GEroNIMO and RUMIGEN Joint Final Event

Breeding the Future

Genomics, Epigenomics & Societal Acceptability for Sustainability in Livestock

The sperm epigenome: role in male fertility, transmission, and impact on offspring phenotype

Hélène Kiefer

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Presented on behalf of collaborators (alphabetical order): F. Ali, C. Archilla, A. Asset, F. Besnard, D. Boichard, A. Bonnet, M. Boussaha, A. Chaulot-Talmon, G. Costa Monteiro Moreira, V. Costes, M-C. Deloche, O. Dubois, V. Duranthon, C. Fouéré, S. Fritz, C. Hozé, F. Jaffrezic, H. Jammes, S. Jean-René, H. Kiefer, Y. Klein, L. Laffont, C. Le Danvic, D. Makowski, A. Raja-Ravi-Shankar, M.-P. Sanchez, E. Sellem, V. Sorin

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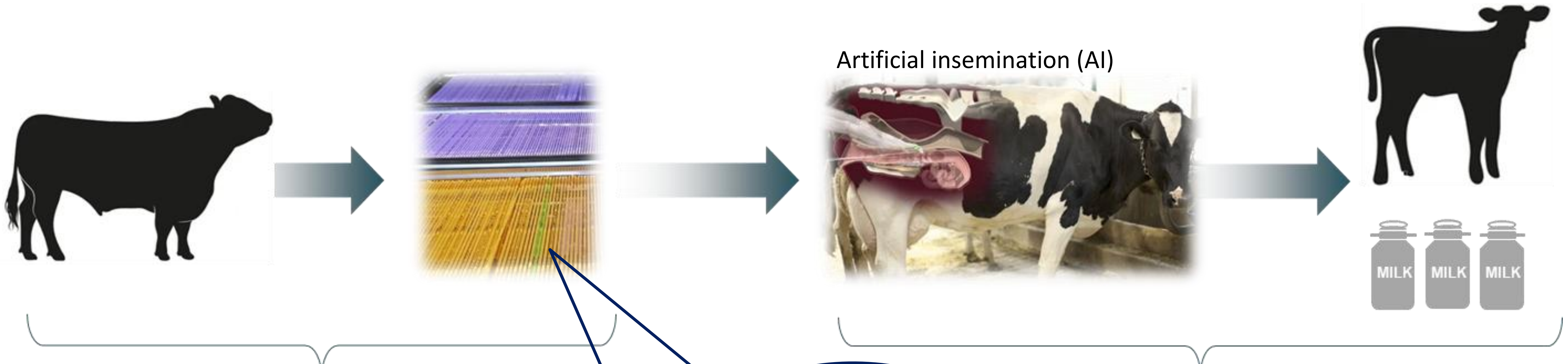
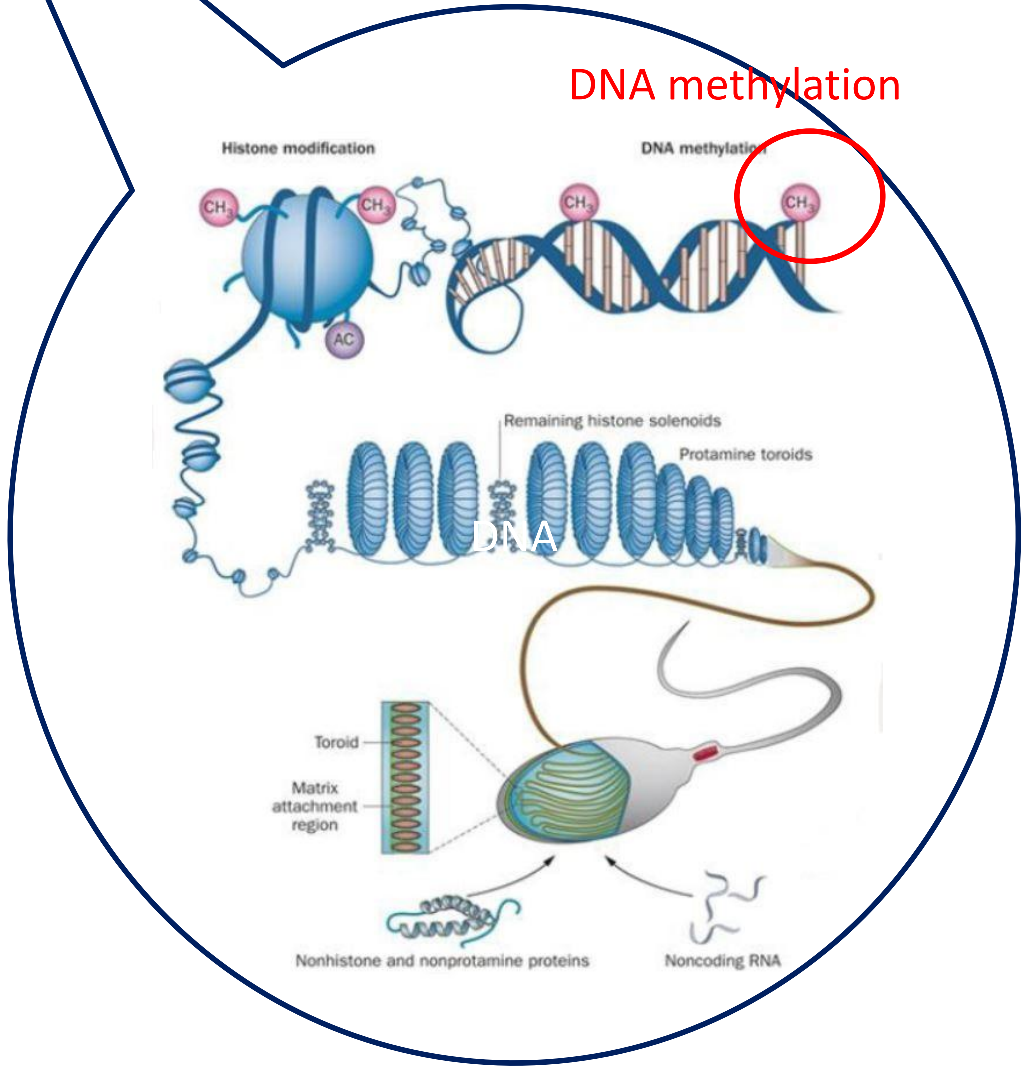
Why does bull sperm epigenome matters?



Breeding company

Farm



Bull semen is an important product for AI industry and farmers

- AI allows the dissemination of high genetic merit sires to many herds
- Reproductive success is crucial for the sustainability of the sector

…But the bull sperm epigenome is overlooked

- Essential for the compaction of the paternal genome
- Essential for male fertility and embryonic development
- Important for the phenotype of offspring

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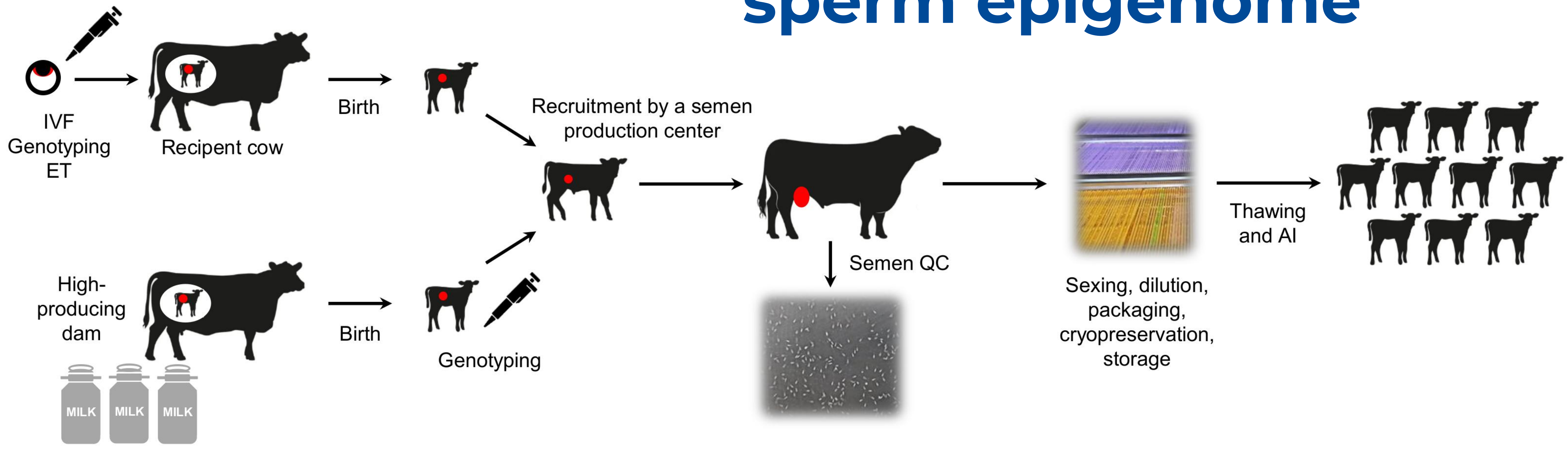
Schagdarsurengin *et al.*, 2012; Carrell, 2012; Champroux *et al.*, 2018

Many steps in a bull's life can modify the sperm epigenome



Impact of embryo biotechnologies

Impact of the maternal metabolism

Impact of environment and nutrition during growth of the male calf

Impact of early semen collection

Impact of semen processing treatments

Widespread diffusion of semen

● Male germ cells

Kiefer et al., 2021

- Impact on bull fertility?
- Transmission to the embryo?
- Impact on offspring phenotype?

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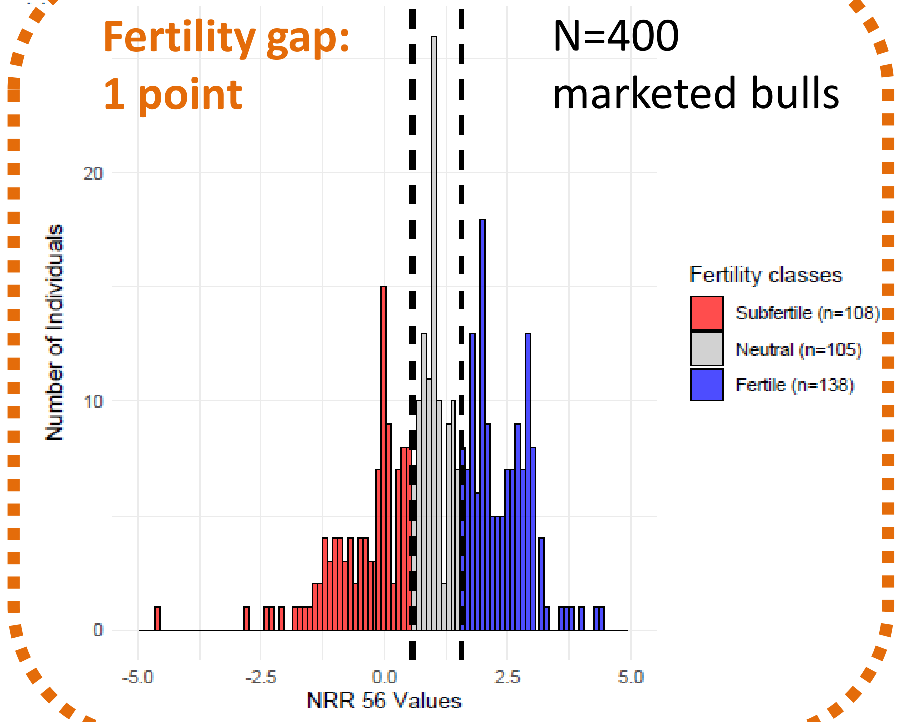
Bull fertility prediction using sperm DNA methylation

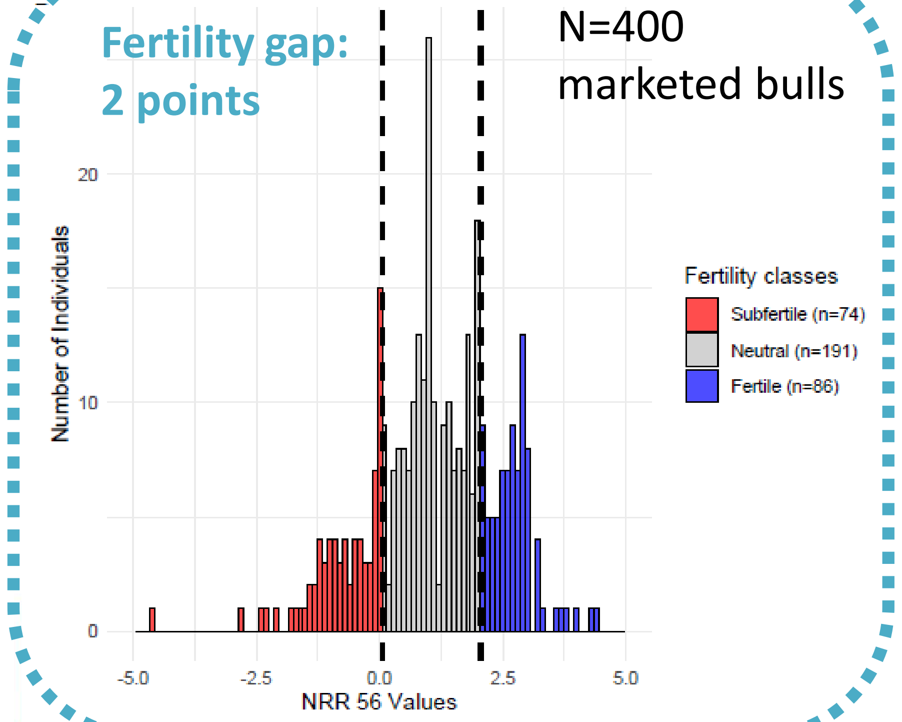
Fertility gap: 1 point

N=400 marketed bulls



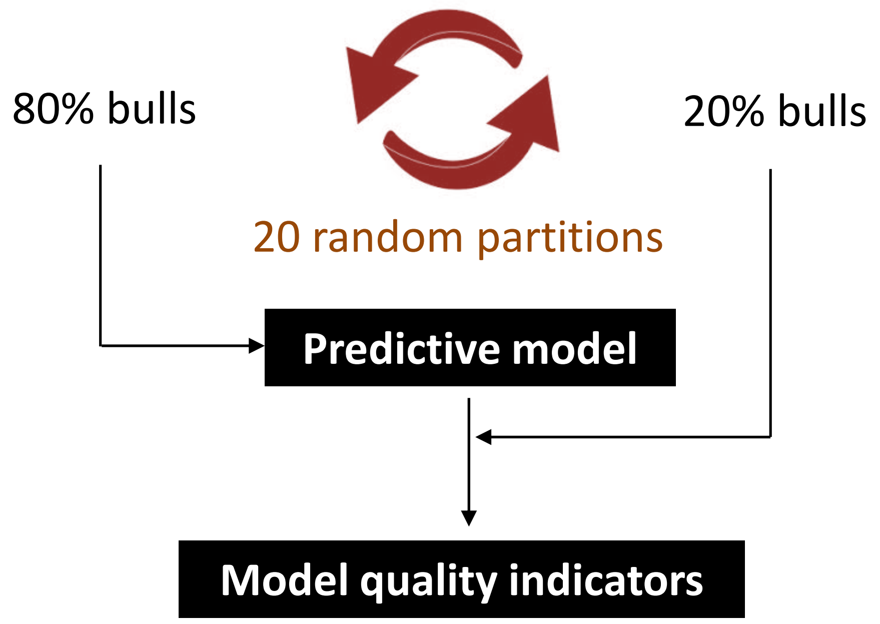
Fertility gap: 2 points

N=400 marketed bulls



Q: is it possible to predict if a bull is subfertile or fertile based on sperm DNA methylation?

Machine learning approach



80% bulls

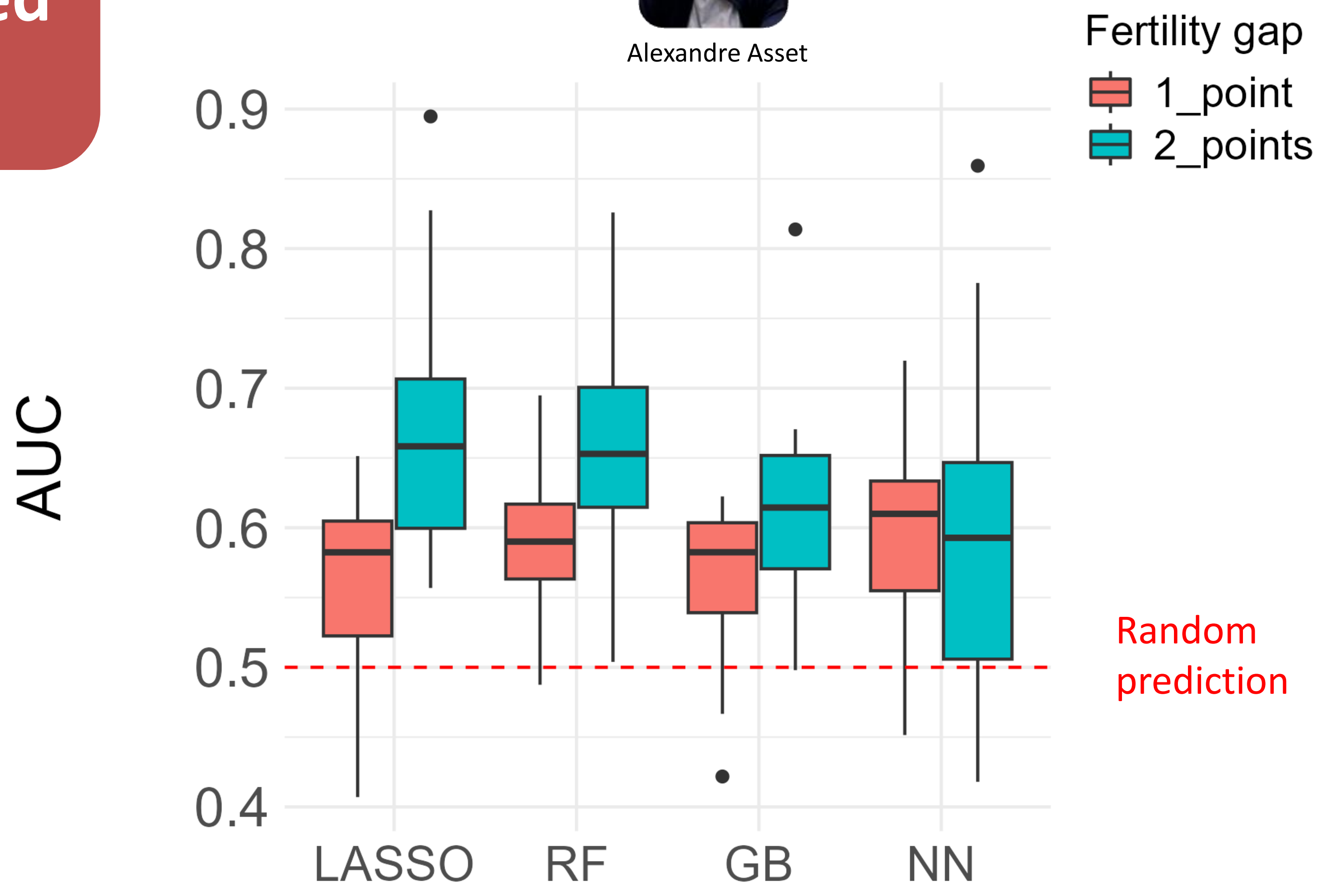
20% bulls

20 random partitions

Predictive model

Model quality indicators

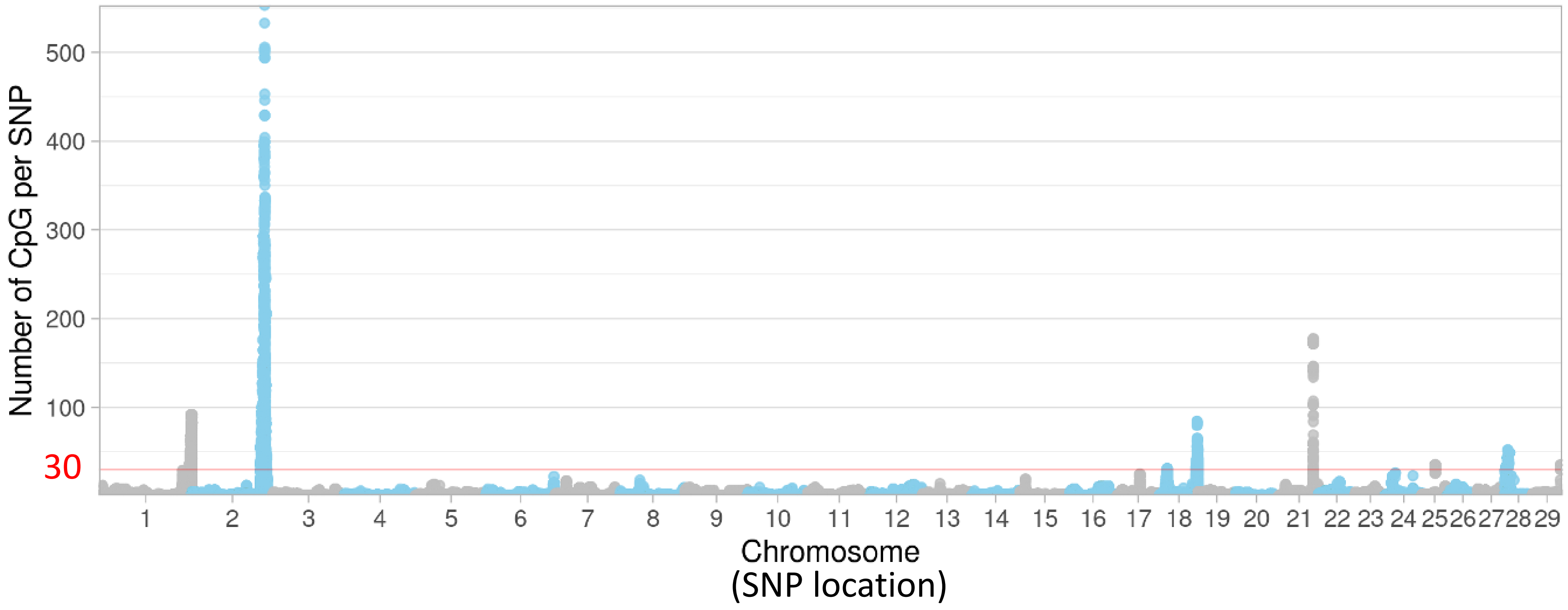
Alexandre Asset



A. Asset, V. Costes, A. Raja-Ravi-Shankar, C. Le Danvic, F. Jaffrezic, H. Kiefer, D. Makowski

Bull sperm DNA methylation is under partial genetic control

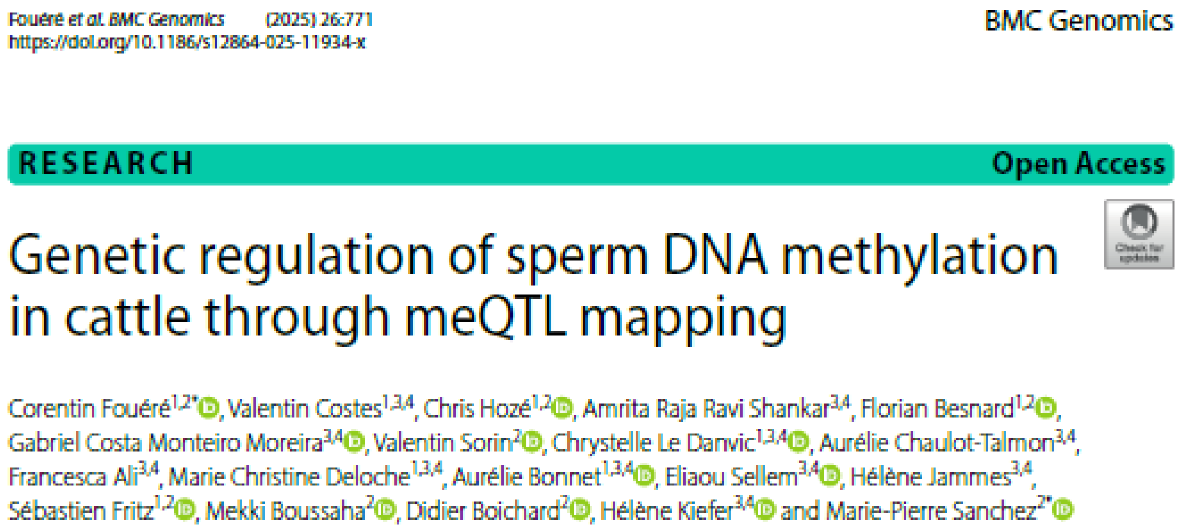
Trans- methylation QTL hotspots



Q: genetic architecture of sperm DNA methylation in cattle?

- Sperm DNA methylation is partly heritable (mean h^2=0.26)
- Cis- and trans- methylation QTLs could be identified
- Trans- methylation QTLs hostspots overlap with genes involved in epigenetic regulation

Corentin Fouéré



Fouéré *et al. BMC Genomics* (2025) 26:771
https://doi.org/10.1186/s12864-025-11934-x

BMC Genomics

RESEARCH **Open Access**

Genetic regulation of sperm DNA methylation in cattle through meQTL mapping

Corentin Fouéré[1,2*], Valentin Costes[1,3,4], Chris Hozé[1,2], Amrita Raja Ravi Shankar[3,4], Florian Besnard[1,2], Gabriel Costa Monteiro Moreira[3,4], Valentin Sorin[2], Chrystelle Le Danvic[1,3,4], Aurélie Chaulot-Talmon[3,4], Francesca Ali[3,4], Marie Christine Deloche[1,3,4], Aurélie Bonnet[1,3,4], Eliaou Sellem[3,4], Hélène Jammes[3,4], Sébastien Fritz[1,2], Mekki Boussaha[2], Didier Boichard[2], Hélène Kiefer[3,4] and Marie-Pierre Sanchez[2*]

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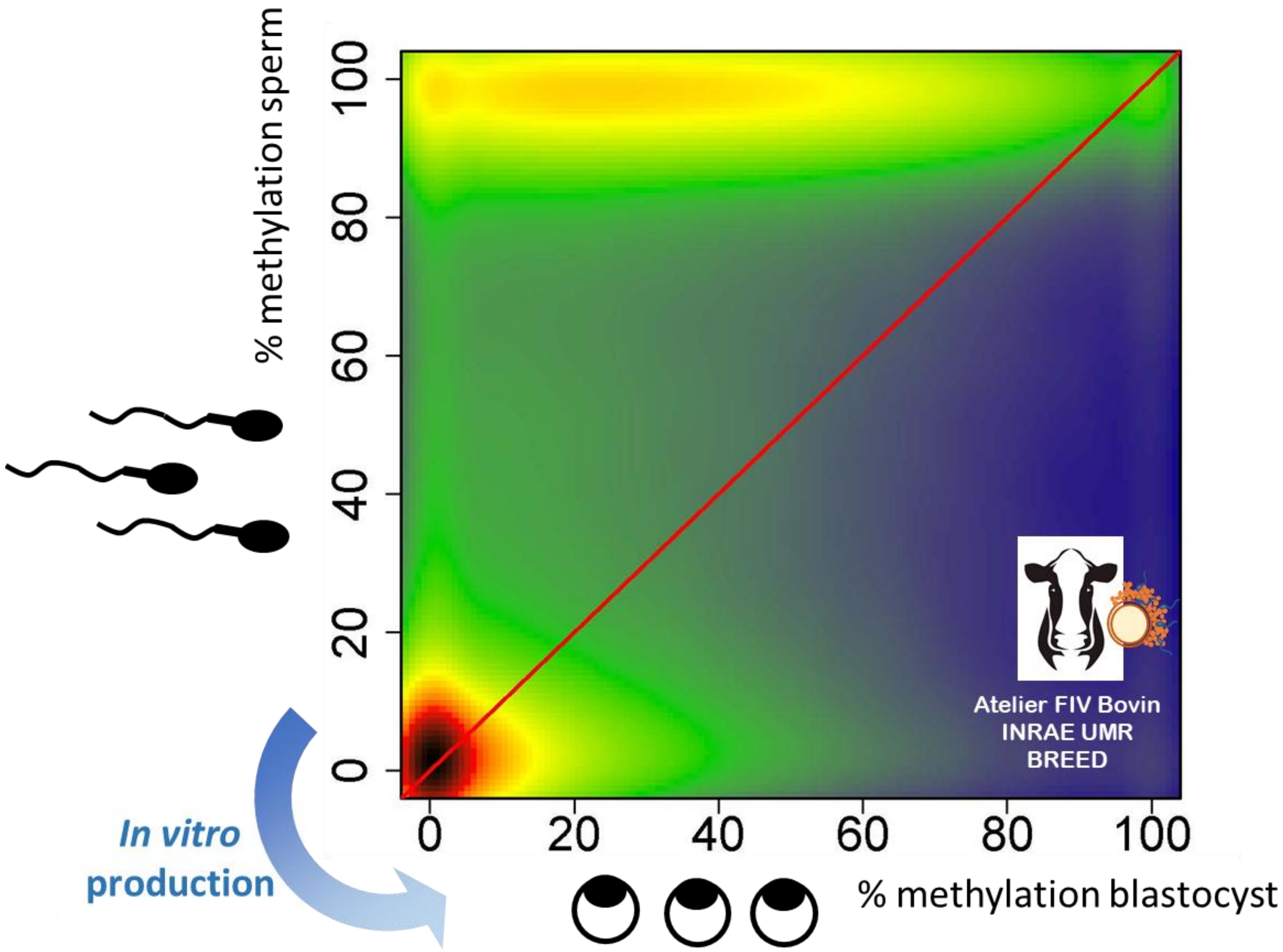
Transmission of bull sperm DNA methylation to the embryo

- Most paternal DNA methylation is erased after fertilization
- DNA methylation reaches a minimum at the blastocyste stage (100 cells)
- Then, specific DNA methylation patterns are acquired during cell differentiation



- **Are methylation changes in sperm transmitted to the embryo?**
- **Are these transmitted features under genetic control?**

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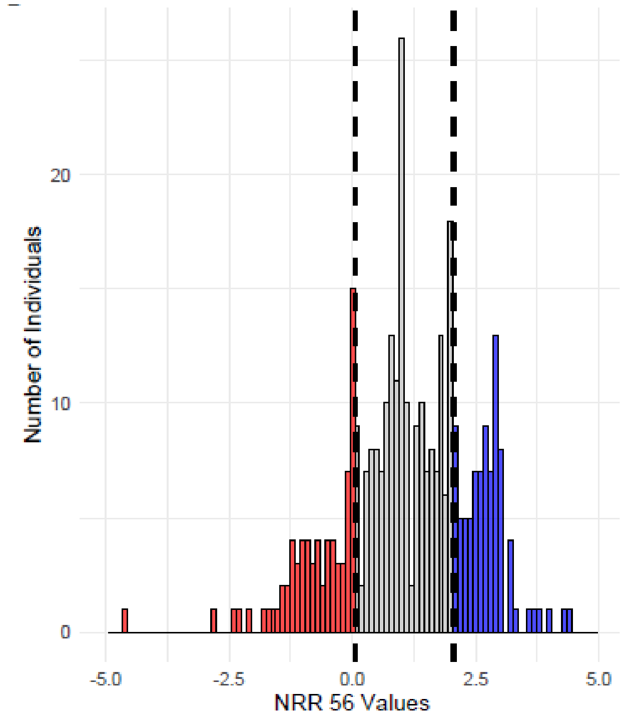
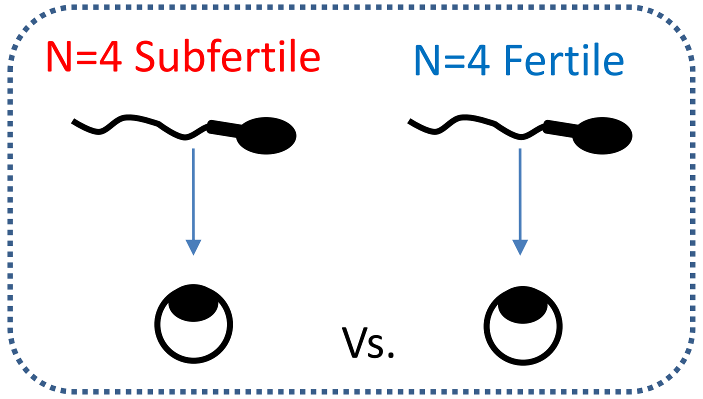
Transmission of sperm DNA methylation patterns to the embryo

A. Raja-Ravi-Shankar



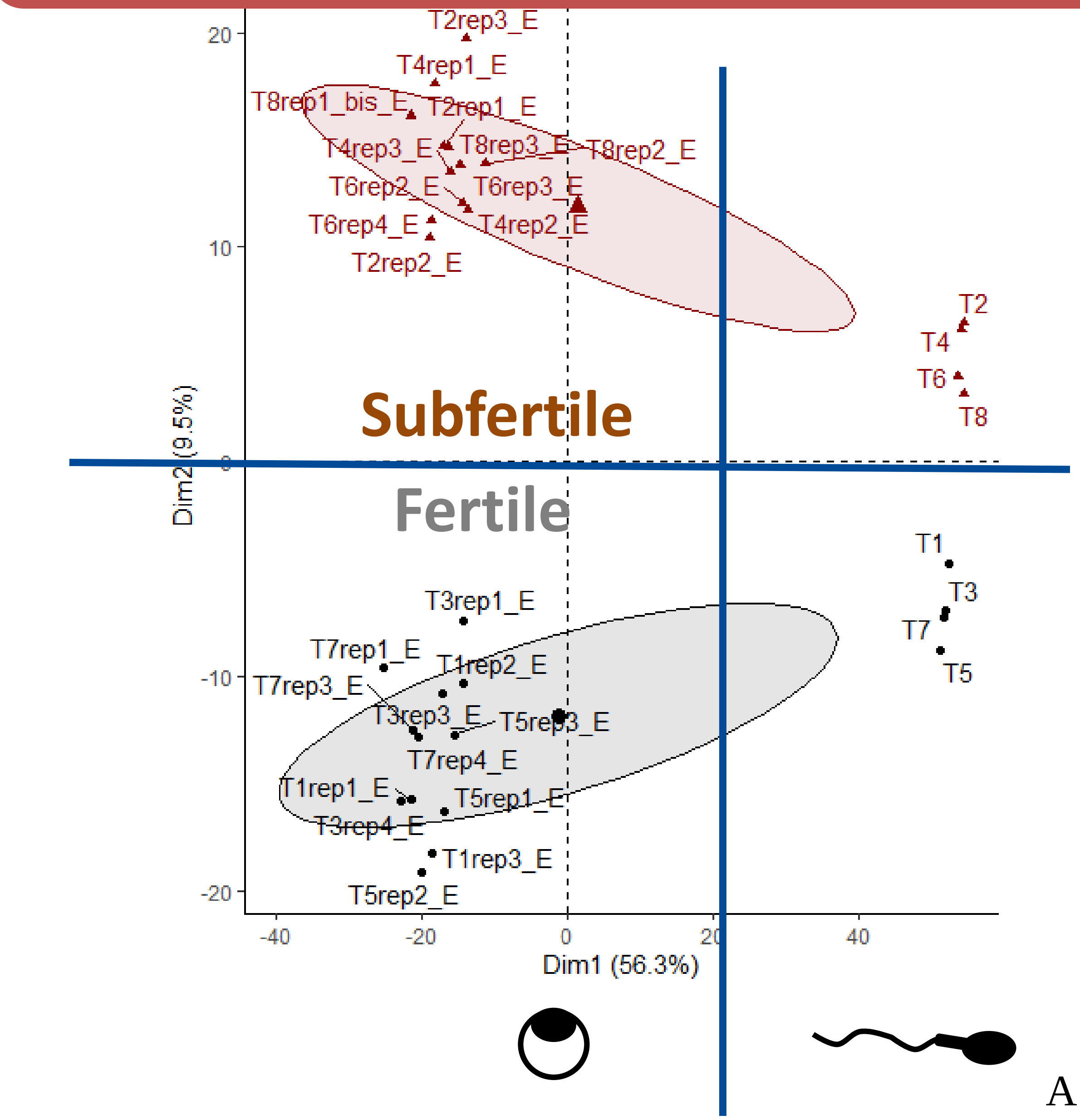


N=4 Subfertile

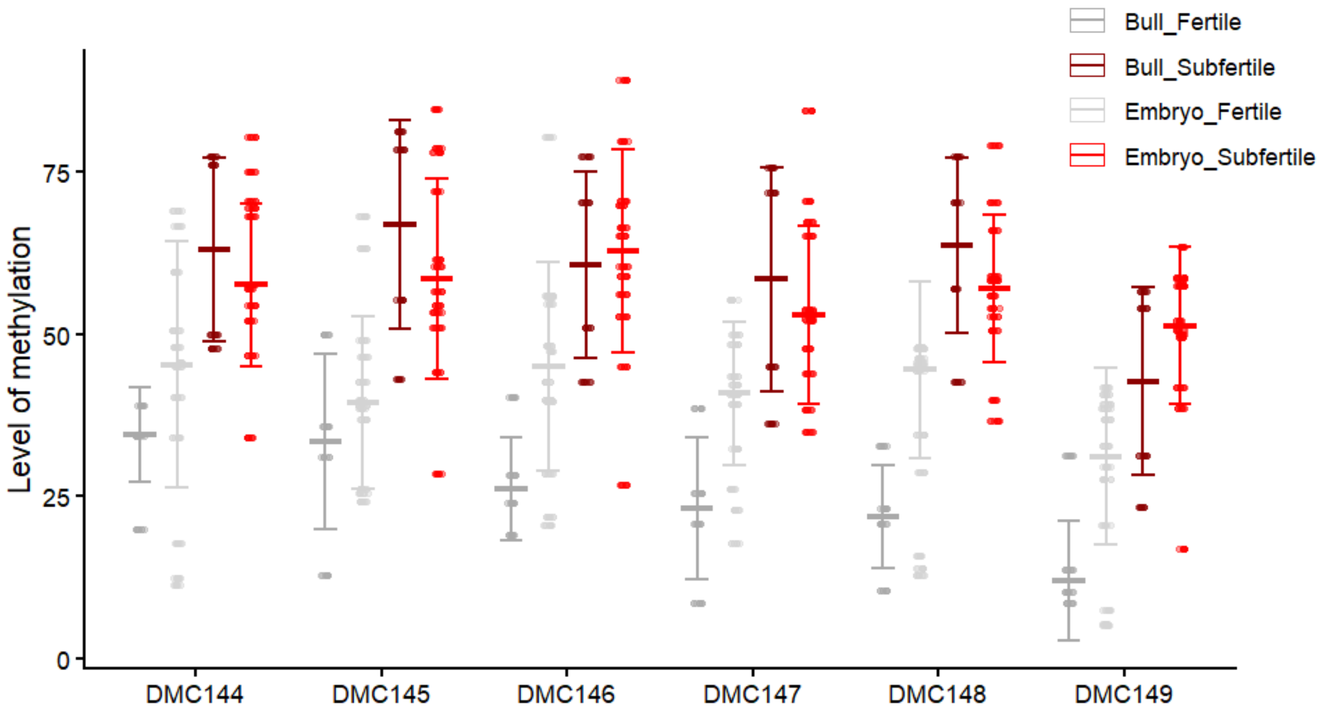
N=4 Fertile

Vs.

DNA methylation is different in embryos issued from fertile vs. subfertile bulls



Some methylation signatures of subfertility are transmitted to the embryo



- For the transmitted signatures: mean $h^2=0.40$ > sperm

A. Raja-Ravi-Shankar, A. Chaulot-Talmon, O. Dubois, MC. Deloche, A. Bonnet, S. Jean-René, L. Laffont, C. Archilla, V. Costes, E. Sellem, C. Fouéré, V. Duranthon, H. Kiefer

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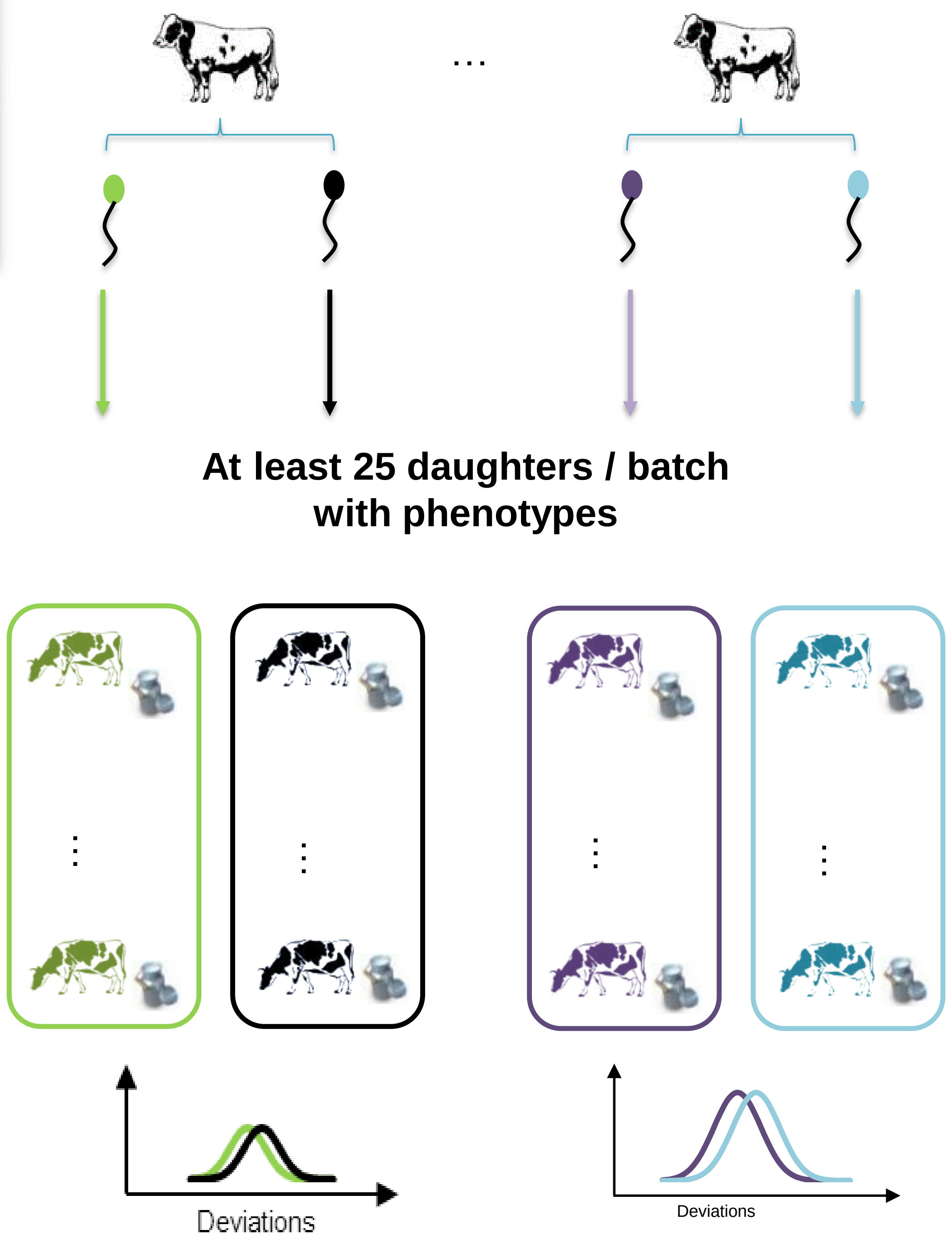
Impact on offspring phenotype

Florian Besnard



At least 25 daughters / batch with phenotypes

Methylation differences between ejaculates
600 samples from 350 bulls

↓

Daughters' phenotypes
75,000 records

- Milk production
- Udder health
- Fertility
- Morphology

Very small effects on milk production, udder health, fertility, and morphology traits

- Daughters' phenotypic variance explained by fathers' sperm methylation <0.4%
- Are the methylation differences between ejaculates sufficient?

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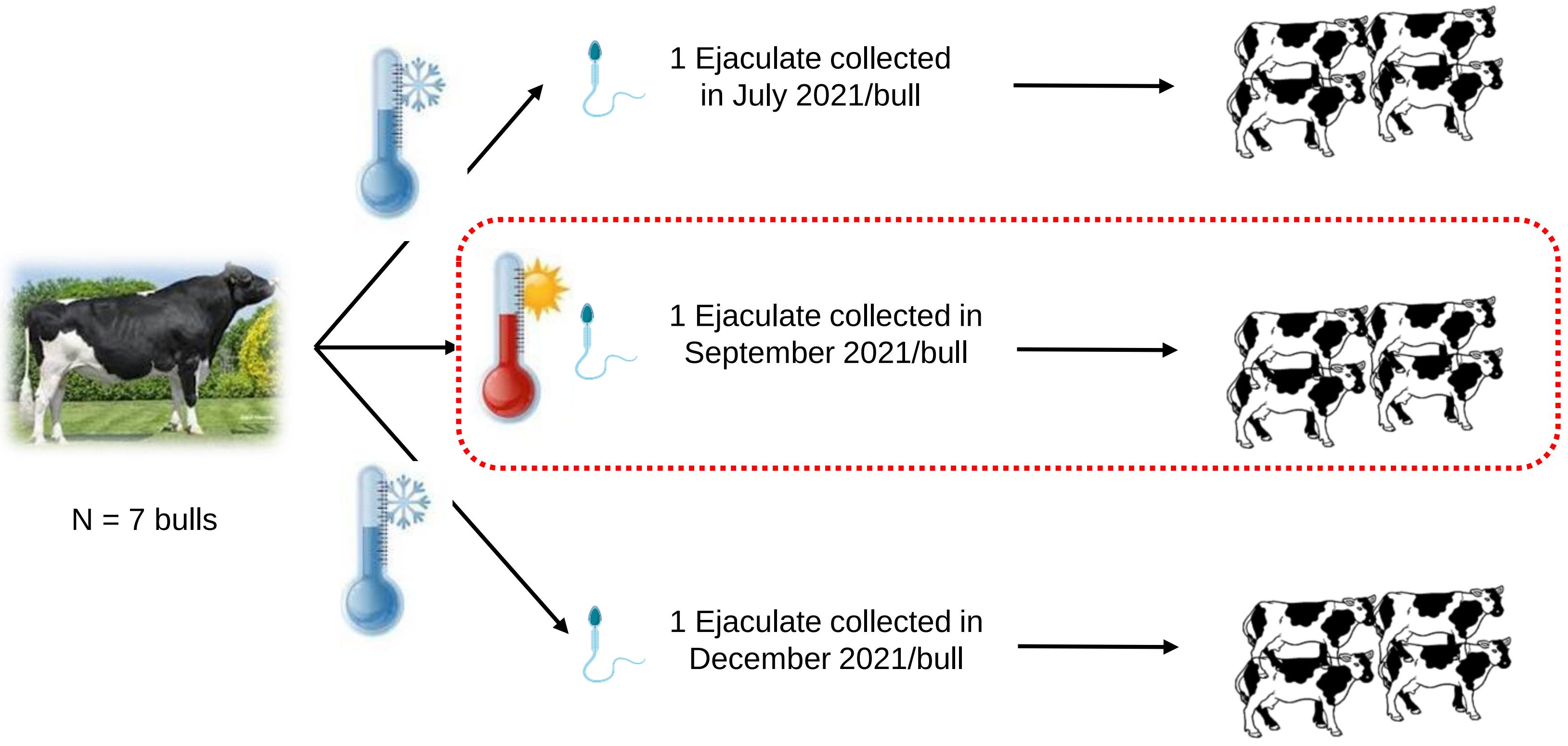
F. Besnard, C. Fouéré, A. Raja-Ravi-Shankar, V. Costes, H. Kiefer, C. Le Danvic, S. Fritz, D. Boichard, M-P. Sanchez

Season effects on the sperm methylome and offspring dairy phenotypes

A. Raja-Ravi-Shankar



1 Ejaculate collected in July 2021/bull

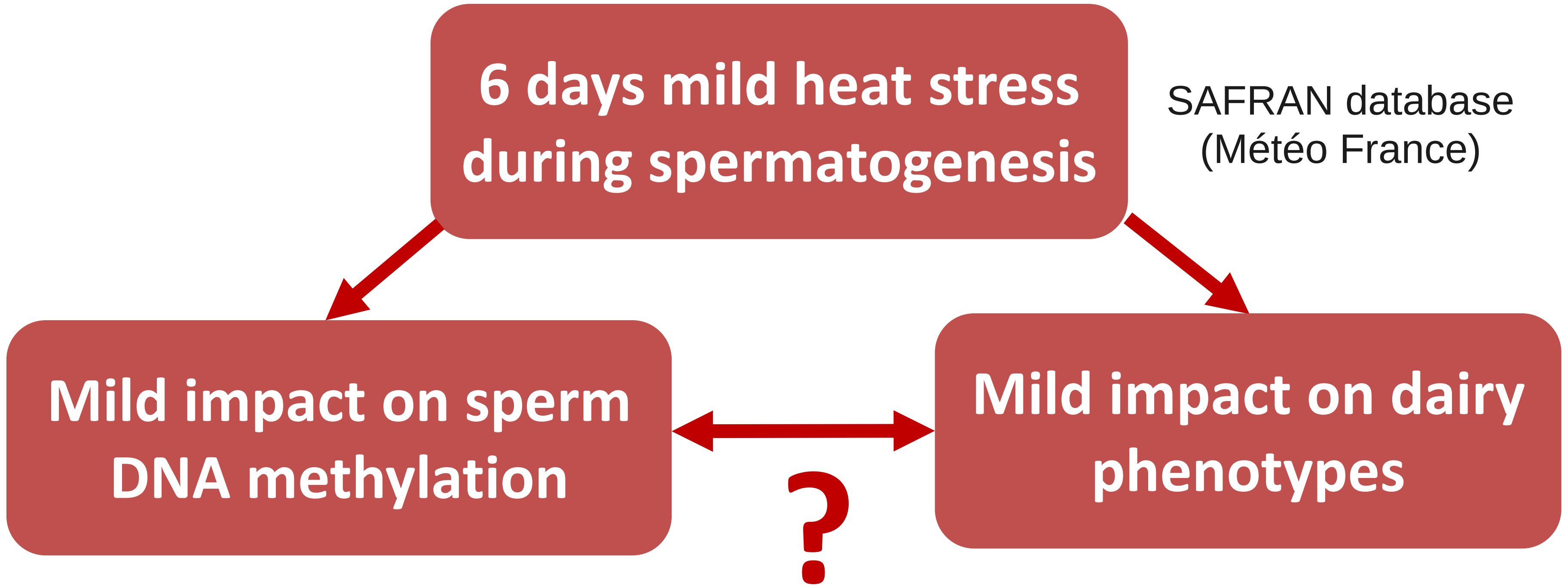
1 Ejaculate collected in September 2021/bull

1 Ejaculate collected in December 2021/bull

N = 7 bulls

Methylation differences between ejaculates
N=21 ejaculates

Daughters' dairy phenotypes
N=1,378



6 days mild heat stress during spermatogenesis

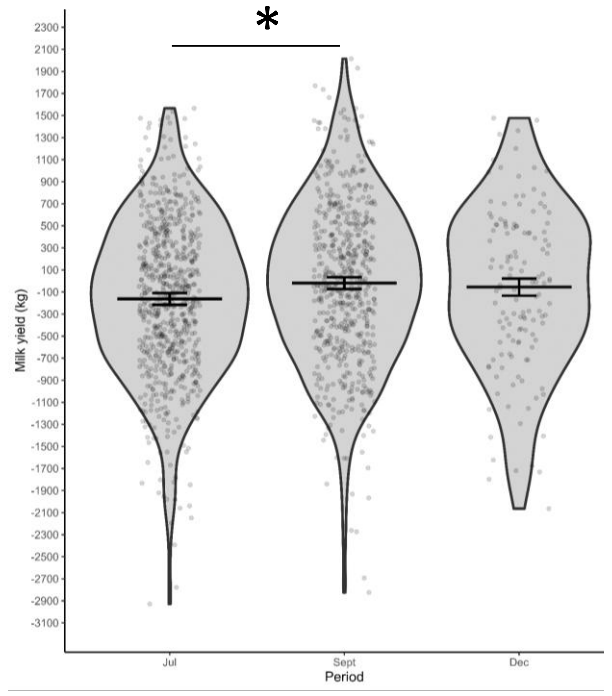
SAFRAN database (Météo France)

Mild impact on sperm DNA methylation

Mild impact on dairy phenotypes

?

- Trend to loose methylation in September



A. Raja-Ravi-Shankar, F. Besnard ,Y. Klein, A. Chaulot-Talmon, F.Ali, V. Costes, D. Boichard, E. Sellem, G. Costa Monteiro Moreira , C. Le Danvic, H. Kiefer

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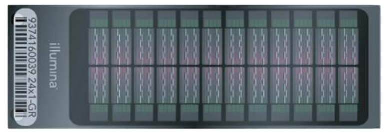
Final message & what's next

- Both genetic and environmental factors shape sperm DNA methylation → attention should be paid to bulls' environment from *in utero* life
- Sperm DNA methylation is a valuable source of male fertility biomarkers → early diagnostic of subfertile bulls?
- Some epigenetic signatures of bull subfertility are found in embryos produced with subfertile semen
  - → Impact on development?
  - → Is it possible to identify more systematically DNA methylation patterns transmitted to the embryo? Ongoing work by Aarhus University
  - → Are these paternal methylation signatures maintained thoughout life?
- Impact of sperm methylation variations on offspring phenotype is limited, important statistical power requirement → levers of resilience for the next generation?
- Production of large datasets, knowledge, methods and concepts → extend to a wider population of bulls, other breeds, using the RUMIGEN EpiChip



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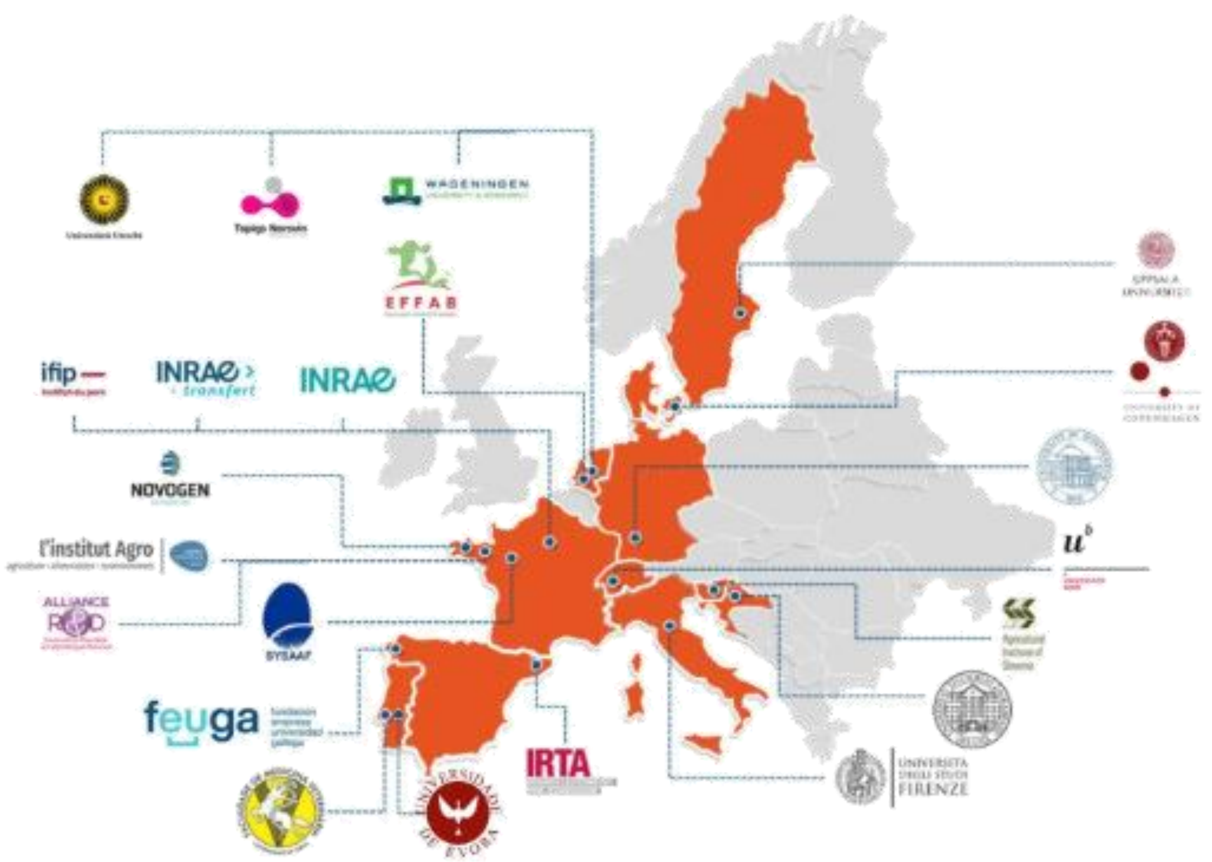
THANK YOU

TOWARDS IMPROVEMENT OF **RUMI**NANT BREEDING THROUGH **GEN**OMIC AND EPIGENOMIC APPROACHES

GENOME AND EPIGENOME ENABLED BREEDING IN MONOGASTRICS



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