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The development of genomics applied to dairy breeding ☆

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ABSTRACT

Genomic selection (GS) has profoundly changed dairy cattle breeding in the last decade and can be defined as the use of genomic breeding values (GEBV) in selection programs. The GEBV is the sum of the effects of dense DNA markers across the whole genome, capturing all the quantitative trait loci (QTL) that contribute to variation in a trait. This technology was successfully implemented in the United States, Canada, New Zealand, Australia, and several European countries with very promising results. The GEBV reliability depends on estimation procedures and models. The different methodologies to estimate SNP effects and GEBV have been extensively tested for many research groups with very promising results. Although GS is a success, many challenges still remain, including integration of GEBV into genetic evaluation programs and increasing GEBV reliability. The aim of this review is to discuss the main aspects involved with GS, including different methodologies of imputation, SNP effect estimation, and the most important impacts of GS implementation in dairy cattle.

1. Introduction

The use of DNA markers for genetic improvement of dairy cattle was first suggested by Smith in the late 1960s (Smith, 1967), particularly for traits that are difficult to improve in conventional breeding programs because of low heritability or difficult-to-measure phenotypes. Affordable high-speed genotyping of large numbers of single nucleotide polymorphisms (SNP) became available for dairy cattle late in 2007, which permitted the development of genomic selection programs as originally described by Nejati-Javaremi et al. (1997) and expanded by Meuwissen et al. (2001). In addition to increasing rates of genetic improvement and reducing costs of progeny testing (Meuwissen et al., 2001; Schaeffer, 2006), genomic evaluations produce estimates of the contributions of individual markers to additive genetic merit. The rapid adoption of this technology has caused profound changes in the dairy cattle industry (Stock and Reents, 2013).

Two major technological advances were critical to the implementation and success of GS. The first was the

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completion of the bovine genome sequence and publication of the reference assembly, which was the basis for accelerated research progress and allowed the identification of several thousands of DNA markers, known as SNP (Elsik et al., 2009). The second one was the development of low-cost SNP chips containing thousands of markers, which enabled the estimation of highly accurate breeding values when combined with phenotypic and pedigree data (Meuwissen et al., 2001).

In a broad sense, GS can be defined as the use of genomic breeding values (GEBV) to make selection decisions. The GEBV can be derived as the sum of the effect of markers across the genome, thereby potentially capturing all the quantitative trait loci (QTL) that contribute to variation in a trait. Reliable estimation procedures are needed for the estimation of allele substitution effects of each SNP for a trait (Hayes et al., 2009; VanRaden, 2008).

According to Schaeffer (2006), one of the main benefits of using GEBV in dairy cattle breeding programs is that selection can be made early in life, sometimes before an animal is born, reducing the generation interval. This can potentially double the rate of genetic gain. In addition, more reliable information about cows can be obtained, which may result in greater genetic progress through the dams of cows selection path (Van Tassell and Van Vleck, 1991).

The objective of this article is to review the principal aspects of GS in dairy cattle, including the most popular methods for GEBV estimation, genotype imputation, potential applications, and future perspectives.

2. Basis of genomic analyses in dairy cattle: linkage disequilibrium and haplotype persistency

In the last decade, dairy quantitative traits began to be studied and selected in many different breeding programs, with the aid of molecular markers. The markers can be direct, exactly marking the causative mutation of a gene, or indirect, marking regions that are nearest to the causative mutation or regions related to these mutations in only a few families (Dekkers, 2004). When working with large SNP panels to analyze quantitative traits most markers will be indirect, but in linkage with causal mutations (Dekkers, 2004). When markers are in linkage with the causative mutations, there is the possibility of recombination between the two. Recombination is a phenomenon that occurs during the formation of gametes (sperm and ovum) and involves the random exchange of genetic material between homologous chromosomes (Griffiths et al., 2007). The rate of recombination between two loci is proportional to the physical distance between them on the chromosome. Thus, the smaller the distance between two loci, the slower it will get to equilibrium of the expected genotype frequencies of these loci, under generations of random mating. The linkage disequilibrium (LD) measure will then indicate a nonrandom association between two loci, based on their genotypic and allelic frequencies (Falconer and Mackay, 1997). The main cause of LD is the "linkage" between loci because of physical proximity. Genomic selection exploits the linkage disequilibrium (LD) between markers, since it assumes that the effects of the analyzed chromosomal segments also represent the LD between the marker and a possible quantitative trait locus (QTL) (de Roos et al., 2008). The extent, distribution, and decay of LD in a population must be characterized before a genomic selection program is implemented.

Studies based on SNPs showed high LD over short distances as reported by McKay et al. (2007) and Bohmanova et al. (2010). Other authors, such as Khatkar et al. (2008) and Qanbari et al. (2010), observed $r^2 \geq 0.2$ in Holsteins for distances less than 100 kb. Santos et al. (2013), working with a panel of 54,000 SNPs, reported r^2 of 0.15, 0.17, and 0.17 for Guzerat ($n=1025$), Gyr ($n=1959$), and Sindhi ($n=116$), respectively. The variation in the extent of LD published depends on several factors, including breed history and population structure (e.g., effective population size) that negatively influence LD (Hayes et al., 2003); the sample size, which can lead to overestimation in small populations (Yan et al., 2009); the density and distribution of markers; the method used to construct haplotypes; the stringency of SNP filtering (e.g., allele frequency thresholds and Hardy–Weinberg equilibrium); and the use of maternal haplotypes or both maternal and paternal haplotypes (Bohmanova et al., 2010). These results indicate that SNP density alone is sufficient to provide LD between chromosome segments determined for prediction of GEBV, especially when the inter-marker distances are less than 100 Kb (r^2 is moderate to high). When proposing GS in its current form, Meuwissen et al. (2001) used adjacent markers with $r^2 > 0.20$ indicating that this LD may explain the variation of the QTL. Calus et al. (2008) used simulated data to evaluate the effect of average r^2 between adjacent pairs of markers on the accuracy of genomic selection (correlation between true breeding values and validation population GEBV). They found that the accuracy of GEBV increased from 0.68 to 0.82 when the average r^2 increased from 0.1 to 0.2. Based on those results, de Roos et al. (2008) estimated that a panel of at least 50,000 SNPs would be necessary to achieve and $r^2 \geq 0.20$ between adjacent markers, which is needed to support efficient GS. Another important use for the LD is the construction of haplotypic blocks and their diversity. These blocks can be used as units for genomic analysis rather than the SNP (Calus et al., 2008), in imputation algorithms (Browning and Browning., 2009), and in genomic detection of lethal alleles (VanRaden et al., 2011a). According to Khatkar et al. (2007), haplotypes are chromosomal regions of high LD and normally have low diversity, typically accounting for regions of low recombination flanked by hotpots of recombination. Generally, the structure provided by the effective size between the breeds, as well as the number of markers used, can influence the assembly of haplotypic blocks.

When LD is estimated in different populations using the same SNPs it is possible to study the persistence of phase (PS) between them. PS refers to how much a chromosomal segment is unchanged over a given physical distance in different subpopulations, breeds, or species. This measure is based on the correlations of r^2 between two populations, along with physical distances (de Roos et al., 2008). Since PS is related to the accuracy of genome-

wide association studies (GWAS) and GEBVs between populations (de Roos et al., 2008), it is possible to evaluate the feasibility of a multibreed genomic evaluation using this measure. Silva et al. (2013) working with Gyr, Guzerat, and Sindhi obtained correlations ranging from 0.40 to 0.56 for 100 kb distances, with an intense decline of PS, suggesting low efficiency for multibreed evaluation based on common SNP effects estimates for the 3 breeds. Despite the low PS observed in some cases, the increased density of the SNP panel markers, may consider high phase correlation between pairs of markers at small distances, as well as the largest LD between markers, making possible the multibreed analyses based on the same SNP effects.

3. Traditional marker-assisted selection versus genomic selection: efficiency, profitability, and use of (pseudo-) phenotype

Progress in animal breeding programs is achieved through the selection of superior individuals for mating. An animal's superiority is generally based on its genetic merit ranking. The accuracy of evaluation methods is one of the main components that determines the rate of genetic gain in a population. Initially, evaluations were based only on phenotypes, i.e., the animals that had better performance were chosen for mating, or in the case of milk production, the sons of the most productive cows were retained for breeding. Breeding values were obtained by multiplication of phenotypic deviations from the herd average with heritability.

In the latter half of the 20th century, selection index methodology was introduced by Hazel and Lush (1943). This methodology considered the correlation between phenotypic measures, as well as the genetic relationships between animals with phenotypes (selection criteria to be used – in the present left hand) and the individuals being evaluated (objective selection – present in the right hand). With this method it was possible to combine many sources of information into a single breeding objective. In the indexes the main properties would decrease the prediction error, maximizing the correlation between the estimated and true (accurate) genetic value and maximizing the probability of correct classification for the predicted genetic value. Thus, there was an increase in accuracy by aggregating information collaterally with other animals. From this methodology we started to give greater importance to the pedigree of animals for use in analysis beyond parent–offspring relationships.

With the development of mixed model methods by Henderson (1949) genetic evaluations began to provide more accurate estimates of breeding value. First, through the sires model that considered sire-progeny relationships, and then through the animal model, which considered all known relationships among animals in the pedigree. Using this methodology it is possible to simultaneously estimate fixed effects (BLUE – Best Linear Unbiased Estimator) and random (BLUP – Best Linear Unbiased Prediction). Thus, the BLUP solution is obtained for all animals present in the pedigree. This methodology has similar statistical properties to selection index, but directly produces estimated breeding values, unlike selection index, in which index weights and breeding values are produced in separate steps. Estimated breeding values (EBV) were widely adopted as a selection tool in breeding programs, where they are commonly presented as predicted transmitting abilities (PTA), which are one-half of EBV.

The use of molecular marker information to increase accuracy and reduce generation intervals has been studied in recent decades, and implemented in a limited fashion in some breeding programs. Marker-assisted selection (MAS) was applied in dairy cattle for the pre-selection of animals, and to select young bulls for entry into progeny testing programs (Kashi et al., 1990a, 1990b; Mackinnon and Georges, 1998). MAS simultaneously uses phenotypic information and data about molecular markers in LD with QTLs, and was adopted to increase annual genetic gain for traits of economic importance in several animal species (Dekkers, 2004). In MAS, BLUP estimates of total genetic value are obtained including marker information as fixed or random effects (Dekkers, 2004), or through an index that combines the two sources of information using weights that can be changed based on the selection objective (Dekkers and van Arendonk, 1998).

Other molecular alternatives are being widely studied. The first recognizable presentation of genomic selection was made by Nejati-Javaremi et al. (1997), and the approach was expanded and popularized by Meuwissen et al. (2001). However, there was considerable lag between the description of the concept and its widespread adoption, which did not occur until panels with thousands of single nucleotide polymorphisms (SNPs) distributed across the bovine genome became available (Van Tassell et al., 2008). SNPs are the most abundant DNA polymorphisms in the genome, and they have become preferred over other types of molecular markers because they have low mutation rates and genotypes can easily be read automatically (Romualdi et al., 2002). In GS, the central idea is to not use specific markers for QTLs, but to use a large number of markers distributed throughout the genome. When many thousands of markers are used it can reasonably be assumed that there are always markers located near causal variants, which means that there are SNPs in LD with the QTL (de Roos et al., 2008). The additive genetic merit of an animal can then be decomposed into a contribution from the markers and a polygenic component that accounts for the variation not explained by the markers. The marker and polygenic effects can be estimated using statistical models similar to those used for breeding value estimation, and performance, pedigree, and genotype information can be combined into genomic breeding values (Meuwissen et al., 2001; VanRaden, 2008). Cole et al. (2009) confirmed that an infinitesimal model is appropriate for most traits of interest in dairy production, and showed that there are few QTL in the traditional sense (loci that explain large proportions of phenotypic variance).

Genomic selection does not have the same limitations as MAS, and GS compared to BLUP provides (1) predictions of breeding values with greater accuracy, particularly for traits that are expressed in one sex or are of low heritability, (2) theoretically lower rates of inbreeding (lesser tendency for family selection), (3) anticipation of the selection process in the case of measured characteristics later in the life of the animals, and (4) facilitate the evaluation of the traits of difficult to measure or high cost

(Daetwyler et al., 2007; Dekkers, 2007; Muir, 2007; Meuwissen, 2007).

Genomic selection has increased the rate of genetic gain in livestock (Weigel et al., 2010). The increase in the accuracy of genomic predictions is best observed in young animals, with no significant changes in the already proven bulls (Schaeffer, 2006). Proofs are used for pre-selection for progeny testing, and also for selection of animals when they are selected by GEBV in the total genomic evaluation. In didactic scheme, the genomic proofs for dairy cattle have a flow that involves a reference population and another population to be selected. Thus, the reference population consists of animals which have, necessarily, accurate information of the trait. This population is used as the genetic basis for predicting the effects of markers.

The determination of the reference population, as its size and its constitution, has great influence on the accuracy of genomic predictions (Hayes et al., 2009; VanRaden et al., 2009). In the case of dairy herds, the constitution is mainly dependent on the composition (bulls and cows) and selective genotyping according to the structure of the response variable. In most countries, only sires, mainly of high accuracy were genotyped and included in the reference population (Loberg and Dürr, 2009). However, the use of more accurate information implies the use the best animals in the reference population. However, simulation studies of dairy cattle (Jiménez-Montero et al., 2011) concluded that the selection of only females with high estimated breeding values or yield deviations produced suboptimal results. This study showed that a better sampling scheme for females is to select from the upper and lower extreme values within the distribution of yield deviations with the usual sampling for males, although these authors have not evaluated this combination with daughter yield deviations (DYD) for sires.

One of the first steps in genomic selection is to generate the response variable for analysis, which depends on the available sources of information (individual performance, of the daughters or parents). Different information can be used, from the phenotype itself, as single records, repeated records, the average of the progeny, or even pseudo-phenotypes such as DYD (VanRaden and Wiggans, 1991), EBV, and deregressed-EBV (Garrick et al., 2009). For dairy traits, pseudo-phenotypes are preferred because lactations are sex-limited and only females have phenotypes. Among these, DYD are the most-used because sires have a larger impact on breeding programs than cows, and their DYDs are more accurate than cow phenotypes (Calus, 2009). The deregressed EBV can be considered a type of deregressed-proof (DRPF) when using sires with information of high accuracy in the reference population because they combine different sources of information about the sires besides daughter records. Generally the DRPFs are considered equivalent to DYD (Sigurdsson and Banos, 1995). The deregressed EBV are used in genomic evaluation of dairy traits when there are cows and bulls in the reference population. However when using any deregressed pseudo-phenotype there is an individual increment disproportionate in response variable that leads to the need to consider the heterogeneity of the residue by statistical models, with weights that range according to the source used to deregress and effects considered (Garrick et al., 2009).

When using genomic evaluations as criteria for pre-selection of animals to progeny test it is possible to reduce spending to prove that animals would have low performance in the test (Hayes et al., 2009), but there is potentially a problem with preselection bias (Patry and Ducrocq, 2011). Dekkers (2007) reported that rates of genetic change can be 3 to 4 times higher with GS than under current progeny test programs, and the savings in logistical costs could be up to 97% of today's cost. Furthermore, genotyping costs are likely to decrease over time, which would make GS easier to administer. Schrooten et al. (2005) reported that genetic progress increased by 19% to 31% compared to progeny testing when the markers explained 50% of the genetic variance. VanRaden et al. (2009) reported that the predictive ability for dairy traits using genomic predictions was 50% versus 27% for traditional PTA. They also reported that gains for proven bulls were highly significant, although smaller than the young bulls because of the higher initial reliability of the proven bulls. Note that GS is already implemented and showing promising results in many countries, including the USA, Canada, New Zealand, and much of Europe (Loberg and Dürr, 2009).

Despite the latest innovations in genomics that are bringing the advantages described above, the molecular data also demands increased statistical and computational resources, limiting the use of such information in many analyses including multi-trait models and test-day models. Although these models are easily applied by replacing the traditional numerator relationship matrix (A) with the genomic relationship matrix (G) (Koivula et al., 2012; Tsuruta et al., 2011), there is not yet a robust approach to multivariate models that consider different variances for each marker, which is one of the greatest prospects for optimization of genomic analyses of the dairy traits.

4. Parentage correction and pedigree errors

For a successful and comprehensive evaluation of individuals in any breeding program, correct parentage and pedigree information are essential because pedigree information is a key part of variance component and breeding value estimation. Pedigree error rates in dairy cattle breeds have been estimated to average 10% to 12% (Banos et al., 2001; Spelman, 2002; Visscher et al., 2002), although reports from the 1970s to the late 1990s estimated values ranging from 5% to about 22% (Christensen et al., 1982; Geldermann et al., 1986; Bovenhuis and Van Arendonk, 1991; Ron et al., 1996). The rapid adoption of micro-satellite parentage testing in the cattle breeding industry probably reduced parentage and pedigree errors, but most commercial (grade) cows are not tested. Although error rates may have decreased over the years, parentage and pedigree inconsistencies of 10% or 11% can lead to reductions in genetic gain of 2–18% (Banos et al., 2001; Visscher et al., 2002).

Before the advancement in high-throughput SNP data, blood groups (Stormont, 1967) and mini- and s (Kashi et al., 1990a, 1990b) were the basic means of inferring parentage. Even though micro-satellites are still used, with the recent availability of SNP markers and with large numbers of sires (Harris and Johnson, 2010; Weigel et al., 2010; Fritz et al., 2013; VanRaden et al., 2013b) and dams (Spelman et al., 2013;

VanRaden et al., 2013b) genotyped in the USA, Canada, Australia, New Zealand, Ireland, and France among others, parentage and pedigree errors are increasingly identified using SNP genotypes. McClure et al. (2012, 2013) have developed methods to impute micro-satellite parentage panels from SNP-based parents panels, which will assist cattle producers as they transition from micro-satellite to SNP genotyping for parental verification.

Parentage assignment is aimed at excluding individuals ("exclusion principle") from the list of potential parents. This means that a large number of potential sires and dams are examined and only one or a few individuals are retained based on their marker data by using simple segregation rules (Kashi et al., 1990a, 1990b; Hayes, 2011). In addition to marker genotypes, additional accuracy can be achieved if information such as birth dates and mating records are considered.

Due to the abundance of SNP marker information and the shift from micro-satellite to small SNP panels, we give a brief description of how SNP information is used to correct pedigrees and infer potential parents. Initial verification of information (parents) obtained from pedigree are to be done to detect parent–offspring inconsistencies. If parent–offspring errors exceed a certain threshold, then loop through all of the genotype data to infer the potential parents. For individuals with no pedigree information, loop through all of the genotype data directly to obtain potential parents.

The algorithm for detecting and inferring parent offspring conflict is based on Mendelian inheritance rules (Calus et al., 2011; Hayes, 2011). This means that, for a bi-allelic SNP, an individual and the prospective parent are both homozygous but for different alleles "opposing homozygotes". For example, if an individual has an A|A genotype, the potential parent should carry the "A" allele (A|A or A|B), however if the potential parent has B|B allele (for more possible parent offspring conflicts per locus) then they have opposing homozygous genotype. Looping across all SNP genotypes, the sum of all "opposing homozygous" is compared to an empirically determined threshold (determined from the genotype error rate). Furthermore, to avoid picking up monozygotic twins in the pairwise comparison (parent–offspring check), information from birth years could be used.

The empirical thresholds are based on the realized distribution of genotyping errors for all parent–offspring conflict checks. Wiggans et al. (2009), Calus et al. (2011), and Hayes (2011) all reported similar distribution of Mendelian errors for the Illumina 50K SNP panel. Wiggans et al. (2009) and Calus et al. (2011) used >200 SNPs and >250 SNPs, respectively, on a 50K panel to exclude parent–offspring conflicts. However, Hayes (2011) used a stringent threshold of >25 SNPs on 50K SNP panel and >8 SNPs on a 3K SNP panel. Additionally, unpublished results from Gyr (Brazilian *Bos indicus* breed) showed a similar distribution when a 50K SNP panel was used. The number of markers within the empirical threshold was <58, however, <200 SNP markers were used as the threshold. The total parent–offspring conflict observed was about 8% in Gyr, and we could infer potential parent for about 2% of these errors. Calus et al. (2011) removed 230 individuals with parent–offspring conflict. Fisher et al. (2009) reported that, about 40 highly polymorphic SNP markers (MAF >0.35) and on-farm information about birth dates and mating periods were needed to correctly assign parentage without any ambiguity.

Using SNP data, (i) recent ancestors errors, (ii) maternal grandsire errors, and (iii) full- and half-sibling errors could also be corrected (Wiggans et al., 2009; Calus et al., 2011; VanRaden et al., 2013a). The reduction in parentage and pedigree errors could go a long way to help reduce the loss in genetic gain (Banos et al., 2001; Visscher et al., 2002) and potentially decrease inbreeding. We conclude that, although there is a dearth of knowledge on the current pedigree errors detected using SNP data in dairy cattle populations, the supposed reason being the lack of interest in publishing pedigree errors, most published materials on genomics (genomic selection, GWAS, etc.) undertake this key component before performing their analysis.

5. Principal traits selected in a dairy breeding program and their results with genomic selection analyses.

Since 2009, the United States in collaboration with Canada has published genomic evaluations based on BovineSNP50 genotypes. More recently these two countries included Illumina's Bovine3K chip genotypes in their GEBV estimations, substantially increasing the number of genomically evaluated animals (VanRaden et al., 2011a). Many countries have implemented GS in their breeding programs and encourage widespread use of young genomically evaluated bulls (Wiggans et al., 2011). Hutchison et al. (2014) have recently shown that the heavy use of genomically evaluated young bulls in the US has greatly reduced the generation interval and improved the rate of genetic gain. The average age of sires of Holstein bulls born in 2012 was 2.7 yr younger than those males born in 2006, and 1.3 yr younger for females. This indicates that dairy producers are willing to use semen from young bulls that rank highly rather than use lower-ranking bulls with progeny tests.

One of the most important requirements for GS implementation is the use of a large reference or training population that include animals with both phenotype and genotype information, thus all the traits routinely evaluated on commercial breeding programs are able to have their GEBV estimated. In the United States, more than 30 traits traditionally estimated and related to health, yield, and fertility of dairy cattle have their GEBV available, including net merit, milk yield, protein yield, fat yield, protein percentage, fat percentage, productive life, somatic cell score and daughter pregnancy rate (VanRaden et al., 2009; Weigel et al., 2010).

Previous results of GS from Australia for protein yield, protein percentage, fertility, Australian Profit Ranking, and Australian Selection Index, demonstrated that GEBV reliabilities estimated with Bayes A and BLUP methodologies were in a range of 0.14–0.48 and 0.18–0.44, respectively. The reliabilities of GEBV were considerably greater than traditional EBV estimates even with a small reference population (approximately 600 animals) (Hayes et al., 2009).

More recent results from the Australian Dairy Futures Cooperative Research Centre demonstrated that the expansion of reference population to 10,000 Holstein and

4,000 Jersey cows could lead to an increase of 0.04 to 0.08 in the reliability of breeding values, depending on the trait (Pryce et al., 2012a).

In a similar study conducted by LIC (Livestock Improvement Corporation) in New Zealand, GEBV for milk production traits, live birth weight, fertility, somatic cell counts, and longevity presented reliabilities for young bulls with no daughter information between 0.50 and 0.67, indicating a increase in the rate of genetic trend of more than 50% compared with traditional EBV (Harris et al., 2008).

As milk production becomes increasingly specialized and competitive, selection objectives will need to include traits related to profitability and animal efficiency. To meet this goal, new traits, not traditionally measured by breeding programs are being evaluated for inclusion in selection programs, such as feed efficiency (De Haas et al., 2012), methane emission (Wall et al., 2010), energy balance (Verbyla et al., 2010), disease resistance (Kirkpatrick et al., 2011; Parker Gaddis et al., 2014), novel fertility traits (Cochran et al., 2013a, 2013b), resistance to heat stress (Dikmen et al., 2013), and calf birth weight (Cole et al., 2014). One limitation on the introduction of novel traits on GS is the low accuracies of the GEBV due to small reference populations.

Calus et al. (2012) evaluated a novel trait with heritability ranging between 0.05 and 0.30 with a moderate-sized reference population and demonstrated that although the accuracies were low (0.15 and 0.43 for traits with heritabilities of 0.05 and 0.30, respectively), the selection response could be substantial depending on the heritability and economic value of the new trait and the genetic correlation with the current breeding goal. Accordingly, to achieve accuracies acceptable in dairy cattle breeding programs, the reference population should be larger.

6. Imputation results on genomic evaluation

Even though the price of genotyping individuals was high about a decade ago, the promise of doubling genetic gain at a lower cost than progeny testing (Schaeffer, 2006) was enough incentive to genotype bulls on the 50K Illumina SNP panel (Matukumalli et al., 2009). However, the extended cost that came along with the requirement of increasing the reference population (training set) and genotyping selection candidate facilitated the need to use alternative SNP panels that were cheaper and preferably efficient for genomic selection. Additionally, the accurate *in silico* genotyping (imputation) of SNP markers in the field of human genetics gave a unique perspective on how genotyping cost could be drastically reduced (Browning and Browning, 2007, 2009; Howie et al., 2009).

Genotype imputation uses population-based linkage disequilibrium (LD), family-based linkage information or a combination of both, to infer genotypes at un-typed marker loci. Population-based imputation algorithms were developed mainly to explore and capture LD information without using a prior family information which might not be available. These methods are very popular in the human genetics field, however, it is also heavily used in the field of animal genetics. The most prominent population-based software includes Beagle (Browning and Browning, 2007, 2009), Impute2 (Howie et al., 2009), MaCH (Li et al., 2010), fastphase (Scheet and Stephens, 2006), and PLINK (Purcell et al., 2007). On the other hand, family-based or a combination of population and family based imputation algorithms have been developed in the field of animal genetics. These algorithms use, *a priori*, the family information and subsequently LD information to infer un-typed markers. Commonly used software includes PHASEBOOK (LinkPHASE and DAGPHASE) (Druet and Georges, 2010), FImpute (Sargolzaei et al., 2012), AlphaImpute (Hickey et al., 2011), Findhap (VanRaden et al., 2011a), and PEDIMPUTE (Nicolazzi et al., 2013).

In dairy cattle breeding programs, to reduce genotyping cost, the Illumina Bovine3K BeadChip (~2900 SNPs) (Illumina Inc., 2011) and Illumina Bovine7K BeadChip (~6900 SNPs) (Boichard et al., 2012) were developed. Imputation accuracies from a lower density SNP panel to higher density SNP panels have been pretty accurate. Dassonneville et al. (2011) reported imputation error rate (allelic error rate) of 3.9%, when they imputed from 3K to 50K in French Holstein (reference population = 3071; validation set = 966) using a combination of Beagle v2.1.3 and DAGPHASE. They also reported 5.5% error rate for Holstein bulls of the three Nordic countries (reference population = 3058; validation set = 1086). Increasing the Reference population with bulls from the EuroGenomics consortium reduced error rate to 2.1% in the French Holstein and 4.0% in Holstein bulls from the Nordic countries. Sargolzaei et al. (2011) also reported imputation error rate (imputing 3K to 50K) between 2.2% to 4.1% in three Canadian dairy cattle breeds (Hosltein, Jersey and Brown Swiss). Error rate was lower (between 0.53% to 1.03%) when the 7K SNP panel was used. Khatkar et al. (2012) also reported error rate of about 3.3% for Australian Holstein using Impute2. Recently, Ma et al. (2013) reported allelic error rate of 3.7% in Swedish and Finish Red dairy cattle for imputing 3K to 50K using beagle v3.3. Studies from three Italian dairy cattle breeds (Hosltein, Brown Swiss and Simmental) by Dimauro et al. (2013) showed a lower allelic imputation error rate for imputing 50K from 3K and 7K compared to the results presented above. Error rates were about 10% for 3K and 5% for HD using Beagle v3.3. Others studies with varying subset of the 50K SNP markers shows error rate of about 2–8% (Weigel et al., 2010; Khatkar et al., 2012). The above studies have been done using *Bos taurus* breeds; however, initial imputation results from Gyr, an important *Bos indicus* dairy cattle breed of Brazil, shows slightly higher allelic error rate (7.0% for 3K and 4.0% for 7K using Beagle v4) than the *Bos taurus* breeds (Boison et al., 2014a), *accepted for the Proceedings of EAAP 2014*. Differences in population structure, number of animals in reference population, choice of imputation algorithms or software have been explicitly shown to account for the observed differences across studies. Furthermore, the higher allelic error rate observed for *Bos indicus* breeds might also be due to ascertainment bias of the 3K, 7K and 50K Illumina SNP panels. This results in a small number of markers being left on the lower density SNP panel (< 2000 for 3K and < 5000 for 7K) as tag SNPs with large inter-marker distances.

To increase accuracies of genomic breeding values more than was observed with the 50K SNP panel for multi-breed genomic, purebreed and crossbreed evaluations, the

BovineHD BeadChip (HD) was introduced. Additionally, the HD SNP panel was to help reduce the ascertainment bias observed for the 50K in *Bos indicus* breeds.

Since most animals were already genotyped on the 50K SNP panel, few but influential sires were suggested to be genotyped on the HD SNP panel and the rest of the population imputed. Goddard and Hayes (2008) suggested an algorithm for efficiently selecting individuals to be genotyped on HD, so that imputation accuracies for the rest of the population would be high. For most breeds, imputing HD genotypes from 50K have been high. Khatkar et al. (2012); Brøndum et al. (2012); Ma et al. (2013); Pausch et al. (2013); Schrooten et al. (2014), and Erbe et al. (2012), all have reported imputation accuracies between nearly zero and 7% when the reference population used in building haplotype library was at least 1/3 of the validation population.

However, accuracies of GEBVs of real data for HD genotypes have been shown to be smaller or sometimes lower than expected in comparison to using the 50K SNP panel (Erbe et al., 2012; Su et al., 2012) regardless of the trait and method of prediction for *Bos taurus* breeds. Initial results in Guzerat, a *Bos indicus* dairy cattle breed of Brazil, have shown an increase in accuracies of about 4–12% for milk, fat and protein yield in kg (Boison et al., 2014b), *accepted for the Proceedings of WCGALP 2014*. The differences in the result might be attributed to the right-skewed nature (lot of markers in low frequency due to ascertainment bias) of the minor allele frequency distribution for the 50K observed in most *Bos indicus* breeds. The HD SNP panel, on the other hand, has markers with high MAF.

Interestingly, the effect of imputation on overall estimates of accuracies of breeding values has been low for imputing 7K to 50K (Khatkar et al., 2012; Dimauro et al., 2013) and 50K to HD (Khatkar et al., 2012; Su et al., 2012), substantially lower for 3K to 50K (Dassonneville et al., 2011; Dimauro et al., 2013). The great reduction in accuracies of GEBV for the 3K to 50K has been attributed to the lower imputation accuracies observed, compared to the imputation accuracies obtained for 7K to 50K and 50K to HD. Low-density genotypes also are most commonly available for young animals with no phenotypes or cows with few phenotypes available, and the resulting low-accuracy PTA may be more responsible for the small gain, rather than the chip itself. Recently, Druet et al. (2014), have shown, with a simulation study, that using imputed sequence data might follow the same trend like the imputed HD (very little loss in accuracy of GEBV). However, they point out in their paper that, effect of QTLs in low frequency might be estimated with lower accuracy than using actual sequence data.

The results from the studies available suggest that, imputing genotypes from 7K to 50K; 50K to HD is feasible and accurate enough for genomic evaluations.

7. Other uses of genomic information

There are a number of applications for genomic information other than the prediction of high-reliability breeding values. Perhaps the most prominent recent application is the use of haplotypes in combination with next-generation sequencing data to identify causal variants associated with recessives. The methodology for identifying recessive haplotypes by searching for a deficit of homozygotes was first described by VanRaden et al. (2011a), and its use in combination with sequence data to identify a causal variant (*APAF1*, associated with the HH1 haplotype) was reported in Adams et al. (2012). Additional details are provided in VanRaden et al. (2012). The US currently tracks 19 recessive haplotypes, and the causal variant for many of those conditions is known (Cole et al., 2013).

While in theory genomic selection should result in lower rates of inbreeding (Daetwyler et al., 2007), that has not proven to be true in practice (e.g., VanRaden et al., 2011b). Sun et al. (2013) have showed that the use of genomic inbreeding coefficients rather than pedigree inbreeding in mating programs results in decreases in expected progeny inbreeding, and the economic value of using genomic relationships is $>$ $3 million per year for US Holsteins when applied to all genotyped females. These results are consistent with the work of Pryce et al. (2012b), who also found that it is beneficial to consider genomic inbreeding when allocating mates. However, Cole and VanRaden (2011) showed that the best chromosomal genotypes generally consist of two copies of the same haplotype, even after adjustment for inbreeding, underscoring the tension between strategies that ensure maximal rates of genetic gain versus those that try to balance selection response against the need to maintain genetic diversity in the population.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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