Review Article

Genomic Selection and Genetic Tools to Improve Fertility Traits

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A B S T R A C T

Improving dairy cow fertility by means of genetic selection is likely to become increasingly important, since it is now well established that declining fertility cannot only be arrested by improved management. Fertility is a major concern in the dairy cattle industry and has been the subject of numerous studies over the past 20 years. Surprisingly, most of these studies focused on rough female phenotypes and, despite their important role in reproductive success, male- and embryo-related traits have been poorly investigated. In recent years, the rapid and important evolution of technologies in genetic research has led to the development of genomic selection. genomic selection (GS) is a form of marker-assisted selection in which genetic markers covering the whole genome are used so that all quantitative trait loci (QTL) are in linkage disequilibrium with at least one marker. GS can increase the accuracy of selection, shorten the generation interval by selecting individuals at the early stage of life, and accelerate genetic progress. With the availability of high density whole genome SNP (single nucleotide polymorphism) chips for livestock, GS is reshaping the conventional animal breeding systems. In many countries, GS is becoming the major genetic evaluation method for bull selection in dairy cattle and GS may soon completely replace the traditional genetic evaluation system. In recent years, GS has become an important research topic in animal, plant and aquiculture breeding and many exciting results have been reported.

Introduction

Genomic selection (GS) is one of the most current progresses in genomics-assisted methods to improve breeding competence and genetic gains. GS provides a genome-wide paradigm for marker-assisted selection (MAS)(1, 2). In GS all genome-wide markers are fitted concurrently in a model that relies on the principle of linkage disequilibrium (LD) to obtain most of the related change all over the genome, whiles MAS focuses on distinct quantitative trait loci (QTLs) that have beforehand been identified, ordinarily in underpowered experiments, and consequently leaving most of the phenotypic variation unaccounted for(3). GS is mostly achieved in three steps: (1) genotyping and phenotyping a 'reference' or 'training population' composed with the development of GS models that permit for prediction of phenotypes from genotypes; (2) validation of the predictive models in a

'validation population', i.e. a set of individuals that did not partake in model training; (3) use of the models to predict the genomic estimated breeding values (GEBVs) of unphenotyped individuals which are selected according to their GEBVs(2). GS has been effectively applied in the breeding of livestock(3, 4) and crops(5, 6) and several studies demonstrated its great potential in forest tree breeding(7, 8). The genomic selection revolution initiated with 2 developments. The first was the sequencing of the bovine genome, which lead to the detection of many thousands of DNA markers, in the form of SNP. Simultaneous with the detection of various SNP markers through the livestock genomes has been a dramatic decrease in the expense of genotyping. The second development was the demonstration that it was probable to make very accurate selection decisions when breeding values were predicted from dense marker data only, by a method termed GS(2). GS has developed modern breeding schemes and has contributed noticeably to the enlarged accuracy of breeding values (BV) particularly for young individuals. So, a decreased generation interval and increased genetic gains For the intended traits (9, 10) (Refs) compared to traditional assessment methods have been observed since the large-scale assumption of GS in routine dairy cattle breeding programs(11, 12). Although the rate of increase in genetic gain from GS can be over 100 % in some cases(13), issues have appeared. One vital subject is the fast decrease in additive genetic variance and more unwanted genetic correlations between important traits(14). This decrease is even more remarkable when genomic information is not used for variance components assessment. The same phenomenon might be responsible for the offered decrease of 33% in heritability in calculations of GS for production yield traits to eschew bias in genomic estimated breeding values (GEBV;(10)). From the start of GS, many ideas were offered and typically tested by simulation, and many of these ideas were later useful to real data sets, first small then large. GS is now extensively practiced across the breeding and genetics industry. This is obvious through large-scale genotyping using cheap SNP chips. As of November of 2019, genotypes were accessible for

over 3 million U.S. Holsteins (https://queries.uscdcb.com/Genotype/cur_freq.html), over 700,000 for American Angus (S. P. Miller, American Angus Association, Saint Joseph, MO, personal communication), and over 100,000 animals per line for some pig and broiler breeding companies. Fertility and reproduction traits are intricate traits that are important for the maintaining of the dairy cattle industry which is affected by many factors involving the entire reproductive cycle from conception to calving and genetics in both sexes(15). Though reproductive records can be mainly affected by management choices, the dairy industry and investigators have been dedicated to developing accurate fertility traits in the past 30 year (16). Nevertheless, the low heritability and low accuracy of selection related to these traits make it hard to attain high rates of maintaining. The low heritability of fertility traits may implicating many effective factors, including the genetic and biological complications of fertility, difficulty and inaccuracy in the evaluation of fertility traits, and the robust correlation with fitness and reproduction(17, 18). Many fertility traits are hard to measure and are mostly affected by managing intentions, including days open, which extremely correlate with conception and pregnancy rates. In addition, variants of fertility is retained at low frequency owing to natural selection on fitness-related traits, thus leading to lesser genetic variation and heritability of fertility related traits (17-20). Also, this low-frequency QTL hypothesis for fertility is supported by the identification of numerous low-frequency embryonic lethal haplotypes by the scientists at USDA-AGIL (21-23). Nevertheless, the differences in fertility between and within cattle breeds, as well as the difference between current Holsteins and those of 50 year ago, propose the existence of genetic variation underlying dairy fertility and indicate the probability of improving the genetic component of fertility without intensely reducing genetic gain for milk production(16, 24). Complex nature of fertility appeals for the use of all accessible resources and tools, containing genetic methods, to comprehend and develop fertility. Several studies have shown

that genetic factors including additive and non-additive effects, contribute to fertility, and sequence-based huge sample analysis will cause the most creative genomic detection and use to improve fertility traits(25, 26). In this review, we aimed to investigate different methods of genomic evaluation in fertility treats in animal.

QTL as Genetic tools to improve fertility traits

Fertility and calving traits are of considerable economic significance in dairy cattle production. It has been shown that poor reproductive function is the most common reason for culling and 26% of all removals in the main dairy breeds in Sweden are owing to impaired fertility (Swedish Dairy Association, 2004). The outcomes of low fertility contain extra inseminations, higher veterinary costs, enlarged culling rate, and higher replacement costs. Calving function and calf survival are significant traits not only for economic causes but also for animal's welfare. Reproduction traits are quantitative traits that are regulated by numerous genes and are influenced by the environment. These traits have a low heritability, typically below 5%(27, 28). Nevertheless, Regard to this, several literatures have shown that the low heritability is because of a big phenotypic and the genetic variation is still entirely large(27-29). Also it has been exhibited that the genetic correlation between fertility and production is mostly negative(28, 30).The environmental effects and the negative genetic correlation create it costly and difficult to achieve a remarkable genetic improvement in reproduction traits through traditional selection relying on breeding values. Molecular methods have made it probable to locateloci involved in the expression of a quantitative trait by genetic markers and the phenotypic pieces of information on a trait. A quantitative trait locus (QTL) is a locus (section of DNA) that correlates with variation of a quantitative trait in the phenotype of a population of. Several literatures have described QTL for reproduction traits in diverse populations(31-33). Marker-assisted selection (MAS) is predictable to be useful in selection for sex-limited traits or traits that are

expressed late in lifespan. MAScan also be used to select for specific QTL that has positive effects on reproduction without contrary effects on production. Thus, MAS may be suitable if could recognize QTL accounting for an important proportion of the genetic variation infertility. Holmberg *et al.,* reported that map QTL influencing fertility and calving traits in the Swedish dairy cattle population. Their results have shown that it is valuable to carry out QTL mapping studies on these traits. Also, it has been founded that it's probable to recognize chromosome regions by the effect on fertility and calving traits in the Swedish dairy cattle population. So, these results provided the first step in detecting the fundamental genes causing the effects. Also, it has been provided a basis for further work to limit the QTL regions. Although reproductive progress depends on several and intricate genetic factors, most of the investigation has been focused on female fertility, exclusively on abnormal phenotypes, such as non-reversal rates(34). It has been expected that genetic studies relying on delicate phenotypes in females, males, and embryos. Also, the collection of big genotyping and whole-genome sequencing (WGS) datasets is considerably increasing the potency of QTL methods and the mining of such databases now provides the detection of recessive embryonic lethal mutations. So, this study presents an overview of the attainments of bovine genetics with a focus on reproduction-related traits.

Detection of QTL for male fertility traits

In spite of the significance of the male role to reproductive success, a remarkably low number of studies has been attentive on male fertility traits(34). However, as for the female, various parameters that could be used as phenotypes for genome-wide association studies (GWAS) are usually calculated to evaluate male fertility, such as the non-return rate (NRR), estimated relative conception rate (ERCR), sire conception rate (SCR) and male reproductive ability (MRA), which are regulated for environmental and genetic effects of female. Besides, some parameters are usually collected

using the AI industry to evaluate semen quality and production. Therefore, several fine phenotypes have been collected for male gametes, including scrotal environment and reparable (i.e. concentration, motility, and morphology) and non-reparable spermatozoid traits that cause subfertility (i.e. nuclear vacuoles, faulty chromatin structure). Highlights include identifying in the Holstein breed of polymorphisms related to ERCR in the fibroblast growth factor 2 (FGF2) and signal transducer and activator of transcription 5A (STAT5A) genes(35) and with SCR in the prophet of Pit 1 (PROP1) gene(36).Remarkably, the second is also related to milk production, providing molecular indication for the reverse association between milk production and fertility. The identify of QTL for scrotal surrounding at 12 and 14 months, which is very associated with sexual maturity, will permit for the selection for prematurity and aid breeding schemes to decrease generation intervals (C. Michot, R. Saintilan, S. Moureaux S. and Fritz, unpubl. data). Finally, the recognition of QTL(37) and candidate mutations (C. Michot, R. Saintilan, S. Moureaux S. and Fritz, unpubl. data) for semen quality, sperm volume, and survival after thawing and five morphology traits also display an exclusive chance to dissect the molecular base of the global phenotypes analyzed so far.

Detection of QTL for phenotypes associated with female fertility

An individual's genotype is the totality of that individual's hereditary material, whereas an individual's phenotype is the individual's appearance. However, the terms genotype and phenotype are usually used in reference to a particular locus or set of loci, and to a particular trait or set of traits. Genotypes are not observed directly, but rather inferred from particular phenotypes. Phenotypes are the observable characteristics of an organism arising from its response to the environment. The distinction between genotype and phenotype was first made by the Danish botanist Wilhelm Johannsen in 1909(38) and disseminated in a later paper in English in 1911 (38). Genotype

imputation is now an essential tool in the analysis of genomewide association scans. This technique allows geneticists to accurately evaluate the evidence for association at genetic markers that are not directly genotyped. Genotype imputation is particularly useful for combining results across studies that rely on different genotyping platforms but also increases the power of individual scans. The main purpose of reproductive management of dairy cows is to maximize the number of parturitions during the useful age of cows and thus increasing profitability. Due to unfavorable genetic correlation between productive and reproductive traits(39) and most emphasis on milk yield in selection of dairy cattle, the reproductive efficiency has decreased since the mid-1980s(40). So today, the main factor of economic losses is to be low reproductive efficiency in dairy cattle herds(41). Fertility in lactating dairy cows is also very sensitive to season, especially in hot climates. Global warming and the breeding of selected animals that are more and more sensitive to environmental effects have made this phenomenon, named heat stress (HS), particularly relevant even in temperate areas(42). Decreasing heat tolerance may be one of the reasons for decline in fertility. One way to counteract this decline is through genetic selection (43). Estimation of genetic trends is necessary to monitor and evaluate selection programs. The estimates of trends in the performance traits of dairy cattle seem to vary from breed to breed and from herd to herd due to differences in locality, management and selection objectives(44). Dairy fertility is a complex phenotype affected by many factors that include nutrition, management, environment, and genetics (45-49). Fertility in dairy cattle is a complex phenotype affected by many factors involving the entire reproductive cycle from conception to calving and genetics in both sexes(15, 50). Although reproductive records can be largely affected by management decisions, the dairy industry and researchers have been devoted to developing accurate fertility traits in the past 20 yr(16, 51, 52). The complex nature of fertility calls for the use of all available resources and tools, including genetic methods, to understand and improve fertility. Many

studies have been conducted to discover causal or tightly linked genetic variants and to apply these genomic discoveries to improve dairy fertility. The genetic components of fertility range from simple monogenic effects of recessive lethal mutations(21, 53) to complex mechanisms that involve multiple genes with additive and nonadditive effects(54-57). As above-mentioned formerly, there have been many studies relying on global phenotypes and on rectified phenotypes in female fertility(34). Because of technical facets, efforts to rectify the phenotypes have focused mostly on the good dissection of periods of time (e.g. pregnancy length or length of anoestrus) or in the well monitoring of pregnancy(58)more than in evaluating the quality and/or quantity of oocytes and embryos in great groups of animals. The major parameters assessed from pregnancy to weaning including age at maturity and at first conception, ovulation rates, fertilization defeat, number of inseminations, embryo loss, fetal losses, pregnancy length, duration of postnatal anoestrus, fertility, and the interval between first and last service (D. Valour, P. Michot, R. Lefebvre, E. Sellem, A. Bonnet, J. Dupont, R. Dalbies-Tran, S. Uzbekova, A. Capitan, S. Fritz, C. Ponsart and L. Schibler, unpubl. data). It is value noting that whiles these traits are recorded in bovines, in most cases, the detection of QTL is executed in AI sires after the alteration of these phenotypes in daughter yield deviations. However, times are altering and the opening up of the genomic selection service for females composed with the extensive utilization of embryo transfer is causing the making of great databases of females with genotype and rectified phenotypes accessible, moreover to the ordinary phenotypes mentioned above. A. Capitan *et al.,* ran an experimental study on 4067 Holstein females with backgrounds accessible for the total number of embryos (Ntot) and the number of viable embryos (Viab) produced after superovulation protocols. (Mean=1.4 protocols per animal; A. Baur, R. Saintilan, F. Guillaume, D. Boichon and S. Fritz, unpubl. data). After regulating the data for various non-genetic effects (i.e. parity, superovulation in the farm, breeding companies, and team of operators), relatively high heritabilities were

attained for Ntot (0.32) and Viab (0.19), suggesting the existence of genetic variants with significant effects on these traits. Then, using a Bayesian sparse linear mixed model (BSLMM) identified markers considerably related to both phenotypes and evaluated their effects on performance genomic selection**.** Remarkably, receptors for LH and GSH (LHCGR and FSHR, respectively), which are the molecules caused to induce superovulation of females, were collocated with the most important QTL for Ntot. The continuous identify of the causative mutations for these QTL will surely greatly enhance our science of folliculogenesis and embryonic development. In parallel, an experimental genomic selection has been applied using 861 markers for Ntot and 875 for Viab that explains 40% of the genetic variance for each trait. So, First, these results (A. Baur, R. Saintilan, F. Guillaume, D. Boichon and S. Fritz, unpubl. data) can cause are incentivizing and their next use by the breeding schemes should gradually increase their efficiency.

Main Fertility QTL on BTA18

The genome-wide association study (GWAS) is a well-established technique for identifying genetic variants of interest, not only for many common complex human diseases but also for traits of interest in animal and plant genetics(59-61). While the GWAS approach is extensively used and generally celebrated, there are still several unresolved statistical challenges in studying the joint effects of that huge number of genetic and environmental variables (62, 63). First, in a typical GWAS, genotypes from some thousands to several millions single nucleotide polymorphism (SNP) markers are determined in subjects in the order of a few thousands, leading to the small *n*, large *p* problem(i.e., many more predictor variables than response variables). It is common in GWAS to perform single SNP regression which leads to very high rates of Type I error (false positives). The standard procedure is then to adjust the significance threshold with some kind of multiple comparison criteria, for example Bonferroni or False Discovery Rate (FDR) corrections. Unfortunately, these

corrections will unavoidably introduce Type II errors (false negatives) and true SNP-associations of moderate and small effects will be erroneously discarded. Therefore, one of the most important issues in contemporary statistical genetics is to find methods that provide a satisfactory balance between false positives and false negatives in large-scale GWAS (64). Secondly, when a large number of SNPs are genotyped on a genome-wide scale, correlated variables (linkage disequilibrium between SNPs) occur both because of biological factors and because of high dimensionality (65). There are several applications of regularized regression methods to GWAS and genomic selection, which is closely related to GWAS but concerned with prediction of genomic breeding values. While in genomic selection the focus is on predicting future performance, the association studies are designed to find genetic makers connected to the trait of interest. Penalized regression methods have been previously used for variable selection in high dimensional studies focused on human genetic data (66-68). (69) compared the performance of elastic net and lasso using uncorrelated predictor variables. (70) examined the influence of penalties in several penalized regression models. To overcome the challenges mentioned above, penalized regression approaches, also called shrinkage or regularization methods, have been developed. Although shrinking some of the regression coefficients toward zero may result in biased estimates, these regression coefficient estimates will have smaller variance. This can result in enhanced prediction accuracy because of a smaller mean squared error (71). Regression coefficients are shrunk by imposing a penalty on their size, which is done by adding a penalty function to the least-squares model. Moreover, some of these procedures enable variable selection such that only the important predictor variables stay in the model (72). Before fertility traits were incorporated into selection, dairy cattle breeding primarily focused on production traits, which resulted in an unfavorable decline in the reproductive performance of dairy cattle. This reduced fertility is constantly challenging the dairy industry on the efficiency and sustainability of dairy

production. Recent development of genomic selection on fertility traits has stabilized and even reversed the decreasing trend, showing the effectiveness of genomic selection. Meanwhile, genome-wide association studies (GWAS) have been performed to identify quantitative trait loci (QTL) and candidate genes associated with dairy fertility, providing a better understanding of the genetic architecture of fertility traits. Because of the polygenic nature of fertility traits, many GWAS of dairy fertility tended to be underpowered. Only 1 major QTL, on BTA18, was identified across multiple studies. This QTL was associated with a range of fertility traits from conception to calving, but the candidate gene or mutation is still missing. Collectively, with the promising success from genomic selection but low power of GWAS on dairy fertility traits, this review calls for continuous data collection of fertility traits to enable more powerful studies of dairy fertility in the future. For more than 40 yr until 2002, increases in Holstein milk production were accompanied by declines in female fertility (46, 73-75). This trend has only recently leveled out and begun to improve (13). Successful conception in Holstein cows now requires approximately 50 d longer than it did 50 yr ago (−1% daughter pregnancy rate = +4 d open) (16). Although reproduction traits generally exhibit low heritability (26, 76-78), the genetic antagonism of milk production and fertility, as well as the unfavorable decline in fertility that occurred during genetic selection, showed the importance of genetic contribution to fertility traits (73, 77-82). In addition, variation in fertility between and within breeds indicated the possibility of improving fertility without severely slowing genetic gain for milk production (24, 29, 46, 79), which has been supported by the stabilization and reversal of the declining trend in daughter pregnancy rate since 2003, when fertility started to be included in the USDA national genetic evaluation (16). of genomic selection and to the efforts of discovering genetic variants associated with fertility but offer only limited coverage of genes and the genome. Genome sequence covers all genes and genomic regions that affect fertility and offers the best power to detect

fertility related variants and regions and to predict fertility traits (83). Sequence-based genomic selection can potentially improve accuracy by increasing the linkage disequilibrium between SNP markers and causal mutations, particularly for fertility traits where causal mutations are of low frequency because of selection (83-89). Large scale sequence-based association studies are ongoing in humans(90-92) and will be the future for livestock animals(25, 92, 93). Several studies reported the QTL on BTA18 to be importantly related to fertility traits. This QTL has the major effect on net merit, a combined trait assessing the final genetic value of an animal, in the US genomic evaluation. More notably, this QTL is related to a range of fertility traits from conception to calving as well as body conformation traits. Although this QTL has been identified by several studies, the causative gene or mutation is still unclear. Candidate genes that are located in this QTL region, including clusters of sialic acid-binding Ig-like lectin genes and zinc finger protein genes; however, definitively the reason for causal genetic variety has not been determined (94-98). So, future studies are still required to identify the candidate genes and mutations fundamental to this big QTL on fertility. Cole *et al.,* also proposed that the pleiotropic effects of this QTL may initiate by the effect on embryo development and growth, which resulted in this QTL having inverse effects on production and reproduction. These antagonistic effects could locate this QTL under adjusting selection to preserve middle frequency, resulting in the main QTL of fertility in the cattle population(94).

Additive and Non- additive effects for fertility traits

The whole genetic value of an individual is the sum of additive (i.e. breeding value) and non-additive (e.g. dominance deviation) effects There is limited science on how much genetic variation is described via non-additive effects in dairy cattle, particularly for fertility traits. Dominance is a non-additive genetic effect that occurs due to the communications between alleles at the same locus(99). If the quota of

dominance effects to the total variance is notable, including dominance effects in genetic evaluation models could progress assessments of additive breeding values and cause better selection decisions. So, the prediction of an animal's future efficiency would be more precise, which would help breeders to select animals for replacements or recognize animals for culling. Besides, to using both additive and dominance effects would be beneficial to select matings and maximize the productive function of the offspring by using the specific combining ability. However, dominance effects are typically disregarded in the genetic evaluation of livestock. In livestock, pedigree information is seldom informative adequate to accurately evaluate dominance effects because it is hard to find large populations with substantial dominance associations such as full-sib families, and these effects are often confused with other non-genetic effects. The prediction of dominance effects by pedigree information is computationally very demanding because it needs great datasets and complex algorithms to calculate and reverse dominance covariance matrices between individuals(100, 101). Evaluations of dominance variance for various traits in livestock by pedigree information vary significantly between traits and studies, but, generally, have a small to medium (1–34 %) influence on the total genetic variance(102). Another object why dominance effects are usually disregarded in the genetic evaluation of animals is that predictable breeding programs pointed at improving the genetic merit of animals rely only on additive gene actions in terms of breeding values, and consequently, the estimate of total genetic values has not been considered. Information from genome-wide single nucleotide polymorphism (SNP) panels have been usually used in dairy cattle to identify additive effects of SNPs in association studies (e.g.(94), or to estimate genomic breeding values of animals for selection purposes (e.g.(75, 103)). The accessibility of large numbers of SNP genotypes is also provided an occasion to study the non-additive gene activities at the individual level. Sun *et al.,* (10) studied the role of dominance effects for eight traits in Holstein and Jersey breeds by SNP

genotypes and indicated that small (5–7 %) proportions of the total phenotypic variance could be explained by dominance variance for yield traits. They also reported very small to zero influence on dominance effects to the variance of non-yield traits in both breeds. Various studies have been shown a significant dominance variance in production and reproduction traits in livestock and up to 28% of the phenotypic variance based on pedigree analysis (e.g., (100, 104-106)., Aliloo *et al.,* (107) using genomic data presented a small dominance variance for fertility trait in Australian Holstein and Jersey dairy cattle. The accessibility of dense genome-wide SNP marker genotypes has provided a chance to evaluate the additive and dominance effects from individual marker genotypes assumed in LD with QTL. It is remarkable that the accessibility of genomic information for bovines enables the study of the role of non-additive genetic effects on fertility and reproduction traits in Canadian dairy cattle. In this regard, it has been observed that dominance variation for fertility traits to be 1.2% of phenotypic variation in Holstein and also detected that the accuracy of estimate of phenotypes was slightly enlarged by including dominance effects in genomic valuation models(107). Therefore, the model that involved additive and dominance effects also resulted in a higher prediction accuracy(10). Also, Aliloo *et al.,* (107) used Spearman's rank associations to compare the rank of animals considered by a model with only an additive genetic effect, to a model in which animals were ranked based on total genetic value. They results shown correlations between the rank of animals to be lesser than 1.0 (≥0.8), proposing that a small re-ranking of animals would happen, particularly amongst the top animals.

Pedigree and population structure

Pedigree includes the animal, sire and dam, and paternal and maternal grandparents. Pedigree provide detailed performance and genetic information about an animal and its ancestors, which has many uses. The pedigree values that mwasure the ability of the sire and dam to transmit their traits

can help you predict the calf's future performance. Pedigree ties together nuclear families, parents and sib-ships in an organized way and summarizes the transmission of trait from generation to generation. The term "population structure" (or "population subdivision") usually refers to the patterns in neutral genetic variation that result from the past or present departure from panmixia of a population. Understanding past population structure is of interest to evolutionary biologists because it can reveal when migration regimes changed in natural populations, thereby pointing to potential environmental factors such as climate changes as driving evolutionary forces. Characterizing the structure of extent populations is also key to conservation genetics as translocation and/or reintroduction decisions must preserve evolutionary stable units. Finally, population structure has important biomedical consequences either when a number of subpopulational groups is locally adapted to particular environmental conditions (and maladapted when exposed to new environments) or represents a confounding factor in the study of the statistical association between genetic variants and phenotypic traits(108). Identify the genetic structure of populations Possibility to investigate the origin Provides formation and communication between populations. Study of the genetic structure of populations with increasing access Facilitated to genomic data (109). Population structure plays also a central role in biomedical applications because it acts as a confounding factor in the study of the statistical association between a genetic variant and a phenotype. Considering that pedigree data continue to benimportant, numerous studies evaluating inbreeding, effective population size, genetic diversity and other important population parameters are available(110-114). Some simple population parameters that depend mainly on management and mating systems have an important impact on the genetic variability of a population. Therefore, studies on population structure may elucidate important factors that affect the genetic evolution of populations(115). Data monitoring is beneficial for maximizing profits and improving the application of selection methods to provide genetic

progress in dairy herds. In addition, precise pedigree control is essential for the correct identification of relationships between the animals, which will help prevent possible high rates of inbreeding in the long term. Inbreeding is caused by the mating of individuals that share one or more common ancestors. High inbreeding rates cause undesirable outcomes, such as a decrease in genetic variance and, therefore, should be avoided(116). Since the adoption of large-scale reproductive biotechnologies, the probability of producing inbred animals has increased considerably because of the diffusion of genetic material from specific breeding herds. Thus, more careful analyses of the structural genealogy of populations are required (117). The population structure is typically determined by calculating the allelic frequencies of the different individuals. To prevent inbreeding, possible changes in the distribution of genetic variability should be constantly monitored (118).

Validation

We use a strategy similar to that used to evaluate non-animal approaches in toxicity and safety testing to discuss the advantages and disadvantages of validating preclinical animal models for proof-of-concept research(119). Both economic and ethical issues come into play, when a potential therapy fails first-in-human or later trials (120). Better (use of) animal models is one way of reducing the high attrition rate (121).

Animal model validity is discussed in terms of the similarity between the model and the human condition it is intended to model, but no formal validation of models is applied. There is a stark contrast here to the use of non-animal alternatives in toxicology and safety studies, for which an extensive validation is required. Roughly speaking, the present approach to model development is based on similarities in the symptoms and/or aetiology of a disease in humans and animals. An animal model is considered to be valid, if it "resembles the human condition in aetiology, pathophysiology, symptomatology and response to therapeutic

interventions" (122). Genome-wide association studies (GWAS) were used to discover genomic regions explaining variation in dairy production and fertility traits. Associations were detected with either single nucleotide polymorphism (SNP) markers or haplotypes of SNP alleles. An across-breed validation strategy was used to narrow the genomic interval containing causative mutations.

There is often pronounced disagreement between different populations in the results obtained from genome-wide association studies (GWAS). The main interest in genome-wide association studies (GWAS) in dairy cattle breeding is to find markers to improve the accuracy of breeding values and to increase the understanding of the genetic control of economically important traits. Identifying the genes that affect traits such as protein yield will also provide insight into the likely effect of selection on these mutations on fitness traits like fertility. Validation of association studies is therefore desired before marker information is incorporated in selection decisions, or before large sums are invested into identification of causal factors. The probability of observing spurious associations between a particular trait and SNPs in multiple populations by chance is small, particularly if significant associations are confirmed in two or more validation populations or breeds(123, 124). As a result of the widespread use of artificial insemination (AI), effective dairy cattle population sizes are relatively small. This has had an effect on patterns of linkage disequilibrium (LD) in dairy cattle breeds.

For example, The Bovine Hapmap Consortium (125) reported low but non-zero levels of LD of up to 1,000 kb in several dairy breeds, in contrast to humans in which LD is found only up to tens of kb(126). Because GWAS exploits LD, it should be possible to find significant associations in dairy cattle with markers positioned every 100 kb or so (127). On the other hand, the level of LD also limits the precision of the QTL location, as SNPs at longer distances will exhibit association due to extended LD with causal mutation. This extended LD is not

expected to exist across breeds, therefore across-breed validation of associations may help to narrow down the QTL interval.

Blup effects for fertility traits

Genomic best linear unbiased prediction (BLUP) is a statistical method that has been used to predict height in humans (128) and breeding values for selection in animal and plant breeding (129). It uses a so called genomic relationship matrix that describes genetic relationships between individuals calculated from genotypes at single-nucleotide polymorphisms (SNPs).

In genomic selection applications (130), those individuals comprise both training individuals that are phenotyped for a quantitative trait and genotyped at SNPs and selection candidates that are genotyped only. Genomic BLUP differs from the traditional pedigree BLUP(131) in the replacement of the pedigree relationship matrix with a genomic relationship matrix. Coefficients of the pedigree relationship matrix describe additive genetic relationships (Malecot, 1948) between individuals at quantitative trait loci (QTL) conditional on pedigree information, but it is not obvious to what extent the genomic relationship matrix explains genetic covariances between individuals at QTL.

Despite this, several authors called the genomic relationship matrix the actual (132) or realized relationship matrix(133-135) as it describes identity by-descent at SNPs (134), assuming an ancient founder population. Improving fertility in dairy cows is becoming increasingly important throughout the world because it has a substantial effect on the overall profitability of dairy cattle production. Reduced fertility is characterized by increased number of inseminations, more veterinary treatments, longer calving interval, and increased rates of involuntary culling (136, 137).

To increase reliability of EBV for a trait with small number of phenotypic records, a multitrait model to use additional information of the correlated traits

could be a good approach. Moreover, genomic selection could be a promising tool to improve the accuracy of estimation of breeding values of fertility traits. Genomic selection refers to selection based on genomic EBV instead of the traditional selection using information on phenotypes and pedigrees to predict breeding values (130) Genomic selection may result in higher rates of genetic gain over traditional selection using BLUP-EBV because genomic EBV have higher reliabilities, especially for young animals that do not have daughter records.

As accurate selection can be performed early in life, genomic selection can greatly reduce evaluation cost and generation interval compared with the traditional progeny test schemes(138, 139). Various models have been used for genomic prediction to use phenotypic information as much as possible for genomic prediction. (140) proposed that the genomic breeding values can be obtained in a single-step genomic BLUP (ssGBLUP) including phenotypic, pedigree, and genomic information, where a pedigree-based relationship matrix (A) in the evaluation procedure is replaced by a matrix (H) that combines A and a genomic relationship matrix (G) (141, 142).

The same procedure also applied by (143), who reported a 3× increase of reliability of EBV prediction by using ssGBLUP instead of traditional BLUP estimation of breeding values for conception rate in US Holstein. Furthermore, studies on Nordic Holstein and Red cattle indicated that ssGBLUP can provide more accurate and simpler estimation of genomic breeding values compared with the multistep genomic prediction methods (144, 145).

Reference and training population

GS is usually done in three steps: (1) genotyping and phenotyping a 'reference' or 'training population' combined with the development of genomic prediction models that permit for an estimate of phenotypes from genotypes; (2) validation of the predictive models in a 'validation population', i.e. a set of individuals that did not contribute in model

training; (3) use of the models to predict the genomic estimated breeding values (GEBVs) of unphenotyped individuals which are then selected according to their GEBVs(2). Numerous studies have been shown that the selection of appropriate statistical methods depends on the real data at hand and the pattern of phenotypic variation in the traits of interest and with reference population used(146, 147).

Nearby statistical methods, other factors are identified to impact the accuracy of genomic prediction models, such as the size of the training population, number of markers employed, and relatedness between the training and validation population and, by extension, to the future selection candidates. Hayes *et al.,*(75) have been reported that for effective population size (Ne), increasing the size of reference population causes improved accuracy of genomic predictions.

The closer relationship between training population and selection candidates has also been reported to causes a higher accuracy of genomic predictions while enlarging the genetic variety of the training population lead to lower accuracy (148).

The number of simulations and experimental studies have revealed that increasing the number of markers can advance the predictive accuracy since Ne also enlarged (146). Nevertheless, increasing the number of markers in small Ne populations causes low or no progress in predictive accuracy (89, 149).

However, collecting these reference populations is probably to be very challenging in some cases where only a confined number of animals is accessible for use in the reference population.

An alternate is to combine different populations of different breeds to increase the accuracy of genomic selection(75, 103, 150). The studies shown that the genomic selection in pigs are more focused on populations with the same or very near genetic base(151-153). The lower the accuracy of the phenotypes, by way of is the case for lower heritable

traits such as fertility(80)and health (49), the lower the accuracy of genomic predictions for the same reference population size (60, 154). For the same reference population size, the larger the relatedness of the reference population to the population where the prediction equations will be used, the larger will be the accuracy of the genomic predictions(155).

Artificial insemination (AI) bulls establish the majority of global dairy cattle training populations because they usually have more accurate predictions of genetic merit and so fewer animals necessary to be genotyped to attain the same accuracy of genomic predictions(60, 154).

The difficulty of using only AI sires is that the traits contained in the genomic predictions are confined to those existent nationally and used to evaluate the sire breeding values. Eased by the multiple trait-across country genetic evaluations (MACE; Schaeffer, 1994) carry out by INTERBULL for dairy cattle, predictions of genetic merit of all international male AI animals on the scale of each country are attainable. So, although a male animal may have no progeny in a given country its MACE assessment might be used as a phenotype for presence in genomic predictions(156) weighted through a function of the MACE reliability.

Nevertheless, the number of AI sires is confined and so natural mating bulls or cows must also be considered for presence in genomic selection reference populations. Cows are involved in the genomic selection reference population in the United States(157)while natural mating bulls are involved in the dairy cattle genomic selection reference population in Ireland (Andrew Cromie, personal communication); the latter is mainly relevant for populations (e.g. some beef populations) where AI is used fewer frequently.

The phenotype involved in all genomic evaluations of dairy cattle is either daughter yield deviations or deregressed estimated breeding values(156) that delete pedigree contributions and inverse the effect of reduction during the BLUP evaluations.

Table.1 The effect of reproductive biotechnologies on genetic gain components

	Accuracy	Intensity	Impact on genetic gain components Accuracy Intensity Variation	Heritability	Generation interval
associations between reproductive technologies and genetic gain	Female genotyping= increased size of reference population (more phenotyped candidates/ females)	More candidates (or females) within a given time period or reduced number of selected candidates	-(Intensive use of a limited number of bulls/dams/embryos) +(Use of assisted mating plans)	Genomic selection on new traits, especially with low heritability	more or less candidates (or females) within a given time period
Genotyping and sexed semen	+++(depending on use of female testing, size of population)	+(more candidates through controlled sex of offspring; detection of elite females)	++ (use of genomic assisted mating plans)	Female traits	+(controlled sex of offspring; early detection of elite females)
MOET	+(depending on use of MOET, nucleus size)	++ (reduced number of selected dams, MOET every 6–7 weeks)	-(increased inbreeding) +(increased number of mating plans)	New traits (donor/ dam, Day 7 embryo)	+(increased number of calves at fixed age) +/- (embryo freezing <fresh)
IVP	+(depending on use of IVP, nucleus size)	++(reduced number of selected dams, OPU once or twice a week)	- (increased inbreeding) +(increased number of mating plans)	New traits (dam, Day 0–7 embryo)	++ (OPU in young, prepubertal heifers)
Embryo cloning		+++(>1 calf from reduced numbers of dams)	-(individual genotype approach)	New traits (dam and clones)	+++(clones from stem/ embryonic cells)
Embryo genotyping	+(depending on use of embryo genotyping, nucleus size)	+++(selection before ET)	+(more candidates), - (embryo selection before ET)	New haplotypes	-(embryo freezing) ++(early candidate selection)

+: positive effects; -: negative effects; MOET: multiple ovulation and embryo transfer; IVP: *in vitro* embryo production; OPU: ovum pick-up; ET: embryo transfer.

The effect of GS in Assisted reproductive technology (ART) on fertility trait

Progress in genetic analysis and mapping technologies have provided the execution of GS in cattle. With this method, animals could be selected for breeding on the foundation of their genomic breeding values (GEBV), that is, their genetic merit predicted by markers labeling the whole genome. GEBV is computed as the sum of the effects of dense genetic markers that are almost equally spaced across the whole genome, so most of the QTL obtained potentially contributes to genetic variation in a trait. GEBV are now being used to recognize and market the best bulls in many countries around the world(158). According to previous studies, the genomic revolution has enabled us to: (1) evaluate the 'meiosisarea' (i.e. the difference between the genetic value of the progeny and the mean parental value) without any progeny testing, with reliability increasing with the development of new computing algorithms; (2) evaluate more selection candidates than allowed with progeny testing; and (3) more efficiently select animals for practical traits that have low heritability, thus paving the way for the maintainable management of populations(159). In this regard, the procedure to generate calves that can be selected for breeding becomes vital, through preserving the genetic variety. One of the most vital developments causing the introduction of genomic testing for dairy cattle is the use of sensibly priced low-density SNP technology to the selection of females to become the milk makers and dams for the next generation(159, 160). Besides, the advantage of genotyping females has been evaluated in terms of their influence on genetic gain through the process of genotyping such as lesser generation interval, and better reliability of breeding values(161). With the decreasing cost of low-density SNP chips, dairy producers can make important selection decisions using sensibly priced genotyping. It has been that, using genome testing and sexed semen in young heifers might be an approach to generate replacement of choice females in a given period of time. Therefore, widely used 'intensive' embryo-based reproductive techniques can be used to increase the number of candidates by repeating the number of flushes in multiple ovulation embryo transfer (MOET) and ovum pick-up (OPU) composed with IVF systems(162). Another problem experienced by breeding organizations in Europe is the finite accessibility of female recipients. In this context, embryo transfer (ET) teams have generally used embryo biopsy technology combined with polymerase chain reaction (PCR)-based sex determination to confine the number of embryos to be transferred (163, 164). As soon as MAS based on a restricted number of microsatellites can be used, benefits of embryo genotyping were found the cause of its potential value for screening the embryo for various traits(165). In the context of GS, the benefits of combining intensive embryo production and genotyping are even higher. Nevertheless, one of the main challenges of using genotype information is the detection of multiple SNPs from a small biopsy sample of a preimplantation stage embryo. Based on recent progress in GS, in this review, we investigated the practice of reproductive technologies, both for commercial aims and genetic schemes, possible side effects, and advantageous influences on reproductive efficiency.

Trends in GS

To date, GS has been used effectively to male pathways of selection in dairy breeding programs. Farmers can attain higher annual rates of genetic gain via gnomically tested bulls in their herds. The main benefit of using GEBV is a decrease in the generation interval, which can cause an increase in the rate of genetic gain over conventional progeny-testing systems(138). At the herd level, female genotyping help to recognizing the best heifers to become herd replacements and to enable a better prediction of the real value of an animal's genetics. High reliability is now acquired for many traits, providing the selection of female replacements on the basis of genotype results. Improved herd profitability can be attained via better sale price and parentage confirmation of individual cows(158, 160). Increased reliability by composed reference populations GS has the potential to promote the

accuracy of selection, genetic gain, also the effect in rate of inbreeding. Nevertheless, increased accuracies of genomic predictions depend on the number of individuals added to the reference population, the reliability of their phenotypes, and the relatedness of the populations that are joined(150, 158). Increasing the size of the reference population by combining closely related populations is particularly suitable for traits with low heritability(150).

Development of haplotype tests for candidate genes associated with reproductive efficiency

Most dairy cattle breeds are genetically small populations originating from a limited number of founders. In recent decades, their genetic pool has been reduced further by the wide use of a limited number of choice sires for insemination. Therefore, the inbreeding rate increased, leading to the appearance of recessive genetic disorders. It has been shown that new recessive defects were revealed in different breeds by investigative haplotypes that had high population frequency but were never homozygous (21, 166, 167). Enormous genotypic and phenotypic datasets let for the efficient discovery of smaller and fewer frequent effects. Haplotype tests can help breeders eschew mating carriers for such faults and decrease future frequencies. Large-scale genotyping makes it probable to accurately detect many genes of interest.

GS as a new decision support tool for reproductive technologies

Use of reproductive technologies in genome-tested females for breeding goals four main factors affect the rate of genetic change in a population undertaking artificial selection. Altogether with GS, combining semen and embryo biotechnologies create it probable to act on all these parameters to improve the rate of genetic gain (Table 1; (168)). Actually, at the population level, one of the most significant features of GS is to noticeably increase the number of estimated candidates subjected to GS to maximize the odds of getting favorable

individuals. This will display a promotor in the selection pressure for those traits. The method by which large numbers of animals are produced becomes vital in the genomic, where animals are assessed on a large number of traits that are less heritable(169, 170). One way to attain a large number of candidates is to use female genotyping, as described above. Large-scaled female testing will let describe the relationships between genotype and new phenotypes. This can contribute to the identity of choice females, be selected for use with sexed semen, and donors for ET, or in vitro production (IVP) technologies. Furthermore, the advantage resulting from the combined use of GS, sexed semen, and embryo biotechnologies in dairy cattle breeding programs have been assessed through simulation studies: the use of sexed semen has been offered to improve the annual genetic gain, particularly when X-chromosome-sorted semen is used for the whole production population(171, 172). Nevertheless, at the level of the nucleus, the effect appears to be low compared to embryo biotechnologies. Indeed, the use of sexed semen mostly actions through increased numbers of selection candidates (which cause a change in selection intensity on bull dams). The use of embryo biotechnologies (ET, IVP) permits an 'intensive' production process on a reduced number of selected top females and so increases the selection intensity on cow dams(172). Compared to MOET, the number of embryos created in a given period of time can even be multiplied by two or three by the use of repetitive IVP periods(169). However, MOET might significantly promote the rate of inbreeding, typically due to repeated embryo production periods from a reduced number of choice females. Shortening the generation interval might also cause an increased inbreeding rate(169, 172). Thus, the use of female genotyping may be limited inbreeding through the use of genomic-assisted mating plans, where relationships between animals are quantified at the genomic level and evade genetic faults that can arise from mating cows to bulls that are known carriers of genetic diseases that are the result of a single lethal mutation(158, 160). As another approach to balance the increase in inbreeding in

dairy herds, crossbreeding has been suggested as an opportunity to increase production and reproductive efficiency(173).

New traits as decision support tools for reproductive biotechnologies

At the population level, a critical purpose remains to improve reproductive competence. Therefore, it should be probable to select donor cows with improved fertility traits, enhanced reproductive efficiency, and or better biotechnology efficiency as a medium-term objective. There are possibly many improvements that can be attained in vivo and in vitro embryo production using the powerful effect of GS. Studies have reported that cross-bred embryos develop higher rates than pure-bred embryos, proposing that cross-breeding can be used to enhance the competence of reproductive biotechnologies(174, 175).

After the introduction of OPU-IVP, many attempts have been made to improve embryo production efficiency. GS provides new methods for improving the efficiency of an OPU-IVP program by selecting donors with high in vitro production results. Heritability for qualitative traits (quality of oocytes, cleavage, and developmental rates) appears to be lower compared to quantitative traits (total number of oocytes, number of embryos;(176). As an example, heritability for the total number of transmissible embryos has been assessed to range from 0.10 to 0.26 between studies, while the phenotypic correlation for the quality of oocytes (based on cumulus investment) appears to be autonomous of the total number of oocytes fertilized(176). Maximal effects observed between genotypes ranged from 5.4% to 12.2% for fertilization rates(177)and from 3.9% to 23.2% for embryo development from cleavage(24), thus indicating the potential interest of GS used to embryo biotechnologies. With the bovine LD SNP Array (Illumina Bovine LD chip; Illumina Inc), a customized list of SNPs could be considered to maximize biotechnology efficiency and to select donor cows with a maximum potential of embryo

production. Another of the main problems is that non-invasive reproductive phenotypes together with in vivo methods discerning fertilization defeat from early embryonic humanity are still missing(169). Another critical topic could be associated with the genetic correlation between reproductive traits and probable side effects on production, longevity, or resistance to diseases(178). Besides, it has been reported that Bos indicus oocytes, embryos, lymphocytes, endometrium, and oviductal cells have more heat tolerance than Bos taurus cells(179).

This genetic variation cause more thermoregulatory ability and cellular thermoresistance in heat-tolerant breeds. Heat-induced oocyte cellular damage happens in both cytoplasmic and nuclear parts. It has been shown that Heat shock reduced oocyte nuclear maturation, induces apoptosis, compromises the oocyte cytoskeleton, and disorders oocyte mitochondrial function and developmental competence. Paula-Lopes *et al.,*(179)have reported that the harmful effects of heat stress on reproductive biotechnologies may be attenuated by genomic tools, including an extra list of SNPs.

When young animals are genotyped, genomic selection has a bigger advantage over genetic selection because anticipated breeding values are more precise than traditional breeding values and the generation interval can be shortened. The increase in reliabilities of GEBV over EBV for bull calves with no daughter records is remarkable, ranging from 2 to 20%.

The increase in reliability of GEBV is being used in 2 ways by bull-breeding companies. In some cases, larger numbers of bull calves are being screened to select a smaller number of calves to go on progeny testing, which decreases the cost of the breeding program and causes some further genetic gain. Other companies are marketing teams of young bulls based on their GEBV alone as soon as they are reproductively capable, which must results in large increases in genetic gain due to reducing the generation interval. Significant challenges and opportunities stay in performance genomic

selection, including conformity of national genetic estimate to include genomic information, genomic selection across breeds, management long-term gain and inbreeding with genomic selection, and computational challenges (e.g., (180, 181)) These are exciting topics for further research.

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