Genomic selection for any dairy breeding program via optimised investment in phenotyping and genotyping

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Abstract

Background: This paper evaluates the potential of maximizing genetic gain in dairy cattle breeding programmes by optimizing investment into phenotyping and genotyping. Conventional dairy breeding programmes focus on phenotyping selection candidates or their close relatives to increase selection accuracy, since this is the main driver of genetic gain and quality assurance for dairy farmers. Genomic selection ~~decoupled~~changed the relative importance of breeding actions and selection parameters ~~henotyping and selection and through this enabled~~and ~~increased~~through this doubled genetic gain per year compared to the conventional selection. However, genomic selection requires a large initial investment, which limits the adoption of genomic selection for some breeding programmes. Here we evaluate the possibility of optimizing the investment in phenotyping and genotyping to enable genomic selection in a case-study of a small dairy population and provide suggestions for other dairy breeding programmes.

Results: We simulated a case-study of a small dairy population with a number of equal costs scenarios. The conventional progeny testing scenario had 11 phenotype records per lactation. In genomic scenarios, we reduced phenotyping to record from 10 to 1 per lactation and invested the saved resources into genotyping. We tested these scenarios in settings with or without initial training population for genomic selection. The results show that reallocating a part of phenotyping resources to genotyping increases genetic gain compared to the conventional scenario regardless of the amount and relative cost of genotyping, and the presence of an initial training population. The genetic gain increases with increased investment in genotyping, despite reduced phenotyping.

Conclusions: This study shows that breeding programmes should optimise ~~allocation of resources~~investment into phenotyping and genotyping ~~efforts~~ to maximise return on investment. We argue that investment into genotyping over repeated phenotyping increases return on investment~~xpensive phenotypes, in particular for the e in phenotypinginvestmentto maximise return~~

on d should be genotyped animalsphenotype that most. These conclusions imply that dairy breeding programmes can implement genomic selection without increasing the level of investment.

Background

This paper evaluates the potential of maximizing genetic gain in dairy cattle breeding programmes by optimizing investment into phenotyping and genotyping. All breeding programmes strive to maximize genetic gain, which is a function of selection intensity, accuracy of selection, genetic variation, and generation interval. The conventional dairy breeding programme uses a long and expensive progeny testing that does not allow for high selection intensity. This programme focuses majority of resources into phenotyping to increase the accuracy of sire selection, since this is the main driver of genetic gain. Genomic selection [1, 2] (Meuwissen et al., 2001; Schaeffer, 2006), on the other hand, achieves genetic gain mainly through substantially reduced generation interval, increased selection intensity, and increased accuracy of selection for young animals [2, 4] (Schaeffer, 2006; Obšteter et al., 2019). ~~Although due to earlier selection in genomic selection the accuracy of selection candidates is often lower than that of a progeny test,~~Despite lower accuracy of sire selection, genomic selection doubles the rate of genetic gain per year in dairy cattle compared to the conventional progeny testing [3](Wiggans et al., 2017).

All breeding programmes operate with a certain amount of resources allocated between breeding activities with the aim to maximise return on investment. Genomic selection is now a de-facto standard in well-resourced breeding programmes, but is still challenging to implement for some breeding programmes. The major hurdle is the large initial investment in genotyping to establish a training population, but maintaining this population on a yearly basis can also be a challenge~~a hurdle~~.~~to yearly update it.~~ These breeding programs need to evaluate priorities and reorganise phenotyping and genotyping to maximise return on investment.

I think we have different ideas of what we want to show here. You want to show with fixed resources and I want to show what happens when we cut down (for phenotyping). My idea was to show that:

1) **reducing repeated phenotyping does not significantly affect accuracy.** My idea was to show this independently from the reallocating to phenotyping (genotyping) more animals.

1.1) I show this in a conventional programme – what happens, when we reduce repeated phenotyping and use it for SOMETHING else. The point is → nothing dramatic happens. If I show an example with fixed resources, where I reallocate this money to phenotype more daughters with less phenotypes, I am not really phenotyping less and cutting down. Here I am using an example with 100daughters per bull and 100 bulls = **10,000 phenotyped females** and **maximum resources for 100,000 phenotypes**. Then I cut down to use money for something else than phenotyping.

1.2) I show the same thing for a genomic example. Cutting repeated phenotyping does not significantly affect the accuracy. Here I am AGAIN using an example with **10,000 females in TP** and **maximum resources for 100,000 phenotypes**

2) **we can benefit from reallocating resources from phenotyping to genotyping**

For this I take the **100,000 cows phenotyped once**, which again equals to the **maximum resources for 100,000 phenotypes.** This increases the accuracy compared to 10,000 cows phenotyped 10-times. HOWEVER – this is not totally true – when we increase the number of genotyped animals from 10,000 to 100,000, we also need to phenotype them! So should 10,000 cows each phenotyped 10-times equal to 50,000 genotyped cows each phentyped once???

3) **Despite reduced accuracy, genomic selection still increases genetic gain- I removed this**

For this I take the example from above: 10,000 females, each phenotyped 10-times = **maximum resources for 100,000 phenotypes**

This then covers everything that drove us to do this – we believed that repeated records don't contribute that much and that is better to invest into genomic selection, since it increases genetic gain (through parameters other than accuracy).

The accuracy of conventional pedigree-based estimates of breeding values increases with increasing heritability and increasing number of phenotype records per animal or its closest relatives (e.g., [5]Mrode, 2005). To illustrate, assume a female-expressed trait with the heritability of 0.25, ~~repeatability of 0.35~~, and progeny testing in a population with 100 sires each tested on 100 daughters each (10,000 cows in total). Collecting 10 phenotype records per daughter gives the expected accuracy of sire selection of 0.98 and the accuracy of non-phenotyped progeny of 0.66. If we decrease the number of phenotype records per daughter to 5, 2, or 1, the accuracy of sire selection respectively decreases to 0.97, 0.96, or 0.93, and the accuracy of parent average to 0.64, 0.59, or 0.56. This shows that repeated phenotype records have diminishing returns and that there is a scope for optimising return on investment.-

THE ABOVE EXAMPLE IS WITH A FIXED NUMBER OF DAUGHTERS PER BULL, SO YOU ARE COMPARING PROGRAMMES WITH RESOURES FOR 100*100*c(10, 5, 2, 1) = c(100K, 50K, 20K, 10K) PHENOTYPES.

Yes – again, I think that "fixed resources" example is not the best here – since we are later not testing programmes that have fixed resources for phenotyping – but we are cutting the phenotyping resources.

I suggest you now expand this paragraph by describing what happens when you have resources for 10K phenotypes. Make sure this does not prolong the paragraph too much. Or should you immediately start with the fixed 10K phenotypes case? - I can prepare this, but I think we should show what happens, when we cut resources for phenotyping

The accuracy of genome-based estimates of breeding values also increases with increasing heritability and increasing number of phenotype records per genotyped animal, but also with increasing training population of phenotyped and genotyped animals, decreasing genetic distance between training and prediction individuals, and decreasing number of effective genome segments (Daetwyler et al. 2008; Goddard, 2009; Habier et al., 2010; Clark et al, 2011; Goddard et al., 2011).

The latter dictates linkage disequilibrium between markers and causal loci, which drives accuracy of genomic evaluation and prediction. Recombination, mutation, migration, drift, and selection change linkage disequilibrium and decrease the accuracy of genomic prediction across generations if the training population is not updated (Meuwissen et al., 2001; Calus, 2010). While the accuracy of genomic prediction decays slower than with pedigree prediction, we still observe a substantial decrease (Habier et al., 2010; Wolc et al., 2011). To prevent the drop in the accuracy, marker effects must be continually re-estimated and the training population must be continually updated with new animals.

Following the previous example, assume 10,000 effective genome segments, trait repeatability of 0.35, and a training population of 10,000 cows. Recording 10 phenotype values per cow increases the heritability of training phenotypes to 0.60 and results in the expected genomic prediction accuracy of 0.61 for a non-phenotyped animal. By reducing the number of phenotype records per cow to 5, 2, or 1, we respectively reduce the heritability of training phenotypes to 0.52, 0.37, or 0.25, and genomic prediction accuracy to 0.59, 0.52, or 0.45. This example again shows that replicated phenotyping has diminishing returns and that there is a scope for optimising return on investment also with genomic breeding programmes. We can also invest the resources saved by reducing phenotyping into ~~o compensate for reduced genotyping~~ ~~If we~~ genotyping. If we ~~simultaneously increase~~increase **the number of genotyped** ~~animals~~cows to ~~, t, genomic prediction with~~ 100,000 ~~cows in the training population~~, each phenotyped once, ~~results in the~~we increase the expected genomic accuracy ~~of~~to 0.85. While these genomic prediction accuracies are lower than with progeny testing, shorter generation interval enables larger genetic gain per unit of time [2](Schaeffer, 2006). ~~Despite this, the genomic selection this increases genetic gain. For example, if we assume 10,000 females each phenotyped 10-times and 5% of males selected, a conventional progeny testing with 100 sires, generation interval of 6 years and accuracy of 0.98 gives the expected genetic gain of 0.34 units of genetic standard deviation per year. Genomic selection with the same intensity of male selection, generation interval of 2 years and accuracy of 0.59 gives the expected genetic gain of 0.61 units~~

genetic standard deviation per year. However, the calculations above hold for when all individuals in the training population are genotyped and phenotyped. In reality, breeding programmes consist of individuals with only phenotype, genotype, or both types of information. To handle this, we use single-step genomic prediction that combines all phenotypic, pedigree, and genomic information and in turn increases prediction accuracy even further (Gao et al., 2012, Gray et al., 2012; Lourenco et al., 2015). However, even with it we can not predict the actual accuracies and genetic gain of complex breeding programmes with overlapping generationsns,.

Pedigree-based nor genomic prediction exploit all the available information, since for some animals in the breeding programme we have only phenotype, genotype, or both types of information. Single-step combines all phenotypic, pedigree, and genomic information and in turn increases prediction accuracy even further (Gao et al., 2012, Gray et al., 2012; Lourenco et al., 2015).

Repeated phenotyping could be an internal financial reserve that enables any breeding programme to implement genomic selection. In dairy breeding programs, the most repeatedly and extensively recorded phenotypes are milk production traits. There are different milk recording methods that differ in the authorisation forto recording, sampling scheme, recording frequency, sampling frequency, and the number of milkings per day (ICAR, 2017). The recording interval ranges from daily recording to recording every nine weeks, which translates to between 5 and 44 recordings per lactation. However, the prices of milk recording are not standardized and differ between recoding systems, countries, and their regions. Some organizations require payment of a participation fee plus the cost per sample, while others include the fee in the sample cost or cover the costs in other ways.

The aim of this study was to evaluate the potential of maximizing genetic gain by optimizing investment into phenotyping and genotyping in dairy breeding pogrammes. Since milk recording is an example of a repeated phenotype with diminished returns, we aimed to evaluate the optimal investment into milk recording and genotyping. To this end we have compared a dairy breeding

programme with conventional progeny testing or genomic testing under equal -cost. To support ~~resource~~ genomic selection we reduced the number of milk records per cow per lactation and invested the saved resources into genotyping. We compared these strategies in a small cattle breeding programme as this is a challenging case to implement genomic selection. The results show that reallocating a part of phenotyping resources to genotyping increases genetic gain regardless of the cost and amount of genotyping, and the availability of initial training population. The genetic gain also increases with increasing investment into genotyping, despite reduced~~ing~~ phenotyping.

Methods

The study aimed to evaluate the effect of different investment into phenotyping and genotyping with a simulation of a case-study of a small dairy breeding programme. The simulation mimicked a real dairy cattle population of ~30,000 animals analysed in our previous study [4]Obšteter et al. (2019). We evaluated 36 genomic scenarios against the conventional scenario, all with equal costs, but varying extent of phenotyping and genotyping. The conventional scenario implemented progeny testing and collected 11 phenotype records per lactation, while genomic scenarios reduced phenotyping and invested saved resources to genotyping. The genomic scenarios differed in i) the number of phenotype records per cow per lactation; ii) the relative cost of phenotyping and genotyping; and iii) the availability of an initial training population. All tested scenarios were compared based on their genetic gain and accuracy of selection.

Simulation of the base population, phenotype and historical breeding

The simulation mimicked a small dairy cattle breeding programme of ~30,000 animals with ~10,500 cows, where introduction of effective genomic selection is difficult. We use this population as a challenging case study to optimize investment into phenotyping and genotyping. The breeding programme aimed to improve dairy performance, which we simulated as a single polygenic trait. For this we used a coalescent process to simulate whole genome comprised of 10 cattle-like chromosomes, each with 10^8 base pairs, 1,000 randomly chosen causal loci and 2,000 randomly chosen marker loci. We sampled the causal loci effects from a normal distribution and constituted animal's breeding value (a_i) for dairy performance (y_{ijkl}). We assigned permanent environment (p_i), herd (h_j), herd-year (hy_{jk}), herd-test-day (htd_{jkl}), and residual environment (e_{ijkl}) effects to the trait:

$$y_{ijkl} = a_i + p_i + h_j + hy_{jk} + htd_{jkl} + e_{ijkl}.$$

We sampled the permanent environment effects from a normal distribution with zero mean and variance equal to the additive genetic variance (σ^2_A). We sampled herd, herd-year, and herd-test-day

effects each from a normal distribution with zero mean and variance 1/3 σ^2_A. Finally, we sampled residual environment effects from a normal distribution with zero mean and variance σ^2_A. This sampling scheme gave a trait with heritability 0.25 and repeatability of 0.50. With the simulated genome and phenotype architecture we have initiated the dairy cattle breeding programme and ran it for 20 years of a conventional selection with progeny-testing based on 11 cow phenotype records per lactation. The detailed parameters of the simulation are described in [4]Obšteter et al. (2019). In summary, in the breeding programme we selected 3,849 out of 4,320 new-born females as cows and 139 as bull-dams during their second, third and fourth lactation. We generated 45 male calves from elite matings and out of these chose 8 for progeny testing of which 4 were eventually selected as elite sires. We made all selection decisions based on pedigree-based estimates of breeding values. The 20 years represented historical breeding and provided a starting point for evaluating future breeding scenarios, which we ran for additional 20 years.

Scenarios

We evaluated 36 genomic scenarios against the conventional scenario, but varying the extent of phenotyping and genotyping. All scenarios had equal costs. The conventional scenario continued the breeding scheme from historical breeding. It used progeny testing and 11 phenotype records per lactation (named C11), corresponding to the standard ICAR recording interval of 4 weeks (ICAR, 2017). We assumed that this scenario represented the total amount of resources available for generating data. We then created genomic scenarios that distributed the total resources between phenotyping and genotyping - we reduced phenotyping and invested the saved resources into genotyping. In the genomic scenarios we selected females as in the conventional scenario and males based on genomic testing. We varied the number of genomically tested male ~~calves~~candidates depending on the resources and always selected the best 5 as elite sires solely on genomic prediction. We evaluated the genomic scenarios under a range of factors: number of phenotype records per lactation, cost of genotyping, and the availability of an initial training population.

Genomic scenarios reduced phenotyping of the conventional scenario and varied the number of phenotype records per lactation between 10 and 1. The scenarios followed ICAR standards of 9, 8, and 5 records per lactation, corresponding to recording intervals of 5, 6, and 9 weeks. Additionally, we created three non-standard recording systems collecting 10, 2, and 1 records per lactation, ~~scorresponding to recording intervals of 4.4, 22, and 44 week.~~ We named the scenarios as "GX" with X being the number of records per lactation. The reduction in phenotyping and the relative cost of phgenotyping to genotyping dictated the amount of saved resources and therefore the number of genotyped animals (Table 1). We invested the saved resources into genotyping females and males in ratio 7:1 based on our previous work [4]Obšteter et al. (2019). If the resources for genotyping females exceeded the cost of genotyping all first parity cows, we did not reallocate the excess to male genotyping. We genotyped first parity cows. This maximized the accuracy of genomic prediction, since it reduced the genetic distance between training and prediction population, prevented the loss of information due to culled heifers, and minimized the time to obtain a phenotype. To maximise the genetic gain, we genotyped male calves from elite matings and high parent average matings.

Genomic scenarios next varied the relative cost of phenotyping ($P) ~~relative to the cost of~~ to genotyping ($G). We compared the cost of one genotype to the cost of 11 phenotype records (recording every four weeks) per lactation. Based on a survey of several breeding programmes, milk recording organizations, and genotyping providers we have considered three cost ratios of $P:$G: 2:1, 1:1, and 1:2. The pricing of every additional milk recording decreased, hence the first recording was the most expensive and the cost of each subsequent control was 95% of the preceding control.

~~in a sense of reducing genetic distance between training and prediction population, ,accuracy of genomic predictionthe We invested the saved resources into genotyping females and males in ratio 7:1 based on our previous work [4]Obšteter et al. (2019) and available resources (Table 1). To maximise highand sustain theaccuracy of genomic prediction we genotyped first parity cows. To~~

maximise the genetic gain, we genotyped male calves from elite matings and high parent average matings.

Lastly, we created scenarios with and without an initial training population for genomic prediction. With an initial training population available, we genotyped all active cows (10,653) and progeny tested sires (100) before the first evaluation. Without an initial training population available, we yearly genotyped a designated number of first parity cows until the training population reached 2,000 cows. Once we reached this goal, we genotyped both females and males as specified in Table 1.

Estimation of breeding values

We selected the animals based on their estimated breeding values that we estimated with a pedigree or single-step genomic (Legarra et al., 2009) repeatability model with breeding value, permanent environment, and herd-year as random effects. We did not fit the herd-test-day effect as data structure of this small population did not enable its accurate estimation. We estimated breeding values once a year with blupf90 (Misztal et al, 2002) with default settings. In the estimation we included all available phenotype and pedigree records for all active, phenotyped, or genotyped animals and additional three generations of their ancestors. However, we used at most 25,000 genotyped animals due to a maximum number of animals allowed in the non-commercial software version. When we accumulated more than 25,000 genotyped animals, we removed the oldest animals in favour of the latest genotyped cows and male selection candidates.

Table 1. NThe number of genotyped animals per year by scenario and relative cost of phenotyping to genotyping.

Relative cost	Scenario					
	G10	G9	G8	G5	G2	G1

$P:$G = 1:2	160 F	350 F	590 F	1610 F	3230 F	3850 F
	22 M	50 M	85 M	235 M	465 M	565 M
$P:$G = 1:1	310 F	700 F	1180 F	3230 F	3850 F	3850 F
	45 M	100 M	165 M	465 M	925 M	1125 M
$P:$G = 2:1	620 F	1400 F	2360 F	3850 F	3850 F	3850 F
	90 M	295 M	335 M	925 M	1845 M	2245 M

Scenarios are named "G" for genomic, followed by the number of phenotype records per lactation. The number of phenotype records and the relative cost of phenotyping to genotyping ($P:$G) dictated the number of genotyped animals. We genotyped females (F) and males (M) in 7:1 ratio.

Analysis of scenarios

All scenarios had equal costs and we compared them based on their genetic gain, which indicated return for the same level of investment, and accuracy of selection. We measured the genetic gain as an average true breeding value by year of birth and standardized it to have zero mean and unit standard genetic deviation in the first year of comparison. We measured the accuracy of breeding values as the mean correlation between true and estimated breeding values of the evaluation years. We obtained the accuracy of: i) male candidates, that is genotyped non-phenotyped male calves; ii) females candidates, that is non-genotyped non-phenotyped female calves; iii) sires, that is sires currently used in artificial insemination; and iv) dams, that is all active phenotyped females (cows and bull dams). We repeated simulation of the base population and each scenario 10 times and summarised results across the replicates.

Results

Genomic scenarios increased the genetic gain of the conventional scenario regardless of the number of phenotype records per lactation, relative cost of phenotyping to genotyping, and the availability of an initial training population. ~~The results compare the impact of optimizing the investment into phenotyping and genotyping on genetic gain and prediction accuracy. Specifically, the results compare the impact of varying the number of phenotype records per lactation, relative cost of genotyping, and the availability of an initial training population for genomic prediction.~~ Despite reduced phenotyping, genomic scenarios with an existing initial training population increased the genetic gain of the conventional scenario by up to 143%. Genetic gain increased with increasing investment into genotyping, hence more animals genotyped. Compared to the ~~baseline~~conventional scenario, implementing genomic selection also increased the accuracy for non-phenotyped selection male and female candidates, and dams. Scenarios without an~~Removing the~~ initial training population ~~did not change the~~followed the overall trend for genetic gain and~~or prediction~~ accuracy. Although these scenarios had~~it resulted in a~~ slightly smaller genetic gain due to a delay in the implementation of genomic selection, they~~it~~ still increased the genetic gain of the conventional scenario by up to 134%.

Genetic gain with an initial training population

Table S1. Genetic gain by scenario, ~~an,d~~ relative cost of phenotyping to genotyping, and availability of initial training population.

Scenario*	Relative cost of phenotyping ($P) to genotyping ($G)		
	$P:$G = 1:2	**$P:$G = 1:1**	**$P:$G = 2:1**
C11	$3.01_{0.22}^{a,A}$	$3.01_{0.22}^{a,A}$	$3.01_{0.22}^{a,A}$
With initial training population			
G10	$5.43_{0.20}^{b,A}$	$5.41_{0.29}^{b,A}$	$6.50_{0.20}^{b,B}$
G9	$5.58_{0.26}^{b,A}$	$6.30_{0.17}^{c,B}$	$7.02_{0.24}^{c,C}$
G8	$6.35_{0.25}^{c,A}$	$6.62_{0.25}^{d,B}$	$7.02_{0.17}^{c,C}$
G5	$6.78_{0.21}^{d,A}$	$7.07_{0.20}^{e,B}$	$7.26_{0.19}^{c,B}$

G2	$7.13_{0.29}^{e, A}$	$7.33_{0.26}^{e, A}$	$7.28_{0.17}^{c, A}$
G1	$7.11_{0.16}^{e,A}$	$7.27_{0.28}^{e, A}$	$7.24_{0.22}^{c,A}$
Without and initial training population			
G10	$3.93_{0.22}^{b, A}$	$4.54_{0.14}^{b, B}$	$5.61_{0.25}^{b, C}$
G9	$4.64_{0.18}^{c, A}$	$5.75_{0.28}^{c, B}$	$6.52_{0.17}^{c, C}$
G8	$5.61_{0.28}^{d, A}$	$6.24_{0.19}^{d B}$	$6.70_{0.25}^{cd, C}$
G5	$6.43_{0.21}^{e, A}$	$6.90_{0.22}^{e, B}$	$7.05_{0.27}^{de, B}$
G2	$6.81_{0.28}^{f, A}$	$6.96_{0.17}^{e, A}$	$7.00_{0.30d}^{e, A}$
G1	$6.78_{0.29}^{f,A}$	$6.92_{0.26}^{e, A}$	$7.01_{0.23}^{e,A}$

*The table presents the means and standard deviations (subscript) across 10 replicates for the conventional (C) and genomic (G) scenarios, with numbers indicating the number of phenotype records per lactation, within three relative costs of phenotyping to genotyping ($P:$G). The genomic scenarios differ in the availability of the initial training population Lower-case letters denote statistically significant differences between scenarios within the same $P:$G and upper-case letters between different $P:$G within the same scenario.

Genomic scenarios with an initial training population increased the genetic gain of the conventional scenario between 79% and 143% for the same level of investment. The genetic gain increased with the increasing investment in genotyping, despite reduced phenotyping. We show this in Figure 1 and Table S1 with ~~the~~ genetic gain by scenario and the relative cost of phenotyping to genotyping with an initial training population. When the cost of phenotyping was the same as the cost of genotyping ($P:$G = 1:1), the genomic scenarios increased the genetic gain of the conventional scenario between 79% and 143%. By ~~one phenotype record, hence collecting ofsaving resources 10~~cutting down to ~~ent~~10 phenotype records per lactation (G10), hence saving resources of one phenotype record, we could genotype 355 animals per year, of which 45 were male candidates. Compared to the conventional scenario, this increased the selection intensity for males from 0.73 to 1.65 and increased the genetic gain by 79% (from 3.01 to 5.41). By ~~two or three phenotype recordsaving resources of s,~~ cutting down to ~~collectinghence~~ nine or eight phenotype values per lactation (G9 or G8) and ~~saving resources of two or three phenotype records,~~ we could respectively genotype 800 or 1,345 animals per year, of which 100 or 165 were male candidates.

This respectively increased the selection intensity of males to 2.02 or 2.20, and genetic gain by 109% or 120% (from 3.01 to 6.30 or 6.62). We achieved the highest genetic gain, between 135% and 143% of the conventional scenario (between 7.07 and 7.33), when we collected five, two, or one phenotype records per lactation. In these three scenarios we could genotyped between 3,230 and 3,850 (all) females and between 465 and 1,125 male candidates per year and achieve the selection intensity of males between 2.63 and 2.93.

We observed a similar trend for genetic gain when the cost of phenotyping was half or twice the cost of genotyping. Changing the relative cost of phgenotyping to genotyping had the largest effect in the scenario with the smallest amount of genotyping (G10). In this scenario, when phenotyping was twice or half the cost of genotyping, we could respectively genotype 182 or 710 animals, of which 22 or 90 were males, and increased the genetic gain of the conventional scenario for 80% (from 3.01 to 5.43) or 116% (from 3.01 to 6.50). When we maximized the investment into genotyping (G1), we genotyped all females at all three price ratios and between 565 and 2,245 male candidates. Correspondingly, we achieved a comparable genetic gain, between 136% and 143% of the conventional scenario, regardless of the relative cost of phenotyping to genotyping and different intensities of male selection.

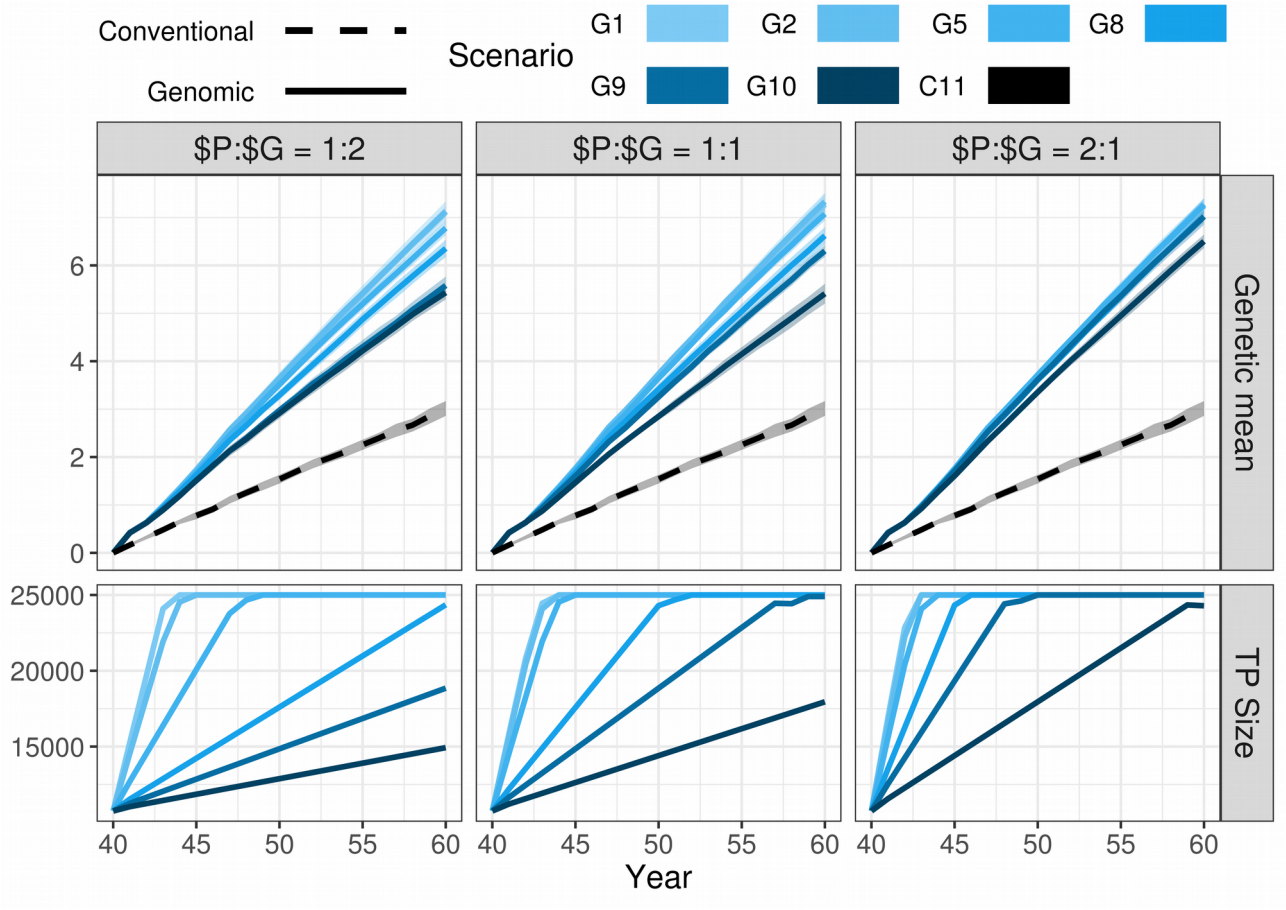

Figure 1 Genetic gain and training population size by scenario and relative cost of genotyping with initial training population. The figure presents the means (lines) and 95% confidence intervals (polygons) across 10 replicates for the conventional (C) and genomic (G) scenarios, with numbers indicating the number of phenotype records per lactation, within three relative costs of phenotyping to genotyping ($P:$G). TP = training population.

Accuracy with an initial training population

Table S2 Selection accuracy by scenario, relative cost of genotyping, and the availability of initial training population.

	Relative cost of phenotyping ($P) to genotyping ($G)					
	With initial TP			Without initial TP		
	$P:$G = 1:2	$P:$G = 1:1	$P:$G = 2:1	$P:$G = 1:2	$P:$G = 1:1	$P:$G = 2:1
Male candidates						

C11, S1	$0.37_{0.04}^{a,A}$	$0.37_{0.04}^{a,A}$	$0.37_{0.04}^{a,A}$	$0.37_{0.04}^{a,A}$	$0.37_{0.04}^{a,A}$	$0.37_{0.04}^{a,A}$
C11, S2	$0.94_{0.01}^{b,A}$	$0.94_{0.01}^{b,A}$	$0.94_{0.01}^{b,A}$	$0.94_{0.01}^{b,A}$	$0.94_{0.01}^{b,A}$	$0.94_{0.01}^{b,A}$
G10	$0.89_{0.03}^{c,A}$	$0.90_{0.02}^{bc,AB}$	$0.91_{0.01}^{bc,B}$	$0.81_{0.03}^{b,A}$ *	$0.84_{0.01}^{b,B}$ *	$0.87_{0.01}^{b,C}$ *
G9	$0.90_{0.03}^{bc,A}$	$0.91_{0.02}^{bc,A}$	$0.91_{0.01}^{bc,A}$	$0.85_{0.02}^{c,A}$ *	$0.87_{0.01}^{bc,B}$ *	$0.90_{0.01}^{bc,C}$ *
G8	$0.91_{0.01}^{bc,A}$	$0.91_{0.01}^{bc,A}$	$0.91_{0.01}^{bc,A}$	$0.86_{0.01}^{cd,A}$ *	$0.89_{0.01}^{c,B}$ *	$0.90_{0.01}^{bc,B}$
G5	$0.91_{0.01}^{bc,A}$	$0.91_{0.00}^{bc,A}$	$0.91_{0.01}^{bc,A}$	$0.90_{0.01}^{d,A}$	$0.91_{0.01}^{c,A}$	$0.91_{0.01}^{c,A}$
G2	$0.91_{0.01}^{bc,A}$	$0.91_{0.00}^{bc,A}$	$0.90_{0.01}^{bc,A}$	$0.90_{0.01}^{d,A}$	$0.90_{0.01}^{c,A}$	$0.90_{0.01}^{bc,A}$
G1	$0.89_{0.01}^{c,A}$	$0.90_{0.01}^{c,A}$	$0.89_{0.01}^{c,A}$	$0.89_{0.01}^{cd,A}$	$0.89_{0.01}^{c,A}$	$0.89_{0.01}^{bc,A}$
Female candidates						
C11	$0.45_{0.02}^{a,A}$	$0.45_{0.02}^{a,A}$	$0.45_{0.02}^{a,A}$	$0.45_{0.02}^{a,A}$	$0.45_{0.02}^{a,A}$	$0.45_{0.02}^{a,A}$
G10	$0.48_{0.01}^{ab,A}$	$0.48_{0.01}^{ab,A}$	$0.51_{0.01}^{b,B}$	$0.46_{0.02}^{ab,A}$ *	$0.47_{0.02}^{ab,AB}$	$0.49_{0.01}^{b,B}$ *
G9	$0.49_{0.02}^{b,A}$	$0.50_{0.01}^{b,B}$	$0.52_{0.01}^{b,C}$	$0.47_{0.02}^{ab,A}$ *	$0.49_{0.02}^{bc,B}$	$0.52_{0.01}^{bc,C}$
G8	$0.51_{0.01}^{b,A}$	$0.51_{0.01}^{b,A}$	$0.54_{0.01}^{bc,B}$	$0.49_{0.02}^{bc,A}$ *	$0.52_{0.01}^{cd,B}$	$0.53_{0.01}^{cd,C}$
G5	$0.51_{0.01}^{bc,A}$	$0.55_{0.01}^{c,B}$	$0.57_{0.01}^{c,C}$	$0.52_{0.01}^{cd,A}$	$0.55_{0.01}^{de,B}$	$0.57_{0.01}^{d,C}$
G2	$0.55_{0.01}^{cd,A}$	$0.57_{0.01}^{c,B}$	$0.57_{0.01}^{c,B}$	$0.55_{0.01}^{d,A}$	$0.56_{0.02}^{e,AB}$	$0.57_{0.01}^{d,B}$
G1	$0.56_{0.01}^{d,A}$	$0.56_{0.01}^{c,A}$	$0.56_{0.01}^{c,A}$	$0.55_{0.01}^{d,A}$	$0.56_{0.01}^{e,A}$	$0.56_{0.01}^{d,A}$
Dams						
C11	$0.48_{0.03}^{a,A}$	$0.48_{0.03}^{a,A}$	$0.48_{0.03}^{a,A}$	$0.48_{0.03}^{a,A}$	$0.48_{0.03}^{a,A}$	$0.48_{0.03}^{a,A}$
G10	$0.56_{0.02}^{b,A}$	$0.59_{0.02}^{b,B}$	$0.63_{0.01}^{b,C}$	$0.53_{0.01}^{b,A}$ *	$0.56_{0.01}^{b,B}$ *	$0.61_{0.01}^{b,C}$ *
G9	$0.59_{0.03}^{bc,A}$	$0.63_{0.02}^{c,B}$	$0.70_{0.01}^{c,C}$	$0.57_{0.02}^{bc,A}$ *	$0.62_{0.02}^{c,B}$	$0.68_{0.02}^{c,C}$ *
G8	$0.62_{0.02}^{c,A}$	$0.67_{0.02}^{c,B}$	$0.74_{0.02}^{d,C}$	$0.60_{0.02}^{c,A}$ *	$0.66_{0.01}^{d,B}$	$0.73_{0.02}^{d,C}$
G5	$0.70_{0.02}^{d,A}$	$0.77_{0.01}^{d,B}$	$0.79_{0.02}^{e,C}$	$0.69_{0.02}^{d,A}$	$0.76_{0.01}^{e,B}$	$0.78_{0.02}^{e,B}$
G2	$0.76_{0.02}^{e,A}$	$0.79_{0.02}^{d,B}$	$0.78_{0.01}^{e,AB}$	$0.76_{0.01}^{e,A}$	$0.77_{0.02}^{e,A}$ *	$0.77_{0.01}^{de,A}$
G1	$0.77_{0.02}^{e,A}$	$0.77_{0.02}^{d,A}$	$0.77_{0.01}^{de,A}$	$0.76_{0.01}^{e,A}$	$0.76_{0.02}^{e,A}$	$0.76_{0.02}^{de,A}$
Sires						
C11	$0.86_{0.05}^{a,A}$	$0.86_{0.05}^{a,A}$	$0.86_{0.05}^{a,A}$	$0.86_{0.05}^{a,A}$	$0.86_{0.05}^{a,A}$	$0.86_{0.05}^{a,A}$
G10	$0.75_{0.04}^{b,A}$	$0.75_{0.03}^{b,A}$	$0.73_{0.05}^{b,A}$	$0.67_{0.08}^{bc,A}$ *	$0.68_{0.05}^{cde,A}$ *	$0.67_{0.06}^{b,A}$ *
G9	$0.76_{0.04}^{b,A}$	$0.72_{0.06}^{bc,AB}$	$0.69_{0.05}^{c,A}$	$0.70_{0.05}^{b,A}$ *	$0.72_{0.05}^{bc,A}$	$0.71_{0.05}^{b,A}$
G8	$0.76_{0.03}^{b,A}$	$0.69_{0.05}^{cd,B}$	$0.68_{0.06}^{c,B}$	$0.71_{0.05}^{b,A}$ *	$0.74_{0.05}^{b,A}$ *	$0.70_{0.07}^{b,A}$
G5	$0.68_{0.07}^{c,A}$	$0.67_{0.08}^{de,A}$	$0.69_{0.04}^{c,A}$	$0.68_{0.05}^{bc,A}$	$0.69_{0.05}^{cd,A}$	$0.69_{0.03}^{b,A}$
G2	$0.67_{0.05}^{c,A}$	$0.67_{0.05}^{de,A}$	$0.67_{0.04}^{c,A}$	$0.65_{0.06}^{c}$	$0.64_{0.07}^{e,A}$	$0.69_{0.05}^{b,A}$
G1	$0.66_{0.06}^{c,A}$	$0.63_{0.05}^{e,A}$	$0.67_{0.04}^{c,A}$	$0.67_{0.04}^{bc}$	$0.67_{0.03}^{de,A}$	$0.69_{0.05}^{b,A}$

*~~entional (C) and genomic (G) scenarios with numbers indicating the number of phenotype records per lactation.~~ The table presents the means and standard deviations (subscript) across 10 replicates for the conventional (C) and genomic (G) scenarios, with numbers indicating the number of phenotype records per lactation, within three relative costs of phenotyping to genotyping ($P:$G)~~across ten replicates~~. Conventional selection implemented two-stage selection for males, hence we present the accuracy of pre-selection of males for progeny testing (S1) and the accuracy of selection of proven sires (S2). Lower-case letters

denote statistically significant differences between scenarios within the same $P:$G and upper-case letters between different $P:$G within the same scenario. Stars denote whether removing an initial training population significantly reduced prediction accuracy for an animal group within the same scenario and $P:$G.

Compared to the conventional scenario, genomic scenarios ~~with equal intermediateinvestment split between intogenotyping and and genotypingphenotyping~~increased ~~selection~~ accuracy for young non-phenotyped male and female candidates, and dams, but decreased accuracy for sires. We show this in Figure 2 ~~and Table S2~~ with the accuracy for male candidates, female candidates, sires, and dams with an initial training population and equal cost of phenotyping and genotyping. ~~–~~In Table S2 we compare the genetic gain at all three relative costs of phenotyping to genotyping. When the cost of phenotyping was equal to the cost of genotyping, the accuracy for young genomically tested male candidates ranged between 0.90 and 0.91 and did not depend on the amount of phenotyping and genotyping. This was 0.53-0.54 higher compared to the first stage of male selection in the conventional scenario, that is selection of young un-phenotyped male candidates for progeny testing (same age point). However, compared to the second stage of male selection in the conventional scenario, that is selection of proven sires for wide-spread use, genomic testing resulted in a 0.03 - 0.04 lower accuracy (same selection point). In contrast, the accuracy for sires decreased with decreasing phenotyping and increasing genotyping. We observed the lowest accuracy for sires, 0.63, when we invested the most into genotyping ~~(G1)~~, and the highest, 0.75, when we invested the most into phenotyping ~~(G10)~~. Compared to the conventional scenario, the genomic testing decreased the accuracy of proven sires between 0.11 and 0.23. The accuracy for female candidates increased with increasing genotyping, despite reduced phenotyping. We observed the highest accuracy for female candidates, between 0.55 and 0.57, when we recorded five, two, or one phenotype record per lactation and invested the rest into genotyping. Compared to the conventional scenario, the genomic scenarios increased the accuracy for female candidates between 0.03 and 0.11. The accuracy for dams followed the same trends, but with higher values. We observed the highest accuracy for dams,

between 0.77 and 0.79, by collecting five, two, or one phenotype record per lactation and investing the rest in genotyping. Compared to the conventional scenario, genomic scenario increased the accuracy for dams between 0.11 and 0.29.

Changing the relative cost of phenotyping to genotyping affected primarily the accuracy for female candidates and dams. Here we observed that in the majority of scenarios the accuracy increased with decreasing the relative cost of genotyping, hence genotyping more animals. We observed the largest difference of 0.06 for female candidates and 0.12 for dams when we changed the relative cost of phenotyping from half to twice the cost of genotyping. Changing the relative costs, however, did not change the trends.

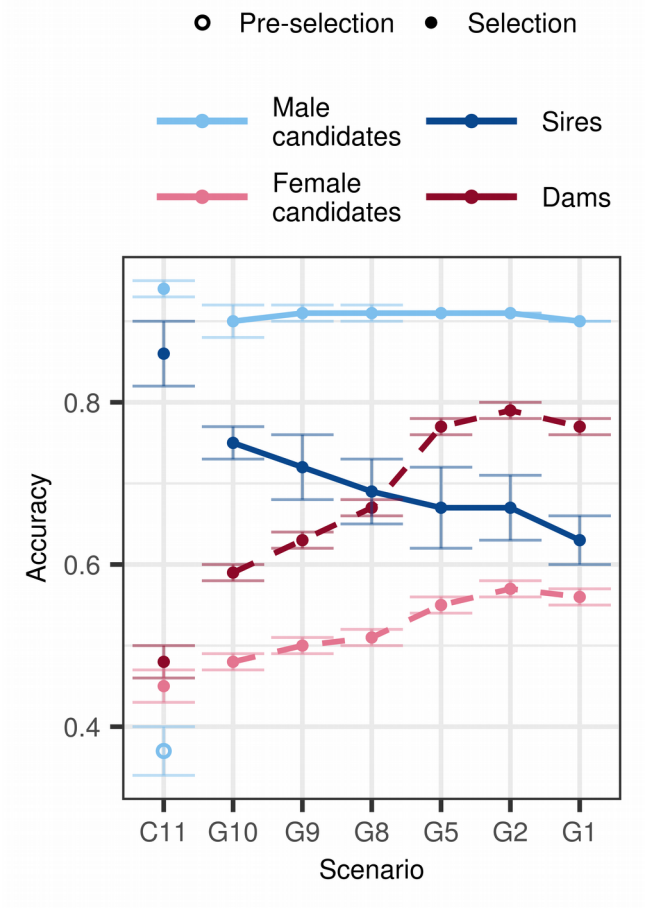

Figure 2 Accuracy by scenario with initial training population and equal cost of phenotyping and genotyping. The figure presents the means (lines) and 95% confidence intervals (errorbars) across 10 replicates for the conventional (C) and genomic (G) scenarios with numbers indicating the

number of phenotype records per lactation. Conventional selection implemented two-stage selection for males, hence we present the accuracy of pre-selection of males for progeny testing (empty point) and the accuracy of selection of proven sires (solid point).

Genetic gain and accuracy without an initial training population

Genetic gain

When an initial training population was not available, we increased the genetic gain of the conventional scenario between 31% and 134% by optimizing investment in phenotyping and genotyping. We show this in Figure 3 with the genetic gain, training population size, and accuracy by scenario without an initial training population and equal cost of phenotyping and genotyping. The observed trends were in line with what we observed with an initial training population, that is, increasing genotyping increased genetic gain despite reduced phenotyping. However, all corresponding scenarios achieved between 2~~.4~~% and 28% smaller genetic gain than when an initial training population was available. We show this in Tables S1 and S2 that compare the genetic gain and accuracies of all scenarios.

When the cost of phenotyping was equal to the cost of genotyping, genomic scenarios increased the genetic gain of the conventional scenario between 51% and 131%. Compared to when we had an initial training population, the corresponding scenarios achieved between 2% and 16% lower genetic gain. We observed the largest difference in the scenario that invested the least into genotyping ~~(G10)~~. In this scenario we ~~waited~~needed six years to build an adequate training population and implement genomic selection, since we only genotyped 355 animals per year. Increasing the investment into genotyping decreased th~~e~~is difference ~~with corresponding scenarios that had an initial training population~~. Scenario with maximum investment into genotyping ~~(G1),~~ implemented genomic selection in the first evaluation year and achieved only 5% smaller genetic gain than when we had an initial training population, which was 229% of the baseline.

Changing the price of genotype did not change the overall trend. When the cost of phenotyping was half the cost of genotyping, the genomic scenarios increased genetic gain of the conventional scenario between 86% and 133%. The corresponding scenarios achieved between 4% and 28% lower genetic gain than when we had an initial training population. When the cost of phenotyping was twice the cost of genotyping, the genomic scenarios increased the genetic gain of the conventional scenario between 31% and 126%. The corresponding scenarios achieved between 3% and 14% lower genetic gain ;than when we had an initial training population.

Accuracy

As when we had an initial training population, genomic scenarios without an initial training population increased the accuracy for non-phenotyped male and female candidates, and dams. We show this in Figure 3 with the accuracy without an initial training population and equal cost of phenotyping and genotyping. In Table S2 we compare the accuracies with and without an initial training population. When the cost of phenotyping was equal to the cost of genotyping, the accuracy for male candidates ranged between 0.84 and 0.91. In contrast to scenarios with initial training population, the accuracy increased with increasing the investment into genotyping and was significantly lower in the scenario that invested the least into genotyping. The accuracy for sires ranged between 0.64 and 0.74. Contrary to when we had an initial training population, we observed no clear trend of either increasing or decreasing accuracy. For female candidates the accuracy ranged between 0.47 and 0.56, and for dams between 0.56 and 0.76. For female candidates and dams the accuracies followed the trends of when we had an initial training population, where increasing genotyping increased the accuracy.

As in the scenarios with an initial training population, changing the relative cost of phenotyping to genotyping affected the accuracy for female candidates and dams, but also male candidates. Here, decreasing the relative cost of genotyping and genomically testing more animals increased the accuracy in the majority of the scenarios, particularly the low-genotyping ones.

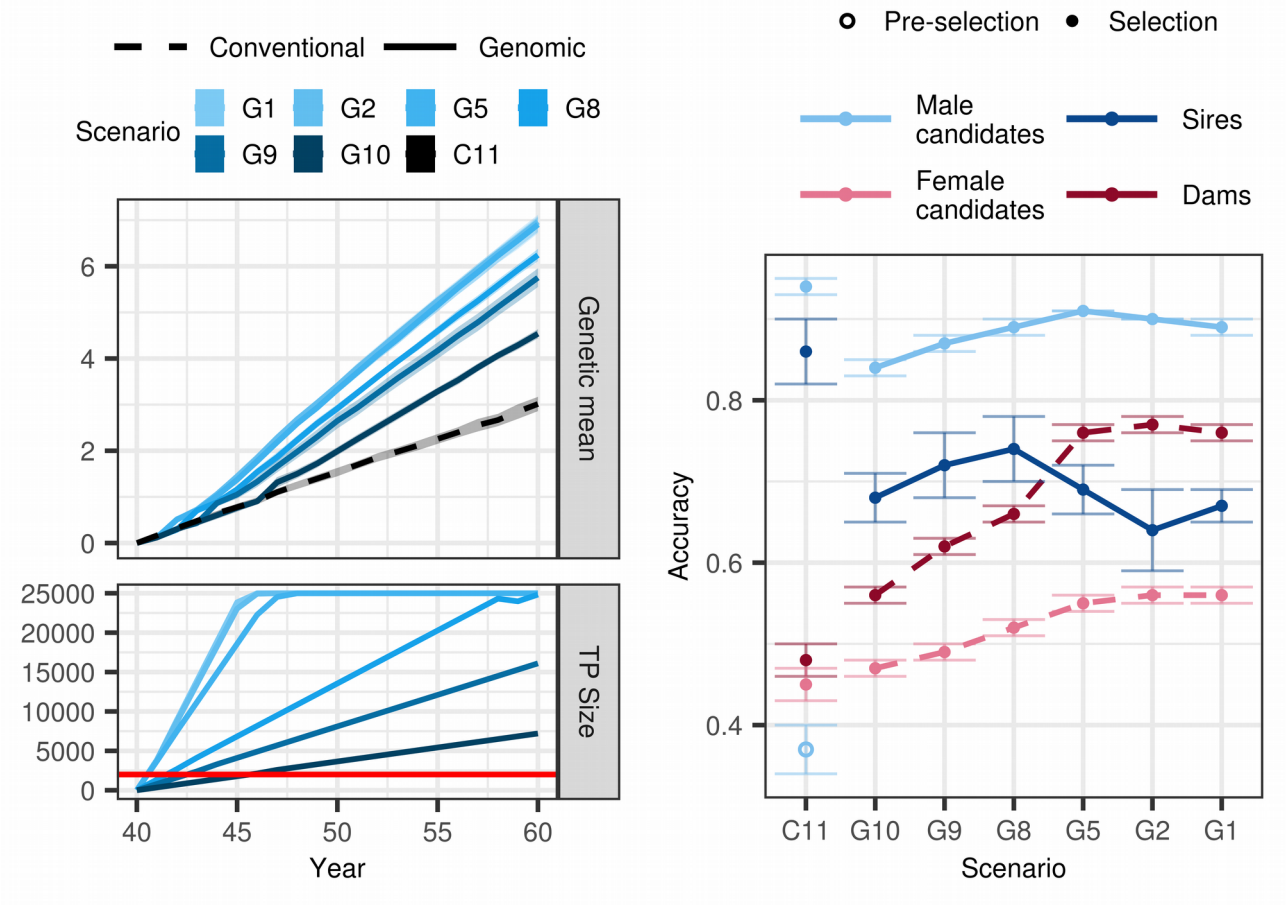

Figure 3 Genetic gain, training population size, and accuracy by scenario without initial training population and equal cost of phenotyping and genotyping. The figure presents the means (lines / points) and 95% confidence intervals (polygons / errorbars) across 10 replicates for the conventional (C) and genomic (G) scenarios with numbers indicating the number of phenotype records per lactation. The red line marks the condition of 2000 animal in the training population (TP) to implement genomic selection. Conventional selection implemented two-stage selection for males, hence we present the accuracy of the pre-selection stage for progeny testing (empty point) and the accuracy of selection for proven sires (solid point).

Discussion

- Since the selection intensity in the dams of dams selection path is very low and the dams of sires are selected after the collection of their own phenotypes, we assumed that the female genotypes are mostly used to update the training population, whereas the male genotypes were used for selection.

1 Genetic gain

- reference yes: this mirrors the existence of international reference populations,
- **genetic gein increases with increased genotyping** (despite reduced phenotyping, regardless genotype price and existence of initial training population) **– why?**
  - compared to the baseline: reduced generation interval, higher accuracy of male candidates, higher intensity
  - among the genomic scenarios: accuracy does not increase with increasing genotyping, hence has to be the increasing intensity of selection
  - reducing phenotyping does not reduce accuracy enough to contradict the benefits
  - no reference: gain shoots up when we start with genomic selection of males
- **genetic gain reaches a plateau** – accuracies are 0.9 for selection candidates (can not improve more), all females are genotyped in the top XX scenarios (no room for improvement), intensity is high
- **same maximum genetic gain achievable for all $G:$P ratios** – largest relative difference between the price ratio in the scenarios that remove only one or two phenotypes

2 Accuracy

- **general**: accuracy does not drop despite reduced phenotyping → because more animals genotyped
- accuracy for male candidates persists high –
  - why is it high regardless the amount of genotyping and price ratio?
- the accuracy for the dams and female candidates:
  - **higher than conventional –** more animals genotyped, higher connectedness
  - **increases with genotyping**. This could be explained with first a growing reference population and secondly, more females genotyped and included in the gEBV prediction, higher connectedness
- WHY IS ACCURACY FOR **FEMALE CANDIDATES THAT MUCH LOWER THAT THE MALE CANDIDATES**? MALE CANDIdaTES are all GENOTYPED, FEMALE NOT
  - when all females (cows) genotyped, the accuracy closer to the one of male candidates (also all genotyped)
- accuracy for sires – inconsistent, slight increase – why?
  - Due to a small number of sires their accuracy varied considerably and the results implied a softer trend of decreasing accuracy with decreased phenotyping. The accuracy for sires decreased with reduced phenotyping, despite increased genotyping. This is a consequence of us trying to rank (distinguish between) sires (animals) in the tail of the distribution, where details matter – and every additional phenotype helps to correctly

differentiate between sires. However, since this is the accuracy after the selection has been made, it is not of great interest for the breeders.

- **Without initial reference** – the accuracy decreases when minimal genotyping for males candidates
  - small reference population + “low” heritability of the phenotype (only 1 recording)
  - once it hits XX, accuracies high → XX animals for update enough to keep the accuracy high
- Compare to theoretical accuracies

3 Recommendations for the Yes/No reference – for breeding organizations

4 Limitations and remarks

- limitations: 25K limit
- genotypes could be used also for parentage verification
- Genomic data also for management – monogenic diseases, caseins, inbreding / mating control
- phenotypes also for management → but it we cut the last one – the cows are already almost through the lactation, keep the recordings in the critical period

- However, repeated records enable the estimation of individual's permanent effect due to non-additive genetic effects or individual specific environmental effects. Repeated records also enable prompt management

- future work: selective phenotyping?

Mention developments in the developing world (Africa) and cite Owen's paper, maybe also Maria's spatial paper and Ante's EAAP abstract.

5 Implications

As already mentioned, the estimation of breeding values requires financial resources for the collection of data. Breeding programs have to assure continuous cash inflow, since the data has to be updated to maintain high accuracy of prediction. While the funding for phenotyping is usually secured in breeding programs, the funding for genotyping is not yet well established to initiate and / or regularly update the training population for genomic prediction. Internal reallocation of resources seems like (the only) viable option. However, breeding programs constitute of many crucial actions, many of them can not be manipulated with or omitted. Since increasing the number of phenotypic records increases the accuracy in a diminishing manner, repeated measurements of the phenotype identifies as a plausible candidate for a reduction and financial reallocation.

Good point! I like the "large initial investment" bit!!! All of this (which porgramme is more expensive) is also rather relative as depends who is paying – make a note about this for a discussion point – some folk might say that this paper is not needed, but it actually is very important for many programmes that have "intricate" funding mechanisms.

All phenotyped animals should be genotyped to increase the value of phenotype investments (a phenotype itself is useful for 1-3 generations with the pedigree model, but many more generations

with the marker model – can we make some simple calculations to show this – based on Daetwyler formulas? Also, can we show the value for a farmer if he is investing in multiple dairy records vs genotype – something that uses h2 and accuracy for selection and e2 for the level of variation that management can address?

Phenotypes are important, but investments should be balanced and most phenotyped animals should be genotyped to make better use of the phenotype investment.

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Conclusions

TODO~~List of abbreviations~~

~~Declarations~~ Acknoweldgement

The authors acknowledge support from the BBSRC to The Roslin Institute (BBS/E/D/30002275) and The University of Edinburgh's Data-Driven Innovation Chancellor's fellowship.~~Ethics approval and consent to participate~~

~~Consent for publication~~

~~Availability of data and materials~~

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