

Novos Enfoques Symposium
“Genomic Information to Improve Fertility in Dairy Cattle”

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Introduction

Genetic evaluation and selection in dairy cattle has largely focused on production traits such as milk and protein production for many years. Genetic improvement causes an average US Holstein cow born in 2014 to produce over 14,000 pounds more milk in one lactation than her ancestors born in 1960. However, the fertility and health of dairy cows cannot be included among these success stories, at least not yet. Between 1960 and its low point in 2000, the phenotypic fertility of dairy cattle declined by 14.7 percentage points while the genetic fertility declined by 15.1 percentage points. In response, Dairy researchers (USDA/AIPL) and cattle breeders responded by developing national genetic evaluation programs for a number of fertility traits including Daughter Pregnancy Rate (DPR), Heifer Conception Rate (HCR) and Cow Conception Rate (CCR) among others. The availability of these fertility traits and the incorporation of them in multi-trait indexes helped US dairy breeders reverse the trend. Continued enhancements of these predictions and the incorporation genomic information today presents an unprecedented opportunity to improve fertility using genetic and genomic information. Improving fertility and health traits through genetic selection presents a compelling opportunity for dairy producers to improve the reproductive performance and profitability of the herd when coupled with sound management practices. This publication documents the available genetic predictions for fertility traits in the US Genetic Evaluation and discusses some key concepts and strategies to utilize these predictions to improve fertility with emphasis in female selection.

Implementation and Key Benefits of the Genomic Evaluation in United States

Implementation of genomic evaluation has caused profound changes in dairy cattle breeding. Today, the majority of young bulls are selected and commercialized by major artificial insemination organizations based upon the genomic evaluation. Reliability of this genomic prediction can reach 75% for yield traits, which is adequate for marketing semen of 2-yr-old bulls or select replacement heifers using this genomic information.

In short, the first official USDA genomic evaluations were released in 2009 for Holsteins, Jerseys, and Brown Swiss. These predictions included genotypes derived from tissue samples and DNA is extracted from the samples by Zoetis Genetics and other labs. The extracted DNA then is placed on a chip developed by Illumina (San Diego, CA), USDA's Bovine Functional Genomics Laboratory (Beltsville, MD), and other research partners (Wiggans et al 2011). That chip provides genotypes on more than 50,000 single nucleotide polymorphisms (SNPs) evenly distributed across all 30 chromosomes; of these SNPs, nearly 40,000 are informative for Holsteins. The genotypes document which genes each animal

inherited, and this completely new source of information is now included in genetic evaluations. The phenotypic (i.e. observed milk production or confirmed pregnancy dates) and genotypic (DNA) information for a reference population is then used to estimate SNP effects (Wiggans et al 2011). Animals from the reference population are genotyped animals with usually high reliable traditional evaluations. The SNP effects estimated from a reference population can be used to calculate genomic evaluations for animals without traditional evaluations (VanRaden, 2008; Wiggans et al 2011). An animal's genomic evaluation includes a genomic prediction (estimates of SNP) and information from traditional evaluations which is included in a second step in the genomic information. A selection index is used to combine the genomic prediction and traditional evaluation (VanRaden et al., 2009; Wiggans et al 2011).

The use of genotypes as a source of information in assessment of an animal's genetic merit has a number of advantages. The simplest is that since an animal's genotype is available at birth and unchanging, we can assess that animal's genetic potential long before any other sources of data are available. This is a critical component of this technology in reducing the effective generation interval by identifying superior animals, and equally important, animals that likely possess inferior genetics, early, and reducing resources invested in animals that should contribute little to genetic progress. This is part of the reason the major artificial insemination organizations now use genomics so extensively in selecting sire candidates, such that the risk of developing and progeny testing sires is mitigated through prescreening.

The use of genomics may also provide predictions of genetic merit with greater reliability than could be sensibly achieved using traditional progeny-based evaluation systems. This is particularly relevant for lowly heritable traits where genomic predictions can provide more information than could ever be achieved in the lifetime of a typical animal. Recalling the results presented in Table 1, a prediction for daughter pregnancy rate in a young female with reliability of 68% would be equivalent to more than 184 daughters in a traditional genetic evaluation (CDCB 2016). Few dairy cows will ever produce that many daughters and yet this degree of reliability is achievable with genomic testing. Therefore, the increased reliabilities and shortened generation interval from using genomic evaluations are the most important factor in increasing the rate of genetic improvement in dairy breeding.

Table 1: Comparison of December 2016 genomic and traditional evaluations (n= 731,443 Holstein heifers; CDCB 2016).

Traits	Reliability (%)			
	Genomic average	Traditional average	Difference ¹	Genomic DE ²
Net merit (\$)	72	26	46	42.9
Milk (pounds)	75	28	48	32.5
Fat (pounds)	75	28	48	32.5
Protein (pounds)	75	28	47	33
Productive life (months)	71	24	47	102.7
Somatic cell score	73	25	47	75
Daughter pregnancy rate (%)	68	22	46	184.8

Final score	73	23	50	31.5
Sire calving ease	57	27	30	44.6
Daughter calving ease	54	23	31	52.7

¹Genomic minus traditional.

²DE = daughter equivalents (the number of daughters with records that the genomic information is worth).

In summary, the incorporation of genomics in the evaluation of dairy cattle genetics is giving to the US dairy industry a good base of knowledge for informed decisions.

Genetic evaluation for Fertility (Traits, Indexes, Haplotypes)

Daughter Pregnancy Rate (DPR)

Daughter Pregnancy Rate allows herd managers to measure how quickly their cows become pregnant again after having a calf and is defined as the percentage of nonpregnant cows that become pregnant during each 21-day period (CDCB 2014). A DPR of 1 implies that daughters from a given bull are 1% more likely to become pregnant during that estrus cycle than a bull with an evaluation of 0. Data to evaluate DPR have improved in recent years as more herds report all inseminations and pregnancy check results. Calculation of DPR begins with days open, the interval between calving and a successful breeding date. Days open can be converted to a pregnancy rate as follows, pregnancy rate = $21 / (\text{days open} - \text{voluntary waiting period} + 11)$, where voluntary waiting period is the initial phase of lactation during which no inseminations occur (assumed to be 60 days). The factor of +11 adjusts to the middle day of the 21-day cycle so that cows that conceive during the first cycle receive 100% credit on average (CDCB 2014). For instance, a cow with 154 days open would have $154 - 60 + 11 = 105$ days in which the herdsman was trying to get her bred. In those 105 days, $105 / 21 = 5$ heat cycles are expected. Thus, the pregnancy rate for this cow would be $1 / 5 = 20$ percent. This approach is later converted in a simpler linear approximation, pregnancy rate = $.25(233 - \text{days open})$ is applied to adjusted data for days open before animal model analysis so that solutions are expressed as DPR (VanRaden et al 2002).

The heritability of DPR is 4 percent which indicates the proportion of observed variation in the trait that is due to genetics. Environmental and management factors have a major influence on reproduction in dairy cows. However, given the significant economic importance of reproduction efficiency on dairy herd profitability and the availability of genetic evaluations for daughter pregnancy rate, sire and female selection criteria should include the use of bulls and cows that will improve cow fertility.

Other Fertility traits (USDA)

Heifer conception rate (HCR): heifer's ability to conceive defined as percentage of inseminated heifers that become pregnant at each service; an HCR of 1 implies that daughters of this bull are 1% more likely to become pregnant as a heifer than daughters of a bull with an evaluation of 0 (CDCB 2014).

Calving to first insemination (CFI): Lactating cow's ability to start cycling defined as days from calving to first insemination (CDCB 2014).

Cow conception rate (CCR): Lactating cow's ability to conceive defined as percentage of inseminated cows that become pregnant at each service; a CCR of 1 implies that daughters of this bull are 1% more likely to become pregnant during that lactation than daughters of a bull with an evaluation of 0 (CDCB 2014).

Fertility Index (Holstein)

A fertility index was developed by USA Holstein Association which combines the 4 previously mentioned fertility traits into one overall index. By definition this index describes the ability to conceive as a heifer, ability to conceive as a lactating cow, and a cow's overall ability to start cycling again, show heat, conceive, and maintain a pregnancy. The Fertility Index is derived from the formula: Fertility Index = 18% Heifer Conception Rate (HCR) + 18% Cow Conception Rate (CCR) + 64% Daughter Pregnancy Rate (DPR)

Haplotypes Affecting Fertility

Rapid discoveries of new recessive defects that affect fertility and stillbirth have been recently described in detail (VanRaden et al., 2013; Cole et al., 2016). As part of the genetic test offering, breeders have the opportunity today to access haplotype information that are routinely reported to track the carrier status of these animals and also to identify new recessive disorders. A recent study by Cole et al., 2016 demonstrated that fertility haplotypes generated economic losses of almost \$11 million due to reduced fertility and perinatal calf death. Importantly, these economic losses can be avoided by using genomic information in concert with mating systems to avoid mating carrier by carrier without sacrificing genetic merit.

Table 2 illustrates the current recessive haplotypes affecting fertility reported in the U.S. genomic evaluation system, the frequency of the less common haplotype, and the location.

Table 2: Haplotype tests for recessive disorders that affect fertility in US dairy breeds reported by the US genomic evaluation (Cole et al., 2016).

Breed	Haplotype	Functional /gene name	Frequency (%)	Chromosome	Region (bp)	Reference
Ayrshire	AH1	PIRM/UBE3 B	13	17	65,921,497	Cooper et al. (2014), Venhoranta et al. (2014)
Holstein	HH1	APAF1	1.92	5	63,150,400	Adams et al. (2012)
	HH2	-	1.66	1	94,860,836 – 96,553,339	VanRaden et al. (2011), McClure et al. (2014)
	HH3	SMC2	2.95	8	95,410,507	Daetwyler et al. (2014), McClure et al. (2014)

	HH4	GART	0.37	1	1,277,227	Fritz et al. (2013)
					93,223,651 –	Cooper et al.
	HH5	TFB1M	2.22	9	93,370,998	(2013), Schütz et al.
						(2016)
Jersey	JH1	CWC15	12.1	15	15,707,169	Sonstegard et al. (2013)
					8,812,759 –	
	JH2	—	1.3	26	9,414,082	VanRaden et al. (2014)

Incorporation of Fertility in Multi-Traits Indexes (Life Time Net Merit NM\$)

Selection indexes have been developed to simplify the process of selecting sires and cows. Several selection indexes are provided in the US genetic evaluation and through the dairy breed associations. Breeders can choose specific selection indexes based on how closely the relative weights for the traits in the index represent the breeding goals for their herds.

Developed by USDA, Net Merit (NM\$) estimates lifetime profit combining the incomes and expenses for each trait into an accurate measure of overall profit relevant for dairy producers. NM\$ utilizes economically relevant traits related to yield, health, longevity and calving ease. Specific traits used in the index include fat and protein yield (therefore also milk), productive life, daughter pregnancy rate, somatic cell score, udder composite, feet & leg composite, body size, and calving ability (including stillbirth information). Net Merit \$ index expresses the expected lifetime profit of sires and females compared to the breed base.

In August 2003, service sire calving ease (SCE), daughter calving ease (DCE), and daughter pregnancy rate (DPR) were included in NM\$ calculations. Measures of fertility in merit indexes now include HCR and CCR along with DPR. Relative emphasis in NM\$ for traits HCR, CCR, and DPR are 1.5, 1.7, and 7.0%, respectively (Table 3), with PTA standard deviations of 2.4, 2.8, and 2.3. The combined emphasis for the 3 fertility traits is around 10% (VanRaden and Cole 2014).

Table 3 shows the traits, units, standard deviation, updated economic and relative values in the NM\$ implemented in December 2014 US genetic evaluation (VanRaden and Cole 2014).

Trait	Units	Standard deviation (SD)	Value (\$/PTA unit)	Relative value (%)
Protein	Pounds	18	4.14	20
Fat	Pounds	25	3.22	22
Milk	Pounds	672	-0.006	-1
PL	Months	2.4	29	19
SCS	Log	0.21	-122	-7
Udder	Composite	0.9	31	8
Feet/legs	Composite	1.03	10	3
Body size	Composite	1.03	-16	-5
DPR	Percent	2.3	11	7

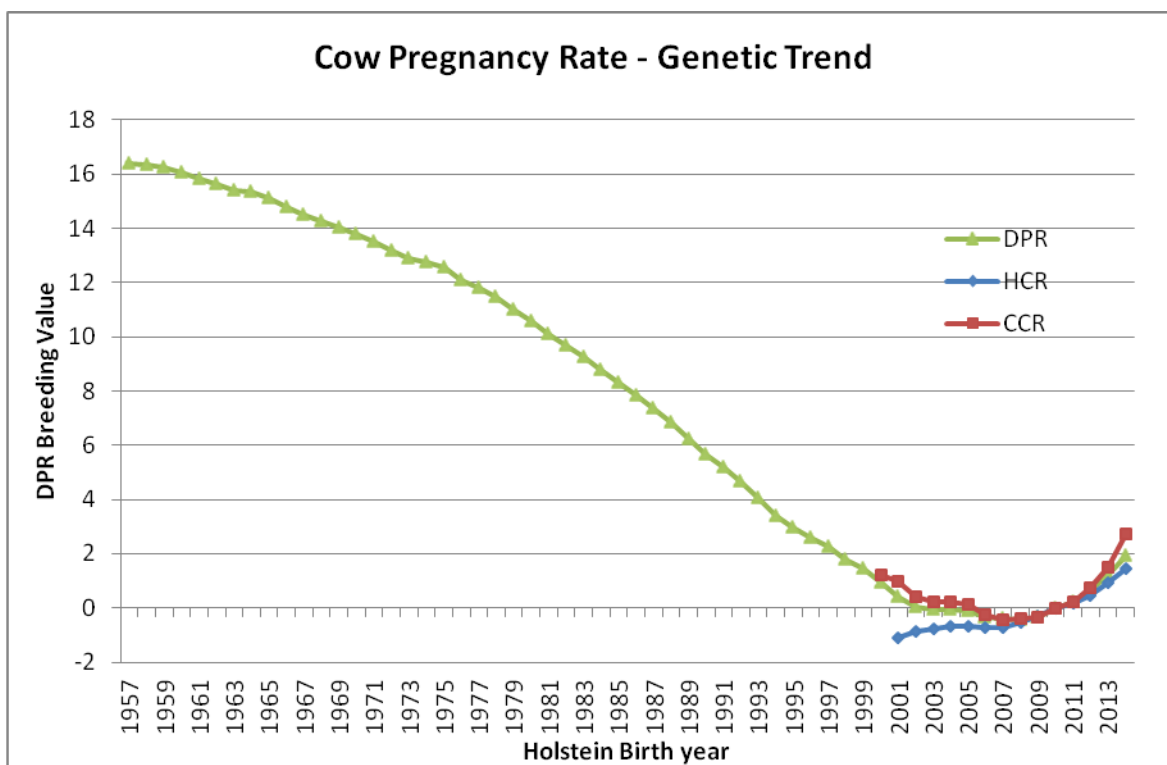
HCR	Percent	2.4	2.3	2
CCR	Percent	2.8	2.2	1
CA\$	Dollars	18	1	5

Genetic Trends of Fertility traits

As previously mentioned, over time the US dairy industry has experienced an overall decline in dairy fertility across diverse production systems. Several reasons may have contributed to this decline such as greater milk production, nutritional management, husbandry management practices, increased herd size and absence of genetic and genomic selection for fertility traits. Importantly, the development and implementation of a US national evaluation for Daughter Pregnancy Rate in 2003, and other related traits as a productive life (PL) and additional fertility traits in recent years (HCC, CCR and CFI) enhanced by genomic information have stop this trend and we have seen a reversal in the genetic potential of US Holsteins during the last 8 years.

Although reproductive performance is strongly influenced by the environment, the incorporation of fertility traits into the genetic evaluation followed by the notorious improvement in genetic trend is a clear evidence to support the influence of genetics on reproductive performance. Furthermore, this improvement occurred even with a continued increase in milk production per cow.

Figure 1 shows the remarkable improvement in the genetic trend of Daughter Pregnancy Rate, and Heifer and Cow Conception Rate (Adapted from CDCB 2016).



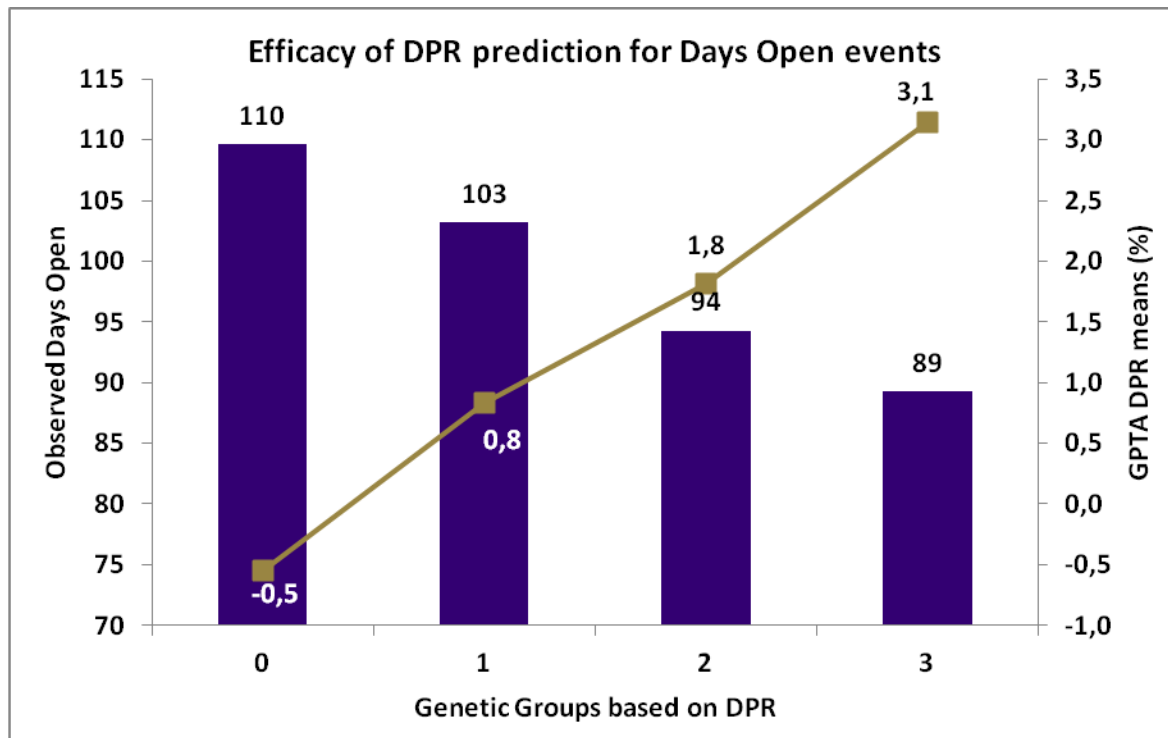
Associations between DPR and Reproductive Outcomes

A fresh approach to demonstrate the value of this information and gain farmers and veterinarian's confidence in these fertility predictions is to determine the relationship between genomic predictions and observed performance of the evaluated animals (Weigel et al., 2015). Thus, we conducted a study to evaluate the association between DPR and days open in commercial US Holstein cows. The objective of this study was to demonstrate the ability of fertility trait predictions to accurately predict reproductive performance (Days Open) in a population of commercial US Holsteins within the first 305 days of lactation.

Eleven large (average 4,180 lactating cows) Holstein herds distributed across the major dairy producing regions of the United States were enrolled in this study including 200 first parity and 100 second parity calving events between September 1st and December 31st of 2015. A random subset of these animals was selected within age group and a tissue sample was collected for genetic testing. In total, 3462 animals were sampled from these eleven herds and all samples were run through the CDCB to ensure compatibility with animal identification (ID), parentage and breed from the US national database. Days Open and other fertility events were collected from on-farm herd management software. Tissue samples from were genotyped with the Zoetis LD Chips by the Zoetis Genetics Laboratory in Kalamazoo, Michigan. Animals were nominated, along with pedigree and genotype to the Council for Dairy Cattle Breeding (CDCB) to obtain CDCB genetic evaluation predictions. Daughter Pregnancy Rate predictions were used to assign cows to percentile based groups of equivalent size, similar to what has been reported by others (Weigel et al., 2015). Furthermore, animals were assigned to percentile fertility based groups (i.e. Bottom 25%, 25-50%, 51-76%, Top 25%) within herd and age group in order to account for the lack of independence between animal and both age group and herd. The data analysis of this paper was generated using SAS Software 9.3 (SAS Institute, Cary NC). For all analyses, differences were considered statistically significant when $P < 0.05$. Least squares means of the STA by group were estimated using PROC MIXED in SAS 9.3 (SAS Institute, Cary NC) where the Days Open was designated as the response variable and the percentile based DPR trait group, lactation, herd and parity group designated as class variables. Animal was nested within herd to account for the lack of independence between animal and herd and both were included in the statistical model as a random effect using the repeated statement.

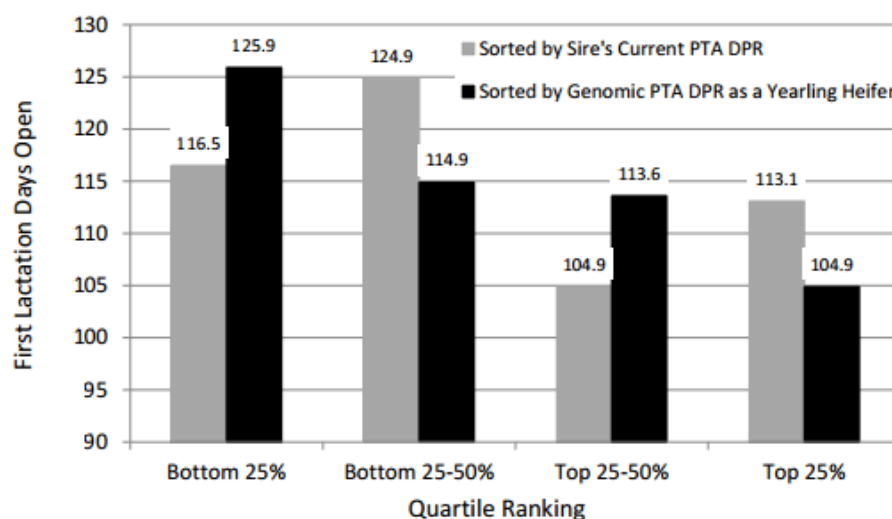
Figure 2 shows least squares means per DPR group (genetic fertility group) and observed Days Open. Differences in observed days open (indirect measure of reproductive efficiency) were statistical significant $P < .0001$ between the genetic groups for Daughter Pregnancy Rate. As shown in Figure 2, the raw difference between the top and bottom DPR quartiles was 20 days in current days open when cows are sorted by DPR. These results indicate that genomic data of young calves and heifers can be used to effectively predict future reproductive performance

Figure 2: least squares means per DPR group (genetic fertility group) and observed Days Open.



Results in this study are similar to previous reports quantifying differences in the Days Open (Weigel et al., 2015) where the authors also include the quartile for sire's current PTA for daughter pregnancy rate in addition to quartile for genomic PTA for daughter pregnancy rate. Weigel et al., 2015 reported 21.0 days difference in actual days open in first lactation when heifers were sorted by genomic PTA (Figure 3). When they sorted animals by sire PTA, this difference was only 3.4 days, so genomic predictions were significantly more accurate as predictors of future reproductive performance

Figure 3: difference in actual days open in first lactation when heifers were sorted by DPR genomic PTA , (Weigel et al., 2015)



Similar results were obtained by Silvestre and Di Croce 2013 (Zoetis Data in File 2014) where authors quantified differences in the conception risk, pregnancy rate and services per conception (Table 4). They reported 13 and 11% difference in conception risk and pregnancy rate respectively, in first lactation when heifers were sorted by genomic PTA.

Table 4 illustrates the association between genomic group for fertility based on DPR GPTA and Reproductive Outcomes in a commercial US dairy (Silvestre and Di Croce 2013)

Genomic Group for Fertility	n ¹	AI Risk ²	Conception Risk (CR) ³	Pregnancy Rate (PR) ⁴	Services per Conception
DPR <0	4336	59%	32%	19%	3.1
DPR 0-1	2707	62%	39%	24%	2.5
DPR >1	531	63%	45%	30%	2.2
Overall	7574	60%	36%	22%	2.8

¹n – Total number of breedings

²AI (Insemination) Risk = number of cows bred / number of eligible cows

³Conception Risk – 10/15/12 & 10/15/13

⁴ Twenty-one day Pregnancy Rate

Selection Strategies to improve fertility using genomic information

Understand the variation

In order to understand the genetic variation from genomically enhanced predictions including fertility, the standard deviation (SD), range of female performance and the economic value of differences in performance are described in Table 5. At the risk of starting too basic, the expected difference between heifers/cows that are 1 SD above the mean as compared to 1 SD below the mean (roughly, cows in the 15th Percentile compared to cows in the 85th Percentile); as such, there are 2 standard deviation between them. For instance, for protein pounds that means 18*2=36 pounds difference in PTA between the cows. As we are reflecting female prediction in this example, necessarily we need to double everything to put it on a Breeding Value basis so that 36 becomes 72 pounds. In other words, the difference between those cows 1 SD below average and those 1 SD above average would be about 10% if our herd average is about 700 pounds for protein. However, if we look at DPR and considering an average pregnancy rate of 25%, the difference between those 1 SD below average would be 20% and 1 SD above would be at 30%. Importantly, selecting for improved reproduction can produced substantial changes in the reproductive performances

Table 5: Heritability, Standard Deviation, Range of Female Performance and Value of Differences in performance (Weigel 2015 – Data on File)

Trait	Units	Heritability	Standard Deviation (SD)	Range of Female Performance (=2*2*SD)	Value of Differences in Performance
Protein	Pounds	.20	18	72	\$298
Fat	Pounds	.20	25	100	\$322
Milk	Pounds	.20	672	2,688	
PL	Months	.08	2.4	9.6	\$278
SCS	Log	.12	0.21	0.84	\$102
DPR	Percent	.04	2.3	9.2	\$101
HCR	Percent	.01	2.4	9.9	\$23
CCR	Percent	.02	2.8	11.2	\$25
CA\$	Dollars	.07	18	\$72	\$72

Development of Genome-Enhanced Selection Strategies

An effective method for selecting for improved cow fertility is to incorporate the fertility traits (DPR) with other economically important traits (production, health) into a selection index such as Net Merit (NM\$), Total Performance Index (TPI) or Jersey Performance Index (JPI) using genomically enhanced prediction (GPTAs).

Selection Criteria: Use Selection Indexes that include fertility traits (DPR)

Dairy cow fertility can be improved through genetic selection using selection indexes along with all many economically important traits (production, health, etc.). Selection indexes are a critical component of many selection strategies as they provide a path for dairy producers to select for comprehensive genetic improvement across many economically important traits including fertility

Rank the animals based on Selection Indexes (Net Merit) and make selection decisions

The simplest application of genomic-enhanced technologies is to better inform selection decisions.

- **Which animals do I keep or buy, and which ones do I cull?**

Replacement heifers are one of the largest costs for commercial dairy producers, so keeping the wrong heifers is a poor investment. Cattle that lack genetic potential don't get pregnant and don't stay in the herd long enough to recover raising costs. Not all heifers represent a genetic upgrade. Therefore,

- Keep the right number of replacements to optimize inventory
- Select those heifers to keep early in life based on reliable data to control development costs in females with limited genetic potential

- **Which bull should I breed this heifer or cow to?**

Select proper bulls to fit in your genomic plan. Using genomic information in concert with mating systems allows minimizing inbreeding and avoiding recessive haplotypes without sacrificing the genetic merit.

- Make strategic breeding decisions using genomic data to identify bulls that complement existing strengths and address apparent weaknesses

- **How many progeny do I want from this female this year?**

The use of genomic data to inform selective breeding of heifers and cows with sexed or beef semen generates many profitable options and scenarios and at the same time accelerates the genetic progress

- Preferentially allocate sex sorted semen to the best females
- Use genomic data to inform selection of donor and recipient females in embryo transfer and IVF programs

Monitor the genetic progress

How much improvement in fertility I can make selecting for Net Merit?

In Brazil, progressive breeders are improving Lifetime Net Merit GPTA at a rate of \$88 by year. This means an average increase in lifetime profit per cow of \$176 (88×2) yearly. In terms of fertility this NM\$ progress also means an yearly increased pregnancy rate by 0.45% meaning a reduction of 2 days open per year in addition of all other trait progress such as an increased genetic merit for milk production by 269 lbs. per lactation with 16 more lbs. of fat and 11 more lbs. of protein, concurrent improvement in somatic cell counts and udder composite and improved longevity with projected average of 1.5 months longer survival in the herd.

Table 6: Expected response to selection expressed in units of the underlying trait associated with selection using NM\$ at a rate of \$88 by year.

Trait	NM\$
Milk	280.5
Fat	16.7
Protein	10.6
PL	1.54
SCS	-0.06
BDC	-0.03
UDC	0.30
FLC	0.22
DPR	0.42
CA	8.55
HCR	0.50
CCR	0.75

Take Home Message

- Improving fertility through genetic selection presents a compelling opportunity for dairy producers to help manage low reproduction performance and improve profitability when coupled with sound management practices
- The incorporation of genomics in the evaluation of dairy cattle genetics is giving to the US dairy industry a good base of knowledge for informed decisions.
- Fertility haplotypes generate economic losses of almost \$11 million due to reduced fertility and perinatal calf death. Importantly, these economic losses can be avoided by using genomic information in concert with mating systems to avoid mating carrier by carrier services without sacrificing the genetic merit.
- Although reproductive performance is strongly influenced by the environment, the incorporation of fertility traits into the genetic evaluation followed by the notorious improvement in genetic trend is a clear evidence to support the influence of genetics on reproductive performance
- Association studies between genomic predictions and observed reproductive performance indicate that genomic data of young calves and heifers can be used to effectively predict future reproductive performance.
- Selecting for improved reproduction can produce substantial changes in the reproductive performances. An effective method for selecting for improved cow fertility is to incorporate the fertility traits (DPR) with other economically important traits (production, health) into a selection index such as Net Merit (NM\$), Total Performance Index (TPI) or Jersey Performance Index (JPI) using genomically enhanced prediction (GPTAs).

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