Designing a reference population to accelerate genetic gains for novel traits in Canadian Holstein

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Abstract

Genomic selection has played a major role in Canadian dairy cattle breeding programs and has substantially increased the industry competitiveness worldwide. The development of the national health-recording program and various ongoing research projects funded by several Canadian and International organizations have led to the collection of a large number of phenotypes for novel traits. In order to remain a world leader in the competitive international market, it is key to include those traits in future breeding programs. Some novel traits (e.g., clinical mastitis and metabolic diseases) have been recently included in the Canadian national genetic evaluation, while other traits such as digital dermatitis, feed efficiency, immune response, methane emission, and fertility disorders are expected to be included in the near future. The size of the reference population (both phenotyped and genotyped animals) for these traits has a major impact on the accuracies of genomic estimated breeding values (GEBVs), and is presently the greatest limitation. Our current potential female reference population amounts to 20,000 cows for health traits, with an increase of approximately 4,000 cows per year. The number of genotyped cows with hoof health records is much smaller (below 5,500 cows). Therefore, the main goal of this project is to advance the rate of genetic progress for novel traits by enlarging the size of the female reference population for a variety of novel traits. The most cost effective strategy is to select cows that already have phenotypic records for novel traits (as well as the traditional traits), have not been preferentially treated based on their genetic merit, and are from herds that do not have any genotyped animals or are only partially genotyped. Thus, in addition to increasing the size of the reference population, it is key to design it in an efficient way by genotyping non-preferentially treated cows and individuals from herds that do not routinely genotype their animals but do collect phenotypes for traits of interest. A new genotyping strategy will be developed to maximize the imputation accuracy from low to medium density SNP panels, by integrating the right balance of low density and medium density genotyping within a given herd. The newly genotyped cows, in addition to the current reference population based on proven bulls, will allow more accurate estimation of genomic evaluations. A single step genomic evaluation is expected to be more useful for novel traits with limited recorded populations. By improving the accuracy of GEBVs, the rates of genetic progress will be accelerated, thereby reducing the economic concerns and improving health, production efficiency, and welfare of Canadian dairy herds.

Keywords: Genotyping strategies, novel traits, female reference population, production efficiency.

Introduction

Which breeding goals should be prioritized to design the cow of the future? The answers to this question have changed substantially over time and across countries (e.g., Miglior *et al*., 2005; Egger-Danner *et al*., 2014; Miglior *et al*., 2017). In a rapid growing society, with changing habits, and environmental conditions challenged by the consequences of industrial and technological advancements, efficient food production with reduced footprints is a top priority in the third millennium. The dairy cattle industry is expected to play a major role in this scenario. Fortunately, the majority of traits related to production efficiency in dairy cattle are under genetic control (Egger-Danner *et al*., 2014) and in the past decades, sophisticated selection methods (e.g., genomic selection; Meuwissen *et al*., 2001) and advanced reproductive technologies (Thomasen *et al*., 2016) have enabled accurate assessment of genetic variability to advance genetic progress in various livestock species. The worldwide dairy cattle industry has excelled in the implementation of these novel technologies. However, key advancements are still needed to efficiently face new challenges and remain sustainable and competitive in the long term.

Genomic selection (GS) has been successfully implemented in Canadian dairy cattle and the rates of genetic gain have doubled for various economically important traits (Canadian Dairy Network, 2017), such as production, conformation, longevity and fertility traits (Figure 1). A key factor for this success was the development over the last decade of a well-designed and large size reference population (i.e., animals genotyped and measured for the traits of interest) for various traits that are routinely measured in Canada and other countries within the Intercontinental Consortium. This consortium includes Canada, USA, UK, Italy, Switzerland and Japan. All genotypes are routinely shared among all those countries, thus allowing each country to add foreign bulls to their local bull reference population.

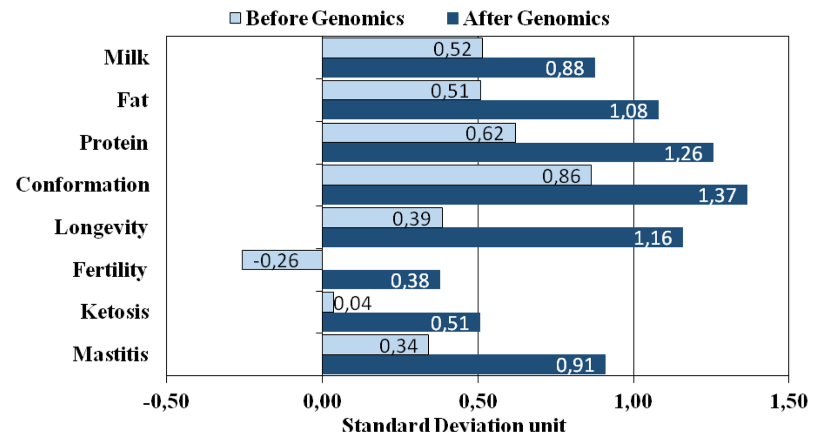

Figure 1. Impact of genomics on genetic progress for selected traits in Canadian Holstein cattle.

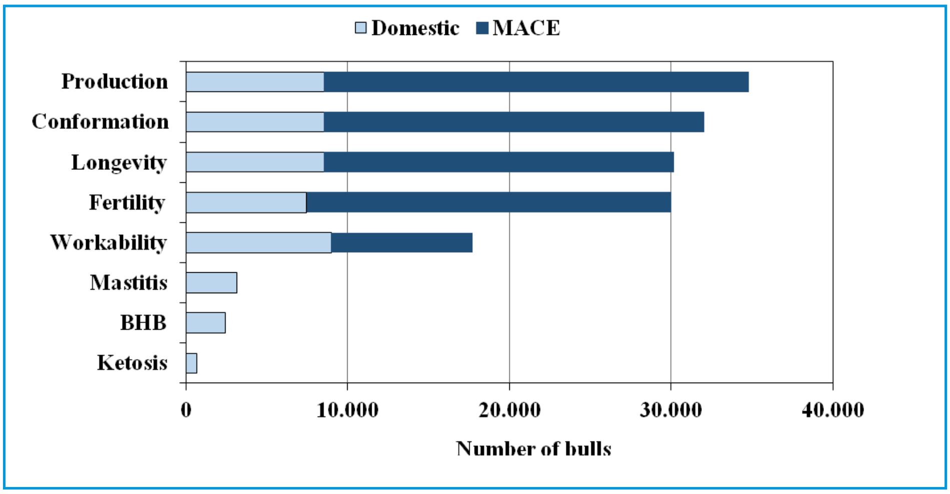

Figure 2. Size of male reference population by selected trait for Canadian Holstein cattle (April 2017 run).

In the April 2017 official genetic evaluation run, CDN (Canadian Dairy Network, www.cdn.ca) used the following reference bull populations for various group of traits in Holstein (Figure 2): 35,000 for production; 32,000 for conformation; 30,000 for longevity and fertility; 18,000 for workability; 3,000 for mastitis resistance; 2,400 for Beta HydroxyButyrate (BHB); and 600 for ketosis (the last three traits included only Canadian proven bulls while the remaining used international MACE evaluations as pseudo-phenotypes). For health traits and other novel traits, genomic selection (GS) is still limited, given that a) so far Canada and UK are the only countries evaluating those phenotypes within the Intercontinental consortium, and b) data collection has started relatively recently in Canada, thus a much smaller group of bulls have been evaluated for those traits. Such a limited reference population has a direct effect on the accuracy of genomic evaluations. Therefore, the objective of this paper is to present and discuss the work-in-progress and the near future plans of the Canadian dairy cattle industry to implement GS for a variety of novel traits aiming to address new challenges for sustainable production, and to address societal demands.

Novel challenges, novel breeding goals

As shown in Figure 3 with some traits taken as examples, genetic trends for various traits in Canadian Holstein cattle have substantially increased over time, highlighting the success of the adopted selection and breeding methods. However, livestock industries, including dairy cattle, are currently facing new challenges, which need to be addressed in order to remain competitive and sustainable in the long term. Little genetic improvement has likely been achieved for various traits known to significantly affect the economic efficiency of dairy cattle production such as feed efficiency. This is mainly due to the difficulty and cost to accurately measure this trait (or indicator traits) in a large number of animals. Furthermore, small or negative genetic response has been observed for some low heritability traits such as fertility, reproduction and disease resistance. This might be due to: a) the lack of accurate phenotypes for these traits; b) non-inclusion (or insufficient weighting in the national selection indexes) of these traits in the breeding objectives. Additionally, the effects of climate change have become more evident, highlighting the need to genetically select for adaptation to

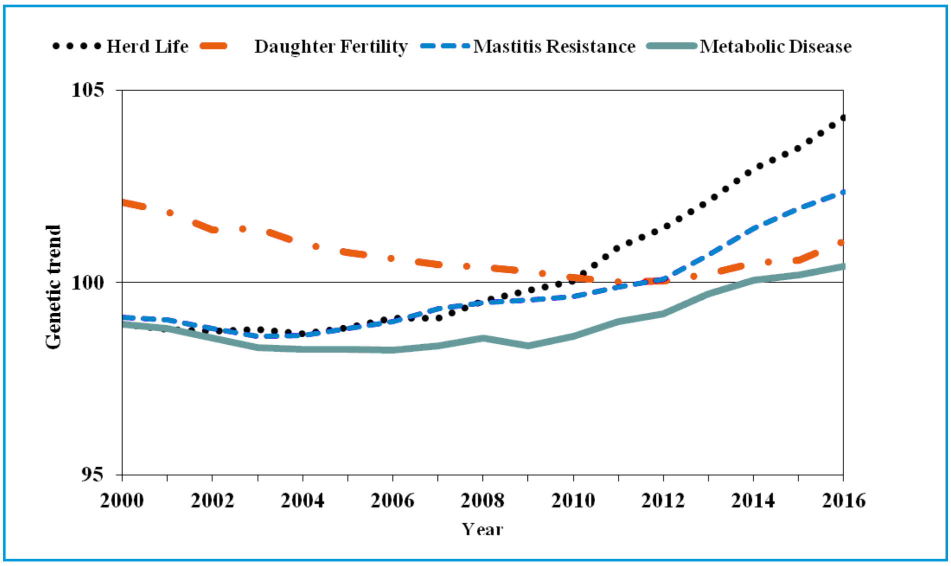

Figure 3. Genetic trend for selected traits in Canadian Holstein cattle (SD =5 for included traits).

extremer temperatures and harsher environments (Misztal, 2017). There is an opportunity to use novel strategies to advance genetic progress more rapidly for traits related to animal health, fertility, welfare, nutritional properties of milk and reduced environmental footprints.

The development of the Canadian national health-recording program in 2007 and various undergoing research projects funded by several Canadian and international organizations have led to the collection of a sizeable number of phenotypes for novel traits. These traits include feed efficiency, methane emission, clinical mastitis, metabolic diseases (ketosis, displaced abomasum, and indicator of disease, i.e., milk BHB), fertility disorders (metritis, cystic ovaries, and retained placenta), and hoof health (digital dermatitis and other hoof lesions). It has been estimated that the inclusion of genomic selection for novel economically important traits will generate an additional $200 million/year in annual net benefits to the industry due to increase in genetic progress for new relevant traits (Chesnais, 2016).

How to implement or increase the efficiency of genomic selection for novel traits?

A large reference population is essential for a precise and accurate estimation of marker effects, which leads to reliable genomic estimated breeding values (GEBVs) (Meuwissen *et al.*, 2001; Goddard, 2009; Hayes *et al.*, 2009). Despite the large size of the Canadian reference population for routinely measured traits (i.e., performance, reproduction and conformation), there is still a great need to increase the size of the reference population for novel traits of relevance to the industry, as already described.

Various alternatives to increase the size of reference populations for GS have been sought worldwide. One is to enlarge the reference population by including individuals from the same breed but from different countries (Cooper *et al.*, 2016). However, there are limitations to the implementation of this strategy for novel traits in Canada. Due to great advancements in the Canadian dairy breeding programs, the novel traits of interest here are also novel traits elsewhere, which means that there are not many phenotypes available in other countries to allow a shared reference population yet, even though there are important initiatives in progress. Another option is to combine the breed-specific reference population with other breeds (Hayes *et al.*, 2009; Olson *et al.*, 2012; Hozé *et al.*, 2014). However, the great majority of dairy cattle in Canada are Holstein, which limits the feasibility of multi-breed reference populations. A third option is to include cows in the reference population (Pryce *et al.*, 2012; Calus *et al.*, 2013; Cooper *et al.*, 2015), which is considered the best alternative at the moment.

It has also been reported that when only a small part of the population has both phenotypes and genotypes and other related animals are also phenotyped, single-step genomic evaluation methodology gives more accurate results than other methods. Currently, there are around 50,000 Holstein cows with production records genotyped in the CDN database, with a yearly increase of around 10,000 cows. Given that 40% of milk recorded herds collect health data, we can assume that we currently have a potential female reference population of 20,000 cows for health traits, with a yearly increase of 4,000 cows. The number of cows with hoof health records is currently much smaller (total of ~ 6,500 cows genotyped and phenotyped).

Female reference populations

Cows that are usually genotyped by breeders used to be elite cows, which could cause a preferential treatment bias. Because of concerns about biased elite cow traditional evaluations, females have not been included in the reference populations in Canada (Schenkel *et al.*, 2009), Germany (Reinhardt *et al.*, 2009), and New Zealand (Spelman *et al.*, 2010). A feasible solution is to genotype non-elite cows and also animals from herds that record phenotypes but have not yet started genotyping their animals.

The importance of developing a large and well-designed reference population for novel traits based on females' data can be further justified, as with the wide use of genomics bull reference populations are expected to become less informative (i.e., on average smaller breeding value reliabilities of bulls and cows). This is due, among other factors, to the random progeny testing programs that have stopped or reduced drastically since the adoption of genomics and the smaller number (on average) of daughters per proven bulls. In addition, it is important not only to increase the size of the reference populations for novel traits, but also to design them effectively in order to maximize the benefits of genomic selection. This can be achieved by creating a random and least-selected reference population covering the whole genetic variability of the population. A quick start in genomic evaluations for these new traits is only possible using genotyped animals with own performance, which includes the development of a female reference population.

Some studies have investigated alternatives to the inclusion of cow information in genomic programs. As discussed by Chesnais *et al.* (2016), for traits that are expensive or difficult to record (e.g., feed efficiency, methane emission, immune response), genotyping all animals with phenotypes is more efficient than using, for example, only the genotypes of their sires, even if those are already available. The use of a cow reference population is, therefore, the most cost-effective way to generate genomic evaluations for such traits (Van Grevenhof *et al.*, 2012; Calus *et al.*, 2013).

The development of these reference populations for novel traits will become more feasible as technological advancements make it easier to collect phenotypes for many of these traits (Chesnais *et al.*, 2016). For instance, some new traits/measurements are derived from sensors on farm (e.g., locomotion, heat detection, rumination), derived from additional data analyzed by labs (e.g., spectral data, hormones' status), collected by veterinarians, producers and technicians (e.g., disease incidence or claw health collected by hoof trimmers and health traits recorded by farmers). For such traits, the main challenges are ensuring national standardization of data collection and the development of data pipelines and expansion of a national database (Chesnais *et al.*, 2016; Miglior *et al.*, 2016). There are many herds in Canada that have measurements for various traits mentioned above; however, some of those herds are still not genotyping their cows. Therefore, genotyping thousands of non-elite cows originating from these herds with known history of excellent quality of recording for (some) novel traits, in addition to other routinely recorded traits, is a priority for the Canadian dairy industry.

Strategies to incorporate cows into reference populations have been reported. For instance, using simulated data, Montero *et al*. (2012) studied optimal genotyping designs that includes females in the reference population and suggested that two-tailed strategies (i.e. genotyping based on extreme phenotypes for the traits of interest) are preferable to increase the reliability of genomic selection (Jenko *et al.*, 2017). Another possible approach is to select a group of genotyped cows in the same breed that mimics the population structure in which selection for the novel trait will be applied. This should be done for both reference and candidate animals. It would not matter that these animals do not have a novel phenotype, as long as the structure of the population resembles what will eventually occur in practice (Chesnais, 2016).

Thomasen *et al*. (2014) reported that the inclusion of cows in the reference population increased monetary genetic gain and decreased the rate of inbreeding. In addition, they showed that genotyping cows is a profitable investment. Buch *et al*. (2012) showed that a reference population consisting of cows with a specific phenotype resulted in higher reliability compared with a reference population only including the sires of these cows. Similarly, to maximize the accuracy of GEBV, Van Grevenhof *et al*. (2012) found that the same individuals should be genotyped and phenotyped instead of genotyping parents and phenotyping their progeny. The inclusion of cows in the reference population will also decrease the generation interval in the dam-bull pathway and significantly contribute to genetic gain within the population as a whole. Moreover, validation studies based on random samples of genotyped Holstein cows in North America showed that the accuracy of genomic prediction using a cow reference population is even larger than that predicted by the Daetwyler formula (Chesnais *et al*., 2016).

What else is needed for successful breeding schemes incorporating genomics?

Other than enlarging the reference populations for novel traits, there are other methodologies that need to be applied to increase the accuracy of GEBVs. Firstly, all cows that are genotyped using a lower-density panel can be successfully imputed to 50K and up to whole-genome sequence (Larmer *et al*., 2012, 2016; VanRaden *et al*., 2012). This imputed genotype data can be used for genome-wide association analysis (GWAS) and further fine mapping aiming to identify causal mutations affecting the traits of interest. The inclusion of more informative SNP markers and/or more trait phenotypes to train the SNP effects can be incorporated into the Canadian dairy cattle breeding programs to further increase the accuracy of GEBVs. A functional analysis of the identified gene will improve the biological understanding of the genetic control of the traits. There is indeed a growing interest in examining interactions among genes and networks of genes that underlie traits of interest (Fortes *et al*., 2011).

Other sources of information that can be incorporated into genomic evaluations need to be investigated and the recent developments and availability of "omics" technologies provide new opportunities for generation of relevant additional information. This information could characterize either the animal itself, or its microbial environment involved in nutrition as the rumen flora or in infectious diseases such as mastitis or metritis. Some applications have already been investigated. For instance, to predict meat quality (Guillemin *et al.*, 2011), as well as different kinds of diagnostic tests for infectious diseases (e.g., Koskinen *et al.*, 2009).

Single-step genomic BLUP (ssGBLUP) is a method that combines the pedigree relationship matrix (A) with the genomic relationship matrix (G). By including genotyped and non-genotyped animals simultaneously in the evaluation, ssGBLUP method has the potential to yield more accurate and less biased genomic evaluations (Aguilar *et al.*, 2010; Christensen and Lund, 2010). In addition, other benefits of ssGBLUP include simplicity of application (another BLUP), avoidance of double counting, and (at least partially) accounting for pre-selection on Mendelian sampling (Legarra *et al.*, 2014).

Building the future

Research projects and initiatives led by Canadian institutions are aiming to generate tools to accelerate the rate of genetic progress for novel traits by designing an enlarged female reference population for genomic prediction of novel traits via ssGBLUP and to investigate the incorporation of additional "omics" data in Canadian dairy cattle breeding programs. The most cost effective strategy seems to be to select cows that already have phenotypic records for the novel traits, have not been preferentially treated based on their genetic merit, and are from herds which do not have any genotyped animals or are already partially genotyped. The majority of the animals will be genotyped with lower-density SNP chip panels and accurately imputed to 50K and then up to the whole-genome sequence genotypes (Larmer *et al.*, 2014, 2016). In addition, various other ongoing research projects have been generating other "-omics" data for a variety of important traits (e.g., fertility, feed efficiency and methane emission) that can potentially be incorporated to genomic evaluations in order to increase the accuracy of genomic breeding values.

Conclusions

A major constrain in the application of genomic selection for novel traits is assembling large enough reference populations to enable accurate predictions. Alternatives to enlarge reference populations for novel traits in Canadian Holstein have been investigated. By improving the accuracy of GEBVs, the rates of genetic progress will be accelerated, which is expected to generate an additional $200 million/year in annual net benefits to the industry and bring more health, production efficiency, and welfare into Canadian dairy herds.

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