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REVIEW & INTERPRETATION

Perspectives for Genomic Selection Applications and Research in Plants

Nicolas Heslot, Jean-Luc Jannink, and Mark E. Sorrells*

ABSTRACT

Genomic selection (GS) has created a lot of excitement and expectations in the animal- and plant-breeding research communities. In this review, we briefly describe how genomic prediction can be integrated into breeding efforts and point out achievements and areas where more research is needed. Genomic selection provides many opportunities to increase genetic gain in plant breeding per unit time and cost. Early empirical and simulation results are promising, but for GS to deliver genetic gains, careful consideration of the problem of optimal resource allocation is needed. Consideration of the cost-benefit balance of using markers for each trait and stage of the breeding cycle is needed, moving beyond only focusing on recurrent selection with GS on a few complex traits, using prediction on unphenotyped individuals. With decreasing marker cost, phenotype data is quickly becoming the most valuable asset and marker-assisted selection strategies should focus on making the most of scarce and expensive phenotypes. It is important to realize that markers can also improve accuracy of selection for phenotyped individuals. Use of markers as an aid to phenotype analysis suggests a number of new strategies in terms of experimental design and multi-trait models. GS also provides new ways to analyze and deal with genotype by environment interactions. Lastly, we point to some recent results showing that new models are needed to improve predictions particularly with respect to the use of distantly related individuals in the training population.

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Abbreviations: ASI, anthesis-silking interval; BLUE, Best Linear Unbiased Estimator; CD, coefficient of determination; CSR, canopy spectral reflectance; G*E, genotype by environment interactions; GBLUP, genomic best linear unbiased prediction model; GEBV, genomic estimated breeding values; GS, genomic selection; MARS, marker-assisted recurrent selection; NIRS, near-infrared spectroscopy; PEV, predicted error variance; QTL, quantitative trait loci; RKHS, reproducing kernel Hilbert spaces; TPE, target population of environments.

Use of molecular markers as an aid to selection has been an active area of research for several decades now (Stuber et al., 1982; Tanksley et al., 1989; Lande and Thompson, 1990) and has generated a lot of expectations, but early results have been quite disappointing for complex quantitative traits (Moreau et al., 2004; Bernardo 2008), such as yield in crops. The concept of genomic selection (GS) (Meuwissen et al., 2001) fostered great hopes and opened new ways to use molecular markers in breeding for complex traits. Initially, most of the research was conducted in the animal breeding community, where the high cost of phenotyping (e.g., progeny testing in dairy cattle breeding), as well as the impossibility to replicate individuals, made it attractive. In addition, partly because of the impossibility to replicate individuals, animal breeders implemented mixed model methodology early on to analyze their data using the available pedigree information (Henderson,

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1984). In plant breeding, the use of mixed models is more recent and not yet as widespread (Smith et al., 2005; Piepho et al., 2007). As a consequence, organizations, infrastructures, and people were more prepared to embrace GS in animal breeding than in the plant community. We briefly summarize what is known about GS in plants, advocate for a systematic approach in the use of markers, and attempt to identify where GS could deliver improved genetic gains beyond recurrent selection. We also point out areas where more research is needed for GS to effectively deliver increased genetic gain per unit time and cost.

WHAT IS KNOWN

Marker-assisted recurrent selection (MARS) refers to several breeding schemes using markers to select unphenotyped individuals and then crossing them to generate the next generation of selection candidates. Initial work with MARS used biparental or multi-population quantitative trait loci (QTL) detection and then tried to pyramid QTL (Servin et al., 2004). Only markers significantly associated with the trait were used in the recurrent selection process. As a consequence, some GS reports make a distinction between MARS and GS, but it is more logical to consider GS as a tool to carry out MARS and other uses.

We define GS or prediction as the simultaneous use of genome-wide markers to predict an individual's genotypic or breeding value for both observed and unobserved individuals. Multi-trait GS models can make use of information on correlated traits to improve prediction accuracy (Jia and Jannink, 2012). Early work on GS in plants was mainly focused on unobserved individuals, in the MARS context. GS can be beneficial for observed individuals as well if entry-mean heritability is low (Endelman et al., 2014).

Genomic selection can be performed with a variety of statistical methods as reviewed in (Lorenz et al., 2011). Those methods are concerned with the same so-called "large p small n" problem; There are many more predictor (marker) effects to be estimated than there are observations. Most approaches to this problem involve some type of penalized regression. Early research on GS in plants focused on prediction power measured through cross-validated accuracy using existing data (Lorenzana and Bernardo, 2009; Heffner et al., 2011; Heslot et al., 2012) trying to verify that GS was potentially more effective than classical marker-assisted selection schemes or use of pedigree (Crossa et al., 2010; Asoro et al., 2013). Results clearly indicated that GS was more predictive than classical marker-assisted selection in cross-validation and that, with empirical data, all GS methods had very similar prediction power. Currently, the most widely used model is the genomic best linear unbiased prediction model (GBLUP) (Habier et al., 2007). With GBLUP, markers are used to estimate the covariance between individuals. That information is further used in a mixed model analysis to predict performance of observed and unobserved individuals. The GBLUP model has the advantages of relative simplicity, limited computing time, and well-known optimality properties of mixed models for selection (Fernando and Gianola, 1986).

A classic mixed model for genetic evaluation can be written:

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \varepsilon \qquad [1]$$

$\mathbf{y}$ is a vector of phenotype, β is a vector of non-genetic effects such as environments with design matrix $\mathbf{X}$. $\mathbf{u}$ is a vector of genetic effects with design matrix $\mathbf{Z}$, and ε is a vector of residuals. If all m individuals are replicated in all t locations and β is a vector of location effects, then $\beta = \mathbf{I}_t \otimes \mathbf{1}_m$ and $\mathbf{u} = 1_t \otimes I_m$. $\mathbf{I}_t$ is an identity matrix with t rows, and $\mathbf{1}_m$ is a vector of ones with length m. $\otimes$ is the Kronecker product. The error variance is usually $\mathrm{var}(\varepsilon) = \mathbf{I}\sigma^2_\varepsilon$. The simplest form of this model does not use pedigree or markers and assumes that individuals are unrelated such that $\mathrm{var}(\mathbf{u}) = \mathbf{I}\sigma^2_g . \sigma^2_g$ is the genetic variance. The estimate of $\mathbf{u}$ would then be a simple adjusted phenotypic mean. This estimate can be further refined by assuming that individuals are related such that their performances are not independent from each other. Then, $\mathrm{var}(\mathbf{u}) = K\sigma^2_a$ with σ^2_a additive genetic variance, and K is kinship, which can be based on pedigree (then often called relationship matrix) or on markers (then often called the realized relationship matrix). If $\mathbf{W}$ is the centered markers score matrix with m rows and as many columns as markers, then $K = \dfrac{\mathbf{W}\mathbf{W}'}{2\sum_k p_k(1-p_k)}$, p_k is the frequency of the minor allele (VanRaden 2008). There are some other possibilities for K to capture some non-additive effects (de Los Campos et al., 2009). If some individuals are not phenotyped, they still can be predicted by the model. In that case, some columns of $\mathbf{Z}$ contain only zero elements. Predictions are obtained by solving the mixed model equations once the variances are estimated:

$$\begin{pmatrix}\hat{\beta}\\ \hat{u}\end{pmatrix} = \mathbf{C}\begin{pmatrix}\mathbf{X}'y\\ \mathbf{Z}'y\end{pmatrix} \text{ with } \mathbf{C} = \begin{pmatrix}\mathbf{X}'\mathbf{X} & \mathbf{X}'\mathbf{Z}\\ \mathbf{Z}'\mathbf{X} & \mathbf{Z}'\mathbf{Z} + K^{-1}\dfrac{\sigma^2_\varepsilon}{\sigma^2_a}\end{pmatrix}^-$$

This model can be further extended to predict hybrid performance by adding an additional random effect such that

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z}_1 u_1 + \mathbf{Z}_2 u_2 + \varepsilon \qquad [2]$$

$\mathbf{y}$, β, and ε are as before, and u_1 and u_2 are, respectively, male and female genetic effect such that $\mathrm{var}(u_1) = \mathbf{K}_1\sigma^2_{a1}$ and $\mathrm{var}(u_2) = \mathbf{K}_2\sigma^2_{a2}$ with σ^2_{a1} and σ^2_{a2} additive genetic variance in the male and female groups, respectively, and $\mathbf{K}_1$ and $\mathbf{K}_2$ relationship matrices are based on pedigree or markers for each group (Albrecht et al., 2014).

Model 1 is calibrated on non-inbred material, and for model 2 an additional random effect u_3 can be fitted to capture dominance effects, such that $\mathrm{var}(u_3) = \mathbf{K}_3\sigma_d^2$ with σ_d^2 dominance variance and $\mathbf{K}_3 = \frac{\mathbf{VV}'}{2\sum_k p_k^2(1-p_k)^2}$ with $\mathbf{V}$ centered marker design matrix for the dominance effect such that each column of $\mathbf{V}$ corresponds to a marker with minor allele a of frequency p coded $\{aa, Aa, AA\} = \{-2p^2, -2p(1-p), -2q^2\}$ (Vitezica et al., 2013). While $\mathbf{K}_1$ and $\mathbf{K}_2$ correspond to kinship between males and females for example, $\mathbf{K}_3$ has one row per hybrid.

Depending on breeding cycle length (time between new crosses) and time necessary to phenotype, using markers to select individuals can greatly shorten the selection cycle (Schaeffer, 2006; König et al., 2009; Heffner et al., 2010) and thus increase genetic gain per unit time and cost compared to phenotypic selection.

A shortened selection cycle raised concerns that GS might increase the rate of loss of genetic diversity (inbreeding) and negatively impact long-term selection gain alleles (Jannink, 2010). In simulation of recurrent selection with GS, long-term gain is reduced compared to phenotypic selection because GS cannot take into account rare alleles (Jannink, 2010). Rare alleles are only present in a few individuals, and, thus, their effect cannot be well estimated by the model.

A selection index can be used including the estimated marker effect and allele frequency to prevent the loss of low-frequency alleles to preserve long-term gains (Goddard, 2009). Because of the steep decline in accuracy with cycles of selection (Muir, 2007; Long et al., 2011), the model will require frequent updating with new phenotypic information. Frequent updating should limit the problem of long-term gains and inbreeding but requires further investigations with simulations.

For a given number of individuals used as parents in each generation, selection causes more rapid inbreeding than random mating because there is generally a positive covariance between relatives for a selection criterion. Thus, the criteria cause relatives to be co-selected more frequently than they would be at random. When the selection criterion is the observed phenotype, the only covariance between relatives for that criterion is due to shared alleles among the relatives. In contrast, BLUPs estimated using covariance matrices calculated from pedigree or marker data have an additional component of covariance due to information sharing from ancestors and collateral relatives. Consequently, both pedigree and marker-based BLUP methods generate selection criteria that have higher covariance between relatives than direct phenotypic evaluation. The key difference between pedigree versus marker-based BLUP methods in this regard is the relative weight that they place on information from parents versus from the so-called Mendelian sampling term of the selection candidates themselves. Pedigree-based methods place no weight on the latter because they have no information on it. Markers, however, record Mendelian sampling, and so they can place weight on it (Daetwyler et al., 2007). Therefore, selection criteria calculated using markers should have lower covariance between relatives than criteria calculated using only the pedigree. From lowest to highest inbreeding caused by this covariance, we have random mating, selection on own phenotype, selection on marker-based criteria, and finally selection on pedigree-based criteria. Because livestock breeding programs are moving from pedigree to marker-based criteria, their rates of inbreeding will likely go down. In contrast, crop breeding programs are moving from phenotype to marker-based criteria, and their rates of inbreeding may well go up.

Research has also focused on training population size and marker type and density required for GS (Lorenz et al., 2011). Briefly, larger training populations and higher marker density are beneficial in theory. In practice, accuracy usually reaches a plateau with increased marker number (Lorenz et al., 2012), and larger training populations do not always generate higher prediction accuracies (Riedelsheimer et al., 2013). Marker type and potential ascertainment bias have a limited impact on prediction accuracy as long as markers are at high density and well-distributed across the genome (Heslot et al., 2013c). Finally, with GS, phenotyping is done to train a model, not to directly select. As a consequence, the unit of evaluation has shifted from the individual to the allele (Heffner et al., 2009; Lorenz et al., 2011). The objective of phenotyping to train a model is not to thoroughly evaluate the individuals in the training population but to best estimate the alleles' effects to identify the best individuals among the selection candidates. This shift has raised questions on how to best design training populations under budget limitations (Rincent et al., 2012). The shift also has suggested new ways to deal with unbalanced historical data where alleles most likely were replicated across environments (Heslot et al., 2013b), even if individuals were not.

URGENT NEED FOR A COMPLETE COST-BENEFITS APPROACH

Reflecting on the disappointing results of marker-assisted selection for complex traits, the apparent lack of success was due not only to inadequate statistical methodology to deal with many small effect loci for which GS provides a solution, but also to a number of practical problems that GS has not eliminated (Xu and Crouch, 2008; Bernardo, 2008). Among those practical problems are the choice of germplasm on which to apply marker-assisted selection, integration of information on multiple traits, trade-off between family sizes and number of families created for marker-assisted selection, balance between phenotypic

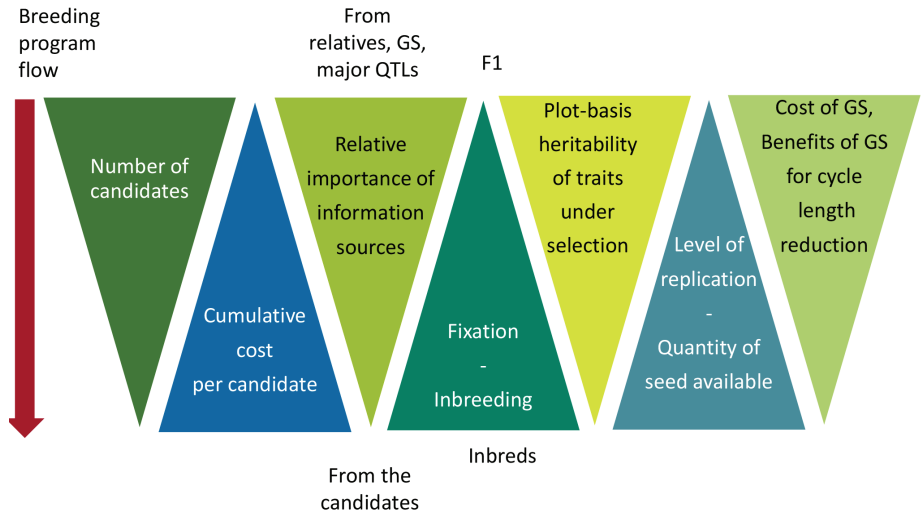

Figure 1. Key parameters and changes during a breeding cycle, to consider in implementing genomic selection (GS). The triangles indicate increase or decrease of the quantity considered. QTL, quantitative trait loci.

selection and marker-assisted selection at constant budget, disconnection between the population used to detect QTLs and the elite breeding germplasm, and logistical issues involved in the integration of marker-assisted selection in breeding programs.

Behind most of those issues is the problem of resource allocation between phenotyping and genotyping and between traits and number of lines. Figure 1 presents the key parameters to consider when implementing the use of markers in a plant breeding program. Most key variables are trait-specific and vary during the breeding cycle. A breeding cycle starts with a cross (generation of new variability) and ends with the release of new commercial products and crosses between them.

Figure 1 describes a trade-off between an increased benefit of using markers to select early in the breeding cycle on low heritability traits, such as yield, and thereby reduce the length of the breeding cycle, versus a higher cost of GS applied in early generations. The increased cost arises because the selection candidates are much more numerous and they are not fully inbred, making the logistics of genotyping and prediction more complicated. This trade-off is even stronger in a phenotypic breeding program, because large populations early in the cycle are combined with high selection intensity on highly heritable traits (high plot-basis heritability), which can be extremely efficient and relatively inexpensive. It probably is beneficial to use markers to select on a low heritability trait, such as yield, early in the cycle; in most crops, yield cannot be measured accurately on segregating populations, single plants, or small plots. At the same time, most of the individuals in early generations can be discarded efficiently using inexpensive phenotyping. An extreme example of the usefulness of at least limited phenotypic evaluation in early generations is dairy cattle. Phenotype is still needed on all selection candidates before release to eliminate congenital defects caused by rare alleles becoming homozygous and novel mutations with large effects (Hayes et al., 2009a). This is probably also necessary for recurrent genomic selection in plants. These requirements should be taken into account when implementing GS in a breeding program.

Effective use of markers to achieve breeding gains requires consideration of the genetic gain achieved overall by the breeding program, with and without GS. Implementing GS in dairy cattle can generate enough savings in phenotyping expenses to pay for genotyping. The cost of testing a bull was estimated to be $50,000 (Schaeffer, 2006). In other animal species, cost-effective GS requires complex optimization strategies. In pig, implementing GS was found beneficial only if the breeding program budget was high (Tribout et al., 2013). In their simulations, below a given threshold, additional resources were better allocated to more phenotyping. Without a cost-benefits approach, looking only at accuracies, it seems clear that using GS in addition to the current breeding scheme will increase genetic gain. A cost-benefits approach will take into account that at constant budget, genotyping all selection candidates might require reducing the size of the breeding population and negatively impact breeding gains. In salmon, pre-selection of candidates based on pedigree before GS was evaluated as a means to limit costs (Lillehammer et al., 2013) and found to be of interest. Similar studies are needed in plants.

Figure 2 presents a schematic of breeding inbred lines using doubled haploids. For each stage, the figure presents side-by-side characteristics of classic breeding (in black) and potential applications of GS (in orange). Clearly, GS can be of some use at each stage of cultivar development. Nevertheless, most of the attention and empirical validation of GS has been focused only on marker-assisted recurrent selection (rapid cycling GS on Fig. 2) for one trait (Moreau et al., 2004; Bernardo and Yu, 2007; Massman et

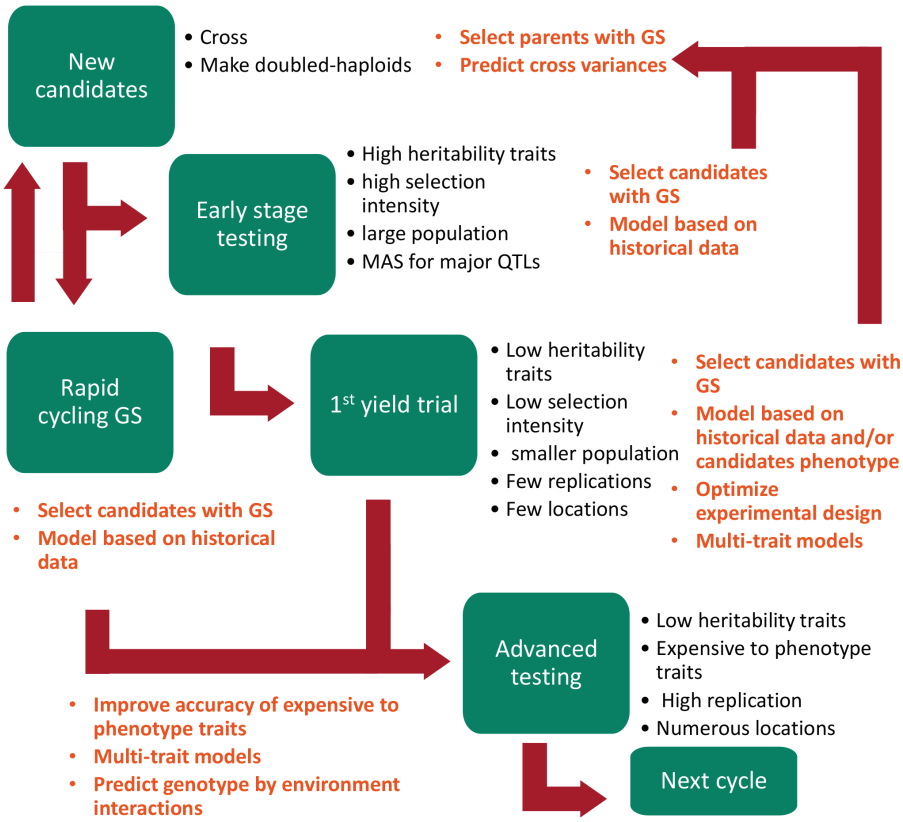

Figure 2. Simple scheme of a breeding cycle with what genomic selection (GS) could bring for each stage (orange). Arrows indicate the flow of germplasm. Upward arrows correspond to early re-crossing. For the sake of simplicity, the scheme uses doubled-haploids. MAS, marker-assisted selection; QTL, quantitative trait loci.

al., 2012; Asoro et al., 2013; Combs and Bernardo, 2013). The relevance of those applications depends on budget size and relative costs of phenotyping and genotyping. Consideration of the cost-benefit balance is needed to leverage the strength of both phenotypic and marker-assisted selection. Simulations could be used to compare multiple GS breeding strategies at a constant budget, for example (Endelman et al., 2014). A decisive step toward better resource allocation would also be the ability to identify the most promising crosses based on expected mean and variance (Zhong and Jannink, 2007).

MARKER-ASSISTED RECURRENT SELECTION WITH GS

Early molecular breeding efforts were based on QTL mapping in biparental or connected populations such as partial diallel for a few traits of interest. Practical application focused on recurrent selection schemes aided by markers to quickly pyramid identified QTLs (Servin et al., 2004). With the advent of GS, efforts have been devoted to make those recurrent selection schemes work without identification of QTLs (Bernardo and Yu, 2007; Bernardo, 2009). Usually, a narrowly based population is created, such as a biparental population or connected crosses, and phenotyped or predicted with a GS model built using historical data. Some individuals are selected, intermated, and used directly for more advanced testing (rapid cycling GS on Fig. 2). The main benefit of such an approach is the reduction in cycle length and phenotyping expenses. A few validation experiments of marker-assisted recurrent selection with GS have been published recently, and a number of others are under way (Massman et al., 2012; Asoro et al., 2013; Combs and Bernardo, 2013). Overall, these studies confirmed the efficiency and superiority of GS over classical marker-assisted selection but did not consider a case where resources used for GS would be allocated to more phenotyping or increased population sizes.

A number of practical issues remain to be considered for efficient use of marker-assisted recurrent selection. Selfing might be required after a cycle to generate enough seed for crosses in the next cycle, slowing down the cycle. Selection on multiple traits, including high heritability traits such as height and flowering time, should be included to effectively deliver genetic gain (Asoro et al., 2013; Combs and Bernardo, 2013). Because prediction accuracy decreases quickly with the cycles of recurrent genomic selection (Muir, 2007; Long et al., 2011), the optimal number of cycles is unclear. Further, phenotyping some of the selection candidates to update the training population will increase the breeding cycle length and costs.

Identifying adequate training populations for those recurrent selection schemes is another area to be

investigated. In the classical marker-assisted recurrent selection scheme based on QTL detection, biparental or connected crosses were phenotyped and used as training data (Xu and Crouch, 2008). Published marker-assisted recurrent selection schemes with GS have mostly used a similar approach (Massman et al., 2012; Combs and Bernardo, 2013). This approach requires that resources are concentrated on a small fraction of the breeding population. Models using historical data for training to predict within families would increase the efficiency of GS in recurrent selection. New models need to be developed to address this issue, as empirical results (Riedelsheimer et al., 2012; Massman et al., 2013) indicate that current models have highly variable prediction accuracies within families if no member of the family is included in the training population or that very large training datasets are needed (Hickey et al., 2014).

IMPROVED USE OF PHENOTYPE WITH MARKERS

Until recently, it was not realistic to consider genotyping all phenotyped individuals because of the high cost and low throughput of the earlier genotyping technologies. In that context, the use of markers was restricted to small, thoroughly phenotyped population subsets.

However, as the cost of whole-genome genotyping has dropped very significantly, e.g., (Elshire et al., 2011), emphasis should be shifted to maximizing the value of expensive phenotypes (Myles et al., 2009). It is likely that genotyping costs will continue to decrease in the future with the advancement in new sequencing technologies. On the contrary, it is unlikely that phenotyping costs will decrease because of increased energy, labor, equipment, and land costs. As a consequence, phenotypes increasingly will be the most valuable asset, and molecular markers should be used to extract all possible information useful to selection from these phenotypes. Molecular markers provide a way to estimate the covariance between the performances of individuals. That information can be used to increase accuracy of selection (Endelman and Jannink, 2012) to maximize the value of the phenotype data available, especially for traits with low entry-mean heritabilities. As replication increases, usefulness of markers decreases, especially if the number of markers is low because the covariance between individuals is poorly estimated. It has been argued that models predicting non-additive effects, such as reproducing kernel Hilbert spaces (RKHS) (de Los Campos et al., 2009), are needed, especially as selection candidates approach commercial release; it is the genotypic, not the breeding value, that is important to create a successful cultivar. However, as an individual approaches commercial release, the amount of phenotype data available on the individual itself greatly reduces the usefulness of information from relatives, even with non-additive models.

Adequately combining information from markers and phenotype for phenotyped individuals might seem to be a challenge. Early molecular breeding work advocated for an index combining phenotypic performance and marker information (Lande and Thompson, 1990). However, because of mixed model optimality properties, the index weights should be 0 for the phenotype and 1 for the GS prediction. For a detailed demonstration, see the supplement in (Endelman et al., 2014). This demonstration makes the assumption that the covariance between individuals is well estimated by the model. This assumption might not be true, for example, at low marker density or if there are some non-additive effects. In practice, this means that if a trial or set of trials is analyzed by GBLUP, the genomic estimated breeding values (GEBV) for those individuals contain all the information available in the phenotype, and the GEBV should be used directly to make a selection.

NEW PHENOTYPING STRATEGIES ARE NEEDED

In the context of marker-assisted recurrent selection with GS, phenotyping is done to train a model, not to directly select (Lorenz et al., 2011). As a consequence, the unit of evaluation is not the individual but the allele. This was first proposed in the context of QTL mapping (Knapp and Bridges, 1990) and suggests that new phenotyping strategies, maximizing the replication of alleles over the replication of individuals, are needed. If the unit of evaluation is the allele, this would favor unreplicated experimental designs over more replications of the same genotypes. More generally, when markers are used to help analyze phenotypes, the switch to allele evaluation is not as clear. The unit of selection remains the individual, and markers provide a way to share information between relatives to improve accuracy of prediction of individuals' performance. Systematic analysis of phenotypic data with markers has a number of consequences for phenotyping strategies. Because trials are analyzed with markers, the assumption used in experimental design, that individuals are independent, is no longer valid. Early work with simple pedigrees showed that equivalent optimal designs are not equally statistically efficient when individuals are not independent (de S. Bueno Filho and Gilmour, 2003). In some cases, a design optimized under the assumption of independent individuals was not optimal for related individuals. This result strongly suggests that current experimental designs need to be reassessed for efficiency.

Given simple assumptions on heritabilities, the mixed model equations can be used to predict the precision of a genetic evaluation before phenotyping with criteria such as the predicted error variance (PEV) or the coefficient of determination (CD) (Laloë, 1993; Laloë et al., 1996).

From the mixed model equations for Model 1, if we write $\mathbf{C} = \begin{pmatrix} \mathbf{C}_{11} & \mathbf{C}_{12} \\ \mathbf{C}_{21} & \mathbf{C}_{22} \end{pmatrix}$, $\text{PEV} = \text{var}(u - \hat{u}) = \mathbf{C}_{22}\sigma^2_\varepsilon$, and $\text{CD} = 1 - \frac{\text{PEV}}{\sigma^2_a}$. In the animal breeding literature, the CD is often referred to as "reliability" and its square root as expected accuracy.

Both the CD and the PEV can be computed for each individual in the dataset given a hypothesis on heritability. Those criteria were used in a genotyped maize population to select an optimal subset of individuals to be phenotyped, such that they would best predict those not phenotyped (Rincent et al., 2012). Those criteria can be used in conjunction with a limit on phenotyping budget or a required precision of evaluation to choose which individuals to phenotype and the experimental design. Mixed model derived criteria were proposed to optimize unreplicated field trials, taking into account the spatial correlation between the residuals (Cullis et al., 2006). In that paper, they note that their method can also be used to take into account relatedness information. In a genomic prediction context, markers could be used to estimate relatedness between individuals before phenotyping to best randomize plots in a field trial.

There are two caveats to this approach. First, it assumes that the covariances among individuals are known, when in fact they are estimated. Given this assumption, adding more individuals or observations to the training population is never detrimental to those optimization criteria. There is empirical evidence that adding more individuals, e.g., from a distinct breed in dairy cattle, is sometimes detrimental to observed within-breed accuracy (Hayes et al., 2009b).

Thus, the mixed model (e.g., PEV) criteria are not useful to select an optimal subset of existing phenotypic data because the criteria will always point to using all data. Only external criteria, such as when there is a budget constraint, might suggest that a subset of data will be better than all data. The last section of this review discusses in more detail the issue with the estimation of the covariance between individual performances. Second, in a breeding context, what matters for breeding gains is the prediction accuracy on both phenotyped and unphenotyped individuals (Endelman et al., 2014)—not only on unphenotyped individuals. Mixed model criteria used in Rincent et al. (2012), such as the mean of the PEV on unphenotyped individuals, can be modified to measure the overall accuracy of the experiment on both phenotyped and unphenotyped individuals.

In the private sector, it has been suggested that GS could be used to increase the size of the breeding programs. For example, large doubled-haploid full-sib families can be developed and a subset of each family phenotyped to predict the remaining. This seems an appealing strategy on paper, but it is not necessarily a good use of resources, depending on relative costs of markers, family development, and phenotyping. Current reports in the literature indicate that, depending on relative costs, it is usually more efficient to phenotype all the individuals in a preliminary yield trial but with fewer replications and more environments if all individuals are genotyped (Lorenz, 2013; Endelman et al., 2014). A scenario where the genotyping budget is used instead to increase population size or phenotyping was also considered in (Endelman et al., 2014), showing that genotyping was not always beneficial, depending on the cost of markers and selection intensity.

EFFICIENT SELECTION ON MULTIPLE TRAITS

The integration of information from different traits for selection purposes requires renewed interest. This is not a new issue, and the theory of selection based on indices (Falconer and Mackay, 1996) is well studied and developed, but more research is needed to apply it in practice and identify the weights to give to the different traits in the index to simplify selection.

In animal breeding, indices are widely used, probably because most of the information is available at once on many traits with varying degrees of accuracy and has to be used to make a selection decision on very large populations. The use of indices in plants is less common, because selection traditionally occurs on different traits at different times. In wheat (*Triticum aestivum*, L.) phenotypic selection on traits such as yield is usually not available from the preliminary trials used to select on plant height, flowering time, and agronomic type. In contrast, with GS, information on many traits will become available at the same time, and selection will be needed on large sets of individuals, necessitating the use of indices to make optimal use of that information.

The use of indices can be more important for GS because GEBVs are not on the same scale as the raw phenotypic data. They include shrinkage of the random effect prediction accounting for the varying amount of information available for each individual and are centered on zero. This shrinkage can be better understood by considering how to unshrink or deregress GEBVs: following (Garrick et al., 2009) $\overline{u}_i = \hat{u}_i / \mathbf{CD}_{ii}$ with $\hat{u}_i$ GEBV for individual i, $\overline{u}_i$ deregressed GEBV, and $\mathbf{CD}_{ii}$ CD for individual ii (ith diagonal element of the **CD** matrix described above). $\overline{u}_i$ is approximately equal to a BLUE (Best Linear Unbiased Estimator), a fixed effect estimate with no shrinkage (Garrick et al., 2009).

Because of shrinkage, GEBVs are optimal for truncation selection (Searle et al., 1992). However, this is a complication for traits where phenotypic selection is based on a threshold value determined with a few check individuals. A check individual will have more phenotypic data than most individuals and, as such, its GEBV value will

be less shrunken toward the mean of the population than most other individuals. Perhaps a distinction is needed between a population improvement task for which truncation selection based on GEBV is optimal and commercial product development in later stages for which comparison to checks is important.

Developing indices might seem to be a difficult task if economic weights had to be identified for every trait. However, breeders already subjectively select genotypes based on performance for multiple traits, such that the historical data for breeding programs contain this information. Retrospective selection indices describing selection already practiced in a population and quantifying the relative trait weights used intuitively by a breeder were proposed (Bernardo, 1991). Those indices should be more accessible to plant breeders now because they can be calculated with a mixed model analysis of the historical breeding data. A limitation of such an approach is that it makes current selection pressure rely on past breeding decisions.

GS ENABLES MULTI-TRAIT MODELS IN PRACTICE

Integration of information on multiple traits is needed for selection purposes, but the covariance between traits can also be used to increase prediction accuracy. Briefly, the mixed model described in the first section of this review can be extended to analyze several traits simultaneously. The single trait model for trait 1 can be written:

$$y_1 = \mathbf{X}_1\beta_1 + \mathbf{Z}_1u_1 + \varepsilon_1$$

and for trait 2:

$$y_2 = \mathbf{X}_2\beta_2 + \mathbf{Z}_2u_2 + \varepsilon_2$$

as described previously. Assuming equal design matrices, no missing records, and independent errors, the multi-trait model can be written:

$$\mathbf{Y} = \mathbf{XB} + \mathbf{Z}\gamma + \varepsilon$$

with γ normally distributed with covariance $G \otimes K$. K is the covariance between individual's performance as before and can be based on pedigree, markers, or an identity matrix.

$$\mathbf{Y} = \begin{pmatrix} y_1 \\ y_2 \end{pmatrix},\ \mathbf{X} = \begin{pmatrix} \mathbf{X}_1 & 0 \\ 0 & \mathbf{X}_2 \end{pmatrix},\ \mathbf{B} = \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix},\ \mathbf{Z} = \begin{pmatrix} \mathbf{Z}_1 & 0 \\ 0 & \mathbf{Z}_2 \end{pmatrix},$$

$$\gamma = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}, \text{ and } \varepsilon = \begin{pmatrix} \mathbf{I}\sigma^2_{e1} & 0 \\ 0 & \mathbf{I}\sigma^2_{e2} \end{pmatrix}$$

with σ^2_{e1} and σ^2_{e2}, respectively, error variances of trait 1 and 2. G is the covariance between traits.

The theoretical background for multi-trait models has existed for a long time (Henderson and Quaas, 1976). However, it has seldom been deployed in plants because the lack of balance of the data made it difficult, or impossible, to fit when individuals were assumed to be independent. The use of markers to estimate the covariance between individuals greatly simplifies the implementation of multi-trait models because it gives a simple way to deal with unbalanced data in which not all individuals are phenotyped for all traits. Those multi-trait mixed models should prove useful to increase the accuracy of selection for traits difficult and expensive to phenotype (Calus and Veerkamp, 2011; Jia and Jannink, 2012). A correlated trait with higher heritability, such as yield under non-stress conditions, could be used to increase accuracy of selection for yield under drought by analyzing both traits together in a multi-trait GS model.

Similarly, drought tolerance could be predicted using multi-trait GS models combining markers, the available yield under drought data, and inexpensive assays, such as canopy spectral reflectance (CSR). Recent empirical results indicate that direct selection for maize yield under drought with GS would be more efficient than indirect phenotypic selection on correlated traits such as anthesis-silking interval (ASI), leaf senescence, or leaf chlorophyll content (Ziyomo and Bernardo, 2013). However, using markers and correlated traits in a multi-trait model at the same time should deliver the most gain.

Another application is where traits of interest are so expensive to phenotype that phenotypic selection uses correlated traits for most of the breeding cycle. For example, malting and baking qualities in small grains and ethanol yield in maize for biofuels are usually evaluated through near-infrared spectroscopy (NIRS) or through cheap indirect chemical assays. Individuals are tested in industrial conditions only in the very late stages of cultivar development. Multi-trait models could be used to deliver a prediction of end-use quality at an early stage by combining marker data and the currently used correlated traits. Higher accuracies for mycotoxin content in wheat, an expensive trait to phenotype with low heritability, were reported by combining markers and simple disease scores (Rutkoski et al., 2012).

Finally, genotype by environment interactions (G★E) can be analyzed in the multi-trait context by considering performances in different environments as different correlated traits (Falconer, 1952). Genetic correlations can then be used to increase the accuracy in different target regions (Piepho and Möhring, 2005; Cullis et al., 2010; Burgueño et al., 2012).

ACCOMMODATING G*E IN GS

Genotype by environment interaction (G★E) is not a new issue in plant breeding (Cooper and Hammer, 1996) but it presents specific opportunities and challenges for GS. G★E is the differential response of individuals to environments. In the case of crossover G★E individuals changing

ranks between environments, there might not be one individual performing best everywhere.

Genomic prediction allows the use of historical phenotypic data to make a selection, thus basing the selection on a broader set of environments than the typical few years of data used by classical phenotypic selection (Heffner et al., 2009). Genomic selection should be beneficial in breeding for stability, because even if an individual has not been tested in a specific environment, some of its relatives may have been, allowing estimation of its performance in that environment.

Underlying the problem of assessing genotype stability, there is the issue of correctly sampling and defining the target population of environments (TPE) (Podlich et al., 1999; Tardieu, 2012). The TPE is the mixture of environments, defined by both abiotic (e.g., weather and soil) and biotic (e.g., weed and disease) parameters, that are likely to occur in the region where breeding program cultivars will be grown. Genetic gains for performance in the TPE can be impacted, in the presence of G*E, if the data used for selection is not a representative sample of the TPE or if the TPE structure is not taken into account in the analysis. It is likely that not all historical data is relevant for performance in the TPE (Heslot et al., 2013b). Defining the TPE may be more critical with GS than with phenotypic selection; in the latter, typically data are used only to select or discard the specific breeding line on which they were measured. Thus, if a particular year of data is a bad sample of the TPE, it will impact genetic gain for only a short period of time. For GS, in contrast, the unrepresentative data may affect genetic gain over a longer period of time, as it will influence marker effect estimates or performance of relatives that, in turn, will affect selection criteria going forward.

Genomic selection also opens new ways of analyzing and coping with G*E. As noted previously, analysis of G*E with multi-trait models becomes more tractable with markers by helping to cope with unbalanced data (Burgueño et al., 2012). Considering allele replication rather than individual replication, marker effects in each environment can be used to cluster environments and identify outliers in highly unbalanced phenotypic data sets (Heslot et al., 2013b).

Genomic selection provides an opportunity to integrate environmental covariates (e.g., climate data) to predict G*E deviations for unobserved environments (Heslot et al., 2013a). Genome-wide marker effects can be considered as a function of environmental covariates that are estimated using GS methods. This approach can in turn allow prediction of individual stability, identification of important stresses, and investigation of the TPE structure that is critical for breeding strategies (Podlich et al., 1999).

NEED FOR IMPROVED PREDICTION MODELS

A lot of attention in GS was initially devoted to statistical models (Gianola et al., 2009), but current GS models behave similarly on empirical data (Heslot et al., 2012). The GBLUP model seems efficient in most situations, but additional research would be beneficial as described below.

First, major QTLs are known for a number of traits in plants. Applying GS in that context might seem problematic. However, (Bernardo, 2013) showed in simulations that it is beneficial to fit the known QTLs as fixed effects only when they each explain more than 10% of the genetic variance. Because their simulations assume that major QTLs are known and in complete linkage disequilibrium with a marker, the practical threshold probably will be higher. Overall, this indicates that GS should be effective for most traits, even when large QTLs are present and without the need for identification or special treatment of the large QTLs.

A more subtle shortcoming of GBLUP was recently identified. Optimality of GBLUP is based on knowledge of the true covariance between individuals. The true covariance between individuals for a given trait depends on the relationship at causal loci and not on the whole genome relationship (Endelman and Jannink, 2012). Recently, it was demonstrated that even for a complex trait at very high marker density, the whole genome relationship can poorly approximate the relationship at causal loci for distantly related individuals (Hill and Weir, 2011; de los Campos et al., 2013). This disjunction between the relationship at causal loci and its whole genome approximation is a potential explanation of why prediction across breeds in dairy cattle does not seem to work with GBLUP (Erbe et al., 2012) and why sometimes adding more individuals to the training set actually decreases prediction accuracy (Riedelsheimer et al., 2013; Habier et al., 2013).

If the true covariance was used for the analysis, accuracy should not decrease with increasing training population size. Adding more individuals to the training population—e.g., very distantly related individuals—should not be detrimental to prediction accuracy. Training population mixed model optimization criteria assumes that covariance is known. As a consequence, adding more individuals is always beneficial for those optimization criteria. For example in dairy cattle, predicted accuracies based on mixed model criteria were good predictors of observed accuracies for within breeds models but not for between-breeds models (Hayes et al., 2009b). This observation reveals an interesting connection between training population design and covariance estimation. If the covariance is better estimated, more individuals can be useful in the training population.

The apparent difficulty to adequately predict within families when no individuals of the family are phenotyped (Massman et al., 2013) is also likely linked to the issue of poor relationship approximation at causal loci for distantly related individuals with GBLUP.

There are two potential strategies for overcoming this problem of estimation of the relationship at causal loci.

One would be to use complete sequencing (Meuwissen, 2010) so that the causal loci would be in the data and variable selection methods could be used to identify them. However, empirical, simulation, and theoretical studies put into doubt the value of this approach (Gianola, 2013; Wimmer et al., 2013) because of the large excess of marker effects to be estimated compared to the number of observations. Nevertheless, it cannot be ruled out that variable selection methods could be useful.

To help identify the causal loci for prediction purposes, other sources of information can be used, such as p-values from genome-wide association studies on different datasets (de los Campos et al., 2013) or from other genomic sources. Prior information about the potential effect of a polymorphism in coding sequence in humans can be obtained with the use of software such as Polyphen (Adzhubei et al., 2010). Similarly, polymorphisms determined to be in regulatory regions can be given a higher prior probability of contributing to the trait than polymorphisms in non-coding, non-regulatory regions using results from the ENCODE project in humans (Maurano et al., 2012). Similar approaches could be developed in plants to derive informative priors for marker effects for genomic prediction purposes.

Another avenue of research would be to develop new covariance estimators. If two individuals are distantly related based on pedigree, the observed kinship coefficient is a poor estimate of the covariance at causal loci. Counter-intuitively, the same observed kinship coefficients but between two highly related individuals is a good estimate of the covariance at causal loci (Hill and Weir, 2011; de los Campos et al., 2013). These differences could be taken into account by shrinking certain coefficients of the realized relationship matrix.

CONCLUSIONS

Genomic selection provides tremendous opportunities to increase genetic gain in plant breeding. Early empirical and simulation results are promising, but for GS to work, consideration of the cost-benefit balance of using markers is needed. It is also important to understand that markers can be used to improve accuracy of selection even for phenotyped individuals. Use of markers for that purpose suggests a number of new ways to improve phenotyping strategies in terms of experimental design and multi-trait models. Genomic selection also provides new ways to analyze and deal with G*E. Finally, more work is needed to develop better prediction models for distantly related individuals. These ideas form the core of what we know at this stage in GS research and will provide fruitful avenues for future research.

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