Implementation of genomic selection in the poultry industry

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Implications

- This paper describes and discusses implementation of genomic selection in broilers and layers, emphasizing distinctive features of the poultry industry.
- We discuss various practical aspects of implementation, from development of tools and calculation of costs from the experimental stage up to actual implementation in commercial settings.
- Experimental implementations have shown that genomic data can indeed be used to improve the accuracy of estimated breeding values and lead to greater response to selection than traditional selection methods.
- Opportunities to reduce generation intervals are, however, limited, in particular for broiler breeding programs.
- We also identify several challenges of practical implementation of genomic selection, such as maintaining accuracy with large-scale DNA collection and labeling, genotyping costs, collecting accurate phenotypes for training, and meeting high requirements in terms of data storage and analysis.
- Currently, genomic selection has been implemented for routine evaluation in the poultry industry, but we are looking forward to further developments in technology, analytical tools for maximizing genetic gain while constraining inbreeding, and costs of running genetic improvement programs in poultry.

Key words: broilers, genomic selection, layers

Introduction

Genomic selection using high-density SNP panels was first implemented in dairy cattle breeding programs. It provided benefits in terms of reduced generation intervals, improved accuracies of selecting young animals, and reductions in costs associated with the requirement of progeny testing bulls in traditional breeding programs (Hayes et al., 2009). Several distinct features of the poultry breeding industry differ markedly from dairy cattle breeding and influence the manner in which genomic selection can be used for genetic improvement in poultry breeding:

- Traditional genetic improvement programs in poultry already have short generation intervals (multiple overlapping generations per year with selection every 6 wk in broilers, non-overlapping annual generations in layers). There is some scope for shortening the generation interval in layers but not as much as was the case for dairy cattle breeding where bull pathways could be reduced in length from greater than 6 yr to less than 3 yr (Schaeffer, 2006, Schefers and Weigel, 2012).


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- Very large numbers of selection candidates and high selection intensities, combined with low marginal revenues from a single selection candidate; in poultry breeding programs, tens of thousands of selection candidates are generated per line per generation, with only 1 to 3% of males selected for breeding. Thus, to be economically viable, genotyping has to be relatively inexpensive.
- In poultry, genetic progress created in pure lines is disseminated through a comprehensive crossbreeding multiplication pyramid that impacts large numbers of commercial layers and broilers. Thus, a single line only contributes 25% of the genes in commercial poultry compared with 100% in the purebred production systems in dairy cattle.
- In dairy cattle, large numbers of doses of semen are sold from the top bulls due to both the large volume of semen that can be produced by a bull and the ability to cryopreserve the semen for storage, shipment, and later use. In poultry, no efficient method of cryopreservation is available. Thus, highly selected males can be utilized only locally, and each rooster can only inseminate a limited number of hens and for a limited time.
- In the poultry industry, there is no pedigree information on commercial descendants of the pure lines. Thus, it is difficult to track individual contributions to improved performance at the commercial level. In contrast, the dairy industry has pedigreed individual performance records on large numbers of commercial cows.

All these factors have to be carefully considered before implementation of any new technology, including genomic selection. The challenges for implementation of genomic selection in livestock were summarized by Misztal et al. (2013) with the following statement: "Methodology for genomic selection in a commercial situation is dependent on attention to detail, using the mature methodology, and knowledge of issues of genomic selection specific to a given population."

In poultry, routine implementation of genomic selection has been preceded by several carefully planned multi-generational selection experiments in both layers and broilers (Misztal et al., 2013; Heidaritabar et al., 2014; Wolc et al., 2015). These experiments enabled verification of the promises of genomic selection in terms of increased accuracy, increased response to selection, and opportunities to redesign breeding programs to maximize the benefits from this technology. These initial experiments also provided lessons on practical application of genomics-based breeding programs, such as large-scale genotyping with proper sample tracking.

In this paper, we review some lessons from the experimental phase of genomic prediction and selection in poultry and provide information on practical implementation of genomic selection in breeding programs for layers and broilers. We will focus here primarily on the implementation of genomic selection by Hy-Line Int. and Aviagen Ltd., which are among the largest international breeding programs in layers and broilers, respectively, and members of the EW group. However, implementation of genomic selection has also been pursued by other major players in the international poultry breeding industry.

Development of Tools

SNP genotyping tools

Genomic selection is not possible without development of high-density SNP chips, which provide means for rapid, massive, and relatively inexpensive genotyping. The chicken was the first livestock species sequenced (Hillier et al., 2004), and simultaneously, several million SNPs were identified (Wong et al., 2004). The first chicken SNP chip had only 3,000 (3K) SNPs (Muir et al., 2008), which was soon found to be insufficient. After a series of privately developed higher-density chips (Fig. 1), two medium-sized chips were developed that have had a major impact on genomic selection research and its implementation: a 60K chip de-

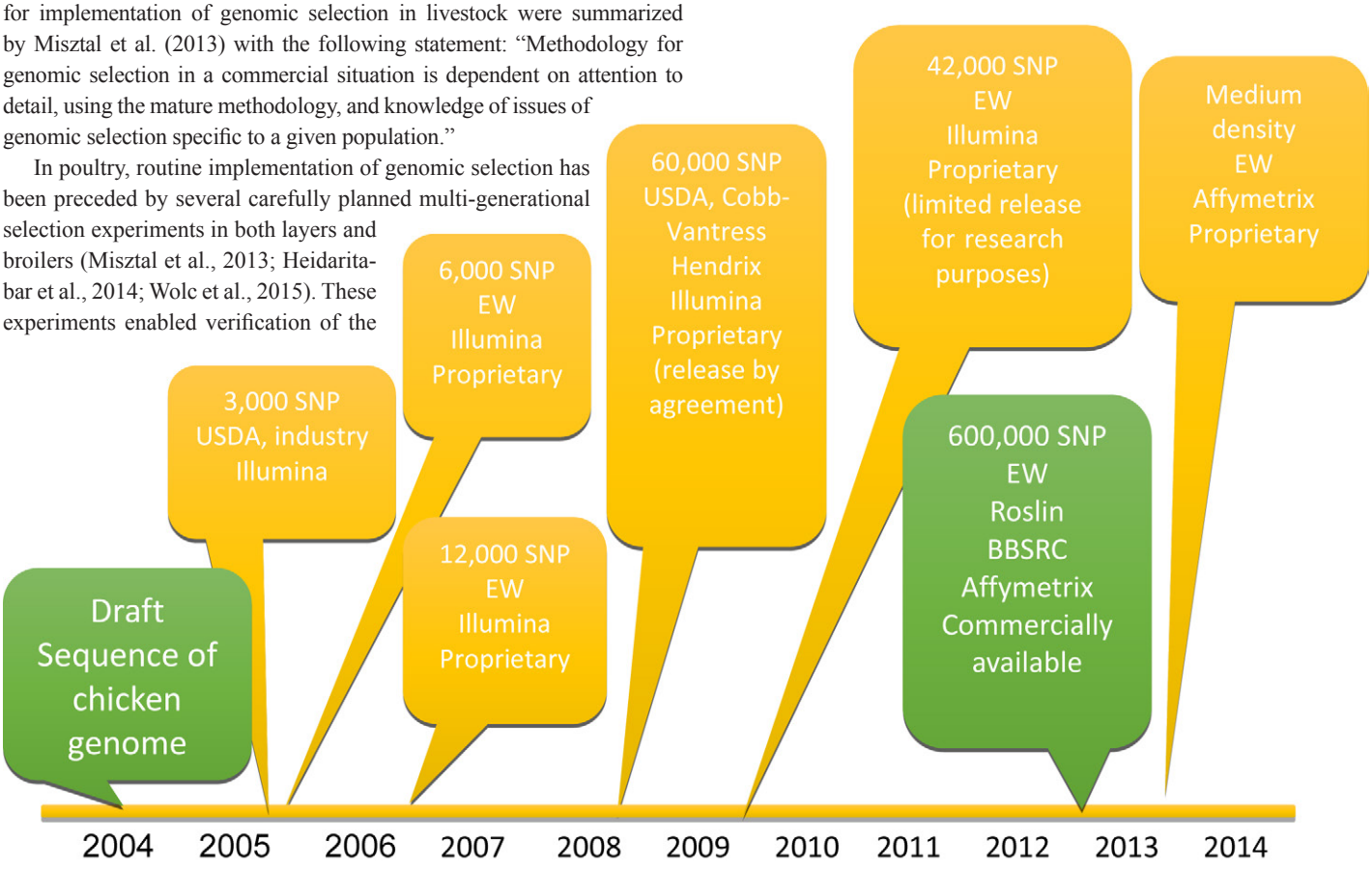
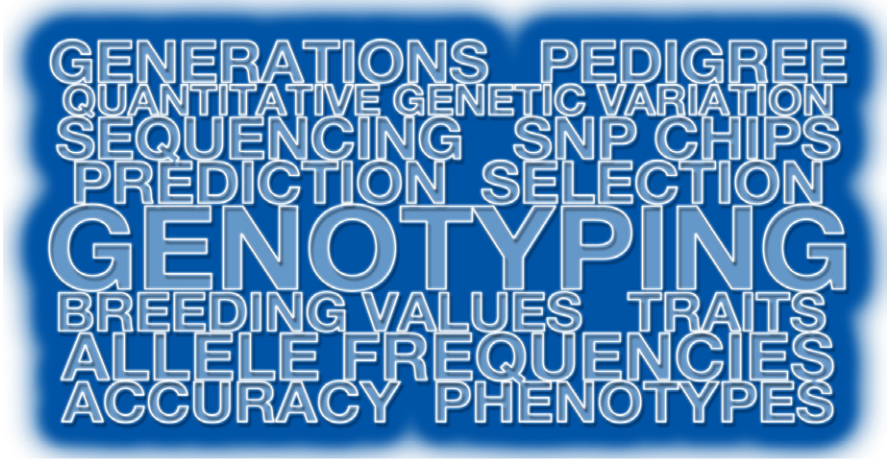


Figure 1. History of SNP chips for poultry.



veloped with USDA funding and used by the Cobb and Hendrix groups, with release by agreement for research purposes (Groenen et al., 2011), and a 42K chip developed by the EW group for internal use and limited release for research. Both of these chips were designed to include genetic variation in both broiler and layer lines. These developments were recently crowned with the first publicly available high-density 600K chip, developed with support from the BBSRC and the Roslin Institute (Kranis et al., 2013), which includes variants from both brown and white egg layer breeds and from broiler breeds. Because of the still relatively high cost of these high-density SNP chips, their initial implementation in poultry breeding capitalized on the much lower cost of low-density SNP chips and the ability to impute selection candidates up to higher density from densities as low as 400 SNPs across the genome (Habier et al., 2009).

Interestingly, after the rapidly increasing density of SNP chips, the latest chips that are used for routine implementation of genomic selection in poultry breeding are back to having medium density, containing tens of thousands of SNPs. For the EW programs, these SNPs are, however, carefully selected subsets from the 600K chip, tailored for specific lines. There are three explanations for this shift back to medium density. The first is that, thanks to technology advancements, the cost of medium-density panels has dropped considerably and is now comparable with that of low-density arrays. Second, the accuracy of prediction of genomic breeding values within line or breed, as a function of SNP density, appears to plateau at several tens of thousands of SNPs (Ilska et al., 2014), at least with training sets of the size currently used. Finally, the use of a single medium density panel without the need for imputation from low to higher densities (Habier et al., 2009) simplifies the genomic prediction workflow. Thus, for the short-term future, medium density arrays are an attractive option for large-scale implementation of genomic selection in poultry. However, these advantages of medium- over high-density arrays must always be weighted against the fact that using only medium-density chips could impact the ability to precisely localize the genes that are responsible for quantitative genetic variation. To mitigate this risk, arrays could be designed to have increased marker density in genomic regions of interest, if prior information is available, or to enable accurate imputation up to higher density or even full sequence.

Analysis software

In addition to genotyping technology, computing resources and software are important components of the implementation of genomic prediction and selection. The first computational step involves genotype calling and quality control using software developed by SNP chip developers, i.e., GenomeStudio for Illumina and AxiomAnalysisSuite for Affymetrix. Additional quality control steps, such as inspecting parent-offspring mismatches, testing for unexpected changes in allele frequencies between generations, and calculating the variance of imputed genotypes, can be performed with the publicly available software PLINK (Purcell et al., 2007) or other self-developed tools.

A wide range of software is available for genotype imputation and for estimation of breeding values based on genomic information, genomic estimated breeding values (**GEBV**). Some programs for genotype imputation that are capable of handling industry-scale amounts of data include Beagle (Browning and Browning, 2007), AlphaImpute (Hickey et al., 2012), and FImpute (Sargolzaei et al., 2014). Programs for large-scale GEBV estimation include GenSel (Garrick and Fernando, 2013), which allows a range of Bayesian Variable Selection Methods; BLR (Pérez et al., 2010), which implements Bayesian Ridge Regression and LASSO methods; BGLR (Pérez and de los Campos, 2014), which implements various parametric Bayesian models and semi-parametric procedures in a unified framework; the BLUPF90 family (Misztal et al., 2014), which implements the Single Step GBLUP approach (Misztal et al., 2009); DMU (Madsen et al., 2014), MIX99 (Lidauer et al., 2011), and ASReml4 (Gilmour et al., 2014), which implement REML-type algorithms to solve mixed-model equations. The methods implemented in these software programs for GEBV estimation mostly differ in prior assumptions on SNP effects and the ability to use phenotypes from non-genotyped animals. Validation of GEBV and re-estimation of effects and of regularization parameters are often applied after each new batch of data is added to training over time, as genomic prediction appears to present more convergence problems and can be less robust to errors in phenotypes or to sample misidentification than was the case with conventional pedigree-based genetic evaluation analyses.

Cost to Implement Genomic Selection

Through the development of new genotyping platforms, the cost of genotyping has steadily decreased. However, cost of genotyping remains one of the major challenges that limits widespread application of genomic selection to poultry breeding. Thus, many aspects, including which animals should be genotyped and on which size panel, genotyping costs, expected accuracy of genotype imputation, and expected accuracy of GEBVs, must be carefully considered when designing genomic selection breeding programs for poultry.

Calculation of the cost of the initial implementation of genomic selection in a single pure line of layer chickens is provided here as an illustrative example, including comparison of strategies for high-density (**HD**) and low-density (**LD**) genotyping and imputation and implications for size of the training dataset that is generated for initial implementation. The following population and cost structures were assumed: 200 sires, 2,000 dams, and 10,000 selection candidates per year; HD genotyping is three times more expensive than LD genotyping. Several scenarios were considered in terms of which animals should be genotyped on the HD panel and the accuracy of imputation. These were contrasted with a scenario in which all selected parents from eight ancestral generations

plus selection candidates from the current generation were HD genotyped (Fig. 2). The imputation accuracies represent imputation from approximately 400 SNPs to the 42K panel. Additional details on scenarios and accuracies are in Wolc et al. (2011a), but three scenarios with stronger constraints on costs were added in this example: i) HD genotyping of only three generations of males and LD genotyping of all dams and selection candidates; ii) HD genotyping of five generations of males and LD genotyping of all dams and selection candidates; iii) HD genotyping of only the parental generation and LD genotyping of selection candidates. Note that, although having only the parental generation HD genotyped for initial implementation of genomic selection resulted in a good accuracy of imputation to cost ratio, it may provide insufficient data for training genomic predictions.

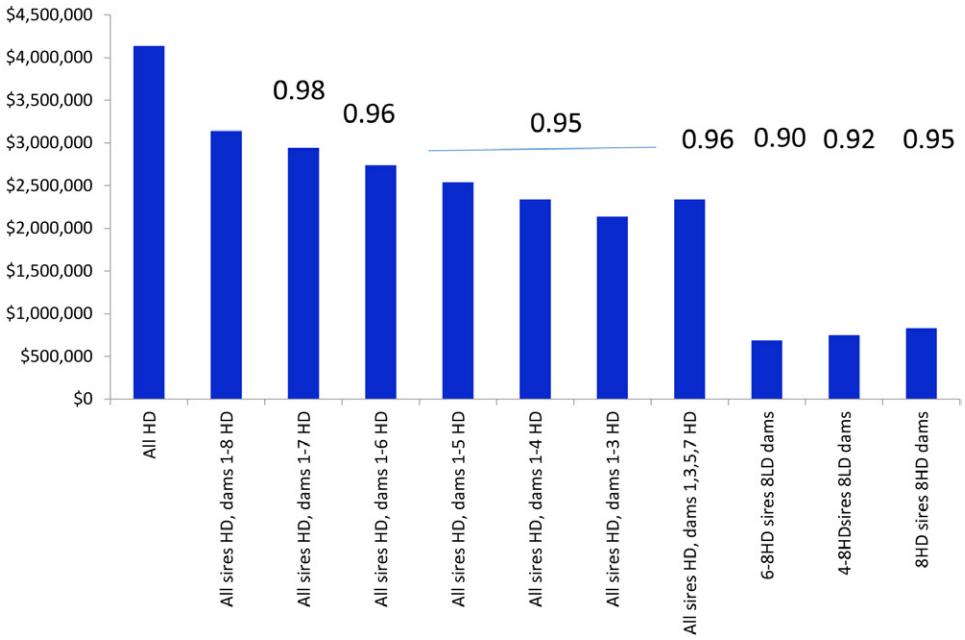


Figure 2. Genotyping costs for initial implementation of genomic selection and accuracies of imputation of selection candidates from generation nine (above the bars) of an experimental line of layer chickens for different scenarios of high-density (HD) and low-density genotyping. For the first eight bars from the left, eight generations of sires used for breeding are high-density genotyped, listed generations of dams are high-density genotyped, and the remaining dams are genotyped on a low-density panel. For the three bars on the right, only the generations listed are genotyped. Except for the "All HD" scenario, selection candidates are genotyped using a low-density panel of 400 SNPs.

Lessons from Genomic Selection Experiments

Comparison of genomic prediction methods

Because of limited opportunities to reduce generation intervals, the major benefit of genomic selection over pedigree-based evaluations in poultry is based on increases in the accuracy of estimated breeding values at puberty and for sex-limited traits. Accuracies of GEBVs in layers and broilers for production, product quality, reproduction, and welfare traits have been evaluated using single-step methods (Chen et al., 2011a, 2011b), Bayesian variable selection methods (Wolc et al., 2011b; Wang et al., 2013), Bayesian LASSO (Liu et al., 2014), non-parametric methods (González-Recio et al., 2008), methods that dissect genetic variance into that from coding and non-coding regions (Abdollahi-Arpanahi et al., 2014), and approaches that capitalize on and include annotation information (Morota et al., 2014). In all these studies, GEBVs were more accurate than pedigree-based EBVs, but there was no clear superiority among the different genomic-based methods, i.e., no method consistently outperformed other methods across traits and populations. The use of genomic prediction was, however, particularly promising for traits that were sex limited, hard to measure, expensive to measure, or measured late in life. For traits for which phenotypes are not available on selection candidates (i.e., egg production and quality in roosters), genomic predictions capture information on Mendelian sampling terms and thus allow within-family selection, in contrast to traditional pedigree-based predictions.

Need for retraining

The initial enthusiasm for genomic selection based on simulation studies (Solberg et al., 2009) was dampened when it was found that the persistency of accuracy of GEBVs across generations was not as good in real data as reported in simulations, although it was greater than for pedigree-based EBV (Wolc et al., 2011c). Thus, the possibility of creating a single static training population for traits such as disease resistance and abandoning phenotyping was found not to be effective with current methods and data for genomic prediction.

It has now been well established that the prediction accuracy of genomic models erodes over time (e.g., Habier et al., 2007; Wolc et al., 2011c). Consequently, genomic prediction models are often re-trained every generation. In commercial implementations, data accumulates over time and a question that has recently emerged is how many generations back one should go when re-training genomic prediction models. On the one hand, including more generations increases sample size, and this should, in principle, lead to higher accuracy of GEBV. However, if linkage disequilibrium patterns and allele frequencies change over generations, or in presence of genotype-by-environment interactions, SNP effects may change (Fragomeni et al., 2014, Rome et al., 2015), in which case using only data from recent generations may provide more accurate GEBV for current selection candidates.

To address this question, a study was conducted by the Aviagen Group (de los Campos et al., 2012). Data consisted of measurements of body weight adjusted for estimates of systematic and contemporary group effects and genotypes at roughly 50 thousand SNPs. This dataset was created by combining data from five consecutive batches (denoted as SET_1–SET_5). Using these data, four partitions of data into a training and a testing dataset were considered: Partition I used data from SET_1– SET_4 for training, and validation was in SET_5; on the other extreme, Partition IV used the first batch of data (SET_1) for training, and validation was performed in SET_2– SET_4. Training used Bayesian Lasso (Park and Casella, 2008), as implemented in the BGLR R-package (Pérez and de los Campos, 2014).

The results from this study are in Table 1. These can be viewed from different angles:

Table 1. Effects of training dataset size and of distance to the testing dataset on prediction accuracy (accuracies are expressed as % of the prediction accuracy achieved for SET 5 with training on partition I).

Training set partition	Training set size	Validation data			
		SET 2 (1655)	SET 3 (1758)	SET 4 (3400)	SET 5 (3492)
I = SET 1,2,3,4	16,794				100.0
II = SET 1,2,3	15,036			122.6	91.4
III = SET 1,2	11,636		114.0	95.1	77.2
IV = SET 1	8144	96.7	86.9	81.4	68.3

Note: SET 1,…,SET 5 represent five disjoint batches of data defined based on week of birth. Partitions I, II, III, and IV use SET 1-SET 4, SET 1-SET 3, SET 1-SET 2, and SET 1 for training, respectively. For each partition, prediction accuracy was assessed in each of the sets of data not used for training. Source: de los Campos et al. (2012).

a) Fixing the partition (rows in Table 1) and moving along columns (validation sets) gives an assessment of how the accuracy of GEBV erodes over generations. In this respect, results in Table 1 confirm previous reports from simulations (Habier et al., 2007) and real data analyses (Wolc et al., 2011a) that accuracy erodes quickly over generations. Thus models for genomic prediction need to be re-trained as often as possible.
b) Fixing the validation dataset (i.e., columns in Table 2) and moving along partitions (rows in Table 1) gives an assessment of the joint effects of reducing the size of the training dataset and increasing genetic distance between training and validation data. Results show a fast decrease in accuracy as the training dataset becomes smaller and more distantly related to the validation data.
c) Finally, using results along the diagonal of Table 1 (i.e., validation in SETS 5, 4, 3, and 2, with training on partitions I, II, III, and IV, respectively), we can address the question how many generations back should be used for training. Although the comparison of prediction accuracy in different testing sets is subject to sampling variability because the testing sets are disjoint, the results in Table 1 suggest that there may be an optimum, with maximum accuracy attained in Partition II with validation in SET 4.

Similar observations were made by Weng et al. (2014) in layers, where addition of information from distant relatives had very limited impact on the accuracy of genomic predictions of selection candidates in the current generation.

Multiple line predictions

Opportunities to increase training data size by combining data from multiple lines were tested by Calus et al. (2014), with the conclusion that closely related lines may slightly increase accuracy of predictions while more distant lines did not improve accuracy and may actually be harmful. In a single step setting, multiline data can also be utilized provided the genomic relationship matrix is scaled correctly (Simeone et al., 2012). Based on simulation studies, it is expected that the use of sequence data will alleviate some of the problems of inconsistent SNP effects across generations and populations, as the actual causative mutations would be genotyped, although initial empirical results using a limited amount of sequence data have not shown too much improvements in accuracy (Heidaritabar et al., 2015).

Empirical response to genomic selection

In contrast to other livestock species, poultry breeders have been able to directly compare response in breeding programs using genomic vs. pedigree selection methods. In parallel breeding programs, improvements from genomic selection over pedigree-based selection were observed in terms of both a higher average index value for the genomic-selected line after two generations of selection (Heidaritabar et al., 2014) and higher performance under uniform environmental conditions (Wolc et al., 2015). In addition to greater responses to selection, the use of genomic data provided better insight into the combining ability of lines and a means to predict heterosis for individual sires. However, between-line variation accounted for 99% of heterosis and differences between sires within lines were small (Amuzu-Aweh et al., 2015).

Redesign of breeding programs with genomic selection

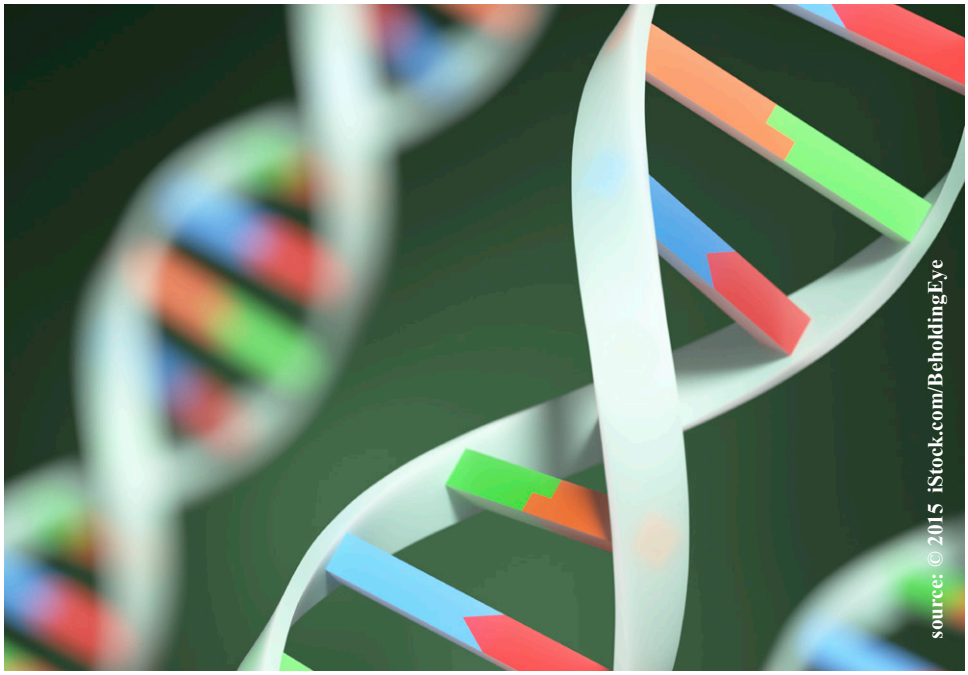
In addition to increasing accuracy of EBV, the use of genomic data also allows a re-design of breeding programs. For example, with genomic selection, the mating structure is no longer restricted to classical hierarchical mating, as cross-classified mating with parentage testing can be implemented, which both reduces inbreeding and increases the effective number of recombinations (Hsu et al., 2015). Another feature of genomic selection that has been explored in layers is shortening the generation interval from 1 yr, which is required for female candidates to be phenotyped for egg production traits, to 6 or 7 mo, which is the age at puberty. Based on experimental implementation, it was concluded, however, that, although possible, halving the generation interval for females may be not practical in a commercial setting but may be a promising option on the male side (Wolc et al., 2015).

Wolc et al. (2015) also reported on opportunities to substantially reduce the size of the breeding program in layers with the use of genomic selection because of its ability to reduce rates of inbreeding for a given number of parents used for breeding. Compared with a traditional breeding program that raises 3,000 females and 1,000 males, with 60 males and 360 females selected for breeding, Wolc et al. (2015) showed by simulation that a genomic selection program that raises only 300 males and 300 females per generation and uses 50 males and 50 females for breeding was expected to result in half the rate of inbreeding per generation, while maintaining the same rate of response per generation, resulting in equal rates of inbreeding per year and a doubling of response if generation interval was halved in the genomic selection program. The reduced rate of inbreeding for genomic selection is the result of its ability to generate information on Mendelian sampling terms, which is particularly important for selection of males, since they are selected entirely based on family information in pedigree-based programs. Implementation of these two programs in parallel lines on an experimental basis demonstrated that genomic selection indeed achieved the predicted reduction in rate of inbreeding per generation, at least up to the last generation (five) of the selection experiment. Practical implementation of genomic selection, however, will likely not involve substantial changes in the size of breeding programs, at least in the short term.

Practical Implementation in Layer Breeding Programs

In 2013, Hy-Line Int. performed the first round of genomic selection in a commercially relevant line (Hy-Line Int., 2013). This was preceded by 3 yr of genomic selection in an experimental line (Wolc et al., 2015), as

described in the previous section, which allowed development of procedures and techniques necessary for blood collection and DNA extraction on a large scale and at low cost, with high quality sample tracking. This initial implementation involved HD genotyping (600K panel) of several generations of selected males and grand dams of selection candidates, followed by low-density genotyping (1,000 SNPs, in-house genotyping) of selection candidates and their dams, with subsequent imputation to 600K. This panel of 1,000 SNPs was carefully chosen from high quality 600K SNPs using information on LD block structure, minor allele frequencies, distance between SNPs, and imputation accuracy. With the chosen data structure, the accuracy of imputation was around 98%. Multiple genomic prediction methods were validated in the target population, and the method with the highest accuracy in validation was selected for a given trait to provide GEBVs. Averaged across multiple traits, changes in accuracies for different methods ranged from negative (for complex multitrait models with genomic information, which failed to converge) to a 40% increase over pedigree-BLUP for BayesB with $\pi = 0.99$. In the subsequent generation, a slight increase in the average accuracy of GEBVs was observed due to the increase in the amount of training data. For animals without genotypes, a single-step method was implemented, resulting in a slight, but consistent, improvement in accuracy of about 1 to 2% for non-genotyped selection candidates. Thanks to advances in genotyping technology, it is possible now to use a medium-density panel for both parents and selection candidates, containing tens of thousands of SNPs, as described previously. Such an approach is competitively priced (with no loss in accuracy of GEBV compared with imputed 600K data) and removes the necessity of imputation, which is a time-consuming step and risks introduction of imputation errors, which are more common than genotyping errors. With the observed gains in accuracy of GEBV, genomic selection has subsequently been implemented in additional lines. Other layer breeding companies have also performed research on genomic selection in their populations with promising results (Sitzenstock et al., 2013; Vissher, 2015).



Practical Implementation in Broiler Breeding Programs

Studies on the application of genomic selection in broilers have been performed by the two major breeding companies Aviagen and Cobb-Vantress. With already very short generation intervals in broilers, the major impact of genomic selection is on the accuracy of EBV, particularly for traits that are not available on selection candidates at the point of selection. These include reproductive performance and disease resistance.

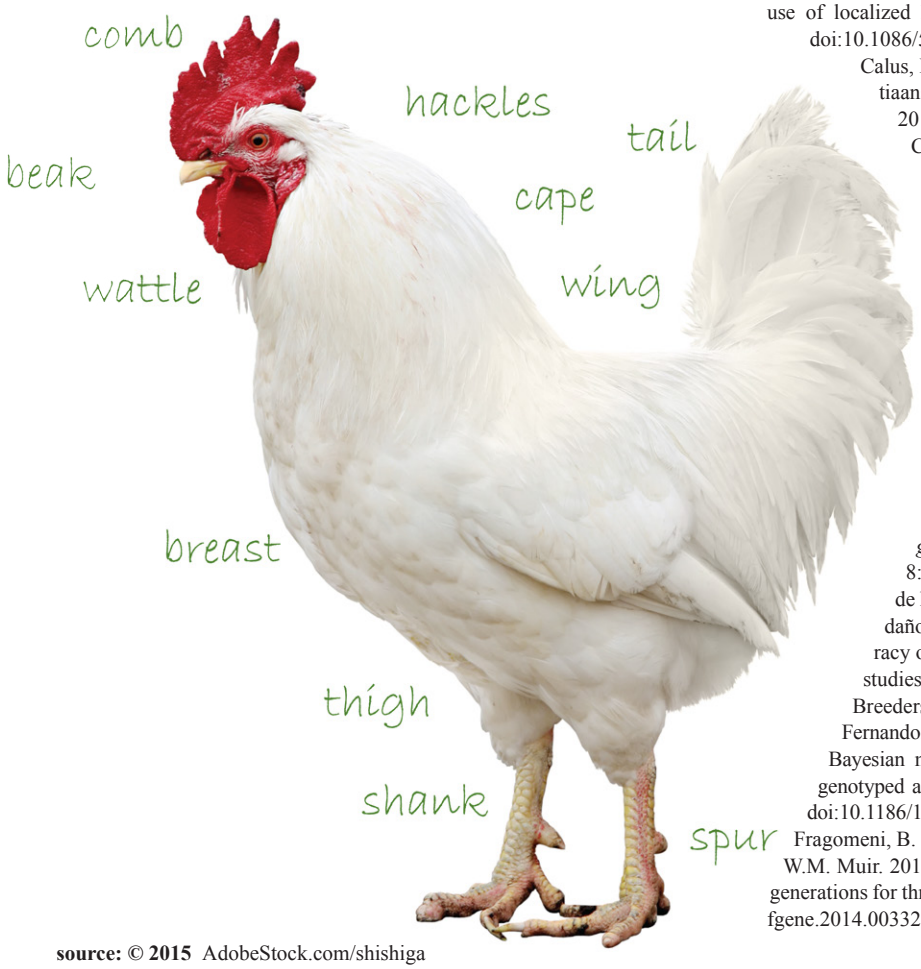
Shortly after the publication of the chicken genome project in 2004, Aviagen pioneered research on the application of genomics in broiler breeding. Capitalizing on advances in technology, it was feasible to accumulate dense genotypes on a large number of animals. That dataset allowed the efficacy of genomic selection in real populations to be validated and produced promising results (Avendaño et al., 2010, 2012). The next step was to focus efforts on developing pipelines to incorporate the analytical tools into a streamlined process for routine evaluations; these were originally implemented using the BLR software (Pérez et al., 2010) and more recently with BGLR (Pérez and de los Campos, 2014). The success of this effort enabled Aviagen in 2012 to become the first broiler breeding company to announce that genomic selection had been implemented in selection procedures for pedigree broiler lines (Aviagen, 2013).

Due to the prolificacy of chickens, a major constraint was the cost of genotyping of selection candidates. Imputation methods were crucial for alleviating this cost (Hickey et al., 2013). Even when selection candidates were genotyped with less than 400 markers and imputed up to 42K, the accuracy of imputed genotypes was in the range of 97% (Wang et al., 2013), with results for the sex chromosomes being even higher (Hickey and Kranis, 2013). Increasing the number of SNPs in the low-density array to 3K further increased the accuracy of imputation up to 600K to 99% (Wolc et al., 2014).

Extensive comparisons of the accuracy of GEBV predicted by different methods indicated that for broilers, as for layers, there are no clear advantages for any specific method (Wang et al., 2013). Due to the large size of datasets in broilers, other factors, such as scalability of the algorithms and robustness of the programs must be considered when deciding which method to choose for routine evaluation. This is where methods such as single-step BLUP appear attractive, as they allow multi-trait evaluation using the well-understood framework of mixed models. Results from numerous large-scale evaluations have established a clear advantage of GEBV in terms of accuracy compared to pedigree-based EBV in broiler populations. The relative improvement appears to be trait-specific, presumably related to the genetic architecture and control of the trait. Hence, for traits that have moderate heritability, the relative improvement in accuracy can range from 20% for fertility to 45% for egg productions, while for highly heritable traits, such as feed intake, this improvement can be greater than 50% (Wang et al., 2013; Wolc et al., 2014). Similar results have also been reported for other broiler traits, including body weight (Chen et al., 2011a), where the boost in accuracy was around 50% relative to pedigree-based EBV.

Looking Forward

Although genomic selection has been implemented in several layer and broiler breeding programs, it is still a rapidly developing area. With the recent progress in sequencing, turkeys will likely be the next poultry species in which genomic selection will be implemented (Dalloul et al., 2010). Currently, new models are being tested in poultry data, including Bayesian single step (Fernando et al., 2014), haplotype and QTL models (Sun et al., 2014; Zeng et al., 2014), and non-additive models (Zeng et al., 2013). Another emerging opportunity is the use of genotyping by sequencing (**GBS**) (Gorjanc et al., 2015). Genotyping by sequencing based on random sequence has some appeal, as it can remove the ascertainment bias that is inherent to most SNP arrays and also implies that most causative variants will be included in the predictor set. Furthermore, with the rapid drop in sequencing costs, GBS may become a viable alternative or a replacement for SNP arrays when coupled with efficient imputation algorithms. The combined effect of capturing all variation and large training datasets can lead to identification of the causal mutations underlying genetic variation, which could result in a step change in the accuracy of GEBVs. Current methods are based on SNP variation, but some studies suggest that other types of genetic variation such as copy number variation may be important for trait determination and are worth exploring for selection (Zhang et al., 2014).



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