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Feature Review

Genomic Selection in Plant Breeding: Methods, Models, and Perspectives

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Genomic selection (GS) facilitates the rapid selection of superior genotypes and accelerates the breeding cycle. In this review, we discuss the history, principles, and basis of GS and genomic-enabled prediction (GP) as well as the genetics and statistical complexities of GP models, including genomic genotype × environment (G × E) interactions. We also examine the accuracy of GP models and methods for two cereal crops and two legume crops based on random cross-validation. GS applied to maize breeding has shown tangible genetic gains. Based on GP results, we speculate how GS in germplasm enhancement (i.e., prebreeding) programs could accelerate the flow of genes from gene bank accessions to elite lines. Recent advances in hyperspectral image technology could be combined with GS and pedigree-assisted breeding.

The Role of Genomic-Enabled Prediction in Plant Breeding

Beginning during the 1980s, the development of different molecular marker systems drastically increased the total number of polymorphic markers available to plant breeders, and to molecular biologists in general. The most notable high-throughput genotyping (HTG) system is single nucleotide polymorphisms (SNPs), which have been used intensively in **quantitative trait locus** (QTL; see Glossary) discovery. More than 10 000 QTLs using different marker systems have been reported in more than 120 studies covering 12 plant species [1] that aimed to improve quantitative traits of economic importance. Initially, molecular markers were integrated in traditional phenotypic selection (PS) by applying **marker-assisted selection** (MAS). For simple traits, MAS comprises selecting individuals with QTL-associated markers that have major effects; markers not significantly associated with a trait are not used. However, attempts to improve complex quantitative traits by using QTL-associated marker detection have been unsuccessful due to the difficulty of finding the same QTL across multiple environments (due to QTL × environment interactions) or in different genetic backgrounds [2].

Linkage analysis for QTL mapping is done on biparental populations, but has low power for detecting marker–trait association due to chromosomes with low recombination rates. Therefore, association mapping started during the early 2000s with the objective of overcoming the low power of linkage analysis, thus facilitating the detection of marker–trait associations in

Trends

In recent years, the global climate has changed, resulting in drastic fluctuations in rainfall patterns and increasing temperature. Sudden climate changes can cause significant economic losses to countries worldwide.

Genetic improvement of several economically important crops during the 20th century using phenotypic, pedigree, and performance data was very successful. However, signs of grain yield stagnation in some crops, especially in drought-stressed and semi-arid regions, are evident.

Genomic selection offers the opportunity to increase grain production in less time. International Maize and Wheat Improvement Center (CIMMYT) maize breeding research in Sub-Saharan Africa, India, and Mexico has shown that genomic selection can reduce the breeding interval cycle to at least half the conventional time and produces lines that, in hybrid combinations, significantly increase grain yield performance over that of commercial checks.

Public and private investment in crop genomic selection research should increase to successfully develop in less time germplasm that is adapted to sudden climate change.

nonbiparental populations and fine-mapping chromosome segments with high recombination rates. However, the main problem of fine-association mapping is the low power for detecting rare variants that may be associated with economically important traits [2]. Thus, the challenge of association mapping and QTL detection resides in identifying and quantifying rare QTLs with small effects for economically important traits that are highly affected by the environment. However, because the cost of SNP assays has dramatically decreased, the possibility of using high-density SNP **arrays** (tens of thousands) has resulted in the development of statistical models to predict marker–trait association accurately, depending on the genetic architecture of the predicted trait.

Contrary to QTL and association mapping, **GS** uses all molecular markers for GP of the performance of the candidates for selection. Therefore, the aim of GS is to predict breeding and/or genetic values. GS combines molecular and phenotypic data in a training population (TRN) to obtain the **genomic estimated breeding values** (GEBVs') of individuals in a testing population (TST) that have been genotyped but not phenotyped [3]. Figure 1A depicts the two basic populations in a GS program: the TRN data, whose phenotype and genotype are known, and the TST data, whose genetic values are to be predicted. GS is used in place of phenotyping for a few selection cycles. The main advantages of GS over phenotype-based selection in breeding are that it reduces the cost per cycle and the time required for variety development. In terms of cost reduction in maize breeding, the breeder can testcross 50% of all available lines, evaluating them in first-stage multi-locational trials, and can then use the phenotypic data to predict the remaining 50% by GS. Figure 1B shows the advantage of GS over PS for: (i) reducing costs, up to 50%; and (ii) saving time by selecting lines directly for stage II instead going through stage I (used in PS). This significantly reduces the cost of testcross formation and evaluation at each stage of multi-location evaluations. The time efficiency over PS could come from the second cycle of selection, which uses the TRN from the previous cycle to predict the new doubled haploid (DH) lines, thus excluding testcross formation and first-stage multi-location evaluation trials. Based on GS, the best lines could go directly to the second stage of multi-location evaluations.

GS predicts the breeding values (BVs) of the candidates for selection. BVs have two components: the parental average (the mean BV of both parents) and the deviation of progeny performance from this average that is due to Mendelian sampling. In conventional breeding, the parental average is quantified by pedigree information (if the genealogy is available), from which a relationship matrix ***A*** between the individuals can be derived. Mendelian sampling assesses within-family variation that is quantified by testing the progeny in multienvironment field trials. GS takes advantage of dense markers to quantify Mendelian sampling, thus avoiding the need to extensively phenotype the progeny. This saves time by reducing the cycle length, while enhancing the expected **genetic gain** and the selection response per unit time; it also uses less resources compared with extensive phenotyping. GS has the potential to quickly improve complex traits with low heritability as well as to significantly reduce the cost of line and hybrid development. GS can also be used for simple traits with higher heritability than complex traits, for which high GP accuracy is expected. The application of GS in plant breeding could be limited by two main factors: (i) genotyping costs; and (ii) unclear guidelines as to where GS can be efficiently applied in a breeding program.

GS and GP have been applied using two different approaches. One focuses on predicting additive effects in early generations of a breeding program ($F_{2:3}$) to achieve a rapid selection cycle with a short interval (i.e., GS at the F_2 level of a biparental cross). In this case, researchers are interested in predicting the additive values (BVs) rather than the total genetic value; therefore, additive linear models that summarize the effects of the markers are sufficient. The other approach predicts the complete genetic values of individuals considering both

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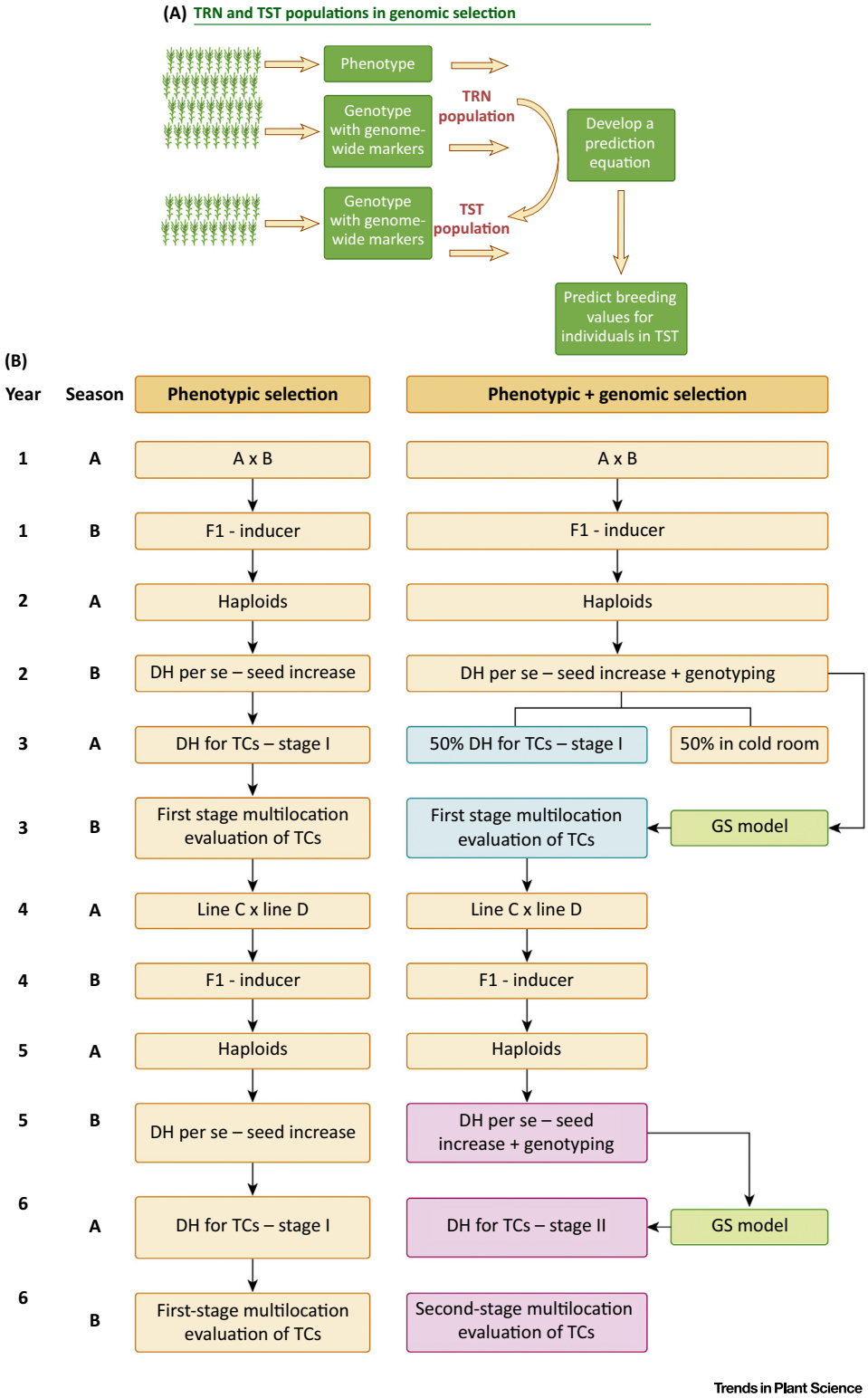

Figure 1. Populations Used in Genomic Selection and a Scheme of Phenotypic and Genomic Selection in Maize Breeding. (A) Genomic selection (GS) requires a training population (TRN) that has been genotyped and phenotyped and a testing population (TST) that has only been genotyped but not phenotyped. (B) Reduction of cycle length through GS in maize using doubled haploids (DH) crossed with a tester (TC).

Glossary

Breeding value (BV): the worth of an individual as estimated by the average performance of its progenies.
Array: high-throughput genotyping platform containing either genome-wide SNPs (SNP array) or coding variants (exome array).
Genetic gain: the amount of increase in performance that is achieved through genetic improvement programs between consecutive selection cycles.
Genomic estimated breeding value (GEBV): breeding value of an individual calculated using genome-wide marker data to capture small genetic effects dispersed over the genome.
Genomic selection (GS): a type of breeding methodology that selects the best candidates as parents for the next selection cycle based on their predicted breeding values computed given: (i) their genotypes; and (ii) the phenotypes and genotypes of their relatives.
Genotyping-by-sequencing (GBS): a highly multiplex genotyping system that involves DNA digestion with enzymes followed by construction of a reduced representation library, which is sequenced using a next-generation sequencing platform.
Heterotic group: a group of genotypes, irrespective of their genetic relatedness, that display similar combining ability and heterotic response when crossed with genotypes from other genetically distinct germplasm of the same group.
Linkage disequilibrium (LD): the nonrandom associations of alleles at two loci that can occur even if the two genes are unlinked.
Marker-assisted selection (MAS): a process for selecting individuals based on trait-linked markers.
Marker-assisted recurrent selection (MARS): a type of MAS that allows the simultaneous identification of associated alleles as well as the accumulation of superior alleles from both parents.
Quantitative trait locus (QTL): a gene (DNA section also called locus) that is associated with variation in a phenotype.

additive and nonadditive (dominance and epistasis) effects, thereby estimating the performance (commercial value) of the cultivars. Genetic values of lines are predicted for some environments using an incomplete (sparse) multienvironment testing scheme.

Several genetic and statistical factors complicate the practical application of GP. Genetic difficulties arise from the size and diversity of the TRN population and the heritability of the traits to be predicted. Statistical challenges are related to the high dimensionality of marker data, where the number of markers (p) is much larger than the number of observations (n) ($p>>n$) and the multicolinearity among markers (adjacent markers are highly correlated). For more details, see 'The complexity of genomic selection and prediction' and 'Solution to an inverse problem' in the supplementary information online.

Here, we review advances in GS and GP theory in light of the above considerations and evaluate recent examples from GP applied to cereal and legume breeding programs. We describe the evolution and main features of GP models, including complexities, strengths, and weaknesses. We then illustrate the use of GP using examples from crop breeding programs with genomic **G × E interactions**, as well as results of genetic gains from rapid cycle GS in maize. We also speculate on the prospects for GS and GP in plant breeding. Most of the results presented in this review include studies performed on maize and wheat from the International Maize and Wheat Improvement Center (CIMMYT), as well as on chickpea from the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT)

Genomic-Enabled Prediction Models and Applications: Coping with Complexity

The complexity of applying GP in breeding occurs at different levels and is influenced by several factors. When a trait is affected by a large number of loci, GP accuracy depends on several genetic factors: (i) the size and genetic diversity of the TRN population and its relationship with the TST population [4]; that is, whether the cultivars in the TRN are relatives (close and/or distant) of cultivars in the TST set; (ii) the heritability of the trait(s) under selection [complex traits with low heritability and small marker effects are suitable for GS and GP, whereas less complex traits (with high heritability) can be predicted by a few markers with relatively large effects); and (iii) for complex traits with large numbers of markers that are not in **linkage disequilibrium** (LD) with the QTL, GP accuracy is lower [5] and increases when the heritability and TRN size increase. Studies have shown the importance of selecting an appropriate TRN population that optimizes the accuracy of the predictions of the nonphenotyped cultivars in the TST set [6]. Depending on the trait, the increase in GP accuracy reaches a plateau as the population size increases. A similar trend was found for the number of markers [7,8].

One important genetic-statistical complexity of GP models arises when predicting nonphenotyped individuals in specific environments (site–year combinations) by incorporating G × E interactions into the statistical models. Equally important is the genomic complexity related to G × E interactions for multi-traits; these interactions create trait and environmental structures that should be dealt with by using statistical-genetic models that exploit multi-trait, multi-environment variance-covariance and genetic correlations between environments, between traits, and between traits and environments, simultaneously. Untangling the complexity of multi-trait genomics and multiple environments requires a theoretical framework that accounts for these complex interactions [9] (see 'Bayesian multi-trait multienvironment genomic model for normal phenotypes' in the supplementary information online). Interestingly, the use of GP to improve disease resistance has been challenging in wheat for two reasons: (i) selection for major resistance genes can be ephemeral due to changes in pathogen races; and (ii) breeding for minor resistance genes with small effects throughout GS (which provides durable resistance) may face the usual complexities encountered in GS [10].

Another level of complexity occurs in GS statistical prediction models because the number of markers (p) is larger than the population size (n) and the predictors (markers) are highly correlated. This situation results in a matrix of predictors that is rank deficient, making it impossible to compute least-square estimates for marker effects. The complexity arises from factors such as the course of dimensionality [11]; that is, under models with $p>>n$, which are not likelihood identified and are prone to overfitting, spurious features and data structures may be captured (see 'The complexity of genomic selection and prediction' and 'Solution to an inverse problem' in the supplementary information online). Solutions to these problems include the use of: (i) penalized regression; (ii) variable selection; and (iii) dimensionality reduction (e.g., principal components), such that a new set of predictors that are not correlated is generated from the original one (markers), thus allowing the use of univariate distributions and decreasing the computation time of the estimates and the prediction [12]. A fourth solution is to use statistical models that assess GP complexities and high-density marker platforms with G × E interactions, thereby adding power to the GP models (see the next section).

GP models based on basic quantitative genetics describe the phenotypic response as the sum of a genetic value (linear additive models) and a residual value. A large body of GP research has focused on developing efficient parametric and nonparametric statistical and computational models with increased accuracy for predicting nonphenotyped genotypes [13]. In general, these theoretical studies show reasonably good prediction accuracies for complex traits such as grain yield and other traits evaluated by means of independent random cross-validation data partitioning. In contrast to the widespread use of GP to predict the performance of one trait in the TST populations using data from the same trait observed in the TRN populations, the complexity of extending this to multi-trait GP indices has not received much attention, except for a method proposed by Cerón-Rojas *et al.* [14] that is based on the multi-trait Genomic Best Linear Unbiased Estimator (GBLUP) selection index, which worked well when applied to simulated and real data sets.

With advances in GS and GP, data volumes and complexity have increased dramatically, leading to novel interdisciplinary research efforts to integrate computer science, machine learning, mathematics, physics, statistics, genetics and quantitative genetics, and bioinformatics. Such work has emerged as a new field of research (commonly known as 'data science' or data-driven science) that aims to unify statistics with data analysis, data mining, and so on. The interdisciplinary researchers in data science focus on computing more accurate predictive values by using statistical models or machine-learning models (R. McDowell, MSc thesis, Iowa State University, 2016). Neural network methods are common prediction tools in machine learning. Neural networks comprise layers of interconnected neurons, where the output of each neuron is expressed as the sum of a certain number of inputs to a neuron located in a specific network layer, with a weight plus a bias; the sum of all inputs is weighted by an activation function.

When neural networks are applied to GP, the input layer is each marker with one neuron per marker; each of the neurons (markers) in the input layer is connected to all the neurons in the first hidden layer, and these are connected to all neurons in the second hidden layer, and so on, up to the output layer, which is one hidden neuron layer with the prediction of each of the phenotypes. Recent developments in neural networks and speedier computer processing have allowed the addition of new layers to the neural network (deep machine learning) to capture small cryptic correlations between inputs [15], which in GP are interactions between markers. Initial applications of machine-learning and neural networks in GP were demonstrated by Gianola *et al.* [16,17], González-Camacho *et al.* [18,19], Pérez-Rodríguez *et al.* [20], Ornella *et al.*, [21], and González-Recio *et al.* [22]. Recent results for deep machine learning applied to GP can be found elsewhere (R. McDowell, MSc thesis, Iowa State University, 2016).

The Accuracy of GP Models, and Genetic Gains Achieved by GS

The GP models assess different prediction problems that attempt to mimic what happens when predictions are made in real situations. Different random cross-validation schemes have been designed to simulate the prediction problems that researchers may face when performing GS. There are four basic scenarios arising from combinations of tested (observed) lines (LT), untested (unobserved) lines (LU) with tested (observed) environment (ET), or untested (unobserved) environments (EU). Predicting newly developed lines (or cultivars) in environments where they were not tested is a case of LU-ET (random cross-validation 1, CV1). Another problem is to predict lines in some environments but not in others; this is LT-ET (random cross-validation 2, CV2), which attempts to mimic one of the objectives of GP: sparse testing. Another problem comprises predicting lines in untested environments; that is, LT-EU (random cross-validation 0, CV0). Finally, there is the problem of predicting lines never observed in never-observed environments, LU-EU (cross-validation 00, CV00) [23–27].

Simulation and empirical results obtained by random cross-validation suggest that GS enhances genetic gains by shortening the breeding cycle (rapid selection cycle) and/or enhancing testing efficiency in field evaluations [3,28–31]. Results of using random cross-validation on maize and wheat breeding data indicate that GS can significantly enhance prediction accuracy related to pedigree and MAS for low-heritability traits [13,18–20,32–43]. Results of applying GS in maize and wheat breeding indicate its effectiveness in selection [44–48].

Breeding programs worldwide have been studying and applying GS and GP in several crops. In parallel, extensive research has resulted in novel statistical methods that incorporate pedigree, genomic, and environmental covariates (e.g., weather data) into statistical-genetic prediction models. GBLUP models [49,50] are widely used in GP, and the extension of GBLUP for incorporating G $\times$ E interactions has improved the accuracy of predicting unobserved cultivars in environments [23,24,51–56]. New models for assessing the GP accuracy of discrete response variables (e.g., ordinal disease data, such as rates, count data, and so on) were proposed [57–61] together with Bayesian genomic models for analyzing multiple traits and multiple environments. A computationally efficient Markov Chain Monte Carlo (MCMC) method that produces full conditional distributions of the parameters, leading to exact Gibbs sampling for the posterior distribution, has also been developed [9]. Results from simulated and (two) extensive data sets show that, when the correlation between the traits is high, a proposed model with an unstructured covariance matrix is preferred over the diagonal and standard methods to help improve the prediction accuracy for grain yield. However, when correlations are low, it is enough to use the standard model [9].

Depending on the complexity of the trait and the prediction scenario, more sophisticated models result in moderate-to-high gains in prediction accuracy. In several studies, complex models increased prediction accuracy by $>$10% at no additional cost. The use of simple models may miss important data features and cause losses of prediction accuracy for complex traits, where nonlinear models usually give significantly higher prediction accuracy than linear models [20,36,55,56]. One of the first assessments of GP in wheat breeding was performed on a collection of 599 wheat lines evaluated in four environments using pedigree and genomic information with two different models [34]. The models were the standard GBLUP with the linear genomic matrix G and a nonparametric model, Reproducing Kernel Hilbert Spaces (RKHS) regression with a nonlinear genomic matrix, the Gaussian kernel (GK) [62]. The most complex model, RKHS using a GK nonlinear kernel, including pedigree and marker information, gave the highest prediction accuracy, ranging from 15% to 36%, with respect to the pedigree model alone. The GP model RKHS with GK, pedigree, and markers has been used for predicting resistance to leaf, stem, and stripe rust, septoria, tan spot, and *Stagonospora nodorum* blotch

in wheat; compared with standard least-squares multiple regression methods, RKHS gave increases in accuracy of 42% and 48% in the two reported studies [63,64], respectively.

Based on the encouraging results obtained in some major cereals, preliminary steps have been taken to deploy GS to develop superior lines more quickly and enhance the rate of genetic gain in a few legume crops, such as pea, soybean, chickpea, groundnut, and pigeon pea [65]. The recent availability of cost-effective, high-throughput sequencing has facilitated the development of large-scale genomic resources in most legumes. Soybean was the first legume crop where GS was deployed for improving yield and agronomic traits using **genotyping-by-sequencing** (GBS) in a breeding program [25]. To assess the utility of GS in soybean breeding programs and understand the effect of marker selection and genotype imputation, prediction accuracies were calculated for two genomic prediction models, namely, the standard GBLUP model with additive effects and an extended GBLUP with additive-by-additive epistasis. High prediction accuracy (0.64) indicated the potential of using GS to improve grain yield [25].

In the case of chickpea, a collection of 320 elite breeding lines was genotyped using Diversity Array technology (DArTseq) and phenotyped for yield-related traits in two environments with two different treatments (i.e., rainfed and irrigated) in two different seasons [65,66]. Various statistical models (RR-BLUP, Kinship GAUSS, Bayes Cπ, Bayes B, Baysian LASSO, and random forest regression or RFR) resulted in high prediction accuracies for the traits of interest; however, not much variation in prediction accuracy among the different models was observed [65,66]. When population structure was included in the model, prediction accuracies improved slightly for days to maturity (DM), days to flowering (DF), and seed dry weight (SDW), but not for seed yield (SY).

In general, early statistical models developed for GP in animal breeding were based on single-environment assessments. However, in plant breeding, G × E interactions are of paramount importance. Just as G × E interactions are a fundamental challenge in plant breeding, they are also increasingly recognized as a major complexity in GP models.

GP Incorporating Genotype × Environment Interaction

Including high-density marker platforms with G × E interactions increases the accuracy of GP models; this has been extensively studied in bread wheat, maize, and legumes [23–27,55,56,67]. In all GP models that incorporate G × E interactions, accuracy with respect to single-environment analyses increased 10–40% on average in all three crop species. The main models used to assess GP accuracy by incorporating G × E interactions and their application to real data are described below.

Multienvironment trials for assessing G × E interactions have an important role in plant breeding for selecting high-performing and stable lines across environments. Burgueño *et al.* [23] were the first to use marker- and pedigree-based GBLUP models for assessing G × E interactions under genomic prediction, while Heslot *et al.* [52] incorporated crop-modeling data to study genomic G × E interactions. A reaction norm model, where the main and interaction effects of markers and environmental covariates are introduced using high-dimensional random variance-covariance structures of markers and environmental covariates, was developed by Jarquín *et al.* [24] as an extension of the well-known GBLUP model.

The baseline model for phenotypes evaluated in different environments (y_{ij}) can be described using Equation 1:

$$y_{ij} = \mu + E_i + L_j + EL_{ij} + \varepsilon_{ij} \quad [1],$$

where μ is the overall mean, E_i (i=1, . . . ,I) is the random effect of the i^{th} environment, L_j is the random effect of the j^{th} line (j=1, . . . ,J), EL_{ij} is the interaction between the i^{th} environment and the j^{th} line, and e_{ij} is the random error term. The assumptions are as follows: $E_i \overset{iid}{\sim} N(0, \sigma^2_E)$, $L_j \overset{iid}{\sim} N(0, \sigma^2_L)$, $EL_{ij} \overset{iid}{\sim} N(0, \sigma^2_{EL})$, and $\varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2_\varepsilon)$, with $N(.,.)$ denoting a normal distribution, and 'iid' standing for independent and identically distributed. However, when the number of environments is small, it may be better to assume it as a fixed effect.

Markers can be introduced in Equation 1 such that the effect of the line (L_j) can be replaced by g_j expressed as a linear regression on marker covariates (it approximates the genetic value of the j^{th} line). The vector containing the 'genomic values' is $\boldsymbol{g} \sim N\left(\mathbf{0}, \mathbf{G}\sigma^2_g\right)$, where σ^2_g is the genomic variance, and **G** is a genomic relationship matrix. Also, the effect of the line (L_j) can be replaced by a_j, with $\boldsymbol{a} \sim N(\mathbf{0}, \mathbf{A}\sigma^2_a)$, where **A** is the numerical additive relationship matrix derived from pedigree, and σ^2_a is the additive variance. The interaction covariance matrix is the Hadamard product of two covariance structures, one describing relationships between lines based on genetic information (pedigree or genomic) and the other relating environments by means of environmental covariates. When the environmental effect is assumed as fixed, the interaction term is the Hadamard product of the fixed effect of environments and the covariance matrix of lines that was built with the genetic information. When environmental covariables are used, the named reaction norm is justified because the genotypic effect is a reaction to those environmental covariables, whereas, when environmental covariables are not used, the reaction norm models have unknown environmental deviations.

This reaction norm model [24] has been applied successfully using pedigree and molecular markers in multienvironments adding environmental covariates, for example, in cotton trials with environmental covariates [68], in GP of extensive wheat gene bank accessions [69], in GP of Fe and Zn in wheat grain [70], in GP of bread wheat lines in sites located in diverse agroecological zones [27,25], in GP prediction of wheat lines evaluated in Mexico and predicted in locations in South Asia [71], and in GP of extensive field trials in wheat on different continents [67]. The reaction norm model was also extended to G × E interactions with maize and wheat disease ordinal and count data by Montesinos-López *et al.* [57–60] (see 'Bayesian genomic-enabled prediction models for ordinal and count data incorporating genotype × environment interaction' in the supplementary information online). The increase in GP accuracy of the reaction norm model with G × E interactions was on average 7–20% relative to the prediction accuracy of the GBLUP without including G × E interactions.

In areas such as Kansas, USA, wheat production is impacted by yearly climate factors, such as extreme temperatures and erratic precipitation. Yearly effects are not repeatable and represent the dynamic part of the G × E interactions, whereas site effects represent the static repeatable component. The accuracy of predicting unobserved historical sites in the wheat breeding program of Kansas State University reaches 0.54, but unobserved years can be predicted with only 0.17 accuracy [26]. Results of using the reaction norm model with pedigree and genomic information for predicting 400–500 bread wheat lines in South Asian locations using approximately 60 000 lines trained in different Mexican environments indicated that GP is more accurate (~0.35) than PS for predicting unobserved wheat lines in different South Asian locations (~0.20) [71]; perhaps this last result is the simplest proof of the concept that GP works better than PS.

GP Incorporating Marker × Environment Interaction Models

The G × E interaction model described by López-Cruz *et al.* [53] decomposes the marker effects into components that are common across environments (stability) and environment-specific deviations (interaction) [see 'The G × E (or M × E) model with linear kernel' in the supplementary information online]. This model borrows information from across environments

while allowing marker effects to change in each environment. It can be implemented using shrinkage methods as well as variable selection methods and, thus, can be used to identify genomic regions whose effects are stable across environments and other regions that are responsible for G × E interactions [54]. The G × E interaction model of López-Cruz *et al.* [53] is best suited for the joint analysis of positively correlated environments and was used to analyze three CIMMYT wheat data sets. The prediction accuracy of the G × E interaction model was greater than across-environment or single-environment analyses (5–29% when predicting each of the environments). Recently, this genomic G × E interaction model was used to predict untested durum wheat lines in environments, as well as a variable selection model to identify genomic regions whose effects are stable across environments and others that are environment specific [54].

In the models of Jarquín *et al.* [24] and López-Cruz *et al.* [53], the kernel used is the linear kernel GBLUP. In a new study, Cuevas *et al.* [55] proposed a G × E interaction model similar to that of López-Cruz *et al.* [53] but with a nonlinear kernel, the Gaussian kernel (GK), which is similar to that used in the RKHS [62] [see 'The G × E model of López-Cruz *et al.* (2015) with a non-linear Gaussian kernel method' in the supplementary information online]. Using two extensive data sets, the authors found that, for the wheat data sets, the GK gave prediction accuracies up to 17% higher than the GBLUP linear kernel. For the maize data set, the GK was on average 5–6% higher than the GBLUP linear kernel. The advantage of the GK over the GBLUP is that it is a more flexible kernel that accounts for small and complex marker main effects and specific interactions.

One weakness of both G × E interaction models with a linear [53] and nonlinear kernel [55] is that positive correlations between environments are assumed. However, when the correlation between environments is low or negative, these models do not increase the prediction accuracy of environments with negligible or negative correlations. The strength of the Bayesian models with G × E interactions used under the linear kernel GBLUP or under the nonlinear Gaussian kernel (GK) is that they overcome the limitation of the previous models when associations between environments are negligible or negative, as shown by Cuevas *et al.* [56]. These authors proposed considering the genetic effects ($\boldsymbol{u}$) described by the Kronecker product of variance-covariance matrices of genetic correlations between environments and genomic kernels through markers under two linear kernel methods: linear (GBLUP) and Gaussian (GK). An extension includes the same genetic component as the first model ($\boldsymbol{u}$), plus an extra residual genetic component, $\boldsymbol{f}$, which captures random effects between environments that were not accounted for by the random effects $\boldsymbol{u}$ (see 'Multienvironment genotype × environment interaction model with linear and nonlinear kernels' in the supplementary information online). Results of the analyses of five data sets showed that: (i) G × E interaction models always had significantly higher prediction accuracy than single-environment models; and (ii) the prediction accuracy of G × E models with $\boldsymbol{u}$ and $\boldsymbol{f}$ over the multienvironment model with only $\boldsymbol{u}$ was higher 85% of the time with GBLUP and 45% of the time with GK across the five data sets. Results indicated that including the random effect $\boldsymbol{f}$ was still beneficial for increasing GP accuracy after adjusting for the random effect $\boldsymbol{u}$. Prediction accuracy of the G × E interaction model methods (GBLUP or GK) increased up to 85% over the accuracy of the single-environment model.

Machine Learning for Genomic Prediction

In an applied GS context, the focus should not be on predicting all individuals, but rather on classifying individuals into upper, middle, or lower classes, depending on the trait under selection. Using classifiers in GS is attractive because they are trained to maximize the probability of an individual being a member of the target class, rather than searching for its overall performance [21]. González-Camacho *et al.* [18] used a radial basis neural network on an extensive genomic maize data set comprising several traits in different environments and compared the results with RKHS

and with a linear regression model. The accuracy of neural network methods was similar to that of RKHS and slightly higher than that of the linear regression.

In a recent study, two neural network classifiers (a multilayer perceptron, MLP, and a probabilistic neural network, PNN) were compared for predicting the probability of an individual member of a target phenotypic class, using 33 maize and wheat genomic and phenotypic data sets [19]. The authors focused on the 15th and 30th percentiles of the upper and lower classes to select the best individuals, as commonly done in GS (for traits such as grain yield, the upper classes are the target; for diseases, the focus is on the lower classes). The criterion for assessing the prediction accuracy of MLP and PNN was the **area under the receiver operating characteristic curve** (AUC). The parameters of both classifiers were estimated by optimizing the AUC for a specific target class. The PNN was found to be more accurate than the classifier MLP for assigning maize and wheat lines to the correct upper, middle, or lower class. Results for the wheat data set with continuous traits split into two and three classes showed that the performance of PNN with three classes was better than PNN with two classes when classifying individuals into the upper and lower (15% or 30%) categories. Depending on the maize trait–environment combination, AUC for PNN30% or for PNN15% upper trait (grain yield) was higher than the AUC of MLP. For the lower class, flowering (male and female) traits, PNN15% and PNN30% always had better AUC than MLP15% and MLP30% [19].

Genetic Gains from Rapid Selection Cycle GS: CIMMYT Maize Biparental Populations

The fundamental goal of using GS in breeding is to achieve greater genetic gains at a lower cost and in less time than with conventional pedigree breeding. To achieve a shorter interval cycle, a favorable use of GS is prediction within full-sib families, because biparental populations have high LD between marker alleles and trait alleles with no group structure.

There are few studies that measure the genetic gains achieved through use of a GS-based rapid selection cycle. The first study confirming the promise of a rapid selection cycle in GP of biparental populations, as well as previous findings from random cross-validation studies, was conducted by Massman *et al.* [44] and showed that GS improved maize genetic gains per unit of time. Genetic gains were also reported by Asoro *et al.* [45] in oat and by Rutkoski *et al.* [48] in wheat, which showed that GS and PS provided similar realized genetic gains per unit of time.

Genetic gain studies comparing GS cycles C_0, C_1, C_2, and C_3 with pedigree selection on eight CIMMYT tropical biparental maize populations in Sub-Saharan Africa were conducted by Beyene *et al.* [47] under drought conditions. The authors showed that: (i) the average gain per cycle (across all eight biparental populations) from GS was 0.086 t/ha under managed drought conditions; (ii) the average grain yield of C_3-derived hybrids was significantly higher than that of hybrids derived from C_0; and (iii) three GS cycles can be achieved in 1 year. The authors concluded that hybrids derived from C_3 produced 7.3% higher grain yield than those developed through conventional pedigree breeding. By contrast, the average gain per cycle using **marker-assisted recurrent selection** (MARS) across ten populations was 0.051 t/ha per cycle under managed drought stress. Extensive field trials were conducted in several managed drought environments in Sub-Saharan Africa to evaluate the grain yield performance of maize hybrids derived from GS-based lines selected from different populations. Lines derived from cycle C_3 GS in hybrid combination produced significantly higher average grain yield than lines from C_0 GS in hybrid combination (Y. Beyene, 2017).

Another example of genetic gains from rapid-cycle GS on CIMMYT maize is two biparental maize populations ($F_{2:3}$) from Asia (CAP1 and CAP2) that were developed and evaluated for testcross performance under drought and optimal conditions [72]. The genetic gains per year for PS versus GS in drought environments were 0.067 t/ha versus 0.124 t/ha, respectively, for

CAP1, and 0.076 t/ha versus 0.104 t/ha, respectively, for CAP2. The corresponding genetic gains per year for PS versus GS in optimal environments were 0.084 t/ha versus 0.140 t/ha, respectively, for CAP1, and 0.123 t/ha versus 0.13 t/ha, respectively, for CAP2. Results of this study confirmed that GS of superior plant phenotypes produced rapid genetic gains in drought tolerance in maize.

Genetic Gains from Rapid Selection Cycle GS: CIMMYT Multiparental Populations

Most GS results in maize have been achieved by rapid cycling of biparental populations (e.g., $F_{2:3}$ segregating populations crossed with a tester from the opposite **heterotic group**). Five years ago, the Global Maize Program of CIMMYT designed a GS rapid cycle of multiparental crosses. Fifteen elite tropical maize lines were crossed in diallelic fashion to form cycle 0 (C_0), which was genotyped using GBS markers and phenotyped at two locations in Mexico; plants with the best phenotype were selected to form the parents for GS cycle 1 (C_1). The C_1 parents were intercrossed and the progeny genotyped with the same GBS markers used for the C_0 population [73].

Two cycles per year were completed and, at the end of the second year, seeds from cycles C_0, C_1, C_2, C_3, and C_4 were collected, assembled, and sown at two locations in Mexico. Fifty entries per genomic cycle were sown at each location, together with two widely used commercial tropical maize hybrids. Average genomic grain yield gains reached 0.134 t/ha, with C_0 producing 6.653 t/ha. Grain yield of C_1 was slightly lower (6.488), and cycles C_2, C_3, and C_4 produced mean yields of 7.022, 6.879, and 7.126 t/ha, respectively. The realized grain yield from C_1 to C_4 reached 0.225 t/ha per cycle, which the authors considered equivalent to 0.1 t/ha per year over a breeding period of 4.5 years. A slight decline in genetic diversity was detected at C_4 compared with C_0.

Prospects for Enhanced Use of GS in Plant Breeding

To accelerate the deployment of GS in crop breeding while reducing the cost of line and hybrid development, here we examine the combined use of GS with high throughput phenotype (HTP) for early-generation testing in plant breeding. In addition, we examine the application of GS in germplasm enhancement and prebreeding using gene bank accessions.

Combining Multi-Trait Multienvironment GS with High-Throughput Phenotyping: The CIMMYT Case

In modern agriculture, high-resolution cameras are used to obtain hundreds of reflectance data measured at discrete narrow bands (wavelengths) to cover the whole spectrum. This information is used to construct vegetation indices (e.g., Green Normalized Difference Vegetation Index or NDVI) to predict primary traits (e.g., grain yield). However, these indices use only certain bands and are cultivar specific; thus, they fail to capture considerable information or perform robustly for all cultivars. The advantage of this imaging technology is that massive numbers of phenotypes can be screened inexpensively during early-generation testing.

The main objective of GS is to reduce phenotyping costs by using markers and accelerate genetic gains, whereas the aim of HTP is to measure high-density phenotypes in very large numbers of individuals or breeding lines across time and space using remote or proximal sensing. This can increase both the accuracy and intensity of selection and, subsequently, the selection response, while decreasing phenotyping costs. The main idea of HTP is to use secondary traits related to grain yield, disease resistance, or end-use quality that may be useful in early-generation testing of lines. A recent study [74] found that the highest accuracy when predicting grain yield is achieved by the use of broader selection of wavelengths (see 'Predicting grain yield using canopy hyperspectral reflectance in wheat breeding data' in the supplementary information online).

Using HTP platforms with vegetation indices as predictor traits in pedigree and GS models can increase the prediction accuracy for grain yield [75]. Prediction during early-generation testing is important to enhance genetic gains during early stages of the breeding cycle, but GS is economically unfeasible at those stages due to the large number of plants in the field; thus, while assessing pedigree relationships has the advantage of not costing anything, their use fails to exploit Mendelian sampling, in contrast to GS. Therefore, using multivariate pedigree-based prediction models that incorporate such predictor traits while using an HTP platform offers a low-cost solution for predicting grain yield among and within families in early-generation testing, as demonstrated by Rutkoski *et al.* [75]. These authors found that within-environment secondary vegetative indices increased prediction accuracies for grain yield by 59% using pedigree relationships and by 70% using genomic relationships. These results indicate that secondary traits measured by HTP and used with pedigree can improve the prediction accuracy of primary traits during the early stages of breeding. Reynolds and Langridge [76] found that HTP techniques are effective for evaluating genetic resources for complex trait expression.

HTP platforms are useful to measure secondary traits that are genetically correlated with grain yield and that can be incorporated in multivariate pedigree and genomic prediction models, improving indirect selection for grain yield. Sun *et al.* [77] used a statistical model that estimated BVs of secondary traits together with multivariate pedigree and genomic models; the authors found a 70% (on average) improvement in the accuracy of selection for grain yield, including secondary traits in both TRN and TST populations.

A recent study developed statistical models to assess hyperspectral wavelength × environment interactions in HTP, incorporating genomic and pedigree G × E interactions [78]. Although little GP accuracy was achieved, important hyperspectral wavelength × environment interactions were observed, demonstrating that GS coupled with HTP can be a powerful tool applied to early-generation testing of a large number of selection candidates. The full conditional distributions for modeling the three-way trait × G × E interaction model of Montesinos-López *et al.* [9] can be adapted to include the hyperspectral bands in the functional regression approach recently described by Montesinos-López *et al.* [74,78].

Exploring the Application of GS to Gene Bank Accessions for Germplasm Enhancement

Although the accessions stored in gene banks represent a rich resource for breeders, alleles need to be extracted from the accessions for cultivar development, which is time-consuming and expensive [79,80]. Lengthy prebreeding programs are required to develop lines that combine favorable alleles from the germplasm bank with good agronomic performance and that can be used as parents in a breeding program. Based on the simulation of various prebreeding options, germplasm enhancement breeding programs can start directly from landraces or from landraces crossed with elite testers [81].

The GP accuracy of 8416 Mexican wheat landrace accessions and 2403 Iranian wheat landrace accessions from the CIMMYT gene bank were examined by Crossa *et al.* [69]. The authors measured two traits in two environments and several highly heritable traits in a single optimum environment. The GP accuracy for several traits (maturity, quality traits, and grain yield and yield components) under the different prediction scenarios was high, ranging from 0.5 to 0.7. In soybean, Jarquín *et al.* [25] analyzed the USDA soybean collection using different cross-validation schemes and grouping factors (trials, states, and genetic subpopulations); results showed relatively high prediction accuracies that should help breeders to introgress useful genetic variation (Box 1).

These preliminary results of the accuracy of GP of gene bank accessions favor the idea of applying GS to introgress landrace accessions in elite germplasm and form gene pools and

Box 1. An Example of GS Deployment in Prebreeding

Results from using a large number of Mexican and Iranian landraces stored in the wheat gene bank of CIMMYT indicated that prediction accuracies for traits evaluated in one environment for TRN20-TST80 design ranged from 0.407 to 0.677 for Mexican landraces and from 0.166 to 0.662 for Iranian landraces. Also, prediction accuracies of the 20% core set were similar to those obtained for TRN20-TST80, ranging from 0.412 to 0.654 for Mexican landraces and from 0.182 to 0.647 for Iranian landraces. Interestingly, the correlations for complex GYSM traits were approximately 0.4 for both Mexican and Iranian landraces. Results of correlations when incorporating G × E interactions for days to heading and days to maturity for TRN20-TST80 were approximately 0.61 for Mexican landraces and 0.60 for Iranian landraces. The 20% core set had correlations of approximately 0.58 for Mexican landraces and 0.50–0.59 for Iranian landraces.

Prediction accuracies of the 10% and 20% diversity and predictive core subsets were generally of a magnitude that appeared useful for predicting the value of gene bank accessions and for breeding. The first application would be to predict the genetic value of all genotyped accessions in a gene bank and then phenotype only those that have the highest predicted genetic values. Then, a breeder could begin prebreeding following several strategies. For example, one decision would be to initiate a prebreeding conversion approach by crossing the best accessions among themselves to improve the accessions per se until they become elite. Another strategy could be to start an introgression approach by crossing selected accessions to elite materials.

Nevertheless, application of GS for germplasm enhancement will have to be performed in combination with standard introgression of exotic to elite germplasm and, possibly, a series of backcrosses to the elite material. Extracting the best accessions directly from the gene banks and forming productive gene pools may be the first stage before refining the gene pools and evaluating them under different environmental conditions.

Outstanding Questions

How can GS have an important role in enhancing the rate of genetic gain?

Are currently available GS models capable of providing the most accurate predictions?

How can GS accelerate the flow of favorable alleles directly from the gene bank to breeding programs?

Are we ready to deploy GS in prebreeding and germplasm-enhancement programs?

Is it possible to combine GS and pedigree selection with HTP to accelerate genetic gains and save resources when developing lines during early-generation testing?

populations suitable for prebreeding and germplasm enhancement programs. However, further research is required in this area.

Concluding Remarks

Many statistical methods have been developed to predict unobserved individuals in GS. In general, linear models (e.g., GBLUP) and machine-learning algorithms have been successful in recognizing complex patterns and making correct decisions based on data. Kernel-based methods, such as the RKHS, have extensively delivered good genomic predictions in plants. Several statistical models based on the standard GBLUP that incorporate G × E interactions in genomic and pedigree predictions have provided substantial increases in the accuracy of predicting unobserved individuals in environments. These GS prediction models can help scientists in different disciplines to develop drought- and heat-tolerant plants by exploiting positive G × E interactions. Modeling multi-trait multi-environment is essential for improving the prediction accuracy of the performance of newly developed lines in future years.

The use of statistical models in extensive hyperspectral image technology for HTP, together with genomic and pedigree information in early-generation testing, offers an opportunity to accelerate genetic gains by increasing the intensity of selection. Deep machine-learning methods using neural networking appear promising to increase the accuracy of genomic-enabled prediction. Genomic selection has a clear-cut advantage over pedigree breeding and MAS to enhance genetic gains for complex traits. The appropriate use of genotyping platforms combined with precise phenotyping platforms will also help enhance prediction accuracy and accelerate genetic gains by shortening the breeding cycle. Further research is required to incorporate GS with HTP as a routine component in plant breeding programs.

Developing GP models for gene bank accessions will be important to access unexplored diversity and fast-track useful portions into breeding programs (also see Outstanding Questions). Currently, GS is the most-promising breeding method to speed the development and release of new genotypes; therefore, the use of GS to form gene pools and populations from rich gene bank accessions merits extensive and intensive study, especially given the vulnerability of elite lines and hybrids to severe climate change effects.

Acknowledgments

The authors are grateful to their colleagues, collaborators, and by using field and lab technician from CIMMYT and ICRISAT, as well as scientists in National Programs who collected the valuable data used in the various studies. The authors would like to thank Kevin Pixley, Daniel Gianola, and four anonymous reviewers for their positive, careful, and detailed reviews of the manuscript; their comments, editing, and suggestions significantly improved the quality and readability of the manuscript. The authors also thank Michael Listman for editing the revised version of the manuscript.

Supplemental Information

Supplemental information associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tplants.2017.08.011.

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