# Genetics, Genomics and Beyond: What to Expect from New Technologies in Dairy Cattle

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## Take Home Messages

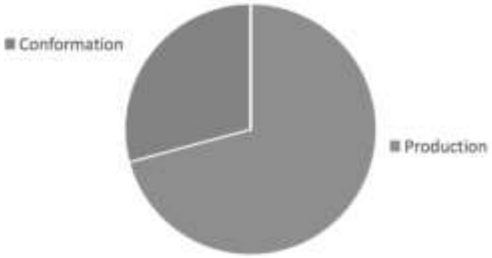
- Genetic improvements can help build and sustain profitable dairy production. If anything is lacking, such as poor calf care, poor management, or poor quality feed, animals will not reach their full genetic potential.
- Implementation of new technologies in routine breeding programs can allow for more exact trait definitions, and permit further genetic gains in both production traits and low heritability traits like health and fertility.
- Many new technologies are emerging, each of which much be carefully scrutinized with regards to associated cost/benefits.
- Exact, well-measured phenotypes which are as close as possible to the biology of the cow remain an integral part of breeding value estimation.
- Genetic diversity, economics, and societal acceptance will play an increasing role in how selection programs evolve.

## Introduction

Many developments have helped to transform and advance the dairy cattle industry. Besides improved management and feeding regimes, as well as other environmental progress, genetic selection for traits with clear economic value, high genetic variation between individuals, and which can be distinctly defined, measured and consistently recorded have contributed greatly to the increase in production efficiency of dairy cattle. The economic value of traits has driven genetic selection in the past; early selection programs were designed to achieve maximum genetic change in production, with additional but lesser emphasis on conformation traits. Simultaneous selection for other traits came only recently (figure 1; adapted from *Miglior et al., 2017*), mainly from the recognition that increased production is associated with a deterioration in cow health and fertility.

Since genetic selection began, the number and type of traits considered for selection in dairy cattle populations have evolved as a response to changes in the needs of producers, consumers, and society. The rapid developments in automated data recording technologies, modern analytical techniques, and genomic information over the past decade are setting the stage for a new era in dairy cattle breeding. The implementation of new technologies in routine breeding programs will not only further accelerate genetic gains in traditional milk production traits, but also, and perhaps more importantly, in low heritability traits like health, fertility, and workability. As the demand for high-quality dairy products increases, dairy breeders will need to optimize the use of available technologies and to consider the emerging forces driving our industry.

A) Relative emphasis of breeding objectives in 1960



B) Relative emphasis of breeding objectives in 2010

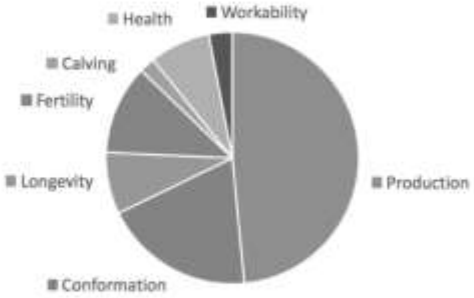


**Figure 1. Relative emphasis of traits included in an average selection index in 1960 (A) and 2010 (B) (adapted from *Miglior et al., 2017*).**

Here we briefly review technologies that will help shape new dairy breeding programs, along with those in development. Powerful tools have emerged in the areas of on-farm data collection, genotyping and sequencing, genetic modification, and bioinformatics. Although many of these technologies bring encouraging opportunities for genetic improvement and transformation of the dairy cattle population, their applications and benefits need to be weighed with their impacts on economics, genetic diversity, and society. Background information on genetic and genomic selection is given, as well as an overview of novel traits and technologies that will affect our industry in the future.

## ■ Genetics as a Tool to Improve Dairy Cattle

Pedigree, dairy production recording programs, and a "good eye" provided the initial data for comparing and choosing dairy cattle. With time, a better understanding of inheritance in dairy cattle evolved into the science of breeding. Major methodological developments, such as the introduction of selection index theory and Best Linear Unbiased Prediction, helped accelerate genetic advancements.

The concepts of genetic variation and heritability are pivotal to the rate of genetic progress possible within a selection program. Traits vary in the amount of both phenotypic and genetic variation observed, and they may be more or less heritable. Heritability defines the proportion of phenotypic variance observed in a given trait which is attributed specifically to genetics. This means that important environmental factors, such as management, nutrition, etc. are corrected for and thus removed from the calculations. Traits may also be dependent on each other. There may be either positive or negative correlations between traits, and they can be strong or weak. Such correlations are exploited by the use of indicator traits, which may be favored if they are simpler or cheaper to measure than a trait of interest.

The easiest traits to improve genetically are those that show high genetic variance between animals, and can be directly, accurately, and consistently measured. These traits are likely controlled by only a few genes. Examples of such traits include milk, fat and protein production, and to a certain extent, some conformation traits. As shown in Figure 2 (adapted from *Miglior et al., 2017*), heritabilities for both production and conformation traits are markedly higher than those for other traits. Health, fertility, and workability traits are more challenging to improve genetically, as they are not well defined and often much more difficult to measure cost-effectively. In some cases, the heritability of these traits may not be precise, as "fuzzy" trait definitions limit proper partitioning of environmental and genetic variance.

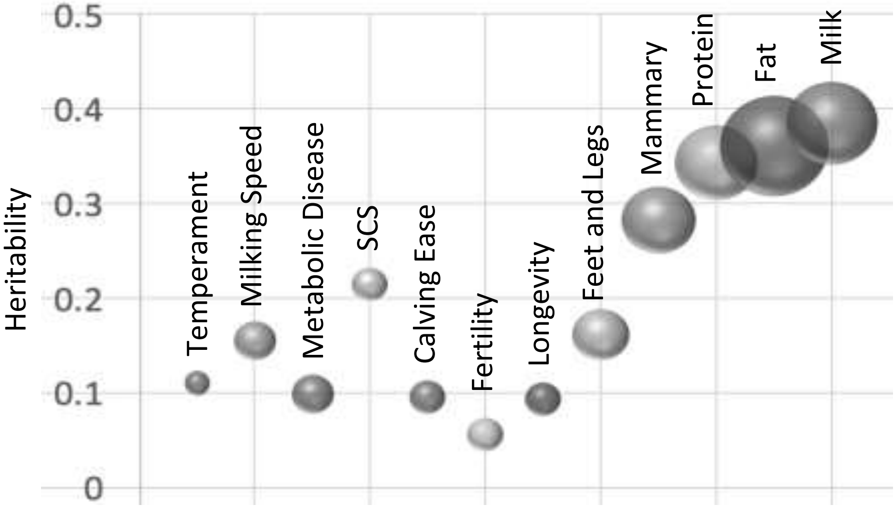


**Figure 2. Ranges in heritabilities for various traits used in current Interbull evaluations (April 2017 run, Interbull, Uppsala, Sweden). Bubble size indicates variance of heritability values across countries (adapted from *Miglior et al., 2017*)**

Despite these difficulties, improvements in health, fertility, and workability traits through genetic evaluation are attainable. When these traits are included in selection indices, we can see genetic progress (see Figure 3; adapted from *Miglior et al., 2017*). We are still challenged with further improving measurement techniques, trait definitions, and data collection for these types of traits, however initial efforts have shown measurable success. Technological developments in the area of on-farm sensors and data collection methods have the potential to improve this situation, however there are a number of logistical and data quality-related issues which must be addressed before the full potential of such technologies can be attained.

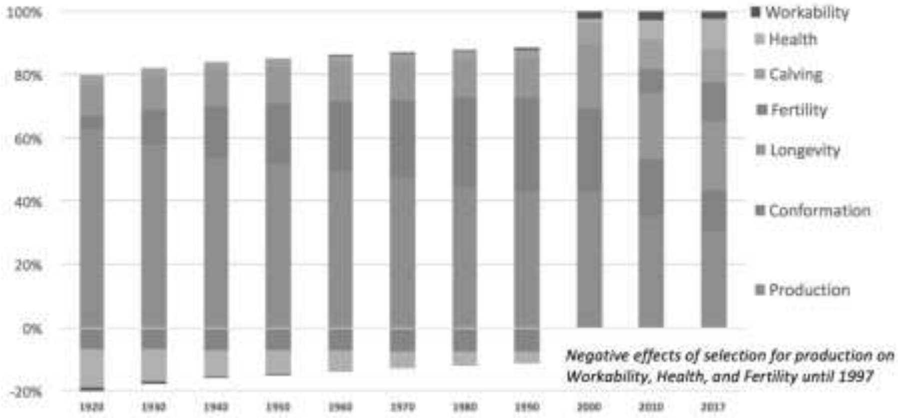


**Figure 3. Schematic representation of the proportion of estimated selection response for various trait categories over time (summing to 100%) (adapted from *Miglior et al., 2017*)**

## ▪ From Genetics to Genomics

The emergence of genomic technologies was initially slow, but has dramatically increased in the last decade. In contrast to genetics, which generally refers to the study of inheritance using conventional theoretical principles and models, genomics uses high throughput molecular information to analyze the function and structure of entire genomes. Various types of molecular markers were initially used for parentage verification and for genetic defect testing. One specific type of genetic marker, the single nucleotide polymorphism (SNP), is found where different nucleotide bases appear at a given position in a DNA sequence. Inexpensive, highly prevalent in the bovine genome, stably inherited, and suitable for high throughput analysis, SNP markers currently provide the information required for genomic selection, as they are often either linked to or directly within many of the genes responsible for phenotypic variation.

The release of the Illumina Bovine SNP50 chip in 2008 allowed efficient genotyping of over 50,000 SNP simultaneously, which were highly polymorphic in different breeds and evenly spaced across the genome. While these SNP represent only a small fraction of genomic variation within the bovine genome, they provide enough information to increase the accuracy of genetic evaluation models. The implementation of genomic selection strategies in dairy breeding have successfully accelerated the rate of genetic gain in many traits of interest in dairy cattle (Figure 4; adopted from *Beavers & van Doormaal*), and thus have changed the landscape of genetic selection. However, accuracies achieved in genomic selection can still be improved.

Genomic selection is based only on those variants that have been discovered and included on SNP arrays. There is still a long way to go before all the information within the genome (totaling approximately 3 billion base pairs per animal) can be understood and implemented in selection programs.

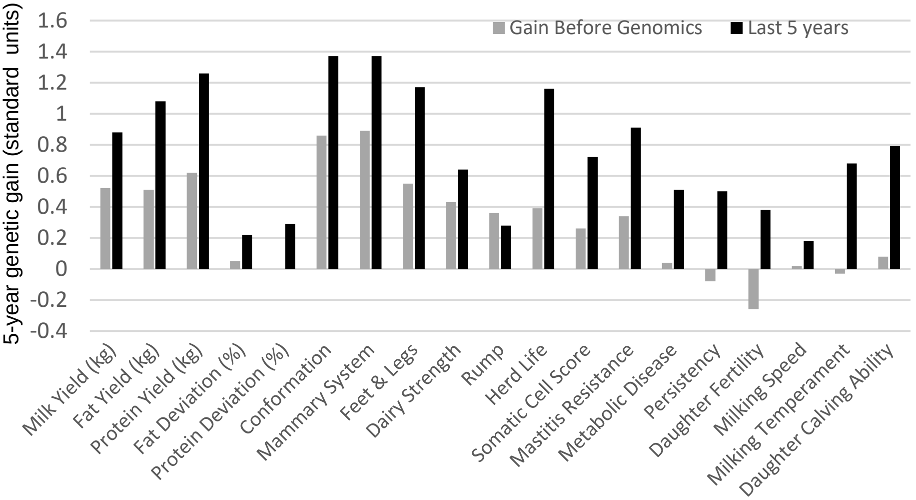
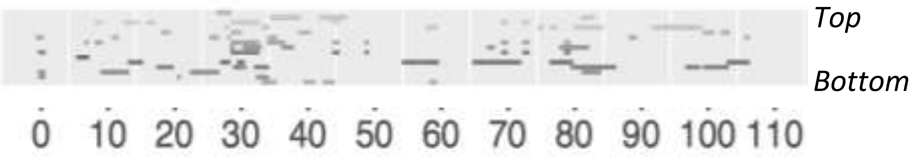


**Figure 4. Relative genetic gain by trait realized during the past 5 years (2011-2016) and before genomics (2004-2009). (Adopted from *Beavers and Van Doormaal, CDN Article, 2017*)**

## ■ From Genotypes to Phenotypes

In the age of genomic selection, the ability to identify exact regions of DNA which have an effect on a particular trait is improving rapidly. The genome-wide association study (GWAS) is a tool used frequently over the past decade to identify and map SNPs with a significant effect on a given trait. One of the most impressive findings using GWAS was the localization of the Diacylglycerol O-acyltransferase 1 (DGAT1) gene on chromosome 14 of the bovine genome, which explains up to 50% of genetic variation in fat yield and up to 10% of genetic variation in milk yield (*Grisart et al., 2002*). While most SNPs explain only a small amount of variation in a given trait, DGAT1 is a picture-perfect example of identifying and harnessing the genetic architecture underlying economically important quantitative traits. As the identification of measurable and consistent biological markers impacting economic traits of interest improve, so too will the precision of associating genomic regions with these traits.

Similarly, the ability to identify long stretches of homozygous DNA (termed "runs of homozygosity" or ROH) is also improving rapidly, as is the ability to associate such regions with traits of interest (e.g., *Howard et al., 2017*). These types of analyses will help us to understand exactly which regions of the genome have negative or positive effects on traits of interest when ROH are present. For example, Figure 5 shows the homozygous regions on bovine chromosome 11 which have an effect on various calving and fertility traits. It can be seen that some specific regions are associated with many different traits affecting calving and fertility in both heifers as well as first parity cows. These areas can now be identified and further investigated with more powerful analyses to find the specific causal mutations.



Position (mbps) of ROH on Chromosome 11. Traits defined below (from top to bottom).

**Figure 5. Location of Runs of Homozygosity (ROH) on chromosome 11 with an effect on various fertility traits. Lines represent traits as follows (from top to bottom: ac0 & ac1 = age at calving (heifer & 1st parity, respectively); afs0 = age at first service (heifer); ctfs1 = calving to first service (1st parity); cz0 & cz1 = calf size (heifer & 1st parity, respectively); do1 = days open (1st parity); fstc0 & fstc1 = first service to calving (heifer & 1st parity, respectively); gl0 & gl1 = gestation length (heifer & 1st parity, respectively); ns0 & ns1 = number of services (heifer & 1st parity, respectively); sb0 & sb1 = still birth (heifer & 1st parity, respectively) (Marras et al., in preparation)**

## ■ Novel Traits

For a long time, selection in dairy cattle focused on the improvement of highly heritable production and conformation traits. Selection goals have since broadened to include economically important traits with low heritability or that are expensive to measure (Figure 1 & 2; adapted from *Miglior et al., 2017*). This is partly due to the realization that such traits can indeed be genetically improved and partly due to the fact that modern and automated technologies can be used to provide more data. Genomics also provides a mechanism for improving such traits. By thoroughly measuring phenotypes in reference populations and extrapolating the results to the national herd (e.g. *Cole et al., 2014*), accurate and reliable breeding values can be achieved if the reference population is large enough. *Chesnais et al*. (2016) provided a description of novel traits expected to be implemented in national evaluations in North America within the next 5 years (Table 1; adapted from *Chesnais et al. 2016*).

**Table 1. Novel traits with ongoing research or official evaluations in Canada (adapted from *Chesnais et al. 2016*)**

| **Trait** | **Definition** |
|---|---|
| Udder Health | Mastitis Incidence (recorded by producer or veterinarian)<br>Alternative predictors of mastitis (conductivity, mid infra-red (MIR), etc.)<br>Hoof Health (hoof trimming, locomotion, lameness) |
| Other Health Traits | Reproductive disorders (retained placenta, metritis, cystic ovaries)<br>Predictors of reproductive disorders (activity monitors, hormone measures, etc.)<br>Metabolic diseases (ketosis, displaced abomasum)<br>Predictors of metabolic disease (BHB, fat:protein ratio)<br>Resistance to Johne's disease (*Mycobacterium avium* ssp. *Paratuberculosis*)<br>Immune response (antibody, cell-mediated) |
| Feed Efficiency | Individual feed intake (DMI, residual feed intake, energy balance)<br>Predictors of feed intake (production, direct or indirect cow weight, MIR)<br>Emission of methane (calorimeter, other methods)<br>Predictors of methane emissions (e.g. MIR) |
| Other Novel Traits | Workability (Milking speed, temperament)<br>Profitability (number of embryos, profit per cow, milk composition, etc.) |

“In the age of the genotype, the phenotype is king” (*Mike Coffey*, personal communication). We are currently challenged to identify traits that measure phenotypes of interest more exactly, more cost-effectively, and more comprehensively than those in our current index. This implies a clear and quantitative breeding objective and involves carefully considering the cost of measurement, potential gain through implementation in a selection program, ease of measurement, genetic variance, phenotypic and genetic correlations to other traits, and long-term effects of selection. We then need to understand the trade-offs between including these traits or not including them in our selection index. Genetic gains are cumulative, and small improvements provide cumulative savings to all farmers, particularly those using selection indices to combine many different traits (*Egger-Danner et al., 2015*).

## ▪ Novel Technologies

Novel technologies have had, and continue to have, a huge impact on the industry. Many facets of dairy farming have been revolutionized through technology. From implements for field work, feed harvesting, feed storage, feed mixing, and feed additives to milking equipment and housing systems, all the way to waste management techniques, dairy farmers are avid implementers of new technologies. Reproductive technologies, such as artificial insemination, sexed semen, embryo transfer, and cloning, are readily available to producers and have become an integral part of our industry. These technologies, when used properly, can boost farm efficiency substantially, while saving time and money.

A myriad of sensors and gadgets are available, most of which are designed to help herd managers better control their herds. Common sensors include those measuring real-time body weight, online milk composition/amount, behavioural sensors (heat detection, etc.), and rumination and heart-rate sensors. Sensors can provide diagnostics or simply gather information; data flow is normally a variation of the following: 1) collect data, 2) transfer data to a program, 3) implement algorithms within the program to calculate a likely physiological interpretation and, possibly, a recommended action, and finally 4) execution a decision by the herd manager based on the summarized information. While helpful for management, the information collected is often only of limited suitability for genetic and genomic analyses. Some sensors are more accurate than others, however they are very rarely standardized across suppliers and data extraction from the provider’s software is often difficult. Another question is data ownership – does it belong to the farmer, or the provider, or both? Automatic data collection is an area of huge potential, but standardized, correct, and curated data is a major caveat that needs to be addressed before any real advances can be made in this area.

New molecular technologies such as those used to conduct next-generation sequencing, methylation and gene expression analyses are being developed at an unprecedented rate. Although they are currently being used as research tools, they have the potential to expand into wide-spread applications. In a report by the McKinsey Global Institute, the use of next generation genomics was listed the 7th most potentially economically disruptive technology on the horizon. Despite initial public denunciation, various methods of genetic modification are under development. The first genetically modified animal, the Aqua Advantage Salmon, has been introduced into the human food chain after federal regulators in both Canada and the United States considered it fit for consumption in 2015. This would have been unthinkable only a decade ago.

## What to Expect in the Future?

Understanding the influence of various genes and genomic variants on phenotypes will bring forth many future opportunities for the genetic improvement of quantitative traits. For example, analyses on gene editing have expanded in the literature and some researchers are hypothesizing developments that may soon be applied in livestock breeding (*Van Eenennaam, 2017*). Many possible applications of the technology are the same as those already considered in current breeding programs, but with targeted efforts on known causative variants. In particular, the use of novel technologies to improve the health and welfare of livestock are strong public arguments which highlight the power of these technologies positively. Examples of edited dairy cattle include cattle with increased resistance to tuberculosis (*Wu et al., 2015*), the knockout of the beta-lactoglobulin gene (*Yu et al., 2011*), and enhanced mastitis resistance (*Liu et al., 2014*). A promising first use of gene editing in the dairy industry to address welfare issues may be the production of hornless dairy cattle through the introduction of the POLLED allele, which is nearly fixed in some beef breeds but low in frequency in Holsteins (*Carlson et al., 2016*). Other animal agriculture fields are also editing animals, including pigs resistant to porcine reproductive and respiratory syndrome virus (*Whitworth et al., 2016*).

Finally, only 2% of the population is directly involved in agricultural food production; the other 98% represent consumers, who are increasingly removed, both literally and figuratively, from the farming industry. Despite this fact, the changing needs, wants, and demands of the consumer play an integral role in the future of our industry. There are marked differences between consumer cohorts of the past and the large, critical, information-seeking cohort currently entering the marketplace. They are driven by incentives different to those of previous generations, which will affect what technologies we use, as well as how we select, breed and raise livestock in the future.

## Conclusions

New technologies, both in terms of those applied to studying the molecular basis of inheritance, as well as those used to measure various physical characteristics of animals, have had, and will continue to have, disruptive effects on livestock breeding practices. Advances in technologies are being made at an unprecedented rate and large-scale implementation of these technologies will affect both the genetic diversity of future livestock populations and the economics of genetic improvement. Furthermore, with an active, information-seeking consumer cohort entering the marketplace, past breeding goals centred on production may no longer be attractive and new phenotypes will need to be collected on a large scale. The implications of increasing the use of reproductive and genomic technologies, as well as applying novel technologies and methodologies in livestock breeding populations, must be carefully considered. In particular, the effects on the genetic diversity of livestock populations, the financial implications for all stakeholders, and the societal acceptance of these technologies and their wide-spread use must be evaluated. Despite these caveats, the use of these technologies, together with their integration in breeding, could contribute to sustainable and further genomic improvements, if properly managed.

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