

Genomic Developments: Past, Present, Future



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Past

- Very fast evolution of science and its applications
- 2001 : publication of the genomic evaluation by Meuwissen et al, Genetics, 57, 1819

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Prediction of Total Genetic Value Using Genome-Wide Dense Marker Maps

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- No practical consequences until the publication of the bovine genome sequence (2006) and the discovery of many new markers

2007 : Release of the bovine 50k SNP chip [®] by Illumina



FIGURE 1: BOVINESNP50 BEADCHIP



The BovineSNP50 BeadChip features more than 54,000 evenly-spaced SNPs across the entire bovine genome.

Single Nucleotide Polymorphism

Substitution of one DNA basis

1

..GAATCTGCTATACATAATTATATACTAAT**C**GGGTATTGTTCTTAT..

2

..GAATCTGCTATACATAATTATATACTAAT**A**GGGTATTGTTCTTAT..

↑
SNP



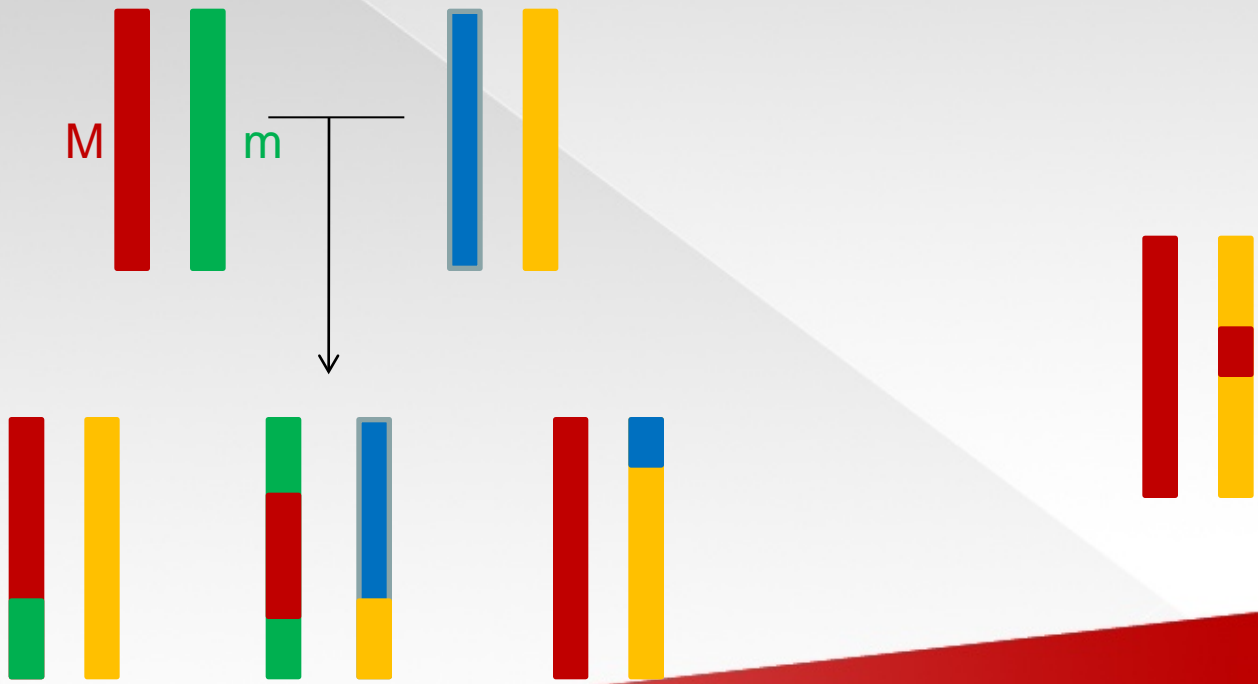
Information provided by markers

Distinguish both chromosomes

Follow transmissions

Measure relationships

Measure inbreeding



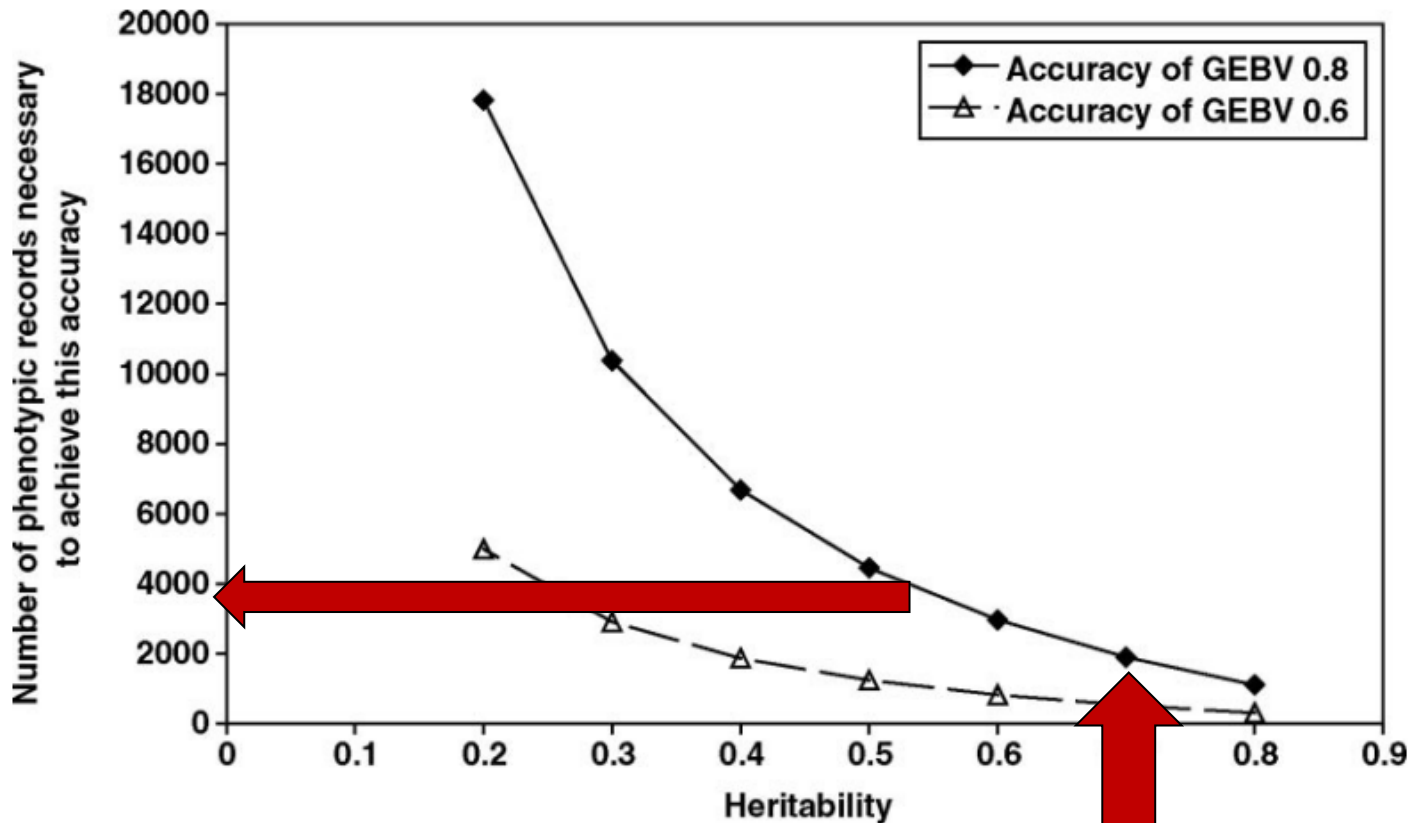
Principle of Genomic Selection (GS)

- Genomic selection = Selection based on breeding values estimated from dense markers covering the whole genome
- **Reference Population :**
 - Population with both genotypes (=SNP information) and phenotypes (=traits measurements)
 - Estimation of marker effects with a statistical procedure
- **Candidates to selection**
 - Genotyped animals
 - From a Population presenting the same associations
 - Prediction of breeding values from estimated marker effects



Reference populations

- Build from several thousands of progeny tested bulls



(Hayes et al, JDS, 2009)



Reference populations

- A strength for the Holstein: thousands of bulls with DNA and accurate phenotypes
- Large consortia: North America, EuroGenomics...
- Accurate GEBV, for all selected traits
- No further need of progeny test, genomically evaluated bulls can be used immediately

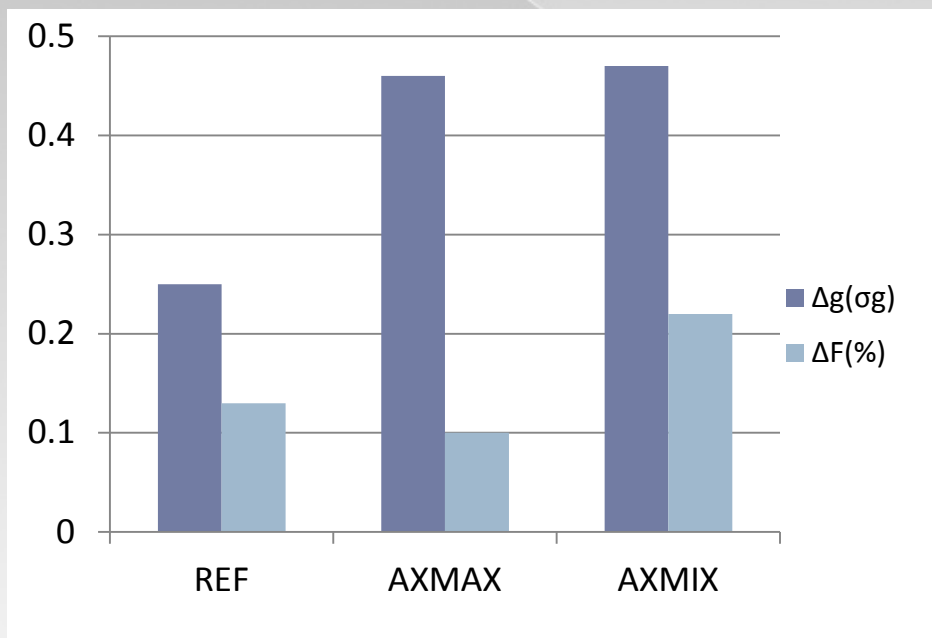


Why GS is so favourable in dairy cattle ?

- 1) Decrease in generation interval
- 2) Good accuracy ($R^2=0.6-0.7$)
- 3) Selection of males and females with similar accuracy
- 4) Cheap genotyping => strong selection intensity
(about 50 genotypes to select one AI bull)
- 5) Good accuracy for **all** traits included in the breeding objective, little dependent on h^2
- 6) Genetic gain is nearly doubled, and more balanced across traits



Expected annual genetic trend and inbreeding



- REF : GS for preselection, and progeny test
- AXMAX : only young bulls, every young bull also bull sire
- AXMIX : 50% AI by young bulls, 50% by older bulls with progeny information

⇒ Stop progeny test

⇒ Don't use bulls when they have progeny information (in competition with their sons and even grandsons...)



Practical implementation: the situation in France

- 1) Results made official for bulls in June 2009
- 2) No new progeny test after 2009
- 3) Change in total merit index,
 - with less emphasis (30-35%) on production (target = to keep the same gain in production)
 - more emphasis on functional traits
 - (in addition to the gain in reliability)
- 4) Use of many young bulls, with limited number of doses and short activity
 - 30% in 2010, 50% in 2011, 70% in 2012
- 5) Use of young bulls as bull's sires



Big changes in the selection practices

- Many bulls on the market, of very high merit
- Strong bulls replacement rate, limited length of career
 - ⇒ individual bulls have less impact and are less popular than before
 - ⇒ Semen availability is limited in time and space
- The end of the « star system »
- Young bull dams are distributed over a much larger number of herds than before
- By the way, pedigree become more complex and their analysis requires computing tools...



Towards a generalization to females

1) Interest for the farmer

- Better choice of replacement heifers
- Maximum interest when a good selection pressure is applied => Maximum gain with sexed semen
- Profitable only if cheap

2) Interest for the population

- Replacement of the reference population
- Selection for new traits

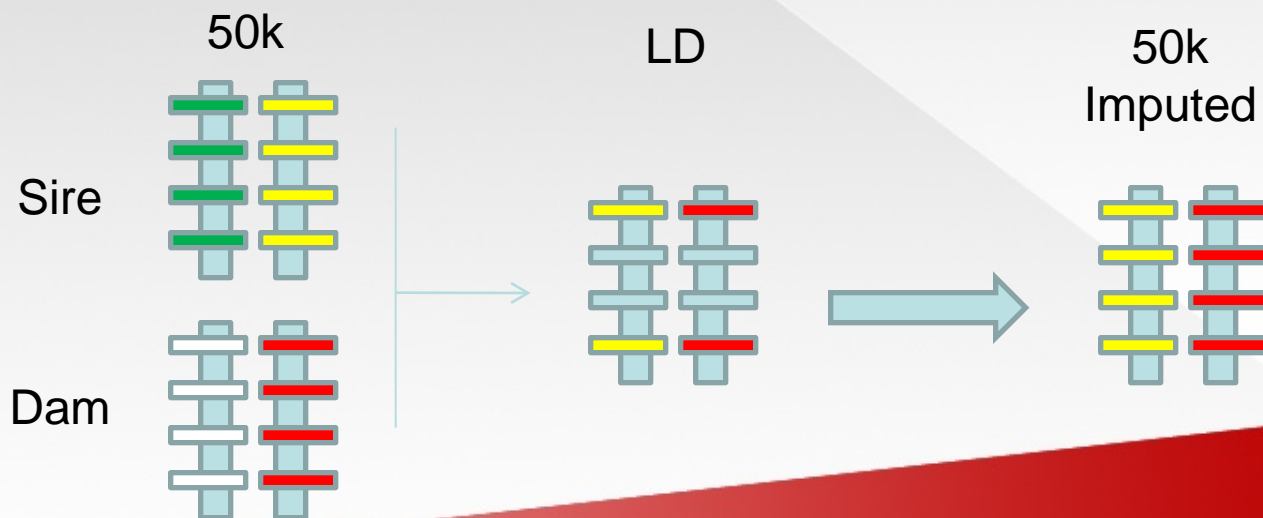
⇒ We have to encourage female genotyping

My guess : in 2 years, 50% of the heifers
genotyped



The Low Density (LD) chip

- 1) Strong need to decrease the cost for a generalized use within herd
- 2) Optimized for efficient imputation to 50k
- 3) Made available by Illumina in fall 2011
- 4) It is important to keep 50k genotypes for marketed bulls, to ensure a highly efficient and sustainable system



And about the future ?

- 1) Generalization of female genotyping
- 2) New traits recorded and selected for
- 3) New relationships between actors
- 4) Reference population sharing
- 5) Across breed evaluation systems
- 6) New tools for population management
- 7) Prediction of G x E interactions



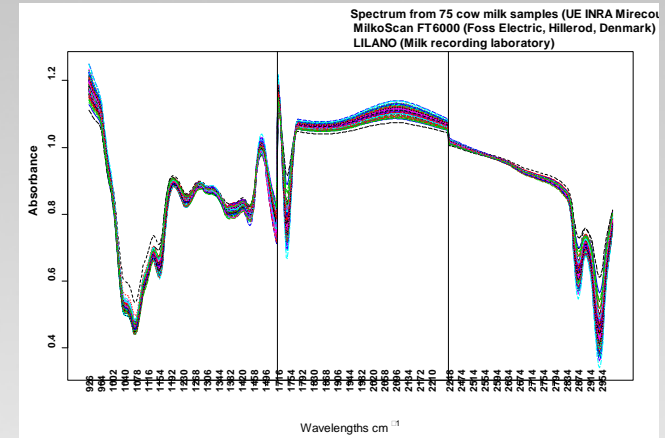
New traits

- 1) Genetic gain is strongly increased => room available in the breeding objective
- 2) Traits are easier to record in reference populations (several thousand animals) than in the whole population
- 3) Selection is less sensitive to heritability: some traits become new targets to selection
- 4) New demands from the market and the society
- 5) New opportunities from precision farming



New traits examples

- 1) Milk composition: fatty acids and protein profile, estimated from Mid Infrared (MIR) spectrometry
- 2) Health related traits:
 - Hoof affection (generated at trimming)
 - Information collected in the sanitary notebook of each herd => All diseases (mastitis, milk fever, ketosis, metritis, etc...)
 - Dedicated designs: Johne's disease...
 - Genetic defects, much easier to detect and eradicate than before, as soon as several cases are observed => dedicated observatories
- 3) Feed efficiency and methane production
Efficiency of the digestive process



New relationships between actors

- 1) Selection will depend on reference populations
- 2) Phenotypes will be the limiting factor
- 3) Investments in phenotyping will benefit to selection
- 4) Several possible economic models
 - Merging / agreement between recording and breeding organizations
 - Increase in size for a better control over the reference population / to decrease the relative cost of the reference population
 - Increased collaborations for the same reasons
 - Incentive / payments for phenotypes
 - Intellectual property attached to reference populations (present situation in France)



Reference population sharing

- 1) The bigger, the better
- 2) Examples of the North American or the EuroGenomics consortia => a way to maximize accuracy while sharing the investments
- 3) A trade-off between an initial advantage (e.g. a new trait, favouring differentiation on the market) and cost sharing
- 4) Sharing is compulsory for traits that are very expensive or difficult to measure, such as methane production
 - 1) Between organizations, between countries
 - 2) Between breeds



Across breed genomic evaluation

- 1) Goal: to use all available information, within and across breeds, to estimate the breeding values within breed
- 2) Interest:
 - 1) to share costs,
 - 2) to maximize accuracy (particularly for difficult traits),
 - 3) to use all the genetic variability (e.g. the effect of a rare variant could be more accurately estimated)
 - 4) It will require more efficient methods, robust to lack of relationships and to generations, and therefore very beneficial within breed
 - 5) It will make genomic selection possible in other breeds, and therefore, contribute to maintain diversity



Across breed genomic evaluation

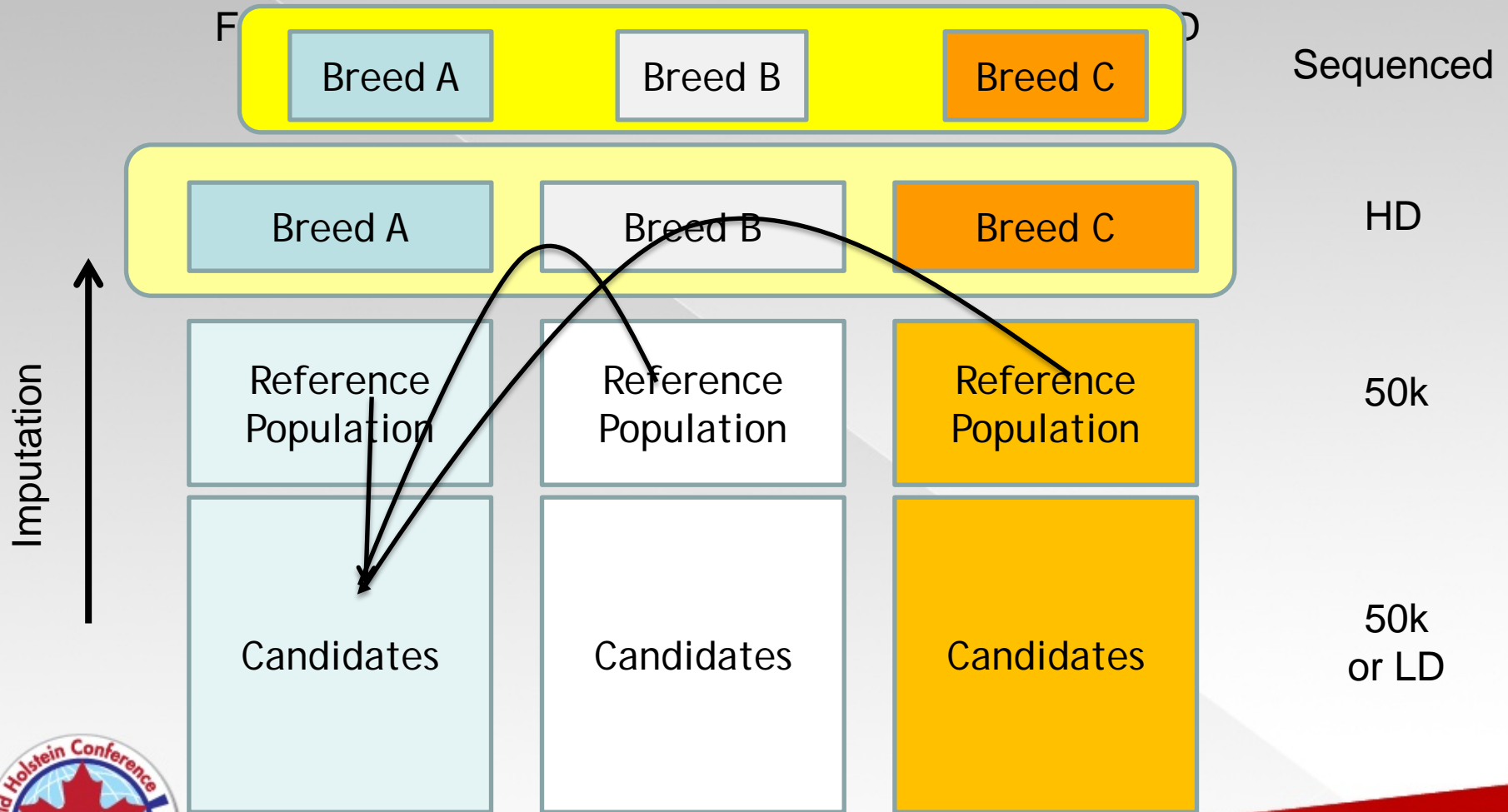
Method:

1. Most current approaches, and especially GBLUP, do not work
2. They are very sensitive to the relationship between the candidates and the reference population
3. Future approaches will rely more on high Linkage Disequilibrium (LD) between causative mutations and their closest markers
4. Two conditions:
 - Increase marker density (HD chip and sequencing) to access shared chromosome segments across breeds (<10 kb)
 - Other statistical methods, still to invent, explicitly accounting for short distance LD, probably more related to present Bayesian methods



Across breed genomic evaluation

« 1,000 bulls genomes » project (B Hayes)



New tools for population management

- Many bulls to use
- Replacement and reproduction policy
- Within herd selection will make it possible to deviate more from the overall objective (large range of bulls, many evaluated traits, selection of cows)
- Females are accurately evaluated, for many traits => many criteria for mating plan
- True relationship known
- True inbreeding known
- Genotype pyramiding, i.e. accumulation of targeted genes over generations



GxE interactions

- **One risk:** a reference population in a specific environment different from the average production environment
- **One opportunity:** many cows genotyped, over a large range of environments => it may become possible to derive prediction equations not only for the average breeding value but also for a component specific of the environment (G x E)



Conclusions

- Genomic has been a revolution in dairy cattle
- Very fast switch from research to practice
- Many changes already observed in selection practices and organizations
- Many changes expected in the future
 - New traits and breeding objectives
 - Management on the farm



Collaborators and sponsors

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CartoFine, AmasGen,
Gembal, CartoSeq projects

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(2) Presently at Illumina

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