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Evaluation of measures of correctness of genotype imputation in the context of genomic prediction: a review of livestock applications

M. P. L. Calus[1†], A. C. Bouwman[1], J. M. Hickey[2], R. F. Veerkamp[1] and H. A. Mulder[3]

[1]*Animal Breeding and Genomics Centre, Wageningen UR Livestock Research, PO Box 135, 6700 AC Wageningen, The Netherlands;* [2]*Royal (Dick) School of Veterinary Studies, The Roslin Institute, The University of Edinburgh, Easter Bush, Midlothian, EH25 9RG, Scotland, UK;* [3]*Animal Breeding and Genomics Centre, Wageningen University, PO Box 338, 6700 AH Wageningen, The Netherlands*

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In livestock, many studies have reported the results of imputation to 50k single nucleotide polymorphism (SNP) genotypes for animals that are genotyped with low-density SNP panels. The objective of this paper is to review different measures of correctness of imputation, and to evaluate their utility depending on the purpose of the imputed genotypes. Across studies, imputation accuracy, computed as the correlation between true and imputed genotypes, and imputation error rates, that counts the number of incorrectly imputed alleles, are commonly used measures of imputation correctness. Based on the nature of both measures and results reported in the literature, imputation accuracy appears to be a more useful measure of the correctness of imputation than imputation error rates, because imputation accuracy does not depend on minor allele frequency (MAF), whereas imputation error rate depends on MAF. Therefore imputation accuracy can be better compared across loci with different MAF. Imputation accuracy depends on the ability of identifying the correct haplotype of a SNP, but many other factors have been identified as well, including the number of genotyped immediate ancestors, the number of animals with genotypes at the high-density panel, the SNP density on the low- and high-density panel, the MAF of the imputed SNP and whether imputed SNP are located at the end of a chromosome or not. Some of these factors directly contribute to the linkage disequilibrium between imputed SNP and SNP on the low-density panel. When imputation accuracy is assessed as a predictor for the accuracy of subsequent genomic prediction, we recommend that: (1) individual-specific imputation accuracies should be used that are computed after centring and scaling both true and imputed genotypes; and (2) imputation of gene dosage is preferred over imputation of the most likely genotype, as this increases accuracy and reduces bias of the imputed genotypes and the subsequent genomic predictions.

Keywords: genotype imputation, livestock, genomic prediction

Implications

Genomic selection is rapidly adopted in breeding programs around the world. It relies on genotyping a reference population with known phenotypes and genotyping selection candidates. The latter is costly if the number of selection candidates is large. Costs can be reduced by genotyping them with a lower-density single nucleotide polymorphism (SNP) panel and impute them to commonly used 50k SNP panels. In this review paper, we show that the accuracy of this imputation step should be measured as the correlation between true and imputed genotypes, to infer the impact of using imputed *v.* measured genotypes on accuracy of subsequent genomic selection.

† E-mail: mario.calus@wur.nl

Introduction

Genomic selection (GS) is rapidly changing breeding programs around the world. Application of GS requires having dense genotypes on selection candidates and on a reference population (RP) of preferably at least a few thousand animals with known phenotype. As a result, thousands of animals may need to be genotyped per year, resulting in high genotyping costs for breeding programs. These costs may be lowered considerably by using a combination of high and low-density single nucleotide polymorphism (SNP) panels, where animals genotyped with the low-density SNP panel are imputed up to high density (Goddard, 2008; Habier *et al.*, 2009). Large numbers of individuals can then be genotyped at relatively low cost, which allows for instance to cost-effectively screen large numbers of potential selection

candidates to increase selection intensity (e.g. Huang *et al.*, 2012a). Imputation of low density to 50k SNP panels, is common practice in genomic breeding programs for dairy cattle (Wiggans *et al.*, 2012), pigs (e.g. Huang *et al.*, 2012a) and poultry (e.g. Fulton, 2012), and has been investigated for sheep (Hayes *et al.*, 2012). At the same time, imputation from 50k to SNP panels with even higher density (e.g. Hozé *et al.*, 2013; Pausch *et al.*, 2013; Pryce *et al.*, 2014), or to whole genome sequence (van Binsbergen *et al.*, 2014) is under investigation.

Many different imputation methods have been applied in livestock, and several studies have compared different imputation methods (e.g. Johnston *et al.*, 2011; Khatkar *et al.*, 2012; Mulder *et al.*, 2012). Some methods fully rely on LD, whereas others use family information in addition (for an overview of methods used; see Table 1). It should be noted that most of the programs that use pedigree information, such as FImpute, are also often applied without using pedigree and therefore relying fully on LD in those cases. Performance of imputation methods is generally evaluated as follows. A subset of the individuals genotyped with the targeted high-density panel are selected into a validation data subset. In this validation subset, genotypes of loci that are not included on the panel with lower density, are masked. The remaining individuals with high-density genotypes are used as a RP in the imputation step. In the imputation step, the masked genotypes in the validation data are imputed. Genotypes may be imputed with discrete values, for instance by using the most likely genotype. Alternatively, probabilities for each genotype can be used to calculate predicted genotypes on a continuous scale, hereafter referred to as gene dosage, and often shortened as simply dosage or sometimes called gene content. Correctness of imputation is generally calculated for each imputed SNP by comparing the masked true genotypes to imputed genotypes across animals. In literature, several different ways to compare true and imputed genotypes have been reported. In some studies the percentage of incorrectly imputed alleles or genotypes is reported, and termed allelic or genotype imputation error rate (e.g. Zhang and Druet, 2010). Other studies report the percentage of correctly imputed genotypes, and call this imputation accuracy (Weigel *et al.*, 2010a), while also the (squared) correlation between true and imputed genotypes is often called imputation accuracy (Druet *et al.*, 2010; Calus *et al.*, 2011; Mulder *et al.*, 2012). Other measures that have been developed or suggested include the imputation quality score (Lin *et al.*, 2010) and those that are derived internally in imputation algorithms. The imputation packages MaCH and Beagle compute a measure that attempts to predict the imputation R^2 value based on the posterior distribution of the Gibbs sampler, without having any information of the true genotypes. Little is known about the usefulness of the different measures to evaluate correctness of imputation although it was suggested that the correlation between true and imputed genotypes is independent from the allele frequency at the imputed locus, and may therefore be a measure with more desirable properties than allelic imputation error rates (Browning and Browning, 2009; Hickey *et al.*, 2012).

Table 1 *Different imputation programs that have been applied for imputation of genotypes in livestock*

Imputation program	Family information	Reference
AlphaImpute	x	Hickey *et al.* (2011)
Beagle[1]		Browning and Browning (2007)
CHROMIBD	x	Druet and Farnir (2011)
DAGPHASE[1]	x	Druet and Georges (2010)
fastPHASE		Scheet and Stephens (2006)
FImpute	x	Sargolzaei *et al.* (2011)
Findhap	x	VanRaden *et al.* (2011)
IMPUTE[2]		Howie *et al.* (2009)
Merlin	x	Abecasis *et al.* (2002)
Minimac		Howie *et al.* (2012)
Multivariate BLUP	x	Calus *et al.* (2011)
PedImpute	x	Nicolazzi *et al.* (2013)
Phasebook	x	Druet and Georges (2010)

[1]Genotype information of parents can optionally be used explicitly.
[2]Is part of PHASEBOOK.

The objective of this paper is to review different measures of correctness of imputation, and to evaluate their utility considering that the imputed genotypes will be used for genomic prediction. This paper is organized as follows. We start with comparing correctness of imputation measures, more specific the correlation between imputed and true genotypes *v.* the (allelic and genotypic) imputation error rate. Thereafter, factors affecting imputation accuracy are discussed, and the link between correctness of imputation of an individuals' genotypes and its accuracy of subsequent genomic predictions is evaluated. Finally, computation of individual-specific imputation accuracy, as opposed to locus-specific imputation accuracy, is discussed. Evaluation of the properties of measures of correctness of imputation is performed both analytically and empirically using examples. Recommendations are given as to which measures are preferred in the context of genomic prediction. Results of previous studies are reviewed throughout the paper.

Imputation accuracy v. imputation error rate

Throughout the remainder of the paper, we will use the term 'imputation accuracy' for the Pearson correlation coefficient between true and imputed genotypes. As indicated before, other authors have used this term to denote rates of correctly imputed alleles or genotypes. We prefer to use this term solely for the correlation between true and imputed genotypes, because this definition is in line with the definition of the accuracy of breeding values, which is commonly used in the context of animal breeding.

Imputation error rate is computed per locus as the percentage (or proportion) of alleles or genotypes that is

Table 2 *Proportion of alleles 1 and 2 that are imputed as 1 or 2 based on allele frequencies*

	Imputed allele		
Observed allele	1	2	Sum
1	p_i^2	$p_i(1-p_i)$	p_i
2	$p_i(1-p_i)$	$(1-p_i)^2$	$2(1-p_i)$
Sum	p_i	$2(1-p_i)$	1

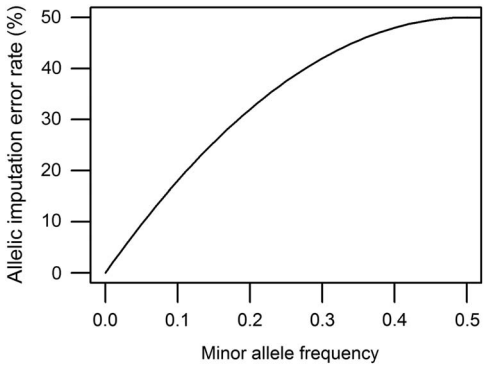

Figure 1 Allele imputation error rate as function of the allele frequency of one of the alleles, considering that imputation is based on the population allele frequencies.

imputed incorrectly. A closely related measure is the percentage of correctly imputed alleles or genotypes, which can simply be calculated as 100% minus the imputation error rate. The error rate measured at the level of alleles is approximately half the error rate measured at the level of genotypes, as explained in detail in Supplementary Material S1.

The difference between the allele imputation error rate (AIER) and the imputation accuracy can be evaluated as follows. Consider a situation where genotypes are imputed for one locus across multiple individuals, based on population allele frequencies, where p_i and $1-p_i$ are the frequencies of respectively alleles one and two at locus *i*. As the measures are computed per locus across animals, the considered imputation error rates and accuracies are termed to be locus specific. When imputing is based on population allele frequencies, an allele at locus *i* is imputed as allele 1 with probability p_i and as allele two with probability $(1-p_i)$. In Table 2, we give for each allele the probability that this allele was imputed as allele one or two. The proportion of correctly imputed alleles is the sum of the diagonal values in Table 2, which after rearrangement is $2p_i^2-2p_i+1$. Using this formula, the proportion of correctly imputed alleles depends directly on p_i, and so does the AIER, as shown in Figure 1. This dependence is such that the AIER of loci with a low minor allele frequency (MAF) is expected to be low. An arbitrary adjustment to the AIER or genotype imputation error rate has been proposed (Hayes *et al.*, 2012; Badke *et al.*, 2013) that removes the dependency on MAF. This adjustment corrects for the proportion of genotypes or alleles that is expected to be imputed correctly by chance.

Computation of imputation accuracy as the correlation between true and imputed alleles requires the variance of the true and imputed alleles, and the covariance between true and imputed alleles. The covariance between true and imputed alleles is calculated from the following general formula to calculate the covariance between two variables *x* and *y*:

$$\frac{\sum(xy)-\frac{\sum x\sum y}{n}}{n-1}$$

The expectation of this covariance between true (*y*) and imputed alleles (*x*), considering imputation based on population allele frequencies, can be derived using the expectations in Table 2 multiplied with the number of individuals in the validation data (*n*), yielding:

$$\begin{aligned}
&\frac{n(1\times 1\times p_i^2+1\times 2\times p_i(1-p_i)+2\times 1\times p_i(1-p_i))}{n-1}\\
&+\frac{n(2\times 2\times (1-p_i)^2)-\frac{(n(1\times p_i+2\times (1-p_i)))^2}{n}}{n-1}\\
&=\frac{n(p_i^2+4p_i(1-p_i)+4(1-p_i)^2)-n(p_i+2(1-p_i))^2}{n-1}\\
&=\frac{n(p_i+2(1-p_i))^2-n(p_i+2(1-p_i))^2}{n-1}=0
\end{aligned}$$

This shows that imputation based on population allele frequencies results in a covariance between true and imputed alleles, that is always equal to zero, and therefore the imputation accuracy is also equal to zero. An alternative derivation, based on genotypes instead of alleles, is shown in Supplementary Material S2.

The above demonstrates that the imputation accuracy has an expected value of zero when imputation is only based on allele frequencies, and therefore does not depend on MAF, while the imputation error rate is clearly affected by MAF (Figure 1) (Hickey *et al.*, 2012). This shows that imputation accuracy and AIER are different measures for correctness of imputation, and using either of the two might lead to different inferences. Note that correctness of imputation based on population allele frequencies can be regarded as the lower bound for the expectation of more sophisticated imputation methods.

To further illustrate the above findings, and to demonstrate that these patterns are indeed observed after imputation using sophisticated imputation software, we empirically evaluated the relationship between locus-specific imputation accuracies and AIER at different levels of MAF for a simulated data set. Details of the simulated data were described in Calus *et al.* (2011). The simulated data consisted of two replicates of one chromosome each with a total of 36 loci on the low-density panel and 177 imputed loci, with distances of ~0.1 cm between loci and an average r^2 value of 0.31 between the loci

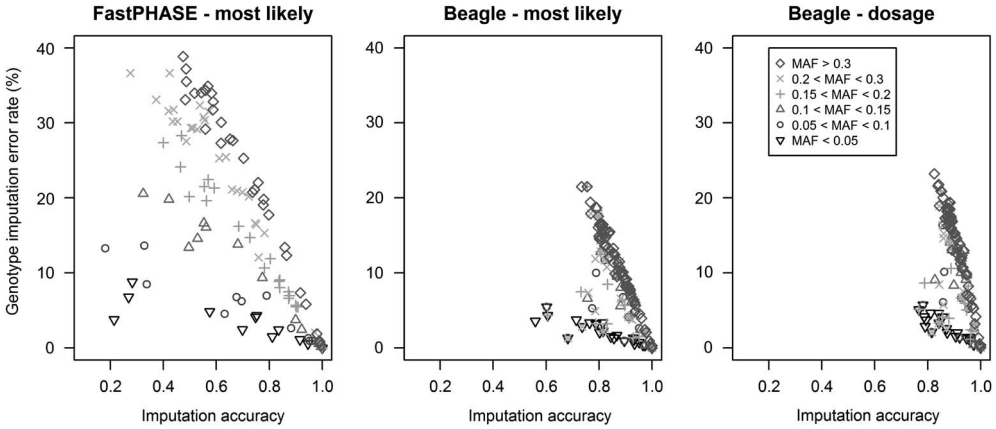

Figure 2 Genotype imputation error rate *v.* imputation accuracy, using the most likely genotype imputed by FastPHASE or Beagle, or the imputed gene dosage imputed by Beagle.

Table 3 *Intercept, slope and* R^2 *value of regressions of imputation accuracy and error rate on minor allele frequency*

Measure	Imputation method	Intercept	s.e.	Slope	s.e.	R^2
Accuracy	FastPHASE – most likely	0.717	0.033	−0.192	0.112	0.018
	Beagle – most likely	0.855	0.013	0.044	0.044	0.006
	Beagle – gene dosage	0.899	0.008	0.034	0.030	0.007
Error rate	FastPHASE – most likely	0.038	0.016	0.592	0.054	0.430
	Beagle – most likely	0.018	0.006	0.237	0.021	0.423
	Beagle – gene dosage	0.025	0.007	0.281	0.024	0.441

(i.e. the 'dense' scenario in Calus *et al.*, 2011). We here used three sets of imputed genotypes, for which imputation accuracies and AIER were calculated for each imputed locus. The first set was obtained using the most likely genotypes imputed by fastPHASE (Scheet and Stephens, 2006). The second and third set were obtained using Beagle (Browning and Browning, 2007), either containing the most likely genotypes or the gene dosage.

For each set of imputed genotypes, the calculated genotype imputation error rates are plotted against the imputation accuracy in Figure 2. This figure shows that the relationship between imputation error rate and accuracy depends on the MAF. At high MAF, there is a much stronger, almost linear relationship between imputation error rate and imputation accuracy than at low MAF. Regressing both the imputation error rates and imputation accuracies on the MAF (Table 3) confirmed that the imputation error rate has a strong relationship with the MAF while imputation accuracy has virtually no relationship with MAF.

Several studies have shown that imputation accuracy tends to increase with higher MAF, suggesting that imputation of SNP with low MAF is more difficult, while imputation error rates in fact increase with higher MAF, suggesting that imputation of SNP with low MAF is easier (Brøndum *et al.*, 2012; Hickey *et al.*, 2012; Ma *et al.*, 2013). This apparent paradox is a result of the dependency of AIER on the MAF. The observed increase in AIER with higher MAF in those studies agrees with our regression coefficients in Table 3, while the observed increase in imputation accuracy with increased MAF was not observed in our regression coefficients. The most likely explanation for this difference in results is that for a given MAF, the variation in observed imputation accuracies is much greater than for imputation error rates, because imputation accuracies have no relationship with MAF. This is also what the R^2 values of our regressions suggest (Table 3). As imputation accuracy gives more credit to correctly imputing a rare allele compared with a common allele, while AIER does exactly the opposite, we conclude, in agreement with the suggestions of Hickey *et al.* (2012) and Mulder *et al.* (2012), that the imputation accuracy is preferred as a measure of correctness of imputation over the percentage of (in)correctly imputed alleles or genotypes. It is worthwhile noting that this conclusion is even more important for imputation of sequence data that has a much greater proportion of loci with low MAF than SNP data.

Factors affecting imputation accuracy

Several studies have investigated imputation accuracy and AIER. We have summarized published results for dairy cattle data in Table 4 and for beef cattle, pigs, layers, broilers and sheep in Tables 5 (imputation accuracy) and 6 (AIER). Whenever results of multiple imputation methods on the same data were reported, average results across those imputation methods are reported in Tables 4 to 6 (for a more

Table 4 *Overview of imputation accuracies and allele imputation error rate for imputation of 50k genotypes in dairy cattle*

	Population			Accuracy			AIER (%)[1]		
Reference	Breed	Ref.	Val.	384	3k[2]	6k[3]	384	3k[2]	6/7k[3]
Dassoneville *et al.* (2012)	MON	997	222	–	0.94	0.97	–	2.6	1.0
	HF	3071	966	–	0.93	0.96	–	2.6	0.9
Jiménez-Montero *et al.* (2013)	HF	1632	834	–	–	–	–	3.1	1.3
Chen *et al.* (2011)	HF	3589	458	–	–	–	–	3.1	–
	HF	14 385	1019	–	–	–	–	2.5	–
	HF	32 597	1881	–	–	–	–	2.7	–
Weng *et al.* (2013)	HF	1098	1010	–	–	–	–	7.2	3.4
Weigel *et al.* (2010a)	JER	1446	316	–	–	–	13.3	4.4	–
Berry and Kearney (2011)	HF	4725	764	–	0.96	–	–	2.6	–
Berry *et al.* (2014)	HF	2424[4]	31	–	–	0.93	–	–	4.6
Mulder *et al.* (2012)	HF	5304	4074	0.62	0.80	0.83	15.0	9.2	8.1
Segelke *et al.* (2012)	HF	11 670	388	–	–	–	–	3.8	2.2
	HF	14 405	1019	–	–	–	–	3.3	1.7
	HF	31 597	1881	–	–	–	–	2.7	1.2
	HF	14 405	1019	–	–	–	–	1.6	0.6
Johnston *et al.* (2011)	BS	1270	209	–	–	–	–	3.0	–
	HF	7224	20 000	–	–	–	–	2.0	–
Gredler *et al.* (2011)	BS	3015	723	–	–	–	–	3.3	–
	MIX	3817	936	–	–	–	–	5.6	–
Nicolazzi *et al.* (2013)	HF	15 671	4233	–	–	0.99	–	–	0.7
Ma *et al.* (2013)	NR	2931	977	–	0.82	–	–	4.8	–
Average				0.62	0.86	0.94	14.4	3.9	2.6

MON = Montbéliarde; HF = Holstein; JER = Jersey; BS = Brown Swiss; MIX = is a combined data set containing Simmental, Swiss Fleckvieh and Holstein; NR = Nordic Red.
When multiple imputation methods were used on the same data, then average results are presented.
[1]Allele imputation error rate (AIER) is computed as half the genotype imputation error rate for studies that provided the latter measure.
[2]This is the Bovine3K (Illumina Inc., San Diego, CA), or an *in silico* 3k panel designed within the study (Weigel *et al.*, 2010a; Mulder *et al.*, 2012). Dassoneville *et al.* (2012) used both the Bovine3K and *in silico* panel.
[3]This is the BovineLD with 6909 single nucleotide polymorphisms (Illumina Inc.), or an *in silico* 6k panel designed within the study (Dassonneville *et al.*, 2012; Mulder *et al.*, 2012).
[4]This is a multibreed reference population (including: 195, 140, 526, 189, 688, 506 and 180 bulls for Aberdeen Angus, Belgian Blue, Charolais, Hereford, Holstein-Friesian, Limousin and Simmental, respectively).

detailed overview with results for different imputation accuracy methods, see Supplementary Tables 1 and 2, respectively). Imputation accuracy from low density to 50k was reported to be in the range of 0.58 to 0.98, while reported allelic imputation error rates ranged from 2.1% to 40.0%.

Several factors have been reported to affect imputation accuracy. The most important factor in livestock is the number of genotyped immediate ancestors (Hickey *et al.*, 2011; Huang *et al.*, 2012a). When there are no or few immediate ancestors with genotypes, the total number of animals at the imputed density becomes important, that is, having too few animals with genotypes at the imputed SNP density yields poor imputation results (Hayes *et al.*, 2012; Wang *et al.*, 2012). Conversely, the impact of having only a small number of animals available at the imputed SNP density on imputation accuracy may be limited if those animals are close relatives, for example, immediate ancestors, of the imputed individuals (Duarte *et al.*, 2013). Other factors include the SNP density on the low and high panel (Mulder *et al.*, 2012), the MAF of the imputed SNP (van Binsbergen *et al.*, 2014) and whether imputed SNP are located at the end of a chromosome or not (Badke *et al.*, 2013; Cleveland and Hickey, 2013; Wellmann *et al.*, 2013). These factors contribute to the probability that the correct haplotypes are identified and to the LD between imputed SNP and SNP on the low-density panel (Pei *et al.*, 2008). For very low-density SNP panels (e.g. 384 SNP), the impact of the LD between imputed SNP and SNP on the low-density panel can also be reduced considerably if the animals genotyped at the imputed density are close relatives of the imputed individuals (Hickey and Kranis, 2013; Wang *et al.*, 2013; Wellmann *et al.*, 2013).

When imputing using software that does not explicitly utilise pedigree information, other important factors affecting imputation accuracy include the number of individuals with genotypes at the imputed density (Zhang and Druet, 2010), and the relationship between imputed individuals and individuals genotyped at high density (Hickey *et al.*, 2012). Most of these factors interact with each other. For instance, imputation accuracy increases when the density of the low-density panel increases (Berry *et al.*, 2014), which implies that the required number of genotyped individuals at the

Table 5 *Overview of imputation accuracies for imputation of 50k genotypes in livestock species other than dairy cattle*

		Population		Low-density panel						
Species	Reference	Ref.	Val.	384/450	741	1000	1468	3k[1]	5k	6k/7k[2]
Beef cattle	Dassonneville *et al.* (2012)	754	237	–	–	–	–	0.88	–	0.92
	Huang *et al.* (2012b)	183	57	–	–	–	–	0.97	–	–
		249	62	–	–	–	–	0.84	–	–
Pigs	Berry *et al.* (2014)	2424	111	–	–	–	–	–	–	0.94
	Huang *et al.* (2012a)	2699	98	0.94	–	–	–	0.97	–	0.98
	Wellman *et al.* (2013)	795	100	0.89	0.93	–	0.95	0.98	–	–
	Duarte *et al.* (2013)	399	932	–	–	–	0.96	0.97	–	0.98
	Badke *et al.* (2014)	64	900	–	–	–	–	–	–	0.94
		900	900	–	–	–	–	–	–	0.97
Broilers	Wang *et al.* (2013)	1091	160	0.94	0.97	–	–	–	–	–
	Hickey and Kranis (2013)	1017	164	0.95	–	–	–	–	–	–

When multiple imputation methods were used on the same data, or when the same data was used to impute equally sized groups of animals from different breeds, then average results are presented.
[1]This is the Bovine3K (Illumina Inc.) (Dassonneville *et al.*, 2012; Huang *et al.*, 2012a, 2012b), or an *in silico* 3k panel for all other studies.
[2]This is the BovineLD with 6909 single nucleotide polymorphisms (SNPs) (Illumina Inc.) (Huang *et al.*, 2012a), the GeneSeek Genomic Profiler (containing 10k SNPs of which 6890 were retained for analysis; Badke *et al.*, 2014), or an *in silico* 6k panel for all other studies.

Table 6 *Overview of allele imputation error rate[1] for imputation of 50k genotypes in livestock species other than dairy cattle*

		Population		Low-density panel						
Species	Reference	Ref.	Val.	384/450	741	1000	1468	3k[2]	5k	6k/7k[3]
Beef cattle	Dassonneville *et al.* (2012)	754	237	–	–	–	–	4.8	–	2.5
	Sun *et al.* (2012)	2281	777	–	–	–	–	–	–	3.3
	Wang *et al.* (2012)	22	2224	–	–	–	–	9.9	–	–
		225	2021	–	–	–	–	7.7	–	–
		449	1797	–	–	–	–	6.5	–	–
		1123	1123	–	–	–	–	6.4	–	–
	Berry *et al.* (2014)	2424	111	–	–	–	–	–	–	4.0
	Ventura *et al.* (2014)	350	100	–	–	–	–	–	–	5.8
		350	100	–	–	–	–	–	–	11.4
Pigs	Wellman *et al.* (2013)	795	100	6.7	4.0	–	2.7	1.1	–	–
	Badke *et al.* (2013)	64	200	–	–	–	–	–	–	4.9
Layers	Vereijken *et al.* (2010)	57	249	12.4	–	8.6	–	4.9	–	–
Sheep	Hayes *et al.* (2012)	40	19	–	–	15.0	–	11.5	9.8	–
		155	52	–	–	19.5	–	16.5	12.5	–
		153	51	–	–	20.0	–	19.0	19	–

When multiple imputation methods were used on the same data, or when the same data was used to impute equally sized groups of animals from different breeds, then average results are presented.
[1]Allele imputation error rate is computed as half the genotype imputation error rate for studies that provided the latter measure.
[2]This is the Bovine3K (Illumina Inc.) (Dassonneville *et al.*, 2012; Wang *et al.*, 2012), or an *in silico* 3k panel for all other studies.
[3]This is the BovineLD with 6909 single nucleotide polymorphisms (SNPs) (Illumina Inc.) (Sun *et al.*, 2012; Ventura *et al.*, 2014), the GeneSeek Genomic Profiler (containing 10k SNPs of which 6890 were retained for analysis; Badke *et al.*, 2013), or an *in silico* 6k panel for all other studies.

high density to reach a certain level of imputation accuracy decreases when the density of the SNP at the low-density panel increases. Another example is that when pedigree information is not explicitly used the increase in the number of haplotypes in the reference panel tends to especially increase the imputation accuracy of SNPs that are in low MAF (Badke *et al.*, 2013).

The impact of relationships of the imputed animal with the RP on its imputation accuracy can also be derived theoretically from the characteristics of an imputation model as demonstrated in Supplementary Material S3. This demonstrates that if there is a large variation in the relationships of imputed animals with the RP, imputed genotypes come from a mixture of distributions. To avoid this affecting the imputation accuracy computed as a Pearson correlation, it is advisable to compute imputation accuracy within classes of animals that have comparable relationships with the RP. Such classes could, for instance, be having one parent in the RP, having two parents in the RP, having one grandparent in the RP, etc. Alternatively, animals can be grouped by a score representing

Table 7 *Reported reliabilities based on imputed genotypes and observed 50k genotypes from several studies*

Species	Reference	Method	Imputation[1]	# Traits	384/450	741	1468	3k	6k/7k	50k
Dairy cattle	Jiménez-Montero *et al.* (2013)	GBLUP	Beagle	4				0.48	0.49	0.47
		R-Boost	Beagle	4				0.48	0.49	0.51
	Weigel *et al.* (2010b)	Bayesian LASSO	IMPUTE2.0	3	0.19	0.30	0.42	0.47		0.50
	Mulder *et al.* (2012)	BSSVS	DAGPHASE	10	0.22			0.37	0.38	0.39
		BSSVS	DAGPHASEgc	10				0.37		0.39
		BSSVS	CHROMIBD	10				0.37		0.39
		BSSVS	MBLUP	10				0.29		0.39
	Segelke *et al.* (2012)	GBLUP	Findhap	1				0.48	0.53	0.55
		GBLUP	Beagle	1				0.53	0.55	0.55
Pigs	Badke *et al.* (2014)	GBLUP	Beagle	3					0.63	0.63

GBLUP = genomic BLUP; MBLUP = multivariate BLUP.
[1]Imputation methods.

the expected proportion of the genome inherited from reference individuals (Zhang and Druet, 2010), also termed 'traceability' (Mulder *et al.*, 2012). This measure has a much stronger relationship with imputation accuracy than, for example, the average relatedness of imputed animals with the RP (Berry and Kearney, 2011).

Some imputation procedures (e.g. probabilistic Hidden Markov models such as MaCH, Beagle, Impute2 or mixtures of probabilistic and heuristic such as AlphaImpute) compute and use a probability for each of the possible genotypes on a locus. These genotype probabilities can be used to impute the genotype with the highest probability, that is, the most likely genotype. Alternatively, the genotype probabilities can be used to weigh each of the genotypes, to calculate a predicted gene dosage. When the genotypes are imputed using a BLUP model (Gengler *et al.*, 2007), genotypes are predicted as gene dosages. Given that these predicted gene dosages are BLUP estimates implies that they are unbiased (in the BLUP sense), whereas most likely genotypes are not. This can also more generally be derived from standard statistical theory (Aulchenko *et al.*, 2010). In addition, it has been shown that imputation accuracies computed based on gene dosages are higher than based on the most likely genotypes, while the AIER tends to be higher when using dosages (Mulder *et al.*, 2012). Several studies have shown that use of predicted gene dosages in subsequent genomic prediction leads to higher accuracies and lower bias of the obtained genomic breeding values compared with when using the most likely genotypes (Berry and Kearney, 2011; Mulder *et al.*, 2012; Pimentel *et al.*, 2013; Wang *et al.*, 2013). Based on these observations, using predicted gene dosages appears to give superior results compared with using most likely genotypes. Collapsing dosage into the most likely genotype essentially throws information away and is in most cases not necessary given that statistical methods to predict genomic breeding values generally can deal with probabilistic data.

The observed increase in accuracy of direct genomic values (DGV), due to using predicted gene dosage instead of most likely genotypes, was reported to be higher for animals that had a low imputation accuracy, for instance because they had no (grand)parents available in the 50k reference data (Berry and Kearney, 2011). This increase in DGV reliability corresponded well with the increase in the imputation accuracy, while the allelic error rates actually showed the opposite (Mulder *et al.*, 2012).

Imputation accuracy and accuracy of subsequent genomic prediction

Several studies have computed DGV based on imputed genotypes, and compared those to the DGV obtained using true 50k genotypes. Those studies report either the reliability of the DGV based on true and imputed 50k genotypes (Table 7), or the correlation between the DGV based on true and imputed 50k genotypes (Table 8) or both. The latter measure directly illustrates the loss in genetic gain due to using imputed instead of true 50k genotypes information (Cleveland and Hickey, 2013), just like the imputation accuracy, that is expected to be linearly related to the DGV accuracy (Mulder *et al.*, 2012). Most studies that reported reliabilities were based on dairy cattle (Table 7), illustrating that the concept of reliability of individual breeding values is especially important in dairy cattle breeding. Most studies on pigs and poultry reported the correlation between the DGV based on true and imputed 50k genotypes (Table 8). The correlation between the DGV based on true and imputed 50k genotypes was ~0.96 in most studies, indicating only a minor loss in genetic gain due to using imputed genotypes, as also reported by Cleveland and Hickey (2013).

In terms of within breed genomic prediction, use of imputed 50k genotypes typically yields 85% to almost 100% of the reliability obtained with a 50k panel in dairy cattle, provided that the low-density panel contains at least 3k genotypes (Table 7). Other studies in dairy cattle have shown that further imputation to 777k SNPs yielded at most a limited further increase in reliability of genomic breeding values for within breed genomic prediction (Erbe *et al.*, 2012; Su *et al.*, 2012; VanRaden *et al.*, 2013). Thus, imputation is especially

Table 8 *Reported correlation between genomic breeding values based on imputed genotypes and observed 50k genotypes from several studies*

Species	Reference	Method	Imputation[1]	# Traits	384/450	741	1468	3k	6k/7k
Dairy cattle	Segelke *et al.* (2012)	GBLUP	Findhap	1				0.94	0.98
		GBLUP	Beagle	1				0.96	0.98
	Berry and Kearney (2011)	GBLUP	Beagle	16				0.96	
	Mulder *et al.* (2012)	BSSVS	DAGPHASE	10	0.83			0.98	0.99
		BSSVS	DAGPHASEgc	10				0.98	
		BSSVS	CHROMIBD	10				0.99	
		BSSVS	MBLUP	10				0.91	
Pigs	Cleveland and Hickey (2013)	ss-GBLUP	AlphaImpute	1	0.90			0.95	0.96
				1	0.74			0.78	0.77
	Wellmann *et al.* (2013)	GBLUP	Beagle	11	0.45	0.60	0.61	0.62	
			own method	11	0.60	0.62	0.63	0.62	
Broilers	Wang *et al.* (2013)	BayesA	Habier *et al.* (2009)	2	0.97	0.99			
		BayesB		2	0.96	0.98			
		BayesC		2	0.97	0.98			
		GBLUP		2	0.98	0.99			

GBLUP = genomic BLUP; MBLUP = multivariate BLUP.
[1]Imputation methods.

valuable for GS to reduce genotyping cost, by imputing low density up to commonly used 50k SNP panels.

Individual-specific imputation accuracy

When the goal is to use imputed genotypes for genomic prediction, then it is desirable that imputation accuracy reflects the accuracy of the subsequent genomic predictions, relative to the scenario where an individuals' genotypes are known without uncertainty. This means that imputation accuracy needs to be assessed per individual, that is, across loci for a single individual, rather than locus specific, that is, across individuals for a single locus. It is worthwhile noting that almost all studies that are reviewed here, did not report imputation accuracies per individual. Mulder *et al.* (2012) did report individual imputation accuracies, and observed that individual-specific imputation accuracies computed as the correlation between true and imputed genotypes across loci appear to be overestimated, since the average of those individual accuracies is higher than the average of the locus-specific accuracies. This was also observed by Bouwman *et al.* (2014) and Van Binsbergen *et al.* (2014). Mulder *et al.* (2012) suggested to overcome this by subtracting the mean genotype per locus, both from the true and imputed genotype. Bouwman *et al.* (2014) showed that this adjustment of the genotypes indeed yields considerably lower individual imputation accuracies. The desired characteristics of true and imputed genotypes when computing individual-specific imputation accuracies, follows directly from its definition. The (individual specific) imputation accuracy, as defined in this article, is computed as the Pearson correlation coefficient between imputed and true genotypes. The Pearson correlation coefficient assumes that two variables for which the correlation is computed are bivariate normal distributed. When computing individual-specific imputation accuracies, this implies that at each locus for both true and imputed genotypes the mean and the variance need to be standardized, for example, such that adjusted genotypes at each locus follow the same distribution (see Supplementary Material S4 for a more detailed explanation). It should be noted that such adjustment gives more weight to errors at loci with a low MAF, in a similar way as standardizing genotypes in genomic prediction gives more weight to loci with low MAF (VanRaden, 2008). Thus, centring and scaling of genotypes leads to an individual imputation accuracy that rewards correct imputation of genotypes at low MAF loci where genotypes are hard to impute, while it gives less credit to correctly imputing genotypes at easy to impute loci with high MAF.

To demonstrate the impact of (not) centring and scaling true and imputed genotypes on the realized imputation accuracy, a 'golden standard' measure for imputation accuracy is needed. The DGV accuracy (r_{DGV}) is linearly related to the imputation accuracy (r_{imp}), as: $r_{DGV} = r_{imp} \times r_{SNP}$, where r_{SNP} is the accuracy of the estimated SNP effects (Mulder *et al.*, 2012). Note that this formula is very similar to the formula presented by Goddard (2009) to compute the accuracy of a genomic breeding value, with the only difference that r_{imp} in our formula replaces $r(T, T_m)$ in Goddard's formula, that represents the (average) linkage disequilibrium between markers and QTL. Thus, if we can create a situation in which we know r_{SNP} and we can compute r_{DGV} based on imputed genotypes that are in one scenario centred and scaled and not in another scenario, then we can easily compute for both scenarios the value r_{imp} both from the formula above and by computing the correlation between true and imputed genotypes. If both values for r_{imp} are similar in one of both scenarios, then this indicates that the genotypes were treated properly in that particular scenario. Using simulations, we can easily create data with known true SNP effects where $r_{SNP} = 1$, and therefore following the

Table 9 *Summary statistics of comparing DGV and imputation accuracy, based on a simulation where the single nucleotide polymorphism effects were assumed to be known without error*

Accuracy	DGV		Imputation	
Centring and scaling	No	Yes	No	Yes
Average	0.925[a]	0.925[a]	0.966[b]	0.922[a]
s.d.	0.006	0.006	0.001	0.003
Minimum	0.900	0.898	0.962	0.912
Maximum	0.945	0.945	0.970	0.932
$r(r_{DGV}, r_{imp})$[1]			0.396	0.391
Intercept[2]			−1.171	0.118
Slope[2]			2.169	0.875

DGV = direct genomic values.
In all, two scenarios were considered, where genotypes were either defined on the original 0, 1, 2 scale or centred and scaled.
[a,b] Values with different superscripts indicate significant differences at $P < 0.05$.
[1]The correlation between DGV accuracy (r_{DGV}) and individual-specific imputation accuracy (r_{imp}).
[2]Intercept and slope of regressing the DGV accuracy on the individual-specific imputation accuracy.

above described formula, $E(r_{imp}) = r_{DGV}$. This estimate of r_{imp} will be used as a golden standard. In turn, r_{DGV} can also be computed as the correlation between the simulated and predicted DGV. In this sense, it is a measure across animals, so it is important to have a 'homogeneous' group of animals that are expected to have similar values for r_{imp}.

To apply the procedure as outlined above, we performed some straightforward simulations. The simulated data contained genotypes for a single chromosome. The last generation of animals had genotypes for 20 loci, while the two preceding generations, that included the parents of the last generation, had genotypes for all 2000 loci. The simulation was replicated 10 times using AlphaDrop (Hickey and Gorjanc, 2012). A description of the simulations is given in Supplementary Material S5. The genotypes of the animals of the last generation were imputed using AlphaImpute (Hickey *et al*., 2011). On this simulated data, for each animal with imputed genotypes, the predicted DGV was calculated using imputed genotypes on the 0 to 2 scale. In addition, simulated and imputed genotypes were centred and scaled per locus. Within each of the 10 replicates, the DGV accuracy and the individual-specific imputation accuracy, before and after scaling the genotypes, was calculated for 10 000 bootstrapping samples, to obtain proper estimates of the standard errors of the computed accuracies. Thereafter, within each replicate across bootstrapping samples the DGV accuracies were regressed on the individual-specific imputation accuracies. The correlation between DGV accuracies and individual-specific imputation accuracies had a value of only 0.39 to 0.40, indicating that the accuracy of predicting the DGV accuracy with the individual-specific imputation accuracy was low, regardless whether genotypes were scaled and centred or not (Table 9). The regression coefficients, however, clearly indicated that computing imputation accuracy as correlation without scaling and centring the genotypes is a very biased predictor of the DGV accuracy (intercept = −1.171 and slope = 2.169), while after scaling and centring the genotypes it is an almost unbiased predictor (intercept = 0.118 and slope = 0.875). This is also shown by the averages of the estimated imputation accuracies measured as a correlation between true and imputed genotypes. This average imputation accuracy was very close to the 'golden standard' imputation accuracy ($E(r_{imp}) = r_{DGV}$), when centring and scaling was applied, while it was significantly inflated by ~0.04 if genotypes were not centred and scaled (Table 9). These results indeed confirm that individual-specific imputation accuracies should be computed from genotypes that are centred and scaled.

Concluding remarks

Imputation of high density, using true genotypes from a lower-density panel, has received a lot of attention in livestock genetics research in recent years, because it can reduce genotyping costs considerably while generally only a minor loss in genetic gain is expected because of imputation inaccuracy. Across this body of literature, several important messages can be extracted. First of all, imputation accuracy, measured as the correlation between true and imputed genotypes, is preferred over measures that count the number of correct or erroneously imputed alleles or genotypes. This follows readily from the observations that (1) imputation based solely on allele frequency quite naturally leads to an imputation accuracy of zero while the resulting imputation error rate depends on the MAF of the locus; and (2) that imputation accuracy is more sensitive to errors at loci with increasingly lower MAF, while imputation error rate actually shows the opposite relationship. The latter feature may be even more important in the near future, when imputation may be primarily targeting whole genome sequence data that holds relatively much more low MAF loci, compared with currently used SNP panels.

When imputation accuracy is assessed as a predictor for the accuracy of subsequent genomic prediction, we recommend that: (1) individual-specific imputation accuracies should be used that are computed after centring and scaling both true and imputed genotypes; and (2) imputation of gene dosage is preferred over imputation of the most likely genotype, as this increases accuracy and reduces bias of the imputed genotypes and the subsequent genomic predictions. Measuring imputation performance correctly will be increasingly important in the future when many of the imputation tasks will involve sequence data. Sequence data has a much greater proportion of loci with low MAF than SNP data and therefore metrics that depend on MAF will give very misleading results.

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Supplementary Material

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