Genomic Selection for Crop Improvement

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ABSTRACT

Despite important strides in marker technologies, the use of marker-assisted selection has stagnated for the improvement of quantitative traits. Biparental mating designs for the detection of loci affecting these traits (quantitative trait loci [QTL]) impede their application, and the statistical methods used are ill-suited to the traits' polygenic nature. Genomic selection (GS) has been proposed to address these deficiencies. Genomic selection predicts the breeding values of lines in a population by analyzing their phenotypes and high-density marker scores. A key to the success of GS is that it incorporates all marker information in the prediction model, thereby avoiding biased marker effect estimates and capturing more of the variation due to small-effect QTL. In simulations, the correlation between true breeding value and the genomic estimated breeding value has reached levels of 0.85 even for polygenic low heritability traits. This level of accuracy is sufficient to consider selecting for agronomic performance using marker information alone. Such selection would substantially accelerate the breeding cycle, enhancing gains per unit time. It would dramatically change the role of phenotyping, which would then serve to update prediction models and no longer to select lines. While research to date shows the exceptional promise of GS, work remains to be done to validate it empirically and to incorporate it into breeding schemes.

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Abbreviations: BLUP, best linear unbiased predictor; EBV, estimated breeding value; G×E, genotype × environment GEBV, genomic estimated breeding value; GS, genomic selection; LD, linkage disequilibrium; MAS, marker-assisted selection; QTL, quantitative trait locus; RR, ridge regression; SR, stepwise regression; TBV, true breeding value.

The use of marker-assisted selection (MAS) in plant breeding has continued to increase in the public and private sectors. Most applications, however, have been constrained to simple, monogenic traits (reviewed by Xu and Crouch, 2008). While MAS has had significant impacts in backcrossing of major genes into elite varieties (Holland, 2004), backcrossing is regarded as the most conservative of breeding methods because improvement occurs through the pyramiding of only a few target genes (Lee, 1995). Gene pyramiding is inefficient for quantitative traits that are often controlled by many small-effect quantitative trait loci (QTL; Kearsey and Farquhar, 1998).

Current MAS methods are better suited for manipulating a few major effect genes than many small-effect genes (Dekkers and Hospital, 2002). Unfortunately, these small-effect genes underlie the complex polygenic traits that are crucial for the success of new crop varieties (Crosbie et al., 2003). Two primary limitations to MAS are (i) the biparental mapping populations used in most QTL studies do not readily translate to breeding applications and (ii) statistical methods used to identify target loci and implement

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MAS have been inadequate for improving polygenic traits controlled by many loci of small effect. The application of genomic selection (GS) proposed by Meuwissen et al. (2001) to breeding populations using high marker densities is emerging as a solution to both of these deficiencies. We review here current GS methods and their performance. In addition, we present future directions for GS research and some exciting opportunities GS provides that could revolutionize crop improvement.

CURRENT MAS LIMITATIONS

The most common method of QTL detection is the use of a biparental mapping population. While these studies are important to the understanding of genetic architecture, building mapping populations distinct from breeding populations often strains the resources of a breeding program. Available resources limit the size of mapping populations and, consequently, the accuracy of QTL position and effect estimates (Dekkers and Hospital, 2002; Schön et al., 2004). Also, allelic diversity and genetic background effects that are present in a breeding program will not be captured with a single biparental population. Therefore, multiple mapping populations are needed, QTL positions require validation, and QTL effects must be reestimated by breeders in their specific germplasm. The validation in locally adapted germplasm is important because poor estimates of the numerous small-effect QTL will lead to gains from MAS that are inferior to traditional phenotypic selection (Bernardo, 2001). Therefore, the resources required for QTL detection coupled with validation and effect reestimation limit the effectiveness of biparental population derived QTL for MAS in plant breeding populations (reviewed by Holland, 2004).

To avoid this disconnect between biparental and breeding populations, linkage disequilibrium (LD)–based mapping can be used for dissecting complex traits in breeding populations that already have extensive phenotypic data across locations and years (Jannink et al., 2001; Rafalski, 2002). This strategy avoids the need to develop special mapping populations that impose an additional burden on breeding programs. Also, mapping within breeding populations will allow for QTL identification and allelic value estimates that can be directly utilized by MAS without the need for extensive validation (Breseghello and Sorrells, 2006; Holland, 2004). However, low heritability, small population sizes, few large-effect QTL, confounding population structure, and arbitrary significance thresholds found in current association mapping efforts allow identification of only a few QTL with overestimated effects (Beavis, 1998; Schön et al., 2004; Xu, 2003a).

To minimize the limitations for successful MAS, Lande and Thompson (1990) proposed a visionary two-step approach: (i) select significant markers from large marker sets, and (ii) combine phenotypic information with significant markers in a selection index that would explain a significant proportion of additive genetic variance. In the first step, they were unable to estimate all marker effects simultaneously with simple regression due to the lack of degrees of freedom. Therefore, they proposed selecting the most significant markers from the previous generation via multiple linear regressions and then reestimating effects of the selected markers in the current generation with independent multiple regressions (Lande and Thompson, 1990).

Lande and Thompson (1990) introduced this two-step approach to handle large marker sets because they estimated that hundreds of molecular markers would be needed to capture a significant proportion of the additive genetic variance. In the early 1990s, genomewide marker coverage was a limiting factor for MAS, but in recent years, plant breeders have encountered a major shift in the amount of genomic information available due to the rapid advances in marker technologies. Although genotyping is still a major expense, the declining costs per marker data point have facilitated large-scale genotyping efforts in breeding programs. For example, the Monsanto Company (St. Louis, MO) reported that from 2000 to 2006, they experienced a sixfold decrease in cost per marker data point and increased the volume of their marker data by 40-fold (Eathington et al., 2007). The availability of abundant markers and the reduction of genotyping costs will present new tools for plant breeders only if statistical methodologies for the utilization of genomewide marker coverage are developed.

GENOMIC SELECTION FOR BREEDING VALUE ESTIMATION

The two-step process of Lande and Thompson (1990) has been criticized as an inefficient use of available data (Meuwissen et al., 2001): one would rather want to use all available data in a single step to achieve maximally accurate estimates of marker effects. Genomic selection is a form of MAS that simultaneously estimates all locus, haplotype, or marker effects across the entire genome to calculate genomic estimated breeding values (GEBVs; Meuwissen et al., 2001). This approach contrasts greatly with traditional MAS because there is not a defined subset of significant markers used for selection. Instead, GS analyzes jointly *all markers* on a population attempting to explain the total genetic variance with dense genomewide marker coverage through summing marker effects to predict breeding value of individuals (Meuwissen et al., 2001).

The central process of GS is the calculation GEBVs for individuals having only genotypic data using a model that was "trained" from individuals having both phenotypic and genotypic data (Fig. 1; Meuwissen et al., 2001). The population of individuals with both phenotypic and genotypic data is known as the "training population"

as it is used to estimate model parameters that will subsequently be used to calculate GEBVs of selection candidates (e.g., breeding lines) having only genotypic data (Fig. 1). These GEBVs are then used to select the individuals for advancement in the breeding cycle. Therefore, selection of an individual without phenotypic data can be performed by using a model to predict the individual's breeding value (Meuwissen et al., 2001). To maximize GEBV accuracy, the training population must be representative of selection candidates in the breeding program to which GS will be applied.

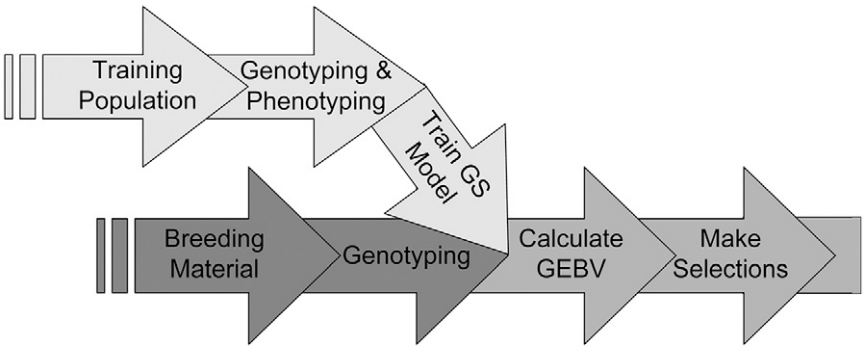

Figure 1. Diagram of genomic selection (GS) processes starting from the training population and selection candidates continuing through to genomic estimated breeding value (GEBV)–based selection. Note that while we show here a single occurrence of model training, training can be performed iteratively as new phenotype and marker data accumulate.

Historically, estimated breeding values (EBVs) for quantitative traits have been calculated by best linear unbiased prediction (BLUP) based only on phenotypic data of individuals and their relatives (Henderson, 1984). The use of EBVs via BLUP has been popular in animal breeding and in recent years has been used by plant breeders (reviewed by Piepho et al., 2007). However, data on markers linked to known QTL can also be used for calculation of EBVs (Fernando and Grossman, 1989); this method was predicted to increase gains from selection in animal breeding up to 38% (Meuwissen and Goddard, 1996). These results were encouraging, but they require extensive prior QTL discovery efforts in non-breeding populations.

MARKER DENSITY AND LINKAGE DISEQUILIBRIUM

Genomic selection differs from current MAS strategies because instead of only using markers that have a predefined significant correlation with a trait, all markers are used to estimate breeding values for each genotype. Consequently, dense marker coverage is needed to maximize the number of QTL in LD with at least one marker, thereby also maximizing the number of QTL whose effects will be captured by markers. Target marker density will be dictated by the rate of LD decay across the genome, as assessed by the relationship between intermarker coefficient of determination, r^2, and genetic distance.

Rate and pattern of LD decay are affected by population characteristics such as evolutionary history, mating system, population size, admixture, recombination rate, and selection effects (Gaut and Long, 2003). Therefore, LD decay rates are highly variable among species, populations, and genomic regions. Examples of this variability in LD decay rates include the following: 75 to 500 kb in a diversity panel of rice (*Oryza sativa*; Mather et al., 2007), 10 to 20 cM (roughly 50–100 Mb) in elite cultivars of wheat (*Triticum aestivum;* Chao, 2007; Maccaferri et al., 2005), 0.1 to 1.5 kb in diverse inbred lines of maize (*Zea mays* ssp. *mays;* Remington et al., 2001; Tenaillon et al., 2001), and 15 to 20 kb in a diversity panel of sorghum (*Sorghum bicolor*; Hamblin et al., 2005). Examples from diversity panels may give rough predictions of LD decay in a species, but because many factors affect LD, individual breeding programs will need to determine LD decay rates on a case-by-case basis in their specific breeding populations.

Linkage disequilibrium estimates can be used to determine target marker densities for GS. For example, Calus and Veerkamp (2007) used the average r^2 between adjacent markers as a measure of their marker density relative to the decay of LD. They found that for a high heritability trait, average adjacent marker r^2 of 0.15 was sufficient, but for a low heritability trait, increasing the r^2 to 0.2 improved the accuracy of GEBV predictions. These marker densities may still be out of reach for some crops or populations. Looking to the near future, however, high throughput sequencing has made marker discovery affordable for most crop species, and the continued reduction of genotyping costs will facilitate dense genomewide marker coverage for all crop species (reviewed in Zhu et al., 2008). Note that the conditions of complete genome saturation and of at least one marker in LD with each QTL need not be met to derive useful prediction models for GEBV. While it is tempting to surmise a minimum number of markers needed to obtain useful GEBVs, the many factors affecting this number and the lack of empirical results currently available would make any guess meaningless. Clearly, this subject requires urgent attention.

STATISTICAL MODELS AND PERFORMANCE

The challenge of QTL analysis is the selection of the appropriate statistical model to identify QTL and estimate their effects (Broman and Speed, 2002). In breeding programs, statistical methods for GS will need to simultaneously estimate many marker effects from a limited number of phenotypes. A greater number of explanatory

variables (markers) than observations (phenotyped lines) leads to a lack of degrees of freedom that must be handled through the selection and use of the most appropriate statistical model, that is, the model that results in the highest GEBV accuracy with consideration of model complexity and computation requirements. In the assessment of model performance, GEBV accuracy has a precise definition, namely, the Pearson correlation between the GEBV and the true breeding value (TBV). Accuracy defined in this way is directly proportional to gain from selection when selecting on the GEBV, that is, $R = ir\sigma_A$, where R is the response, i is the selection intensity, r is the accuracy defined above, and σ_A is the square root of the additive genetic variance of TBV (Falconer and Mackay, 1996, p. 189). We briefly describe here three models: stepwise regression, ridge regression, and Bayesian estimation.

Stepwise Regression for MAS

Traditional MAS considers marker effects as fixed, requiring stepwise regression (SR) approaches that avoid the lack of degrees of freedom problem by fitting markers singly or in small groups. After the model selection process during which markers are added or removed from the model on the basis of arbitrary significance thresholds, nonsignificant markers are assigned an effect of zero and significant marker effects are simultaneously tested to estimate their effects. This stepwise approach to set nonsignificant marker effects to zero is critical for maintaining model estimability (Lande and Thompson, 1990). Significance thresholds that may maximize response to selection cannot be determined analytically, although guidelines have been established through simulation (Hospital et al., 1997; Moreau et al., 1998). The general guideline is that liberal p-value thresholds improve selection gain (Hospital et al., 1997; Moreau et al., 1998). Nevertheless, when only significant marker effects are estimated, only a portion of the genetic variance will be captured (Goddard and Hayes, 2007) and effects retained in the model can be greatly overestimated (Beavis, 1998; Hayes, 2007), particularly when many effects are tested.

Limitations of SR for MAS in practice were reported by Moreau et al. (2004). In 300 test-crossed maize progenies evaluated in 14 trials over 11 locations for dry grain yield and grain moisture, they discovered 16 QTL for dry grain yield and 12 QTL for grain moisture explaining 50% of the total phenotypic variance of both traits. When using an index combining phenotypic and marker information for a single cycle followed by two cycles of marker-only selection, they observed no genetic gain from the two cycles of marker selection (Moreau et al., 2004). They suggested that this inefficiency of MAS could be caused by fixation of major effect loci in the first cycle of selection and inaccurate estimation of remaining effects resulting in no gain from the cycles of marker selection (Moreau et al., 2004). These complications were probably consequences of SR that detects only large effects and that overestimates effects.

In a GS simulation by Meuwissen et al. (2001), SR resulted in low GEBV accuracy due to limited detection of QTL. The simulated outcrossing population had an effective population size of 100 with a trait heritability of 0.5. After 1000 generations of random mating to establish mutation-drift equilibrium, generation 1001 had a population size of 200 (100 males; 100 females). Two generations (1002 and 1003) of size 2000 with 20 half-sib families of size 100 individuals were then simulated. Generations 1001 and 1002 were used to train the model while GEBV accuracy was calculated on generation 1003. Genotypic data consisted of 101 multi-allelic markers on each of 10 chromosomes of length 100 cM. Adjacent pairs of markers were considered haplotypes such that 50,000 haplotype effects were estimated. The accuracy of GEBV for SR (0.318) was less than that expected for strictly phenotype-based BLUP (about 0.4; Meuwissen et al., 2001). In agreement with Lange and Whittaker (2001), Meuwissen et al. (2001) concluded that SR's procedure to identify marker subsets is suboptimal for MAS in situations where the majority of the additive genetic variance is generated by many QTL. Note, however, that the GEBV accuracy of SR depends on the details of the analysis: using the Meuwissen et al. (2001) simulation design, Habier et al. (2007) found that SR produced an accuracy of 0.61. Habier et al. (2007) attributed this difference to the use of a less-stringent significance threshold than was used by Meuwissen et al. (2001). This conclusion was supported by simulations showing prediction accuracy changes with changes in significance thresholds (Piyasatian et al., 2007).

Ridge Regression BLUP for Genomic Selection

The ridge regression BLUP (RR-BLUP) method can simultaneously estimate all marker effects for GS (Meuwissen et al., 2001; Whittaker et al., 2000). Rather than categorizing markers as either significant or as having no effect, ridge regression shrinks all marker effects toward zero (Breiman, 1995; Whittaker et al., 2000). The method makes the assumption that markers are random effects with a common variance (Meuwissen et al., 2001; Table 1). Equal variance does not assume that all markers have the same effect (Bernardo and Yu, 2007) but that marker effects are all equally shrunken toward zero. Nevertheless, the assumption that individual markers have the same variance is unrealistic, and therefore, RR-BLUP incorrectly treats all effects equally (Xu, 2003b). Despite the incorrect assumption of equal marker variance, RR-BLUP is superior to SR because it can simultaneously estimate effects for all markers: by avoiding marker selection, it avoids the biases that go with that selection (Whittaker et al., 2000).

Also, a ridge regression approach is more appropriate than SR for instances in which there are few or no large effects and many small effects (Breiman, 1995), as is the case with most quantitative traits.

In the simulation by Meuwissen et al. (2001), RR-BLUP had a GEBV accuracy of 0.732, which was 41 and 33% greater than SR and phenotype-based BLUP, respectively. With higher SR significance thresholds, Habier et al. (2007) reported that RR-BLUP resulted in 4 and 11% increase in GEBV accuracy compared to SR and traditional BLUP, respectively. In addition to these studies, Muir (2007) simulated 512 genotypes with a low heritability trait ($h^2 = 0.1$) in each of four training generations. These conditions resulted in an even higher RR-BLUP GEBV accuracy of 0.83 despite the lower heritability. This gain in GEBV accuracy was attributed to the four training generations used by Muir (2007), as opposed to two generations used in previous studies (Habier et al., 2007; Meuwissen et al., 2001).

In a GS simulation on a population derived from a biparental cross of maize inbreds, Bernardo and Yu (2007) found that relative to phenotypic selection, the increase in selection gain from RR-BLUP was 18% greater than that from SR for a highly heritable trait ($h^2 = 0.8$) controlled by 20 QTL. For a trait with low heritability ($h^2 = 0.2$) controlled by 100 QTL, the increase in selection gain from RR-BLUP was 43% greater than that from SR (Bernardo and Yu, 2007). Similar results were observed by Piyasatian et al. (2007), who found that in the first round of selection in a simulated cross between two inbred parents, gain from selection from RR-BLUP was 109 and 32% greater than that of traditional BLUP and SR, respectively.

Bayesian Estimation

The simplifying assumption of equal and fixed marker effect variances allows RR-BLUP parameters to be efficiently computed using maximum likelihood methods (Meuwissen et al., 2001). While RR-BLUP can provide a conservative EBV by shrinking all marker effects equally (Muir, 2007), the presumably incorrect assumption that underlies it can lead to overshrinking of large effects (Table 1; Meuwissen et al., 2001; Xu, 2003b). Bayesian methods have been adopted to relax this assumption and better model marker effects of differing sizes (Hayes, 2007). Here, a separate variance is estimated for each marker, and the variances are assumed to follow a specified prior distribution (Meuwissen et al., 2001).

Meuwissen et al. (2001) proposed two types of prior distribution for the marker variance. The first type of prior (BayesA) uses an inverted chi-square distribution with degrees of freedom and scale parameters chosen so that the mean and variance of the distribution match the expected mean and variance of the marker variances. In the simulation design described above, BayesA outperformed both SR and RR-BLUP with a GEBV accuracy of 0.798. Different parameter values for the BayesA inverted chi-square prior distribution have also been proposed that place much higher density on marker variances close to zero, thereby forcing more marker effect estimates close to zero (ter Braak et al., 2005; Xu, 2003b).

The BayesA method of Xu (2003b) was applied to data from a doubled haploid barley (*Hordeum vulgare*) population of 145 lines with 127 single nucleotide polymorphism markers covering 1500 cM for yield, heading date, maturity, test weight, lodging, and kernel weight. Xu (2003b) reported that SR and BayesA both found large-effect QTL but that BayesA provided better QTL location and effect estimation. Also, in simulation of a population derived from a biparental inbred cross, ter Braak et al. (2005) found that BayesA prior parameters forcing more marker effect shrinkage gave better estimates of QTL effects than did the Meuwissen et al. (2001) parameters. A comparison of these different prior parameterizations in an association genetics rather than linkage mapping context has not been done.

The second type of prior distribution Meuwissen et al. (2001) proposed (BayesB) contrasts with BayesA by having a prior mass at zero, thereby allowing for markers with no

Table 1. General characteristics and trends of performance for traditional best linear unbiased predictor (BLUP) and genomic selection methods. Note that these are general summaries based on current understanding of model performance.

Method	Marker effect; variance assumptions	Proportion of markers fitted in model	Performance with increased		Large-effect QTL	Small-effect QTL	Inbreeding depression; loss of diversity
			Marker density	QTL† number			
Traditional BLUP	N/A	N/A	N/A	N/A	Captured only by phenotype	Captured only by phenotype	Yes
Stepwise regression	Fixed	Subset	Reduced	Reduced	Overestimated	Excluded	Marginally Reduced
RR-BLUP‡	Random; Equal	All	Reduced§	Increased	Underestimated	Captured	Reduced
BayesA	Random; Unique All > 0	All	?	Reduced	More accurately estimated	Captured	Reduced
BayesB	Random; Unique Some = 0	All	Insensitive§	Reduced	More accurately estimated	Captured	Reduced

†QTL, quantitative trait locus.

‡RR, ridge regression.

§Source: Fernando (2007).

effects. The inverted chi-square prior of BayesA may be set to strongly regress variances toward zero, but it does not permit the value of zero itself. BayesB thus presents a more realistic prior because we expect that some regions of the genome will carry no QTL, so that some markers should have estimates of zero effect. The results from Meuwissen et al. (2001) showed that BayesB had a GEBV accuracy of 0.848, greater than all other methods tested. Of the Bayesian methods, BayesB not only was more accurate but was also less computationally demanding. Meuwissen et al. (2001) concluded that Bayesian methods outperformed RR-BLUP through better estimation of large-effect QTL by allowing for unequal variances.

de Roos et al. (2007) used Bayesian modeling as described by Meuwissen and Goddard (2004) in actual dairy cattle data for a single chromosome containing 32 markers with one being a known causal mutation for fat percentage. They compared Bayesian GS that used all marker information to regression on the genotype at the known causal mutation and to traditional BLUP with no markers. Using a cross validation population of 1135, they concluded that Bayesian GS and regression on the causal mutation had similar accuracies (0.752 and 0.746, respectively), with both being superior to traditional BLUP (EBV accuracy of 0.508). Interestingly, the GS analysis often did not place the causal mutation in the correct marker bracket but was nevertheless able to calculate accurate GEBV. This robustness of GEBV accuracy provides evidence that GS can perform well for breeders in the absence of the discovery of QTL (de Roos et al., 2007).

In the future, genotyping costs will decrease, but it is unlikely that phenotyping costs will also decrease, thus shifting goals toward reducing phenotyping and increasing genotyping. Bernardo and Yu (2007) suggested this shift would be feasible when the cost of a marker data point is 5000 times less than the cost of phenotyping a single entry. Regardless of the threshold, it is desirable to decrease the number of phenotypic records needed for training models for accurate GEBVs. Simulations by Meuwissen et al. (2001) showed that with 2200 phenotypic records, RR-BLUP and BayesB had GEBV accuracies of 0.732 and 0.848, respectively. When the number of phenotypic records was reduced to 500, RR-BLUP and BayesB GEBV accuracies decreased to 0.579 and 0.708, respectively (Meuwissen et al., 2001). Thus, the effect of low numbers of phenotypic records was less severe for BayesB than for RR-BLUP. In addition, Fernando (2007) found that in contrast to RR-BLUP, BayesB's GEBV accuracy did not decline as the number of markers increased. These findings suggest that Bayesian methods may be better suited to handling situations with increased colinearity between markers caused by extremely large markers sets and limited phenotypic records (Table 1). Computational issues may arise for Bayesian methods under high marker densities and colinearities; these will need to be resolved by improved statistical methods (ter Braak et al., 2005).

INCLUSION OF A POLYGENIC EFFECT TERM ACCOUNTING FOR KINSHIP

Phenotypic information from relatives contribute to an individual's EBV because EBVs vary according to the additive relationship (**A**) matrix, that is, a matrix that contains for each pair of individuals the proportion of alleles for which they are identical by descent (van Arendonk et al., 1994; Lynch and Walsh, 1998, p. 751). When markers are introduced into the analysis, some genetic effects will be captured by markers in LD with QTL, but residual genetic effects will still be assumed to vary according to the **A** matrix. These residual effects can be captured by including a polygenic term in the model. In association mapping, the inclusion of this matrix has been popularized as a statistical control for population structure and familial relatedness (Yu et al., 2006; Zhao et al., 2007).

The **A** matrix can be calculated on the basis of the pedigree or the marker data, with pedigree information providing exact expected relationships and markers providing estimated realized relationships. When marker number is high enough that marker sampling plays a minor role (i.e., relationship estimates on the basis of markers are accurate), marker-estimated relationships will better reflect true relationships than will pedigree-expected relationships. In particular, four mechanisms lead realized relationships to diverge from their expectation: random Mendelian segregation, segregation distortion, selection, and pedigree recording errors. For example, parental contributions to inbreds vary from their expected 50% because of random Mendelian segregation during selfing. For the genomes of maize and wheat, there is a 10% probability that single seed decent–derived inbreds will have less than 38 and 43% genome contribution from one parent, respectively (Frisch and Melchinger, 2007).

The value of including a polygenic effect term in the model will depend strongly on marker density available in the study for two reasons. First, if density is such that all QTL are in strong LD with a marker, all genetic effects will be absorbed by markers and none will be left for the polygenic term to capture (Bernardo and Yu, 2007; Meuwissen et al., 2001; Zhong and Jannink, 2007). Second, even markers that are in linkage equilibrium with all QTL carry information about relationships among individuals, and this information contributes to the accuracy of GEBV (Habier et al., 2007). Indeed, this contribution depends on the number of markers included in the GS method, and because SR uses only a subset of markers, it benefits least from genetic relationship contributions to GEBV accuracy (Habier et al., 2007).

Research to look explicitly at the value of including a polygenic effect term used adjacent-marker r^2 as a measure

of marker density. For a high heritability trait ($h^2 = 0.5$), the polygenic effect term increased GEBV up to an adjacent-marker r^2 of 0.14, while for a low heritability trait ($h^2 = 0.1$), the term made no difference already at an r^2 of 0.11 (Calus and Veerkamp, 2007). At lower adjacent-marker r^2, the polygenic term fulfills its role of explaining genetic variance not absorbed by markers, and it therefore contributes to GEBV accuracy (Calus and Veerkamp, 2007; Villanueva et al., 2005).

SELECTION INDEX THEORY APPLIED TO GENOMIC SELECTION

A selection index integrates and weights multiple traits to achieve greater gains than if traits with independent thresholds are individually or collectively selected (Hazel and Lush, 1942; Hazel, 1943). Selection indices can incorporate marker data as indirect selection traits (Lande and Thompson, 1990; Neimann-Sorensen and Robertson, 1961; Smith, 1967). However, current MAS applied to loci selected by SR violates the selection index assumptions of multivariate normality and small changes in allele frequencies because selection is based on only few large effect loci (Dekkers, 2007; Lande and Thompson, 1990). Because GS is based on many markers distributed throughout the genome, index selection assumptions are met, providing an opportunity to use index selection theory to predict response to GS (Dekkers, 2007).

Dekkers (2007) used selection index theory by adding marker-derived breeding values as a separate correlated trait to the selection index (Lande and Thompson, 1990). In a simulated pig breeding program, selection on only marker data could outperform phenotypic selection for low heritability traits (0.1) even with moderate GEBV accuracy (0.55). When marker and phenotypic data were both used for a single trait, even greater accuracies were observed. This increase was due to marker information that allowed for within family selection (Dekkers, 2007).

For two negatively correlated traits with heritabilities of 0.3 and 0.1, Dekkers (2007) found using only markers increased gains from selection over phenotypic selection by 8.5% for the index of the two traits and 66% for the low heritability trait alone. Using both markers and phenotype increased gains from selection over phenotypic selection by 21% for the index of the two traits and 80.5% for the low heritability trait alone. These results show the potential of GS to increase gains for multiple traits especially in cases where phenotypic data is available on selection candidates and traits have low heritability.

MAINTAINING GENETIC DIVERSITY AND REDUCING INBREEDING DEPRESSION

Gains from selection can be increased by raising the selection intensity or the accuracy of EBV of breeding lines. Increased selection intensity reduces the number of lines selected, thus lowering the effective population size and thereby increasing the loss of genetic variability. Traditional BLUP increases EBV accuracy by incorporating ancestor and collateral relative phenotypes in the calculation (Henderson, 1984). But including family information in EBV calculation increases the correlation between EBV of family members, making it more likely that multiple sibs will be selected (Wray and Thompson, 1990). Sibling coselection, in turn also reduces effective population size. Therefore, while increased selection intensity and a higher EBV accuracy lead to greater short-term gains from selection, they both may reduce long-term gains by decreasing genetic variation and increasing rates of inbreeding (Quinton et al., 1992).

Daetwyler et al. (2007) reviewed these issues and determined that GS differs from simple phenotypic selection and traditional BLUP by using markers to more accurately estimate Mendelian sampling variation, that is, deviations between siblings within families. Mendelian sampling variation, generated by random segregation, is created anew each generation. Selecting strictly on this variation therefore enables sustained genetic progress by decreasing coselection of sibs and thus reducing inbreeding and the loss of genetic variation (Woolliams et al., 1999). Optimized selection schemes have been proposed where parent combinations are restricted by their level of coancestry to limit the loss of genetic variation and the rate of inbreeding (Grundy et al., 1998; Meuwissen, 1997). In these schemes, an individual's selective advantage depends largely on the Mendelian sampling term, that is, on its performance relative to its siblings (Avendaño et al., 2004). Unlike traditional BLUP based on pedigree data that account for average relationships, tracking markers enables GS to also track the random segregation that makes up the Mendelian sampling term. The benefit is both more accurate EBVs and decreased correlation between EBVs within families, countering the mechanism whereby the use of family information increases loss of genetic diversity (Daetwyler et al., 2007). Note that the greater emphasis placed by GS on the Mendelian sampling term does not completely negate variable long-term genetic contributions among individuals and its consequent increase in inbreeding rate. In particular, superior individuals carry superior alleles, and selection of those alleles will, in turn, lead their carriers to leave more offspring behind (Daetwyler et al., 2007). Thus, it still may be advisable to manage rates of inbreeding (e.g., Avendaño et al., 2004) even in the context of GS. Nevertheless, the advantages of GS in regard to inbreeding and the maintenance of genetic diversity should prove valuable for crops such as alfalfa (*Medicago sativa*) that suffer from inbreeding depression and for maintaining genetic variation in advanced cycle breeding programs.

GAINS FROM SELECTION PER UNIT TIME

Marker-assisted selection strategies increase gain mainly through gain per unit time, rather than gain per cycle (Bernardo and Yu, 2007; Edwards and Johnson, 1994; Hospital et al., 1997; Koebner and Summers, 2003; Meuwissen et al., 2001; Muir, 2007). To ascertain GS's impact on gains per unit time, Schaeffer (2006) suggested a plan for implementing GS into a dairy breeding program. Through reduction in time and costs needed to prove the value of a bull, assuming a GEBV accuracy of 0.75, Schaeffer (2006) determined that GS could provide a twofold increase in rate of genetic gain and save 92% of the costs of the current progeny test based breeding program.

In plants, the importance of generation time varies between crops, but the goal of reducing cycle time remains. In maize, a crop that uses doubled haploids and off-season nurseries, test cross performance selection still requires at least 2 yr (Bernardo and Yu, 2007), providing an opportunity for GS to reduce unit time per selection cycle by reducing the need for progeny test data in every cycle. In the more extreme case of oil palm (*Elaeis guineensis* Jacq.), which takes 19 yr to complete a cycle of selection, Wong and Bernardo (2008) reported that GS reduced the selection cycle to 6 yr. Even with small population sizes ($N = 50$) that adversely effected GEBV accuracy, their simulations indicated that GS would outperform MARS and phenotypic selection when considering gain per unit cost and time.

GENOTYPE × ENVIRONMENT INTERACTIONS AND EPISTASIS

Genotype × environment (G×E) interaction is a challenge in plant breeding because the large number of experimental lines and environments, that is, locations and years, make it impossible to test a line in all possible environmental conditions of a breeding program's target region (Allard and Bradshaw, 1964). Consider, however, that the genotype of any line is composed of alleles that, over time, will have been evaluated in a larger sample of target environments than would be feasible for any particular line. Thus, it may be possible to accurately predict GEBV even in the presence of high G×E. As an extreme example, for winter annual crops, a severe winter may only occur once a decade. Variety releases for the region need to be hardy to such winters because crop failure even once per decade is too frequent. With GS, a given generation of experimental lines need never experience a test winter if the alleles they carry were characterized during a severe winter. Similar cases include the infrequent but devastating conditions caused by severe drought, flooding, disease pressure, and insect infestation. The broader insight that these examples illustrate is that with GS, lines are not evaluated solely on the basis of their own phenotypic performance, but on the basis of information shared across other lines, other years and locations, and even possibly other breeding programs. This information sharing should provide GS with stability in the face of G×E.

Anticipating the effect of epistasis on the potential of GS is difficult. Almost all GS prediction accuracy evaluations derive from simulations that adopted additive genetic models. There is current debate, at both theoretical and empirical levels, of the likely importance of epistasis in the architecture of quantitative traits (Carlborg and Haley, 2004; Hill et al., 2008; Holland, 2007; Mackay, 2008). To examine this issue, it is essential to distinguish between the genotypic value versus the breeding value of a line (Falconer and Mackay, 1996). The genotypic value is the expected phenotype of the line given its genotype and includes additive and nonadditive genetic effects. The breeding value is the expected phenotype of line's progeny and includes only additive effects. The additive models used by GS should predict the breeding value rather than genotypic value (Goddard and Hayes, 2007). Consequently, correlations between GEBVs and line phenotypes may well be lower than those obtained in additive effect simulations, but they should nevertheless reflect a line's value as a parent. For cases in which estimates of genotypic value are desired in the presence of epistasis, methods are currently being developed and tested (e.g., Gianola et al., 2006; Gianola and van Kaam, 2008; Gonzalez-Recio et al., 2008). Further empirical evaluation of the prediction accuracies of these methods should help address the ongoing debate over the importance of epistasis in the mapping of genotype to phenotype. Because of the small contribution that epistasis makes to breeding value (Holland, 2001), GS using simpler additive models should be effective for maximizing gain from selection.

FUTURE DIRECTIONS

Statistical Methods

A statistical model will more faithfully capture QTL information as its assumptions about the underlying genetic architecture, made explicit in the prior distributions of QTL effects or variance, are more correct (Meuwissen et al., 2001). There are two obstacles to translating this fact into improved models. First, GS may gain in accuracy not just by capturing more QTL information but also by better capturing relationship information (Habier et al., 2007). There may be a tradeoff between the kinds of prior distributions of effects that promote the use of these two information sources (Habier et al., 2007). Second, we simply do not know, for any complex trait, what the underlying genetic architecture is, and thus, we do not have adequate prior knowledge at our disposal. Therefore, statistical models that are relatively insensitive to the underlying architecture may be optimal for most populations, although identifying those models remains challenging.

Finally, the marker technologies on which GS methods depend are constantly changing. Next-generation sequencing technologies and improvement of genotyping platforms present breeders with powerful tools for characterizing the genetic composition of their germplasm. As these technologies continue to evolve, they will provide quantitatively and qualitatively different information (e.g., copy number and epigenetic variation; Stranger et al., 2007; Zhang et al., 2008), and statistical machinery will also need to evolve to use this information efficiently to increase prediction accuracy.

Software and Database Development

While statistical methods of prediction must be continually advanced, an integral part of their performance will be the software packages used to implement them. In conjunction with this software, robust databases that can efficiently link breeding lines, testing environments, genotypic data, phenotypic data, and breeding programs will need to be developed to simplify flow and use of information. While private breeding companies have invested heavily in data management systems that will likely be efficient in executing GS (e.g., Eathington et al., 2007), public sector breeding programs also need database software that integrates the wide variety of data they generate (Heckenberger et al., 2008; Tinker and Yan, 2006). Recent developments in the public sector are promising, such as the Barley Coordinated Agricultural Project Hordeum Toolbox (http://hordeumtoolbox.org/), the GDPDM database schema that links with the association analysis software TASSEL (http://www.maizegenetics.net); the German GABI-BRAIN project (http://brain.uni-hohenheim.de/eng/indexeng.html), and the Canadian COOL-DUDE (Yan and Tinker, 2007). Adaptation of these tools to link with GS and development of user-friendly GS analyses themselves are needed to take GS from theory to practice.

CHANGES TO BREEDING PROGRAM STRUCTURE

The accuracies of GEBV observed in research offer the possibility that future elite and parental lines will be selected on their GEBV rather than on their phenotypic records from extensive field testing. The most immediate impact of this circumstance would be a great increase in the speed of the breeding cycle (Fig. 2; Wong and Bernardo, 2008), thereby increasing selection gains per unit time. This shift would also fundamentally alter the role of phenotyping in plant breeding (Fig. 2). Note that Fig. 2 offers a somewhat futuristic view of the use of GS, contingent on its validation in practice. We do not, at this point, advocate dispensing with phenotypic evaluation before parent selection.

The purpose of phenotyping now is to select the best lines from a segregating population and to evaluate fewer lines with greater replication in each cycle of selection. But in a GS driven breeding cycle, the purpose of phenotyping is to estimate or reestimate marker effects. It is far from clear at this point whether it will be advantageous to evaluate only the best lines or to evaluate few lines with high replication. Figure 2 therefore separates the germplasm improvement cycle from the prediction model improvement cycle. Indeed, if we use the guidelines for optimal QTL linkage mapping, evaluation should include not just the best but the best and the worst lines

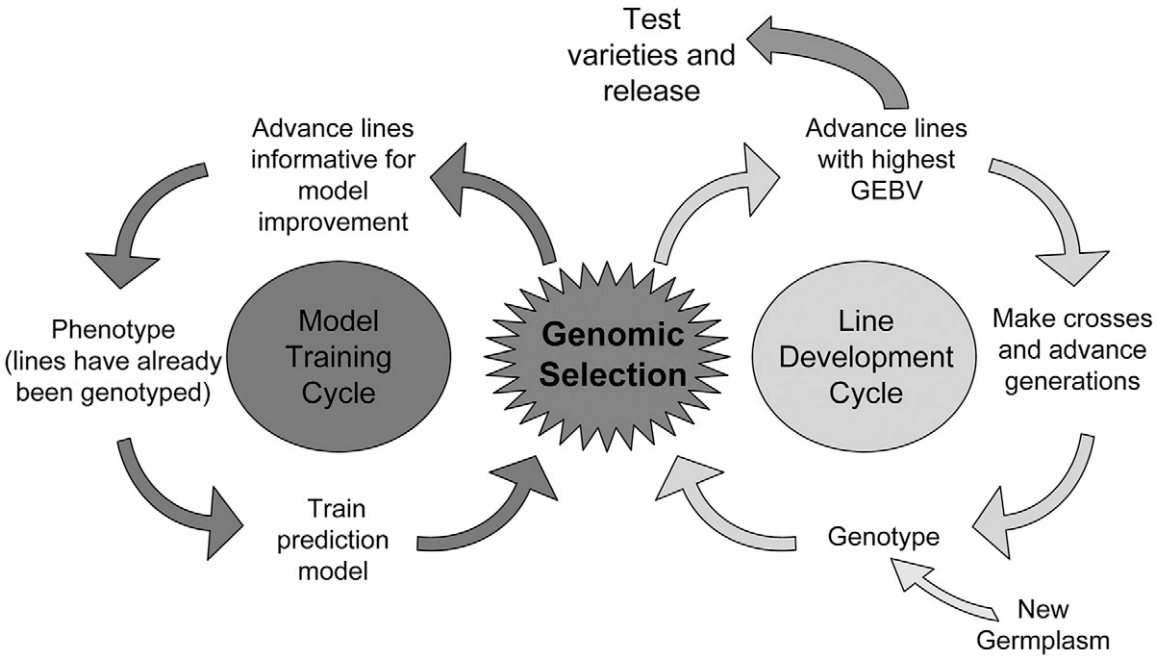

Figure 2. Flow diagram of a genomic selection breeding program. Breeding cycle time is shortened by removing phenotypic evaluation of lines before selection as parents for the next cycle. Model training and line development cycle length will be crop and breeding program specific. (GEBV = genomic estimated breeding value.)

(Darvasi and Soller, 1992; Lander and Botstein, 1989) and many unreplicated lines instead of few replicated lines (Knapp and Bridges, 1990). Figure 2 also emphasizes the need for model updating and reevaluation. Marker effects may change as a result of allele frequency changes (Muir, 2007) or of epistatic gene action. Model updating with each breeding cycle should mitigate reduced gains from GS caused by these mechanisms. Thus, GS could radically change the practice of field evaluation for breeders. Of course, regardless of the breeding method used, final field evaluations of varieties across the target environments will be needed before they are distributed to farmers.

GS may also diminish the need for breeders to select parents strictly from the set of lines evaluated in their target environments (Goddard and Hayes, 2007). Once a predictive linear model is established for their target environments, any genotype with high target environment specific GEBV will become a candidate. Thus, GS should facilitate germplasm exchange and increase the probability of selecting useful germplasm.

CONCLUSIONS

It has been predicted for more than two decades that molecular marker technology would reshape breeding programs and facilitate rapid gains from selection (Stuber et al., 1982; Tanksley et al., 1989). The failure of current MAS to significantly improve polygenic traits has thwarted this prediction. Genomic selection looks to fulfill it by using genomewide marker coverage to accurately estimate breeding values, accelerate the breeding cycle, and introduce greater flexibility in the relationship between phenotypic evaluation and selection. To do so, however, GS must shift from theory to practice. As evident in this review and interpretation, GS has almost exclusively been tested through simulation, and therefore, its potential value should be assessed with cautious optimism. The accuracy of GS and its cost effectiveness must now be evaluated in breeding programs to provide the empirical evidence needed to warrant the addition of GS to the plant breeders' toolbox.

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