

Genomic selection in dairy cattle: impact and contribution to the improvement of bovine fertility*

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Abstract

Genomic selection has revolutionized the dairy cattle breeding industry, with ripple effects that have greatly impacted dairy herd management. Rate of genetic progress has increased markedly, especially in Holstein and Jersey breeds, for production, health, and fertility traits. Genomic testing of young bulls and heifers provides greater accuracy of selection decisions involving traditional fertility traits, such as daughter pregnancy rate, while creating the opportunity to improve novel traits, such as fetal loss. Cameras, wearable sensors, and other precision livestock farming technologies will allow selection for traits such as estrus duration and intensity that require high frequency phenotyping. At the same time, synergies between genomic testing and advanced reproductive technologies have led to rapid and widespread adoption of sexed semen, coupled with mating of females whose offspring are not needed as herd replacements to beef sires. This strategy produces added-value crossbred calves for the beef supply chain, while allowing genetically inferior mature cows that are still producing at a high level to remain in the herd for additional lactations.

Keywords: Fertility, genomic testing, selection

Impact of genomic selection on dairy cattle improvement programs

Genomic selection using tens of thousands of single nucleotide polymorphism markers dispersed across the bovine genome has transformed dairy cattle breeding programs over the past 15 years, due to commercial availability and widespread adoption of inexpensive genomic testing using DNA microarrays. This technology was first used by artificial insemination (AI) companies to assess the genetic merit of young bulls and potential embryo transfer or in vitro fertilization donors, as well as by pedigree breeders who wished to sell calves, heifers, and cows with high breeding values for production and conformation traits at a premium price. These efforts were highly successful in increasing the reliability of genetic predictions for young bulls and heifers, relative to pregenomic era, because the Council on Dairy Cattle Breeding (CDCB; Bowie, MD) very rapidly incorporated genomic data from commercial testing laboratories into routine national genetic evaluations for dairy cattle. The immediate impact was a decrease in generation interval, particularly in the 'sires of bulls' and 'dams of bulls' pathways, where generation

intervals were reduced from ~ 7.5 and 4.5 years, respectively, to 2.5 and 2.0 years (Figure 1). Average generation interval in the 'sires of cows' pathway also declined, albeit at a slower rate, from ~ 7.0 years to 4.5 years (Figure 1).

Because generation interval is in the denominator of the 'Breeders Equation' for calculating rate of annual genetic progress that features genetic variation, accuracy, and selection intensity in the numerator, average genetic gain per year in key traits such as protein yield accelerated with the switch to genomic selection (Figure 2). Annual genetic change in female fertility, as measured by daughter pregnancy rate (a function of days open), declined from 1975 to 2000. This downward trend stalled between 2000 and 2010 and began to reverse after genomic selection began in 2009 (Figure 2), indicating genomic selection can yield an increase in the rate of genetic improvement for female fertility and augment phenotypic gains achieved through improved reproductive management practices. Increased genetic progress by genotyping potentially elite young bulls and heifers represented an early win for the applications of genomic technologies in dairy cattle improvement programs.

Fifteen years prior to the advent of genomic selection, dairy cattle breeders realized that selection for increased revenue

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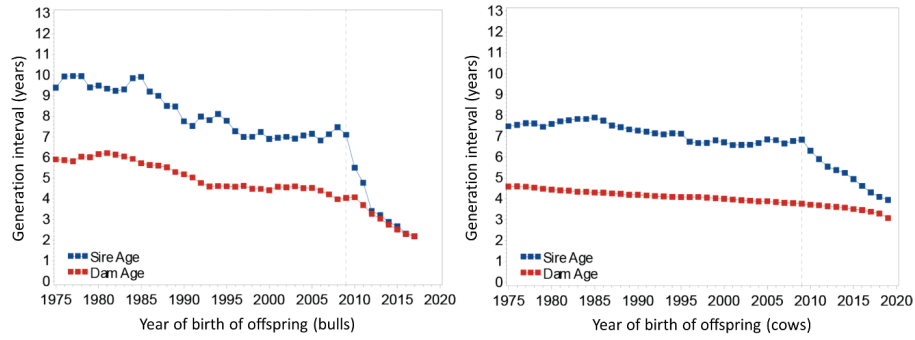


Figure 1. Average generation intervals by year of birth for US Holstein bulls and cows from 1975 to present; dashed vertical line indicates when genomic selection was implemented, adapted from Guinan et al: 2023.¹

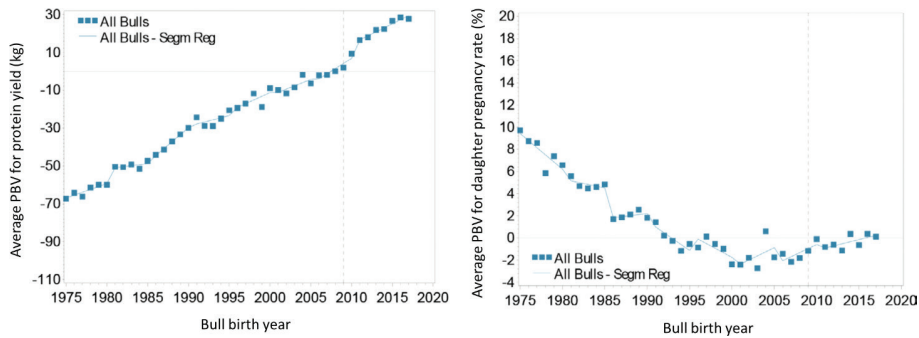


Figure 2. Average predicted breeding value (PBV) by year of birth for US Holstein bulls for protein yield and daughter pregnancy rate from 1975 to present; dashed vertical line indicates when genomic selection was implemented, adapted from Guinan et al: 2023.¹

	Relative emphasis on trait (%)										
	PD\$ (1971)	MFP\$ (1976)	NM\$ (1994)	NM\$ (2000)	NM\$ (2003)	NM\$ (2006)	NM\$ (2010)	NM\$ (2014)	NM\$ (2017)	NM\$ (2018)	NM\$ (2021)
Milk	52	27	6	5	0	0	0	-1	-1	-1	0
Fat	48	46	25	21	22	23	19	22	24	27	22
Protein		27	43	36	33	23	16	20	18	17	17
PL			20	14	11	17	22	19	13	12	15
SCS			-6	-9	-9	-9	-10	-7	-7	-4	-3
BWC				-4	-3	-4	-6	-5	-6	-5	-9
UDC				7	7	6	7	8	7	7	3
FLC				4	4	3	4	3	3	3	1
DPR					7	9	11	7	7	7	5
SCE					-2						
DCE					-2						
CA\$						6	5	5	5	5	3
HCR								1	1	1	1
CCR								2	2	2	1
LIV									7	7	4
HTH\$										2	2
RFI											-12
EFC											1
HLIV											1

Figure 3. Relative economic weights for production and fitness traits in the Predicted Difference (PD\$) and Net Merit (NM\$) indices used by US dairy farmers from 1971 to present. Fitness traits include productive life (PL), somatic cell score (SCS), body size/weight composition (BSC/BWC), udder composite (UDC), foot and leg composite (FLC), daughter pregnancy rate (DPR), sire calving ease (SCE), daughter calving ease (DCE), calving ability (CA\$), heifer conception rate (HCR), cow conception rate (CCR), livability (LIV), producer-reported health disorders (HTH\$), residual feed intake (RFI), early first calving (EFC), and heifer livability (HLIV). Negative values indicate that lower values of a given trait are preferable, adapted from VanRaden et al: 2021.²

per cow, in the form of higher production traits such as milk, fat, and protein yields, was not the optimal way to improve farm profitability. Genetic evaluations of physical conformation, such as udder composite and foot and leg composite, had been available for decades, but no direct measures of fitness were part of the breeding goal until 1994 (Figure 3). In that year, national genetic evaluations for somatic cell score and length of productive life were provided to US dairy farmers, and the latter allowed indirect selection for improved reproductive performance through its favorable genetic correlations with traits such as conception rate and days open. A direct measure of female fertility, namely daughter pregnancy rate, was added to the breeding goal in 2003, as was calving ability that included direct and maternal aspects of calving ease and stillbirth rate. Two more direct measures of female fertility, cow conception rate and heifer conception rate, were added into the breeding objective in 2014. It is important to note that some other countries, particularly those in Scandinavia that had national veterinary recording systems, implemented national genetic improvement programs for traits such as fertility, calving ability, and mastitis resistance long before these traits received substantial attention in North America.

Although genetic evaluations for many of the fitness traits were introduced after genomic testing became available, most of them could have been implemented without genomics. That is not the case for traits such as feed utilization efficiency or enteric methane emissions, which require expensive measurement equipment and are too difficult and expensive to record routinely on commercial farms. Data from research farms can be combined with genomic testing information from the same animals, allowing implementation of national genomic evaluations for novel traits that cannot be measured on commercial farms. This strategy of enlisting research farms or contract herds with specific data capture technologies can also be used for novel measures of specific aspects of female fertility.

Impact of genomic testing on dairy herd management

Initially, genomic testing was used only for potentially elite animals that were expected to be superior based on their pedigrees, performance, or progeny. The AI companies tested their current and prospective bulls immediately, as well as most current and prospective donor dams, but the impact of genomics on commercial dairy farms was limited to indirect gains conferred by increased merit of the bulls represented in their semen tanks. That changed between 2015 and 2020, when farmers began aggressively using semen from beef bulls to mate excess females, which needed a pregnancy to initiate the next lactation but were genetically too inferior to be used as dams of the next generation of replacement heifers. This practice allowed mature cows whose time had passed, genetically speaking, to stay in the herd for additional lactations if they were still producing milk at a high level. In addition, the resulting crossbred calves brought added value upon entering the beef supply chain, relative to the purebred calves that would have been created otherwise, especially in the Jersey breed.³

By 2021 (Figure 4), majority of first and second inseminations of yearling heifers involved sexed Holstein semen and, although many first and second inseminations of young cows still relied on conventional Holstein semen, a rapid shift toward beef semen was observed in the repeat inseminations of older cows. Market for conventional dairy semen has

become relatively small, as the proportions of inseminations to sexed dairy semen and conventional beef semen continue to increase.

Potential advances in improvement of female fertility

Although selection for improved female fertility using national genetic evaluations for daughter pregnancy rate, heifer conception rate, and cow conception rate can help stem the decline in reproductive performance observed in previous decades, these traits can be influenced heavily by environmental and management factors, such as length of the voluntary waiting period, presence or absence of heat abatement systems, and hormonal synchronization protocols. At the same time, marked phenotypic improvements in reproductive performance have been achieved through advances in reproductive management practices, specifically hormonal synchronization of estrus and ovulation, followed by timed AI.⁵ Many commercial dairy farms today are achieving levels of reproductive success that would have been unimaginable 20 years ago, but these programs bear short-term costs of additional labor and supplies, and they present a long-term risk of consumer backlash.

One aspect of female fertility that has eluded direct genetic selection thus far is pregnancy loss. Pregnancy losses during the first 42 days of pregnancy are typically referred to as embryonic loss, whereas pregnancy losses after 42 days of pregnancy are commonly known as fetal loss. Rates of embryonic loss are typically higher, around 25 to 40%, than rates of fetal loss that usually range from 8 to 14%.⁶ However, because fetal losses occur later in pregnancy, their economic impact is much greater, and fetal loss is a heritable trait that could be considered in selection programs. Recently, genetic parameters were estimated⁷ for fetal loss in US Holstein cattle by applying linear and threshold models to data from nulliparous heifers and primiparous and multiparous lactating cows that were confirmed pregnant on day 42 after an insemination event (Figure 5). Fetal loss phenotypes were considered as binary (0 = pregnancy maintained, 1 = pregnancy lost after day 42) or ordinal (0 = pregnancy maintained, 1 = pregnant on day 42 but nonpregnant on day 150, 2 = pregnancy lost after day 150). Heritability estimates were low in nulliparous heifers, but threshold model estimates for the binary phenotypes were 8 and 16%, respectively, in primiparous and multiparous cows, indicating the potential for improvement through genetic selection.

Opportunities may also exist to select for estrous behavior, duration, or intensity, which could in turn improve insemination and conception rates. It is known that high-producing dairy cows tend to have shorter estruses than low-producing cows or yearling heifers. For example, it has been reported⁸ that cows producing 46.4 ± 0.4 kg milk/day had estruses of shorter duration (6.2 ± 0.4 hours) than cows producing 33.5 ± 0.3 kg milk/day (10.9 ± 0.7 hours), with fewer standing events (6.3 ± 0.4 versus 8.8 ± 0.6 , respectively). High-producing cows also had lower intensity of estrus, as measured by the number of standing events per hour, than low-producing cows, such that 53.4% of high-producing cows that estruses characterized as short duration / low intensity (< 8.7 hours and < 2.7 standing events per hour), 23.3% had estruses characterized as long duration / low intensity (≥ 8.7 hours and < 2.7 standing events per hour), and 15.8% had estruses characterized as short duration / high intensity (< 8.7 hours and ≥ 2.7 standing events per hour). Estruses that are

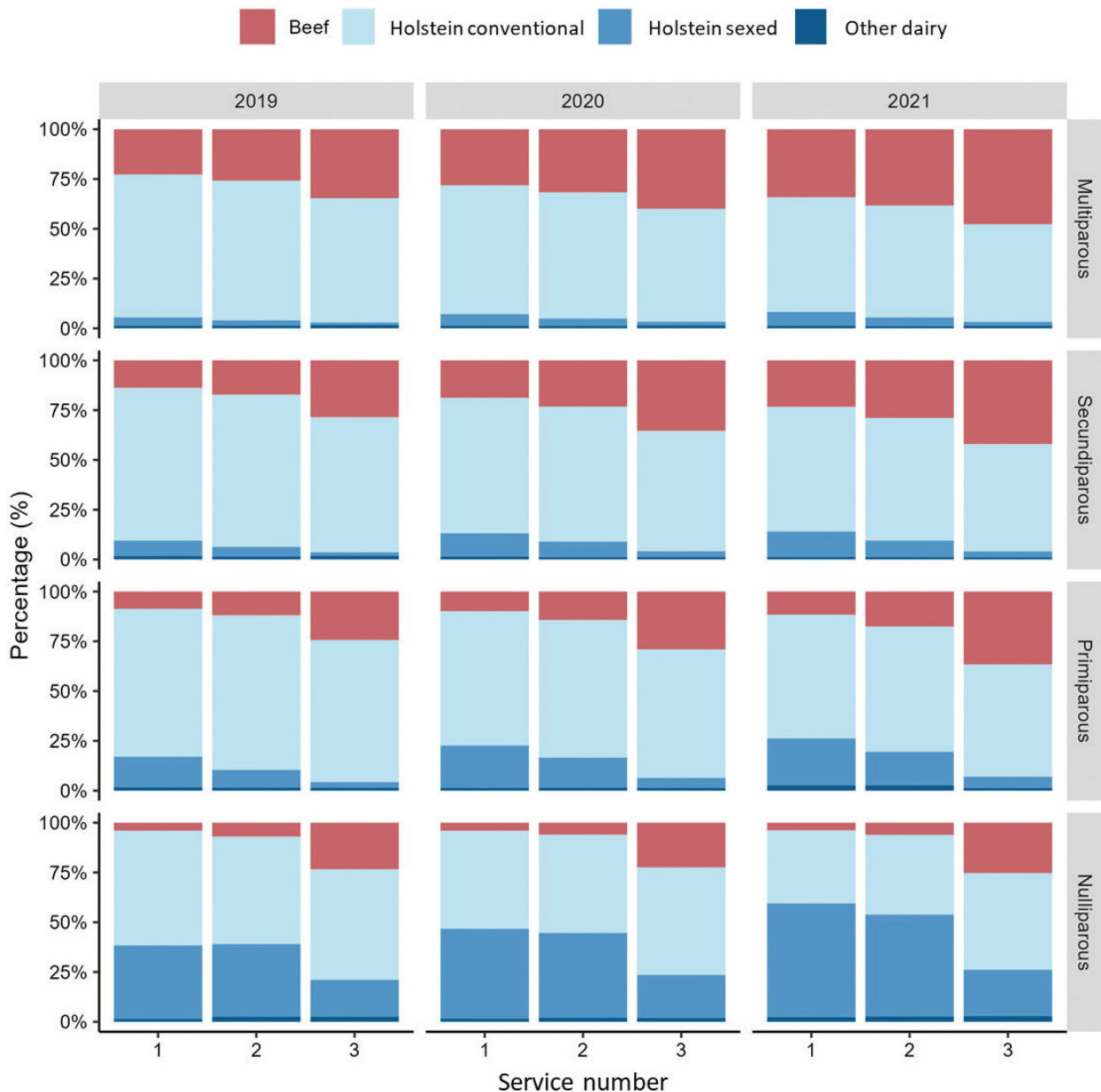


Figure 4. Relative frequencies of beef, conventional Holstein, sexed Holstein, and other dairy semen inseminations of yearling Holstein heifers and first parity, second parity, or third and later parity Holstein cows in the US from 2019 to 2021, by service number, adapted from Lauber et al: 2023.⁴

short in duration or low in intensity make visual heat detection very challenging, and they can lead to missed estrus events when using pedometers or accelerometers for automated estrus detection. This can, in turn, lead to greater reliance on hormonal synchronization and timed AI programs, which are highly effective but may not be viewed favorably by consumers of dairy products.

Portfolio of tools available for reproductive management of lactating dairy cows have been reviewed^{5,9} with specific focus on the use of data from wearable sensors, noting that these systems provide the opportunity to study associations estrus duration, estrus intensity, and pregnancy outcomes. Data from a large commercial farm with an accelerometer system were used¹⁰ to quantify estrus duration, as well as activity strength (intensity of

the increase in activity) and rumination strength (intensity of the decrease in rumination) during estrus, with the latter phenotypes measured relative to a cow's baseline activity and rumination levels prior to estrus. Increases in probability of pregnancy by lactation number and semen type, according to activity strength at the time of insemination are described (Figure 6). In every scenario, cows with greater activity strength had higher conception rates, and similar results (not shown) were observed for estrus duration and rumination strength, indicating the possibility of enhancing the duration and intensity of estrus through genetic selection that could lead to less reliance on hormonal synchronization programs.

While this article focuses largely on novel female fertility traits under study by our research group at the University of

Wisconsin-Madison, other research groups have pursued different traits that may also be strong candidates for improvement through genomic selection. For example, heritability estimates of 0.31 and 0.25 for antral follicle count in lactating Holstein cows and nulliparous Holstein heifers, respectively, have been reported¹¹ indicating the potential for increasing the number of healthy follicles and oocytes through selection. Substantial relationship between anogenital distance and pregnancy status in a seasonal, pasture-based system, has been reported¹² suggesting it may have potential as an indicator trait in genetic selection programs. Positive associations between plasma concentrations of antiMüllerian hormone (AMH) and

maintenance of pregnancy or pregnancy rate have been reported¹³; and candidate genes associated with AMH concentration and embryo development in Holstein cattle have been reported.¹⁴ Thus, genomic selection can be applied to a broad array of novel fertility traits if a reference population of animals with genotypes and phenotypes can be established.

Potential advances in improvement of male fertility

Although selection programs have focused primarily on improving female fertility, significant variability also exists in the male's contribution to pregnancy. Preselection of AI bulls occurs routinely, based on AI company benchmarks for semen quantity and quality,¹⁵ so the observed differences between bulls in on-farm conception rates reflect the remaining variation in sperm quality after internal control measures have been applied. For the past 15 years, CDCB has provided sire conception rate evaluations that are phenotypic (rather than genetic) predictions of fertility of semen from individual bulls after accounting for accounting for known environmental and management factors.¹⁶ Farmers can use this information when purchasing semen, and AI companies can monitor these data to identify or confirm challenges with the semen of individual bulls at a given time. Furthermore, it has been reported¹⁷ that sires with low versus high evaluations for sire conception rate differ in blastocyst development rate, as well as percentages of unfertilized oocytes and degenerated embryos, in an in vitro experiment.

Widespread genomic testing of US dairy cattle has facilitated rapid and highly effective investigation of inherited conditions affecting embryonic or fetal loss that can be subsequently managed using the genomic data of AI bulls. In some cases, the functional mutation can be identified, and its mode of inheritance can be deduced, whereas in other cases, only the association between a specific haplotype (haploid stretch of

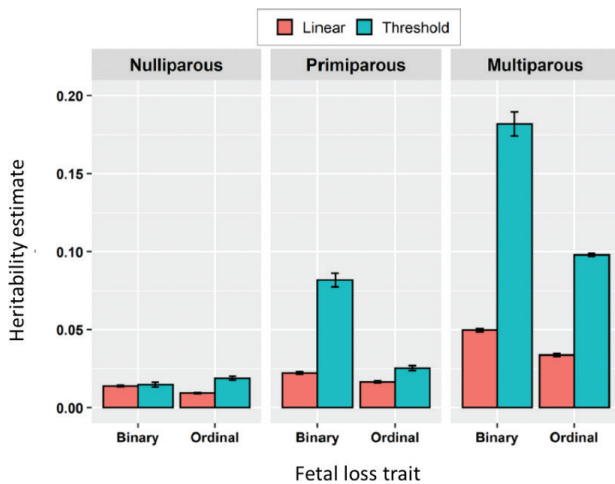


Figure 5. Heritability estimates for fetal loss in nulliparous, primiparous, and multiparous Holstein cattle, using linear or threshold models and considering fetal loss phenotypes as binary or ordinal, adapted from Sigdel et al: 2022.⁷

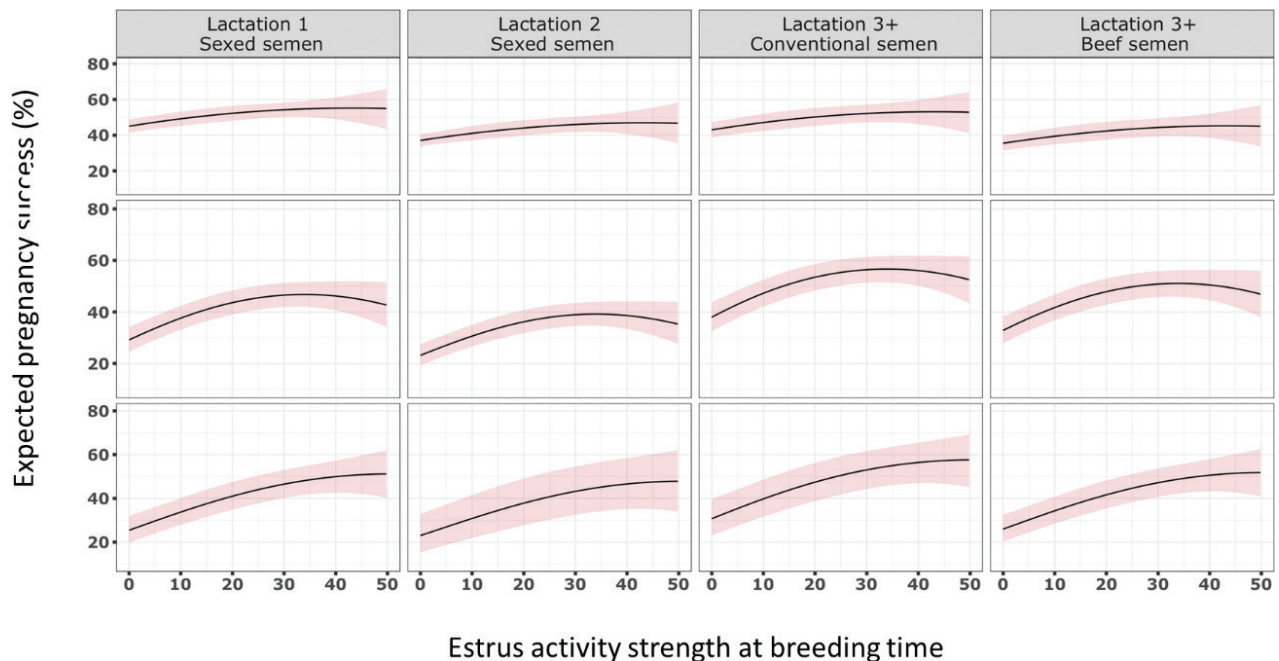


Figure 6. Predicted probability of pregnancy for cows in lactation 1, 2, or 3+ when inseminated with sexed, conventional, or beef semen, according to accelerometer-based measures of the increase in activity during estrus relative to the cow's preestrus baseline activity, adapted from Chasco et al: 2023.¹⁰

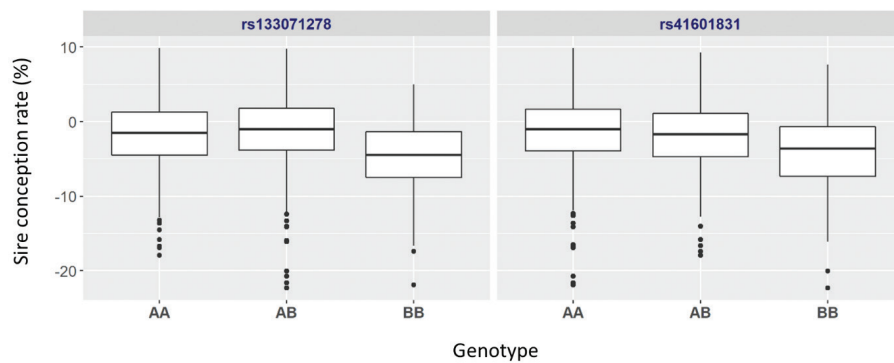


Figure 7. Sire conception rates of Italian Brown Swiss bulls carrying 1 or 2 copies of the undesirable allele at single nucleotide polymorphism loci on chromosomes 6 (left panel) and 26 (right panel), adapted from Pacheco et al: 2022.¹⁹

DNA carried by the sperm or egg) and a reproductive outcome can be identified. A novel approach was proposed¹⁸ to detecting genomic regions associated with impaired fertility, in which haplotypes that appear frequently in the population in heterozygous form, but for which no living homozygotes have been reported, are targeted for further investigation. With additional research, many of these putative genetic defects can be confirmed and attributed to underlying functional mutations. Breed associations maintain lists of genetic variants that are known to affect fertility, coat color, polled status, and many other conditions, and these can be managed at the farm level using computerized mating programs that incorporate genomic data.

Research aimed at understanding the underlying genetic basis of observed differences in male and female fertility continues at a rapid pace. Recently, genomes of 1,102 Italian Brown Swiss bulls using high-density genotypes (454,556 single nucleotide markers per bull) were scanned¹⁹ and it was detected that regions on chromosomes 6 and 26 that were strongly associated with sire conception rates and seemed to indicate nonadditive inheritance. Bulls that were homozygous for the unfavorable allele at each location had significantly ($p < 0.05$) poorer male fertility than their contemporaries (Figure 7). Widespread genomic testing in cattle and other farm animals, coupled with advances in statistical models and machine learning algorithms, will allow continued advances in our understanding of the roles of specific genetic and epigenetic factors associated with male and female fertility in the future.

Conclusion

Genomic selection of dairy cattle has led to monumental changes in dairy cattle breeding programs, especially when coupled with advanced reproductive technologies. Widespread genomic testing and advanced reproductive technologies have led to more rapid genetic progress for most economically important traits, and new opportunities have arisen regarding selection for novel phenotypes that are too difficult to measure on commercial farms, as well as those that can be captured electronically using cameras, accelerometers, and other sensor technologies. Farmers have shifted quickly to coupling sexed dairy semen with beef semen for generating high-merit replacement heifers for their dairy operations and added-value crossbred calves for the beef supply chain. Together, genome-based selection tools and precision livestock farming

technologies will continue to aid in the improvement of reproductive performance on dairy farms and the sustainability of our dairy industry.

Conflict of interest

Authors declare no conflict of interest.

References

1. Guinan FL, Wiggans GR, Norman HD, et al: Changes in genetic trends in US dairy cattle since the implementation of genomic selection. *J Dairy Sci* 2023;106:1110-1129. doi: 10.3168/jds.2022-22205
2. VanRaden PM, Cole JB, Neupane M, et al: Net merit as a measure of lifetime profit: 2021 revision. AIP Research Report NM\$8 (05–21). Available from: <https://www.ars.usda.gov/ARUserFiles/80420530/Publications/ARR/nmcalc-2021ARR-NM8.pdf> [cited 16 August 2023].
3. Berry DP: Invited review: beef-on-dairy—the generation of crossbred beef × dairy cattle. *J Dairy Sci* 2021;104:3789-3819. doi: 10.3168/jds.2020-19519
4. Lauber MR, Peñagaricano F, Fourdraine RH, et al: Characterization of semen type prevalence and allocation in Holstein and Jersey females in the United States. *J Dairy Sci* 2023;106:3748-3760. doi: 10.3168/jds.2022-22494
5. Giordano JO, Sitko EM, Rial C, et al: Symposium review: use of multiple biological, management, and performance data for the design of targeted reproductive management strategies for dairy cows. *J Dairy Sci* 2022;105:4669-4678. doi: 10.3168/jds.2021-21476
6. Wiltbank MC, Baez GM, Garcia-Guerra A, et al: Pivotal periods for pregnancy loss during the first trimester of gestation in lactating dairy cows. *Theriogenology* 2016;86:239–253. doi: 10.1016/j.theriogenology.2016.04.037
7. Sigdel A, Bisinotto RS, Peñagaricano F: Genetic analysis of fetal loss in Holstein cattle. *J Dairy Sci* 2022;105:9012-9020. doi: 10.3168/jds.2022-22000
8. Lopez H, Satter LD, Wiltbank MC: 2004. Relationship between level of milk production and estrous behavior of lactating dairy cows. *Anim Reprod Sci* 2004;81:209-223. doi: 10.1016/j.anireprosci.2003.10.009

9. Cerri RLA, Burnett TA, Madureira AML, et al: Symposium review: linking activity-sensor data and physiology to improve dairy cow fertility. *J Dairy Sci* 2021;104:1220-1231. doi: 10.3168/jds.2019-17893
10. Chasco JA, Chebel RC, Weigel KA, et al: Estrus expression in dairy cows: phenotyping, genetic variability, and association with reproductive performance. *J Dairy Sci* 2023;106 (Suppl. 1):53.
11. Walsh SW, Mossa F, Butler ST, et al: 2014. Heritability and impact of environmental effects during pregnancy on antral follicle count in cattle. *J Dairy Sci* 2014;97:4503-4511. doi: 10.3168/jds.2013-7758
12. Grala TM, Price MD, Kuhn-Sherlock B, et al: Investigating anogenital distance and antral follicle count as novel markers of fertility within a herd of cows with positive or negative genetic merit for fertility traits. *J Dairy Sci* 2021;104:12939-12952. doi: 10.3168/jds.2020-19948
13. Ribeiro ES, Bisinotto RS, Lima FS, et al: Plasma anti-Müllerian hormone in adult dairy cows and associations with fertility. *J Dairy Sci* 2014;97:6888-6900. doi: 10.3168/jds.2014-7908
14. Gobikrushanth M, Purfield DC, Colazo MG, et al: The relationship between serum anti-Müllerian hormone concentrations and fertility, and genome-wide associations for anti-Müllerian hormone in Holstein cows. *J Dairy Sci* 2018;101:7563-7574. doi: 10.3168/jds.2017-13940
15. Harstine B, Utt M, DeJarnette JM: Review: integrating a semen quality control program and sire fertility at a large artificial insemination organization. *Animal* 2018;12:s63-s74. doi: 10.1017/S1751731118000319
16. Kuhn MT, Hutchison JL: Prediction of dairy bull fertility from field data: use of multiple services and identification and utilization of factors affecting bull fertility. *J Dairy Sci* 2008;91:2481-2492. doi: 10.3168/jds.2007-0743
17. Ortega MS, Moraes JGN, Patterson DJ, et al: Influences of sire conception rate on pregnancy establishment in dairy cattle. *Biol Reprod* 2018;99:1244-1254. doi: 10.1093/biolre/bfy141
18. VanRaden PM, Olson KM, Null DJ, et al: Harmful recessive effects on fertility detected by absence of homozygous haplotypes. *J Dairy Sci* 2011;94:6153-6161. doi: 10.3168/jds.2011-4624
19. Pacheco HA, Rossoni A, Cecchinato A, et al: Deciphering the genetic basis of male fertility in Italian Brown Swiss dairy cattle. *Sci Rep* 2022;12:10575. doi: 10.1038/s41598-022-14889-1