CREATION OF VALUE FOR THE INDUSTRY FROM THE USE OF GENOMICS IN ANIMAL BREEDING

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SUMMARY

The creation of value for the industry from the use of genomics in animal breeding will increase but large differences between breeding organizations in terms of the use of genomic technology, the overall investment in breeding and in the amount of risk taken, will remain. The value will be driven by increasingly complex breeding goals, opportunities to reduce cost and optimal use of genomic information in the context of a quantitative breeding program.

INTRODUCTION

Genomic projects in animal breeding are the result of ‘push or pull’. In the case of ‘push’, a technology company or research group has technology with perceived value and tries to convince the industry to validate and use that technology. In the case of ‘pull’, the industry has defined its objectives and tries to figure out what the best way is to achieve that objective. The objective of the collaboration between technology provider and the industry is to be able to provide the total package from project design to integration of results in existing programs. Industry will be driven by business success while research organizations are more interested in technical success. The gap between both groups can be enormous. This makes it sometimes difficult to transfer the results from research to the industry and to create real value. Starting point is the definition of what has value for the industry.

RESEARCH GROUPS IN RESEARCH ORGANIZATIONS AND INDUSTRY

Research groups tend to have their own culture in terms of focus and perspective. Some research programs are very narrowly defined with emphasis on genomics and a specific trait while other programs have a broad perspective of genomics in the context of a breeding program and a large number of traits. The evaluation of success can be based on technical or business success.

Industry is in general interested in the animal as a whole and will be driven by business success. Markers with significant effects on traits but with small economic impact have little value and even markers with reasonable economic impact have reduced value if it can not be converted into profit.

Research organizations are more interested in technical success which can be achieved more easily if focus is on a very specific trait or problem. Technical success leads to publications, recognition and future funding. This difference explains why industry sometimes feels that money is being wasted by the research organizations while the research organizations don’t understand why industry is not more interested in their discoveries.

RESEARCH AND PRODUCT DEVELOPMENT ACROSS SPECIES

Differences between industries are large due to the existing industry programs, the amount of money available and the amount of genomics information in the public domain. Still, there are some features that hold true for the animal breeding industry in general.
Traits. Most traits tend to be complex traits where component traits such as ovulation rate, survival, robustness, lean deposition etc. contribute to the trait of interest. Genes tend to impact underlying traits but only the impact on economically relevant traits is of importance.

Breeds. The traits we are interested in are the result of a number of pathways where different genes play a role. Different breeds and lines have different genetic bottlenecks and because of that, different genes and chromosomal regions appear to play a role. On the other hand, a viable hypothesis is that we detect important line/breed differences because we know too little. If we would have a fuller understanding of the pathways and genes involved, we would again see more similarities between breeds/lines. Nevertheless, for each species and breed (line), markers will need to be validated against the primary and correlated traits, before they can be used in a development program.

Money. Breeding companies do not like to spend money on external projects and royalties unless it is obvious that they cannot ignore the opportunity or the threat. Some companies will look more at the opportunities (technology leaders, added value objective) while others are more concerned about threats (followers, low cost strategy).

Genetic margin. The payment for genetic superiority is in general not directly related to the creation of genetic progress and only a small fraction of the value generated ends up in the hands of the breeding company.

The product. We need to understand what has value for the different industries. The first question is whether product development (using the genetic variation within a generation) or genetic improvement (accumulating dG) is the key driver. The next question is how important genetic superiority is relative to other aspects and services that have an impact on the competitive position of the breeding organizations.

Genetic margin opportunity. In general there is a certain genetic margin opportunity that exists in an industry. This genetic margin opportunity is not easy to change but can be redistributed between existing and new players.

Program cost. The cost of programs for a certain species depends on what information is in the public domain and the cost of certain technologies such as sequencing (SNP detection). For information poor species it might be important to wait until more information comes into the public domain and/or costs come down.

RELEVANT PLAYERS
Depending on the structure of the industry we might have 1) breeding organizations that want to sell more germ plasm (animals, semen, embryos) at a higher price, 2) marketing organizations that want to sell validated markers to the industry, 3) genomics service providers that want to do the gene expression work, genotyping, sequencing etc. and 4) research groups that develop new opportunities.

Genomic service providers. The business of providing genomic services will be increasingly competitive with cost coming down. This should be compensated by volume (number and/or scale of projects) as the cost/value ratio will improve. With the cost of genomic services coming down, aspects such as quality, reliability and sharing risk, become more important. It will be increasingly difficult for research groups and even research organizations to justify running their in-house genomic service as it requires specialist companies to use the latest technology and provide the best value for money.
Marketing organizations. The role of marketing organizations will depend on the species. Their general role is to bundle the results from several research programs into one product that can be used by the customer. In species such as pigs and poultry, that role will to a large extent be played by the breeding organizations. Marketing organizations will play a larger role in species were the value of a commercial animal is relatively large (cattle, horses) or where the breeding industry is not very structured (sheep, pets).

Cattle breeding. In cattle breeding we have a confusing situation of who runs a breeding program and who should invest in genomics. We have breeding companies, AI organization, national data collection organizations and herdbooks. Ownership of germ plasm is not well controlled as we deal with global populations. In general, the prime objective of a cattle breeding organization is to exploit the genetic variation within one generation in order to produce superior products (proven bulls) that win the competition. Genetic progress is a by-product of this process as well as an objective as long as it is not in conflict with the first objective. AI organizations tend to play the dominating role in cattle breeding.

The cattle industry runs a sophisticated program of estimation of breeding values based on quantitative genetic technology. The total range of not being interested in genomics to the first use of genomic selection exists. The industry does make money and investment in genomics is a realistic proposition.

Pig breeding. A few companies have played the role of technology leader in the pig breeding industry with a significant genomics program including SNP discovery, in-house genotyping and GE studies. Other companies have followed although the role of genomics in line development varies a lot between companies. Over the last 2 years significant shifts have taken place due to mergers and acquisitions and strategy changes. As service providers offer services below the cost of in-house programs, the best strategy now is to run a good quantitative genetic program that results in predictable genetic improvement and in samples and data for genomics projects. In addition specific projects can be designed to collect samples and data for specific objectives outside the scope of the routine breeding program.

The program of the technology leaders did motivate the competition to get involved in genomics. This was perhaps more based on the threat argument than the perceived value of opportunities. Getting seriously involved in genomics now as compared to 10 years ago might be an example of getting involved at the right time.

The main players in the pig breeding industry run sophisticated programs of estimating breeding values based on quantitative genetic technology. The bulk of the pig breeding industry was until very recently not directly involved in genomics and they were lagging behind the innovative sector of the pig breeding industry. That has changed dramatically in the last year.
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few years. This is a good example of the balance between opportunity and threat. The industry was not convinced about potential value. Nevertheless at some point a main player got involved and that threat resulted in other players jumping in. They tend to build their in-house teams now. The industry does make money and investment in genomics is a realistic proposition.

Aquatic breeding industry. This industry is in general lagging behind the terrestrial breeding industry. The salmon breeding industry is leading the field. SyAqua (Sygen) was leading in the shrimp breeding industry, but this has come to an end with the break-up of SyAqua. The aqua breeding industry in general does not run sophisticated line development programs. The industry does not make much money and investment in genomics is very limited. The term ‘shoe string operation’ often applies.

Comparison of industries. The industries can to a large extent be split into two groups: those where breeding companies own and control the germplasm, the trait data and genomics information (pigs, poultry, aquatic) and those that do not (cattle, sheep, horses). Other aspects to look at are the strength of the quantitative program, the investment in a molecular genetic program, the short versus long term perspective and profitability. Indications of these aspects are given in Table 1.

Table 1. A crude characterization of different breeding industries

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Cattle</th>
<th>Sheep</th>
<th>Horses</th>
<th>Pigs</th>
<th>Poultry</th>
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<tr>
<td>Profitability</td>
<td>Good</td>
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<td>Medium</td>
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DELIVERING VALUE
The value of genomics in animal breeding has been described as being negative (long term) to creating a revolution in animal breeding. It is possible to find examples of both extremes. For a trait such as growth rate in pigs, where the recording takes place before selection, Meuwissen and Goddard (1996) calculated an increase of genetic gain due to MAS of 8% in the first generation, dropping to 2% in the 5th generation and longer term it will become negative. For traits such as milk production and fertility, recorded after selection, the gains were 38% in the first generation, dropping to 16% in the 5th generation. One can argue that selection for certain traits using quantitative genetic technology, does not work and the impact of MAS is infinite. So there is the whole range. There are numerous ways to apply genomics in animal breeding and the choice of approach will determine the impact. The examples at the upper end of the success range are appealing. Why has MAS not revolutionized the breeding programs as yet? A large number of reasons can be listed. A few will be discussed here.

Overall breeding goal. The value of a trait depends on its position in the overall breeding goal. If we take the simple situation where breeding goal traits are not related, the value of a trait in a breeding goal depends on the genetic variance (heritability coefficient) and the relative economic value. If a trait is responsible for 1/5th of the breeding goal variance and the impact of MAS is 38-16% in generations 1 to 5, the impact on overall genetic progress is only 8-3%, in generations 1 to 5. The
conclusion can be drawn that we need to incorporate more QTL and more traits (preferably all) in our MAS programs. Genomic selection would solve that problem as effects of a large number of markers for all traits are used in that approach. Still, if the breeding goal is dominated by the ‘easy’ traits, the value of genomic selection will be limited.

**Realized versus predicted.** Model calculations tend to be based on simple models. When single gene effects are studied in detail, we often find that the biological and genetic realities are more complex than initially assumed. Non additive effects, gene interactions, GxE, genetic background effects, epigenetic effects, correlated effects, changing LD, biased estimates etc. all contribute to the reality. Chamberlain and Goddard (2006) report on the results of an empirical test of the gain in selection in dairy cattle due to MAS. Seven QTL regions were involved explaining 30% of the genetic variance of ASI, an economic index of protein, fat and milk yield. The combined QTL effect was estimated with 65% accuracy. The observed improvement in accuracy, comparing a pedigree EBV with and without the use of markers was 1-2% as compared to the expected improvement of 4%. ‘Realized versus predicted’ will depend on how genomics is being applied in animal breeding and the challenge is to close that gap.

**Alternatives.** The use of genomic technology in animal breeding needs to be evaluated in the context of alternatives that are available or can be developed. In a Nucleus breeding program, we can for instance add genetic marker technology at a certain marginal increase of cost or we can increase the size of the Nucleus population with similar increase of marginal cost. When initial population size is low, it is most likely better to increase population size while at large initial population size is will be better to add genetic marker technology.

If markers only affect some of the breeding goal traits and these affected traits only make up a certain percentage of the breeding goal, if the realized impact is smaller than the predicted impact and if alternative use of funds competes with MAS, why bother at all?

**Reducing cost.** The value of genomics is often expressed as percentage improvement of genetic gain that can be achieved. The value of that for the breeding organization needs to be larger than the cost. It is often difficult to convince non-technical financial managers due to the uncertainty of added value and the lack of confidence in the ability to boost market share and/or genetic margin. Reduction of cost while maintaining the quality and competitiveness of the program is often an easier argument to sell. Genomic selection in dairy cattle, increasing the accuracy of matings to breed sires and exploiting the genetic variation between full sib young bulls, could be such an example. The ultimate target would be to eliminate progeny testing. The irony might be that we need progeny test results to ‘train’ and regularly ‘retrain’ the genomic selection model in order to run a breeding program without progeny testing.

**Adding traits due to MAS.** The use of MAS or genomic selection might make it possible to select for traits that are impossible or very difficult to select for in a traditional quantitative selection program. Selection for reproductive longevity could be such an example. The trait has a low heritability, is sex limited, information is available late in life and the appropriate phenotype information is in general not available due to commercially driven culling decisions and is a such difficult and expensive to collect.

**Underlying biological and indicator traits.** The fact that genes tend to have an impact on pathways that contribute to the relevant trait variation, creates an opportunity for MAS or GMAS. Development of genetic markers for underlying biological traits such as protein deposition rate and for indicator
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traits such as biomarkers in blood or milk, is promising as long as the underlying and indicator traits explain a large enough proportion of the genetic variation of the economic trait.

**Complex breeding goals.** Selection during the last few decades has in general been rather simple. Selection for low back fat in pigs, selection for growth rate in broilers and selection for milk production in dairy are good examples. As pointed out by Coffy *et al.* (2006), the breeding goal becomes more complex due to the interest in product quality, suitability for certain production systems, behaviour and welfare, disease resistance and robustness, longevity and environmental footprint. Each aspect translates in a number of traits. The risk of an expanding breeding goal is that we end up with a situation where the sum of small effects for a large number of traits amounts to zero commercial value. The use of markers will allow us to handle a larger number of traits without falling into that trap. This is visualized in figure 1, although the example is hypothetical and not based on model calculations. At some point, the number of traits to select for is too large and development of sub lines needs to be considered with each of them having a more restricted breeding goal. To prove or to disprove this concept (gut feel) would be a nice topic for a PhD project.

![Figure 1. Relationship between the number of traits in the breeding goal and the commercial value of realized genetic improvement, with and without the use of genetic markers.](image)

**Program optimization.** The bottom line is that each organization will need to optimize the genetic improvement program given the available resources and technology. The role of genomics in animal breeding will change as cost of genomic technology comes down and the power increases. Competitive pressures, profitability of the breeding industry, marketing, the structure of the breeding industry and genetic protection of germ plasm will all have an impact. Large differences between breeding organizations in terms of the use of genomic technology, the overall investment in breeding and taking risk will remain.
CONCLUSIONS
Creation of value for the industry from the use of genomics in animals breeding is possible but the route to success if full of potential pitfalls. Realistic arguments in favour and against the use of genomic technology can be given. Each organization will make decisions in the context of their business strategy and available resources. The ultimate battle might be between MAS based on candidate genes and GMAS based on a large number of anonymous markers. The integration and optimization of both into a selective marker assisted selection program (SMAS) is a challenge that needs to be addressed.

REFERENCES