



REPORT ON INTERBULL TECHNICAL WORKSHOP

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Introduction

The use of genomic information in animal breeding has become a matter of great interest among those working with cattle selection schemes worldwide. Some countries have already incorporated genomic information in their genetic evaluations, and genomic breeding values are already in use for both young sire selection and semen marketing. In order to discuss the implication of genomic information on international genetic evaluations Interbull carried out an international workshop in Uppsala, Sweden, January 27 and 28, 2009. The main objectives of the workshop were to set the scientific framework for the use of genomic data in national and international genetic evaluations and to promote the idea and benefits of international collaboration, under the auspices of Interbull, with regards to genomic evaluation and selection. A total of 101 people from 26 countries participated in the workshop, which was open only to a limited number of representatives from Interbull member countries and Interbull committees.

Besides the workshop, important parallel meetings took place in Uppsala in the same week: in January 26, the Interbeef working group met, the Interbull Centre staff presented technical reports on ongoing projects in an open session and the Interbull Technical Committee had a meeting; during January 28 and 29, a strategic planning session took place and Interbull Steering Committee also had an ordinary meeting on the 29; finally, the ICAR Executive Board met in January 29 and 30.

The present report will discuss the main issues debated and summarize major conclusions both from the workshop and the other Interbull meetings.

Workshop Summary

Task Force Report

Interbull Steering Committee established a Task Force to address the issues involving the role of genomic information on genetic evaluations, and this group has been working since September 2008. One of the tasks was to propose the program for the workshop and to establish the goals to be achieved during the event.

The Task Force organized the program with one initial session for presentations and two subsequent sessions for group work. Presentations were focused on the current status of the use of genomics at national levels, examples of cooperation between countries, developments on outstanding questions and one main presentation about the future role of Interbull considering genomics, which was presented by Mike Goddard.

The convener of the Task Force, Georgios Banos, presented a report stressing major technical issues involving the use of genomics in national and international genetic evaluations (genomic selection bias, validation procedures,

data combination, data independence, weighting factors, reliabilities, de-regression, data accessibility, SNP array consistency) and the benefits of data exchange between countries and companies. This report set the grounds for discussion in the working groups during the workshop.

Group work was divided in two moments. Firstly, groups were asked to address different questions:

- Which validation and bias estimation procedures are needed for national genetic evaluations including genomic information?
- How to estimate direct genomic EBVs (DGV)?
- Which methods can be used to combine conventional EBVs and DGVs and to estimate EDCs and reliabilities?
- Which are the expected benefits, opportunities and difficulties of genomic data exchange?

In the final session, all groups debated the same question:

- How should Interbull services evolve to incorporate genomic information (expectations, opportunities)?

Discussions yielded very interesting group reports that will be summarized below.

During the workshop, Reinhard Reents chaired the first session, João Dürr chaired the discussion period in the second session and Jan Philipsson was the chairperson in the last discussion period.

Use of genomic information at national level

In December 2008, Interbull Centre launched a survey among member countries to assess the current status of the use of genomic information in both genetic evaluations and selection of dairy cattle. Anne Loberg presented the results of the survey at the workshop, which are also summarized in an article of the proceedings. Reports from nine countries complemented the assessment of the situation at the national level during the workshop. They were presented by Mike Goddard (Australia), Flavio Schenkel (Canada/US), Vincent Ducrocq (France), Sander de Roos (Holland), Zengting Liu (Germany), Donagh Berry (Ireland), Bevin Harris (New Zealand), Mogens Lund (Nordic Countries) and Joanna Szyda (Poland).

Genomic information is already applied for selection and genetic evaluations for dairy cattle in more than 10 member countries, and this constitutes one of the major changes in the way genetic improvement programs are organized in many years. As stated by Dr. Jan Philipsson during the workshop, the speed of the changes is what impresses most: “if we had this workshop six months ago, there would be little to report; if we waited another six months from now, the workshop would have been too late!” Interbull is the international forum for genetic evaluation of cattle and the timing of the workshop was most appropriate so that countries which are already using genomics could exchange experiences and countries still planning to start could gather valuable directions and advices on how to proceed.

One of the surprising information revealed is that a lot of cooperation between different countries is already ongoing, in contrast with the previous fear that genomic information would be treated as an industrial secret by most of the countries and companies in the business. Examples of cooperation are: United States and Canada; Denmark, Finland and Sweden; Holland and New Zealand; Ireland and New Zealand; and Austria and Germany. The North-American cooperation model is particularly interesting because the major breeding companies decided to integrate their genomic programs in order to optimize resources and speed up development at AIPL and CDN.

Interesting evidence from the country reports was that significant differences in methodology exist between evaluation centers. These differences are related to the type of data and the method of estimating SNP effects, the weighting factors applied, the inclusion of polygenic effect in the model, the estimation of reliabilities and the blending procedure to produce genomic breeding values (GEBVs). A particular case is France, which adopts a procedure incorporating marker assisted selection (QTL) information on the model to predict SNP effects.

Regarding genotyping procedures, most countries have adopted the Illumina Bovine SNP50 Bead Chip, with the exception of the Netherlands, which has developed a customized CRV Illumina 60K Bead Chip to obtain genotypes from bulls in both the Netherlands and New Zealand. Standardizing the DNA readings is regarded as a key issue for those advocating that countries should exchange genotypes through Interbull, in order to facilitate estimation of prediction equations with data from several countries. Currently both low and high density Bead Chips are being developed for different purposes and means to combine information from different arrays will have to be exploited.

The use of genomic information is changing who are the main players in dairy cattle genetic evaluation. Prior to the “genomics era”, genetic evaluations were typically performed by national evaluation centers with data provided by milk recording agencies and breed associations. Now the breeding companies are more actively involved in the process because they own the genomic data in most countries. This situation will force a new equilibrium in the dairy chain, and there is still discussion if we are moving towards a poultry-like or swine-like integration (genetic information is privately owned) or if we are still going to have animals from several companies being compared by a common and independent genetic evaluation procedure. Country boundaries will probably lose importance as companies tend to simultaneously use data from different countries to produce prediction equations. One concern expressed during the workshop about companies taking more control over the breeding programs is the risk of monopoly.

National evaluation centers were asked about the role of Interbull in this new context. Most countries responded that there is still the need for fair comparisons between countries, that genotype by environment interaction is still a major concern for importing countries, that conventional MACE EBVs have to continue being published since some countries may take a longer time to adopt genomic selection and because they are used as inputs to estimate SNP effects.

View to the future

As the main invited speaker, Mike Goddard shared his views on the future of Interbull in the presence of genomic methodologies. He categorically stated that genomic evaluation will become the new standard for cattle selection because it allows faster genetic gain and breeding values can be predicted for any country regardless where bulls are born. In this context, Goddard sees Interbull as possibly playing important international role as a repository of different types of genomic and phenotypic information and providing GEBVs in different country scales.

Cooperation between countries and data exchange

Paul VanRaden was asked to discuss the theme “benefits from across-country collaboration”, based on the successful experience between Canada and USA. Paul also presented the first developments on Genomic MACE (GMACE) that he and Peter Sullivan are working on. If successfully implemented, this methodology will allow international comparisons between GEBVs in a similar fashion as currently practiced by Interbull with conventional EBVs.

Mike Coffey brought a report from the Clubware group, which is working on cooperative software development for genomic evaluation. The Task Force report also presented reasons for data exchange and finally the topic was exhaustively discussed in two discussion groups.

Major benefits associated with genomic data exchange through Interbull can be summarized as:

- Smaller breeds are expected to benefit more from data exchange to become large enough for reliable genomic selection.
- Genomic data are not the same in different countries; SNP effects differ from country to country and DGV and GEBV must be calculated on different country-scales.
- The EU does not allow importations of semen of dairy bulls if their genetic merit was not evaluated according to methods accepted by an internationally reference body (ICAR/Interbull).
- More data-sharing benefits are expected for traits that are difficult to record.

- Since many animals have progeny in more than one country, exchanging data would avoid that the same individuals are genotyped several times, which means optimizing investments.
- Young bulls can receive a genomic evaluation for several countries as soon as genotypes are sent to Interbull Centre, which may allow different selection decisions in different environments.
- If national and international genetic evaluations are biased due to genomic pre-selection, corrections or more robust models are needed and a minimum knowledge of pre-selection intensity is likely to be required.
- Many alternative methodological approaches have been developed worldwide already, and Interbull is the logical forum for exchange of experience for validation of methods and results, and also for standardization of procedures.
- Assuming that different SNP arrays and DNA screening techniques are likely to become available in the future, an international database of genotypes can be the basis for integrating genomic information of different sources.
- Intensive use of genomic selection carries a danger of decreasing genetic variability within breeds and increasing overall inbreeding. Interbull is the only organization capable of monitoring genetic variability and inbreeding worldwide, given that a database of genotypes is in place.
- As a neutral body, Interbull is prepared to maintain an international database of genotypes with restricted access, assuring confidentiality for all participants.

Discussions in the groups indicated that most breeding companies that currently own the genomic information are not willing to share this information since they perceive it as a competitive advantage which resulted from a significant investment. The most sensitive data are the genotypes of the reference population and the SNP prediction equations. There is a general understanding that exchanging direct genomic values (DGV) and GEBVs would be possible immediately.

It was also pointed out that Interbull should be prepared to provide different services for different countries. Some might be only interested in GMACE results, while other countries may wish to be part of an international genomic database, from which Interbull could estimate SNP effects on different country scales. The overall understanding is that all countries will continue to request conventional MACE estimates from Interbull.

Technical issues

The group that discussed validation and bias estimation procedures stressed the fact that possible methods depend on what type of data is going to be available for national evaluation centers and for Interbull. Validation and bias estimation are key procedures to ensure transparency and harmonization in international genetic evaluations and ultimately fair trade of genetic products.

There is a need for validation of SNP prediction equations and also of genetic trends. Reliabilities also lack a satisfactory estimation procedure (some of the values currently used were considered arbitrary) which should be related to correlation between predictor and daughter deviations.

Clotilde Patry presented a study on bias due to genomic pre-selection, clarifying that it leads to the violation of BLUP basic assumptions. It was proposed that a posteriori selection on real data (if available) may indicate how big the bias is, allowing correction of evaluation results.

The discussion group dedicated to estimation of DGVs proposed the establishment of guidelines for national genomic evaluations which would include desirable features of methods to estimate SNP effects (models, reliabilities), criteria to evaluate genomic data quality and possible response variables (phenotypes) for SNP effects estimation.

Methods to combine EBVs and DGVs and methods to estimate EDCs and reliabilities were themes for one discussion group. The group indicated that the ideal situation is to have one joint evaluation procedure which combines the various information sources, avoids bias due to double counting and produces one figure per animal. Meanwhile,

several countries are using a Selection Index approach to combine conventional EBV's and SNP effects as well as the corresponding reliabilities. EDC values should be part of the data files sent to Interbull, however, the EDC estimation depends on the definition of reliabilities and represent a problem if based on genomic information only.

Role of Interbull

In the last day of the workshop, all working groups debated how Interbull services should evolve to incorporate genomic information. Here is a summary of the groups' conclusions.

It became evident that Interbull must have different answers or services for countries in different stages of genomic technologies adoption. For countries or populations without a genomic information program, Interbull should establish an international genotype database, which could optimize investments in genotyping given that these countries agree to trade genotypic information as a means to increase their reference population and allowing that SNP prediction equations be calculated in several country scales at Interbull Centre. For countries or populations that have their own genomic program in place, Interbull should provide methodologies to convert individual bull DGV or GEBVs into foreign scales, as well as serve as the forum for information exchange on methods between countries.

Interbull has also a role in providing recommendations on implementation of genomic evaluation, on selection bias evaluation, and on validation procedures.

In the short term, many groups indicated that Interbull has to provide some kind of international comparison between genomic evaluated bulls, and the choice seems to be the implementation of GMACE procedures. There was an overall feeling that Interbull needs to start working with genomic data immediately, otherwise there is a risk of breeding companies losing interest in international comparisons.

Concerns with the fact that countries have started publishing official GEBVs for young bulls already while European Union regulations only allow imports of progeny tested bulls were expressed by many participants. The fact that European Commission Decision 2376 (2006) establishes that "the statistical methods applied in genetic evaluation must comply with the principles agreed by competent international bodies (for example, the ICAR)", means that ICAR (Interbull) must declare the equivalence between genomic evaluations and classical methodology (progeny testing) before young bulls with only GEBVs can be imported by European countries. As a matter of great urgency, this theme was discussed later in both Interbull Steering Committee and in the ICAR board.

Conclusions

The main conclusions from the workshop may be summarized as:

- Classical evaluation of EBV is base of SNP effect estimation and GEBV calculation.
- Interbull should continue providing MACE-EBVs that contain no genomic information.
- Investigation and consideration of selection bias (caused by intensively preselected test bulls) in national evaluation systems is needed.
- Good definition of reference population with progeny test is crucial, and size of reference sample is dependent on effective population size.
- Collaboration between countries is highly desirable, especially for small populations that need to improve the size of reference population, but also for large populations to compare animals in different scales.
- Interbull should progressively account for genomic information provided by the member countries by:

- developing and implementing a validation check similar to current validation method 3 both at Interbull Centre and at the national evaluation centers comparing stored genomic evaluations with the first progeny test results for the same bulls,
 - applying conversion equations for young bulls without progeny once validation procedures are in place,
 - developing and implementing GMACE in order to express GEBVs in different country scales, and
 - applying different countries prediction equations for the same genotyped animals (either by being a clearing house for prediction equations or by keeping an international database of genotypes and estimating SNP effects from MACE-EBVs).
- Interbull should provide a variety of different services for different countries, depending on the status of national genomic evaluation programs, the needs and the priorities of each member.

As a general conclusion from the workshop, most participants declared their satisfaction with what was accomplished during the two days of the event. While before the workshop some expressed the fear that international cooperation through Interbull could be at risk with the implementation of genomic evaluations, most manifestations after the meeting pointed towards the opposite direction: Interbull as a facilitator of global breeding programs is more needed than ever!

Interbull Technical Committee Meeting

The main objective of the Interbull Technical Committee (ITC) is to identify and review technical issues that may be essential for providing a high quality service to countries participating in the international genetic evaluations.

The topics discussed in this last meeting were: minimum requirement of daughters or minimum requirement of EDC, use of animal model pedigree (AM-pedigree) in MACE, Mendelian Sampling trend validation (MS-trend), direct maternal vs. maternal grandsire effects for calving traits, multiple trait effective daughter contribution (MT-EDC) and revision of the genetic correlation post-processing procedures.

Research results about the first two topics and about use of multi-trait MACE for female fertility traits were presented during the Interbull Centre Reports session that occurred right before the ITC meeting.

Main recommendations made by the ITC were: the MS-trend validation working group should resume their activities and finalize the outstanding issues as soon as possible to allow implementation of the procedure by member countries; to use as minimum requirement criteria either 'number of daughters' or EDC, but not to change the current required minimum number (either 10 or 50); the AM-pedigree must be updated, and another research run should be carried with updated pedigree and newer data (data from the March test run 2007 has been used); a review on the post-processing procedures as currently done at the Interbull Center should be presented by Hossein Jorjani at the ITC-meeting in Barcelona, in August 2009; Jette Jakobsen shall study the correlations among direct maternal and maternal grandsire breeding values for calving traits and report to the ITC; finally, the new MT-EDC program written by Peter Sullivan is ready for testing and should be tested and approved over the summer. It should further be applied for calving traits for the September 2009 test run by all countries currently participating in the evaluation for calving traits. Implementation is aimed for the routine run in January 2010.

Interbull Strategic Plan

Following decision made in the Niagara Falls meeting, Interbull Steering Committee started the process of strategic planning to prepare for the rapid changes in the breeding industry. Besides the members of the Steering Committee,

Interbull Scientific Advisory Committee and some members of the ICAR Executive board were invited to participate. The strategic planning sessions were conducted by Neil Petreny, president of ICAR.

The key strategic issues identified by the group were: genomic evaluation developments, conventional international genetic evaluation services, business operations, strategic communication and marketing, research-development-services, Interbull role in harmonization-monitoring-quality assurance and Interbeef project. The group managed to propose a vision statement, rank the main success factors, elect priorities for each key issue and finally propose short and long term objectives. The document will be reviewed by the Steering Committee in May 2009 and the strategic plan will be presented and discussed at the business meeting at the 2009 Interbull Meeting, in August.

Steering Committee Meeting

Having the results from both the workshop and the strategic planning session in mind, the Steering Committee had an ordinary meeting in Uppsala under the leadership of its chairman, Reinhard Reents.

Regarding genomic evaluations, major decisions were: Interbull shall take proactive steps to incorporate this new technique in its portfolio; Interbull must not risk its excellent reputation as provider of fair comparisons of genetic evaluations across countries and therefore any recommendation of use of GEBVs or DGVs can only be given after validation test for unbiased predictions and unbiased reliabilities are in place; it is realistic that a good validation procedure can be developed until the August 2009 meeting in Barcelona and can be approved at the Interbull meeting in Barcelona in August 2009; a stepwise implementation can be envisioned, starting with the use of conversion formulas (August 2009), continuing with development and implementation of GMACE (early 2010) and finally applying the importing countries prediction equations on genotypes of traded animals (2010/2011).

Other relevant decisions were:

- Interbull will adopt a new evaluation schedule starting in August 2010, and the official release dates will then be the first Tuesday in April, the second Tuesday in August, and the first Tuesday in December.
- The possibility of having a follow up workshop on genomic evaluations will be discussed in the Barcelona meeting.
- Next Interbull industry meeting will be scheduled for next winter in Europe, and the probable theme will be the implementation of services at Interbull relating to genomic information

ICAR Executive Board

The ICAR Executive board also met in Uppsala and discussed the status of genomic breeding values regarding their acceptance as official genetic evaluations. It confirmed the proposal from the Interbull Steering Committee, that DGV or GEBV can only be accepted as substitutes for progeny based EBVs when a validation procedure of Interbull is in place and the system that estimated DGV or GEBV has passed this test. This is particularly relevant because of the European Commission Decision 427, from June 20th, 2006, which defines that

III Genetic evaluation

'1 Principles... The breeding value of an animal is calculated on the basis of the results of the performance of the individual and/or of its relatives. The statistical methods applied in genetic evaluation must comply with the principles agreed by competent international bodies (for example, the ICAR) and guarantee a genetic evaluation unbiased from the influences of the main environmental factors and data structure. The reliability of the genetic evaluation must be measured as the coefficient of determination in accordance with principles agreed by competent international bodies

(for example, the ICAR). When publishing the evaluation results, the reliability as well as the date of evaluation must be given.”

‘2 (a) ... the minimum reliability of the genetic evaluation of AI bulls of the dairy breeds must be at least 0,5 for the main production traits according to ICAR principles taking into account all information from relatives”

Given that such regulation is currently in place, European countries face restrictions to import genetic material from young bulls with no progeny but with an official genomic evaluation in the country of origin.