The use of genome-wide prediction to increase efficiency in plant breeding programs

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1. General Introduction

1.1 The origin and economic importance of wheat and barley

Both bread wheat and barley have their evolutionary origins in the ecologically highly successful and economically important Poaceae family. A short generation time facilitated by an energy-rich endosperm and the lack of investment in woody anatomical structures, high climatic tolerance enabled by C3 and C4 photosynthesis and underground perennial buds that survive frost and fire, and a high diversity of dispersal units due to the variable shape of spikelets that enable migration over long distances are some of the functional characteristics that account for the ecological success of the Poaceae, which manifests itself in a great species richness and presence in almost all climatic zones inhabited by plants (Linder et al., 2018). These are also the characteristics that were used by the first farming humans when bread wheat and barley were domesticated, and thereby fundamentally changed the shape of human existence.

The Poaceae family includes sugar cane, corn, rice, wheat, and barley, the world's most important crops. Cereals, in particular, are the most important share on the global food market with maize, wheat, rice, and barley accounting for ca. 40 %, 28 %, 19 %, and 5 % respectively (FAO, 2022). The domestication of barley began about 10,000 years ago in the fertile crescent region (Haas et al., 2019a), where it was a popular food and feed. Nevertheless, archeological evidence suggests the use of ground barley over 17,000 years ago in the Nile Valley (Wendorf et al., 1979). The cultivated form of barley is derived from *Hordeum vulgare* ssp. *spontaneum*, to which it still looks morphologically very similar (Haas et al., 2019b). In ancient times, barley was valued for its high energy content and, according to tradition, was the staple food of gladiators, who were therefore also called "*hordeari*" (Percival, 1921). In particular, in the last two centuries, the use of barley as a food source has receded in favor of its further use as malt and animal feed. In general, barley has a lower and more difficult-to-digest starch content than corn, but it has more protein, which makes it an attractive feed for poultry, pigs, and cattle (Dehghan-banadaky et al., 2007; Jacob & Pescatore, 2012; Meints & Hayes, 2019). Various initiatives are underway to improve the digestibility of barley to advance its suitability as feed, for example through chemical and physical processing (Dehghan-banadaky et al., 2007) or breeding (Meints & Hayes, 2019).

Unlike barley, wheat plays a consistently important role in the food industry because of its good food processing and product development qualities. Wheat was domesticated in the fertile crescent shortly after barley. The first domesticated form of wheat was einkorn (*Triticum monococcum*) (Weiss & Zohary, 2011). It was cultivated in the geographic region of the Balkan Peninsula around 6,000 BC, and later spelt wheat (*Triticum spelta*) and bread wheat (*Triticum aestivum*) achieved expansion throughout the Mediterranean region (Bonjean et al., 2001). Even before the Romans, the Chinese

Empire of the Shang Dynasty elevated wheat to an essential pillar of society, where it was revered as a sacred plant, just like barley (Igrejas et al., 2020). Wheat is used for the production of various pasta products in almost all parts of the world. In addition, it is used as animal feed and for the production of alcoholic beverages. In the food industry, wheat is used for the extraction of starch, leaving gluten, which in turn can be used as feed or to produce other food products (Igrejas et al., 2020).

1.2 Line breeding in barley and wheat

In general, the term breeding refers to various methods of generating, selecting, and fixing favorable phenotypes that lead to the development of new varieties that meet the needs of consumers and producers (Moose & Mumm, 2008). The simplest and probably oldest method to increase crop productivity might be phenotypic selection. Since then, breeding itself has undergone an evolutionary process which, according to Fernie & Yan (2019), can be divided into three further phases: the era of hybridization, the era of biotechnologies such as marker-assisted selection, genome-wide selection, transgenics and bioinformatics. Finally, there is the era of breeding by designing genotypes according to end-users' demands using genome editing and precision breeding through big data, which allows, for example, the prediction of genotype characteristics under certain environmental conditions.

Both barley and wheat tend to self-pollinate, with outcrossing rates of up to 1.8% observed in wild barley and barley landraces (Abdel-Ghani et al., 2004). No self-incompatibility exists in either species and the mature anthers shed their pollen in the usually unopened flower, resulting in self-pollination. This circumstance facilitates line breeding, which has been used in commercial breeding programs.

Even before Gregor Mendel began experimenting with peas in the 1850s, Vilmorin began line breeding based on a pedigree approach in the 1840s (Gayon & Zallen, 1998). In the pedigree approach, the progeny of a cross is sown in a plot with ample spacing between each plant to determine differences. Beginning in the first segregating F_2 generation, ears from particularly promising individuals are harvested and the corresponding seeds are sown in row plots in the following generation. In this way, offspring can be compared against the background of their pedigree and performance in terms of certain traits in order to select the best. Over several seasons, fewer genotypes are evaluated through the selection process. At the same time, the number of available seeds increases, so that first yield tests can be carried out with potent progeny of a cross in the $F_{2:3}$ generation. Multi-environment trials follow, and as the breeding process progresses, uniformity increases, so that 93.75% homozygosity can be expected in the F_5 generation (Hallauer et al., 2010), implying that a certain stability over generations is present.

Another classic method for line breeding is bulk breeding. Similar to the pedigree approach, the progeny of a cross is sown in a plot. However, selections are not made on the basis of individual plants within the plot, but those plots are selected whose plants perform particularly well with respect to the

target traits. Again, the plants achieve more homozygosity and uniformity with each generation. With sufficient uniformity and homozygosity, the development of lines can now begin by selecting individual ears or plants. For this purpose, the seed of selected ears or plants is sown in rows. A further evaluation step can take place before the plants selected in this step are harvested. Yield tests can now be carried out from this seed.

The advent of double haploid technology has led to a revolution in line breeding over the past three decades (Kalinowska et al., 2019). Double haploids are genotypes that result when haploid cells double their chromosome set. This phenomenon can be induced, for example, by hybridization with another species and the addition of chemical agents. Double haploid technology allows the creation of fully homozygous genotypes after only one generation. In this way, the development of lines can take place, for example, after the F_1 generation. From this point on, seed multiplication and evaluation of genotypes can take place. Double haploid technology has become a routine tool in both barley and wheat. In wheat in particular, the success of double haploid production depends heavily on parental genotypes. Therefore, approaches for rapid breeding have recently come more and more into focus (reviewed in Srivastava & Bains, 2018).

1.3 Heterosis

The term heterosis was coined by George Shull's in the course of his studies on corn breeding (Shull, 1908, 1914). Heterosis describes the higher performance of genotypes resulting as F_1 from a cross of two homozygous, complementary parental lines. It manifests itself in particular in a higher fitness and vigor of the hybrid genotype (Lamkey & Edwards, 1999; Shull, 1952) . Although research on heterosis has been ongoing for more than a century, the biological mechanisms behind the phenomenon are not yet fully understood. The genetic effects causing heterosis can be explained by dominance, overdominance, and epistasis.

When recessive alleles are masked by dominant alleles, this leads to an increase in performance with respect to the trait of interest in the case of positive dominance. This observation is summarized in the dominance hypothesis and identified as one possible cause of heterosis (Bruce, 1910; Davenport, 1908; Jiang et al., 2017; Jones, 1917; Keeble & Pellew, 1910). The epistasis hypothesis explains part of the performance gains observed in hybrids by interactions between different loci, i.e. epistasis (Jiang et al., 2017; Schnell & Cockerham, 1992). Digenic epistasis can be described by three forms of interactions: additive times additive interactions, additive times dominance interactions, and dominance times dominance interactions (Jiang et al., 2017). The overdominance hypothesis substantiates the superiority of hybrids in that the effect of heterozygosity at some loci is more beneficial than that of one or the other allele when homozygous (Crow, 1948; East, 1936; Hull, 1945; Jiang et al., 2017). Most likely, all of the three forces described play a role in the action of heterosis,

although the importance of each component is likely to depend on the investigated species (Schnable & Springer, 2013) and the genetic architecture of the trait.

One way to describe heterosis in a quantitative framework is mid-parent heterosis, which is defined as the deviation of a hybrid from the mean of its homozygous parents (W. Schnell, 1961). Better-parent heterosis, on the other hand, represents the difference between the hybrid and the better-performing parent. From an economic point of view, commercial heterosis is more important: it compares the performance of hybrids with the best line variety on the market.

Heterosis is the basis of hybrid breeding and especially in cross-pollinated species it can bring significant advantages. In maize, for example, a better parent heterosis of 15% was found (Duvick, 1999). In rye, similar values for heterosis could be observed as in maize, ranging from 15-20%. In winter oilseed rape, an average better parent heterosis of 50% was reported for yield (McVetty, 1995).

1.4 Hybrid breeding in wheat

Also in autogamous crops, there has been a great interest in implementing hybrid breeding for a long time. In wheat, hybrid varieties are noted for higher yield while showing higher yield stability (Longin et al., 2012). By crossing two parent lines with complementary resistance to diseases, they can be combined much more easily (Longin et al., 2012). In this way, it is also possible to respond more quickly to changing pathogen populations, for example. From an economic point of view, it is important to note that hybrid varieties have a higher return on investment, since the illegal reproduction of seed is not possible without a massive loss of quality (Hallauer et al., 1988).

Commercial heterosis of wheat hybrids can reach up to 1 Mg ha^{-1}. In line breeding, this would correspond to about 15 years of breeding progress (Laidig et al., 2014; Zhao et al., 2015). The mid-parent heterosis amounts to 10% in wheat (Longin et al., 2012). In 2022, the descriptive variety list of the Bundessortenamt was topped by a hybrid variety in both treated and untreated yield tests (Bundessortenamt, 2023). In addition, there is the lower susceptibility to biotic and abiotic stressors observed in wheat (Longin et al., 2013).

The advantage conferred by heterosis can be released through targeted breeding strategies and the eventual release of hybrid varieties. Continuous improvement of populations of genotypes suitable for hybrid breeding can be achieved through recurrent selection. Recurrent selection is the cyclically repeating selection of potent genotypes and the subsequent intercrossing of these genotypes. The implementation of recurrent selection in hybrid breeding was already proposed by Comstock et al. (1949). By performing recurrent selection, heterosis can be used with a continuing selection gain to improve a population in terms of its combining ability.

Despite the compelling advantages of hybrid breeding in wheat, hybrid wheat breeders are faced with some obstacles, essentially involving the allogamous flowering biology of wheat, which significantly complicates seed production (Whitford et al., 2013). Genotypes with good flowering properties must first be found at great expense. By backcrossing, flowering properties can be introduced into an elite background, which involves a great expenditure of work. In addition, cross-pollination is also dependent on environmental factors such as humidity, temperature, and time of day (Pickett, 1993). The nature of the relatively heavy wheat pollen precludes its transport over longer distances, added to which it is short-lived. These factors complicate the production of hybrid seed in wheat. To be competitive in the market, wheat hybrid varieties must compensate for the high production costs through performance. Effective breeding strategies can contribute to the development of attractive and competitive hybrid varieties.

1.5 Genome-wide selection

The advent of genetic markers has fundamentally revolutionized plant breeding. One element of this new facet of plant breeding is genome-wide prediction and the resulting genome-wide selection. In genome-wide prediction, a set of genetic markers sufficiently covering the genome is used to predict the performance of non-phenotyped genotypes based on genotypes with known phenotype. Generally, the set of genotypes on which the model for genome-wide prediction is based is called the training set. The genotypes whose performance is to be predicted are called the test set. Genome-wide selection is the selection of promising genotypes whose performance is evaluated using genome-wide predictions or genomic estimated breeding values from their marker profile. The concept of genome-wide selection was introduced two decades ago (Meuwissen et al., 2001) and was associated with the goal of performing selections for complex traits controlled by many small effect genes with high precision. Heretofore, other studies have successfully predicted the phenotypic performances of maize hybrids based on their genetic similarity (Bernardo, 1994, 1996).

A major advantage of genome-wide selection is the reduced effort that must be invested to evaluate genotypes based on their performance. This eliminates the need for some of the genotypes in the breeding program to be phenotypically evaluated and multiplied, only to be discarded because other genotypes were more promising. Instead, only those genotypes that have promising genomic-estimated breeding values (GEBVs) regarding a set of desired characteristics are comprehensively tested.

For a successful breeding program, the efficient and sustainable exploitation of two resources is crucial: i) Genetic diversity, the reservoir of heritable factors that are optimally combined in the breeding process for the purpose of increasing performance, and ii) time and experimental plots that ensure highly accurate phenotyping to maximize selection intensity and precision. The essence of this

principle is summarized in the breeder's equation (Lush, 1937): The effectiveness of genome-wide prediction lies in a significant reduction in the time required for a breeding cycle and the reduction of genotypes to be phenotyped, while maintaining a constant selection gain (Heffner et al., 2010). One of the first successful studies on genome-wide selection was published for dairy cattle and predicted a 92% cost reduction from the laborious process of determining the breeding value of a bull based on the milk yield of its progeny (Schaeffer, 2006). In crop plants, genome-wide prediction has been successfully implemented in maize (Massman et al., 2013), wheat (He et al., 2016), barley (Philipp et al., 2016), oat (Asoro et al., 2011), rye (Wang et al., 2014), rice (S. Xu et al., 2014), sugar beet (Hofheinz et al., 2012; Würschum et al., 2013), canola (Jan et al., 2016), and sunflower (Reif et al., 2013).

1.6 Parental selection in line breeding

The concept of the breeding value originates from cattle breeding, where the value of a male animal is estimated by the performance of its progeny. This common problem in animal breeding is very similar to the selection of the most potent parents for the creation of a breeding population in plants. It seems obvious that a high performing offspring population can be produced by combining two particularly high performing parents. Nevertheless, this is only half the truth: a single high-performing genotype produced by a breeding population can justify the entire effort of a breeding program. It is quite possible that a breeding population with a lower mean value will still be more successful, provided that only one genotype performs sufficiently well. Ideally, a breeding population is characterized by a high population mean and a high variance with respect to the trait of interest. These considerations were summarized in the usefulness concept (Schnell & Utz 1975).

1.7 Parental selection in hybrid breeding using genome-wide prediction

Finding well-suited parents for the generation of superior hybrids is one of the core tasks in hybrid breeding. For this purpose, inbred lines that can be considered as parental crossing partners can be characterized based on general combining ability (GCA) and specific combining ability (SCA) effects. The concept of GCA and SCA effects date back to Sprague & Tatum (1942), and were first used in hybrid corn breeding. To determine GCA, potential parental lines are crossed against a set of inbred lines referred to as testers. Each of these crosses results in hybrids in the F_1 generation whose performance is evaluated for the trait of interest. The average performance of all hybrids resulting from these test crosses is referred to as GCA. While the GCA of a parent line remains constant in a defined set of testers, the SCA depends on the combination of the parent line with a specific tester. The difference between the GCA of a parent line and the realized performance of the parent line with a specific tester is called SCA. GCA is essentially driven by additive genetic effects, whereas SCA is due to dominance effects and additive times dominance, or dominance times dominance epistasis.

SCA can be used to select the optimal combination of crossing partners, but it cannot be addressed in breeding terms because it is not due to additive genetic effects. Therefore, the focus of the breeder's interest is to maximize GCA. Only in the last step the suitable parents are selected for the generation of a hybrid based on their SCA. Multi-location tests are necessary for reliable determination of GCA and SCA. In addition to the field trials themselves, seed production represents a high workload. Therefore, efforts are directed at increasing the efficiency of hybrid breeding programs through genome-wide prediction (Albrecht et al., 2011; Reif et al., 2013; Zhao et al., 2015).

In hybrid breeding, the formation of heterotic groups has been established in maize. A heterotic group is a group of genotypes that have similar combining abilities when crossed with genetically distinct other genotypes (Melchinger & Gumber, 1998). A heterotic pattern is defined as two heterotic groups whose genotypes, when crossed, optimally exploit heterosis with respect to a trait. A reasonable goal of hybrid breeding is to maximize heterosis for a specific heterotic pattern.

1.8 Recurrent genomic selection

The term recurrent selection was coined by Jenkins (1940) for intrapopulation improvement, later extended to populations improvement using a tester (Hull et al., 1945, Hallauer et al., 1988, Hallauer et al., 2010). In contemporary terminology, recurrent selection defines cyclically recurring, i.e. returning selections of outstanding genotypes and the subsequent crossing of these genotypes with each other (Hallauer et al., 2010; Lonnquist, 1949). The improvement of the population is achieved by increasing the frequencies of beneficial alleles. The improved population can then be used to derive inbred lines that can either be released directly as varieties or used to produce hybrid varieties. The implementation of genome-wide selection in recurrent selection has been proposed to shorten the time required to complete a selection cycle by reducing the need for phenotyping (Gorjanc et al., 2018; Müller et al., 2017, 2018) but an application-oriented validation study for the implementation of genome-wide selection in hybrid breeding is missing.

1.9 Objectives

The main objective of the presented work was to evaluate genome-wide selection across the breeding cycle to identify opportunities to increase the efficiency of the same. For this purpose, for each of the most important categories of cereal population improvement, namely hybrid breeding and line breeding, a concept presented in the scientific community but not yet tested in practice was evaluated in application-oriented experiments. In particular, the objectives were to:

1) provide an overview of experimental and simulation-based studies exploring the possibilities to integrate genome-wide prediction into recurrent selection in the context of hybrid wheat breeding;

2) discuss possibilities to make use of recurrent selection for inter-population improvement in wheat;
3) investigate the utility of genomic selection to identify superior females through genomic estimation of the general combining ability effects in wheat;
4) evaluate the selection gain for grain yield achieved by recurrent selection for inter-population improvement in wheat,
5) examine the impact of genotype-by-environment interaction effects on the effectiveness of a long-term breeding strategy;
6) analyze a commercial barley line breeding program for the possibilities and limitations of implementing genome-wide selection; and
7) test the potential of genomic prediction for the population mean, variance and the usefulness criterion using data from an applied breeding population for winter barley.

2. Peer-reviewed scientific articles

2.1 Reciprocal recurrent genomic selection: an attractive tool to leverage hybrid wheat breeding

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Abstract

Despite the technological advance of methods to facilitate hybrid breeding in self-pollinating crops, line breeding is still the dominating breeding strategy. This is likely due to a higher long-term selection gain in line compared to hybrid breeding. In this respect, recent studies on two-part strategies splitting the breeding program into a population improvement and a product development component could mark a trend reversal. Here, an overview of experimental and simulation-based studies exploring the possibilities to integrate genome-wide prediction into recurrent selection is given. Furthermore, possibilities to make use of recurrent selection for inter-population improvement are discussed. Current findings of simulation studies and quantitative genetic considerations suggest that long-term selection gain of hybrid breeding can be increased by implementing a two-part selection strategy based on reciprocal recurrent genomic selection. This would strengthen the competitiveness of hybrid versus line breeding facilitating to develop outstanding hybrid varieties also for self-pollinating plants such as wheat.

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ORIGINAL ARTICLE

Reciprocal recurrent genomic selection: an attractive tool to leverage hybrid wheat breeding

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Abstract

Key message **Using a two-part breeding strategy based on a population improvement and a product development component can leverage hybrid wheat breeding.**

Abstract Despite the technological advance of methods to facilitate hybrid breeding in self-pollinating crops, line breeding is still the dominating breeding strategy. This is likely due to a higher long-term selection gain in line compared to hybrid breeding. In this respect, recent studies on two-part strategies splitting the breeding program into a population improvement and a product development component could mark a trend reversal. Here, an overview of experimental and simulation-based studies exploring the possibilities to integrate genome-wide prediction into recurrent selection is given. Furthermore, possibilities to make use of recurrent selection for inter-population improvement are discussed. Current findings of simulation studies and quantitative genetic considerations suggest that long-term selection gain of hybrid breeding can be increased by implementing a two-part selection strategy based on reciprocal recurrent genomic selection. This would strengthen the competitiveness of hybrid versus line breeding facilitating to develop outstanding hybrid varieties also for self-pollinating plants such as wheat.

Abbreviations

SNP Single nucleotide polymorphism
ST Single trait

Introduction

Increasing crop yield is a global challenge to produce sufficient food, feed, and fuel for a growing human population. Hybrid breeding is a promising strategy to increase grain yield through the maximal exploitation of heterosis (Duvick 2001). A successful implementation of hybrid breeding has been realized for outcrossing species such as maize (Troyer 1999), rye (Geiger and Miedaner 1999), sugar beet (Li et al. 2010), or sunflower (Reif et al. 2013). In contrast, the selfing species wheat is bred as pure line varieties with stagnating yield growths (Zhao et al. 2015a). Consequently, the goal of several wheat breeding programs is to implement hybrid breeding in order to boost yield (Zhao et al. 2015b) and yield stability (Mühleisen et al. 2014).

Plant breeders face many challenges when they shift from line to hybrid breeding in selfing species (Longin et al. 2012; Whitford et al. 2013; Ma and Yuan 2015). One major bottleneck is to produce hybrid seeds economically, which entails the development of techniques for hybrid seed production including a re-education of selfing into outcrossing species (Whitford et al. 2013; Tucker et al. 2017). Moreover, hybrids must significantly outperform released line varieties. One key component contributing to the competitiveness of hybrid breeding is the establishment of genetically complementary heterotic groups (Melchinger and Gumber 1998). Zhao et al. (2015a) developed a genome-based three-step strategy to identify high-yielding heterotic patterns. In this three-step approach, genome-wide predictions are used to compile a full diallel matrix of hybrid performances, a simulated annealing algorithm is applied to identify the

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highest yielding heterotic pattern, and optimal sizes of heterotic groups are determined balancing short- and long-term selection gain, and the approach is focused on grain yield but can be expanded to consider also an index of relevant traits.

Hybrid wheat breeding profits from around 10% of mid-parent heterosis (Longin et al. 2012; Jiang et al. 2017) but suffers from longer lasting cycles compared to line breeding (Longin et al. 2014). A central task is therefore to shorten the cycle length in hybrid wheat breeding. The introduction of genome-wide prediction (Meuwissen et al. 2001) has paved the way to accelerate hybrid breeding (Zhao et al. 2014, 2015a, b). Experimental findings in wheat populations showed that accuracies of hybrid prediction are encouraging for grain yield (Zhao et al. 2013, 2015a), disease resistances (Miedaner et al. 2013; Gowda et al. 2014), and quality traits (Liu et al. 2016). Nevertheless, cycle lengths of genomics-aided hybrid wheat breeding are still longer lasting compared to line breeding (Longin et al. 2014).

Gaynor et al. (2017) proposed for inbred lines a two-part strategy by splitting the breeding progress into a recurrent genomic selection and a product development component. The population improvement relies on rapid recurrent genome-wide mass selection in a population of heterozygous genotypes and results in a fast increase in the mean value of the population. Advanced seeds from selected heterozygous plants enter the product development to identify superior potential pure line varieties. The product development corresponds to classical pure line breeding schemes including genome-wide predictions. Genome-wide prediction models are updated using the phenotypic and genomic data generated in the course of the product developing. Performing computer simulations and assuming a restricted budget Gaynor et al. (2017) showed that long-term genetic gain from the two-part strategy increased by a factor of 1.31 times compared with the best performing standard genomic selection strategy. The authors anticipated that completing one cycle of recurrent genomic selection was accomplished within half a year, which could be reduced dramatically for spring wheat by applying speed breeding (Watson et al. 2018) enhancing selection gain.

Due to the increased genetic gain, recurrent genomic selection is not only for intra-population but in particular also for inter-population improvement of interest (Kinghorn et al. 2010; Cros et al. 2015) and may boost long-term selection gain in hybrid wheat breeding. Recurrent genomic selection for inter-population improvement is denoted as reciprocal recurrent genomic selection and aims to increase the hybrid performance of two populations. Owing to its potential, empirical studies on the possibilities of reciprocal recurrent genomic selection are underway, such as in the frame of a comprehensive German public–private hybrid breeding initiative called "Zuchtwert." This stimulated us to review the quantitative genetic theory underlying reciprocal recurrent genomic selection. We introduce the basis of recurrent genomic selection for inbred line breeding programs and discuss the potential and limits of this new breeding strategy in intra-population improvement. Afterward, we summarize principles underlying reciprocal recurrent genomic selection of a hybrid population and highlight future research needs.

Definition of breeding values in recurrent genomic selection for breeding pure lines

A genotype passes only gametes from one to the next generation because of recombination during meiosis. This is considered in the concept of breeding values, which allows measuring the potential contribution of a genotype to the performance of the next generation when crossed with a random sample of genotypes of the population under consideration (Falconer and Mackay 1996). The breeding value reflects the additive component of the genetic effect that can be exploited in a recurrent manner, and is therefore relevant for recurrent genomic selection.

The breeding value in the context of pure line breeding operating at a fully homozygous level depends on the allele frequencies of the population under consideration and on the additive (a) effects of all quantitative trait loci (QTL) underlying the trait. Please note that the dominance (d) effects cancel out if the population comprises individuals with an inbreeding coefficient of one (Wricke and Weber 1986). Consider the one-locus case with two alleles B and b occurring with frequency p and $1-p$, then the average effect of allele B and b is $(1-p)a$ and $-pa$, respectively, and the breeding value of a genotype is then the sum of the average effect of its two alleles. For a population in linkage equilibrium, the breeding values of single loci are summed up yielding the breeding value of a genotype. The breeding value weighs the additive effects with the allele frequencies, and thus, favorable rare alleles are given more value in recurrent genomic selection.

Estimating the breeding values in recurrent genomic selection

Additive effects of relevant QTL are often not known but can be estimated applying genome-wide prediction (Meuwissen et al. 2001). One popular approach for estimating marker effects is ridge regression best linear unbiased prediction, but a plethora of further models has been proposed (Desta and Ortiz 2014). Design matrices for the marker effects can be implemented applying the F_∞ metric (Falconer and Mackay 1996) in order to predict not only additive but also non-additive effects such as additive-by-additive epistasis. For recurrent genomic selection, additive effects are used in

conjunction with the allele frequencies to estimate the breeding values and to select superior parents for the next cycle of selection. In contrast, the aim in product development is to identify individuals with high genotypic values including additive and non-additive effects. Experimental studies revealed that non-additive effects play a role in wheat grain yield (He et al. 2017; Jiang et al. 2018) and should therefore be included in the genome-wide prediction models (Jiang and Reif 2015) in order to identify superior varieties.

Persistency of prediction accuracy in recurrent genomic selection

The potential of recurrent genomic selection for long-term population improvement has been investigated so far exclusively based on computer simulations (Muir 2007; Jannink 2010; Yabe et al. 2016; Gaynor et al. 2017; Müller et al. 2017, 2018; Gorjanc et al. 2018). The studies focused on closed populations, simulated mostly additive gene actions while ignoring epistasis, assumed constant and often-known marker effects, analyzed the persistency of prediction accuracies, and determined the long-term genetic gain. In a nutshell, the simulation studies revealed that the persistency of the prediction accuracy depends on: (1) Effective size and extent of linkage disequilibrium of the ancestral population from which genotypes were sampled for recurrent genomic selection (Schopp et al. 2017); (2) the size of the training population used to (re)calibrate the genome-wide prediction model (Meuwissen 2009) and its relationship to the test set (Müller et al. 2017); (3) the number of parents sampled to initiate the recurrent genomic selection program (Müller et al. 2017); (4) the marker density (Schopp et al. 2017), and (5) the statistical model used to estimate the marker effects (de los Campos et al. de los Campos et al. 2013; Schulthess et al. 2017; Varona et al. 2018). The above-mentioned factors are interacting and determine wether the prediction accuracies are driven by linkage between QTL and SNPs in the base population (Meuwissen et al. 2001), cosegregation between QTL and SNPs due to sample linkage disequilibrium (Habier et al. 2007; Schopp et al. 2017), or pedigree relationships (Habier et al. 2007).

Gaynor et al. (2017) simulated a scenario that reflects an integrated approach of recurrent genomic selection and variety development. The benefit of this integrated approach is an economic strategy to update the genome-wide prediction model during product development. Prediction accuracy converged for a complex trait toward 0.2 (Gaynor et al. 2017). This value is lower compared to accuracies observed for grain yield in wheat within one cycle, which mostly ranged between 0.50 and 0.60 (Heslot et al. 2012; Nakaya and Isobe 2012; Isidro et al. 2015; He et al. 2016). In contrast, the reported prediction accuracy of 0.2 (Gaynor et al. 2017) was comparable to estimates in the case of unrelated training and test populations of wheat hybrids, which was observed within one cycle of selection (Zhao et al. 2015a). Hence, experimental studies are needed to validate ultimately the level and persistency of the prediction accuracies in recurrent genomic selection.

Strategies to maintain the genetic variance in recurrent genomic selection

Maintaining the genetic variance of the population has a strong impact on the long-term genetic gain. Selection that is entirely based on the genomic estimated breeding values causes an erosion of the genetic variance as revealed by simulation studies (Jannink 2010). Consequently, modified selection criteria have been proposed to preserve the genetic variance in long-term recurrent genomic selection programs (Fig. 1). Goddard (2009) suggested to weigh the allele substitution effects with the frequencies of the favorable alleles, so that beneficial rare alleles are preferred, which increased long-term selection gain (Jannink 2010). A further option is to select parents not on their (weighted) estimated genomic breeding value but on their optimal haploid (Daetwyler et al. 2015) or expected maximum haploid breeding value (Müller et al. 2018). Both criteria search for a compromise between the candidate's genomic estimated breeding value and its segregating variance when the genotype is selfed (Müller et al. 2018). In contrast to the optimal haploid value, the expected maximum haploid breeding value assumes finite population sizes and takes the difficulties to combine favorable haplotypes due to a restricted number of recombination events into account (Müller et al. 2018). Goiffon et al. (2017) generalized the optimal haploid value and introduced the optimal population value selection. In optimal population value selection, a group of genotypes is searched that maximizes the selection limit defined by favorable haplotype blocks segregating in this selected subpopulation possessing a predefined size. In contrast, genotype building selection aims to identify a minimal subpopulation, for which all favorable haplotype block alleles are segregating (Kemper et al. 2012).

Alternative concepts developed in the context of animal breeding are optimal contribution selection (Meuwissen 1997), its extension genomic optimal contribution selection (Sonesson et al. 2012), and optimal cross-selection (Kinghorn 2011). Here, genetic gain is balanced versus the need to maintain genetic diversity (Woolliams et al. 2015). This can be accomplished, for example, by maximizing genetic gain at a predefined rate of population inbreeding (Meuwissen 1997) or by maximizing a weighted index that balances genetic gain

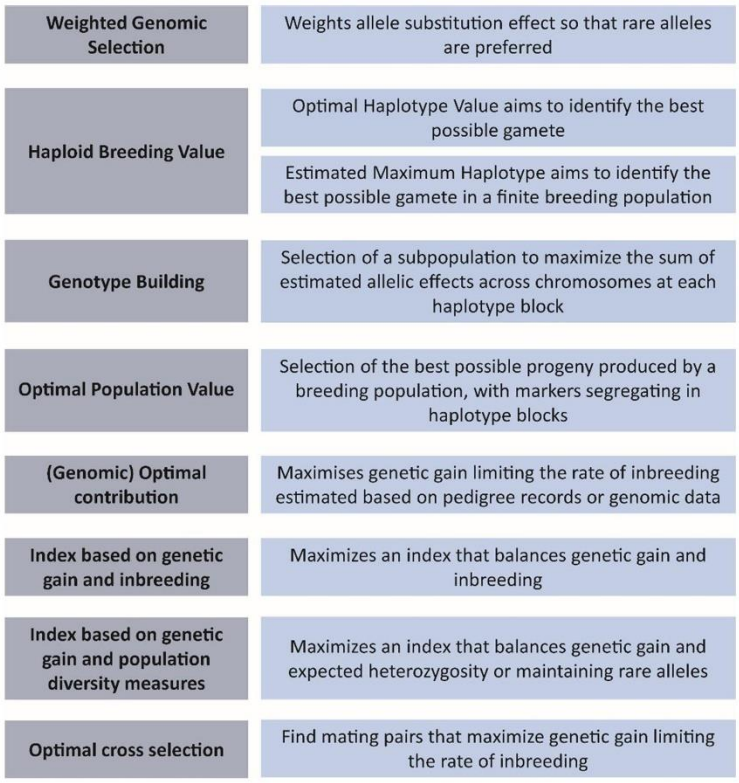

Fig. 1 Schematic overview of selection criteria proposed for recurrent genomic selection

versus inbreeding (Carvalheiro et al. 2010), expected heterozygosity (de Beukelaer et al. 2017), or maintaining rare alleles (de Beukelaer et al. 2017).

No simulation study exists, which compares all suggested selection criteria under relevant scenarios. Nevertheless, taking findings of individual comparisons together (Jannink 2010; Daetwyler et al. 2015; Goiffon et al. 2017; Müller et al. 2018; de Beukelaer et al. 2017; Gorjanc et al. 2018; Akdemir and Sánchez 2016) suggests that the proposed modified criteria boost long-term but sometimes reduce short-term genetic gain in the first selection cycles (Müller et al. 2018). Further extensive simulation studies are needed to guide a proper choice of selection criteria in recurrent genomic selection programs. Moreover, it is of interest to consider scenarios that also take the introgression of novel variation into account, which is in contrast to animal breeding common in plant breeding programs.

Targeted introgression of novel variation in recurrent genomic selection programs is difficult

Wheat breeders make use of the breeders' right and utilize released elite varieties, exotic elite material, and in rare cases also genetic resources as parents for their crossing programs. Consequently, selection gain of competitors is exploited and breeding profits from a diverse population. For recurrent selection, the challenge is how to manage the introgression of novel lines into the else closed breeding population. In wheat breeding, information is available only on the per se performance of novel inbred lines but not on their breeding values. Reliable estimates of the breeding values profit from using the novel lines intensively in breeding programs before integrating them in the recurrent selection programs, which would allow taking

the performance of derived progenies into account. Alternatively, genomic best linear unbiased prediction (VanRaden 2008) and its extension to epistasis (Jiang and Reif 2015) can be used to decompose the genetic value into the breeding value and epistatic components based on the per se performance of the novel inbred lines. Nevertheless, the precision of the estimate of the breeding value for genotypes not embedded in the closed population can be quite low in wheat (Zhao et al. 2015a) and epistasis seems to be relevant (He et al. 2017) hampering their targeted introgression in recurrent genomic selection programs.

Multi-trait recurrent genomic selection profits from multi-stage selection

Recurrent selection can target grain yield or be expanded to consider an index of relevant traits (Moll 1994). This works fine for polygenic traits such as *Fusarium* head blight resistance (Yang et al. 2000). Mono- and oligogenic traits can be improved by genomic or marker-assisted selection (Dekkers 2007) or by combining both approaches (Zhao et al. 2014; Bernardo 2014). An efficient combined recurrent genomic and marker-assisted selection most likely entails multi-stage selection. In the first step, marker-assisted selection is economically beneficial to screen large populations for instance for disease resistances based on a limited set of diagnostic markers. In the second step, genomic selection based on genome-wide markers can target complex traits. The logistic required for implementing such a two-step marker-assisted and genomic selection in a short time interval before flowering is challenging in wheat. A further problem is the temporal dynamics of the effects of diagnostic markers for disease resistances, which can breakdown in the case of mono- or oligogenic mode of inheritance. A promising solution to face these temporal dynamics is high-throughput precision phenotyping screens based on detached leaf assays, which allow assessing the disease resistance for single plants using steadily updated pathogen populations (Douchkov et al. 2014). Further research is required to refine high-throughput precision phenotyping screens for recurrent genomic selection, which is an attractive field of coordinated international activities.

Definition of breeding values in reciprocal recurrent genomic selection for breeding hybrids

Schnell (1965) defined the breeding values for a hybrid population. Here, the allele frequencies in both heterotic groups f (p_f and q_f) and m (p_m and q_m) have to be considered. We first define the effect α_m as $a+(q_m-p_m)d$. The breeding values of the three female genotypes F_{BB}, F_{Bb}, and F_{bb} are then: $F_{BB}=2q_f\ \alpha_m$, $F_{Bb}=(q_f-p_f)\ \alpha_m$, and $F_{bb}=-2p_f\ \alpha_m$. The breeding values of the three male genotypes M_{BB}, M_{Bb}, and M_{bb} are: $M_{BB}=2q_m\ \alpha_f$, $M_{Bb}=(q_m-p_m)\ \alpha_f$, and $M_{bb}=-2\ p_m\ \alpha_f$ with $\alpha_f=a+(q_f-p_f)d$.

We illustrated the interpretation of breeding values for a hybrid population in numerical examples with varying degrees of dominance, i.e., $k=d/a$, and allele frequencies focusing on the breeding values of the female genotypes (Fig. 2). In "Appendix" section, a detailed mathematical derivation of the interpretation of breeding values for different degrees of dominance can be found. Briefly, for $0<k\leq 1$, the breeding values represent an excellent framework to find a compromise between a and d effects and the allele frequencies in the male and female heterotic group. The breeding value of the favorable genotype F_{BB} is increasing with decreasing frequency of the favorable allele in the female pool, which is more pronounced with increasing degree of dominance. Moreover, F_{BB} is higher when the favorable allele occurs with low frequency in the male heterotic group. The selection will fix the favorable allele in both heterotic groups ("Appendix" section, Situation A). For $k>1$, the selection directions are elusive but will eventually lead to the desirable situation, i.e., a fixation of different alleles in the two heterotic groups. Nevertheless, in the case that the frequencies of the favorable allele in both heterotic groups (p_m and p_f) are above or below the threshold $(k+1)/2k$, the selection goal is reached with a delay. The reason is that the selection will start from simultaneous increasing or decreasing the frequencies of the favorable allele in both heterotic groups until one of them passes the threshold. Then, the selection direction will be reversed in one heterotic group and finally fixes different alleles in the two groups ("Appendix" section, Situation B).

Negative dominance effects have been reported for the selfing model species *Arabidopsis thaliana* (Reif et al. 2009; Oakley et al. 2015) and were therefore considered in the following. For $k<0$, selection should aim to avoid genotypes that carry the unfavorable allele. This desirable selection direction can be achieved from the breeding values for loci with $-1\leq k<0$ ("Appendix" section, Situation C). However, for loci with $k<-1$, the selection direction is complicated. Only when the frequency of the favorable allele in both heterotic groups (p_m and p_f) is above the threshold $(k+1)/2k$, the selection guarantees to fix the favorable allele in both heterotic groups. In contrast, when both p_m and p_f are below the threshold, the selection will fix the unfavorable allele in both heterotic groups, which is not desired. In case that the threshold $(k+1)/2k$ lies in between p_m and p_f, the selection will eventually lead to one of the two aforementioned cases, depending on the initial values of p_m, p_f and the selection intensity ("Appendix" section, Situation D).

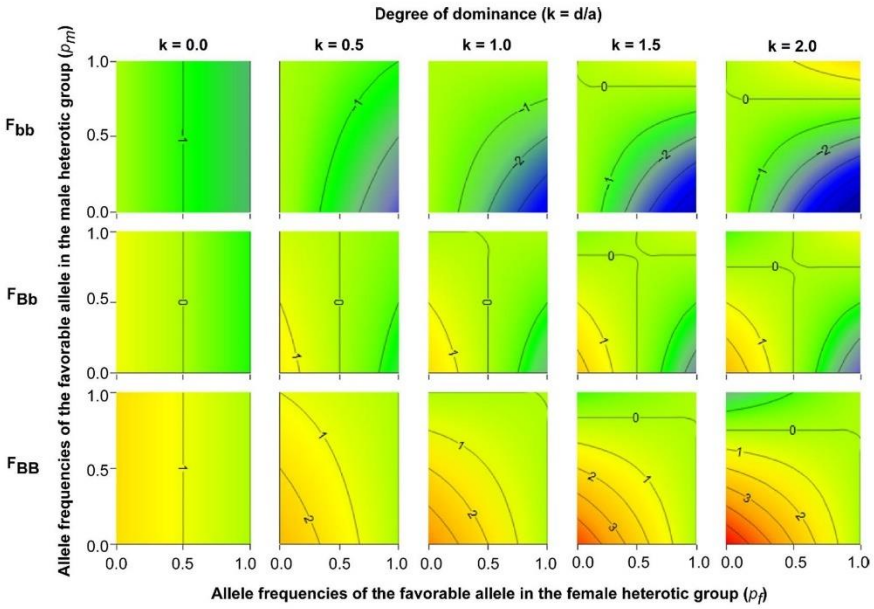

Fig. 2 Breeding values of the three genotypes of female lines (F_{BB}, F_{Bb}, and F_{bb}) as a function of the degree of dominance (we set the additive $a = 1$ and varied the dominance effect d) and the allele frequency of the favorable allele B in the male and female pool for inter-population improvement

Summarizing, the concept of breeding values in hybrid populations as defined by Schnell (1965) provides a framework to combine information on the a and d effects as well as on the allele frequencies of both heterotic groups under the assumption of partial and complete dominance. Additional weighing of the allele substitution effects with the frequencies of the favorable alleles in the vein of the suggestions of (Goddard 2009) represents an approach to increase long-term selection gain. For positive or negative overdominance, selection theory has to be revised in order to optimize reciprocal recurrent genomic selection programs. Moreover, alternative selection criteria have to be developed, which facilitate to prevent an erosion of the genetic variance in the course of the reciprocal recurrent selection. The strategies proposed in the context of intra-population improvement (Jannink 2010; Daetwyler et al. 2015; Goiffon et al. 2017; Müller et al. 2018) represent entry points to tackle this challenge.

Persistency of the prediction accuracy in reciprocal recurrent genomic selection

To our knowledge, no study has been published so far investigating the persistency of the prediction accuracy in the reciprocal recurrent genomic selection considering additive and dominance effects. Nevertheless, if the allele frequencies of the opposite heterotic group remain unchanged, reciprocal recurrent genomic selection behaves like a model with purely additive gene action assuming the absence of epistasis. In this case, results of simulation studies performed for recurrent genomic selection presented above are also relevant for the reciprocal recurrent genomic selection. The assumption of constant allele frequencies of the opposite heterotic group, however, is not reflecting the relevant situation for long-term inter-population improvement.

To gain first insights into the persistency of the prediction accuracy considering additive and dominance effects, we performed a simulation study building upon the genetic makeup of a comprehensive hybrid wheat population (Zhao et al. 2015a). We assumed the absence of epistasis and generated phenotypic data (Y) for the 15 male and 120 female lines and their 1604 single-cross hybrids simulating additive and dominance effects of the 17,372 SNPs, which have been observed in the panel of 135 parental lines, applying the following model:

$$Y = \mu + G_\alpha + G_\delta + e,$$

where μ is the population mean, G_α are the breeding values, G_δ are the dominance deviations, and e are the remaining errors. Please note that the female and male lines do not belong to two divergent populations (Zhao et al. 2015a), and hence, $\alpha = \alpha_f = \alpha_m$. This assumption can be relaxed, and marker effects can be modeled as specific for each parental population (Technow et al. 2012). The prediction accuracies, however, are only marginally affected (Technow et al. 2012), but the genome-wide prediction model is more appropriated for initiating reciprocal recurrent genomic selection in the case of divergent subpopulations. The variance of the breeding value was defined in our simulation study as $\sigma_\alpha^2 = \mathrm{var}(G_\alpha)$, and the variance of dominance deviations is $\sigma_\delta^2 = \mathrm{var}(G_\delta)$. The additive and dominance effects were independently sampled from normal distributions. We simulated directional dominance reflecting 10% of midparent heterosis as observed for grain yield in wheat (Zhao et al. 2015a). We varied the ratio of $\frac{\sigma_\delta^2}{\sigma_\alpha^2}$ from 0.05 to 1, with intervals of 0.05 and set the error variance to $\sigma_e^2 = \sigma_\alpha^2 + \sigma_\delta^2$, which resulted in a broad-sense heritability of 0.5. For each simulation run, the accuracy of genomic best linear unbiased prediction exploiting α and δ effects [for details on the implementation, see Zhao et al. (2015a)] was assessed as the correlation between the predicted breeding values, dominance deviations, and hybrid performance and the corresponding true values using a chessboard-like validation. The chessboard-like validation was performed as follows: The training sets comprised a random selection of 80 out of 120 female and 10 out of 15 male parental inbred lines as well as 610 hybrids derived from them. From the remaining hybrids, three test sets were formed. Test sets included only hybrids not assigned so far that had both parents ($T2$), one female ($T1A$) or male parent ($T1B$) or no parent ($T0$) in

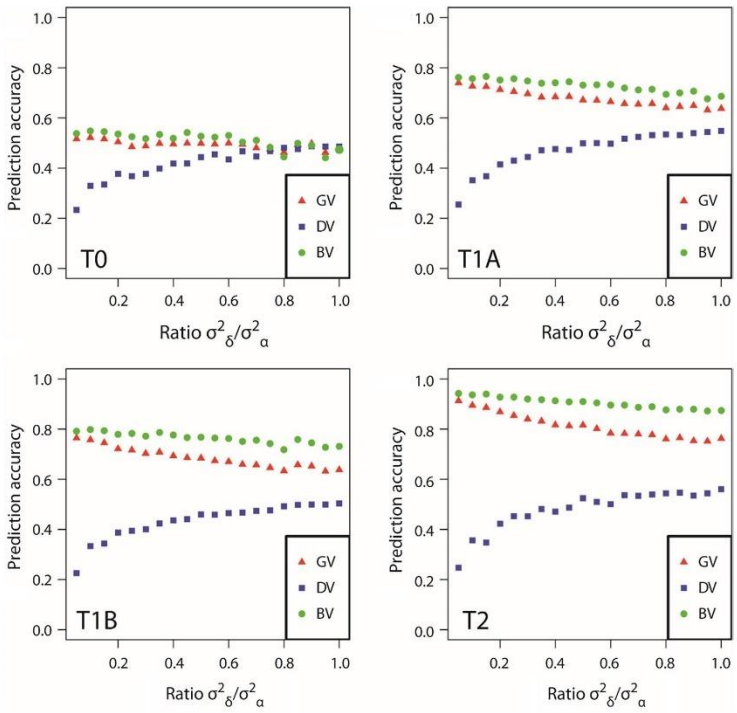

Fig. 3 Prediction accuracies for hybrids obtained using genomic best linear unbiased prediction for different ratios of variance due to dominance deviations and breeding values ($\sigma_\delta^2/\sigma_\alpha^2$). The training sets comprised a random selection of 80 out of 120 female and 10 out of 15 male parental inbred lines as well as 610 hybrids derived from them. From the remaining hybrids, test sets with three successively decreasing degrees of relatedness to the training set were formed. Test sets included only hybrids not assigned so far that had both parents ($T2$), one female ($T1A$) or male parent ($T1B$) or no parent ($T0$) in common with the hybrids in the corresponding training set. The genetic variance (GV) is indicated as red triangles, the variance of the dominance deviations (DV) is indicated as blue squares, and the variance of the breeding values (BV) is indicated as green dots (color figure online)

common with the hybrids in the corresponding training set. For each ratio of $\frac{\sigma_\delta^2}{\sigma_\alpha^2}$, the simulation was repeated 50 times.

The factorial mating design used to generate the mapping population resulted in higher degrees of freedom for G_δ than G_α (Hallauer et al. 2010). Prediction accuracies of G_δ were lower than for G_α for the full range of $\frac{\sigma_\delta^2}{\sigma_\alpha^2}$ when inspecting the related test sets *T*1*A*, *T*1*B*, and *T*2 (Fig. 3). For the unrelated *T*0 scenario, which is the most relevant for the persistency on a long term, prediction accuracy of G_δ is only comparable to G_α for a ratio of $\frac{\sigma_\delta^2}{\sigma_\alpha^2}$ approaching one but else lower. Experimental studies in wheat reported ratios of $\frac{\sigma_\delta^2}{\sigma_\alpha^2}$ in the range of 0.25 (Longin et al. 2013). Consequently, predicting δ versus α effects is less precise, which very likely hampers the development of complementary heterotic groups through reciprocal recurrent genomic selection. Nevertheless, further extensive computer simulations are needed to study this in more detail.

Increasing the competiveness of hybrid versus line breeding with the use of a two-part selection strategy based on reciprocal recurrent genomic selection

A larger long-term selection gain is crucial for the effectiveness of hybrid versus line breeding. The long-term selection gain is a function of the selection intensity, and the additive genetic variance exploited and the heritability (Cochran (1951). Longin et al. (2014) observed that line breeding outperformed hybrid breeding on a long term for scenarios with a restricted budget. Assuming the absence of epistasis and dominance, the superiority is mainly driven by the fact that line breeding makes use of up to twice as much additive genetic variance than hybrid breeding (Longin et al. 2012; Gowda et al. 2012). As outlined above, long-term selection gain in pure line breeding can be increased even by the two-part selection strategy (Gaynor et al. (2017). The benefit results from the rapid cycles in the population improvement component, which causes a faster increase in the population mean compared to the conventional pure line breeding schemes applying genomic selection. Interestingly, the selection gain is enhanced in the population improvement component although only half of the genetic variance (inbreeding coefficient is 0 instead of 1) is exploited compared to conventional pure line breeding. Consequently, it is very likely that the selection gain of a two-part selection strategy is comparable for hybrid and line breeding because both strategies make use of a similar amount of additive genetic variance. Considering that hybrid wheat breeding profits from an additional 10% of midparent heterosis suggests that a two-part hybrid breeding program based on reciprocal recurrent genomic selection is competitive compared to line breeding (Fig. 4). The above considerations rely on the assumption that the persistency of the prediction accuracies is similar for inter- and intra-population recurrent genomic selection. To the current knowledge, this scenario is likely but further research is essential to support this theory. Summarizing, current findings of simulation studies and quantitative genetic consideration suggest that the competiveness

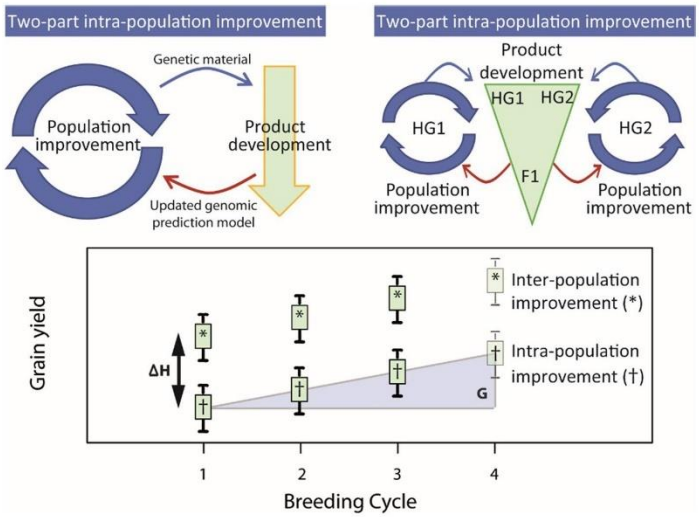

Fig. 4 Schematic representation of the two-part inter- and intra-population improvement. Germplasm in inter-population improvement is split in heterotic group 1 (HG1) and heterotic group 2 (HG2) and profits from the heterosis effect (ΔH). Both, inter- and intra-populations improvement breeding benefits from a recurrent selection genetic gain (G), which results from the population improvement. Genetic material is transferred from the population improvement component to the product development component (red arrow). Updated models from the product development component can be used in population improvement component (blue arrow) (color figure online)

of hybrid versus line breeding can be increased through the implementation of a two-part selection strategy based on reciprocal recurrent genomic selection.

Author contribution statement MR, YZ, YJ, and JCR conceived and designed the study. YZ performed the simulation study. MR and JCR wrote the manuscript. YZ and YJ helped to improve the manuscript. All authors agree with the current statement.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical statement All experiments were performed under the current laws of Germany.

Appendix

In reciprocal recurrent genomic selection, the aim is to develop complementary heterotic groups yielding high hybrid performance. The degree of dominance, i.e., $k=d/a$ with d referring to the dominance and a to the additive effects, at each single locus plays a crucial role to select for complementarity. In order to exploit successfully the dominance effects in hybrid breeding, selection directions have to be chosen carefully. For positive overdominance, the favorable allele should be fixed in one heterotic group but eliminated in the other. In contrast, in the presence of negative or partial dominance, heterozygous genotypes are disadvantageous compared to the homozygous genotypes. Therefore, the aim should be to fix the favorable allele in both heterotic groups so that the hybrid offspring is homozygous at the locus of interest.

Schnell (1965) introduced a concept of breeding value for hybrid populations. Let us denote the favorable allele B and the unfavorable allele B. Assume a male (m) and female heterotic group (f). Following Schnell (1965), the breeding values of genotypes that are homozygous for the favorable allele (BB) are defined for the male and the female heterotic group as:

$$\begin{cases} F_{BB} = 2q_f\alpha_m \\ M_{BB} = 2q_m\alpha_f \end{cases} \quad \text{with} \quad \begin{cases} \alpha_m = a + d(q_m - p_m) \\ \alpha_f = a + d(q_f - p_f) \end{cases}.$$

F_{BB} and M_{BB} refer to the breeding values for the genotypes in the female and the male heterotic group, respectively, carrying the favorable allele. The frequency of the favorable allele B is denoted as p, and the frequency of the unfavorable allele b is denoted as q. The subscripts m and f identify allele frequencies of the male and female heterotic group, respectively. The question arises whether the concept of Schnell (1965) is suited for long-term reciprocal recurrent genomic selection. In the following, we studied the direction of selection for different k in dependency on the allele frequencies in the two heterotic groups. We assume that the initial allele frequencies q_f and q_m are nonzero, i.e., the favorable allele has not been fixed in either of the two heterotic groups. We further assume that $k\neq 0$, otherwise the breeding value is purely contributed by a, and the favorable allele will be fixed through selection in both heterotic groups just like in line breeding.

Situation A $0<k\leq 1$.
Suppose $F_{BB}<0$, then we have $\alpha_m<0$, which is equivalent to $p_m > \frac{k+1}{2k}$. But, $\frac{k+1}{2k} \geq 1$ since $0<k\leq 1$. This implies $p_m > 1$, which is impossible. The same arguments hold true when supposing $M_{BB} < 0$. Thus, F_{BB} and M_{BB} will always be positive. So in this situation the selection will eventually fix the favorable allele in both heterotic groups, which is desirable.

Situation B $k > 1$
There are four possible combinations of positive and negative F_{BB} and M_{BB}:

Situation B1 $F_{BB}<0$ and $M_{BB}<0$
This means $p_m > \frac{k+1}{2k}$, and $p_f > \frac{k+1}{2k}$. Since $F_{BB}<0$, the selection will aim to decrease the frequency of genotypes that are homozygous for the allele of interest, and thus decrease p_f. In parallel, as $M_{BB}<0$, the selection will aim to decrease p_m. Thus, in both heterotic groups the frequencies of the allele of interest will be decreased until one of them goes below the threshold $\frac{k+1}{2k}$. Then, it changes to Situation B2 or B3, depending on the allele frequency p of which heterotic groups decrease below the threshold first.

(i) **Situation B2**, $F_{BB}<0$ and $M_{BB}>0$
This means $p_m > \frac{k+1}{2k}$, and $p_f < \frac{k+1}{2k}$. Since $F_{BB}<0$, the selection will aim to decrease the frequency of genotypes that are homozygous for the allele of interest, and thus decrease p_f. Because $p_f < \frac{k+1}{2k}$, a decrease in p_f will not change the sign of M_{BB}. Thus, we still have $M_{BB}>0$, implying that the selection in the male group will further increase p_m. As $p_m > \frac{k+1}{2k}$, the sign of F_{BB} will also stay negative. Hence, M_{BB} will always favor genotypes carrying two alleles of interest, while F_{BB} will constantly discriminate against these very genotypes. This process finally leads to $p_m = 1$, and $p_f=0$. This is a desirable con-

stellation that allows to produce hybrid offspring that is heterozygous for the allele of interest.

(ii) **Situation B3**, $F_{BB} > 0$ and $M_{BB} < 0$
This means $p_m < \frac{k+1}{2k}$, and $p_f > \frac{k+1}{2k}$. Since $F_{BB} > 0$, the selection will increase the frequency of genotypes that are homozygous for the allele of interest. Because $p_f > \frac{k+1}{2k}$, the breeding value of these very genotypes will stay negative in the male heterotic group. Then, the selection in the male group will further decrease p_m, implying that F_{BB} will stay positive. Eventually, this process leads to $p_f = 1$, and $p_m = 0$. This is a desirable constellation that allows to produce hybrid offspring that is heterozygous for the allele of interest.

(iii) **Situation B4**, $F_{BB} > 0$ and $M_{BB} > 0$
This means $p_m < \frac{k+1}{2k}$, and $p_f < \frac{k+1}{2k}$. Since $F_{BB} > 0$ and $M_{BB} > 0$, the selection will aim to increase the frequency of genotypes that are homozygous for the allele of interest in both heterotic groups. As soon as the frequency of these very genotypes goes above the threshold of $\frac{k+1}{2k}$ in one heterotic group, the sign of the breeding value in the opposite heterotic group will change the sign, and thus, the selection direction will be reversed here, leading back to Situation B2 or Situation B3 and the allele of interest will be fixed in one heterotic group and eliminated in the other. Finally, both heterotic groups are in a complementary genetical constitution.

Situation C $-1 \leq k < 0$

Suppose $F_{BB} < 0$, which is equivalent to $p_m < \frac{k+1}{2k}$. Since $-1 \leq k < 0$, we have $\frac{k+1}{2k} \leq 0$. This implies $p_m < 0$, which is impossible. The same arguments hold true if we suppose $M_{BB} < 0$. Thus, F_{BB} and M_{BB} will always be positive. So as in Situation A, the selection will eventually fix the favorable allele in both heterotic groups.

Situation D $k < -1$
There are four possible combinations of positive and negative F_{BB} and M_{BB}:

Situation D1 $F_{BB} < 0$ and $M_{BB} < 0$
This means $p_m < \frac{k+1}{2k}$, and $p_f < \frac{k+1}{2k}$. Since $F_{BB} < 0$, the selection will aim to decrease the frequency p_f of the favorable allele B. In parallel, as $M_{BB} < 0$, the selection will aim to decrease p_m. Both, p_m and p_f will eventually reach zero. This is problematic because the favorable allele will be eliminated, while the unfavorable allele will be fixed in both heterotic groups.

Situation D2 $F_{BB} < 0$ and $M_{BB} > 0$
This means $p_m < \frac{k+1}{2k}$, and $p_f > \frac{k+1}{2k}$. Since $F_{BB} < 0$, the selection will aim to decrease the frequency of the genotypes carrying the favorable allele in the female heterotic pool, and thus decrease p_f. Here, the selection intensity heavily influences how the selection directions behave. When $p_f \gg \frac{k+1}{2k}$, and low selection intensity is applied, a small decrease in p_f will not change the sign of M_{BB}. This leads to an increase in p_m and eventually F_{BB} will change the sign, which leads to Situation D4. If the selection intensity is large enough, then $p_f < \frac{k+1}{2k}$. As a consequence, M_{BB} will change the sign, e.g., $M_{BB} < 0$, which leads back to Situation D1.

Situation D3 $F_{BB} > 0$ and $M_{BB} < 0$
This means $p_m > \frac{k+1}{2k}$, and $p_f < \frac{k+1}{2k}$. Since $F_{BB} < 0$, the selection will aim to increase the frequency of the genotype carrying the favorable allele in the female heterotic pool, and thus increase p_f. If $p_f \approx \frac{k+1}{2k}$, the increase in p_f can eventually lead to $p_f > \frac{k+1}{2k}$ and finally to a positive breeding value of genotypes carrying favorable allele in the male heterotic group, e.g., $M_{BB} > 0$. This will lead to Situation D4. If $p_f \ll \frac{k+1}{2k}$, a small increase in p_f may not change the sign of M_{BB}. As long as M_{BB} is smaller than zero, p_m will be decreased. If selection intensity in the male heterotic pool is higher enough, then p_m decrease below the threshold before M_{BB} change its sign, F_{BB} will change to negative, which leads back to Situation D1.

Situation D4 $F_{BB} > 0$ and $M_{BB} > 0$
This means $p_m > \frac{k+1}{2k}$, and $p_f > \frac{k+1}{2k}$. Since $F_{BB} > 0$ and $M_{BB} > 0$, the selection will aim to increase the frequency of the genotype carrying the favorable allele in both populations, until $p_m = 1$ and $p_f = 1$. This is the ideal constitution of heterotic groups in the presence of negative overdominance as it leads to hybrids that are homozygous for the beneficial allele.

As a final remark, note that in the above discussion we have assumed that the selection is first applied to the female group and then to the male group. Assuming the opposite (that the selection is first applied to males and then to females) will lead to similar results. However, if the selection is applied simultaneously to both groups, the conclusions are slightly different. More precisely, in Situation B1 and B4, there is an additional case that p_m and p_f could simultaneously change from above to below the threshold $\frac{k+1}{2k}$ and back and forth. Similarly, in Situations D2 and D3, there is an additional case that the frequencies change from $p_m > \frac{k+1}{2k}$, $p_f < \frac{k+1}{2k}$ to $p_m < \frac{k+1}{2k}$, $p_f > \frac{k+1}{2k}$ and back and forth. These additional cases are undesirable as the selection goal will be either delayed, or even can never be achieved.

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2.2 Reciprocal recurrent genomic selection is impacted by genotype-by-environment interactions

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Abstract

Reciprocal recurrent genomic selection is a breeding strategy aimed at improving the hybrid performance of two base populations. It promises to significantly advance hybrid breeding in wheat. Against this backdrop, the main objective of this study was to empirically investigate the potential and limitations of reciprocal recurrent genomic selection. Genome-wide predictive equations were developed using genomic and phenotypic data from a comprehensive population of 1,604 single crosses between 120 female and 15 male wheat lines. Twenty superior female lines were selected for initiation of the reciprocal recurrent genomic selection program. Focusing on the female pool, one cycle was performed with genomic selection steps at the F_2 (60 out of 629 plants) and the F_5 stage (49 out of 382 plants). Selection gain for grain yield was evaluated at six locations. Analyses of the phenotypic data showed pronounced genotype-by-environment interactions with two environments that formed an outgroup compared to the environments used for the genome-wide prediction equations. Removing these two environments for further analysis resulted in a selection gain of 1.0 dt ha^{-1} compared to the hybrids of the original 20 parental lines. This underscores the potential of reciprocal recurrent genomic selection to promote hybrid wheat breeding, but also highlights the need to develop robust genome-wide predictive equations.

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Reciprocal Recurrent Genomic Selection Is Impacted by Genotype-by-Environment Interactions

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Reciprocal recurrent genomic selection is a breeding strategy aimed at improving the hybrid performance of two base populations. It promises to significantly advance hybrid breeding in wheat. Against this backdrop, the main objective of this study was to empirically investigate the potential and limitations of reciprocal recurrent genomic selection. Genome-wide predictive equations were developed using genomic and phenotypic data from a comprehensive population of 1,604 single crosses between 120 female and 15 male wheat lines. Twenty superior female lines were selected for initiation of the reciprocal recurrent genomic selection program. Focusing on the female pool, one cycle was performed with genomic selection steps at the F_2 (60 out of 629 plants) and the F_5 stage (49 out of 382 plants). Selection gain for grain yield was evaluated at six locations. Analyses of the phenotypic data showed pronounced genotype-by-environment interactions with two environments that formed an outgroup compared to the environments used for the genome-wide prediction equations. Removing these two environments for further analysis resulted in a selection gain of 1.0 dt ha^{-1} compared to the hybrids of the original 20 parental lines. This underscores the potential of reciprocal recurrent genomic selection to promote hybrid wheat breeding, but also highlights the need to develop robust genome-wide predictive equations.

Keywords: grain yield, hybrid breeding, long-term selection gain, genotype-times-year interaction, abiotic stress

INTRODUCTION

Since the discovery of the advantages of hybrid breeding through increased performances due to the exploitation of heterosis (Shull, 1908), it has proven to be a successful strategy in allogamous species such as maize (Troyer, 1999), sunflower (Reif et al., 2013), sugar beet (Li et al., 2010), and rye (Geiger and Miedaner, 2015). Besides, hybrids display higher yield stabilities (Mühleisen et al., 2014), especially in marginal environments (Hallauer et al., 1988) and facilitate the stacking of major genes (Longin et al., 2012). These advantages stimulated investments in the implementation

of hybrid breeding also in autogamous species, with the main challenge to develop economically competitive varieties that can compete against the line varieties on the market as the autogamous biology makes economic seed production challenging. Therefore, hybrid varieties must outperform significantly line varieties and the yield surplus must compensate for the higher costs in seed production. Recent advances enabled the introduction of hybrid breeding in autogamous species such as barley (Mühleisen et al., 2013), wheat (Melonek et al., 2021), and most successfully rice (Huang et al., 2017) but a major challenge is the selection gain per unit time: Classical hybrid breeding uses heterosis but exploits less additive variance and the breeding schemes are longer compared to line breeding (Longin et al., 2012).

A promising approach to breed high-yielding hybrids is to maximize the exploitation of beneficial heterosis. The concept of reciprocal recurrent selection (RRS) was originally proposed by Comstock et al. (1949) and optimizes the use of general and specific combining ability by selecting genotypes from one population based on the performance of their progeny resulting from crosses with another population. Ideally, this selection strategy results in a reciprocal shift in gene frequencies among the two populations from which female and male genotypes shall derive. Recurrent selection cycles are applied to further manifest this tendency. The success of RRS has been demonstrated in outcrossing species such as maize (Eyherabide and Hallauer, 1991; Tardin et al., 2007; Souza et al., 2010; Kolawole et al., 2018) and sugar beet (Doney and Theurer, 1978; Hecker, 1985). To the authors knowledge, no studies were published that investigate the potentials and limits of RRS in autogamous cereals such as wheat.

A disadvantage of RRS compared to recurrent selection is the elongation of breeding cycles due to the need to produce sufficient progeny based on which genotypes can be rated. In recurrent selection, the implementation of genomic selection has the potential to shorten the length of selection cycles and raise selection gain (Santantonio et al., 2020; Atanda et al., 2021), but empirical studies providing insights into the long-term effect in recurrent genomic selection are still missing. Research in animal breeding has suggested to complement RRS with genomic selection (Kinghorn et al., 2010). In oil palm, simulations have shown that genomic selection could potentially reduce the generation time of an RRS breeding cycle from 20 to 6 years (Cros et al., 2015). Integration of genomic selection into RRS would furthermore allow the combination of RRS and speed breeding approaches as proposed by Watson et al. (2018). Empirical evidence of the superiority of reciprocal recurrent genomic selection (RRGS) breeding programs, however, is still missing.

Many breeding programs are aimed at producing genotypes adapted to so-called mega-environments. Mega-environments are geographic regions that show similar growing conditions limiting the variance of the interaction effects between genotype and environments (Braun et al., 1996). In Germany, breeders generally aim for genotypes that are capable to meet the requirement criteria of the Federal Plant Variety Office (Bundessortenamt, Hannover), to release registered varieties. The Federal Plant Variety Office tests candidate genotypes in its official trials at up to 15 locations representing wheat growing regions in Germany. It is important to note here that Germany is not further subdivided in the Federal Plant Variety Office tests into target mega-environments for wheat breeding.

This study provides the first empirical results on the potential and limits of an RRGS breeding program in wheat targeted for Germany. The objectives were to (1) investigate the utility of genomic selection to identify superior females through genomic estimation of the general combining ability, (2) evaluate the selection gain for grain yield achieved by an RRGS breeding strategy, and (3) examine the impact of genotype-by-environment interaction on the effectiveness of a long-term breeding strategy.

MATERIALS AND METHODS

Design of the Reciprocal Recurrent Genomic Selection Program

We implemented an RRGS program based on genomic and phenotypic data of a large hybrid wheat population (further denoted as HYWHEAT population) presented in detail in previous studies (Longin et al., 2013; Zhao et al., 2013, 2015; Gowda et al., 2014; Liu et al., 2016, 2020a,b; Jiang et al., 2017; Schulthess et al., 2018; Thorwarth et al., 2018, 2019). Briefly, 120 female and 15 male winter wheat lines adapted to Central Europe were crossed using chemical hybridization agents (e.g., Croisor 100; Kempe et al., 2014) applying standard in house protocols. 1,604 single-cross hybrids were produced. The 1,604 hybrids, their 135 parents, and 10 commercial varieties (As de Coeur, Colonia, Genius, Hystar, JB Asano, Julius, Kredo, Tabasco, Tobak, Tuerkis) were evaluated for grain yield in 11 environments, i.e., 5 and 6 locations (Adenstedt, Boehnshausen, Hadmersleben, Harzhof, Hohenheim, and Seligenstadt), in the growing seasons 2011/2012 and 2012/2013, respectively, in Central Europe, resulting in high quality phenotypic data (Supplementary Table 2 in Zhao et al., 2015). The 135 parental lines were genotyped using a 90,000 SNP array based on an Illumina Infinium assay and after quality tests, 17,372 high-quality SNP markers were retained. The phenotypic and the genomic data were combined, and a ridge regression best linear unbiased prediction (RRBLUP) model was trained fitting additive and dominance effects using the package rrBLUP (Endelman, 2011) in the R software environment (R Core Team, 2020). The implementation of the RRBLUP model was described in detail elsewhere (Zhao et al., 2015). Briefly, the model was:

$$Y = 1_n\mu + Z_A a + Z_D d + e, \quad (1)$$

where Y refers to the grain yield data of the 135 parent lines and their 1,604 hybrids, μ was the overall mean, 1_n was an n-dimensional vector of ones, a and Z_A denoted the additive effects and the corresponding design matrix, and d and Z_D denoted the dominance effects and the corresponding design matrix. The estimated a and d effects were used to predict the genotypic values of the hybrid performances when crossed with the 15 male lines.

In the recurrent genomic selection program, we focused on the female pool and selected 20 out of the 120 female lines. The selection was based on the first-year estimates of general

combining abilities and further criteria such as for example being carrier of the dwarfing gene *Rht2*. The 20 female lines formed the C_0 cycle and were crossed following a single round robin design (A x B, B x C, C x D, …, T x A), i.e., every line was used in two crosses resulting in 20 F_1's. The 20 F_1's were grown in the following season and selfed to the F_2 generation in the green house. Seeds were harvested and around 30 F_2 plants were grown for each of the 20 biparental families amounting to a total of 629 F_2 plants. The 629 F_2 plants were genotyped before flowering using the above-mentioned SNP array. The general combining abilities of the 629 F_2 plants when crossed with the 15 original male lines were estimated using the SNP profiles and the above outlined RRBLUP model. The best 3 F_2 plants per family, i.e., 60 F_2 plants in total, were selected and selfed toward the F_5 generation resulting in 2,886 F_5 genotypes. Descendants from each of the 20 initial crosses were represented in this panel with a mean number of genotypes of 144, ranging from 76 to 277. Seeds of the 2,886 F_5 genotypes were grown in single row plots in the season 2016/2017 and a fraction of 382 $F_{5:6}$ families were visually selected based on overall agronomic performance (disease resistance) and considering plant height and flowering time to facilitate hybrid seed production when crossed with three out of the 15 above outlined male lines. The 382 $F_{5:6}$ families were genotyped using the above-mentioned SNP array. The general combining abilities of the 382 $F_{5:6}$ families when crossed with the 15 original male lines were estimated using the SNP profiles and the above outlined RRBLUP model. Based on the estimated general combining ability effects, 50 outstanding $F_{5:6}$ families were selected (denoted as C_1S). All of the 20 biparental F_2 families were represented in this set of families.

As further reference point besides C_0, 60 F_2 plants out of the above outlined 629 F_2 plants of the 20 biparental families were randomly selected. Here, a total of 3 F_2 plants were randomly drawn from each of the 20 biparental families and selfed toward the F_5 generation resulting in 714 F_5 genotypes. Seeds of the 714 F_5 genotypes were multiplied in single row plots in the season 2016/2017. A subfraction of 30 $F_{5:6}$ families were visually selected considering plant height and flowering time to facilitate hybrid seed production when crossed with three out of the above outlined 15 male lines. The subfraction of 30 $F_{5:6}$ families were denoted as C_1R. The 30 genotypes of the C_1R cycle were genotyped using the above-mentioned SNP array. The integrated data set was filtered by excluding markers with more than 5% missing values, resulting in 4,031 unique and polymorphic markers.

Evaluation of the Selection Gain in Field Trials and Phenotypic Data Analyses

The data set comprised 376 genotypes, including 3 male lines previously used to produce the 1,604 original F_1 hybrids, 20 female lines from C_0, 49 female lines (one out of the above mentioned 50 lines were discarded because hybrid seed production failed entirely) from C_1S, 30 female lines from C_1R, 267 F_1 hybrids, and 7 commercial varieties (Julius, Colonia, Tobak, Elixer, RGT Reform, Hystar, and Genius). The hybrids were derived by crossing the 99 female and the 3 male lines using a factorial mating design. For 267 of the potential 297 single-cross hybrids, enough seeds were harvested for intensive field trials.

All 376 genotypes were evaluated in yield plots for grain yield and plant height at 6 locations in the growing season 2018/2019. The locations were Hadmersleben (latitude 51.98 N, longitude 11.30 E), Mintraching (latitude 48.95 N, longitude 12.25 E), Adenstedt (latitude 52.20 N, longitude 10.18 E), Sossmar (latitude 52.2 N, longitude 10.08 E), Wohlde (latitude 52.8 N, longitude 9.98 E), and Boehnshausen (latitude 51.85 N, longitude 10.95) (**Supplementary Table 1**). The same seeding rate of 230 grains per m^2 was used for both parental lines and hybrids. The plot size ranged from 7.2 to 12 m^2. Harvesting was performed mechanically and adjusted to a moisture concentration of 140 g H_2O kg^{-1}. The field design was an alpha lattice with block size 11 where each environment corresponded to one replication. The yield trials were treated with fertilizers, fungicides, and herbicides according to farmers practice for intensive wheat production.

The quality of the outlier-controlled phenotypic data from each environment was assessed by estimating the genomic repeatability employing the package BGLR (Perez and de los Campos, 2014) in the software environment R (R Core Team, 2020). For this purpose, the following genomic prediction model was used for lines:

$$y = 1_n\mu + g + e, \tag{2}$$

where y was the n-dimensional vector of phenotypic records of each environment, 1_n was an n-dimensional vector of ones, u was a common intercept, g was an n-dimensional vector of additive genotypic values and e was the residual term. It was assumed that u was a fixed parameter, $g \sim N(0, G\sigma_g^2)$ and $e \sim N(0, I_n\sigma_e^2)$, where I_n denoted the $n \times n$ identity matrix and G denoted the $n \times n$ genomic relationship matrix among genotypes as proposed by VanRaden (2008). For each environment, a 5-fold cross-validation scheme was implemented. Therefore, the population of tested lines was randomly divided into five subsets of equal size. One subset was predicted after the model was trained based on the phenotypic and genotypic data from the remaining four subsets. The correlation between the observed and predicted values defined the prediction ability. After performing 100 5-fold cross-validations, genomic repeatability was obtained by the mean of the prediction abilities.

For assessing the quality of the outlier-controlled phenotypic data for the hybrids tested in each environment, genomic repeatability was estimated employing the following model using the package BGLR (Perez and de los Campos, 2014) in the software environment R (R Core Team, 2020):

$$y = 1_n\mu + Z_A a + Z_D d + e, \tag{3}$$

where y was the n-dimensional vector of phenotypic records of each environment, $1_n$was an n-dimensional vector of ones, μ was the common intercept, a and Z_A denoted the additive effects and the corresponding design matrix, and d and Z_D denoted the dominance effects and the corresponding design matrix. The cross validation of hybrids was executed in the same manner as described for lines.

After outlier tests, the following model was used to obtain best linear unbiased estimations (BLUEs) across environments:

$$y_{ijk} = \mu + g_i + r_j + b_k + e_{ijk}, \quad (4)$$

where y_{ijk} referred to the phenotypic performance of the *ith* genotype at the *jth* location in the *kth* block, μ referred to the intercept, g_i referred to the genetic effect of the *ith* genotype, r_j referred to the effect of the *jth* location, b_k referred to the *kth* block in the *jth* location and e_{ijk} denoted the residual. Genotype was treated as fixed and the remaining effects as random. Outlier detection test was performed following the method M4r as described by Bernal-Vasquez et al. (2016), where the standardized residuals were used in combination with the Bonferroni-Holm test to identify an outlier. The detected outliers (3 for grain yield) were removed for further analysis. Moreover, we estimated variance components with the following model:

$$y_{imfnk} = \mu + a + l_n + b_{nk} + p_i + g'_f + g''_m + g_{fm} + (g'l)_{fn} + (g''l)_{mn} + (pl)_{in} + e_{mfink}, \quad (5)$$

where y_{ifmnk} referred to the phenotypic performance of the *ith* genotype at the *nth* location in the *kth* block, l_n referred to the *nth* location, b_{nk} referred to the *kth* block at the *nth* location, p_i referred to the effect of the *ith* parental line, g'_f referred to the general combining ability (GCA) effect of the *fth* female line, g''_m referred of the GCA effect of the *mth* male line, g_{fm} referred to the specific combining ability (SCA) effect of the *fmth* genotype, $(g'l)_{fn}$ referred to the interaction effect between the GCA of the *fth* female and the *nth* environment, $(g''l)_{mn}$ referred to the interaction effect between the GCA of the *mth* male and the *nth* environment, $(pl)_{in}$ referred to the interaction effect of the *ith* parental line and the *nth* environment e_{mfink} referred to the residual. Dummy variables were used to distinguish between checks, lines, and hybrids. Based on the variance components, heritability (h^2) was estimated separately for lines and hybrids as $h^2 = \frac{\sigma^2_G}{\sigma^2_G + \frac{\sigma^2_{GxE} + \sigma^2_\varepsilon}{l}}$, where σ^2_G refers to the genetic variance of lines or hybrids, σ^2_{GxE} refers to the genotype-by-environment variance σ^2_e refers to the residual variance, and l denotes the average number of environments in which the genotypes were tested. Linear mixed models have been executed using ASReml version 4.0 (Butler et al., 2017) in the software environment R (R Core Team, 2020).

GCA_{Female}-by-environment interaction effects were estimated by using the same model as in Equation (5) to further characterize the environments in which the genotypes were evaluated. The GCA_{Female}-by-environment interaction effects were estimated for the experiments of the growing season 2018/2019 only and furthermore in a combined data set consisting of the training environments of the growing seasons 2011/2012 and 2012/2013 and the test environments of the growing season 2018/2019. The GCA_{Female}-by-environment interaction effects were used to perform principal component analyses (PCA) and obtain Euclidean distances based on which the environments were clustered in a complete-linkage approach.

The observed response to selection was estimated as $R_{obs} = \hat{S}$, where $\hat{S} = \mu_{sel} - \mu_{pop}$ denoted the observed selection differential, with μ_{sel} being the phenotypic mean of the selected genotypes and μ_{pop} being the mean of the population from which the selected genotypes were drawn. The C_1 hybrids of the underlying RRGS breeding program have been produced using female lines deriving from a population of 629 genotypes. The capacity for all of the 629 genotypes to produce hybrids has not been estimated in field experiments but only through genomic prediction. For this reason, the mean performance of the C_0 hybrids evaluated in the growing season 2018/2019 has been considered as an approximation for μ_{pop}.

The expected response to selection was estimated as $R_{\exp} = i \bullet h \bullet \sigma_A$, where i denoted the intensity of selection, h refers to the square root of the heritability, and σ_A denoted the standard deviation of the breeding values. Selection intensity was calculated as $i(N, G) = i(\alpha) - \frac{G-N}{2N(G+1)i(\alpha)}$, where N was the number of selected genotypes, G was the size of the population from which the selected genotypes were drawn, and $i(\alpha) = i\left(\frac{N}{G}\right)$ referred to the standardized selection differential according to tabulated values (e.g., Becker, 1975).

Selection was performed in two steps. In the first step, 60 F_2 plants were selected out of a population of 629, resulting in a selection intensity of $i(N, G) = i(60, 629) = 1.78$. Since the selection was based on genomic predictions of the GCA effects of the female lines evaluated in the HYWHEAT experiments, the relevant variance of breeding values corresponds to σ^2_{GCA}, estimated in the experiments of the growing seasons 2011/2012 and 2012/2013 (Zhao et al., 2015). The selection was performed in a population of F_2 plants derived from crosses of genotypes from the aforementioned population. Specifically, three F_2 plants were selected from each family. From quantitative genetic theory, it can be inferred that half of the genetic variance can be exploited if a selection is performed within an F_2 family (Hallauer et al., 2010). It follows that for the first step of selection, $\sigma_{GCA\_F2} = \sqrt{\frac{1}{2}\sigma^2_{GCA}} = 1.2$. The square root of the heritability, h, was assessed using as a conservative estimate the prediction abilities obtained in a chessboard-like cross-validation considering two out of the three different test sets T_2, T_1, and T_0: T_2 test sets included hybrids sharing both parental lines, T_1 test sets comprised hybrids sharing one parental line, and T_0 test sets contained hybrids having no parental line in common with the hybrids in the related training sets. In the RRGS program, male testers were not changed and thus, the C_1 lines reflected a mix between the T_1 and T_2 scenario with a prediction ability of 0.55 and 0.76, respectively. For simplicity, the mean of the prediction abilities for scenarios T_1 and T_2 was considered, resulting in $h = 0.66$.

In the second step of selection, 50 plants were selected from a population of 382 $F_{5:6}$ plants. While h is considered equal to the first step, $i(N, G)$ and σ_{GCA} changed, with $i(50, 382) = 1.63$. According to quantitative genetic theory (Hallauer et al., 2010), the σ_{GCA} exploited in the second step amounted to $\sigma_{CGA_{F5:6}} = \sqrt{\frac{7}{8}\sigma^2_{GCA\_F2}} = 1.1$. The total response to selection was the sum of the responses of the first and second step.

Characterization of Field Locations

In the recent decades, Germany has become more prone to drought events with harmful effects to agro-ecosystems. Personal communication with responsible field technicians indicated adverse field conditions in some of the environments in which the genotypes of the RRGS program were tested. Therefore, GCA_{Female}-by-environment interaction effects were obtained from model (5) to estimate Euclidean distances between each pair of environments.

To further investigate the range in which the environments differed regarding physical stress, we used data from meteorological and satellite-based approaches estimating the plant available water and the condition of the regional vegetation, respectively. The German drought monitor provides data on plant available water beginning from 2015. Information for the plant available water at each location was extracted from the German drought monitor for the growing season 2018/2019 (Zink et al., 2016). In addition, the Vegetation Condition Index (VCI) was employed to quantify the severity of drought stress around the test locations. Geospatial data sets based on the MOD13Q1 images were accessed from the Application for Extracting and Exploring Analysis Ready Samples (https://lpdaacsvc.cr.usgs.gov/appeears/) by USGS. Data from MOD13Q1 images were available for the growing seasons 2011/2012, 2012/2013, and 2018/2019, qualifying them for the comparison of the HYWHEAT and RRGS environments. For each location, an area of 500 ha centered for the coordinates of the test site was selected. The VCI based on the Enhanced Vegetation Index (EVI) was obtained from the equation:

$$VCI_i = \frac{EVI_i - EVI_{\min}}{EVI_{\max} - EVI_{\min}}, \quad (6)$$

where VCI_i referred to the VCI on day i, EVI_i referred to the EVI on day i, $EVI_{\min}$ referred to the minimum EVI in the area observed in the period 2010–2019, and $EVI_{\max}$ referred to the maximum EVI in the area observed in the period 2010–2019. The recommended practice for drought monitoring using the VCI was applied as suggested by the United Nations Office for Outer Space Affairs (2021). The mean value of the selected area around the test site was applied in further considerations.

Based on the data for PAW and VCI, matrices with the individual weather profile of each environment were constructed. From these matrices, principal component analyses were performed, and complete-linkage clusters based on the Euclidean distances were obtained to identify environments with special conditions.

RESULTS

Analysis of Population Structure Revealed Genomic Traces of Selection

The population structure of the 3 male tester lines, the 20 founder female lines (C_0) of the RRGS program, their 30 resulting randomly drawn (C_1R) recombined, and 49 selected progenies (C_1S) was analyzed based on 4,031 polymorphic SNP markers. The principal component analysis derived from the eigenvectors of the parental lines revealed that male and female lines tended to be separated by the first principal component (**Figure 1**). With respect to the second principal component, C_1R was more widely spread than C_1S. Overall, C_1S appeared to be more separated from the male parents than C_1R.

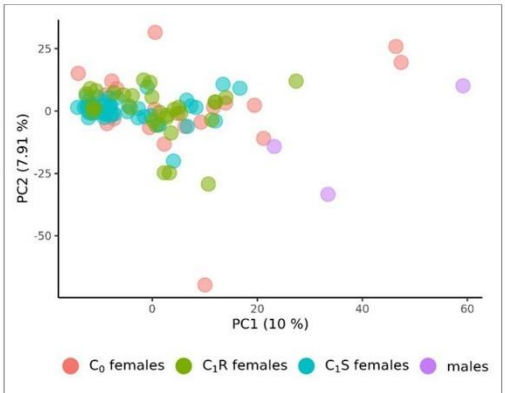

FIGURE 1 | Principal Component Analysis (PCA) of the 20 founder wheat lines (C_0 females), the 3 male lines, the 30 female lines drawn from random after recombining the 20 founder lines (C_1R), and the 49 female lines from the first selection cycles (C_1S). PCA were derived from the eigenvectors of the 3 male and 20 female founder lines. The proportion of variance displayed by the principal components (PC) were presented in brackets.

Phenotypic Data Indicated Pronounced Interactions Between Genotypes and Environments

Genomic repeatabilities were moderate to high, ranging from 0.13 in Wohlde to 0.51 in Hadmersleben with an average of 0.34 in lines and ranging from 0.17 in Mintraching to 0.58 in Adenstedt with an average of 0.34 in hybrids (**Supplementary Table 1**). This underlines the overall high quality of the yield trials. Interestingly, we observed that correlations between grain yields in each environment were low for some pairs (**Table 1**). For example, grain yields of lines and hybrids studied at Wohlde and Hadmersleben were not significantly correlated ($r = 0.09$; $P > 0.36$ for lines; and $r = -0.08$; $P > 0.20$ for hybrids). The grain yield trial conducted at Hadmersleben was not an outlier but correlated significantly with the grain yield trial conducted at Boehnshausen ($r = 0.51$; $P < 0.001$ for the lines; and $r = 0.23$; $P < 0.001$ for the hybrids), a second location in Saxony-Anhalt. These pronounced differences among locations were also visible in the contribution of genotype-by-environment interaction effects (G×E) to the phenotypic variance (**Table 2**). Genotypic variances σ^2_G were significantly greater than zero ($P < 0.01$, **Table 2**) for lines as well as hybrids, with σ^2_G being 5.85-times smaller in hybrids than in lines. The ratio of $\sigma^2_{GxE}/\sigma^2_G$ amounted to 0.81 in lines and the ratio of $\sigma^2_{GCA(Female)xE}/\sigma^2_{GCA\ (Female)}$ to 1.13 for general combining

TABLE 1 | Pearson moment correlations between grain yield of 109 wheat lines (below diagonal) and 264 hybrids (above diagonal) evaluated at six locations in the year 2019 to assess the selection gain of the reciprocal recurrent genomic selection program.

Inbred/hybrid	Adenstedt	Boehnshausen	Hadmersleben	Mintraching	Sossmar	Wohlde
Adenstedt	1.00	−0.01	0.05	0.10	−0.02	0.17**
Boehnshausen	0.42***	1.00	0.23***	0.15*	0.12*	−0.07
Hadmersleben	0.22*	0.51***	1.00	0.13*	0.14*	−0.08
Mintraching	0.29**	0.22*	0.26**	1.00	0.14*	−0.01
Sossmar	0.54***	0.55***	0.39***	0.17"	1.00	−0.01
Wohlde	0.44***	0.12	0.09	0.32***	0.24*	1.00

*", *, **, and *** significantly different from zero at the 0.05, 0.01, 0.001, and 0.0001 level of probability.*

TABLE 2 | Estimates of variance components (residual variance indicated as σ_ε) and heritability ($h2$) for winter wheat for grain yield (dt/ha).

Source	Grain yield (dt/ha) 6 locations	Grain yield (dt/ha) 4 locations
Lines		
σ^2_{LINES}	17.21***	17.91***
$\sigma^2_{LINESxE}$	14.01***	10.05***
h^2(Lines)	0.84	0.76
F_1 hybrids		
σ^2_{SCA}	1.07**	1.05
σ^2_{SCAxE}	6.86**	7.50
$\sigma^2_{GCA(Female)}$	1.73**	2.14*
$\sigma^2_{GCAxE(Female)}$	1.97***	2.20*
$\sigma^2_{GCA(Male)}$	0.00	0.00
$\sigma^2_{GCAxE(Male)}$	1.57^{NS}	1.95^{NS}
$\sigma^2_{HYBRIDS}$	2.94	3.20
$\sigma^2_{HYBRIDSxE}$	10.40	11.65
σ^2_ε	5.73***	5.77***
h^2(hybrids)	0.54	0.44

Parents and checks were grouped together as lines. The panel was evaluated at 6 locations and comprised 109 lines (7 checks, 99 females and 3 males) and 264 hybrids. In a further analysis, only 4 locations with no stressful growing conditions were investigated. NS, Not significant.
*, **, and *** significantly different from zero at the 0.01, 0.001, and 0.0001 level of probability.*

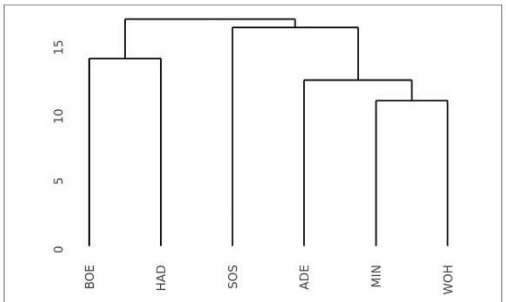

FIGURE 2 | Dendrogram based on the Euclidean distances among six locations estimated using the GCA_{Female}-by-environment interaction effects from the grain yield trials performed in the year 2019 to assess the selection gain of the reciprocal recurrent genomic selection program. The locations were ADE, Adenstedt; BOE, Boehnshausen; HAD, Hadmersleben; MIN, Mintraching; SOS, Sossmar; WOH, Wohlde.

ability effects of the females, which was of special interest during the selection. This underlines the substantial contribution of genotype-by-environment-interaction effects to the phenotypic variance. The estimated heritability (h^2) was high for lines (0.84) and moderate (0.54) for hybrids.

Drought Stress Was Associated With the Pattern of Genotype-by-Environment Interactions

The pronounced differences among locations encouraged us to investigate the pattern of interaction effects between genotypes and environments in more detail. Due to the exploitation of additive effects in the recurrent genomic selection program, we focused on the interaction effects between the GCA effects of females with environments and performed a cluster analysis. The analysis revealed that the Boehnshausen and Hadmersleben locations formed a distinct group, separate from the other locations of the RRGS experiment (**Figure 2**). We assessed the clustering of the locations in more detail by analyzing two published meteorological and satellite-based parameters: the plant available water in the soil (PAW) and vegetation condition index (VCI). Boehnshausen and Hadmersleben were the locations with the lowest PAW during the early growing season (**Figure 3A**) and both locations also clearly clustered separately from the remaining locations when applying a principal component analyses based on the PAW of the entire growing season (**Figure 3B**). A similar picture was observed for the VCI profiles. Boehnshausen and Hadmersleben showed low VCI values throughout the growing season and distinguished from the other locations in particular during the autumn and winter months of the growing season (**Figure 3C**). The principal component analyses based on the VCI profiles of the entire growing season separated the Boehnshausen and Hadmersleben locations from the remaining ones (**Figure 3D**). Thus, the pronounced genotype-by-environment interactions were most

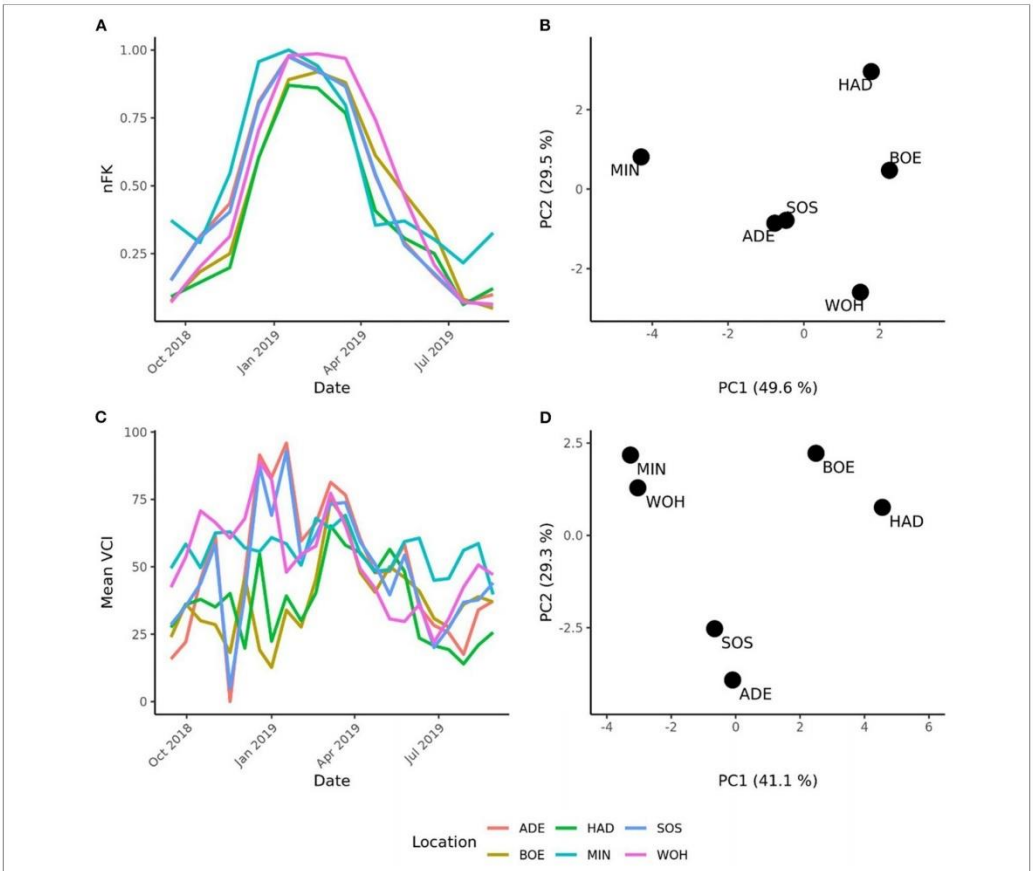

FIGURE 3 | Characterization of the locations used to assess the selection gain of the reciprocal recurrent genomic selection program. **(A)** Line plot of the plant available water (PAW) in the soil and **(B)** a principal component analyses (PCA) based on the PAW profiles of the locations recorded in the growing season [September 1st in the year of sowing (2018) to September 1st in the year of harvest (2019)]. **(C)** Line plot of the mean vegetation condition index (VCI), and PCA based on the mean VCI profiles of the locations recorded in the growing season **(D)**. The locations were indicated as ADE, Adenstedt; BOE, Boehnshausen; HAD, Hadmersleben; MIN, Mintraching; SOS, Sossmar; WOH, Wohlde.

likely caused by severe drought stress occurring in the region of Saxony-Anhalt in the growing season 2018/2019.

Pattern of Genotype-by-Environment Interactions for Integrated Phenotypic Data of the Training and the RRGS Populations

The HYWHEAT training population was phenotyped at five locations in the 2011/2012 season and at six locations in the season 2012/2013, and the RRGS program was evaluated at six locations in the 2018/2019 season. Three overlapping locations albeit in different years were used for both, the HYWHEAT and for the RRGS trials. Interestingly, for the overlapping genotypes (27 for lines and 48 for hybrids) between the HYWHEAT and the RRGS experiments, we observed a much higher correlation between grain yield estimated in the growing seasons 2011/2012 and 2012/2013 within the HYWHEAT experiment ($r = 0.49$; $P < 0.00$ for lines and $r = 0.43$; $P < 0.00$ for hybrids) than between the RRGS experiment and the HYWHEAT experiment in 2011/2012 ($r = -0.04$; $P < 0.80$, for lines and $r = 0.08$; $P < 0.80$, for hybrids) and in 2012/2013 ($r = 0.05$; $P < 0.40$ for lines and $r = -0.17$; $P < 0.80$, for hybrids). A closer look at the correlations between grain yield of the RRGS experiment in each environment

TABLE 3 | Correlations of phenotypic data from single environments of the RRGS experiments (2018–2019) with phenotypic data from HYWHEAT experiments and with single years of the HYWHEAT experiment.

	RRGS: 2018–2019	Hywheat: 2012	Hywheat: 2013	Hywheat: total
Lines	Adenstedt	0.24	0.30	0.40*
	Boehnshausen	0.04	−0.14	−0.11
	Hadmersleben	0.03	−0.30	−0.24
	Mintraching	0.38	−0.07	0.11
	Sossmar	0.11	−0.11	0.03
	Wohlde	0.43*	0.41*	0.54**
Hybrids	Adenstedt	0.37*	0.37**	0.47***
	Boehnshausen	-0.26"	-0.27"	−0.32*
	Hadmersleben	−0.20	−0.23	−0.32*
	Mintraching	−0.20	−0.04	−0.13
	Sossmar	−0.09	−0.07	−0.07
	Wohlde	0.13	0.27"	0.24

A number of 27 overlapping lines and 48 overlapping hybrids were included into the estimation.
*", *, **, and *** significantly different from zero at the 0.05, 0.01, 0.001, and 0.0001 level of probability.*

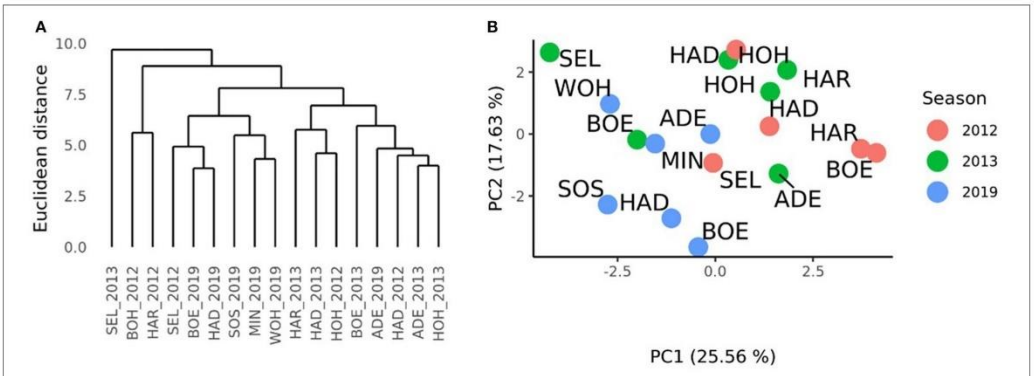

FIGURE 4 | Characterization of the environments of the HYWHEAT and RRGS experiments of the growing seasons 2011/2012, 2012/2013, and 2018/2019, based on the phenotypic performances of overlapping tested hybrids. **(A)** Dendrogram based on the Euclidean distances among 17 location times year combinations (location_year) estimated using the GCA_{Female}-by-environment interaction effects from the grain yield trials performed in the year 2012 and 2013 for the training population (HYWHEAT) and in the year 2019 to assess the selection gain of the reciprocal recurrent genomic selection program. **(B)** PCA based on the GCA_{Female}-by-environment interaction effects of 16 location times year combinations. The locations were indicated as ADE, Adenstedt; BOE, Boehnshausen; HAD, Hadmersleben; HAR, Harzhof; HOH, Hohenheim; MIN, Mintraching; SEL, Seligenstadt; SOS, Sossmar; WOH, Wohlde.

and the HYWHEAT experiments revealed strong interaction effects with years (**Table 3**). The RRGS experiment conducted in Wohlde and Adenstedt showed the highest correlations with the HYWHEAT experiments with a decreasing trend toward Mintraching, Sossmar, Boehnshausen, and Hadmersleben.

A complete-linkage clustering based on the Euclidean distances estimated using the GCA_{Female}-by-environment interaction effects was performed to further investigate the relationships among the environments of the HYWHEAT and the RRGS experiments (**Figure 4A**). The location Seligenstadt in 2013, and Boehnshausen in 2012 and Harzhof in 2012 formed outgroups. Apart from Seligenstadt in 2012, which grouped together with the environments Seligenstadt, Boehnshausen, Hadmersleben, Sossmar, Mintraching, and Wohlde from the RRGS experiment, the remaining HYWHEAT environments constituted a distinguished cluster including the environment of Adenstedt in 2019. A PCA based on the GCA_{Female}-by-environment interaction effects showed that apart from Seligenstadt in 2013, the environments of the HYWHEAT experiment grouped together with the RRGS environments Adenstedt, Mintraching and Wohlde in 2019 (**Figure 4B**). The RRGS environments Boehnshausen, Hadmersleben and Sossmar grouped separately from the remaining environments of the RRGS and the HYWHEAT experiments.

A distance matrix obtained from the VCI profiles of the 17 environments of the RRGS and the HYWHEAT experiments

was calculated. The comparison to the distance matrix derived from the GCA_{Female}-by-environment interaction effects revealed a correlation of 0.17 which was significantly different from zero ($P < 0.01$) according to a Mantel test (Mantel, 1967). The cluster which was derived from the VCI profiles of the 17 environments indicated the presence of two subgroups among the HYWHEAT and RRGS experiments (**Figure 5A**). The environments of the RRGS experiment grouped apart from the HYWHEAT experiments, with the environment of Mintraching in 2019 behaving exceptionally as it was situated within the HYWHEAT experiments. Within the HYWHEAT experiments, the location Adenstedt of the growing season 2011/2012 appeared as outgroup. The remaining HYWHEAT environments formed two subgroups distinguished mostly by the year of the evaluation. A PCA was executed based on the VCI profiles of all environments in which the genotypes were tested during the HYWHEAT and RRGS experiments (**Figure 5B**). This analysis exposed shifts of the growing conditions across the growing seasons in which the genotypes were evaluated. Based on the 1st principal component, the environments in the RRGS experiment showed to be largely separated from all remaining environments from the HYWHEAT experiments. Only Mintraching situated closely to some of the HYWHEAT experiments. The 2nd principal component separated the RRGS experiments into three groups: Mintraching and Seligenstadt, Sossmar and Adenstedt, and Boehnshausen and Hadmersleben. The first principal component explained 32.71% of the variance, the second principal component explained 16.78% of the variance.

Selection of Test Locations Affected the Assessment of Breeding Success

Evaluation of effectiveness of RRGS was conducted at six locations during the 2018/2019 growing season, between which pronounced genotype-by-environment interaction effects were observed. Moreover, the 2018/2019 growing season locations showed high genotype-by-year interactions compared to the HYWHEAT experiments conducted in the 2011/2012 and 2012/2013 growing seasons, based on which the genomic selection model was trained. In particular, the Boehnshausen and Hadmersleben locations of the 2018/2019 growing season showed low correlations to the environments of the HYWHEAT experiment (**Table 3**). By comparing the BLUEs for the overlapping genotypes of the RRGS experiment with the BLUEs from the HYWHEAT experiment, correlations of 0.13 and −0.10 were observed for lines and hybrids, respectively. After excluding the locations Boehnshausen and Hadmersleben from the RRGS experiment, correlations between the RRGS experiment and the HYWHEAT experiment based on overlapping genotypes increased to 0.37 for lines and 0.21 for hybrids. Furthermore, exclusion of the Boehnshausen and Hadmersleben locations resulted in a drop of $\sigma^2_{GxE}/\sigma^2_G$ from 1.13 to 1.02 for the GCA of the female lines, indicating a lower proportion of genotype-by-environment interactions among the remaining locations of the RRGS experiment (**Table 2**). These findings encouraged us to investigate the influence of genotype-by-environment interactions on the selection gain of the RRGS breeding programs. To this end, we estimated the selection gain based on phenotypic data collected in all six environments of the RRGS experiment and alternatively we excluded two environments with negative average correlations to the single environments of the HYWHEAT data set and estimated the selection gain based on the remaining four locations.

Including all six environments from the growing season 2018/2019, the randomly drawn female lines of the C_1 cycle showed comparable ($P > 0.1$) average yields as the female parent lines of the C_0 cycle (**Figure 6A**). The genomically selected females showed no significant differences of 1.0 dt ha^{-1} ($P > 0.1$) average yields compared to the randomly selected female lines. Surprisingly, genomically selected female lines of the C_1 cycle showed lower ($P > 0.1$) average yields than the female lines of the C_0 cycle. Both differed by 1.15 dt ha^{-1}. The average yield of the C_0-hybrids, the genomic-selected fraction of the C_1-hybrids (C_1S) and the randomly drawn fraction of the C_1-hybrids (C_1R) did not show any significant ($P > 0.1$) difference. The midparent heterosis was not significantly ($P > 0.1$) larger for C_1S (10.3%) as compared to C_1R (9.7%) and C_0-hybrids (9.8%) (**Figure 7A**). The same was observed for better parent heterosis (**Figure 7C**).

Excluding the two outlier locations from the growing season 2018/2019, randomly drawn female lines of the C_1 cycle showed comparable ($P > 0.1$) average yields as the female parent lines of the C_0 cycle (**Figure 6B**). Genomically selected female lines of the C_1 cycle and randomly selected female lines of the C_1 cycle showed no significantly different ($P > 0.1$) grain yield performance. The female parent lines of the C_1 cycle performed comparable ($P > 0.1$) to the female parent lines of the C_0 cycle. While C_1R hybrids showed no significant difference ($P > 0.1$) in average yield performance compared to C_0 hybrids, C_1S hybrids outperformed ($P < 0.05$) C_0 hybrids by 1.0 dt ha^{-1}, achieving a selection gain of 1%. Moreover, C_1S hybrids outperformed ($P < 0.1$) C_1R hybrids by 0.7 dt ha^{-1}. Midparent heterosis was not significantly different ($P > 0.1$) in C_1R (11.5%) compared to C_0 (11.3%), while C_1S (12.8%) showed a clear advancement and performed significantly better than C_0 ($P < 0.05$) and C_1R ($P < 0.05$) (**Figure 7B**). A different pattern was observed for better parent heterosis. C_0 (11.3%) and C_1R performed comparable ($P > 0.1$). C_1S (10.0%) did not perform significantly different from C_0 ($P > 0.1$) and C_1R ($P > 0.1$) (**Figure 7D**).

The observed selection differential and hence the observed response to selection varied depending on which environments were considered for the evaluation. When all six environments were included, it amounted to $R_{obs\_6E} = -0.4\ dt\ ha^{-1}$. When environments with severe stress conditions were excluded and only four environments were considered, the observed selection differential and hence observed response to selection was $R_{obs\_4E} = 1.0\ dt\ ha^{-1}$.

DISCUSSION

We conducted one cycle of an RRGS program in wheat, including field evaluation of the resulting hybrids, which took a total of 6 years from the first crosses. It is important to note that each subsequent selection cycle lasts only one additional year at most,

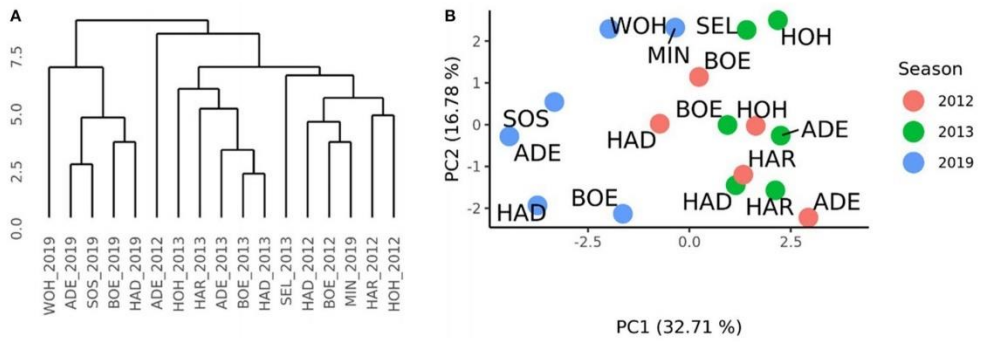

FIGURE 5 | Characterization of the environments of the HYWHEAT and RRGS experiments of the growing seasons 2011/2012, 2012/2013, and 2018/2019, based on satellite-based images. **(A)** Dendrogram based on the mean vegetation condition index (VCI) profiles of 16 location times year combinations (location_year) used to perform grain yield trials in the year 2012 and 2013 for the training population and in the year 2019 to assess the selection gain of the reciprocal recurrent genomic selection program. **(B)** PCA based on the mean VCI profiles of 16 location times year combinations. The locations were indicated as ADE, Adenstedt; BOE, Boehnshausen; HAD, Hadmersleben; HAR, Harzhof; HOH, Hohenheim; MIN, Mintraching; SEL, Seligenstadt; SOS, Sossmar; WOH, Wohlde.

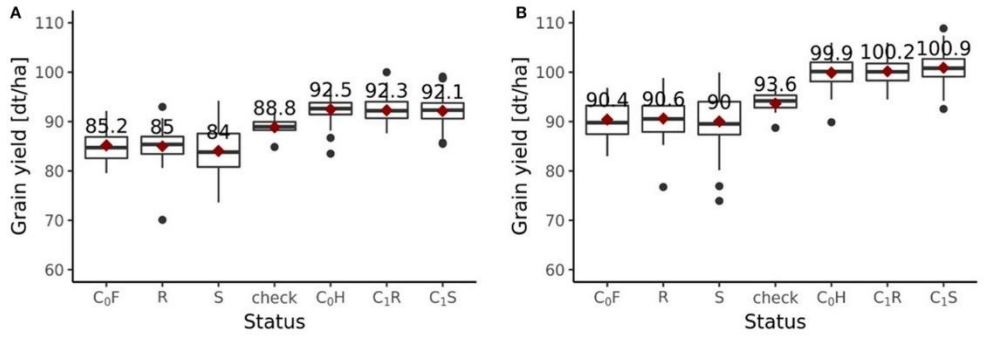

FIGURE 6 | Grain yield performance depending on the status of genotypes evaluated in the 2019 experiment. **(A)** Performances of the fractions from the breeding population with all six environments of 2018/2019 included. **(B)** Performances of the fractions from the breeding population with only 4 environments of 2018/2019 included. Status indicates the affiliation of each group of genotypes to a specific fraction within the breeding program. Female parent lines from the C_0 cycle are indicated as C_0F, female parent lines from the randomly selected fraction of the C_1 cycle are indicated as R, female parent lines from the genomic-selected fraction of the C_1 cycle are indicated as S, checks are indicated as "check," hybrids from the C_0 cycle are indicated as C_0H, hybrids from the randomly selected fraction of the C_1 cycle are indicated as C_1R, hybrids from the genomic-selected fraction of the C_1 cycle are indicated as C_1S.

which illustrates the great opportunity to accelerate classical RRS programs. The RRGS program focused exclusively on the female pool and can be viewed as a special case of RRGS in which only the allele frequencies in the pool of female parent lines have been shifted with respect to the frequencies of favorable alleles in the pool of male parent lines.

This situation implies consequences for the determination of selection directions, especially in the case of overdominance, $k > 1$, with $k = \frac{d}{a}$, where d denotes the dominance effect and a denotes the additive effect. If overdominance is present at a given locus, RRGS aims to fix different alleles in the pool of female parental lines and in the pool of male parental lines, thus guarantees the desired complementarity among the two heterotic groups. For loci with $k > 1$, at which the pool of male parent lines has a fixed allele, RRGS will result in the fixation of the complementary allele in the pool of female parent lines. If the allele is not fixed in the pool of the male lines, and no selection is applied to the pool of male parental lines, complementarity among the heterotic groups cannot be achieved.

If $0 < k \leq 1$, i.e., in the presence of partial dominance, RRGS aims to ultimately fix the favorable allele in both heterotic groups.

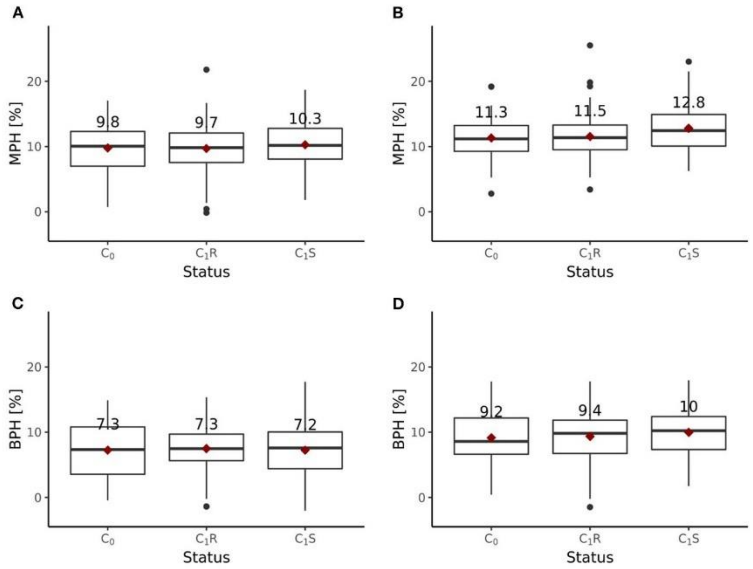

FIGURE 7 | Midparent heterosis (MPH) and better parent heterosis (BPH) for hybrids generated in the reciprocal recurrent selection program. MPH [%] estimated based on trials performed **(A)** at 6 locations and **(B)** 4 locations, excluding 2 stress environments. BPH [%] estimated based on trials performed **(C)** at 6 locations and **(D)** 4 locations, excluding 2 stress environments.

In the case where the male heterotic group is not fixed for the favorable allele, the optimal configuration cannot be achieved if the male heterotic group is not subject to selection.

For loci that exhibit negative dominance, i.e., $k < 0$, the desired selection direction is to fix the favorable allele in both heterotic groups. Complications arise when the unfavorable allele is present in the male heterotic group. Furthermore, if $k < -1$, i.e., negative overdominance is present, RRGS is directed toward fixation of the favorable allele only if the frequency, p, of the favorable allele is above the threshold $p > (k+1)/2k$ (Rembe et al., 2019).

In the present breeding program, the male heterotic group was kept constant between the C_0 and the C_1 cycle. As described above, this approach would not be expedient to reach the ideal allelic configurations between the two heterotic groups. However, the applied selection scheme is capable to evaluate the effectiveness of a selection that is conducted with respect to the allele frequencies within both heterotic groups. Therefore, the experimental design can serve as a model case for an RRGS breeding program.

The results of the field trials indicate that heterosis increased through RRGS (**Figure 7**). The selected fraction of the C_1S hybrids showed significantly higher midparent heterosis than the C_0 hybrids, but no significantly different better parent heterosis. In contrast, the C_1R hybrids did not show increased midparent or better parent heterosis compared to the C_0 hybrids. These findings highlight that the implemented selection models, which focused on additive and dominance effects, had an impact.

To evaluate the success of the RRGS program in more detail, the expected response to selection was compared to the observed response to selection. The expected response considering genomic selection at the F_2 and $F_{5:6}$ levels was $R_{\text{exp}} = 2.6\ dt\ ha^{-1}$, which was much lower than the observed response considering all six environments ($R_{obs\_6E} = -0.4\ dt\ ha^{-1}$) or the four environments ($R_{obs\_4E} = 1.0\ dt\ ha^{-1}$). The difference between R_{obs_6E} and R_{obs_E} clearly suggests that different growing conditions in the environments impacted the assessment of the response to selection. But even R_{obs_4E} was 2.6 times smaller than the expected response of selection R_{exp}, indicating that the implemented RRGS breeding program falls short of expectations. This observation can be mainly attributed to a high amount of genotype-by-year interactions between the 2011/2012, 2012/2013, and 2018/2019 experiments as highlighted in the detailed analyses of the interaction between genotypes and years (**Figures 4**, **5**). Multi-year testing could be an option to reduce the risk of unsuitable selection decisions.

So far, there are no experimental studies that have evaluated the effectiveness of an RRGS breeding program in cereals. In an RGS breeding program in wheat for the less complex trait grain fructans compared to grain yield, significant genotype-by-environment interactions were observed with little

effects on prediction accuracies (Veenstra et al., 2020). In contrast, in an RRS program in tropical maize focusing on grain yield, Kolawole et al. (2018) also observed that genotype-by-environment interactions negatively affected the observed response to selection.

As an alternative approach to estimate the expected response of selection, realized prediction ability was examined as the correlation between predicted average hybrid performances and the observed average hybrid performance of the 30 randomly drawn female parent lines from the C_1 cycle. When all six environments of the season 2018/2019 were included in the analysis, a realized prediction ability of 0.13 was observed. Excluding environments with stressful growing conditions for the 2018/2019 data set resulted in a realized prediction ability of 0.27. These realized prediction abilities of the 2018/2019 growing season are substantially lower than the prediction abilities estimated by cross validations based on the data of the HYWHEAT experiment conducted in the 2011/2012 and 2012/2013 growing seasons (Zhao et al., 2015). This can only partly be explained by the small sample size of 30 randomly drawn female parent lines from the C_1 cycle used to estimate the prediction abilities. Moreover, it is unlikely that the low realized prediction abilities have been caused through recombination. More likely, the lower realized prediction abilities are due to interaction effects between genotypes, locations, and years.

When the prediction abilities estimated based on the 30 randomly drawn female parent lines from the C_1 cycle are used to estimate the expected response to selection, the value decreases to $R_{exp\_6E} = 0.09\ dt\ ha^{-1}$ and $R_{exp\_4E} = 1.22\ dt\ ha^{-1}$, depending on whether stressful environments are included or not. In this case, R_{obs_4E} was only 1.22 times smaller than the expected response of selection R_{exp}. Consequently, it is pivotal to obtain genome-wide prediction models that are not biased due to interaction effects between genotypes, locations, and years. One promising approach to achieve this, is to account for interaction effects between genotypes and environments by implementing environmental cofactors into genome-wide prediction models (de los Campos et al., 2020). This facilitates to reduce the adverse effects due to interactions between genotypes and environments and to develop more sustainable genome-wide prediction models. In addition, aggregation of available medium size genomic and phenotypic data across different projects and perhaps even breeding programs into large data sets can help substantially to reduce confounding effects of genotype-environment interactions (Zhao et al., 2021). These adjustments seem urgently needed to further leverage the potential of RRGS.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://doi.org/10.1093/database/baw033.

AUTHOR CONTRIBUTIONS

JR, EE, EK, CL, PT, and YZ conceived and designed the study. EE, VK, JS, PB, PV, NPh, NH, SK, NPf, and MG acquired and contributed data. MR processed the data, performed the analyses, and analyzed the results. YZ supervised the data analyses. MR, JR, and YZ interpreted the results and wrote the manuscript. EE, PT, VK, JS, PB, PV, EK, NPh, SK, NPf, CL, NH, and MG provided input. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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2.3 The potential of genome-wide prediction to support parental selection, evaluated with data from a commercial barley breeding program

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Abstract

Parental selection is at the beginning and contributes significantly to the success of any breeding work. The value of a cross is reflected in the potential of its progeny population. Breeders invest substantial resources in evaluating progeny to select the best performing genotypes as candidates for variety development. Several proposals have been made to use genomics to support parental selection. These have mostly been evaluated using theoretical considerations or simulation studies. However, evaluations using experimental data have rarely been conducted. In this study, we tested the potential of genomic prediction for predicting the progeny mean, variance, and usefulness criterion using data from an applied breeding population for winter barley. For three traits with genetic architectures at varying levels of complexity, ear emergence, plant height, and grain yield, progeny mean, variance, and usefulness criterion were predicted and validated in scenarios resembling situations in which the described tools shall be used in plant breeding. While the population mean could be predicted with moderate to high prediction abilities amounting to 0.64, 0.21, and 0.39 in ear emergence, plant height, and grain yield, respectively, the prediction of family variance appeared difficult, as reflected in low prediction abilities of 0.41, 0.11, and 0.14, for ear emergence, plant height, and grain yield, respectively. We have shown that identifying superior crosses remains a challenging task and suggest that the success of predicting the usefulness criterion depends strongly on the complexity of the underlying trait.

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The Potential of Genome-Wide Prediction to Support Parental Selection, Evaluated with Data from a Commercial Barley Breeding Program

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Abstract: Parental selection is at the beginning and contributes significantly to the success of any breeding work. The value of a cross is reflected in the potential of its progeny population. Breeders invest substantial resources in evaluating progeny to select the best performing genotypes as candidates for variety development. Several proposals have been made to use genomics to support parental selection. These have mostly been evaluated using theoretical considerations or simulation studies. However, evaluations using experimental data have rarely been conducted. In this study, we tested the potential of genomic prediction for predicting the progeny mean, variance, and usefulness criterion using data from an applied breeding population for winter barley. For three traits with genetic architectures at varying levels of complexity, ear emergence, plant height, and grain yield, progeny mean, variance, and usefulness criterion were predicted and validated in scenarios resembling situations in which the described tools shall be used in plant breeding. While the population mean could be predicted with moderate to high prediction abilities amounting to 0.64, 0.21, and 0.39 in ear emergence, plant height, and grain yield, respectively, the prediction of family variance appeared difficult, as reflected in low prediction abilities of 0.41, 0.11, and 0.14, for ear emergence, plant height, and grain yield, respectively. We have shown that identifying superior crosses remains a challenging task and suggest that the success of predicting the usefulness criterion depends strongly on the complexity of the underlying trait.

Keywords: usefulness criterion; variance prediction; long-term genomic selection; superior progeny

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1. Introduction

An important step in breeding is the selection of promising parents to initiate a breeding cycle [1]. Ideally, genetically complementary parents are crossed to initiate a breeding population from which the best performing candidates are selected to bring new varieties to market. The central question of optimal parental selection for breeding programs is probably as old as breeding itself. Despite an increasing number of theoretical considerations on strategies for selecting parents, few of them have found their way into practice, and many breeders rather rely on basic concepts such as crossing best times best genotypes [2]. Nevertheless, quantitative genetic considerations suggest that attention should be paid not only to a high mean of a potential breeding population, but also to a high variance and consequently response to selection. Both aspects are considered in the usefulness criterion (*UFC*, ref. [1]) which is defined as $UFC = \mu + i \cdot h \cdot \sigma_g$, where μ denotes the mean of a breeding population, i denotes the intensity of selection to be applied in the breeding population, h denotes the square root of the heritability of a specific breeding population, and σ_g denotes the genetic standard deviation of the breeding population resulting from a particular cross. It follows from the definition of the *UFC* that a cross with

a low mean can still be promising because of a greater selection response. There are some pre-genomic studies that employed the *UFC* to empirically compare crossing strategies in maize breeding as an example [3,4]. Nevertheless, the crucial aspect for parental selection, the prediction of the usefulness of a cross, has remained an unsolved problem: While μ can be predicted with high confidence from the midparent value in an additive genetic model, predicting σ_g for more complex traits has been challenging [5].

With the advent of low-cost genome-wide marker systems and the successful application of genome-wide prediction in plant breeding [6–8], the prediction of family means and variances based on marker effects, the components of *UFC*, returned to the forefront of quantitative genetic research. Zhong and Jannink [9], in a pioneering study based on computer simulations, investigated the potential and limitations of predicting means and variances of crosses based on marker effects. The prediction of family means was determined as the average predicted value of parents. Variance was predicted as the sum of the variances of the genetic effects across the segregating quantitative trait loci and twice the summed covariances between all pairs of segregating quantitative trait loci. For the prediction of variance, the recombination frequency of each pair of segregating quantitative trait loci was considered [9].

Subsequent studies have presented approaches to predict family means and variances by simulating progeny populations derived from specific crosses and determined the relevant population parameters by predicting the performances of each genotype belonging to the family based on marker effects [10]. Similar approaches for selecting parents based on their simulated progeny were proposed by Mohammadi et al. [11], Lado et al. [12], and Yao et al. [13]. Lehermeier et al. [14] derived family variances analytically as Bayesian estimates of genetic variances, assuming known allele substitution effects at all quantitative trait loci, and integrated this approach into the prediction of *UFC* [15]. The analytic approach of Zhong and Jannink [9] was implemented in a simulation study and a small-scale empirical experiment [16,17]. All the aforementioned studies showed very promising results but assumed that marker effects were known [10–12,14–16] or estimated marker effects considering genomic and phenotypic data of the populations whose *UFC* should be predicted [17]. In a study on cassava [18], marker effects and *UFC* were estimated in separate training and testing populations, yielding disappointing results.

Here, we present a validation study for the analytical approach of Zhong and Jannink [9] using four years of data from a barley breeding program. Our experiment aimed to evaluate the benefit and ability to predict the family mean, the family variance, and the *UFC* for selecting superior parents. The underlying data allowed us to design different validation scenarios that resemble situations on the basis of which breeders make decisions. The scenarios were implemented for three traits with different heritability and complexity.

2. Results

2.1. Quality of Phenotypic Data

In total, 4488 genotypes were phenotyped in 38–40 environments, with the number of genotypes per environment varying from 72 to 1163. On average, every genotype was tested in 4.3, 3.5, and 3.2 environments for ear emergence, plant height, and grain yield, respectively. All traits approximated a normal distribution and the repeatability estimates ranged for ear emergence, plant height, and grain yield from 0.67 to 0.98, 0.61 to 0.96, and 0.18 to 0.96, respectively (Figure 1). The BLUEs across environments ranged for ear emergence from 47.8 BBCH [19] to 62.9 BBCH with a mean value of 55.7 BBCH, for plant height from 72.0 cm to 115.4 cm with a mean value of 98.0 cm, and for grain yield from 62. 6 dt ha^{-1} to 114.1 dt ha^{-1} with a mean value of 91.7 dt ha^{-1}. Heritability estimates ranged from moderate (grain yield: $h^2 = 0.49$) to high (ear emergence $h^2 = 0.84$; plant height: $h^2 = 0.77$). The coefficient of variation for families was lowest for ear emergence, followed by plant height, and grain yield. Summarizing, for all three traits, the quality of the phenotypic data was excellent, providing a solid basis for our study.

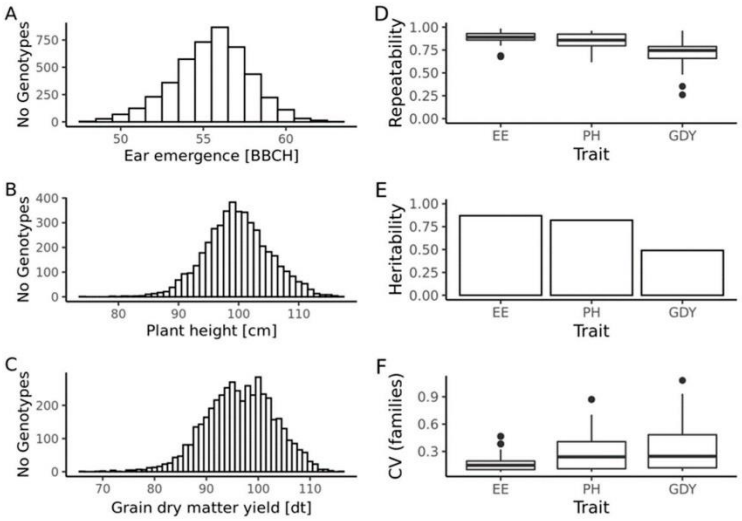

Figure 1. Distribution of phenotypic records (**A**–**C**), distribution of repeatabilities at test environments (**D**), heritabilities (**E**), and coefficients of variation (CV) of the families (**F**) for the traits ear emergence (EE), plant height (PH) and grain yield (GDY).

2.2. Genome-Wide Prediction of Line Performances within and across Breeding Cycles

Five-fold cross-validations were executed for each trait with the complete data set comprising all breeding cycles. Prediction abilities were 0.81 for ear emergence, 0.79 for plant height, and 0.73 for grain yield. Furthermore, leave-one-cycle-out cross validations were conducted and performances of the genotypes from one breeding cycle were predicted based on phenotypic data from genotypes of the remaining cycles (Figure 2). The prediction abilities for ear emergence ranged from 0.65 to 0.87, with the lowest prediction ability for the cycle of 2018 and the highest prediction ability breeding cycle of 2015. For plant height, the prediction abilities ranged from 0.55 to 0.73, with the minimum observed in the cycle of 2016 and the maximum prediction ability in the cycle of 2018. With a range from 0.14 to 0.46, the prediction abilities for grain yield were the lowest among the investigated traits. The highest prediction ability was observed for the cycle of 2018 and the lowest for the breeding cycle of 2016.

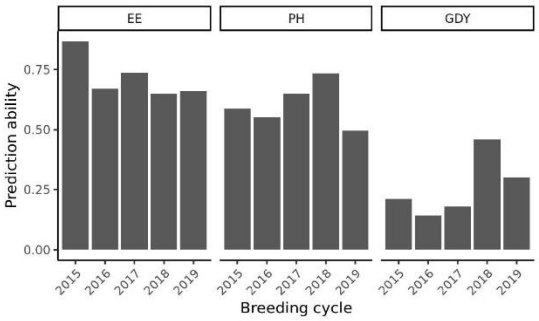

Figure 2. Prediction abilities for the traits ear emergence (EE), plant height (PH) and grain yield (GDY) across breeding cycles, where each breeding cycle was predicted based on a training set comprising only genotypes from the remaining breeding cycles.

2.3. Prediction of the Family Mean, the Family Variance, and the Usefulness Criterion

For the first scenario, the complete data set was used, and the training set was identical to the prediction set. Moderate to high correlations were observed between the predicted and the observed family means. The highest prediction ability was found for the trait ear emergence and the lowest for plant height (Figure 3). The prediction abilities for family means were 0.64 for ear emergence, 0.21 for plant height, and 0.39 for grain yield. In all cases, genomic predictions of the family means performed better than the prediction of the family means based on the midparent value derived from phenotypic records of the parents alone (no implementation of genomic prediction). For the latter, prediction abilities of 0.57, 0.18, and 0.17 were observed for ear emergence, plant height, and grain yield, respectively.

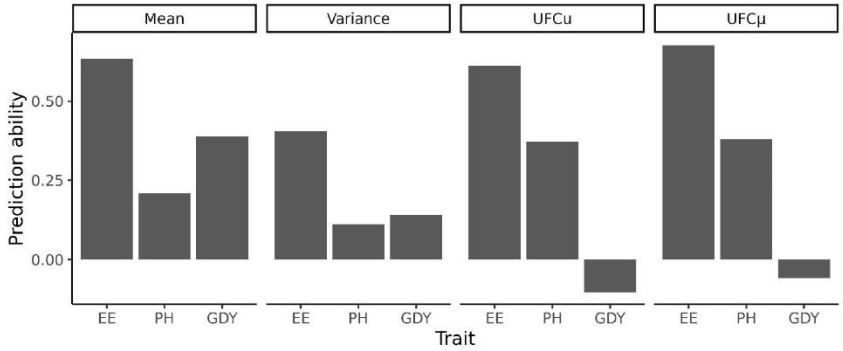

Figure 3. Prediction abilities for the population paramters family means, variances, usefulness criterion (*UFC*) predicted by *UFC* (*UFCu*) and *UFC* predicted by the mean (*UFCμ*) for the traits ear emergence (EE), plant height (PH) and grain yield (GDY) with the training set being identical to the test set employing the complete data set of the breeding program.

Low to moderate values were observed for the correlations between the predicted and the observed family variance. The correlation between the predicted and the observed variance was 0.41 for ear emergence, 0.11 for plant height, and 0.14 for grain yield (Figure 3). Correlations between the predicted and observed usefulness criterion ranged from −0.10 for grain yield to 0.61 for ear emergence (Figure 3).

In the second scenario, the final breeding cycle of 2019 was predicted based on a training set consisting of all previous breeding cycles (Appendix A Table A1). The prediction abilities for family mean ranged from 0.31 for grain yield to 0.64 for plant height. For family variance, the prediction abilities ranged from 0.12 for plant height to 0.44 for ear emergence. The prediction abilities for UFCu ranged from −0.15 for grain yield to 0.67 for ear emergence. For UFCμ, the prediction abilities ranged from −0.13 for grain yield to 0.68 for ear emergence.

To investigate the influence of population size on the prediction ability of family means, family variances and the usefulness criterion (*UFC*), a leave-one-cycle-out validation was performed for the final breeding cycle of 2019 using randomly sampled training sets from the previous breeding cycles with population sizes ranging from 50 to 1000 genotypes (Figure 4). For ear emergence, prediction abilities improved with increased training population size for means, variances, and the *UFC*. We observed that the prediction abilities improved steadily for population sizes ranging from 50 to 200 genotypes and then stagnated at a median value of approximately 0.67. Towards the maximum population size, the variation in prediction abilities was smaller. For the prediction of the genetic variance, a clear upwards trend in prediction abilities was observed at higher sizes of the training set. Nevertheless, no clear trend was observed in the variations of prediction abilities. Similar trends were observed for both ways of predicting *UFC*, either using predicted family means

only or using predicted family means and variances: Prediction abilities increased from a training set population size of 50 to 200, where they settle at a stable level. As the size of the training population increased, the variation of prediction abilities decreased.

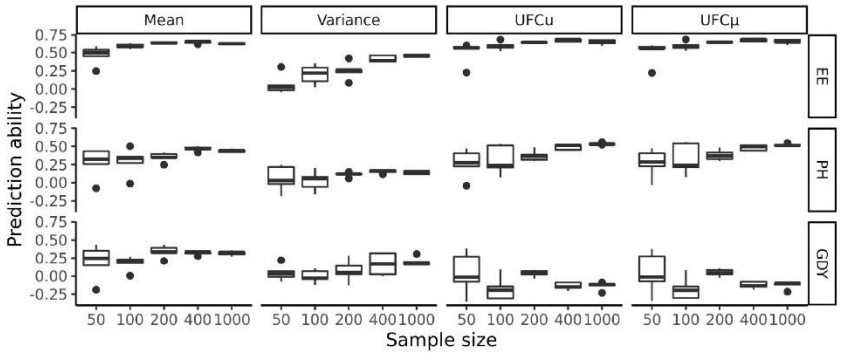

Figure 4. Prediction abilities for family means, variances, usefulness criterion (*UFC*) predicted by *UFC* (*UFCu*) and *UFC* predicted by mean (*UFCμ*) for the traits ear emergence (EE), plant height (PH), and grain yield (GDY). The population parameters of the last breeding cycle were predicted based on data from the previous breeding cycles. Training populations of sizes ranging from 50 to 1000 were randomly sampled five times.

For plant height, the trends for the prediction of means and both ways of predicting the *UFC* were similar (Figure 4). A decreasing distribution of prediction abilities was observed for the prediction of genetic variances, but absence of clear upwards trend of prediction abilities with higher training set population sizes.

We observed a different situation for grain yield. While the trends for predicting family means were similar to the findings for ear emergence and plant height, the trends for the other measures to be predicted drew a more complex picture. As the size of the test populations increased, the prediction abilities for genetic variances improved slightly. In contrast, no clear trend was observed for the variation of prediction abilities. Both methods for predicting the *UFC* showed a decrease in the variation of the prediction abilities with increasing size of the training populations (Figure 4). The median values showed neither an upward nor a downward trend and moved towards zero as the training population increased.

3. Discussion

Besides the mean, the genetic variance of the family resulting from a cross is the most important factor for its superiority and is therefore considered in the *UFC*. Despite an increasing number of publications proposing to predict the family mean and variance for a specific cross based on marker effects, proof of concepts based on comprehensive data sets are scarce. A recent attempt used a dataset from a cassava breeding program and yielded disappointing results [18]. In our study, we investigated the potential and limitations of predicting the *UFC* to identify optimal parent combinations using a data set generated in the course of commercial winter barley breeding. Despite the extensive population size, the use of data from commercial breeding programs also has some drawbacks. For a sufficiently precise study of the genetic variance of families, large and equal family sizes are ideal. The population composition in the present study has not been designed for scientific purposes, so family sizes vary. The contribution of parents to families also varies, and phenotypic selections at early stages can bias estimates of population parameters. The imbalanced nature of the data set made it impossible to consider family-specific genotype-times-environment effects and heterogeneous residual variances which could as well be

a source of bias in the estimation of within family variances. On the other hand, the extensive data allow initial validation of the potential of predicting the *UFC*.

3.1. Leave-One-Cycle-Out Cross-Validations Revealed That Performances of Individual Genotypes Can Be Predicted across Breeding Cycles

Five-fold cross-validations showed high prediction abilities for individual genotype performances for all three traits and amounted to 0.81 for ear emergence, 0.79 for plant height, and 0.73 for grain yield (Figure 2), which was consistent with similar findings from experiments in an elite winter barley panel [20]. For leave-one-cycle-out validation, prediction abilities were lower for most breeding cycles for all three traits, averaging 89% for ear emergence, 75% for plant height, and for grain yield 36% of the five-fold cross-validation scenario that included all breeding cycles combined. For most traits, within cycle genome-wide prediction abilities were reported to be higher than across cycle genome-wide prediction abilities in sugar beet (*Beta vulgaris* L.) [21], maize (*Zea mays* L.), wheat (*Triticum aestivum* L.) [22], and in rye (*Secale cereale* L.) [23]. Except for the breeding cycle of 2015 including a relatively large number of frequently used parental genotypes, which exceeded the prediction ability of the five-fold-cross-validation for ear emergence, no breeding cycle showed higher prediction abilities compared to the five-fold cross-validation. The relatively low prediction abilities for grain yield may be attributed to the comparably low heritability. Additionally, it can be hypothesized that genotype-by-environment interactions play a larger role in this trait, which was shown in a similar data set for barley [24]. Summarizing, the findings indicated that genomic prediction of the performance of individual genotypes is working well for the underlying data set.

3.2. Prediction Abilities of the Family Mean across Cycles Were Lower than Reported in Previous Simulation Studies

In an additive model, it is expected that the mean performance of the parents, i.e., the midparent value, is equal to the mean of the progeny of the respective cross [25]. In our study, the mean of a family was predicted based on the midparent value of genomic estimated breeding values (GEBVs). The correlations were substantially lower than the values reported from the literature. In previous studies, the family means have been predicted based on midparent values based on GEBVs of parental lines for simulated progeny populations [10,11]. In these studies, correlations between the predicted family mean and the family mean of the simulated progeny population was 0.95 for silking date and 0.91 for protein content in *Zea mays* [10], or 0.89 for deoxynivalenol and grain yield in barley [11]. One drawback of these studies is the fact that the simulated progeny populations which functioned as test set were generated based on the same prediction models as the midparent GEBVs that were designed to predict the family mean. Clearly, this concept does not reflect a situation a breeder faces before deciding which crosses to produce. Osthushenrich et al. (2018) observed a correlation of 0.95 for grain yield in a 5×5 factorial design tested in an augmented field design at 5 locations in one year, where the training set was identical to the test set. Neyhart and Smith [26] reported moderate prediction abilities in barley, amounting to 0.46 for *Fusarium* head blight, 0.62 for heading date, and 0.53 for plant height. High prediction abilities of the family mean have been reported in maize with 0.91 for plant height, 0.83 for ear height, and 0.80 for silking date [27]. In the present study, the prediction ability of the mean was lower for all traits, even if the training set was identical to the test set (Figure 3). This can be explained by varying sizes of families, an unbalanced design of field tests, where parents have usually not been tested in the same environments as the progeny populations, and in the case of grain yield by a relatively low heritability.

In another scenario, mimicking the typical situation in breeding, the training set consisted of genotypes from previous cycles and the test set consisted of genotypes from the last cycle of the breeding program. For plant height, the prediction ability was higher compared to the above-described scenario with the training set being identical to the test set (Table A1). For ear emergence and grain yield, prediction abilities were comparable. To ex-

amine the influence of the training set population size, 50, 100, 200, 400, and 1000 genotypes were sampled from the previous cycles of 2016, 2017, and 2018 to predict the final cycle of 2019. At the maximum training population size of 1000 genotypes, the mean prediction abilities for the family mean were 0.62 for ear emergence, 0.43 for plant height, and 0.33 for grain yield (Figure 4). For larger sizes of training populations, the median values of the prediction abilities approach $\sqrt{h^2}$, which corresponds to the theoretical limit of prediction abilities [28].

3.3. Low Ability to Predict the Genetic Variance of Families

The prediction abilities for the genetic variance of families were lower compared to the prediction ability for the family mean for all traits (Figure 3). This trend is consistent with previous results from experiments predicting the genetic variance based on simulated populations. In maize, the prediction abilities for plant height, ear height, and silking date amounted to 0.03, −0.24, and 0.14 [27], and 0.01, 0.39, and 0.48 for *Fusarium* head blight severity, heading date, and plant height, respectively [26]. In both studies, progeny populations of potential crosses were simulated based on estimated marker effects obtained from a training population, and validations were examined through phenotypic analysis of families in subsequent field trials. The results presented in this study were used to validate the prediction ability of family variance based on the analytic approach proposed by [16]. In a field trial-based validation of the analytical approach, this method led to prediction abilities of 0.34 or 0.76 if downwards outliers were removed [17]. However, this scenario does not reflect the scenario breeders typically face, as the training set and the test set were identical.

3.4. Prediction of the Usefulness Criterion

Depending on the trait, the trends for the prediction abilities of the *UFCu* varied strongly. While the prediction abilities for the family variance were lower than those for the family mean in all cases, the prediction abilities for the *UFCu* were comparable to those observed for family mean in ear emergence, higher for plant height, and even negative and therefore lower for grain yield. Since both the mean and the variance determine the value of the *UFC*, it is reasonable to assess the correlation of both measures. For all investigated traits, the correlations between mean and variance were negative for the observed (−0.28 for ear emergence, −0.26 for plant height, and −0.72 for grain yield), as well as for the predicted values (−0.29 for ear emergence, −0.15 for plant height, −0.47 for grain yield), and grain yield showed the lowest correlations in both cases. Several studies report a triangular relationship of mean and genetic variance, where families with extreme, i.e., very low and very high means are associated with low genetic variance, and families with intermediate means are associated with high genetic variance [11,26]. This phenomenon was not observed as clearly in the present study.

The coefficients of variation, i.e., the ratio of the standard deviation to the mean, of the families for ear emergence was comparably low in the present breeding program (Figure 1F). It can be presumed, that the influence of the family variance on the predicted and the observed *UFC* was relatively low. This explains the small difference between the prediction abilities for family mean and *UFCu*.

For plant height, the coefficients of variation of the families were higher compared to the values observed for ear emergence. Consequently, for plant height, the contribution of the family variance to the *UFC* should be larger compared to ear emergence. Even though the prediction ability for family variance was lowest for plant height, the prediction ability of the *UFCu* is larger compared to the prediction ability of the family mean. In comparison to ear emergence and grain yield, the correlations between variance and mean were highest for plant height for observed, as well as for predicted values. Together with the relatively high heritability of the trait of $h^2 = 0.82$, these findings explain the relatively high prediction ability observed for the *UFCu*.

The highest coefficient of variation of the families were observed for grain yield. Similarly, to plant height, this finding points to a relatively large impact of the family variance on the *UFC*. Considering the notable low correlation between predicted family mean and predicted family variance, it is not surprising to observe a major difference in prediction ability of the *UFCu* compared to the prediction of the family mean. Furthermore, in contrast to both previously discussed traits, the phenotypic records of grain yield disclosed a relatively low heritability of $h^2 = 0.49$. The high complexity of the trait grain yield, as well as the resulting quality of phenotypic data, lead to higher degrees of uncertainty in the estimation of marker effects, which are known to play a larger role in second degree statistics, e.g., family variance, as compared to first degree statistics which include the family mean.

Because of the uncertainty in variance prediction discussed above and reported in the literature [18], and the fact that the family mean generally contributes more to the *UFC* than the standard deviation, which is multiplied by the square root of heritability and the selection intensity, the *UFC* was furthermore predicted based on the family mean only, i.e., *UFCμ*. In general, the prediction abilities of the *UFCu* and the *UFCμ* deviated only slightly. For ear emergence and grain yield, prediction abilities increased while it was comparable for plant height (+10% for ear emergence, +3% for plant height, and +13% for grain yield). The relatively low differences between both approaches of predicting the *UFC* are due to the comparably low influence of the family variance on the *UFC* under the given conditions of the breeding program.

To further elucidate the impact of the selection intensity and the square root of heritability on the prediction abilities of both approaches of predicting the *UFC*, the product of both constants was assumed as $c = i \cdot h$, with levels ranging from 0 to 5. For example, at a heritability of $h^2 = 1.0$, c will be 0 if no selection is applied, 1 at a selection fraction of 38%, 2.5 at a selection fraction of 1.61%, and 5 at a selection fraction of 1 out of 1000,000. The constant c was used to calculate the observed *UFC*. Correlations between these hypothetical values of the *UFC* and the predicted values indicate that for all three traits, under medium to high selection intensities, prediction abilities will be higher for the *UFCμ* than the *UFCu*. Both approaches performed similarly for ear emergence and grain yield at very low selection intensities and for plant height at low to medium selection intensities (Figure 5). If at all, a small benefit of the *UFCu* is only given for ear emergence and plant height under the circumstance of low selection intensities. For grain yield, no benefit of predicting the *UFCu* was observed under any selection intensity.

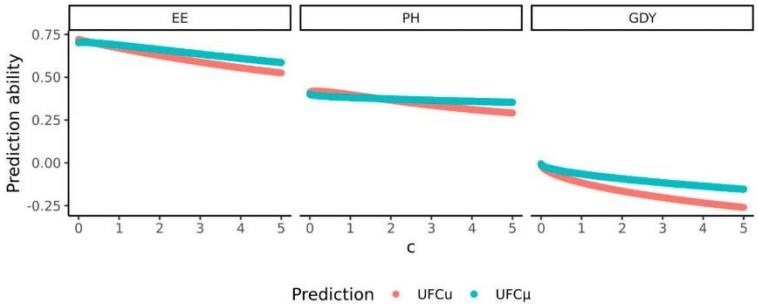

Figure 5. Prediction ability for the *UFC* varies depending on the complexity of the trait (ear emergence (EE), plant height (PH), and grain yield (GDY)), and the product of the square root of heritability and selection intensity given as the constant *c*. Two methods of predicting the *UFC* were applied: *UFCu* (red) and *UFCμ* (blue).

In a breeding program, predictions are based on the inference resting on genomic and phenotypic data from previous cycles or genetically independent populations. Therefore, a further scenario was considered in the present study, in which the performances of the

final breeding cycle were predicted based on the information on the genotypes originating from all previous cycles. In this scenario, *UFCu* performed slightly better than *UFC*μ for plant height. For the remaining traits, trends were similar to the scenario based on the full data set with the prediction and test set being identical. Moreover, to elucidate the influence of the population size, subsamples of the population sizes 50, 100, 200, 400, and 1000 genotypes were drawn which were then used as training set to calibrate models for predicting the final breeding cycle. These experiments confirmed the previously discussed findings of the present study, based on the full data set with the prediction and test sets being identical. In general, larger training set population sizes led to decreased dispersion of prediction abilities for all traits. For nearly all predicted population parameters, increasing population size leads to higher prediction abilities except for grain yield, where both approaches of predicting the *UFC* remain around zero for all training set population sizes. In all cases, the difference between the prediction abilities of the *UFCu* and the usefulness criterium predicted by the family mean was low.

The results presented in the underlying study largely correspond to findings obtained from a cassava breeding program [18]. In cassava, median prediction abilities for the usefulness criterion predicted by the *UFC* ranged from 0.1 to 0.83 in a cross-validated scenario and 95% of the prediction abilities were greater than zero, assuming a heritability of $h^2 = 1$ and varying selection intensities per family. Wolfe et al. [18] similarly described low differences between the prediction abilities for the family mean and the *UFC* and reported a high correlation of both.

4. Materials and Methods

4.1. Plant Material and Field Trials

The plant material used in this study is based on the winter barley breeding program of KWS LOCHOW GmbH (Bergen, Germany) and comprises in total 4500 winter barley lines. Each genotype was generated based on a double-haploid technology using two-, three-, and four-way crosses. Double-haploids were generated using F_1 plants. Genotypes, which originate from the same cross were denoted as a family. In total, a number of 347 families were part of the barley breeding program. The underlying data comprise four breeding cycles, corresponding to the year in which they were phenotyped for the first time. Barley breeding in Europe is not based on closed second breeding within companies. The use of lines also from other breeding programs in combination with the different time for doubled haploid production due to an additional generation for 3- and 4-way crosses compared to 2-way crosses leads to a complex pedigree structure and the parents of the cycles do not necessarily follow each other linearly.

Phenotypic evaluation took place in the years 2015, 2016, 2017, 2018, and 2019 for the traits grain yield (dt ha^{-1}), plant height (cm), and ear emergence (BBCH; [19]) in up to 10 locations. The experimental design of the field trials followed alpha lattice designs. A subset of 433, 1026, 1021, 1020, and 1000 lines were tested in the year 2015, 2016, 2017, 2018, and 2019 in two to four replications. Only sparse information was available for the parents of the first breeding cycle (2015). The dataset was nevertheless considered because it contained information on genotypes that were frequently used as parents in subsequent cycles.

4.2. Genomic Data

An Illumina Infinium 5 k SNP array was used to genotype the lines [3,29]. The mean rate of missing values was 1.4%. Markers with a minor allele frequency of 0.05 or less were excluded. After quality control, SNP markers with a missing rate lower than 5% were imputed based on the allele frequency. The original data set comprised 4501 markers from which 2898 remained after quality control and were used for further analysis.

4.3. Phenotypic Data Analysis

For the analysis of the phenotypic data, we implemented a two-stage approach. After removing outliers following the method of Tukey and Anscombe [30], a linear mixed model was used to analyze the data for each environment:

$$y = 1_n\mu + Zg + Z_B b + Z_R r + e, \quad (1)$$

where y denoted the vector of phenotypic values for each genotype tested in the specific environment, 1_n denoted the n-dimensional vector of 1's and n denoted the number of records in the specific environment, μ was the common intercept, g denoted the vector of genotypic values of the lines tested in the specific environment and was considered as random effect, r denoted the vector of replication effects, considered to be random, and b was the incomplete block effect, which was considered as random effect, and e denoted the random residual. Z, Z_B, and Z_R were design matrices for g, b, and r, respectively. We assumed that all random effects followed an independent normal distribution with different variance components for genotype, replication, and block effects. Repeatability was estimated for each environment as:

$$repeatability = \frac{\sigma_g^2}{\sigma_g^2 + \frac{\sigma_e^2}{n_R}}, \quad (2)$$

where σ_g^2 denoted the genotypic variance, σ_e^2 denoted the residual variance, and n_R denoted the average number of replications per genotype. The best linear unbiased estimations (BLUEs) for genotypes within each environment were obtained using model (1) assuming fixed genotypic effects.

The BLUEs of the genotypes in each environment were used in a second step to fit a further linear mixed model across the environments:

$$y = 1_m\mu + Zg + Z_E u + e, \quad (3)$$

where y denotes the vector of BLUEs that were calculated in the first step for the genotypes in each environment. 1_m denotes a vector of 1's with the length of m which refers to the total number of genotypes across all environments, μ denotes the common intercept, g denotes the vector of genotypic effects for all genotypes, u denotes the vector of environmental effects, and e denoted the vector of residuals. Z and Z_E denote corresponding design matrices for g and u, respectively. μ was assumed to be a fixed parameter, while g, u, and e were assumed to follow an independent normal distribution. The resulting estimated variance components were used to calculate the broad-sense heritability as:

$$h^2 = \frac{\sigma_G^2}{\sigma_G^2 + \frac{\sigma_e^2}{n_E}}, \quad (4)$$

where n_E denotes the average number of environments in which the genotypes were evaluated. Furthermore, the genotypic effects were assumed to be fixed in model (3) in order to calculate the BLUEs across environments.

The genetic variance of the families that were tested in the field was obtained by the following model:

$$y = 1_n\mu + Zg + Z_E u + Z_{EB} b + Z_{ER} r + e, \quad (5)$$

The genotypic variances were estimated separately for each family by assuming $g \sim N\left(0, \oplus_{k=1}^{f} G_k\right)$, $G_k = I_k\sigma_{G_k}^2$ nd $\sigma_{G_k}^2$ was the genotypic variance for *k-th* family. Z_{EB} and Z_{ER} were design matrices for block and replication effects nested into environments, respectively. A model considering family specific variance for genotype-times-environment interaction effects and heterogeneous residual variance was attempted in

the first place but did not converge. For all mixed linear models that were applied in the phenotypic analysis, ASReml-R [31] was employed.

The *UFC* was estimated for each family as the sum of the family mean and response to selection [1]. Response of selection was estimated assuming a selection intensity of $i = 1.27$ and a fixed broad-sense heritability for all families observed in the phenotypic data analyses, because the non-orthogonal data set led to convergence problems and prevented the family-specific estimation of heritability.

4.4. Genome-Wide Prediction within and across Breeding Cycles

The ability of genomic prediction was evaluated using genomic best linear unbiased prediction (GBLUP, [32]). The GBLUP model was given by $y = 1_n\mu + g + e$, where y denoted the vector of BLUEs of the parental genotypes, 1_n denoted an n-dimensional vector of 1's, n was the number of genotypes, μ denoted the common intercept, g denoted the vector of genotypic values, e denoted the residual term. We assumed that $g \sim N\left(0, G\sigma_g^2\right)$, where G denoted the n-dimensional genomic relationship matrix [32] and $e \sim N\left(0, I\sigma_e^2\right)$.

To assess the prediction abilities within the breeding program under study, five-fold cross validations were performed for the entire data set across all breeding cycles. For this purpose, the lines of the breeding program were randomly divided into five subsets, four of which were used as training sets and the fifth as prediction set. The prediction ability was examined as the correlation between BLUEs and predicted genotypic values for the test set. This procedure was repeated 100 times and the mean prediction ability was obtained as the final prediction ability, r_{GP}.

The prediction ability between breeding cycles was investigated by dividing the full data set into the single breeding cycles, i.e., 2015, 2016, 2017, 2018, and 2019. Subsequently, the data of four breeding cycles were used as the training set to predict the genotypic values of the remaining breeding cycle, which functioned as the test set. This procedure was repeated for all breeding cycles.

To estimate the additive effects of single markers, an RRBLUP model with the form $y = 1_n\mu + X\alpha + e$ was applied, where α was the vector of additive effects of markers assuming $\alpha \sim N\left(0, I_p\sigma_\alpha^2\right)$, $e \sim N\left(0, I_n\sigma_e^2\right)$. I_p and I_n were identity matrices of order p and n, with p being the number of markers and n being the number of genotypes.

4.5. Prediction of the Family Mean

The genomic estimated breeding values (GEBV) of each genotype were obtained by the above-mentioned genomic prediction models, GBLUP. To predict the mean of a progeny of a cross, the mean between the genotypes employed as parents was calculated, where the parents were weighted for the expected proportion of contributed genome. For comparison, the midparent value calculated from the phenotypic records of the parents alone was used as a point of reference.

4.6. Prediction of the Family Variance

For the prediction of the family variance, the method suggested by [16] was applied. Briefly, marker effects were estimated using the above-mentioned genomic prediction model, RRBLUP. The predicted variance was then obtained from the estimated marker effects by the following formula:

$$\sigma_G^2 = var(S) = \sum_c \sum_{j,k} cov(S_j, S_k), \quad (6)$$

where S denotes the lines of a family, S_j is two times the additive effect of the maternal or paternal allele, c is summed over the number of chromosomes, j is summed over the number of loci of a chromosome, and j, k is the sum of all locus pairs of a chromosome. The covariance of two linked loci was given by

$$cov(S_j, S_k) = \left(\frac{1}{2}q_{jk} - \frac{1}{4}\right)(m_j m_k + v_j v_k - m_j v_k - v_j m_k), \quad (7)$$

where m_j and m_k denote the effect of maternal alleles at the loci j and k, respectively and v_j and v_k denoted the effect of paternal alleles at the loci j and k, respectively. Following Equation (20) of Osthushenrich et al. [16], the parameter q_{jk} is a function of the linkage disequilibrium between two loci and was calculated for each pair of linked loci assuming zero generations of random mating.

4.7. Prediction of the Usefulness Criterion

The *UFC* was predicted for each family as the sum of the predicted family mean and the predicted response to selection [1]. The response to selection was predicted using the predicted family variance, and assuming a selection intensity of i = 1.27 as well as a fixed broad-sense heritability for all families as outlined above. For predicting the *UFC*, square root of heritability was assumed to be 1. To assess the prediction ability, the correlation of the predicted and the observed *UFC* was calculated. This method of predicting the *UFC* is referred to as *UFCu*. As a further point of reference, *UFC* was additionally predicted using the predicted family means only, hereafter referred to as $UFC\mu$.

4.8. Validating Predictions of the Family Mean and the Family Variance

In the first step, a scenario similar to the study design of [17] was investigated. Marker effects were estimated based on the full data set including all parents and families with available genotypic and phenotypic information. Predictions were validated with data from families derived from two-way crosses, assuming a minimum family size threshold of at least 10 genotypes and an estimated genetic variance greater than 0.01. Data were available from 66 families for ear emergence, 57 families for plant height, and 65 families for grain yield. The correlation between the observed mean and variance and the predicted mean and variance for the families was calculated.

Subsequently, methods for predicting the family means and variances were tested employing a leave-one-cycle-out validation for the final breeding cycle of 2019. The marker effects were estimated based on the full data set, excluding the data for the genotypes originating from the breeding cycle of 2019. The correlations between the observed mean and the observed variance of the family and the predicted mean and variance were calculated for the breeding cycle of 2019.

To elucidate the impact of the population size, an additional leave-one-cycle-out validation was executed. This time, the variances and means of the families from the final cycle of 2019 were predicted based on phenotypic data from the remaining cycles 2015, 2016, 2017, and 2018 with randomly sampled training sets comprising 50, 100, 200, 400, and 1000 randomly sampled genotypes.

5. Conclusions

The reliable prediction of the family variance and the *UFC* based on marker effects remain the pinnacle of any breeding intention. While the prediction of the family mean leads to acceptable or satisfying prediction abilities for all traits, the prediction of the family variance seems to be impeded by several uncertainties. No benefits were obtained for predicting the *UFC* based on analytic approaches, and in complex traits with low heritability, predictions might even harmfully lead to the wrong direction. Our data suggest that selections based on the *UFC* are not advisable in such cases. In accordance with existing literature on the prediction of family variance and the *UFC* based on realistic breeding scenarios, it can be concluded that the applied analytical methods are not well enough developed to be trustworthily recommended to breeders or decisionmakers in the breeding industry.

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and V.K. and provided the data on which the work was based. All authors agree with the current statement. All authors have read and agreed to the published version of the manuscript.

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Appendix A

Table A1. Prediction abilities of population parameters in a scenario where the test set corresponds to the final breeding cycle of 2019 and the training set corresponds to a combination of all previous cycles.

Trait	Mean	Variance	UFCu	UFCμ	N° Families
Ear emergence	0.64	0.44	0.67	0.68	21
Plant height	0.41	0.12	0.55	0.53	17
Grain yield	0.31	0.33	−0.15	−0.13	21

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3. General Discussion

The implementation of genome-wide selection in plant breeding programs can be considered a success story (Marulanda et al., 2016), as reflected by the fact that it has become a standard part of the toolbox of many breeding companies (e.g., He et al., 2017). Genome-wide prediction and selection has been implemented across crop species in the past decade and a half, for example in wheat (He et al., 2016), maize (Massman et al., 2013), barley (Philipp et al., 2016), rice (Xu et al., 2014), and rye (Wang et al., 2014). Here, genome-wide prediction is primarily applied to increase the efficiency of resource allocation by inferring the performance of non-phenotyped genotypes within a breeding cycle at early stages of selection (Figure 1).

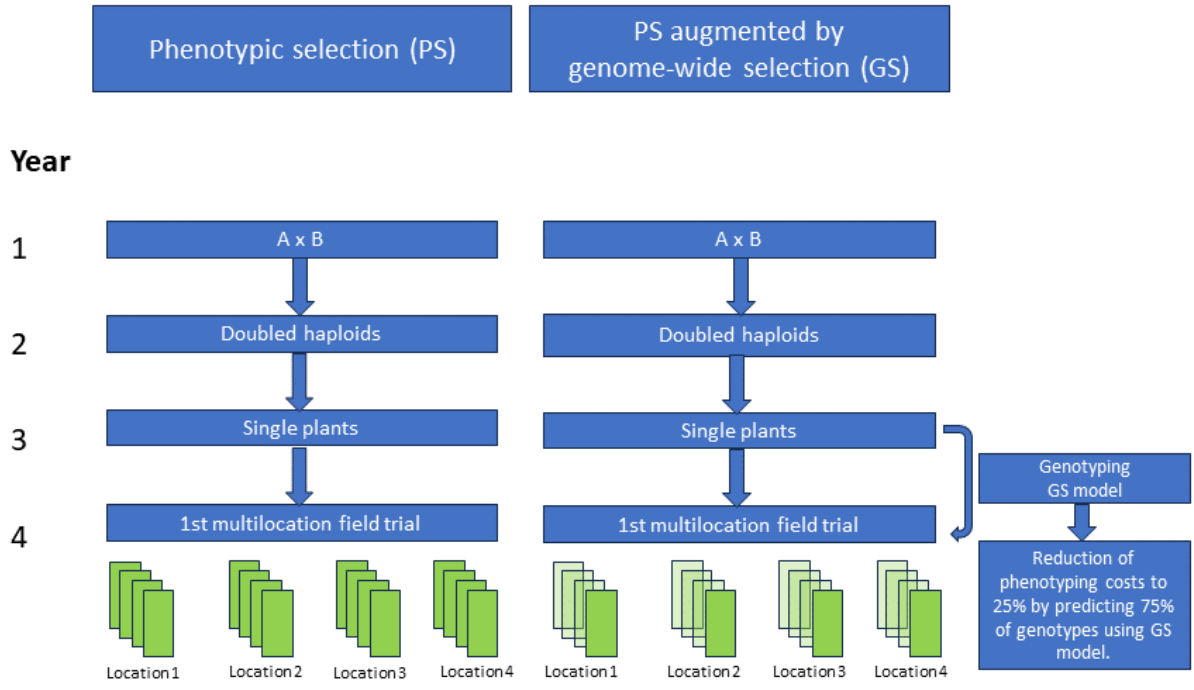

Figure 1: Graphical comparison of phenotypic selection (PS) and PS augmented by genome-wide selection (GS). Accuracy of GS corresponds to 3-4 field trials in complex traits. Costs can be reduced by predicting performances of genotypes based on genome-wide prediction models.

In addition to the use of genome-wide prediction in early selection cycles, genome-wide approaches could also bring competitive advantages in the planning of breeding decisions across breeding cycles. In this case, the selection of promising parents (Heffner et al., 2009) as well as long-term selection strategies (Jannink, 2010) are particularly attractive fields of application for genome-wide prediction. In the past, there were several proposals for these areas of application, which were supported in particular by arguments based on simulation studies (Allier et al., 2019; Lehermeier et al., 2017; Osthushenrich et al., 2017). To determine the actual benefits of a selection strategy in the context of

a user-oriented scenario, multi-year field studies are essential. Despite the absence of such validation studies, breeding strategies are promoted in the literature as a cure-all to solve pressing problems (Hickey et al., 2019; Watson et al., 2018), which can be misleading for recipient stakeholders.

In this work, two implementation options of genome-wide prediction were therefore investigated using extensive experimental data with regard to their prospects of success in industry-relevant use cases: genome-wide prediction of the performance of a cross to aid parental selection, and genome-wide prediction to assist recurrent selection in a hybrid breeding context (Figure 2). The usefulness-criterion is an established concept in quantitative genetics to assess the breeding value of a cross (Longin et al., 2014). Several usefulness-criterion inference methods based on genome-wide prediction have been proposed and tested in simulation studies (Allier et al., 2019; Lehermeier, de los Campos, et al., 2017; Lehermeier et al., 2014; Lehermeier, Teyssèdre, et al., 2017; Osthushenrich et al., 2017). To investigate the applicability of one of these methods in plant breeding, it was tested in a commercial barley breeding program as part of this work. Reciprocal recurrent genome-wide selection is a method for simultaneous improvement of complementary heterotic groups (Rembe et al., 2019), where selection decisions are made based on performance data from test crosses of genotypes from complementary pools. In this work, reciprocal recurrent genomic selection based on theoretical quantitative considerations was identified as a promising tool for increasing the efficiency of hybrid breeding programs, especially in autogamous crops. However, field experiments conducted as part of this work showed that the practical implementation of recurrent genomic selection is challenging.

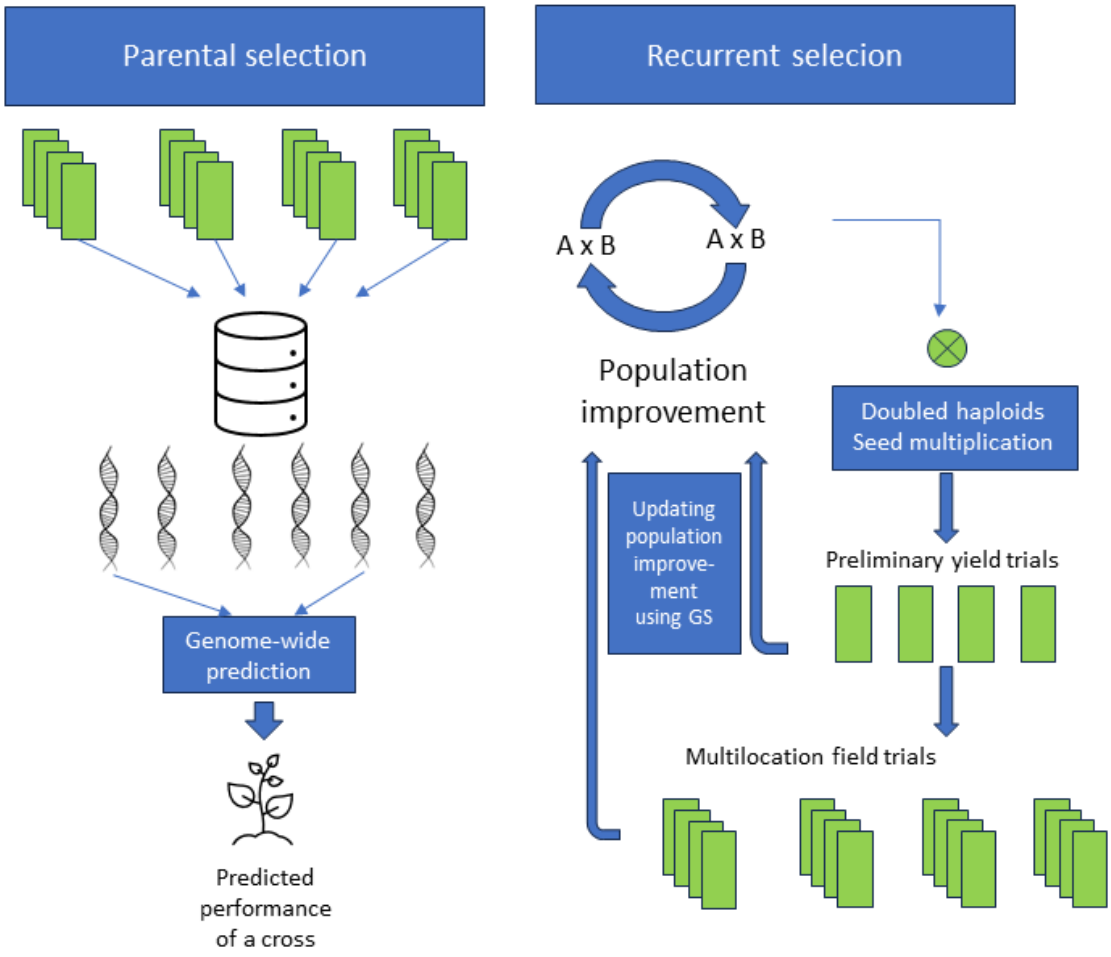

Figure 2: Comparison of two application scenarios of genome-wide selection in plant breeding: parental selection and recurrent selection.

The experience gained in this work suggests the need of feasibility studies for the assessment of long-term selection strategies. They prevent serious mistakes from becoming a risk for long-term investments by society or private stakeholders when major research projects are set up, for example for the utilization of genetic resources or in industrial applications in commercial breeding programs.

3.1 Parental selection strategies using genome-wide prediction in line breeding

In line breeding, the performance of the progeny population determines the value of the parents (Gaynor et al., 2017). Therefore, predicting the performance of the progeny population is critical to selecting promising parents. A progeny population is particularly suitable for the selection of high performing genotypes if it is characterized by a high mean and a high variance with respect to the trait of interest. This observation was formalized in the form of the usefulness criterion by (Schnell & Utz, 1975).

Based on the concept of the usefulness criterion, Zhong & Jannink (2007) developed a method for predicting offspring populations, basically changing the formulation of the usefulness concept so that

the heritability was always 1. The authors of the study tested the method using simulations and found that among the crosses, the variance of the means was substantially greater than the variance of the standard deviations, making the prediction of the standard deviation or variance of the trait of interest less relevant than the prediction of the mean (Zhong & Jannink, 2007).

First approaches to predict the mean and variance of progeny populations based on marker effects were entirely based on simulations: genotypic values of individuals of the progeny population were calculated as a function of the breeding values of their parents and optionally the prevailing linkage disequilibrium. For the entirety of simulated progeny individuals, the population mean and population variance were then calculated and used as a predictor for the actual population parameters to be observed (Bernardo, 2014; Endelman, 2011; Lado et al., 2017; Mohammadi et al., 2015; Tiede et al., 2015; Yao et al., 2018). Simulations are computationally and time intensive and, given the potentially infinite size of progeny populations, there is a risk of sampling errors. On the other hand, simulations of offspring populations allow the prediction of interactions, such as based on epistasis (Yao et al., 2018) or based on interactions with the environment. However, simulations are always based on marker effects and are therefore only as reliable as the estimate of these effects. The prediction of higher degree statistics is also subject to increasing uncertainty: the variance results from the squared deviation of observations from the population mean. Therefore, it can be concluded that in the prediction of variance, the error in the prediction of the mean is squared and also plays a role.

More recently, two methods were published for predicting the usefulness criterion, one based on Markov chain Monte Carlo samples of marker effects from a whole-genome regression model (Lehermeier, Teyssèdre, et al., 2017) and the other based on an analytical approach that considers linkage disequilibrium (Osthushenrich et al., 2017). Allier et al. (2019) expanded the approach of (Lehermeier, Teyssèdre, et al., 2017) for four-way crosses and showed high correlations between predicted and observed trait mean and variance of simulated offspring populations. The approach of Osthushenrich et al. (2017) also showed high correlations between predicted and observed population means and variances in simulation studies, a finding that was further confirmed by field experiments (Osthushenrich et al., 2018).

With regard to the validation based on simulation studies mentioned above, it must be criticized that the performances of the genotypes of each progeny population were simulated based on known marker effects. These effects were subsequently used to predict the population mean and the population variance of the progeny. Nevertheless, this scenario does not correspond to the real-life problem breeders face during a selection decision process. Similarly, regarding the field study by Osthushenrich et al. (2018), it must be stated that training and test populations were always congruent, i.e., that the populations to be predicted were always already used to calibrate the

prediction models. This also does not correspond in any way to an application-oriented situation. It should also be noted that Osthushenrich et al. (2018) do not report heritabilities for the traits studied and removed outliers based on an unspecified procedure. Hence, the presented findings do not allow users to draw any conclusions regarding the real suitability of the published methods for the prediction of the usefulness criterion.

Our study allowed us to extensively test the approach of Osthushenrich et al. (2018) in an applied manner in the context of a commercial barley breeding program that spanned four years from 2016 to 2019 (Rembe et al., 2022). The present data set was well suited to investigate the applicability of the usefulness criterion: phenotypic records and genomic information were of high quality for parents and progeny populations, prediction abiblities were high, both within and between breeding cycles and across the entire data set. We have shown that the prediction abilities for the means and variances of offspring populations were highly dependent on the complexity of the trait under study. In line with the observation of Zhong & Jannink (2007), we found that variance played a minor role in the prediction of the usefulness criterion. The results from Rembe et al. (2022) were consistent with the observed results from Wolfe et al. (2021) showing low correlations between predicted and observed variance of progeny populations for complex traits.

3.2 Selection strategies using genome-wide prediction to improve heterotic pools in hybrid breeding

The goal of hybrid breeding is to optimize the exploitation of heterosis through selection and recombination (Schulthess et al., 2017). If only additive effects are present, the progeny of a cross will have a genetic value equal to the mean of the parent's genetic values. With the presence of epistatic and dominance effects, the genetic value of the progeny can deviate from the mean of the parent's genetic values (Falconer & Mackay, 1996; Hallauer et al., 2010). Thus, the task of hybrid breeding is to configure additive, epistatic, and dominance effects in the best possible way to come up with the ideal hybrid genotype.

To make the best use of heterosis, it is useful to group genotypes according to their heterotic response when crossed with distinct material. The resulting group is called a heterotic group. When genotypes of complementary heterotic groups are crossed with each other, some beneficial effect due to heterosis can be expected depending on the combination suitability. Particularly well-matched heterotic groups whose genotypes produce high-performing hybrids when crossed in a complementary manner are referred to as a heterotic pattern (Melchinger & Gumber, 1998).

Methods to establish heterotic pools were provided by Zhao et al. (2015) and Boeven et al. (2016). These steps are followed by the further development of the heterotic pools. Constant improvement of

heterotic pools can be achieved by recurrent reciprocal selection (Comstock et al., 1949). In this approach, two breeding programs are run in parallel, one for each heterotic pool. Test crosses of complementary genotypes are then used to determine GCA, which in turn serves as a criterion for selection decisions (Comstock et al., 1949). In the context of reciprocal recurrent selection, the implementation of genome-wide prediction appears promising to reduce the cost and time required to determine GCA (Rembe et al., 2019), as demonstrated by several simulation studies in different crops (Ibáñẽz-Escriche et al., 2009; Kinghorn et al., 2010;Cros et al., 2015).

In this work, the efficacy of recurrent reciprocal genome-wide selection was investigated for the first time under application-oriented conditions with extensive field trials (Rembe et al., 2021). A promising accuracy of genome-wide prediction models for wheat hybrid performance has been reported in earlier experiments for different scenarios of data availability (Figure 3A, B) (Zhao et al., 2015). Based on these results an experimental breeding program focusing on the female heterotic pool based on recurrent reciprocal genome-wide prediction was established. In the experiment described in Rembe et al., (2021), increase in mid-parent heterosis was achieved, but better-parent heterosis was not significantly increased. Furthermore, the realized selection gain fell short of the expected one (Rembe et al., 2021). Because Rembe et al. (2021) focused only on improving the female heterotic pool, allele frequencies of the male heterotic pool could not be optimized. In this case, the complementarity of heterotic pools desired in overdominance cannot be achieved if the corresponding alleles are not already fixed in the male pool (Rembe et al., 2019, 2021). In the case of partial dominance or negative dominance, the favorable allele should be fixed in both heterotic pools (Rembe et al., 2019). Again, it should be noted that if the male heterotic pool remains constant, the optimal configuration cannot be achieved unless the corresponding alleles are already fixed (Rembe et al., 2021).

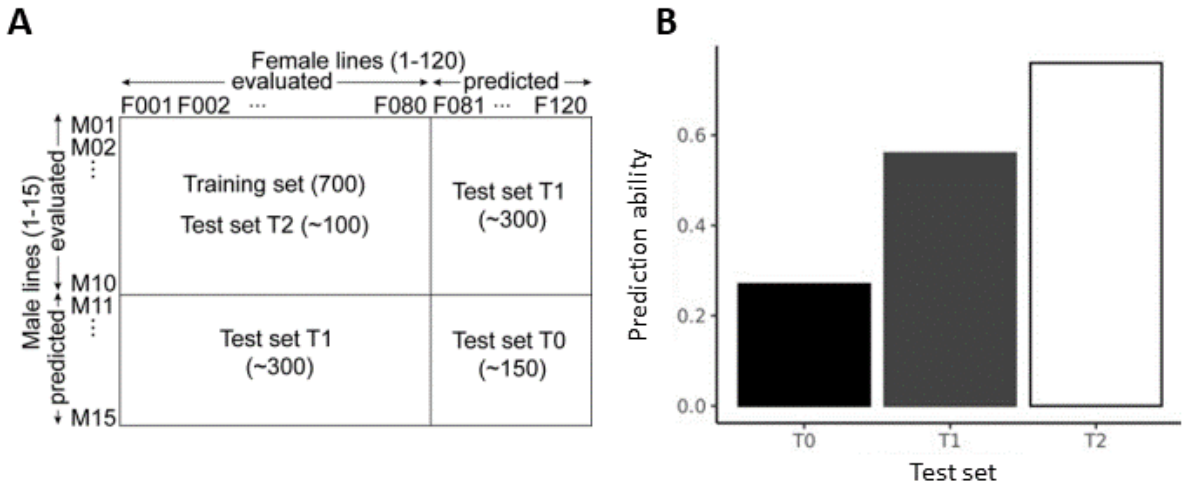

Figure 3: Genome-wide prediction scenarios as reported in Zhao et al. (2015). A: In scenario T2, both male parent lines and female parent lines have been evaluated phenotypically in the field. In scenario T1 only female parent lines or only male parent lines have been tested phenotypically in the field. In test set T0, neither female parent lines, nor male parent lines have been tested in the field (Zhao et al., 2015). B: Prediction abilities for predicting performances of the test sets corresponding to the respective scenarios.

An important aspect that Rembe et al. (2021) focus on to explain the low success of the described breeding program is the low realized prediction accuracy of the models calibrated on 2012 and 2013 data (Zhao et al., 2015) for the performances of overlapping genotypes tested in 2019. Cros et al. (2018) found, based on simulations, that prediction accuracies could be improved when calibrations of the models relied on two preceding breeding cycles. In Rembe et al. (2021), prediction accuracies were also low for those genotypes already included in the 2012 and 2013 training datasets (Zhao et al., 2015). Therefore, it is likely that other influences have had a negative impact on the effectiveness of the breeding program.

Climate change and the growth of the world's population, as well as the shrinking land area available for agricultural purposes associated with both events, demand higher and reliable yields with efficient use of available resources (Lobell & Gourdji, 2012; Misra, 2014; Ray et al., 2019; Zabel et al., 2014). Innovations from agricultural research, of which plant breeding is one, can be used to achieve the ambitious goals associated with this.

Genetic gain is the increase in the average genetic value or in the average phenotypic value within a population over several generations as a result of selection (Hazel & Lush, 1942) and is sometimes also referred to as response to selection. Maintaining genetic gain over as long a period of time as possible is a basic requirement for long-term selection.

Genome-wide selection is a tool that has been routinely used in commercial breeding programs for several years to increase genetic gain. One challenge for the long-term maintenance of genetic gain in genome-wide selection is the reduction of genetic diversity within a population through high selection intensity. However, genetic diversity is an essential prerequisite for long-lasting improvement (Goddard, 2009). The impact of genome-wide selection on genetic variance has been demonstrated in simulation studies (Jannink, 2010). Different approaches to address this problem have been proposed in the literature (Daetwyler et al., 2015; Goddard, 2009; Goiffon et al., 2017; Jannink, 2010; Müller et al., 2018) and contrasted in Rembe et al. (2019). Other approaches for implementing genome-wide prediction in long-term selection include look-ahead selection (Moeinizade et al., 2019) and optimal contribution selection with branching (Santantonio et al., 2020), which were summarized in Labroo et al. (2021). Changing environmental conditions as a result of climate change are a further challenge to the successfulness of long-term selection.

3.3 Genotype-by-environment interactions are expected to have a high impact on the success of long-term breeding strategies

In the work presented, we were able to provide evidence that long-term strategies in plant breeding can be complicated by large changes in environmental conditions (Rembe et al., 2021). Cross-validation is commonly used to test the performance of prediction methods. The resulting prediction ability or prediction accuracy is then used as a guide to estimate how reliable the predicted values are to be used as selection criteria. For cross-validations, the population of genotypes studied is divided into a training set and a test set. Based on phenotypic records and genomic information of the training data set, a model is calibrated, which in turn is used to predict the performance of the genotypes of the test set based exclusively on genomic information. Based on the correlation between the phenotypic records of the test set and the predicted performances, the predictive ability or predictive accuracy is determined.

Nevertheless, since in this approach genotypes of the test set and of the training set originate from the same data set and are therefore produced under the same environmental conditions, the suitability for long-term selection can only be derived from the predictive ability or predictive accuracy to a limited extent. In the past, this circumstance was less relevant because of more stable environmental conditions. Validation studies for long-term selection based on genome-wide prediction were furthermore rare, as in the first decade of genome-wide prediction more attention was focused on other applications of genome-wide prediction.

Recently, genotype-by-environment-times-year interactions have become increasingly important: drought years are accumulating in Central Europe (Shorachi et al., 2022) and extreme weather events with strong local limitation are occurring more frequently (Crespi et al., 2020). When making selection

decisions, a breeder must consider that future environmental conditions may affect his predictions and thus his basis for decision-making. The requirement for validation studies must be that this problem of potential inequality of training environment and test environment is illuminated, and for a fair comparison of prediction methods they must be tested under realistic, application-related conditions.

3.4 Genome-wide prediction to overcome challenges in long-term selection

In the frame of climate change, the classical selection of suitable genotypes based on phenotypic performance alone is increasingly moving into the background in favor of predictive breeding approaches involving phenotype, genotype, environment and the interaction of these components (Y. Xu et al., 2022). Large, multidimensional datasets consisting of structured and unstructured information could play a role in the future to make breeding decisions based on big data and artificial intelligence (Y. Xu et al., 2022). By merging different experimental datasets, prediction accuracies for grain yield in hybrid wheat could be doubled (Zhao et al., 2021). Through the integrative use of in-house and publicly available data sets, breeders could build their predictions on broader basis and, thus, achieve more certainty in decision-making. Along with this, genetic diversity could be exploited, which supplements the gene pool used for breeding with valuable properties, such as adaptations to stress habitats or disease resistances (Schulthess et al., 2022). De los Campos et al. (2020) demonstrated an approach to predict cultivar performances under simulated weather conditions to overcome problems associated to genotype-by-environment interactions by a combined analysis of phenotypic and genomic information with environmental cofactors obtained from weather stations, and provided promising results from validating the method. Promising results were also obtained in predicting the performance of crosses in a commercial hybrid maize breeding program by incorporating weather data using random forest and optimization models (Ansarifar et al., 2020). Approaches that add a component to genotype-by-environment interactions that will take into account applied agronomic practices and, thus, shed light on genotype-by-environment-by-management interactions have recently received greater interest and may facilitate breeders to optimize customer-oriented selection decisions (Beres et al., 2020; Mahmood et al., 2022).

A core problem of using big data in plant breeding is the processing of differently structured data sets with varying quality. Breeding companies have historically generated large data sets that, in addition to the phenotypic performance of genotypes, sometimes provide comprehensive information on environmental conditions prevailing at test locations, such as weather or soil type. The integrative use of these data could lead to more robust predictions involving genotype-by-environment interactions, allowing more reliable long-term selection decisions.

4. Summary

Following the establishment of genome-wide selection in plant breeding programs, the search for areas of application for this promising technology continues. Of particular interest is the use of genome-wide selection to improve populations across generations, for example in long-term breeding programs or in parental selection. This work provides user-based experimental assessments of the utility of genome-wide selection in parental selection in barley under usefulness criterion estimation, and in reciprocal recurrent genomic selection for long-term improvement of complementary populations for wheat hybrid breeding. Empirical evidence suggests that, despite promising performance in theoretical and simulation-based environments, both concepts evaluated here present challenges under application-oriented conditions.

Nachdem sich die genomweite Selektion in Pflanzenzuchtprogrammen etabliert hat, geht die Suche nach Anwendungsbereichen für diese vielversprechende Technologie weiter. Von besonderem Interesse ist der Einsatz der genomweiten Selektion zur Verbesserung von Populationen über Generationen hinweg, z. B. in langfristigen Züchtungsprogrammen oder bei der Elternselektion. Die vorliegende Arbeit liefert anwenderbasierte experimentelle Bewertungen des Nutzens der genomweiten Selektion bei der Elternselektion von Gerste unter Schätzung des Usefulness Criterions und bei der reziproken rekurrenten genomischen Selektion zur langfristigen Verbesserung komplementärer Populationen für die Weizenhybridzucht. Empirische Belege deuten darauf hin, dass trotz vielversprechender Indikatoren in theoretischen und simulationsbasierten Umgebungen beide hier evaluierten Konzepte unter anwendungsorientierten Bedingungen noch große Herausforderungen darstellen.

5. General References

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6. Abbreviations

GCA	General combining ability
GS	Genome-wide selection
PS	Phenotypic selection
RRGS	Reciprocal recurrent genomic selection
SCA	Specific combining ability

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8. Curriculum Vitae

Work Experience

10/2023 KWS SAAT SE & Co. KGaA
- Breeding Information Scientist – Germplasm Management

01/2022 – 08/2022 State Institute of Agriculture and Horticulture of Saxony-Anhalt
- Head of the Laboratory for Seed Accreditation
- Vice head of the department of Seed-Accreditation

02/2017 - 12/2021 Leibniz Institute of Plant Genetics and Crop Plant Research
- Research associate in the group of Prof. Dr. Jochen Reif
- Evaluation of effectiveness of selection strategies
- Curation and imputation of genomic data
- Coordination and planning of field tests for project partners from industry and science
- Biometric analyses of genomic and phenotypic data
- Responsibility for an experimental winter wheat breeding program
- Supervision of students

Education

Since 03/2022 Martin Luther University of Halle-Wittenberg
- Master of Science in Bioinformatics

09/2014 - 05/2017 Martin Luther University of Halle-Wittenberg
- Master of Science in Crop Science

Master's thesis with the topic "Genome-wide Association Mapping and Genome-wide Prediction of Anther Extrusion in a Nested Association Mapping (NAM) Population of Wild x Cultivated Barley"

09/2011 - 09/2014 Leipzig University
- Bachelor of Science Biology
- Bachelor's thesis with the topic "Genome-wide Association Mapping in Summer Barley"

Awards

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2019 Rembe, M., Zhao, Y., Jiang, Y., and Reif, J.C. 2019. Reciprocal Recurrent Genomic Selection: An Attractive Tool to Leverage Hybrid Wheat Breeding. Theoretical and Applied Genetics. https://doi.org/10.1007/s00122-018-3244-x.

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Ich erkläre, an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst, keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. / I declare under penalty of perjury that this thesis is my own work entirely and has been written without any help from other people. I used only the sources mentioned and included all the citations correctly both in word or content.

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