

The RUMIGEN logo features the word "RUMIGEN" in a blue, sans-serif font. The letter "I" is replaced by a stylized green and blue DNA double helix structure.The GERONIMO logo consists of the word "GERONIMO" in a blue, sans-serif font. The letter "O" is replaced by a stylized orange and red DNA double helix structure. To the right of the text are two small white icons of a cow and a pig.

GERONIMO and RUMIGEN Joint Final Event

Breeding the Future

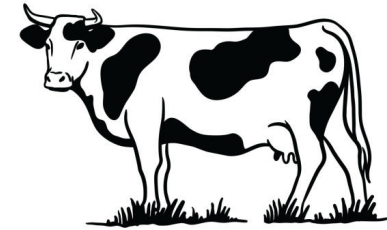
Genomics, Epigenomics & Societal

Acceptability for Sustainability in Livestock

The RUMIGEN EpiChip for prediction of dairy cow performance

M.P. Sanchez, F. Besnard, V. Costes, C. Fouéré, B. Castro Dias Cuyabano, C. Patry, C. Le Danvic, G. Costa-Monteiro-Moreira, A. Asset, A. Raja Ravi Shankar, M. Boussaha, H. Jammes, S. Fritz, H. Kiefer, D. Boichard

The INRAE logo is the word "INRAE" in a bold, teal, sans-serif font.The ELIANCE logo features a stylized lowercase "e" in a red and green circle, with the word "ELIANCE" in a bold, black, sans-serif font below it. Underneath "ELIANCE" is the tagline "Des éleveurs. Une ambition." in a smaller font.The VALOGENE logo consists of a stylized blue and green circle with a white outline, and the word "VALOGENE" in a bold, black, sans-serif font below it.The European Union logo is a blue rectangle with a circle of twelve yellow stars. To its right, the text "Funded by the European Union" is written in a black, sans-serif font.



The DNA methylation BeadChip (**EpiChip**), developed in the H2020 RUMIGEN project



A powerful tool to explore how epigenetic factors influence dairy cow performance

Objectives: assess the contribution of epigenetic biomarkers to phenotypic variation in cows

- 1) % variance explained by methylation
- 2) Impact on the accuracy of predictions in a validation population



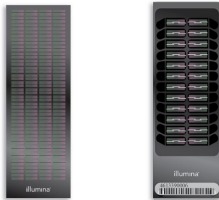


Animals & measurements

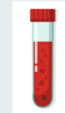
4,943 Holstein cows with EpiChip methylation data

Born between 2013 and 2023 & from 262 French farms

4,484 with
genotypes



Blood methylation
EpiChip



Milk production (n=3,592)



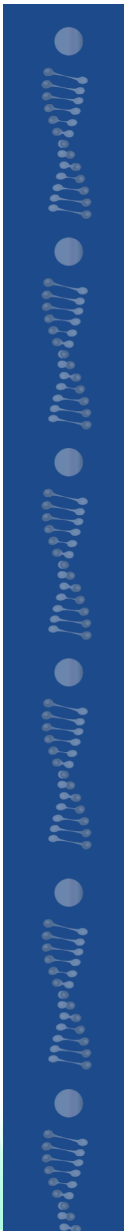
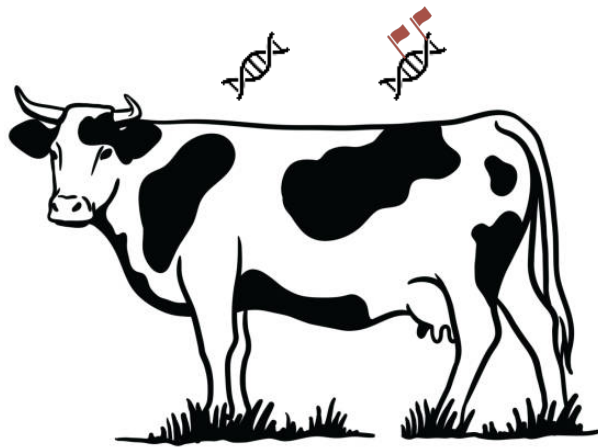
Udder health (n=3,592)



Fertility (n=4,271)

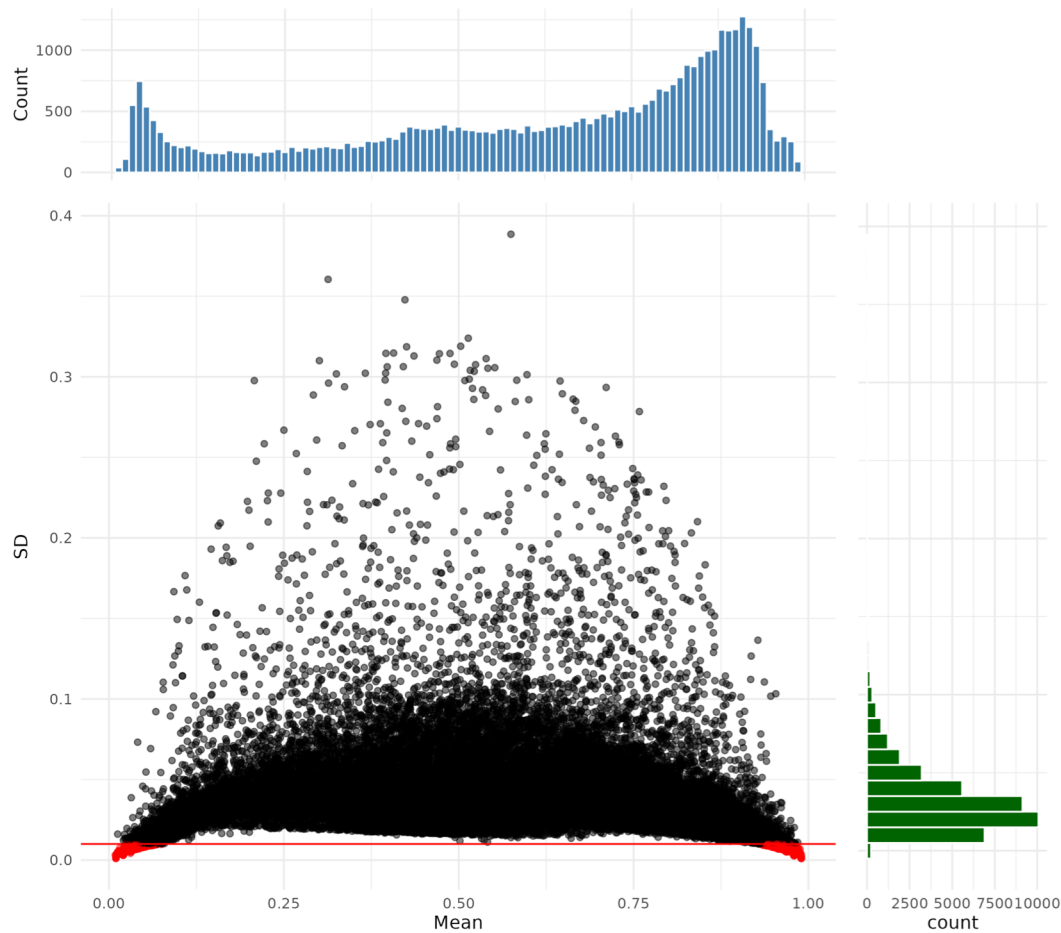


Morphology (n=1,896)



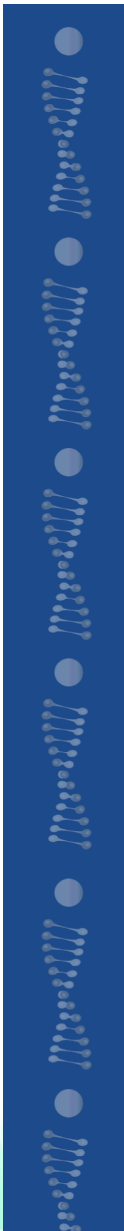


Methylation rates for 44,053 marks



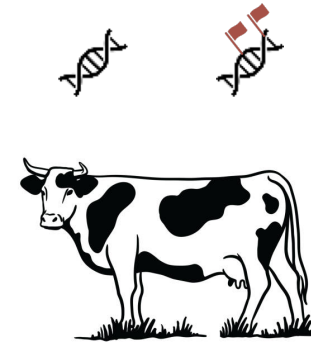
Mean vs SD

≈ 5% of methylation marks showed **little or no variability** between cows





Filtering of data



44,053 marks

4,484 cows

Marks with < 20% missing data

Cows with < 20% missing data

40,933 marks

Marks with SD > 0.01

39,166 marks

4,461 cows

Methylation corrected for leucocyte composition, age of cow, and plate position




Methylation matrix (M)

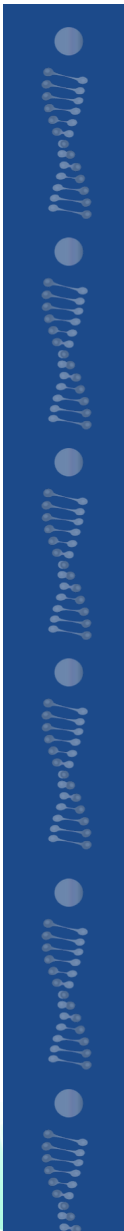
% methylation for mark i and individual j





33 traits analyzed in 1,896 to 4,271 cows

Trait Name	N	Trait Name	N	Trait Name	N
 Milk yield	3,592	Cow non-return rate	4,251	Body condition	1,896
Milk fat yield	3,592	Milking speed	1,896	Dairy form	1,896
Milk protein yield	3,592	Stature	1,896	Body depth	1,896
Milk fat content	3,592	Fore udder attachment	1,896	Locomotion	1,896
Milk protein content	3,592	Udder depth	1,896	Behaviour	1,896
 Somatic cell score	3,587	Front teat distance	1,896	Rear legs rear view	1,896
Heifer conception rate	4,187	Udder balance	1,896	Rear legs side view	1,896
Cow conception rate	4,223	Rear udder height	1,896	Foot angle	1,896
First - last AI interval	4,213	Teat placement	1,896	Rump angle	1,896
AI - calving interval	4,271	Teat length	1,896	Rump width ischiums	1,896
 Heifer non-return rate	4,164	Udder cleft	1,896	Chest width	1,896



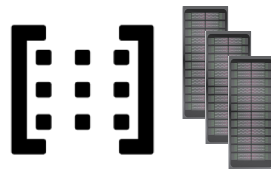


Similarity matrices

Relationship matrices



Methylation
similarity matrix



50k genotypes
similarity matrix



33 adjusted phenotypes (YD)



Bayesian generalized regression (BGLR
R package)

1. Quantify % variance explained by genotypes and methylation
2. Quantify gain in prediction accuracy





2 Models

Genetics (1) vs Genetics + Epigenetics (2)

Model		h^2 % variance explained by genetics	me^2 % variance explained by methylation
(2)	$y = X\beta + Zg + e$	$\frac{\sigma_g^2}{\sigma_g^2 + \sigma_e^2}$	-
(1)	$y = X\beta + Zg + Wm + e$	$\frac{\sigma_g^2}{\sigma_g^2 + \sigma_{me}^2 + \sigma_e^2}$	$\frac{\sigma_{me}^2}{\sigma_g^2 + \sigma_{me}^2 + \sigma_e^2}$

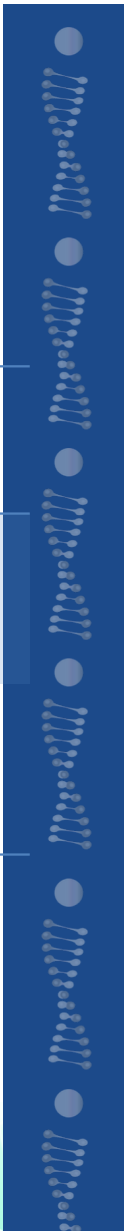
Adjusted phenotypes (YD = Yield deviations)

Fixed effect of birth year

Random genetic effects (genotypes) $N(\mathbf{0}, \mathbf{G}\sigma_g^2)$

Random methylation effects $N(\mathbf{0}, \mathbf{S}\sigma_{me}^2)$

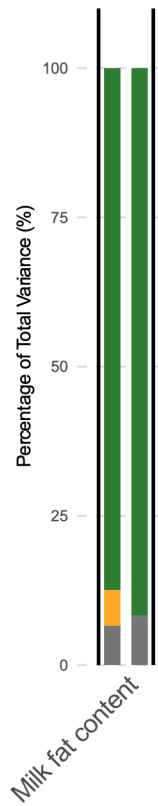
Random residual effects $N(\mathbf{0}, \mathbf{I}\sigma_e^2)$





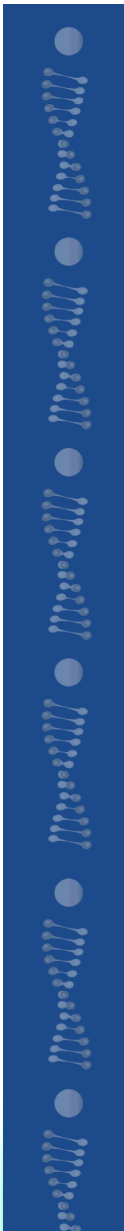
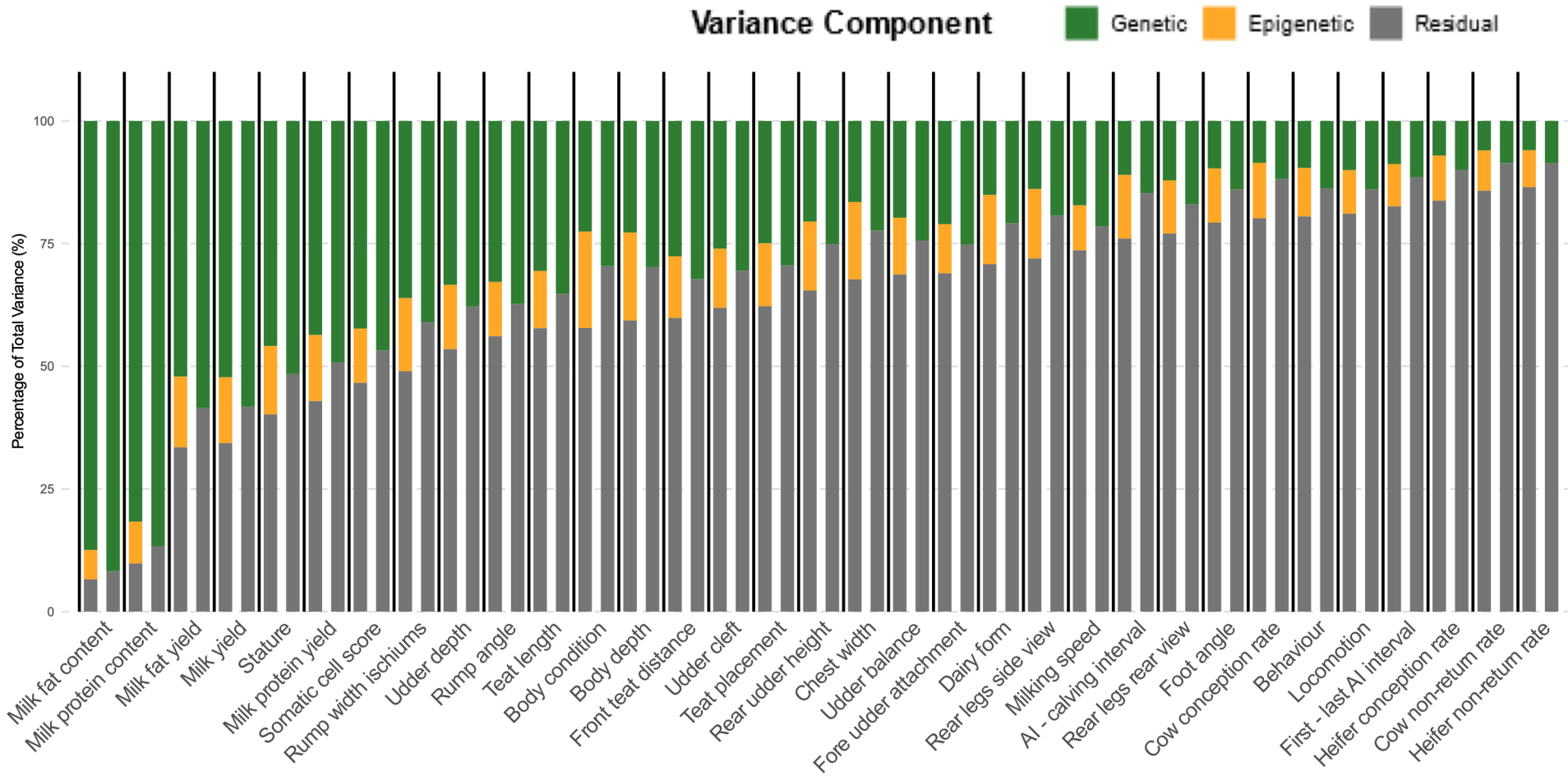
Results: % variance explained

Variance Component Genetic Epigenetic Residual





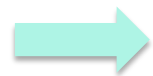
Results: % variance explained





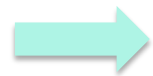
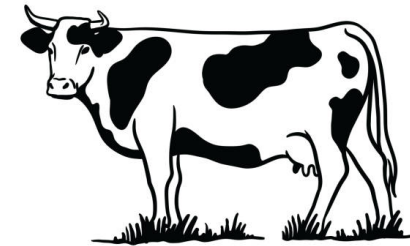
Results: % variance explained

Phenotypes = YD



Model with only genetics:

$$8.6\% < h^2 < 91.7\%$$



Model with both genetics and epigenetics:

$$6.0\% < h^2 < 87.4\%$$

$$6.0\% < me^2 < 19.6\%$$

$$10\% < h^2 + me^2 < 94\%$$



For all traits, more variance is explained by combining genetics and epigenetics

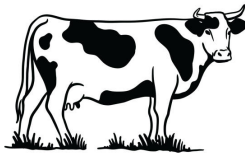




Prediction accuracy

70 sires had daughters in **TRAINING & VALID**

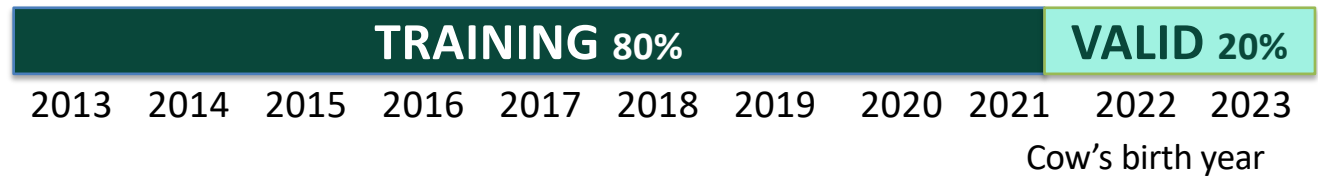
Ex. Milk production



305 sires
3,150 cows

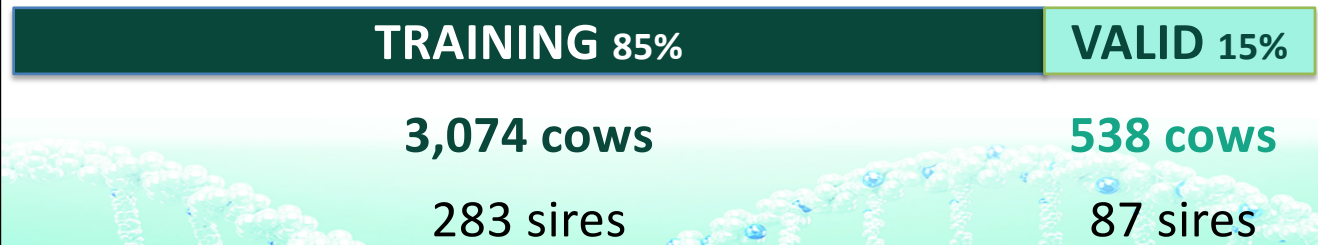


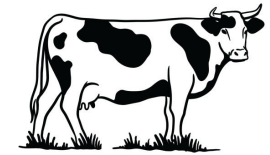
145 sires
788 cows



Separate sire families in **TRAINING & VALID**

	TRAINING	VALID
Milk production	3074	538
Udder health	3070	539
Fertility	3572	662
Morphology	1592	304



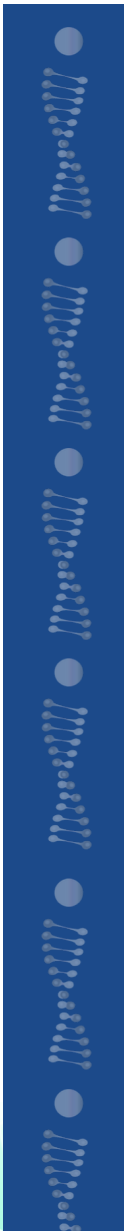
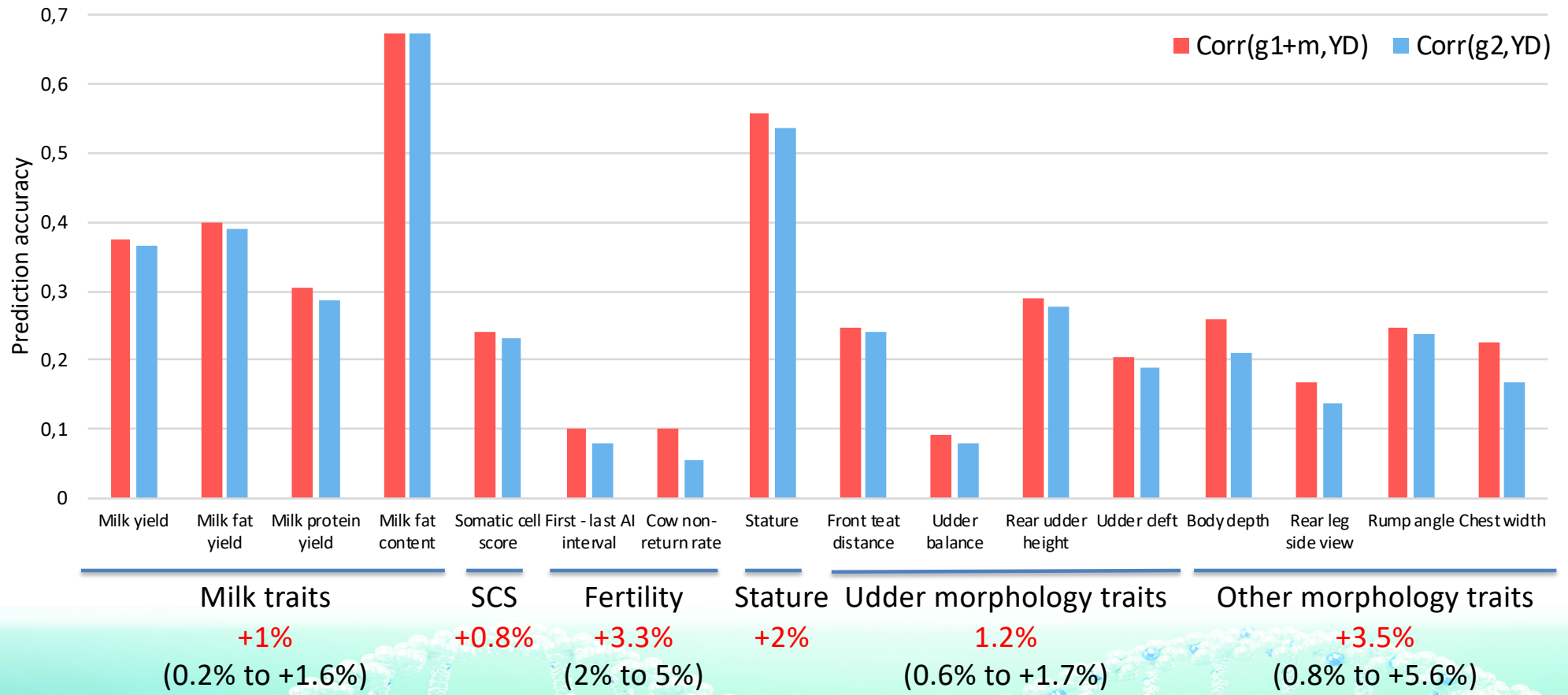


Results: accuracy of predictions

Gain in accuracy for 16 traits: +0.2% to +5.6%

Model (1) $y = X\beta + Zg_1 + Wm + e$

Model (2) $y = X\beta + Zg_2 + e$





Conclusion

Thanks to RUMIGEN, EpiChip usable to large scale

Adding methylation data in prediction models:

- improves the total % of variance explained for all the 33 traits

- improves the accuracy of predictions for 16 traits

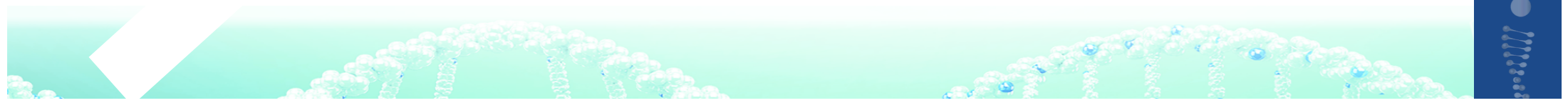
Not all questions were addressed in RUMIGEN:

- Which stage of measurement / tissue are the best for predictions ?

- From EpiChip data: imputation of methylation for missing marks ?

...

Some of them will be addressed in ongoing projects (e.g., ADAAPT)



Rumigen

GERONMO

GERONIMO and RUMIGEN Joint Final Event

Breeding the Future

*Genomics, Epigenomics & Societal
Acceptability for Sustainability in Livestock*

THANK YOU

