Mendelian Sampling variance tests with genomic preselection

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Abstract

Interbull has introduced a new validation test, and provided corresponding software to detect non-zero time trends and outliers years, for estimates of genetic variance. The test is applied separately for cows and AI sires, for all traits included in the Interbull MACE evaluation service. In recent years, AI sires have been genomically preselected, using genotype-based evaluations when they were young calves. Genomic preselection significantly changes the expectation of Mendelian sampling distributions for AI bulls. The new Interbull test is applied to EBV computed without genotypes, which are biased by ignored genomic preselection effects. The purposes of the present study were to apply the new validation test to Canadian data, firstly using official EBV submitted for MACE, and secondly using corrected EBV, after making adjustments to reduce preselection biases in the MS distributions of the most recent AI bulls. For the main traits under selection in Canada, test results were a pass for official EBV, but a fail for bias-corrected EBV. For bull populations with genomic preselection, biased EBV are expected to pass the test, while unbiased data are expected to fail.

Key words: trend validation, international evaluation, Mendelian sampling, genomics, selection bias

Introduction

To ensure high quality standards for the sire comparison services of Interbull, validation tests must be applied and passed before contributing national data into the MACE evaluation system (Schaeffer et al, 1996). There are three trend validation tests (Boichard et al, 1995), which were designed to detect biases in national EBV averages of bulls born in different years. More recently, Interbull introduced a fourth validation test (Tyrisevä et al, 2018), designed to detect biases in variance of EBVs within a year. All countries participating in MACE are required to apply test 4, using software provided by Interbull, but passing the test is not a requirement to contribute data into MACE. Validation test 4 checks if yearly distributions of Mendelian sampling (MS) estimates are consistent with the null hypothesis of homogeneity and normality across all years. In other words, each yearly average for MS should be zero and the MS variance of selected sub-populations should be constant over time. Implied by this hypothesis is that within-family preselection of animals has not occurred within any given year. Prior to the era of genomics, it was nearly impossible to preselect the best full-sib young bulls within a family, which was the reason for structured young-sire sampling and costly progeny-test programs. Since 2008, however, within-family selection of young bulls has become feasible, using genotype-based, genomic evaluations (e.g. VanRaden, 2008). Genomic preselection has grown in both widespread application for dairy sires and in the levels of preselection intensity used. Genomic selection will have clear and strong impacts on the underlying distributions of true MS values of AI bulls, such that homogeneity of these distributions has become an unrealistic premise for testing bias in national EBV.

National evaluations for genomically preselected AI bulls are expected to be biased if the genotypes used to preselect AI bulls are not included in the evaluation data (Henderson, 1984; Sorensen and Kennedy, 1984; Schaeffer et al, 1998), as in the currently required approach for national EBV submitted and used in MACE, and for validation test 4. It is highly anticipated that countries will develop advanced methods to reduce levels of genomic preselection bias in national EBV, and these advances are expected to increase heterogeneity of MS-distributions for more recent years relative to older cohorts of AI bulls. Objectives of the present study were firstly to apply test 4 to the current Canadian EBV used in MACE, and secondly to modified EBV, after making adjustments to reduce expected levels of genomic preselection bias in the MS distributions.

Materials and Methods

The August 2018 national EBV for Hosteins were used in the present study. The Interbull software for validation test 4 was applied to both cow and AI bull populations of many traits, as required. Detailed results are presented here for protein yield of bulls. Results for other traits are discussed in general terms, and relative to the results presented for protein.

The bias in national EBV, caused by ignoring genotype-based data that were used to preselect young AI bulls, was quantified in an approximate way to assess impacts on validation test 4 results. Genetic trends estimated from EBV of recent AI bulls are generally underestimated, due to genomic preselection bias (e.g. deJong, 2018; Mäntysaari, 2018; Masuda et al, 2017; Splichal et al, 2017). The bias appears to be on the order of about 50% reduction in the EBV trend. Correction for such a bias would require doubling the observed EBV trends (i.e. multiplying the trend by 2). The following range of adjustments was considered as a simple way to simulate bias-corrected EBV: multiplying the EBV trend of bulls born since 2009 by 1.00 (no correction), 1.25, 1.50, 1.75 and 2.00. Trend corrections between 1.50 and 2.00 are likely the most realistic. Trends were adjusted by multiplying the yearly average differences from 2009. Hence, EBV for 2009 and older years were not adjusted, adjustments were small for 2010 and increasing up to 2013.

Internal studies have linked downward bias in bull EBV trends as mainly due to downward bias for the poorest bulls, with relatively small biases in the EBV of top bulls. To simulate corrections for this type of bias, EBV trends were increased by shrinking the within-year EBV standard deviations, such that yearly means in EBV were modified as desired while the EBV of bulls 3 standard deviations above the yearly mean were unchanged. This approach increased the percentages of bulls with positive MS values from EBV, to most closely match percentages from GEBV used in preselection, if the assumed corrections to EBV trends were between 1.50 and 2.00.

Results & Discussion

Correcting for genomic preselection bias

Implied assumptions in traditional mixed model equations ignoring genotypes causes a regression of Mendelian sampling deviations for AI bulls towards an expected value of zero. This shows up very clearly in Table 1, where distributions are centred near zero for all recent years of birth for progeny-tested AI bulls. In reality, however, the expected mean of MS in most recent years should be positive for strongly preselected traits like protein. National evaluation systems will likely and eventually be updated to better reflect this reality of genomic preselection in AI bulls.

Scaling the mean and shrinking the SD of EBV for bulls born after 2009 effectively altered the distributions of MS derived from the EBV (Table 1). The altered MS distributions are likely more consistent with a revised expectation accounting for genomic preselection, where MS estimates should be generally positive for the recent years of highly preselected bulls. While it could be argued that the maximum MS is a bit high using a 2.00 EBV trend adjustment, the average MS might be a bit too low with a 1.50 EBV trend adjustment. Realistically, an optimum adjustment for protein is likely somewhere between 1.50 and 2.00.

Table 1. Distributions of Mendelian sampling[z] estimates for protein, based on unadjusted (EBV Trend=1.00) and bias-corrected EBV.

	EBV trend	Birth Year of AI bull				
		2009	2010	2011	2012	2013
Min	1.00	-1.9	-1.9	-1.9	-1.8	-1.6
Ave		-0.1	-0.1	-0.1	-0.1	-0.1
Max		1.5	1.7	1.6	1.7	1.5
Min	1.50	-1.9	-1.6	-1.6	-1.1	-0.6
Ave		-0.1	0.0	0.2	0.4	0.5
Max		1.5	1.7	1.7	1.9	1.8
Min	2.00	-1.9	-1.4	-1.2	-0.5	0.1
Ave		-0.1	0.2	0.5	0.8	1.1
Max		1.5	1.8	1.8	2.2	2.4

[z]stardardized relative to validation software estimate of genetic SD with unadjusted EBV

Impacts of selection on variance

Traditional estimates of genetic variance (e.g. REML) are affected by model assumptions, and in BLUP models accounting for animal genetic relationships, it is assumed that all MS deviations have expectation equal to zero. Variance estimates are not adjusted for, and will thus include the square of any non-zero MS averages. The expected impacts of non-zero averages on variance (and SD) estimates are shown in Figure 1, using a simulated sample of 1000 true MS deviations, and assuming MS distributions of AI-bulls are approximately left-truncated, due to genomic preselection of only the better bulls within genotyped full-sib families. The estimated SD are plotted by increasing levels (from left to right) of truncation selection intensity.

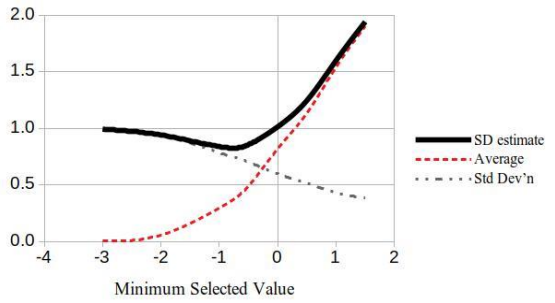

Figure 1. Impacts of truncation selection on estimates of SD that include the contribution of a non-zero average (e.g. REML).

Truncation selection increases the mean (dashed red line) and decreases the mean-adjusted Std Dev'n (dashed-dotted grey line) of MS deviations. With lower intensities of selection, the MS average is close to zero and the SD estimate (solid black line) closely follows the declining mean-adjusted Std Dev'n. However, as selection intensity increases, the contribution of a rapidly increasing average eventually dominates the SD estimate. Thus, REML estimates of variance are expected to initially decrease, but then increase rapidly as genomic preselection intensity increases to very high levels. Validation test 4 might be improved by modifying the null hypothesis for years of genomic preselection, such that the expected variance is adjusted for recent years of AI bulls, as a function of the observed non-zero MS averages.

Validation test results for August 2018

The patterns of expected change in estimated variance demonstrated in Figure 1 match exactly the patterns of change observed in validation test 4 results for Canadian data (Table 2), after applying relatively simple adjustments to reduce genomic preselection biases in protein EBV. These adjustments were an attempt to simulate reduced bias from genomic preselection when genotypes are not included in EBV calculations. The idea was to demonstrate potential future impacts on validation test 4 results, as countries begin to update their national evaluation systems to reduced these biases. Newer EBV models will likely be developed that can account for preselection effects on the distributions of MS deviations of genomically preselected young bulls, without requiring the inclusion of individual genotypes in the EBV analysis.

Table 2. Yearly estimates of variance for protein, relative to (% difference from) the overall estimate with unadjusted EBV, for unadjusted and bias-corrected EBV.

	Multiplier to EBV trend after 2009				
Born	1.00	1.25	1.50	**1.75^{F}**	**2.00^{F}**
2002	2	2	2	2	**2^{L}**
2003	5	5	5	5	**5^{L}**
2004	9	9	9	9	9
2005	-3	-3	-3	-3	**-3^{L}**
2006	8	8	8	8	**8^{L}**
2007	-13	-13	-13	**-13^{L}**	**-13^{L}**
2008	1	1	1	1	1^{L}
2009	-8	-8	-8	**-8^{L}**	**-8^{L}**
2010	-5	-12	-16	**-17^{L}**	**-16^{L}**
2011	-7	-17	**-15^{L}**	-1	24
2012	9	1	**23^{H}**	**75^{H}**	**157^{H}**
2013	-4	-11	**41^{H}**	**152^{H}**	**323^{H}**

^{F}failed trend test, ^{H}detected as a high outlier, ^{L}detected as a low outlier.

Results for other traits under primary selection in Canada (e.g. conformation) would be similar to the results for protein, while relative impacts on variances and on test 4

results would be much smaller for secondary traits undergoing weaker selection.

Canadian EBV passed the test for all traits of Holstein AI bulls, when applied to official EBV used currently in MACE. The official EBV are believed to have strong biases, however, due to genomic preselection effects ignored by the model. Improper expectations are assumed for distributions of MS deviations of genomically preselected bulls. Altering the MS distributions to better reflect genomic preselection in recent AI bulls caused a change in validation test results, from passing to failing for traits undergoing strong selection. Impacts were much smaller for secondary traits undergoing weaker selection. Pass versus fail results for validation test 4 should be treated cautiously, especially for years of genomic preselection in AI bulls, because biased data are more likely to pass the test while unbiased data are more likely to fail.

Conclusions

Interbull has provided very useful software for the application of validation test 4, which checks for non-zero trends in variance and identifies yearly outliers. The null hypothesis used for test 4 is less relevant today, than before the era of genomically preselecting young AI bulls. It should be expected that H0 will be rejected (fail the test) more often if EBV are unbiased and properly reflecting genomic preselection effects on Mendelian sampling distributions of bulls, which are no longer full-normal with a zero mean. In this sense, the rejecting of H0 is not an indication of bias in the EBV, but rather because H0 does not reflect the true underlying expectation for variance of genomically preselected bulls.

Preselection alters the distribution of both true and estimated MS deviations. The distributions of MS for genomically preselected bulls have a mean that deviates significantly from zero, and when selection intensity is very high, the non-zero mean dominates estimated variance, which becomes much higher in recent years than in the years prior to the start of genomic preselection.

Variance outliers for years of genomically preselected bulls are currently being hidden in official EBV, which are used for MACE and for validation test 4, due to genomic preselection biases from a model-forced normalization of MS estimates for preselected bulls. Test 4 fail rates for AI bulls are expected to increase dramatically in the future as national methods are improved to properly account for genomic preselection effects on the distributions of MS estimates and national EBV. Fail results for bulls should not be considered an indication of EBV bias, if the results can be reasonably explained by genomic preselection effects.

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