All Cows are Worth to be Genotyped !

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Abstract

In dairy cattle, genomic evaluation based on male reference populations has the same accuracy for males and females and a similar accuracy for all traits. This provides new opportunities to efficiently implement within herd selection. Much more than before, the farmer can customize his breeding goal due to the larger panel of available bulls and the accurate evaluation of females for all traits. The proportion of genotyped females is very sensitive to the evaluation cost. It is anticipated that, in European conditions, this technology can be generalized to a large proportion of the female population if the cost is below 40€. The genetic benefit and the profitability of this practice are highly dependent on the selection intensity which can be applied within herd. With conventional reproduction, most females are needed for replacement and the interest is limited. With sexed semen, a technology expected to strongly develop, the upper half of the herd (based on the breeding objective of the farmer) can be devoted to produce female calves for replacement whereas the remaining part does not contribute to replacement and can be mated for other purposes, especially for crossbreeding. In practice, it is worth to start genotyping at least all young animals during their first year of life, allowing a gradual increase of the proportion of genotyped animals in the herd. In addition to selection, genotyping females provides useful information for matings (today genetic defects, tomorrow optimal matings based on inbreeding minimization, QTL pyramiding, non additive effects…). Finally, it should be emphasized that these females will contribute to the reference population of the future. Therefore, there is a strong general interest to increase the proportion of genotyped cows and to decrease genotyping cost.

Key words: genomic selection; female genotyping; sexed semen

Introduction

Genomic evaluations are available early in life and are as accurate for females as for males and with a similar range of accuracy for all « conventional » traits (*ie* for all traits with recent progeny test evaluations). The panel of young genomically evaluated bulls proposed by breeding companies is much larger (3-4 fold) than that of proven bulls. As a consequence, within herd selection can be strongly enhanced, and possibly oriented to a customized breeding objective. This is true through the choice of males but also by within herd female selection for replacement.

Female genotyping presents two complementary interests, at the farmer and at the population levels. At the population level, genotyped (and phenotyped) females will form the reference population of the future, because the number of progeny-evaluated bulls will decrease. For most traits (excluding those with very low heritability), the information carried by one progeny tested bull is equivalent to that of 3-7 females with phenotype, depending on heritability. Building reference populations of thousands or tens of thousands of cows is realistic. This is also the only possibility for some new traits, whereas only a limited number of bulls can be progeny evaluated bulls.

Female genotyping is a major opportunity for many breeds, when their male reference population is limited to few hundreds. In France, the male reference population is around 2500 in Montbéliarde or Normande breeds, and less than 500 in the other (non Holstein) French breeds.

Another interest at population level is the much broader screening of the population at a reasonable cost: one can easily afford to genotype an "original" animal than before, when this strategy was hampered by the huge cost of progeny testing. Finally, due to the much larger number of genotyped animals, within herd genotyping will decrease the cost of genotyping for everybody, including for the breeding scheme.

Therefore, there is a strong interest to encourage and find the most appropriate conditions for mass female genotyping.

Within herd selection

For the first time, a clear increase of the dam to cow pathway contribution to genetic gain can be envisioned, as well as a real opportunity to customize the genetic trend at farm level, through the choice of bulls, but also through female selection.

Through genomic evaluation, the accuracy of female evaluation is strongly increased. The real issue is to increase selection intensity, limited by low natural prolificacy (~0.4 female calf / cow / year).

Most young females are needed for replacement. Embryo Transfer is expensive and will not generalize in the future. Under the present conditions, the only solution is through the use of sexed semen. One can expect a big increase in the use of this technique in the near future, in parallel to female genotyping. Indeed, replacement can be made from the top 50% of the herd, based on genomic evaluation and on a breeding goal defined by the farmer. Other females can be bred for other purposes (crossbreeding, sales…).

It is often argued that genotyping is not profitable and results are highly variable in the literature (table 1).

Generalized female genotyping without use of sexed semen is likely not profitable (based on genetic gain arguments), unless at a very low price, due to limited selection intensity and therefore poor use of the information.

Sexing alone is profitable, in spite of its high cost and its negative effect on fertility. Its development is presently not limited by a lack of profitability but by technical and social constraints. This aspect will not be developed here.

Table 1. Summary of the gain due to female genotyping in the literature.

Study	Country	Genotyping cost	Compared to selection on pedigree	Replacement rate	Economic value of 1 TMI σ_g	Gain due to female genotyping
Chesnais (2011)	Canada	CAN$47	NO	10 to 40%	CAN$159	CAN$ 70
Pryce & Hayes (2012)	Australia	AU$50	NO	15 to 30 %	AU$80	AU$ 41
Pryce & Hayes (2012)	Australia	AU$50	YES	15 to 30 %	AU$80	Negative
Weigel et al. (2012)	USA	US$40	YES	10 to 90%	US$396	Huge
Pryce (2012)	Ireland	29 €	NO	select top 50%	62 €	46 €
Pryce (2012)	Ireland	29 €	YES	select top 50%	62 €	-31€

A fair estimation of the value of genotyping heifers must not include the value of sexing, which can be used without genotyping. Therefore, we have to compare a situation with both genotyping and use of sexed semen to an alternative situation with use of sexed semen only without genotyping.

Two scenarios can be envisioned and compared with a scenario with sexed semen but without within herd selection. In Scenario 1, all females in the herd are inseminated with sexed semen, all live heifers are genotyped and only those needed for replacement are selection on the breeding objective and kept for production, whereas the other are sold. This scenario maximizes the short term genetic gain but maximizes reproduction and genotyping costs, and also assumes a good market for heifers in excess.

In scenario 2, all reproducing cows and heifers are genotyped but only those needed to produce replacement females are inseminated with sexed semen whereas the other are inseminated with conventional (possibly beef bull) semen. As only the number of heifers requested for replacement is produced, no additional selection nor culling is possible before first calving. This scenario produces lower genetic gain (-0.04 genetic standard deviations (σ_g) per year), but it requires less genotyping costs (only the new heifers kept for replacement), requires less sexed semen, and is less sensitive to market assumptions and.

For both scenarios, the following technical parameters are assumed:
- a 50% selection pressure on heifers (scenario 1) or on dams (scenario 2) to produce replacement heifers;- a reliability of genomic evaluation of R^2=0.65;
- 100% use of artificial insemination;
- a value of 100€ for one genetic standard deviation, expressed each year.

The simple model used includes 6 categories of females (from 0-1 year to 5-6 years) and one category of males. Simple assumptions are made: fixed female replacement rate, age pyramid, generation interval, and age at calving. The overall breeding scheme is not affected by the farm policy, the bulls genetic merit is initially 1.5 σ_g higher than in the herd and increases by 0.4 σ_g per year. Each female is born from an AI sire and a cow from the herd. The genetic gain is expressed each year of presence of the cow in the herd, after first calving.

Table 2 presents the breakeven cost of genotyping according to scenarios and time horizon, assuming a 4% discounting rate. As mentioned before, no income due to sexing is accounted here. As expected, the genetic gain superiority over scenario 0 without selection is twice larger for scenario 1 than for scenario 2 because selection is applied directly to heifers at the onset of their carrier and not on their dams. However, due to the lower number of genotypes, the breakeven price is higher for scenario 2. According to the present price, 6-7 years are needed to make a positive return. On the longer term, the profitability increases regularly over time.

Table 2. Comparison of genetic merit and breakeven genotyping price according to scenarios and time horizon (S1=scenario 1, S2=scenario 2, S0=reference scenario without genotyping).

	Annual gain difference between scenarios (€)		**Breakeven genotyping price (€)**	
Year	S1-S0	S2-S0	S1	S2
2	0	0	0	0
3	26	13	9	10
4	45	22	18	20
5	58	29	25	28
6	70	35	32	35
8	85	42	41	46
10	98	49	48	53
20	122	61	59	66

Some people argue that one should compare genomic selection with pedigree selection. We do not agree with that and consider that it is more appropriate to assume the absence of within herd cow selection in the reference scheme. Indeed, sire selection is already accounted for in the other pathways and must not be double counted and selection potential on the dam's pathway is very limited.

Genotyping Cost

The cost of genotyping already strongly decreased with the use of LD chips, with very limited loss of accuracy due to efficient imputation. It will continue to decrease with lower sampling cost and larger volumes. A good target (already observed in some countries) is 30€, and an upper bound target is 40-45€. When using both genotyping and sexing, accounting only for genotyping cost and additional genetic gain on a steady state scheme, genotyping is profitable at a 5- to 8-year time horizon.

Other benefits from genotyping

Additional genetic gain is only a part of the return expected from female genotyping, and other consequences should be added to the benefit. Some of these consequences are immediate and, for many farmers, they could be of more value than increased but remote future genetic gain.

All benefits from sexed semen were excluded in our estimation. This is a pessimistic point of view as the joint use of genotyping and sexed semen leads to clear synergies. No change in age distribution or replacement rate was assumed, whereas longevity will be increased.

In the very short term, a high accuracy of GEBV for all traits can be of high interest, especially for adapting the individual management (reproduction, calving, feeding…). Much more accurate mating plans can also be proposed, based on GEBV with a reliability R^2 equal to 0.7 for all traits. Information on major genes and genetic abnormalities are readily available and can be used to favor/avoid some mating. Parentage checking (or even assignation) can be obtained at marginal cost.

In the near future, new tools will be available to compute true parentage and inbreeding coefficients, and new generation mating plans will optimize genomic information (eg, for inbreeding minimization, QTL complementa-tion, non additive effects…).

As mentioned in the introduction, the additional selection intensity available within breed can also be used to define a farmer-specific customized breeding objective, eg on milk composition, mastitis resistance, or fertility, allowing a clear differentiation of the herd or a targeted effort to solve a difficulty.

Present strategy in France

An important piece of the strategy is a custom LD chip called EuroG10K with an add-on developed by INRA, Unceia, Labogena, Liège University, VIT, and Aarhus University. This custom chip includes additional markers for general or targeted imputation, 140 published mutations (for research or for release) all in duplicate, and an increasing number of candidate mutations, derived from research projects. These mutations were selected based on results of association studies and sequencing. In practice, this approach is a cheap and efficient way to first validate and then quickly disseminate results for better predictions. Due to a large use of this EuroG10k within the Eurogenomics consortium, we can afford regular updates of the chip. The second release will be available in October 2013.

Table 3 illustrates some results obtained from the first month of use of release 1 of the EuroG10k chip in spring 2013. No homozygous animal was found in 3849 Holstein, 909 Normand and 2931 Montbéliard for candidate mutations of HH1, HH3, HH4, MH2 embryonic lethal haplotypes, providing a good statistical confirmation/«validation» of these causative mutations. This information was obtained at a marginal cost.

Conclusions

Genotyping will generalize in dairy production, in association with sexed semen. This development will generate a strong synergy between within herd selection, within herd management, reference population set-up and replacement. SNP chips will continue to be enriched with causative variants. New tools will develop to make the best use of this information.

In the mid-term, genotyped females will also form a rich resource for research (gene hunting, gene validation, non additive effects, G x E prediction…) and are the source for the future innovations.

References

Chesnais, J. 2011. Utiliser la génomique pour maximiser les profits des éleveurs laitiers. *Proceedings of "symposium sur les bovins laitiers", Drumondville.*

Pryce, J.E. & Hayes, B.J. 2012. A review of how dairy farmers can use and profit from genomic technologies. *Animal Production Science* 52, 180-184.

Pryce, J.E., B.J. Hayes, B.J. & Goddard, M.E. 2012. Genotyping dairy females can improve the reliability of genomic selection for young bulls and heifers and provide farmers with new management tools. *Proceeding ICAR congress, Cork.*

Weigel, K.A., Hoffman, P.C., Herring, W. & Lawlor, T.J. 2012. Potential gains in lifetime net merit from genomic testing of cows, heifers, and calves on commercial dairy farms. *J. Dairy Sci. 95,* 2215-2225.

Table 3. Frequency of heterozygous individuals for 4 embryonic lethal candidate causative mutations, observed during the first month of use of the EuroG10k chip (note that no homozygous was found).

QTL	Gene	Polymorphism	Holstein	Montbéliarde	Normande
HH1	APAF1	p.Q579X	3.5%	0.0%	0.0%
HH3	SMC2	p.F1135S	6.7%	0.0%	0.0%
HH4	GART	p.N290T	8.0%	0.0%	0.0%
MH2	SLC37A2	p.R12X	0.0%	12.1%	0.0%