

Chapter 6. Marker-assisted selection

6.1 Introduction

Much more has been written with respect to methods for detection and analysis of individual quantitative trait loci as compared to application of these genes in breeding programs. Many of the reviews on this topic that were published were quite pessimistic (Smith and Simpson, 1986; Stam, 1986). In those situations in which traditional selection index works well, little is gained by identification of the individual loci affecting quantitative traits. However, many practical breeding situations are encountered in which trait based selection index is very inefficient or impractical. In these instances marker-based selection can make a very significant gain. In this chapter we will first review the principles of selection index, and then consider the value of genetic gain, which is much higher than generally thought. We will then consider situations for which traditional selection index is not efficient, and consider various possible strategies to apply MAS. Finally we will briefly consider long-term consequences of MAS, and application of MAS together with other possible biotechnological advances.

6.2 Principles of selection index

Lush and Hazel formulated the principles of economic selection index. Although they did not phrase the derivation of selection index in matrix terms, we will do so because it greatly facilitates explanation. For selection on a single trait based only on trait records and relationships among animals, the expected gain is maximized by selecting individuals based on their estimated genetic values, u , which can be computed as follows:

$$u = E(u) + \mathbf{CV}^{-1}[\mathbf{y} - E(\mathbf{y})] \quad \{6.1\}$$

where $E(\cdot)$ denotes an expectation, \mathbf{y} is a vector of trait records, \mathbf{C} is the covariance matrix between u and \mathbf{y} , and \mathbf{V} is the variance matrix of \mathbf{y} . (As previously, matrices will be denoted by **bold type**.) For the case of a single record per individual and no relationships, \mathbf{CV}^{-1} is equal to the heritability of the trait. The expected gain due to one generation of selection, δ , based on u is computed as follows:

$$\delta = i\rho(\sigma_A) \quad \{6.2\}$$

where i is the selection intensity, ρ is the accuracy of the evaluation, and σ_A is the additive genetic standard deviation. For selection based on a single record per individual and no relationships, ρ is the square root of the heritability. Genetic gain per year, ΔG is then computed as follows:

$$\Delta G = i\rho(\sigma_A)/L \quad \{6.3\}$$

where L = generation length in years. Selection index is remarkably efficient under the optimum conditions, high heritability, high fertility, and the possibility to score the quantitative trait on all individuals prior to breeding. However, very few actual situations correspond to these ideal conditions. Although it would seem that if the individual genes affecting the trait were known, that it should be possible to devise a more efficient selection strategy, this is apparently not the case (Weller and Soller, 1981).

We will now briefly consider selection index for a multitrait breeding objective. Assume that for each individual there is a vector \mathbf{y} , of length m , consisting of the individual's breeding values for traits of economic importance and a vector \mathbf{x} of n measured traits to be included in the selection index. Although \mathbf{x} and \mathbf{y} may include the same traits, this does not have to be the case. Assume further that the economic values associated with \mathbf{y} are linear functions of the trait values. We can then define a vector \mathbf{a} , also of length m , consisting of the economic values of the traits in \mathbf{y} . The aggregate economic breeding value, H , can then be computed as $\mathbf{a}\mathbf{y}$. H , the optimum selection index, is a scalar in monetary units. For a given selection intensity, the response to selection will be greatest, in monetary units, if candidates for selection are ranked by H . Since the elements of \mathbf{y} are generally unknown, the goal is to derive the linear index, I_s , of \mathbf{x} , that maximizes the correlation between I_s and H . Specifically, \mathbf{b} is defined as a vector of index coefficients, $I_s = \mathbf{b}\mathbf{x}$. In scalar notation, $I_s = b_1x_1 + b_2x_2 + \dots + b_nx_n$, where b_i is the index coefficient for trait i . The objective is to solve for the vector \mathbf{b} that maximizes the correlation between $\mathbf{b}\mathbf{x}$ and $\mathbf{a}\mathbf{y}$. Defining \mathbf{P} , the $n \times n$ phenotypic variance matrix of the traits in \mathbf{x} ; \mathbf{C} , the $n \times m$ genetic covariance matrix between the measured traits in \mathbf{x} and the breeding values in \mathbf{y} ; and \mathbf{G} , the $m \times m$ genetic variance matrix for the traits in \mathbf{y} ; the selection index coefficients are then derived by the following equation:

$$\mathbf{b} = \mathbf{P}^{-1}\mathbf{C}\mathbf{a} \quad \{6.4\}$$

Brascamp (1984) presents several methods to derive this equation, and summarizes the important properties of the selection index. If economic values are linear functions of the biological trait values, and if no information other than trait values and relationships are known, then selection of parents based on I_s is the most efficient method to increase the mean economic value of the population. The response of the vector of individual traits, δ , to one generation of selection on I_s is computed as follows:

$$\delta = i\mathbf{C}\mathbf{b}/\sigma_{I_s} \quad \{6.5\}$$

where σ_{I_s} is the standard deviation of the selection index. The economic value of this response, $\mathbf{a}\delta$, is computed as follows:

$$\mathbf{a}\delta = i(\mathbf{a}\mathbf{C}\mathbf{a})^{0.5} \quad \{6.6\}$$

6.3 The value of genetic gain

As already noted, many of the studies that have considered MAS are quite pessimistic. In certain breeding programs gains obtained by information on specific genes will be minuscule. Like any other investment, genotyping must be considered in terms of potential gains vs. costs. Genetic gain is unlike all other investments, in that gains due to breed improvement are eternal and cumulative. Unlike investment in new machinery, genetic gain never is "used up" and never has to be replaced. Unlike introduction of a new treatment or process, which must be continually applied, once genetic gain is obtained, no further investment is required to maintain this gain. The annual rate of genetic gain in most domestic species is from about 1 to a 5% of the mean (Lande and Thompson, 1990; Weller and Fernando, 1991). Although these numbers seem small, they in fact represent huge increases in economic value, as is demonstrated below.

The calculations that follow are based on the calculations of Weller (1994) for the value of gains from breeding to the national economy. Consider an ongoing breeding program with a nominal genetic gain of V each year. The *cumulative* discounted returns, R, will be a function of the nominal annual returns, the discount rate, the profit horizon and the number of years from the beginning of the program until first returns are realized. R is then computed as follows (Hill, 1971):

$$R = V \left[\frac{r^t - T^{t+1}}{(1-r)^2} - \frac{(T-t+1)r^{t+1}}{1-r} \right] \quad \{6.7\}$$

Where $r = 1/(1+d)$, d = discount rate, T = profit horizon, and t = years to first returns. For $d = 0.08$, $T = 20$ years, and $t = 5$ year, $R = 32.58V$. That is, the cumulative returns are equal to 33 times the nominal annual returns. For an infinite profit horizon, Equation {6.7} reduces to:

$$R = \frac{Vr^t}{(1-r)^2} = \frac{V}{d^2(1+d)^2} = 124.04V \quad \{6.8\}$$

We will now compare the value of nominal annual genetic gain to annual costs of a breeding program, assuming a fixed nominal cost per year. Costs, unlike genetic gain are not cumulative. Thus, assuming first costs in the year after the base year, C_1 , the net present value of the costs of the breeding program, is computed as follows:

$$C = \frac{C_1r(1-r^t)}{1-r} \quad \{6.9\}$$

Where C_2 = annual costs of the breeding program. Using the same values for T , and d , $C =$

9.82 C_2 . Thus, net profit is positive if $V > 0.31C_2$. For an infinite profit horizon, $C = 12.5C_2$, and profit will be positive if $V > 0.1C_2$.

Thus, a MAS breeding program will be profitable even if the nominal annual costs are several times the nominal annual genetic gain. For example, we will consider the US dairy cattle population, which consists of about 10,000,000 cows. Annual genetic gain is about 100 kg milk/yr. The value of a 1 kg gain in milk production has been estimated at \$0.1 (Weller, 1994). Thus, the annual value of a 10% increase in the rate of genetic gain (10 kg/yr) is:

$$V = (10 \text{ kg/cow/yr})(\$0.1/\text{kg})(10,000,000 \text{ cows}) = \$10,000,000/\text{yr} \quad \{6.10\}$$

The cumulative value with a profit horizon of 20 yr and an 8% discount rate would be \$330 million, and break-even annual costs are \$32,000,000/yr. Thus, it would be profitable to spend quite a lot for a relatively small gain.

These calculations are based on the gain to the national economy. Brascamp et al. (1993) considered the economic value of MAS based on changes in returns from semen sales for a breeding organization operating in a competitive market. In this case a breeding firm that adopts a MAS program can increase its returns either by increasing its market share or increasing the mean price of a semen dose. Although the value of genetic gain will be less, relatively small changes in genetic merit can result in large changes in market share.

6.4 Situations in which selection index is inefficient

The practical situations in which selection index is not efficient can be listed as follows:

1. Low heritability for trait included in the economic objective.
2. Traits that cannot be scored on all individuals (males, juveniles, live animals, disease challenge).
3. Negative genetic correlations among traits.
4. Non-additive genetic variance (dominance, epistasis).
5. Crossbreeding.
6. "Cryptic" genetic variation.
7. Introgression.

We have already mentioned the first two situations above. Many traits of major economic importance have been neglected in breeding programs because of low heritability. Prime examples are fertility traits and disease resistance. Selection index works best on traits with near normal continuous distributions. Thus, traits such as conception rate, number of progeny, or disease have received less emphasis in breeding programs. Selection index is less efficient when the trait is expressed only in one sex, or only in mature individuals. Certain traits cannot be scored on live animals, such as carcass composition. In this case genetic values can only be estimated through records of relatives.

As shown by Falconer (1964) negative genetic correlations among traits included in the

selection objective tend to build up over time. Nearly all commercial breeding programs include traits with negative genetic correlations. The effect of negative genetic correlations among traits included in the selection objective will be considered below in detail.

Clearly, selection index does not utilize non-additive genetic variance, nor does it provide an answer for crossbreeding among strains. The three main goals of crossbreeding are: (1) utilization of heterosis, (2) increased genetic variation, and (3) introgression. The "classical" explanations for heterosis are elimination of inbreeding depression, and overdominance at the level of the individual locus. Even in the absence of these "true" genetic effects, crossbreeding is often more profitable than selection within a single line. Moav (1966) defined five type of "economic" heterosis.

Differently breeds are sometimes crossed to produce a population with increased genetic variance. Selection index can then be used to increase the economic value in future generations. However, desirable genes of individuals with overall inferior phenotypes can be lost through trait based selection. Generally only the economically best breeds will be considered as parental candidates. Again, some breeds with overall inferior phenotypes may carry some desirable genes which will not be found by trait based selection. This is especially true of wild progenitors of domestic species. This "cryptic" genetic variation can be utilized via MAS.

"Introgression" is the process whereby a characteristic, or a specific gene is transferred from one strain to another. The prime example are disease resistance genes from wild relatives of domestic strains. Another example are very advantageous genes that appear by mutation in a domestic population, such as the Barroola gene in sheep. The traditional approach has been to first cross the "wild strain" carrying the desired gene or trait and the otherwise superior cultivar. A series of backcross generations to the cultivar is then performed, while trying to maintain the desired trait for the wild strain. This process can be significantly facilitated by inclusion of genetic markers for the desired gene.

Introgression will be at the expense of selection within the breed. Visscher et al. (1997) simulated introgression for a nucleus swine population under selection for a quantitative trait with a heritability of 0.25. They found that the reduction in genetic gain for the main objective of selection due to introgression without MAS was between one and two generations. If MAS was employed, this loss could be slightly reduced, if the number of generations of backcrossing was less than 5. They did not consider the possibility of reducing the generation interval via MAS, by breeding prior to expression of the introgressed allele.

6.5 Potential contribution of MAS for selection within a breed

Potentially, MAS can increase annual genetic gain by: increasing accuracy of evaluation, increasing selection intensity, or decreasing generation interval. Most of the studies on MAS have dealt with increasing the accuracy of evaluation. Information on the individual genes affecting the trait of interest does increase the accuracy of the evaluation, but the effect decreases as the heritability increases. Assume that marker information is available for QTL affecting some of the traits included in the breeding objective. We will define m as the "net

marker score", which is the sum of the additive effects associated with the markers for a given individual. With information on individual loci in addition to phenotypic trait values, selection index methodology can be used to construct an optimum linear selection index of the form: $b_x'x + b_m'm$, (Lande and Thompson, 1990), where b_x represents the index coefficients for the quantitative trait records, x , b_m represents the index coefficient for m . For single trait selection the relative weights of b_m and b_x are computed as follows:

$$b_m/b_x = (1/h^2 - 1)/(1-p) \quad \{6.11\}$$

where h^2 is the heritability, and p is the fraction of the additive genetic variance associated with the genetic markers. As the heritability tends toward unity, b_m tends to zero, regardless of p . The relative efficiency, RE , of two different indices is defined as the ratio of their expected genetic gains. The RE of a selection index including marker information to a selection index based only on trait values for individual selection is computed as follows (Lande and Thompson, 1990):

$$\left[\frac{p}{h^2} \frac{(1-p)^2}{1-h^2p} \right] \frac{0.5}{1} \quad \{6.12\}$$

As heritability tends to unity, so does RE . For $h^2 = 0.25$, and $p = 0.5$, $RE = 1.5$. Thus, gains for individual selection through MAS can be quite significant. RE computed for selection based on half-sib or full-sib records are much less. With half sib selection, the maximum gain possible, as p tends towards unity is $2[(1-h^2/4)/(1+2h^2)]$. For $h^2 = 0.5$, maximum $RE = 1.58$.

Selection intensity can be increased by selection among individuals without phenotypic expression of trait. For example, milk production is expressed only in females. Therefore selection among males is based only on information from relatives. With only information on relatives two full brothers will have the same genetic evaluation. Information on markers could be used to differentiate between them.

In most animal breeding programs, selection intensities, accuracies of genetic evaluations and generation intervals are different along the for paths of inheritance: sires to sons, sires to daughters, dams to sons, and dams to daughters. In this case, mean annual genetic gain for the population, ΔG , is computed as follows:

$$\Delta G = \frac{\delta_{SS} + \delta_{SD} + \delta_{DS} + \delta_{DD}}{L_{SS} + L_{SD} + L_{DS} + L_{DD}} \quad \{6.13\}$$

Where: δ_x = genetic gain per generation for path x , and L_x = generation interval for path x . The male generation intervals are usually much longer than the biological minimum. Bulls

reach sexual maturity of the age of one year. Most advanced dairy cattle breeding programs are based on a progeny test of young sires based on 50 to 100 daughters. Sires with superior evaluations based on the first crop of daughters are returned to service. However, by the time daughter milk production records are available these sires are five years old. Theoretical studies show that the gain in accuracy obtained by the progeny test outweighs the loss incurred by increasing the generation interval.

6.6 Incorporation of MAS into existing breeding programs

A number of studies have estimated the expected gain from incorporating MAS into existing dairy cattle breeding programs. Most of these studies have assumed only minor modifications of the existing programs. *A priori*, dairy cattle improvement should be nearly an ideal situation for application of MAS, as noted above, because most economic traits are only expressed in females, which have very limited fertility. Meuwissen, and van Arendonk (1992) considered two schemes. The first scheme was a traditional progeny test scheme in which information on markers was used to more accurately evaluate young sires in addition to records on their daughters. In this scheme MAS increased ΔG only 5% when the markers explained 25% of the genetic variance. This result is not surprising considering that the accuracy of sire evaluations based on a progeny test of 50 daughters is already quite high. The advantage of this scheme is that it requires virtually no change in the existing breeding either on the part of AI institutes or farmers, and would therefore meet with no opposition.

Meuwissen, and van Arendonk (1992) also considered both "closed" and "open" nucleus breeding schemes. In nucleus schemes selection is carried out within a relatively small population, and bulls produced from this population are then used to service the general population. Rate of increase in nucleus populations can be greater, chiefly because of application of multiple ovulation and embryo transplant (MOET) to dramatically increase selection intensity along the dam to daughter path. MOET is only economically viable for a small population. Furthermore, it should be possible to obtain more accurate records from a small population maintained specifically for breeding purposes. In closed nucleus schemes only cows from the nucleus population are used as dams, while in open schemes superior cows from the general population are also used. In MOET schemes, progeny testing of sires is not a viable option, and sires are selected based on records of half-sisters. Thus, the accuracy of sire evaluations are much lower, which gives more scope for improvement via MAS. Increase of rates of genetic gain were 26% and 22% for open and closed nucleus schemes if the markers accounted for 25% of the genetic variance. Even without markers, genetic gains were greater for nucleus schemes than traditional progeny testing schemes, although several studies have disputed these claims.

Kashi, Hallerman and Soller (1990) considered a standard progeny test breeding scheme, but used markers to select among young candidate bulls prior to progeny test, in addition to pedigree information. As in the nucleus schemes considered above, there is significant scope for improvement, since the accuracy of young sire evaluations based only on pedigree information is low. This method also has the advantage that it only requires

minimal changes on the part of the AI institutes, and no changes by the farmers. Kashi, Hallerman and Soller (1990) estimate that rates of genetic could be increased up to 30% by this scheme. However, Brascamp et al. (1993) note that Kashi et al. (1990) did not account for the expected differences among estimated breeding values of candidate bulls. Furthermore, Kashi et al. (1990) did not account for the reduction in selection intensity expected along the dam to son path, if many more bulls are considered as candidates a priori. It can be argued that this reduction is expected to be low, because the proportion of cows selected as bull dams will be very low in any event.

6.7 Inclusion of marker information in "animal model" genetic evaluations

Most studies that have evaluated MAS have generally assumed that the genome is first scanned to locate chromosomal regions containing QTL. Using additional markers, the QTL are progressively localized to smaller and smaller chromosomal regions, and finally the actual genes are identified. The identified QTL are then used in selection program (Soller, 1994). Following this approach, or even localization of the QTL to a very small chromosomal segment, recombination in future generations is no longer a problem, but there is a significant time lag until QTL are utilized in breeding programs.

An alternative approach was presented by Fernando and Grossman (1989). Their model, discussed previously in Chapter 2, estimates breeding values of all individuals in the population including information from genetic markers, but does not directly estimate the QTL effects. Instead, they modified a standard individual animal model so that in addition to the polygenic effect of each individual, two "genetic effects" are estimated for the two parental marker alleles or haplotypes pass to each individual for each locus. Rather than representing specific QTL alleles, these genetic effects include uncertainty with respect to the QTL allele received. Following the principles of selection index, selection based on the estimated breeding values including marker information should result in maximum genetic gain in the next generation, even though QTL information is incomplete.

The original model of Fernando and Grossman (1989) could handle any population structure, and could also include "nuisance" effects, such as herd or block, but considered only a single marker and a linked QTL, and assumed that the variance contributed by the QTL and recombination frequency between the QTL and the genetic marker were known. They also assumed that all individuals in the population were genotyped. Weller and Fernando (1991) presented formula to estimate these parameters via restricted maximum likelihood (REML). Goddard (1992) extended this model to consider multiple markers and QTL. Van Arendonk et al. (1994) used REML to estimate QTL variance and recombination frequency, but found that these parameters are confounded for a single marker in a granddaughter design. They also presented methods to incorporate information from animals that were not genotyped.

6.8 Long-term considerations, MAS vs. selection index

Although most studies have looked at the gain obtained by a single generation of MAS a few studies have also looked at the expected long-term effects of MAS. Since the effect of long term selection cannot be solved analytically, all of these studies are based on simulation, and the model used becomes critical. Even though Lande and Thompson (1991) maintain that new additive genetic variance arises by mutation at a rate on the order of 10^{-3} times the environmental variance per generation, all of these studies have assumed that no new genetic variance is generated during the course of the breeding program.

Zhang and Smith (1992, 1993) and de Koning and Weller (1994) both simulated long-term selection for a single trait. Zhang and Smith (1992) assumed that all the genetic variance was due to 100 QTL, while de Koning and Weller (1994) assumed that all the genetic variance was due to 10 QTL. Both studies compared MAS to trait based selection index. Zhang and Smith assumed that the population was genotyped for 100 markers covering a genome of 2 Morgans, while de Koning and Weller (1994) assumed that genotypes for the ten QTL were known without error in the MAS scheme. Zhang and Smith (1992) found that MAS combined with selection index based on relative information always resulted in greater genetic gain than conventional selection index, although differences were slight. Similar results were found by de Koning and Weller (1994) for high heritability traits. For low heritability traits the advantage of MAS was greater. The difference between selection index and MAS decreased over time, but even after ten generations, the relative efficiency of MAS to selection index with heritability of 0.2 was 1.24.

Gibson (1994) employed a infinitesimal model for genetic variance, excluding a single segregating QTL. He found that genetic response was greater via MAS in the early generations, but always greater for traditional selection index in subsequent generations. The apparent explanation is that genetic variance with MAS is reduced relative to selection index in the early generations, which results in less genetic gain in later generations. Although this model assumes an infinite number of loci affecting the quantitative trait, genetic variance is reduced due to inbreeding, fixation is obtained for the segregating QTL, and no additional genetic variance is generated during the course of selection.

6.9 MAS for a multitrait breeding objective

de Koning and Weller (1994) compared selection on known loci affecting quantitative traits to phenotypic selection index for a single and a two-trait selection objective. Two situations were simulated; a single known quantitative locus, and 10 identified loci accounting for all the additive genetic variance. Selection efficiency of marker-assisted selection (MAS), relative to trait-based selection was higher for two-trait selection, as compared to single trait selection. Results are presented in Table 6.1. The advantage of MAS was greater when the traits were negatively correlated. Relative efficiency for a single loci responsible for 0.1 of the genetic variance was 1.11 with heritabilities of 0.45 and 0.2, and zero genetic and phenotypic correlations between the traits. RE of MAS for ten known loci was 1.3 to 1.8 in the first three generations of selection, but declined in each subsequent generation. Allele fixation for MAS was obtained for all loci after 10 generations. Response to trait-based selection continued through generation 15, and approached the response obtained with MAS after ten

generations. The cumulative genetic response by MAS was only 80% of the economically optimum genotype, because the less favorable allele reached fixation for some loci, generally those with effects in opposite directions on the two traits.

Table 6.1 Relative efficiency of MAS with all QTL known for a two trait or single trait selection objective, relative to trait-based selection. The genetic correlation was -0.4, the environmental correlation was 0, and heritability of the two traits were equal, for the two-trait simulations. Results are the means of 10 replicates.

Generation	Two traits		Single trait	
	— heritability —	— heritability —	— heritability —	— heritability —
1	0.05	0.20	0.40	0.40
2	5.10	2.55	1.95	4.10
3	4.50	2.40	1.82	3.84
4	4.15	2.08	1.67	3.52
5	3.58	1.87	1.46	3.27
6	3.14	1.63	1.32	3.08
7	2.71	1.45	1.23	2.85
8	2.42	1.36	1.18	2.71
9	2.21	1.29	1.15	2.50
10	2.02	1.25	1.13	2.27

6.10 Velogenetics - the synergistic use of MAS and germ-line manipulation

In future breeding programs, MAS will probably be combined together with other new technologies affecting reproduction, such as embryo transplant, sexed semen and cloning. Georges and Massey (1991) considered the possibility of combination of MAS with germ-line manipulation. Although spontaneous oocyte maturation and ovulation do not begin until puberty, for cattle this is at the age of close to one year; waves of oocyte growth are seen even *in utero*. Activation of primordial follicles starts at 140 days of gestation. Georges and Massey (1991) considered the theoretical possibility to "grow" mature and fertilize prepubertal oocytes *in vitro*. This procedure could reduce the generation interval of cattle to maybe as little as 3 to 6 months, as compared to the normal biological minimum of two years. By using *in-vitro* fertilization of fetal oocytes by selected, progeny-tested sires, annual responses in milk yield could be doubled compared to conventional progeny testing. They term this procedure "velogenetics", and propose the following breeding scheme.

1. Selection of "bull grandams" based on records and genetic markers.

2. Selection of fetal "bull dams" based on genetic markers.
3. *In-vitro* fertilization of fetal oocytes with semen of elite sires, selected by breeding values based on records of female relatives and genetic markers.
4. Selection among juvenile male calves based on genetic markers.
5. Selected young sires at age of 1-2 yr are mated to cows of commercial population.

Step 3 of this protocol is not possible at present, but until very recently, it was generally considered impossible to clone mature mammals.

6.11 Summary

Again we must emphasize that a little bit of genetic gain can have a huge economic value. Thus, relatively large costs in genotyping can be justified to increase rates of genetic gain by only a few percent. It is not possible to consider within a single chapter all scenarios for MAS, and radically different results can be obtained depending on the breeding scheme and the assumptions employed. There does seem to be a consensus emerging that application of MAS could result in rather significant genetic gains, at least for several generations. Consideration of ten or more generations does not seem very relevant since profit horizons are at most 20 years, and breeding objectives tend to change over time anyway. In addition, with normal rates of spontaneous mutation, it does not appear that fixation of desirable alleles after a few generations of MAS is a serious problem.

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