Il contributo della genetica all'incremento della produttività in zootecnia e alla soluzione dei problemi ambientali causati dall'intensificazione

Paolo Ajmone Marsan

Dipartimento di Scienze Animali della Nutrizione e degli Alimenti - DIANA

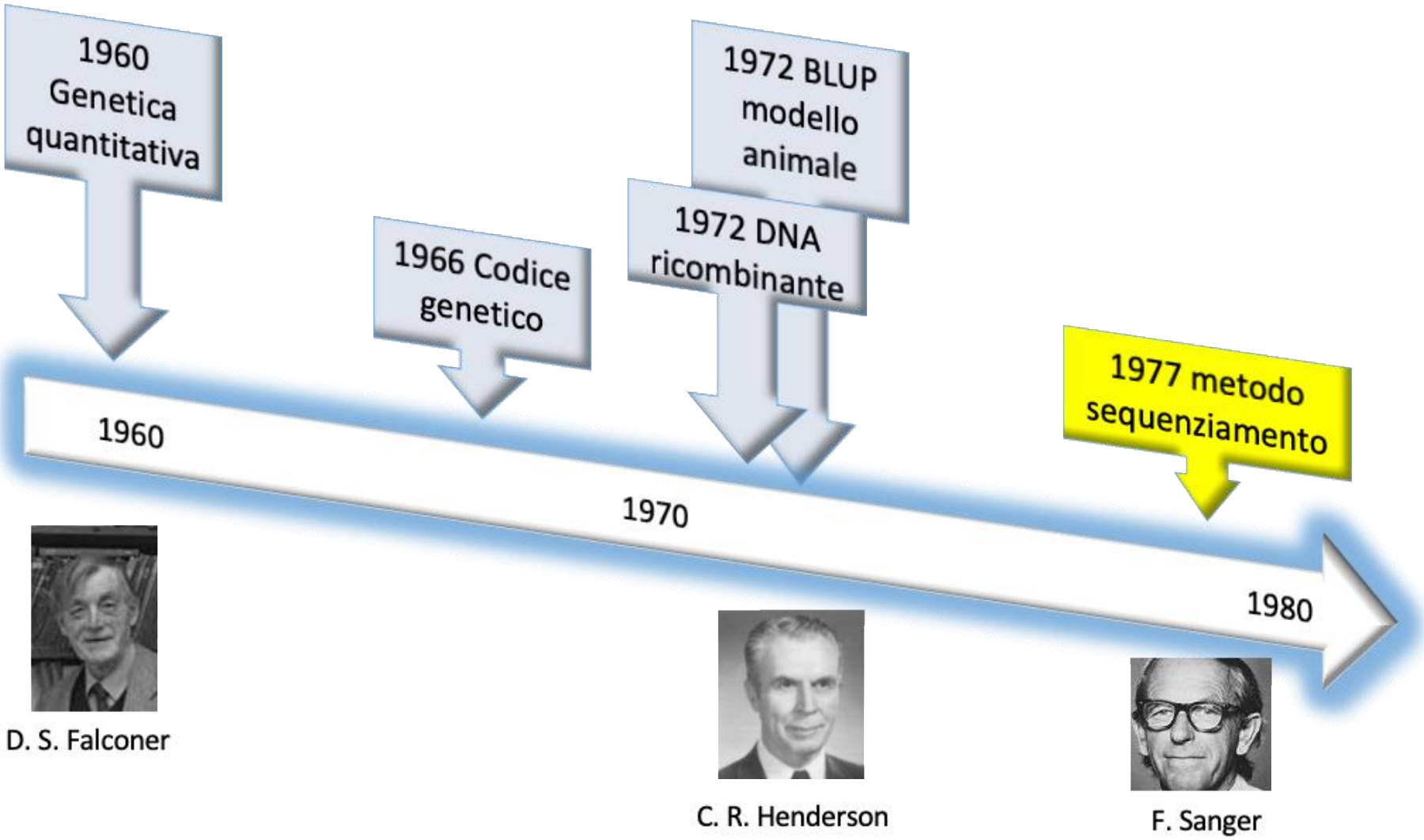
Centro di Ricerca Romeo ed Enrica Invernizzi sulle produzioni lattiero-casearie sostenibili – CREI

Università Cattolica del S. Cuore

Accademia dei Georgofili, Firenze, 14/11/2024

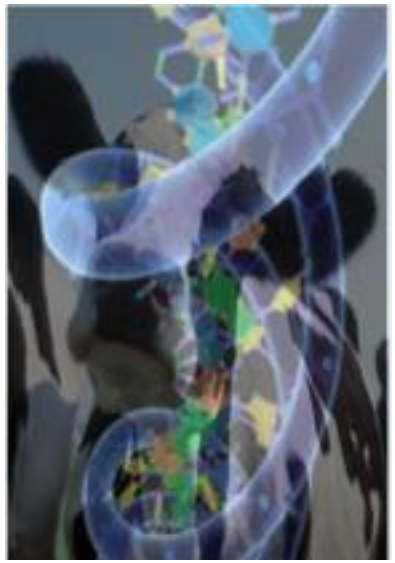
Da dove siamo partiti

Verso l'utilizzo del DNA

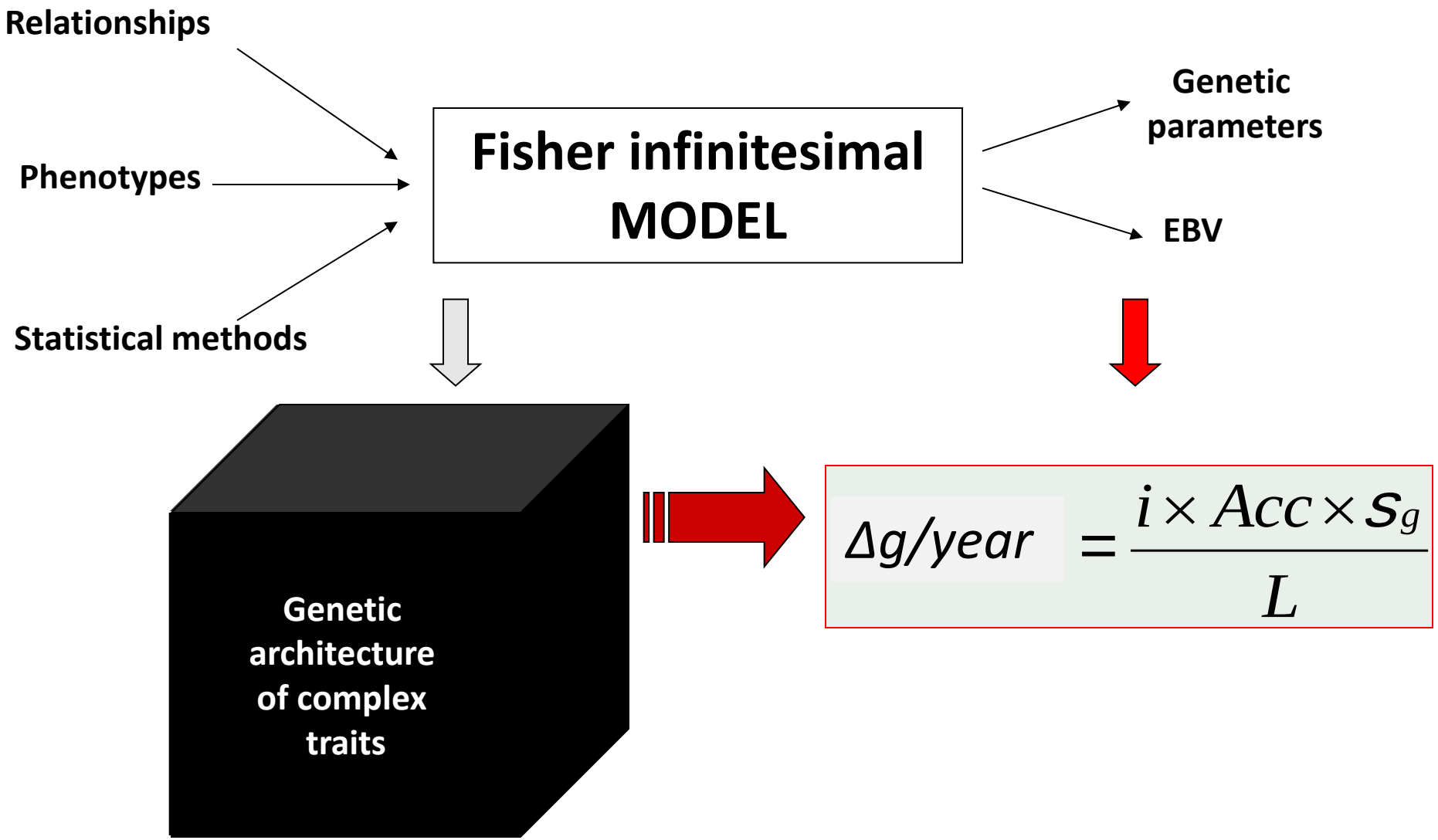


Valutazione genetica

$$P = G + E$$



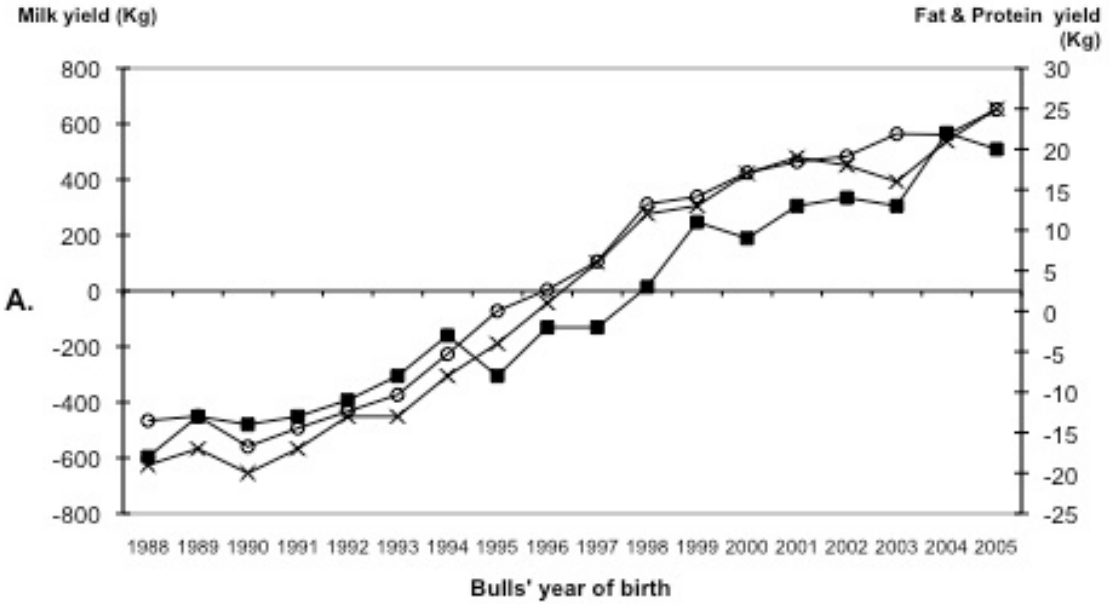
Selezione tradizionale



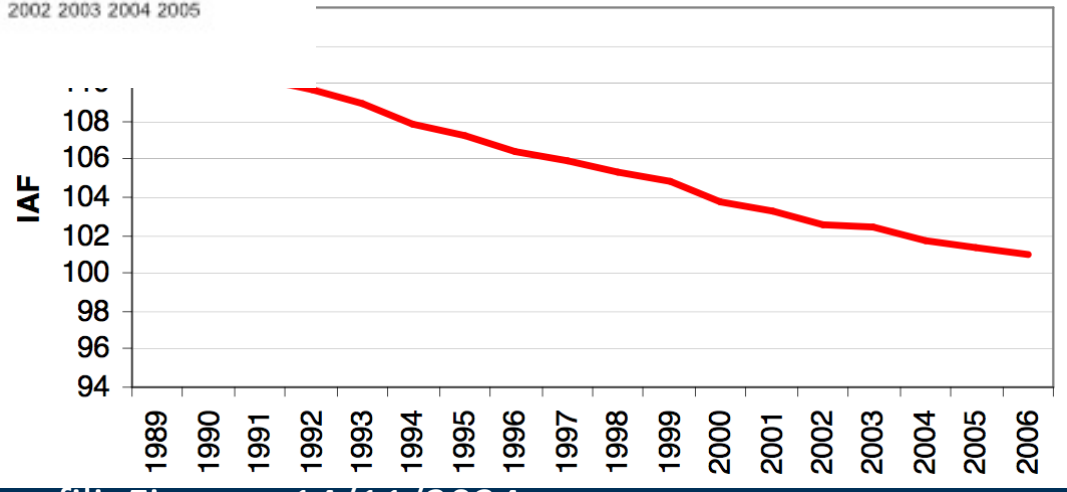
Selezione tradizionale

UNIVERSITÀ CATTOLICA del Sacro Cuore

Milk, Fat and Protein genetic trends



Fertility Index genetic trend



Evoluzione dell'indice di selezione nella Frisona Italiana

Carattere	ILQ 1989-1990	ILQ 1991-1993	ILQM	PFT 2002-2009	PFT 2009-
Latte kg	0	-27	-21	0	0
Grasso kg	33	6	5	12	8
Proteina kg	67	67	54	42	36
Grasso %	0	0	0	2	2
Proteina %	0	0	0	3	3
Tipo	0	0	0	4	4
Mammella	0	0	20	13	13
Arti e Piedi	0	0	0	6	6
Cellule	0	0	0	10	10
Longevità	0	0	0	8	8
Fertilità	0	0	0	0	10

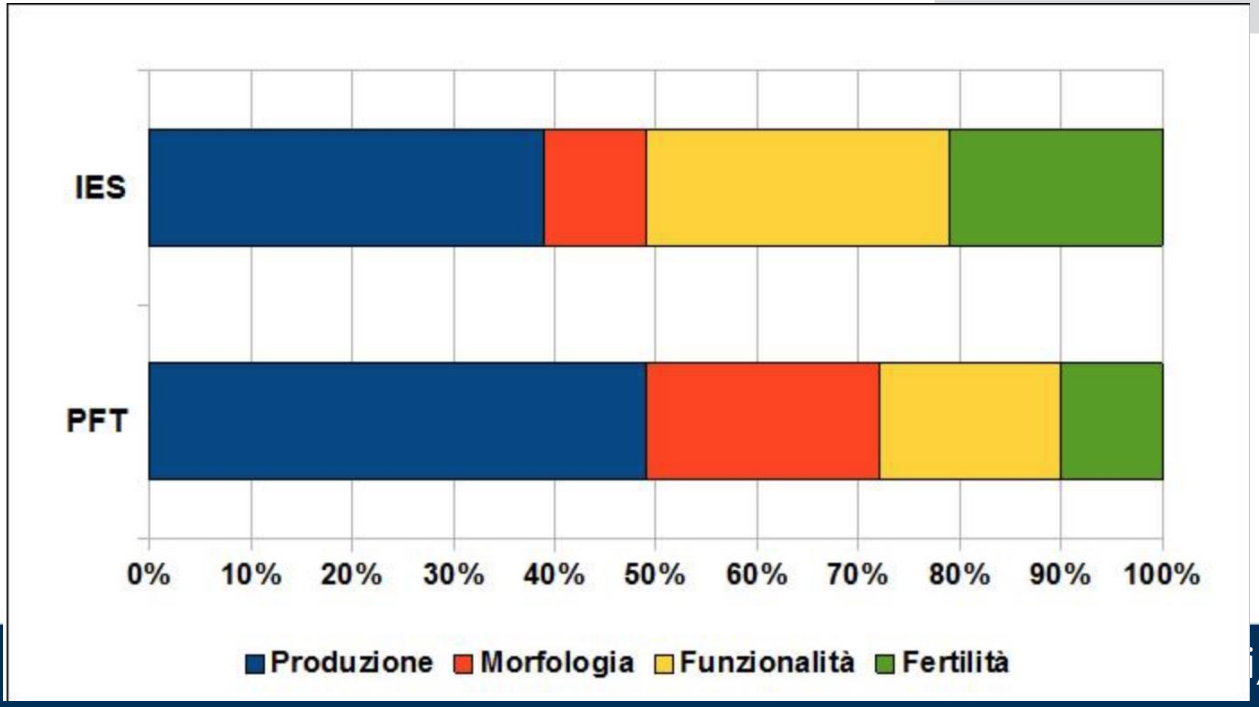
Dove siamo

Frisona, Indice Economico Salute (IES) (2016)

IES = 0,32 * grasso kg + 1,37 * proteina kg + 0,043 * grasso% * 100 +
0,0188 * proteina * 100 - 5 * statura + 4 * locomozione +
1 * profondità mammella + 20,51 * (longevità – 100)/5 +
6 * ((scs-100)/5,7) + 18 * (fertilità -100)/5 + 3,35 * ((bcs-100)/5) +
3,51 * ((facilità parto materna -100)/5)

che determina un rapporto tra produzione, morfologia e funzionalità pari al 39:10:51

PRODUZIONE	PESO	MORFOLOGIA	PESO	FUNZIONALITÀ	PESO
Grasso	8	Statura	-5	Longevità	20,51
Proteina	27,62	Locomozione	4	Cellule Somatiche	6
Grasso %	1	Profondità Mammella	1	Facilità Parto Vacca	3,51
Proteina %	2			Fertilità	18
				Body Condition Score	3,35



IES 39:10:51

PFT 49:23:28

Nuovo millennio: era del DNA

1978 Markers in dairy cattle selection

1983 PCR

1996 clonata pecora Dolly

2000 bozza genoma umano

2015 Editing del genoma con CRISP/Cas9

2022 genoma umano completo

1980 1990 2000 2010 2020

M. Soller

C. Mullis

I. Wilmut

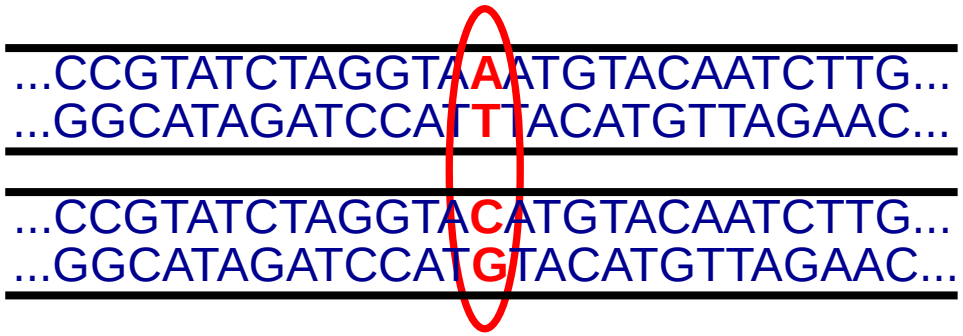
F. Collins

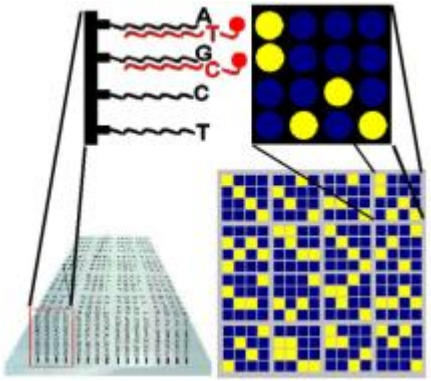
C. Venter

E. Charpentier, J.A. Doudna

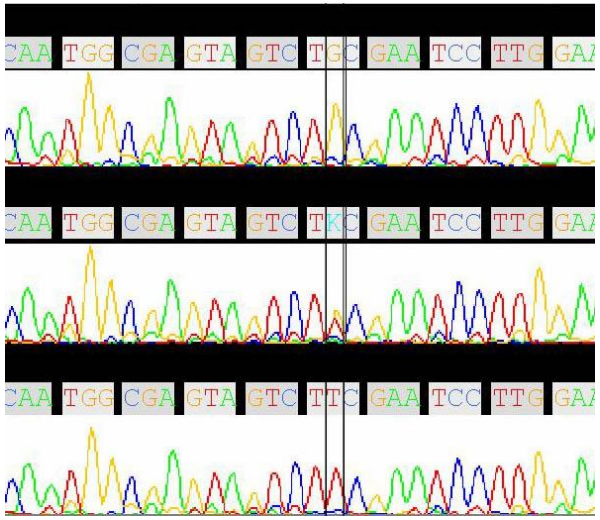
Single Nucleotide Polymorphisms (SNPs)

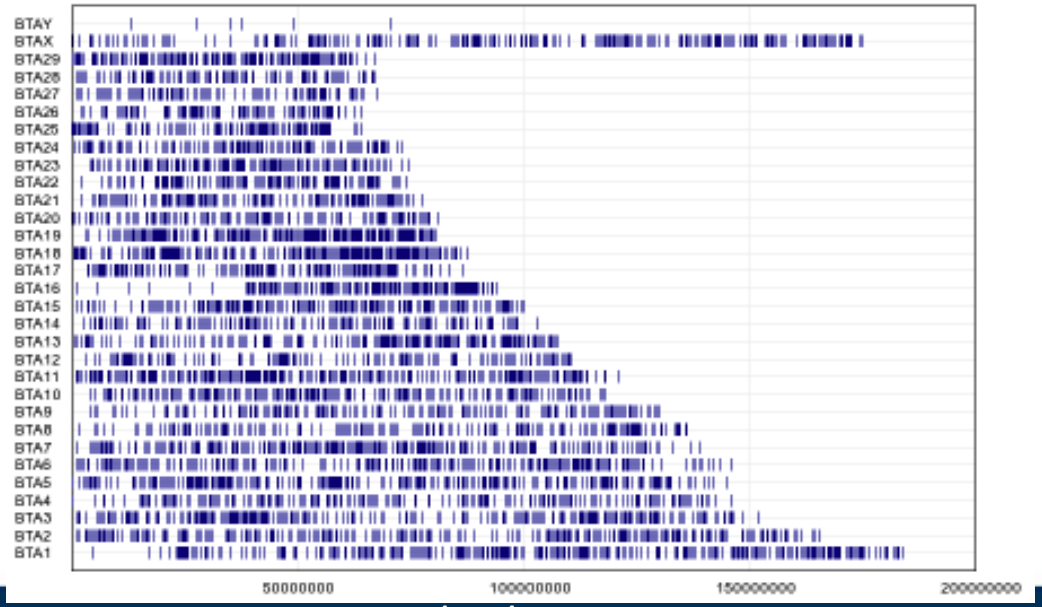
Mutazioni puntiformi in specifiche posizioni lungo il genoma



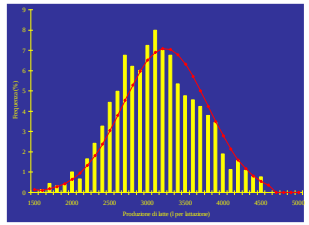


Analisi su chip/microarray

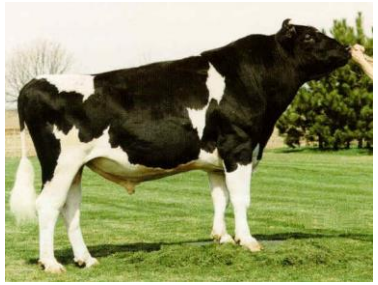




Selezione genomica: un cambio di paradigma

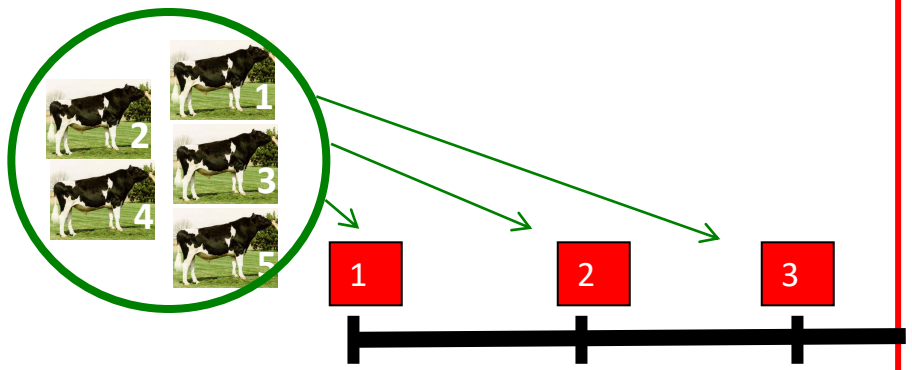


Selezione tradizionale:
Raccolta di fenotipi di molti animali parenti per stimare **il valore dell'intero genoma di un toro o di una vacca**



= EBV

Selezione genomica:
Raccolta di fenotipi di molti animali per stimare parentela e il **valore di marcatori e aplotipi nell'intera popolazione**



G. Mendel

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

T. H. E. Meuwissen,* B. J. Hayes† and M. E. Goddard†,‡

*Research Institute of Animal Science and Health, 8200 AB Lelystad, The Netherlands, †Victorian Institute of Animal Science, Attwood 3049, Victoria, Australia and ‡Institute of Land and Food Resources, University of Melbourne, Parkville 3052, Victoria, Australia

Manuscript received August 17, 2000 Accepted for publication January 17, 2001

ABSTRACT

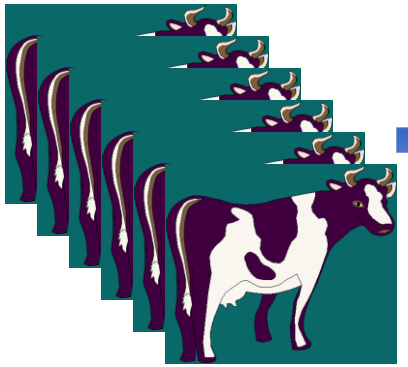
Recent advances in molecular genetic techniques will make dense marker maps available and genotyping many individuals for these markers feasible. Here we attempted to estimate the effects of ~50,000 marker haplotypes simultaneously from a limited number of phenotypic records. A genome of 1000 cM was simulated with a marker spacing of 1 cM. The markers surrounding every 1-cM region were combined into marker haplotypes. Due to finite population size (N_e = 100), the marker haplotypes were in linkage disequilibrium with the QTL located between the markers. Using least squares, all haplotype effects could not be estimated simultaneously. When only the biggest effects were included, they were overestimated and the accuracy of predicting genetic values of the offspring of the recorded animals was only 0.32. Best linear unbiased prediction of haplotype effects assumed equal variances associated to each 1-cM chromosomal segment, which yielded an accuracy of 0.73, although this assumption was far from true. Bayesian methods that assumed a prior distribution of the variance associated with each chromosome segment increased this accuracy to 0.85, even when the prior was not correct. It was concluded that selection on genetic values predicted from markers could substantially increase the rate of genetic gain in animals and plants, especially if combined with reproductive techniques to shorten the generation interval.

Popolazioni di training e di validazione

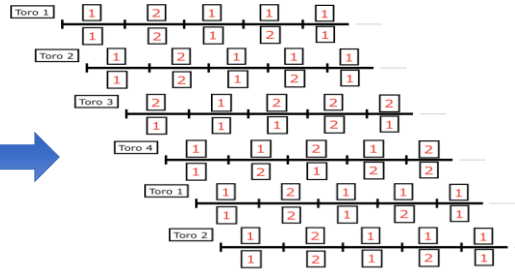
PROGENY TEST

EBV
EBV
EBV
EBV
EBV
EBV

TORI PROVATI



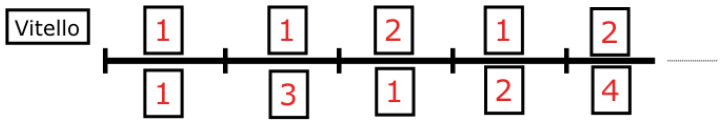
GENOTIPI



$$EBV_i = effetto_{SNP1} + effetto_{SNP2} + \ldots + effetto_{SNP54k} + e_i$$

$$100 = (+1) + (-4) + \ldots + (-2)$$

La Selezione Genomica in azione



$$EBV_i = effect_{SNP1} + effect_{SNP2} + \ldots + effect_{SNP54k} + e_i$$
$$100 = (+1) + (-4) + \ldots + (-2)$$

$$DGV_i = g_{SNP1} * effect_{SNP1} + g_{SNP2} * effect_{SNP2} + \ldots + g_{SNP54k} * effect_{SNP54k} + e_i$$

$$DGV_i = 0 * (+1) + 2 * (-4) + \ldots + 1 * (-2)$$

DGV → **G-EBV**

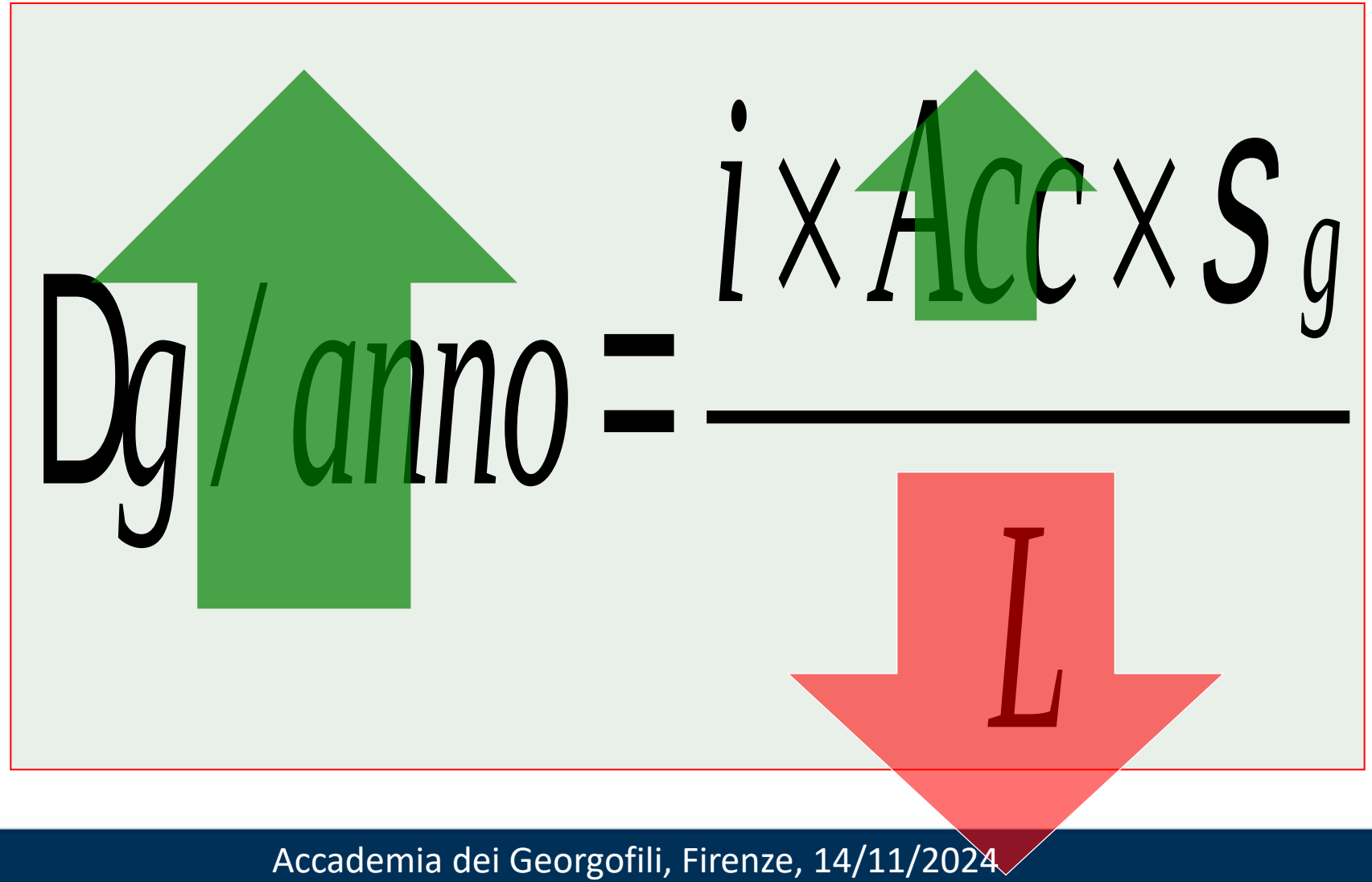
One-step

$$\mathbf{H}^{-1} = \mathbf{A}^{-1}\begin{bmatrix} 0 & 0 \\ 0 & \mathbf{G}^{-1} - \mathbf{A}_{22}^{-1} \end{bmatrix}$$

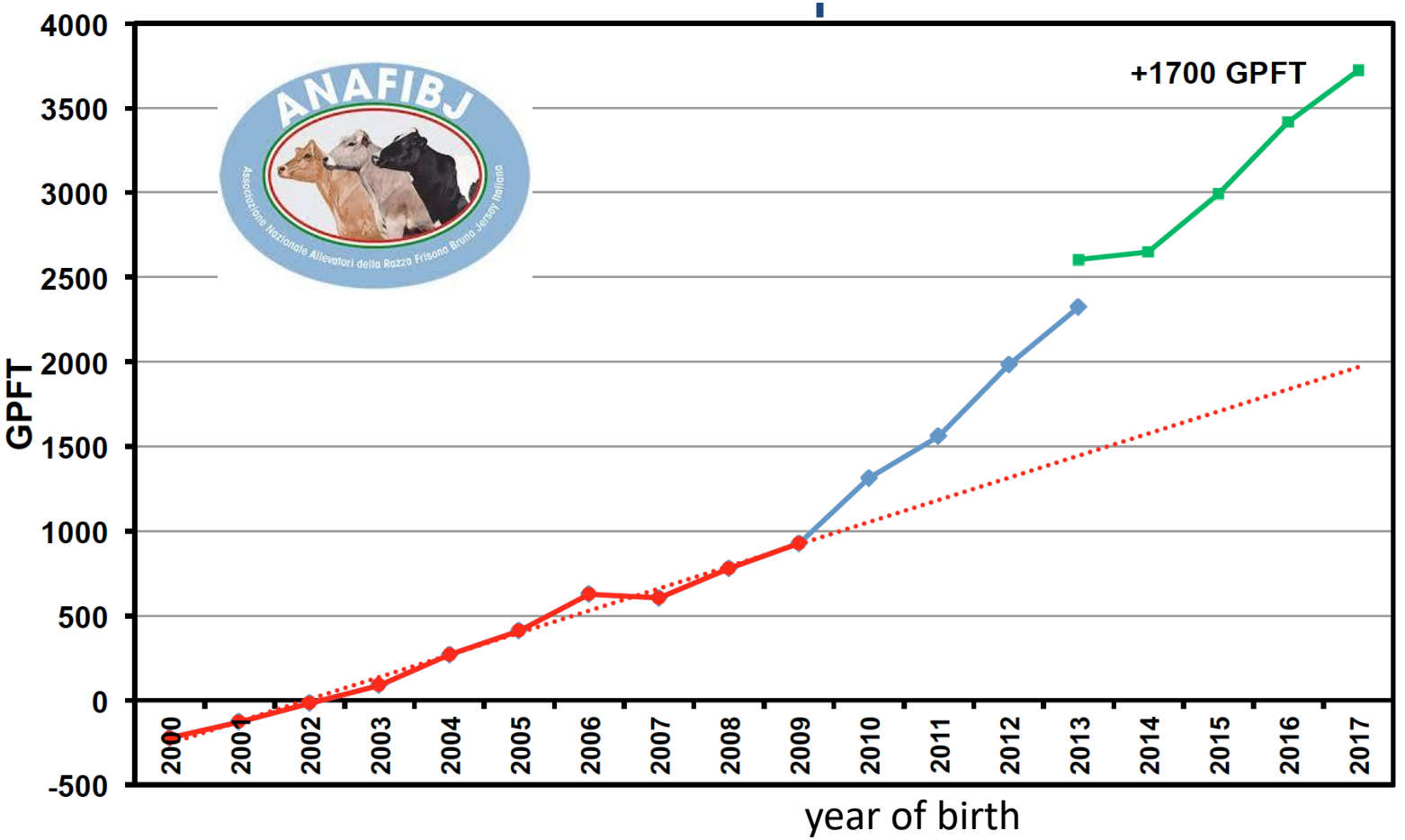
where $\mathbf{G}^{-1}$ is the inverse of the genomic relationship matrix and $\mathbf{A}_{22}^{-1}$ is the inverse of the pedigree-based relationship matrix for genotyped animals. Comparisons involved

Forni et al. 2011 GSE

Selezione genomica



Selezione Genomica



Raffaella Finocchiaro

Jan-Thijs Van Kaam

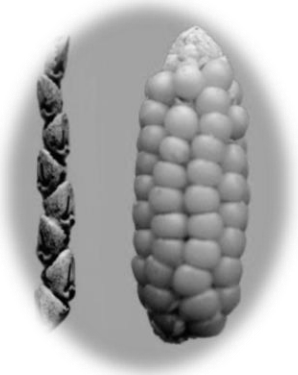
Great impact in (dairy cattle) breedin

Produttività negli ultimi 100 anni

8 Kg/d

1930

1.5 t/ha

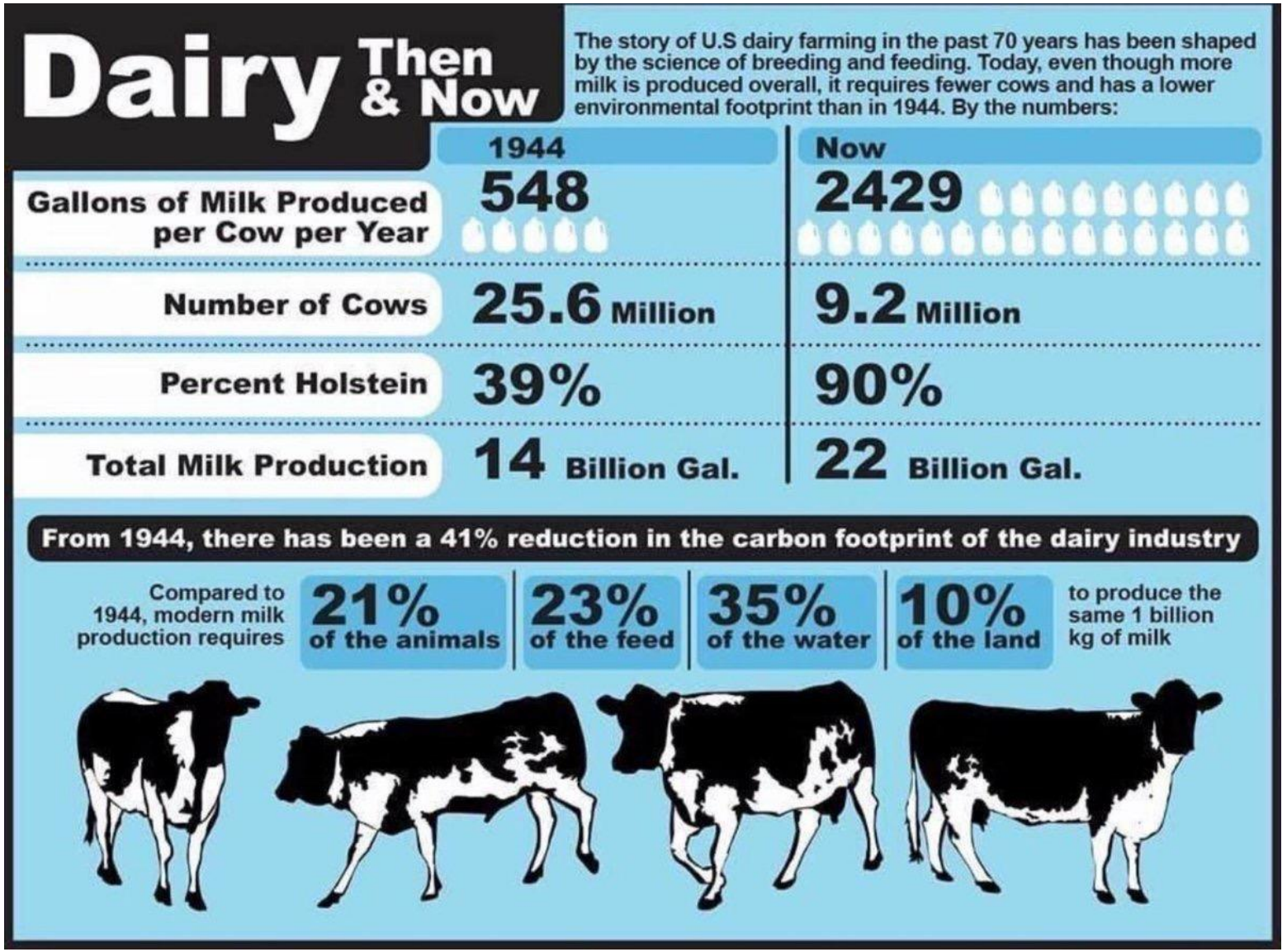


40 Kg/d

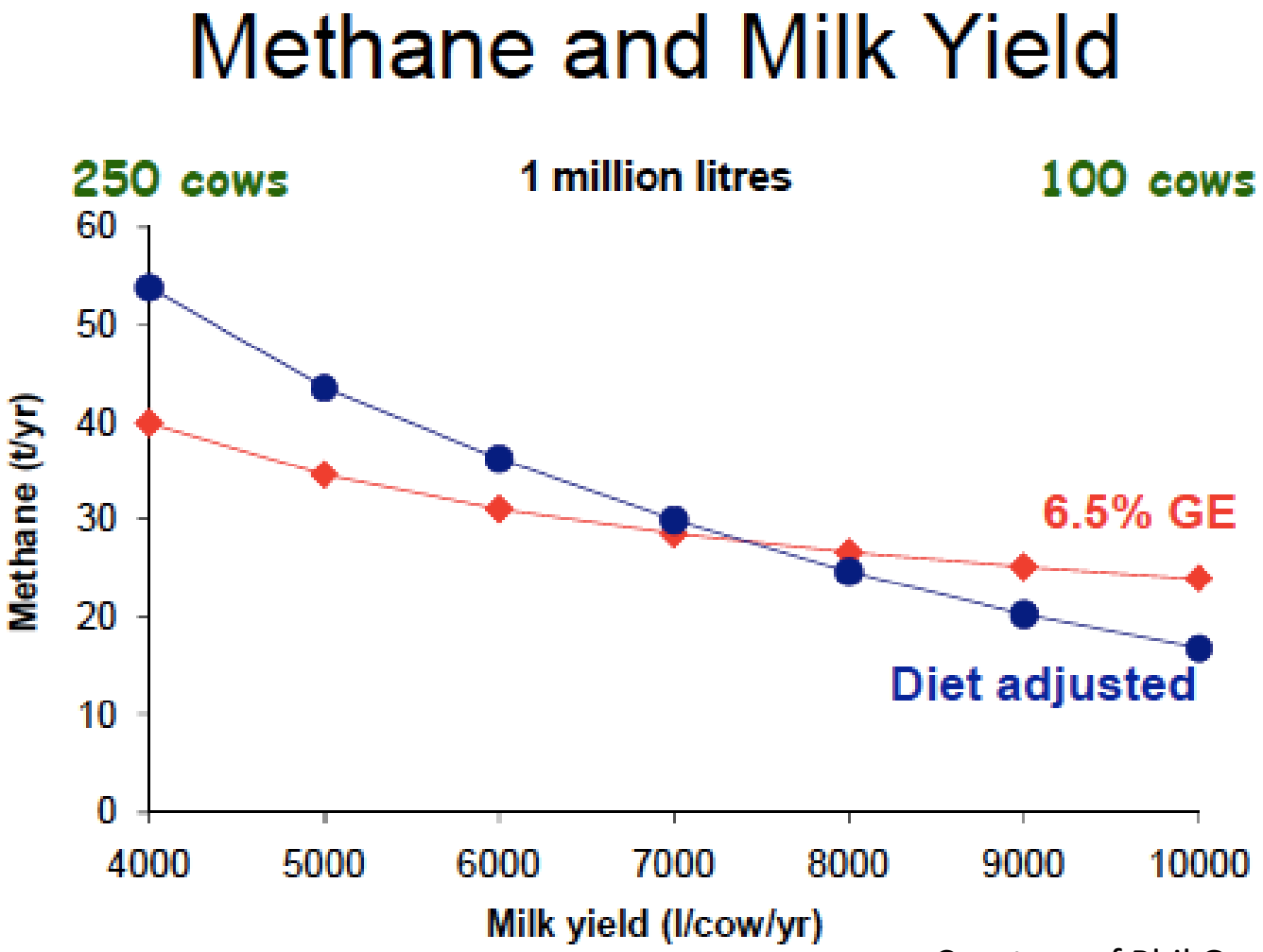
2024

15 t/ha

Produttività negli ultimi 100 anni

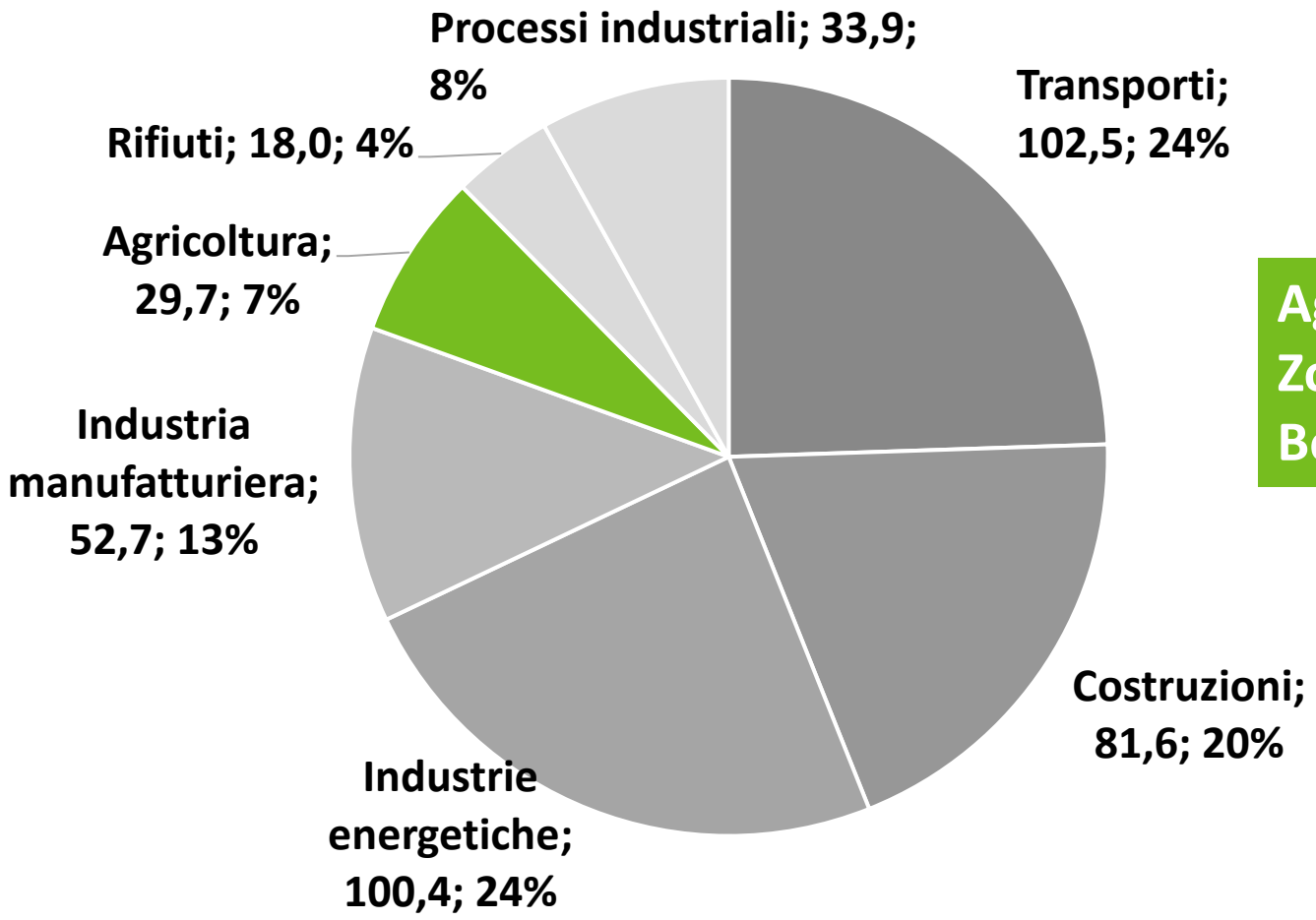


Efficienza e impatto



Courtesy of Phil Garnsworthy

Dati ISPRA



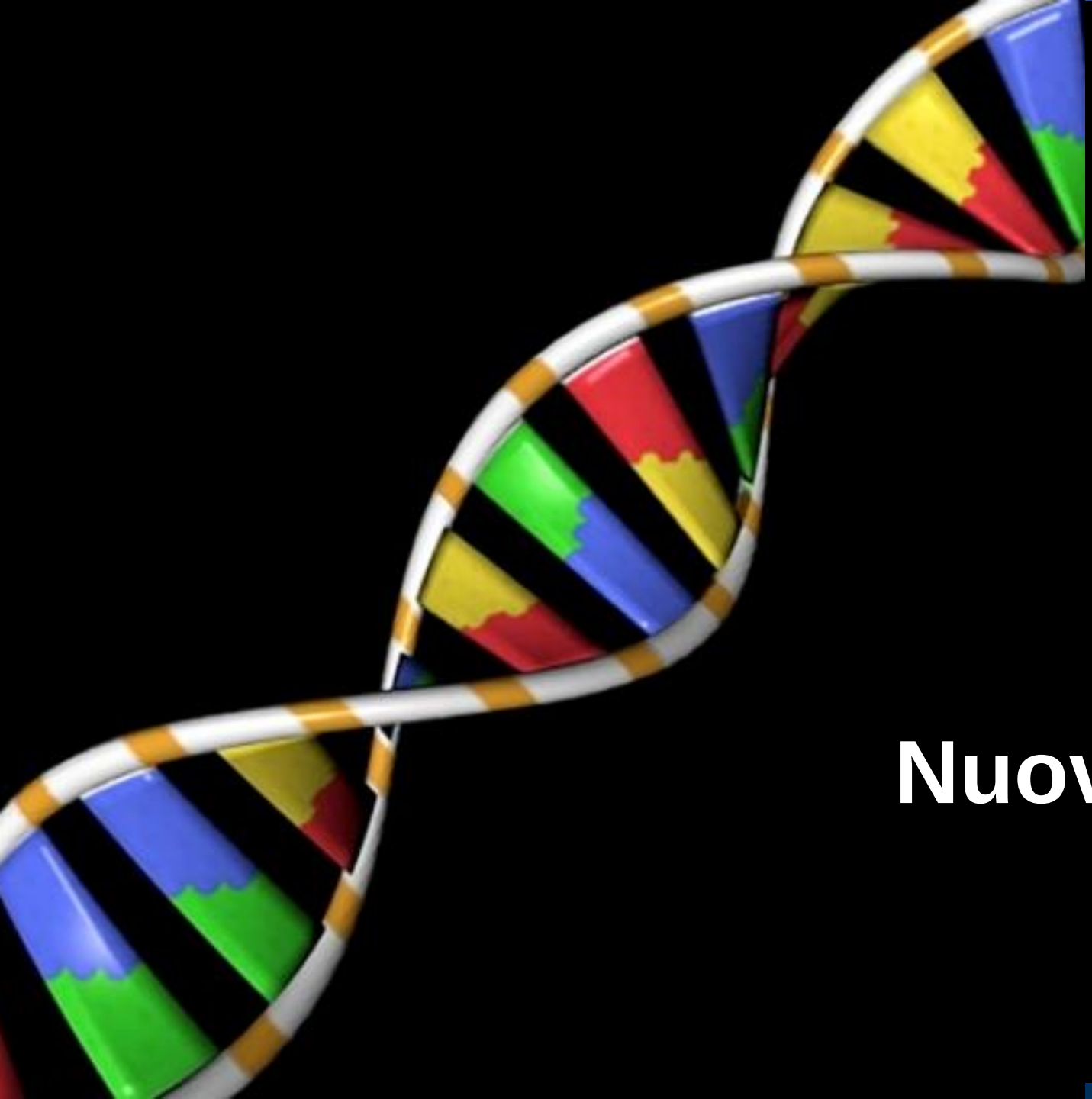
Agricoltura:	29.7 Mt CO_2-eq
Zootecnia:	23.7 Mt CO_2-eq
Bovino da Latte:	12.5 Mt CO_2-eq

4.2%

Food and Agriculture Organization of the United Nations

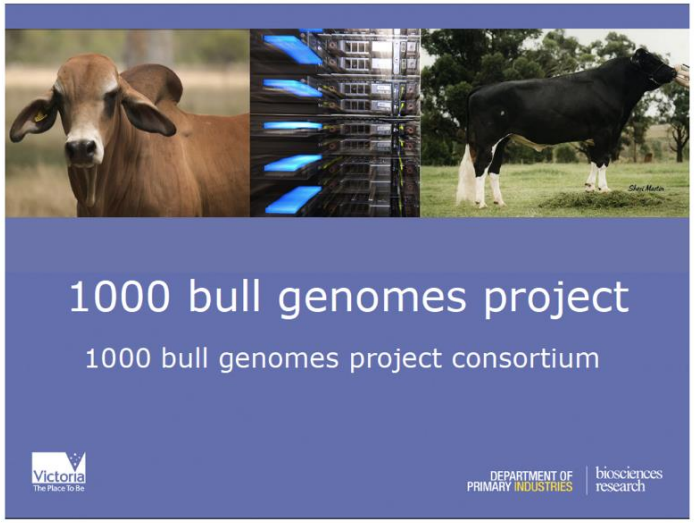
nLCA

Dove stiamo andando

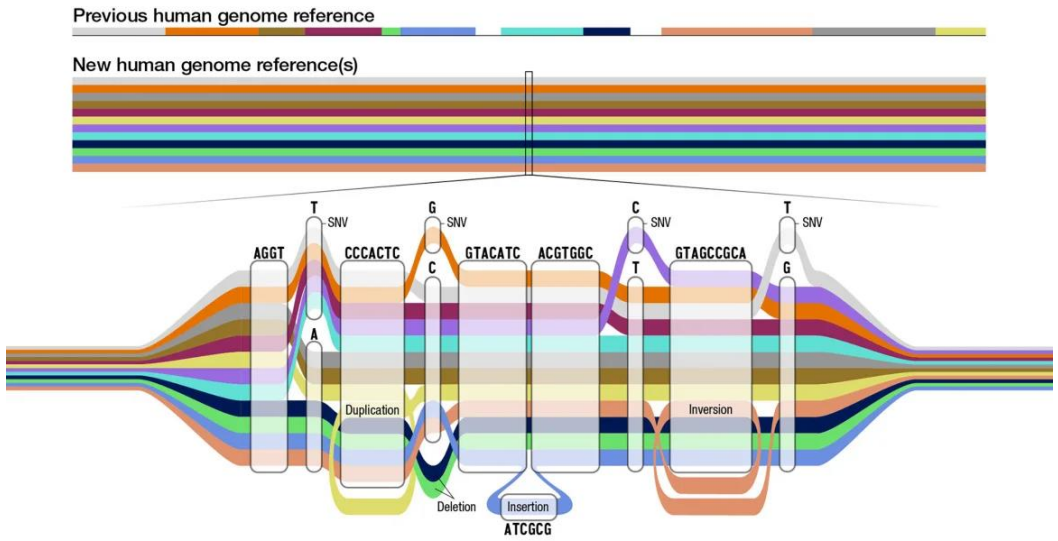


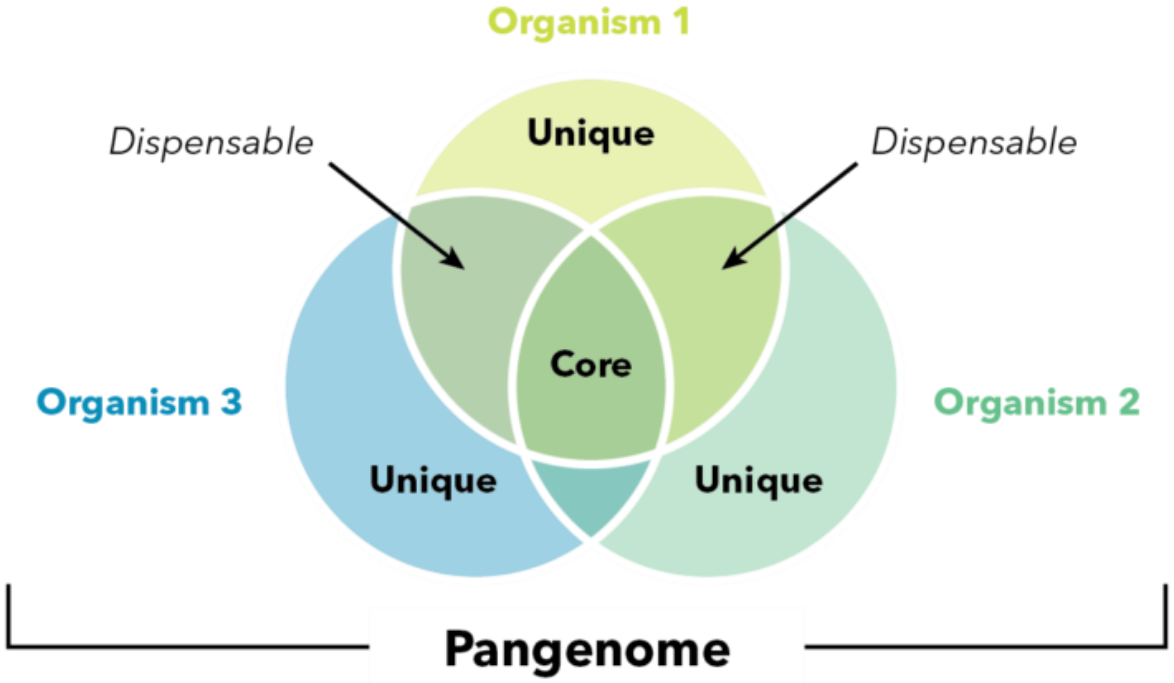
Nuova genomica

From single animals to whole planet

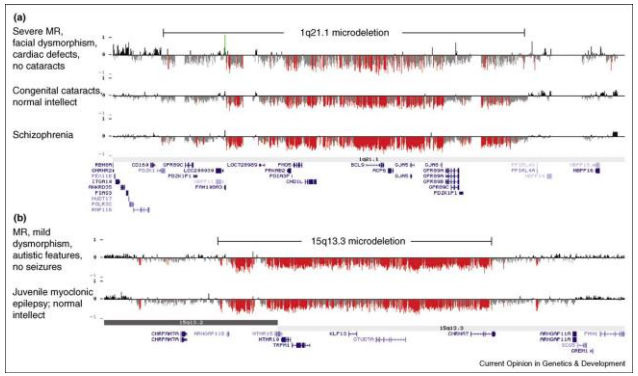


Dal genoma al Pangenoma





Copy Number Variations (CNVs)

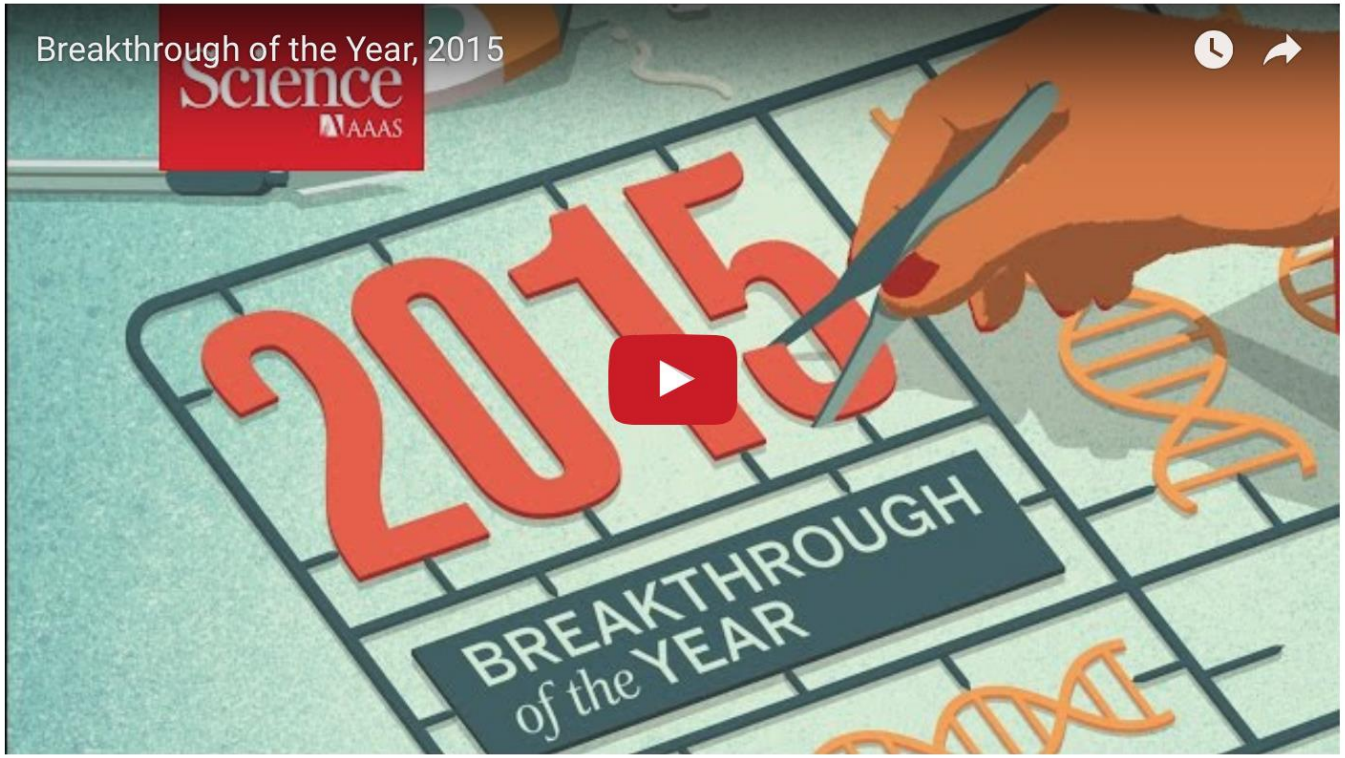


Gene editing

UNIVERSITÀ CATTOLICA del Sacro Cuore

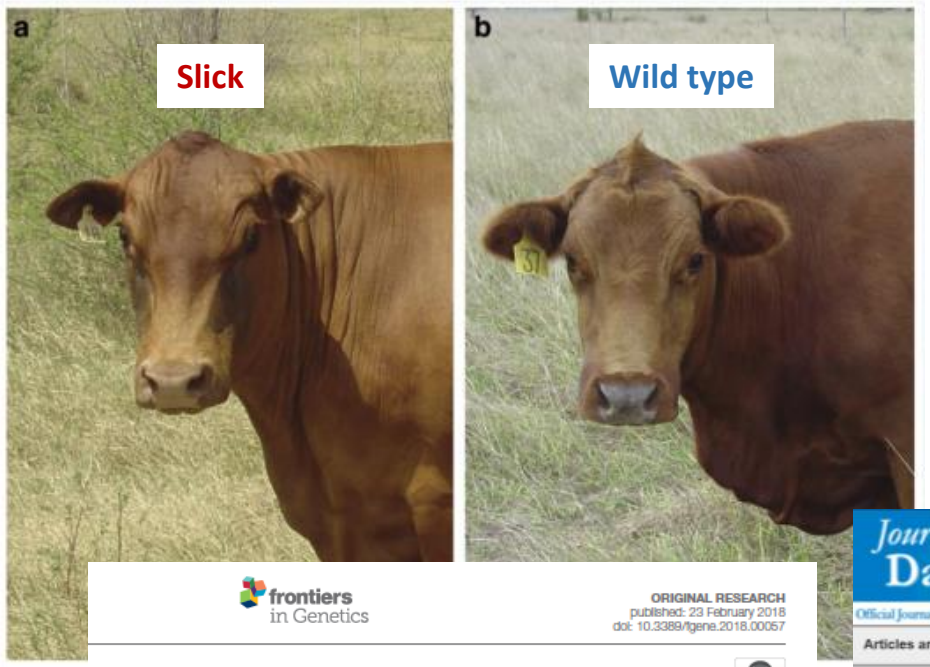
Making the cut

CRISPR genome-editing technology shows its power



And Science's 2015 Breakthrough of the Year is...

La mutazione SLICK



La mutazione **SLICK è insorta naturalmente in bovini di razza Senepol** del Sud America.

SLICK induce un cambiamento nel gene del recettore per la prolattina che conferisce **un'aumentata tolleranza alle temperature elevate.**

frontiers in Genetics
ORIGINAL RESEARCH
published: 23 February 2018
doi: 10.3389/fgene.2018.00057

Convergent Evolution of Slick Coat in Cattle through Truncation Mutations in the Prolactin Receptor

Laercio R. Porto-Neto[1], Derek M. Bickhart[2], Antonio J. Landaeta-Hernandez[3], Yuri T. Utsunomiya[4,5], Melvin Pagan[6], Esbal Jimenez[6], Peter J. Hansen[7], Serdal Dikmen[8], Steven G. Schroeder[9], Eui-Soo Kim[10], Jiajie Sun[11], Edward Crespo[3], Norman Amati[3], John B. Cole[9], Daniel J. Null[9], Jose F. Garcia[4,5,12], Antonio Reverter[1], William Barendse[1] and Tad S. Sonstegard[10]

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Article in Press

The *SLICK* hair locus derived from Senepol cattle confers thermotolerance to intensively managed lactating Holstein cows

S. Dikmen, F.A. Khan[1], H.J. Huson[2], T.S. Sonstegard, J.I. Moss, G.E. Dahl, P.J. Hansen
[1] Present address: Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, ON, N1G 2W1, Canada.
[2] Present address: Department of Animal Science, Cornell University, Ithaca, NY 14853.

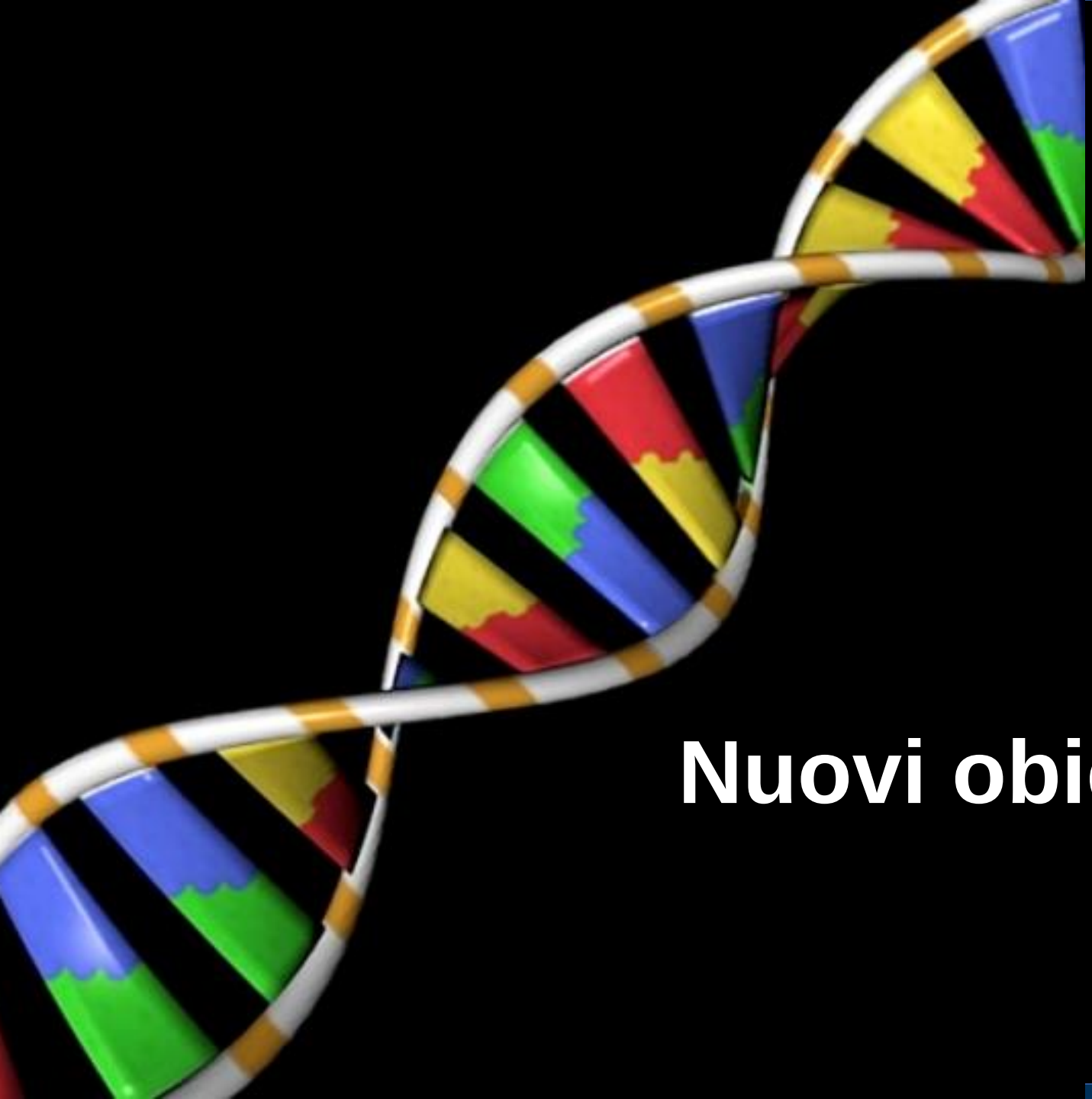
Received: February 27, 2014; Accepted: May 20, 2014; Published Online: July 01, 2014

Morfologia e fisiologia

- ✓ **Heat Tolerance**
  - Gene: *PRLR*
    - ➢ Target: SLICK1, SLICK2, SLICK3, SLICK4, SLICK5
- ✓ **Milk Production**
  - Gene: *GHR*
  - Gene: *DGAT*
    - ➢ Target: High Milk Allele
- ✓ **Size/ Fertility**
  - Gene: *PLAG1*
    - ➢ Target: Small stature / High Fertility
- ✓ **Trypanosoma Tolerance**
  - Gene: *DHRS4*
  - Gene: *FDX2*
    - ➢ Target: Tryps Tolerance
- ✓ **Tuberculosis Resistance**
  - Gene: *IFI16*
    - ➢ Target: Zebu Allele
  - Gene: *IL1A*
    - ➢ Target: Zebu Allele
  - Gene: *IRF3*
    - ➢ Target: Taurus, Zebu Allele, Recombinant Allele
  - Gene: *NOD2*
    - ➢ Target: Taurus, Zebu Allele, Recombinant Allele
  - Gene: *MARCO*
    - ➢ Target: Taurus Allele, Deleterious Allele
  - Gene: *NLRP3*
    - ➢ Target: Zebu Allele

Tad Sonstegard

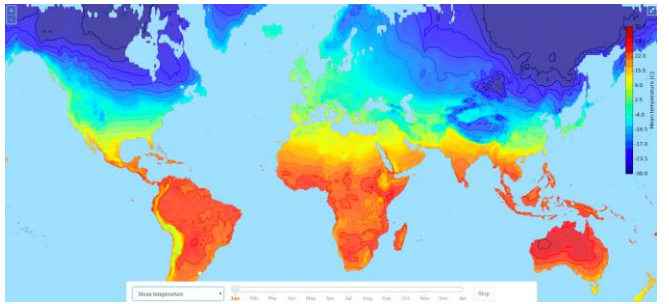
recombinetics™

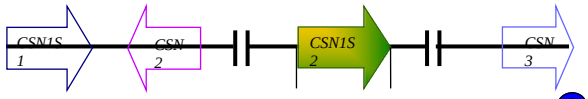


Nuovi obiettivi di selezione

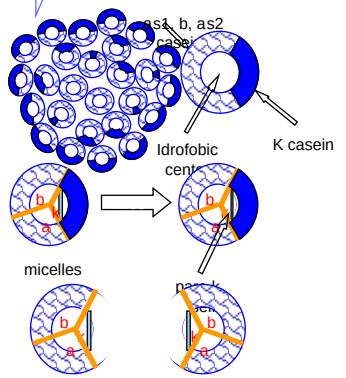
Obiettivi vecchi e nuovi

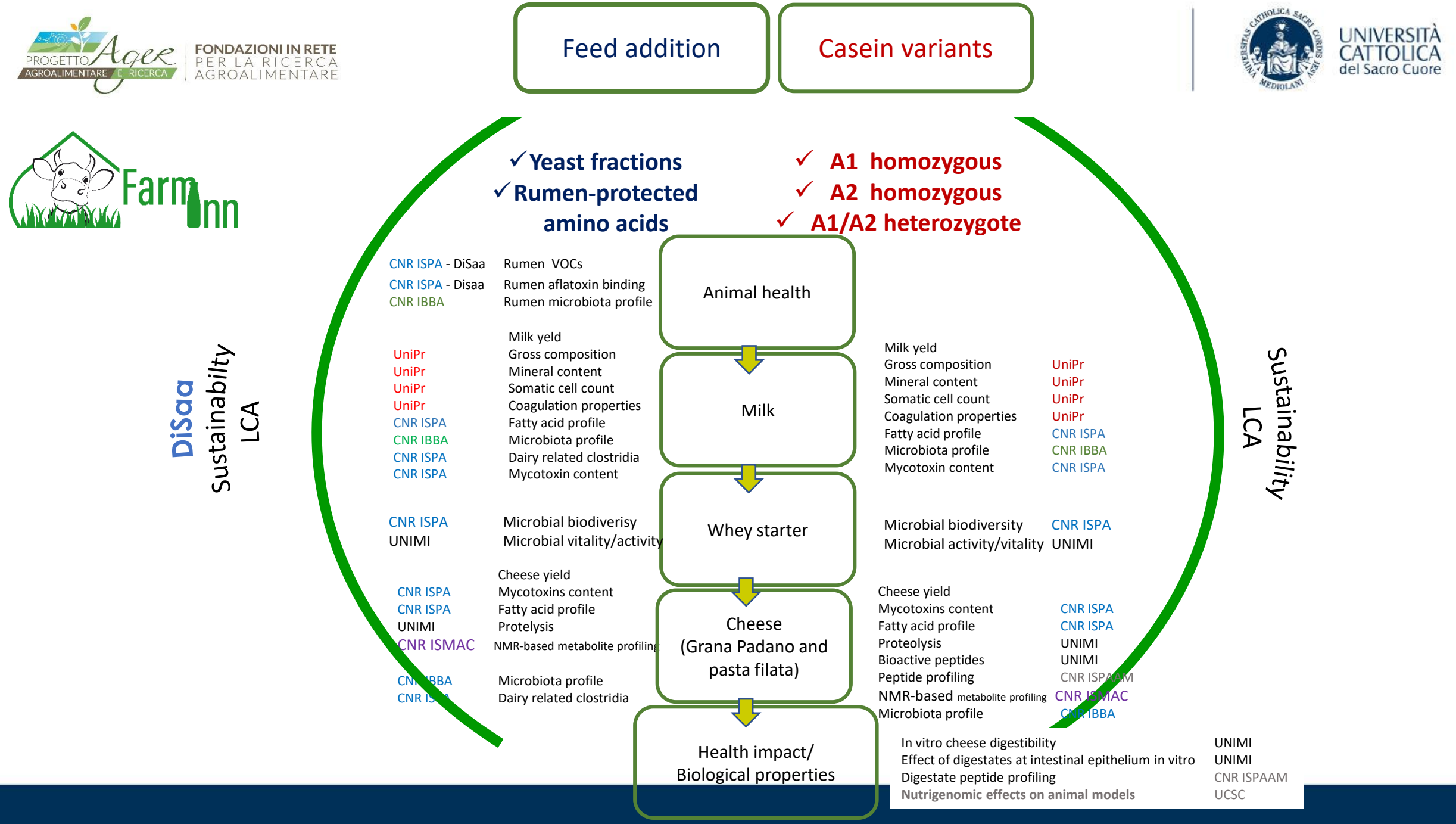
- Benessere animale
  - Adattamento
  - Stress
  - Salute
- Impatto ambientale
  - Antibiotici
  - Gas serra
  - Efficienza
- Qualità
  - Caseificazione

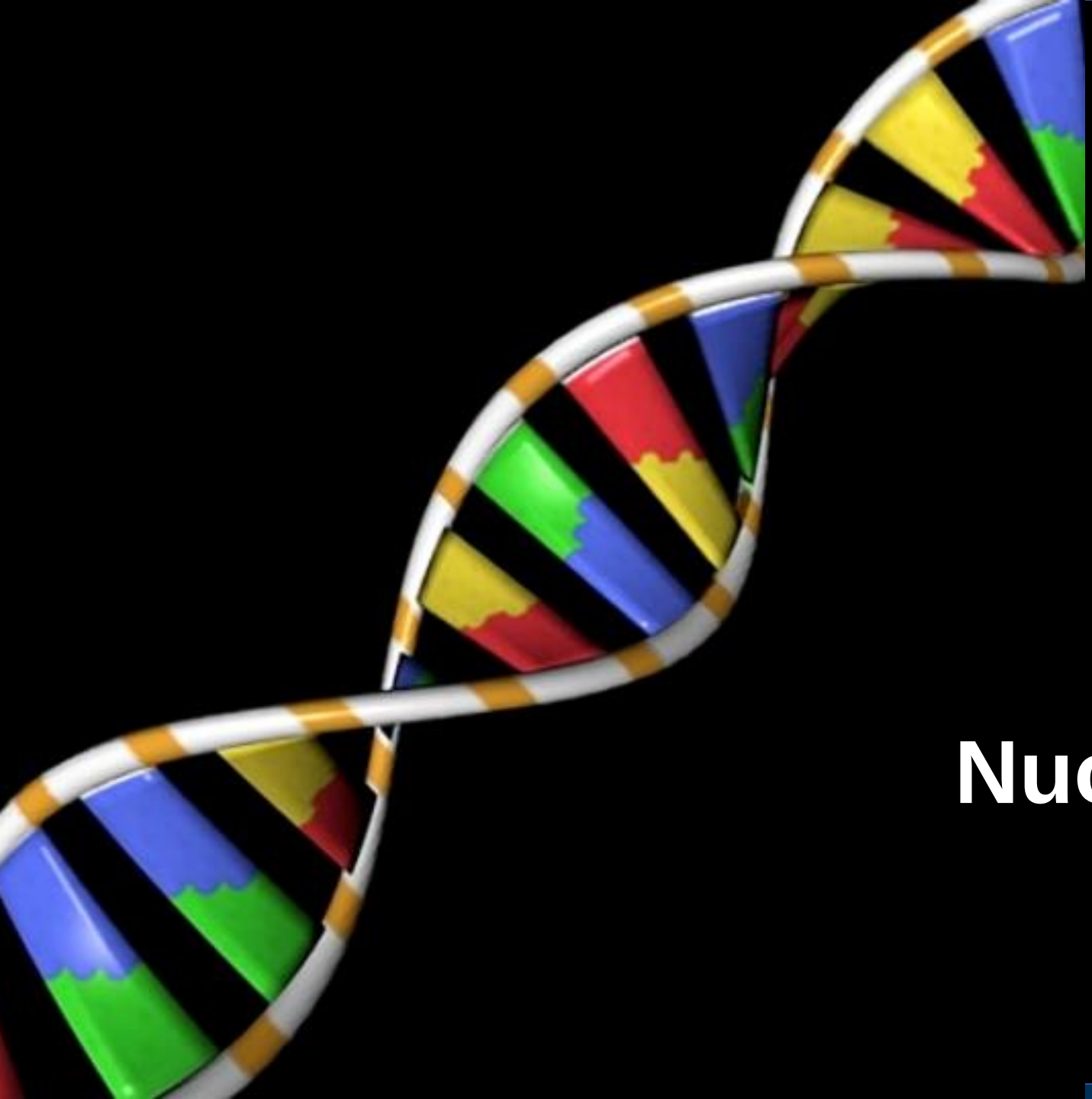




Chromosome 6




Feed addition
Casein variants
✓Yeast fractions
✓Rumen-protected amino acids
✓ A1 homozygous
✓ A2 homozygous
✓ A1/A2 heterozygote
CNR ISPA - DiSaa Rumen VOCs
CNR ISPA - Disaa Rumen aflatoxin binding
CNR IBBA Rumen microbiota profile
Animal health
Milk yeld
UniPr Gross composition
UniPr Mineral content
UniPr Somatic cell count
UniPr Coagulation properties
CNR ISPA Fatty acid profile
CNR IBBA Microbiota profile
CNR ISPA Dairy related clostridia
CNR ISPA Mycotoxin content
Milk
Milk yeld
Gross composition UniPr
Mineral content UniPr
Somatic cell count UniPr
Coagulation properties UniPr
Fatty acid profile CNR ISPA
Microbiota profile CNR IBBA
Mycotoxin content CNR ISPA
CNR ISPA Microbial biodiverisy
UNIMI Microbial vitality/activity
Whey starter
Microbial biodiversity CNR ISPA
Microbial activity/vitality UNIMI
Cheese yield
CNR ISPA Mycotoxins content
CNR ISPA Fatty acid profile
UNIMI Protelysis
CNR ISMAC NMR-based metabolite profiling
CNR IBBA Microbiota profile
CNR ISPA Dairy related clostridia
Cheese (Grana Padano and pasta filata)
Cheese yield
Mycotoxins content CNR ISPA
Fatty acid profile CNR ISPA
Proteolysis UNIMI
Bioactive peptides UNIMI
Peptide profiling CNR ISPAAM
NMR-based metabolite profiling CNR ISMAC
Microbiota profile CNR IBBA
Health impact/ Biological properties
In vitro cheese digestibility UNIMI
Effect of digestates at intestinal epithelium in vitro UNIMI
Digestate peptide profiling CNR ISPAAM
Nutrigenomic effects on animal models UCSC
DiSaa Sustainability LCA
Sustainability LCA



Nuovi fenotipi

Nuovi fenotipi

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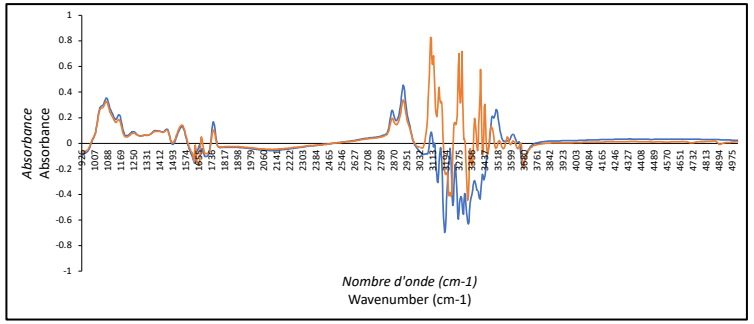
Livestock Environment Opendata

50 milioni di spettri



J. Dairy Sci. 102:11751–11765
https://doi.org/10.3168/jds.2019-16804
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Persistence of differences between dairy cows categ
as low or high methane emitters, as estimated from r
mid-infrared spectra and measured by GreenFeed

J. Dairy Sci. 100:2433–2453
https://doi.org/10.3168/jds.2016-12030
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Invited review: Large-scale indirect measurements for enteric methane emissions in dairy cattle: A review of proxies and their potential for use in management and breeding decisions

J. Dairy Sci. 98:5740–5747
http://dx.doi.org/10.3168/jds.2014-8436
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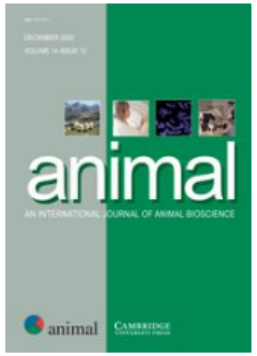
Hot topic: Innovative lactation-stage-dependent prediction of methane emissions from milk mid-infrared spectra



Potential use of milk mid-infrared spectra to predict individual methane emission of dairy cows

Published online by Cambridge University Press: **28 February 2012**

F. Dehareng, C. Delfosse, E. Froidmont, H. Soyeurt, C. Martin, N. Gengler, A. Vanlierde and P. Dardenne

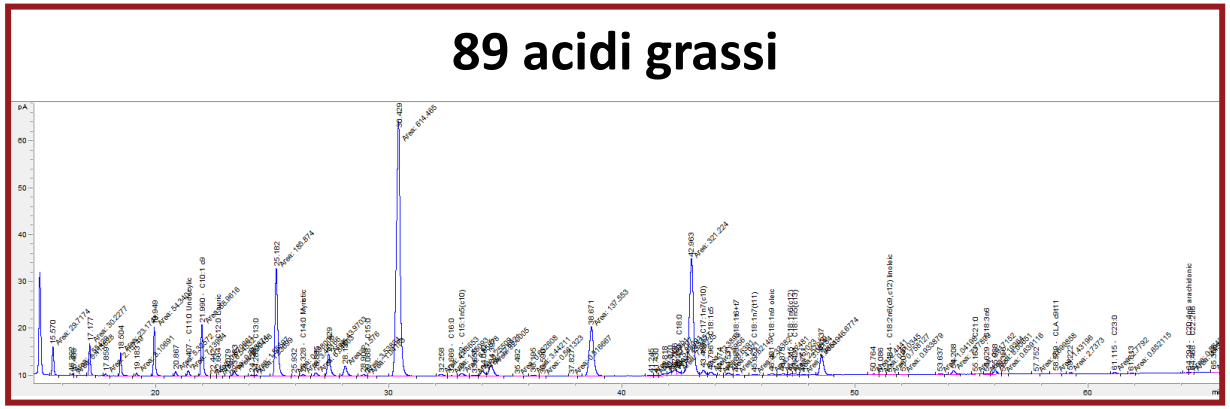
Show author details

Article Metrics

Fatty acids, Lactoferrin, Fat Globule Size
Methane emissions, Dry Matter Intake

Lo studio

89 acidi grassi



8 fattori latenti

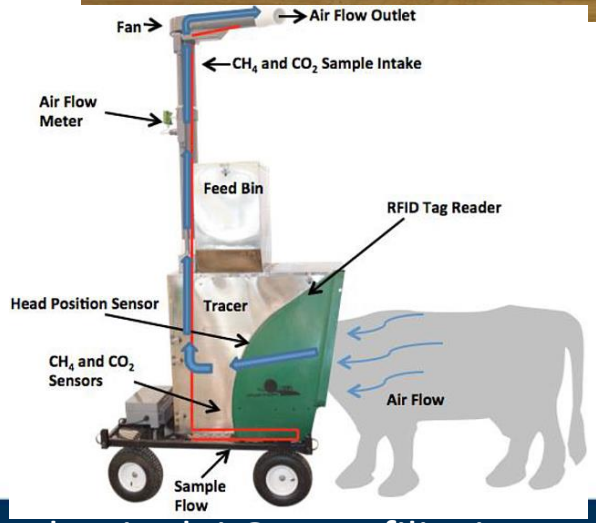
1. Sintesi *de novo*
2. Acidi grassi a catena ramificata
3. Acidi grassi polinsaturi a lunga catena
4. Bioidrogenazione ruminale alternativa
5. Produzione
6. Acidi grassi a corta catena
7. Acidi grassi a catena dispari
8. Bioidrogenazione ruminale

Associazione con:

1. BCS
2. Misure ecografiche epatiche
3. Contenuto pTAG epatico
4. Parametri ematici di:
   a. Energia
   b. Infiammazione
   c. Funzionalità/danno epatico
   d. Stress ossidativo
   e. Minerali

Nuovi fenotipi

Sensori
Podometri
Ruminometri
Telecamere



PRIMA SCALA-MEDI

Funded by European Union

Nuovi fenotipi

PRIMA PARTNERSHIP FOR RESEARCH AND INNOVATION IN THE MEDITERRANEAN AREA

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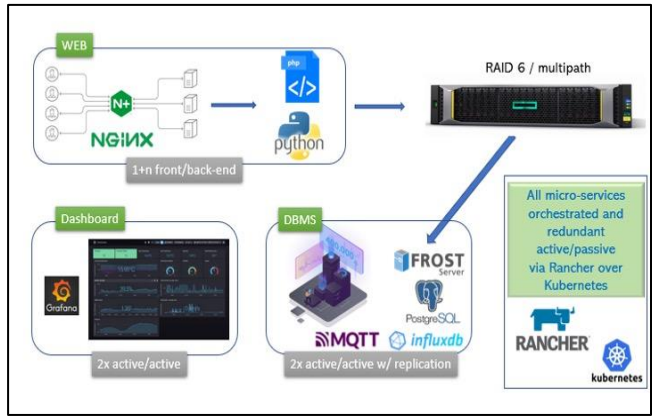
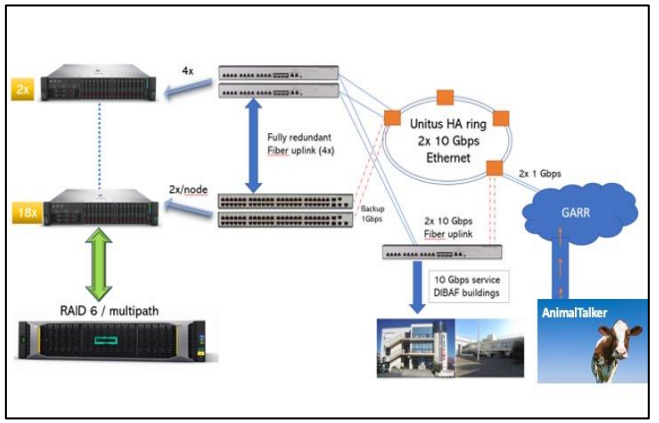
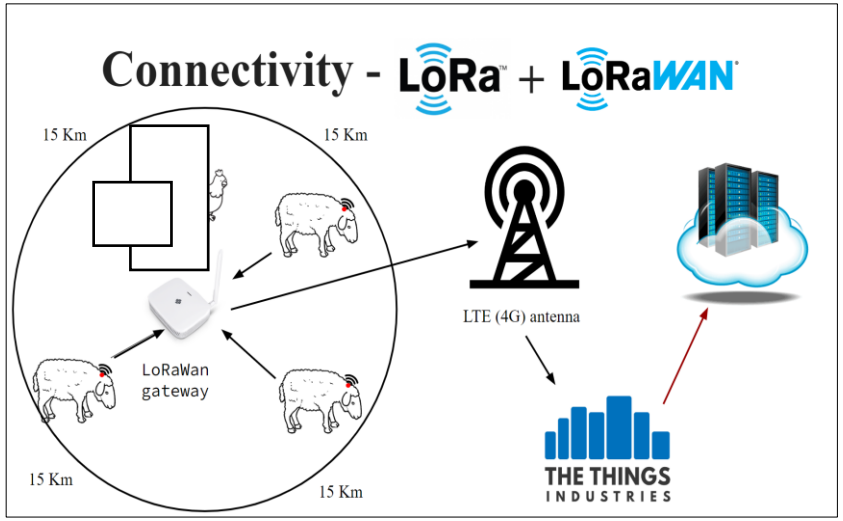
Software



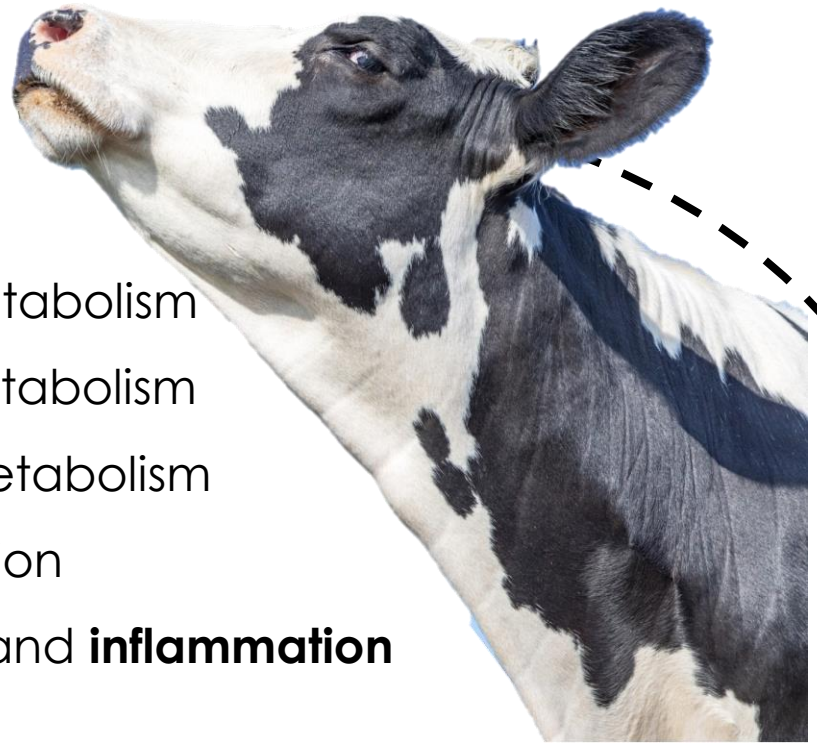
Hardware





Endophenotypes

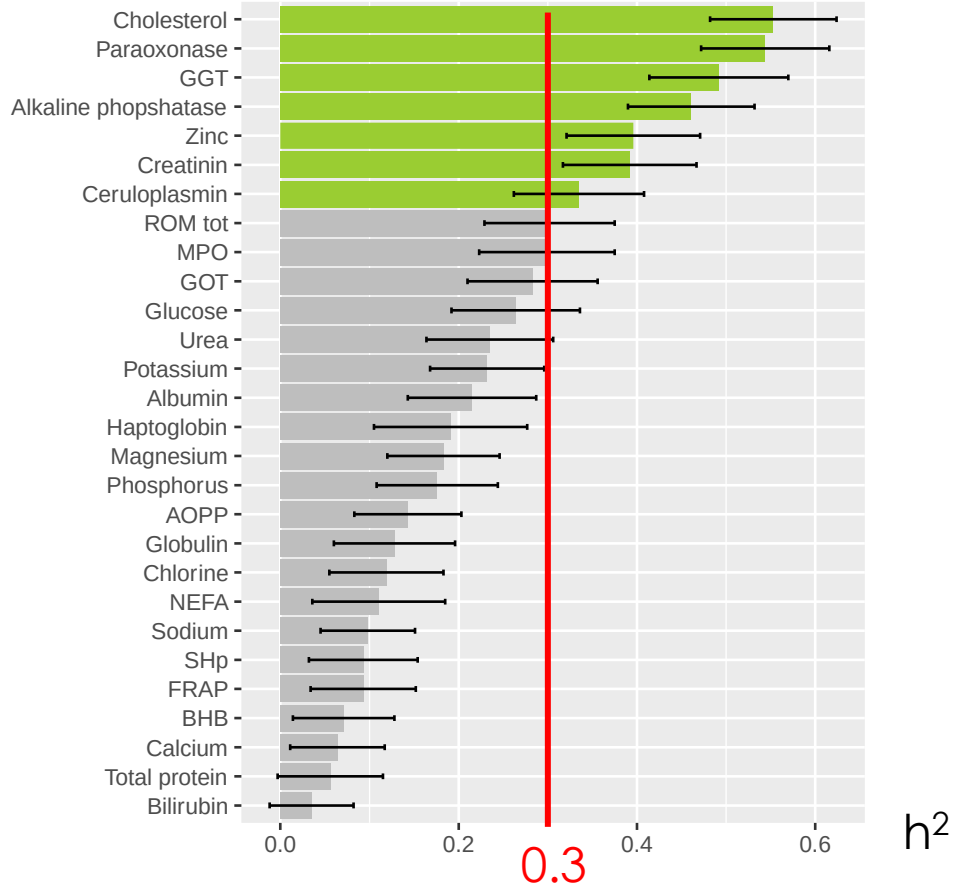
Blood	Milk	Hair
Albumin	BHB	Cortisol
Total bilirubin	Cortisol	
Total protein	Urea	
Globulin		
Paraoxonase		
AST/GOT		
GGT		
Cholesterol		
Glucose		
NEFA		
BHB		
Ceruloplasmin		
Haptoglobin		
Calcium		
Zinc		
Creatinine		
Urea		



- **Energy** metabolism
- **Protein** metabolism
- **Mineral** metabolism
- **Liver** function
- **Immunity** and **inflammation**

Matilde Passamonti

SNP-based heritability (h^2)



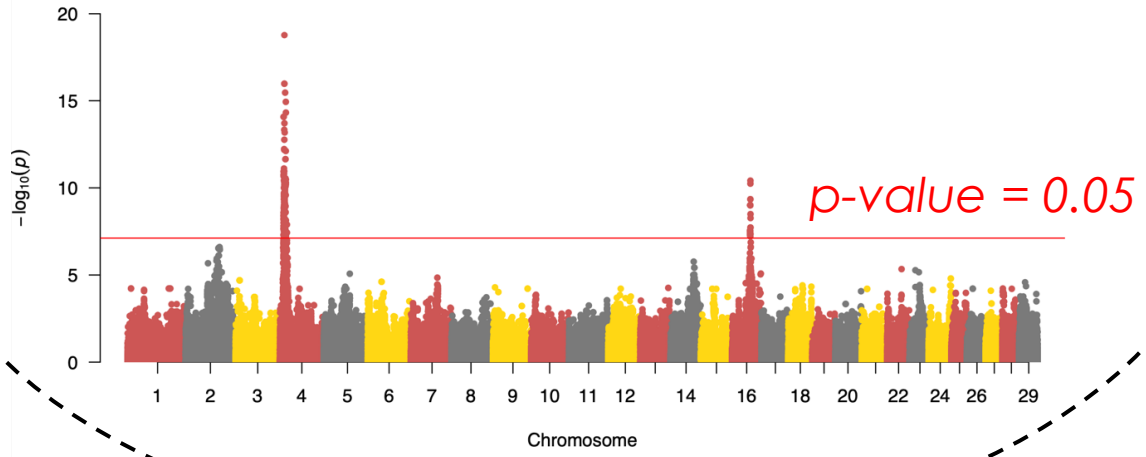
h^2 > 0.3 (medium to high)

h^2 < 0.3

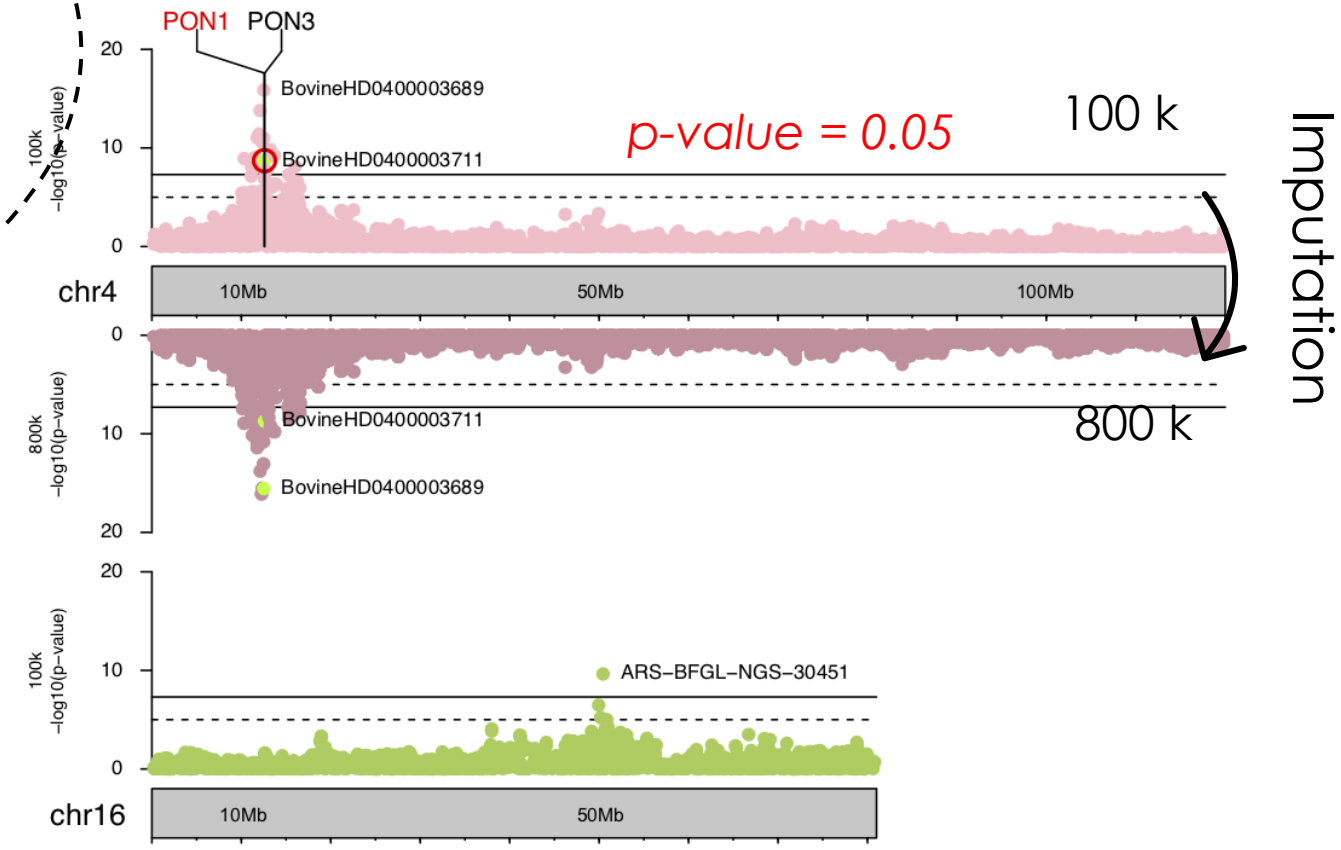
Standard error

Paraoxonase

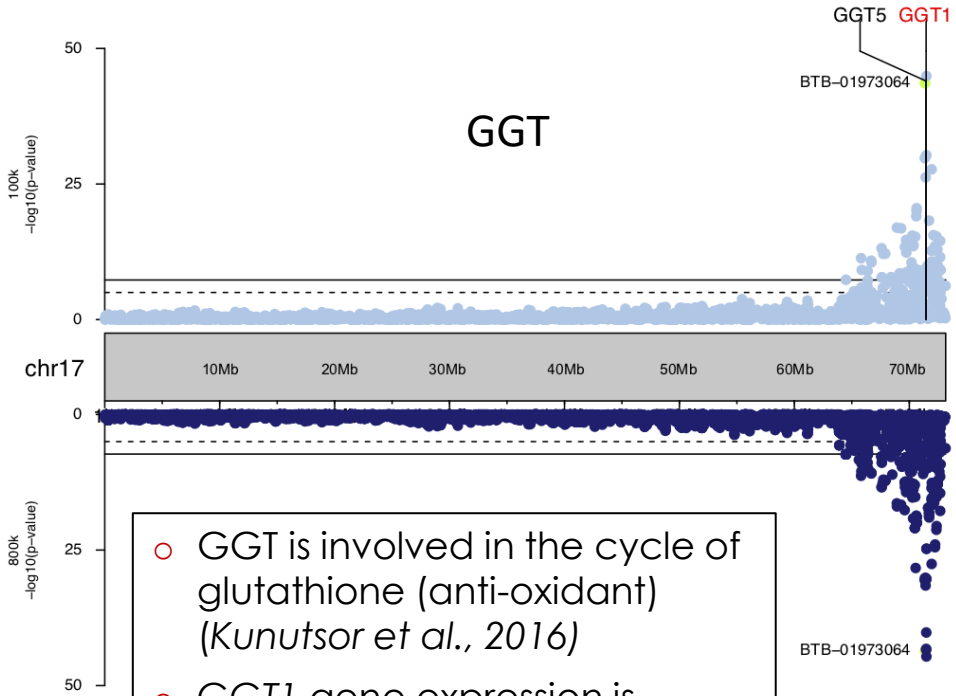
Haplotype-based:



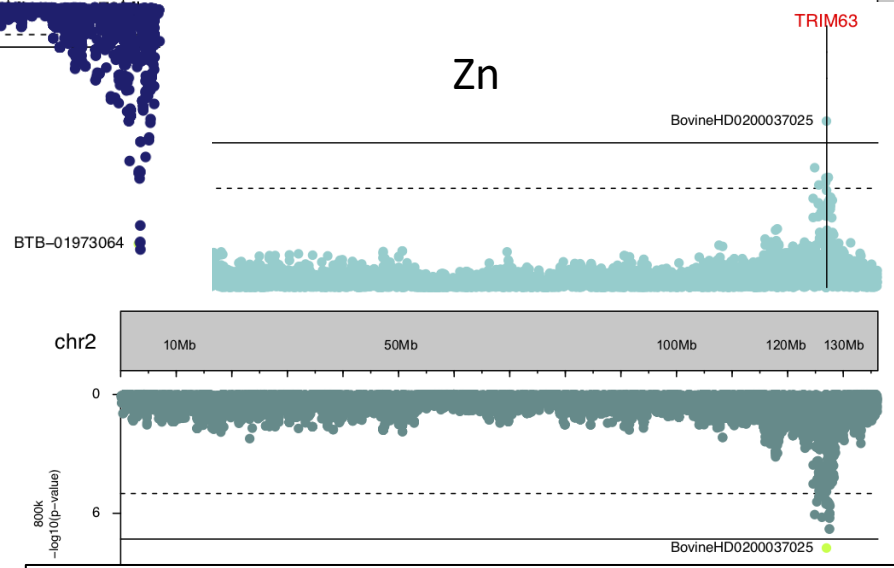
Passamonti et al., Journal of Dairy Science 2024, in press



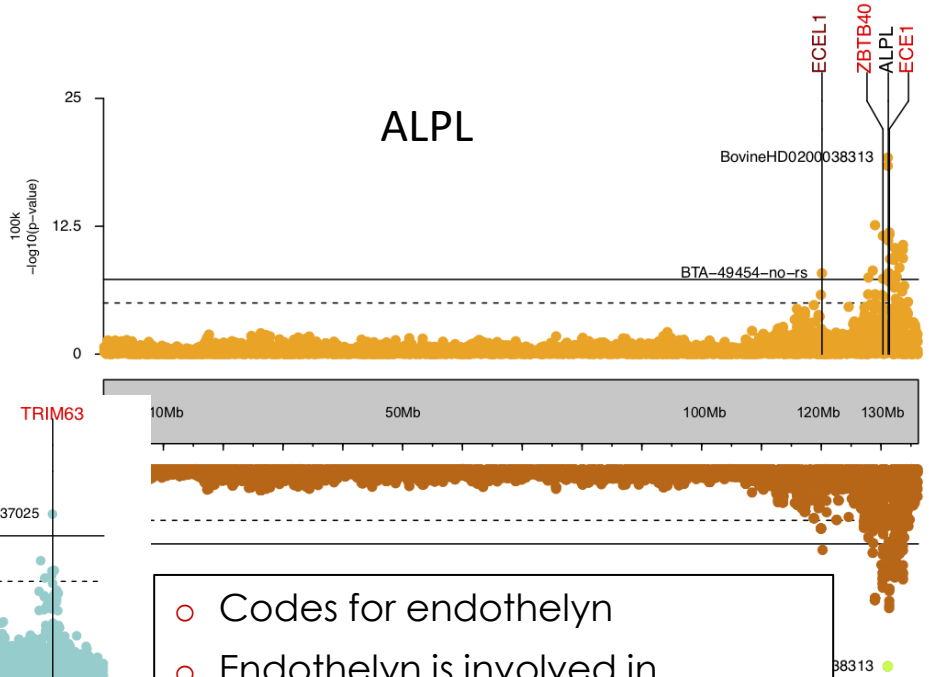
- Paraoxonase protects HDL from oxidation *(Aviram et al., 2000)*
- Low levels of paraoxonase associated with **higher inflammation** in dairy cows *(Bionaz et al., 2007)*
- In mice, **SNPs in *PON1* gene** were associated with **different susceptibility** to **oxidative stress** *(Deakin and James, 2004)*



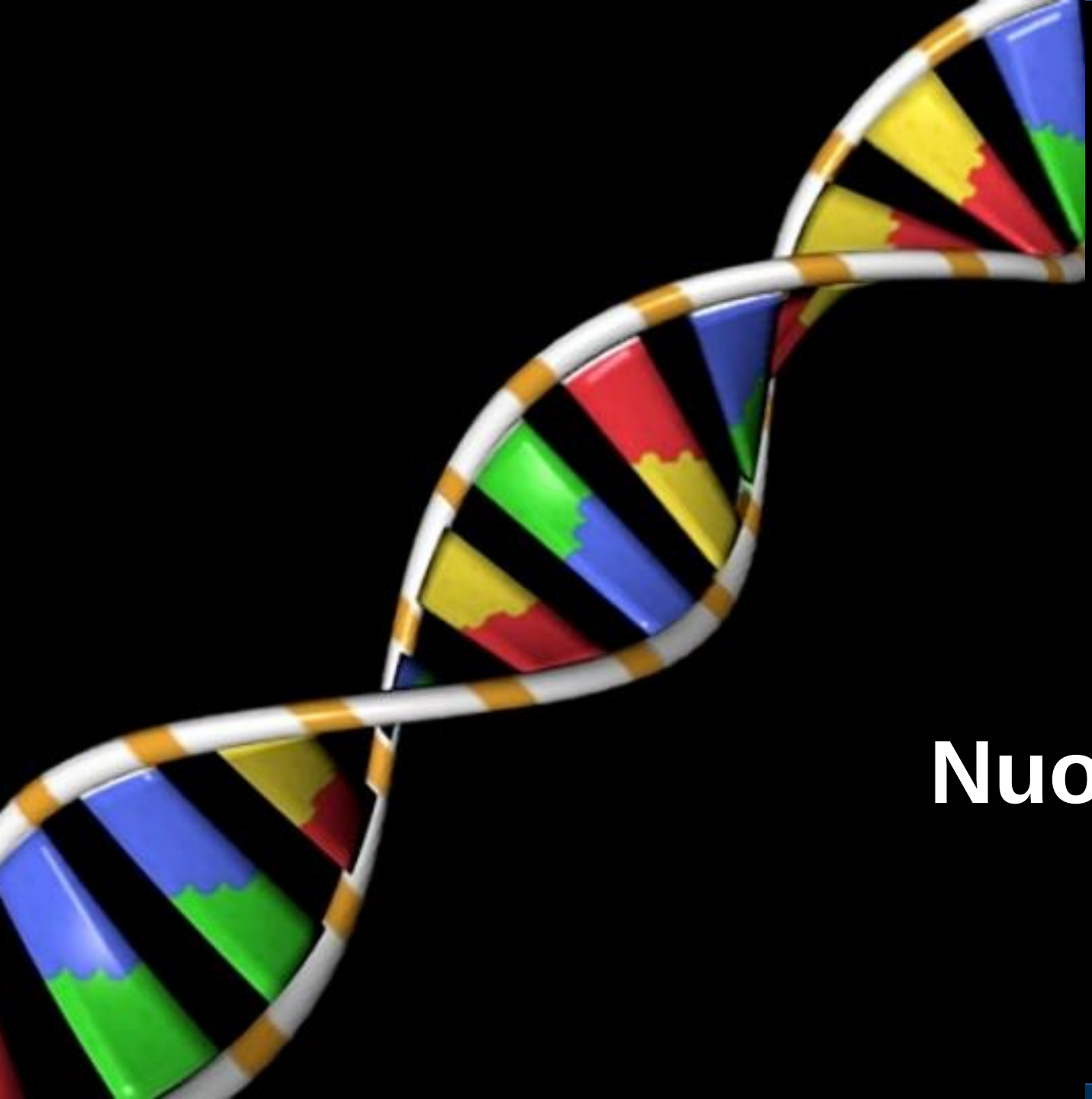
- GGT is involved in the cycle of glutathione (anti-oxidant) *(Kunutsor et al., 2016)*
- *GGT1* gene expression is increased by oxidative stress (adaptive response?) *(Zhang et al., 2005)*



- Codes for a zinc finger protein (MuRF-1)
- MuRF-1 is involved in the breackdown of skeletal muscle proteins, then degradated into peptides and supplied to other tissues (adaptation to negative protein balance condition in dairy cows?) (Kuhla et al., 2011)



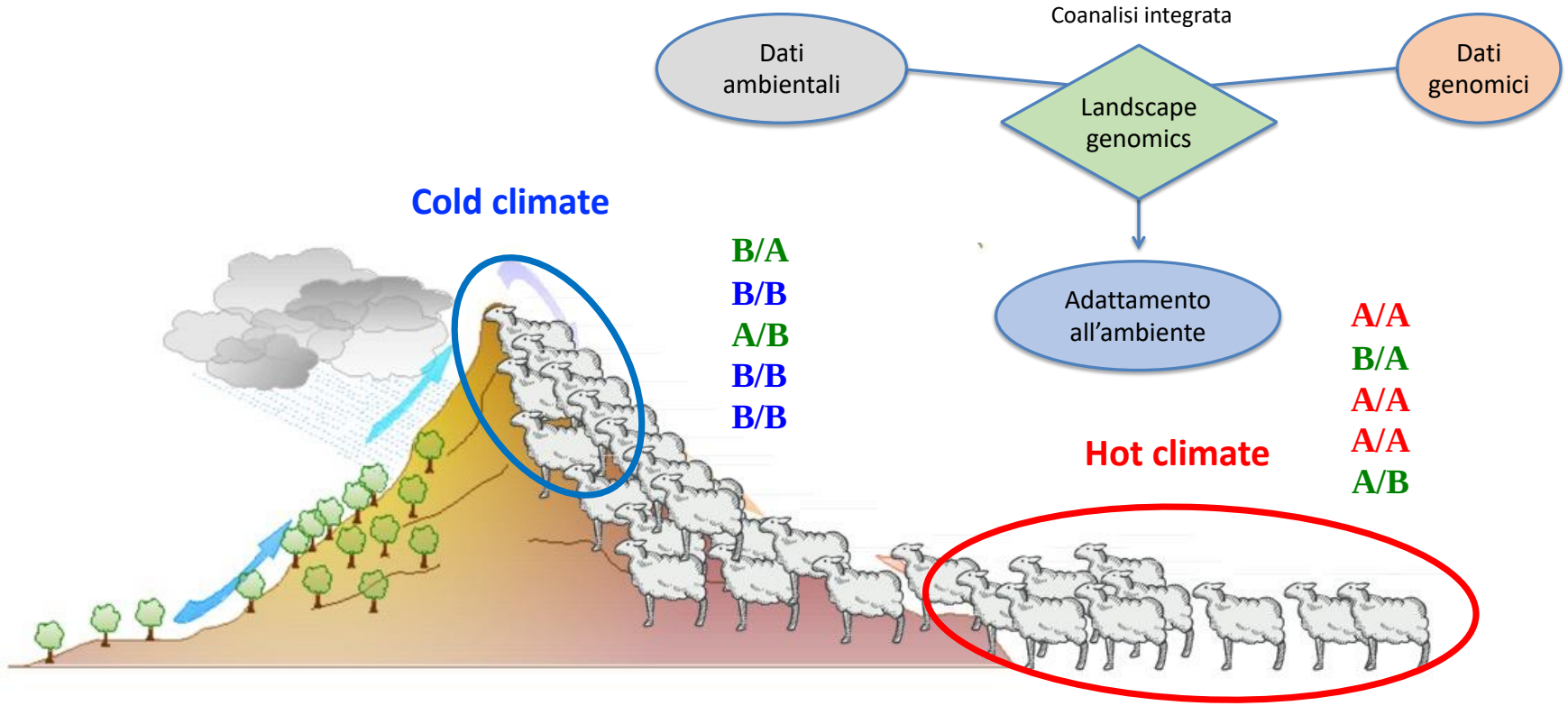
- Codes for endothelyn
- Endothelyn is involved in proliferation of hepatic stellate cells
- Increased ECE1 expression associated with liver injury *(Cho et al., 2019)*
- *ECE1* gene associate with blood ALP concentration in humans (Monti et al., 2022)



Nuovi approcci

Landscape genomics

Comprendere i **meccanismi molecolari** che sottendono **l'adattamento degli animali domestici alle variazioni ambientali** è un fattore chiave per lo sviluppo di un'agricoltura **"climate-smart"**.



La **"Landscape genomics"** cerca di spiegare il pattern spaziale di distribuzione della variabilità genetica in relazione all'**adattamento locale** all'ambiente (Joost et al., 2003).

Landscape genomics

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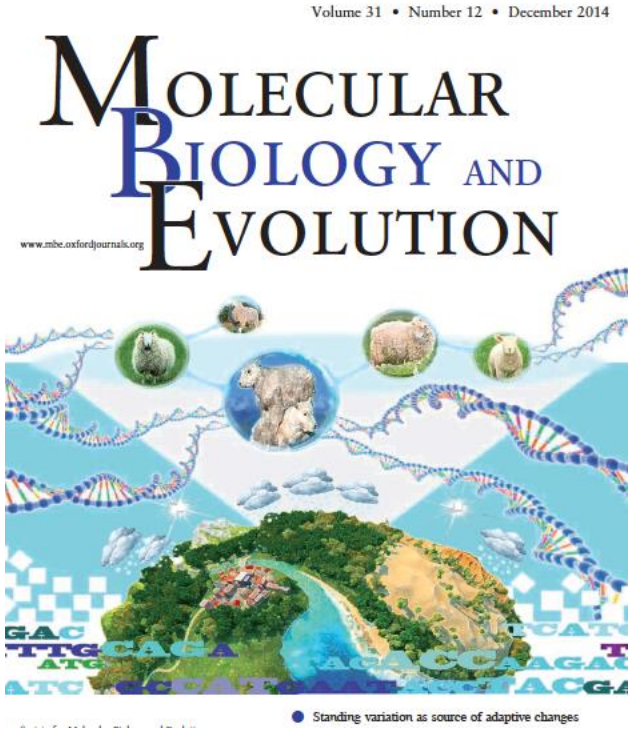
Adaptations to Climate-Mediated Selective Pressures in Sheep

Feng-Hua Lv,[1] Saif Agha,[2,3] Juha Kantanen,[4,5] Licia Colli,[6,7] Sylvie Stucki,[2] James W. Kijas,[8] Stéphane Joost,[2] Meng-Hua Li,*[,1] and Paolo Ajmone Marsan[6,7]



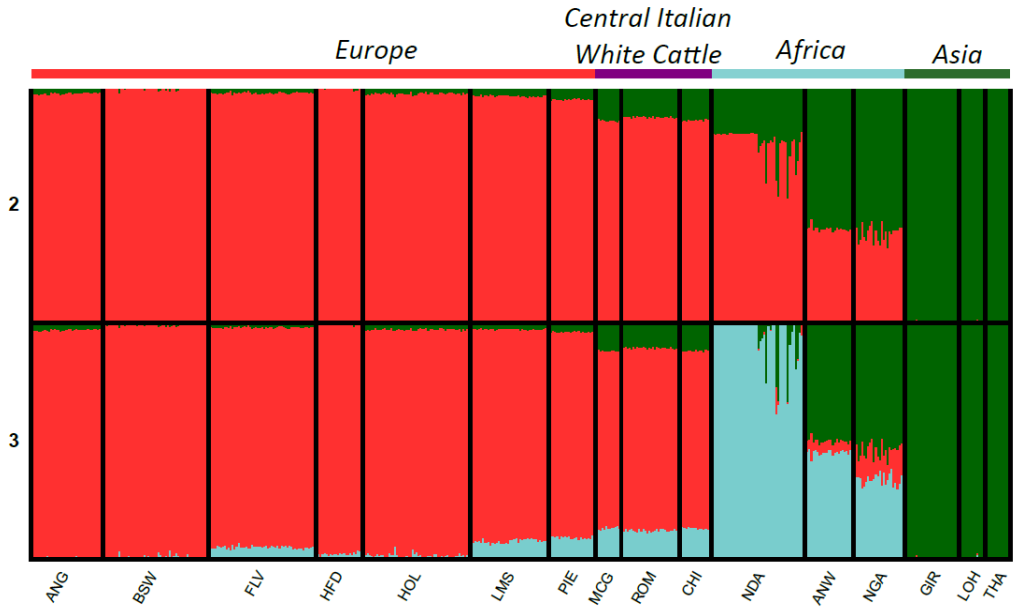
8 genes involved in endocrine and autoimmune regulation.

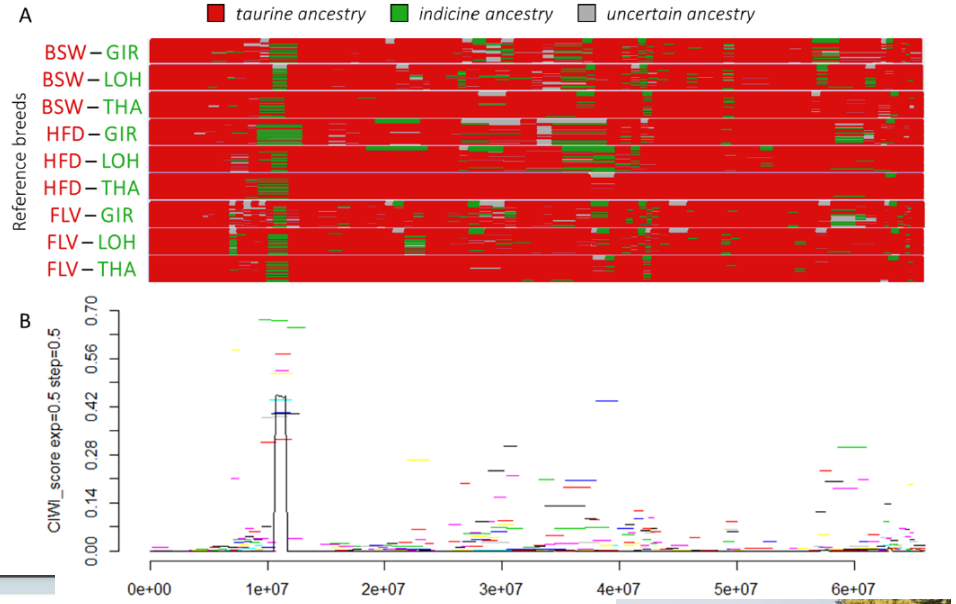
9 genes involved in the biological processes of energy metabolism.

Chr.	Gene	Position (bp)	Gene Size (kb)	SNP	F_{ST}[a]	|z| Score[b]	Max Wald[c]
1	*EVI5*	68957918–69191464	233.50	OAR1_73673800[d]	0.55**	5.35	15.81
2	*FBXO8*	105386295–105423924	37.63	OAR2_113355547	0.37*	9.74	17.59
2	*CHN1*	134023000–134022999	70.92	OAR2_142314137	0.29**	5.42	14.37
				OAR2_143195752	0.46**	5.48	15.62
2	*ACVR2A*	160457581–160549550	91.97	OAR2_170004218	0.35**	6.99	15.06
2	*NMUR1*	232366028–232483197	117.20	s74305	0.51**	11.20	16.41
				OAR2_245260141	0.32*	8.71	17.33
				OAR2_245638268	0.39*	8.35	14.93
				OAR2_245680195	0.42*	10.37	14.57
5	*IL12RB1*	4854306–4869950	15.64	s33778[d]	0.35**	5.40	15.87
5	*ARHGEF18*	13935201–14021434	86.23	s48780[d]	0.38**	8.02	14.88
10	*ALOXSAP*	30365435–30388526	23.09	s18834	0.84**	8.79	17.66
				s68983	0.67**	8.61	18.85
				s12004	0.54**	7.06	14.67
				OAR10_30746533	0.70**	7.24	17.37
10	*EDNRB*	53508345–53534498	26.15	OAR10_53694894	0.23*	6.83	19.21
				OAR10_54710595	0.33**	5.46	17.06
15	*THY1*	29450455–29452173	1.72	s13895	0.36*	6.74	16.08
				s02747	0.38*	6.38	15.70
15	*ARAP1*	50442784–50529042	86.26	OAR15_55184101[d]	0.63**	7.54	15.70
19	*XCR1*	53235736–53236748	1.01	s18532	0.61**	8.60	18.16
				OAR19_56419475	0.27*	5.25	16.21
19	*CXCR6*	53290059–53291081	1.02	s18532	0.61**	8.60	18.16
				OAR19_56419475	0.27*	5.25	16.21
19	*CCR9*	53333188–53340782	7.60	s18532	0.61**	8.60	18.16
				OAR19_56419475	0.27*	5.25	16.21
20	*PRL*	34258080–34266415	8.34	OAR20_37437726	0.57**	9.54	19.18
				s39515	0.62**	9.90	19.15
22	*PLCE1*	15009437–15337740	328.30	OAR22_18841208_X[d]	0.46**	8.24	14.55
				OAR22_18876523	0.53**	7.75	16.38
				OAR22_18929579	0.47**	5.90	15.00
				OAR22_19052408	0.44**	5.89	16.91
22	*TBC1D12*	15398171–15490853	92.68	OAR22_18841208_X	0.46**	8.24	14.55
				OAR22_18876523	0.53**	7.75	16.38
				OAR22_18929579[d]	0.47**	5.90	15.00
				OAR22_19052408	0.44**	5.89	16.91

[a]Based on the F_{ST}-based selection test between the 2 groups of 11 populations (see Materials and Methods).
[b]Based on the LFMM test (Frichot et al. 2013).
[c]Based on the spatial analysis method (Joost et al. 2007).
[d]SNPs within genes.
Significant at the level of *$P < 0.05$ and **$P < 0.01$.

Adaptive introgression





Mario Barbato
(UNICATT)

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SCIENTIFIC REPORTS
nature research

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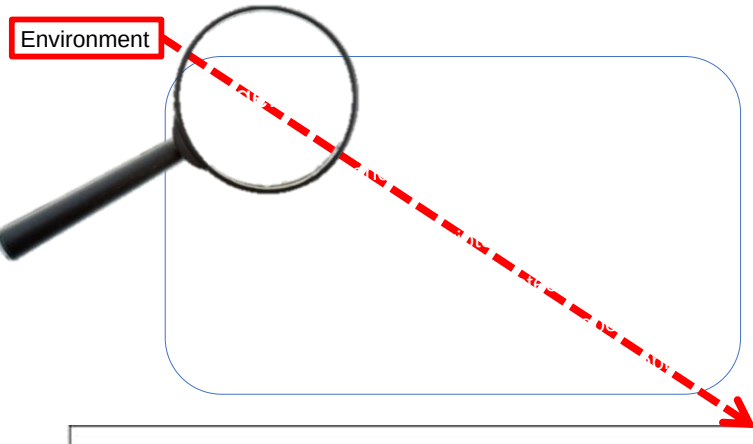
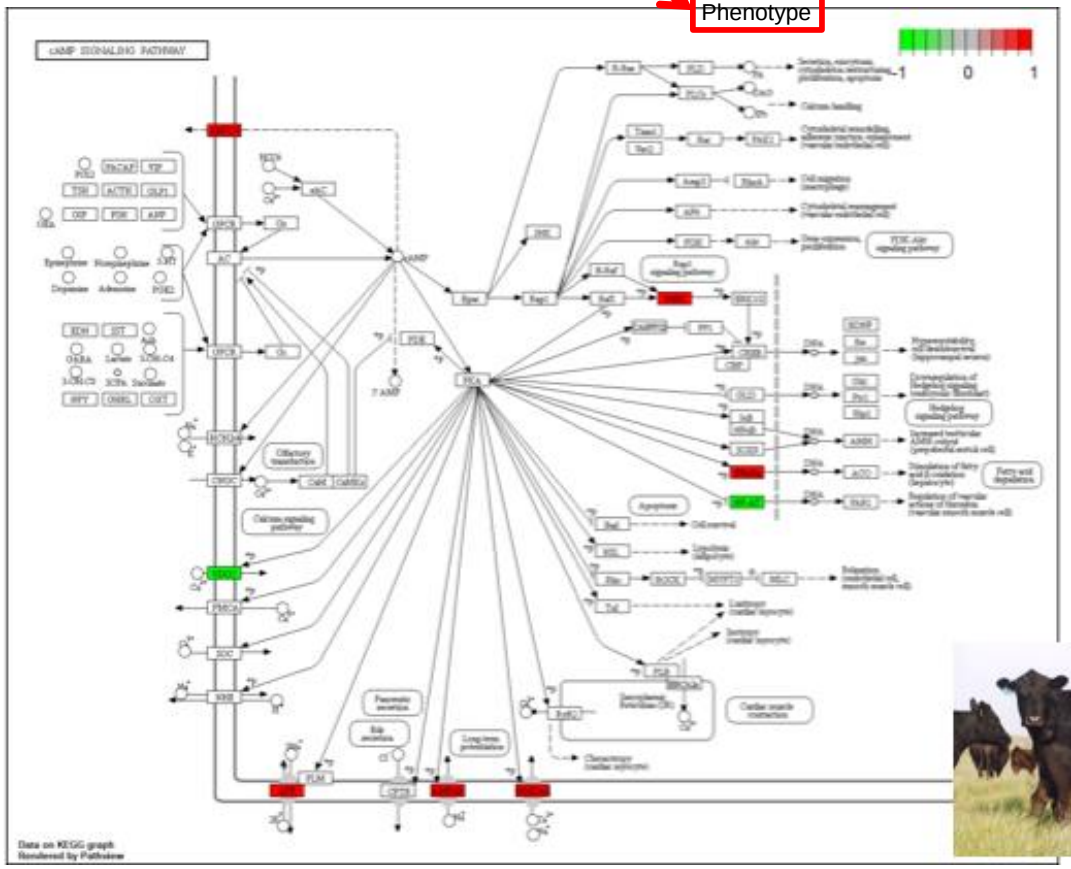
Adaptive introgression from indicine cattle into white cattle breeds from Central Italy

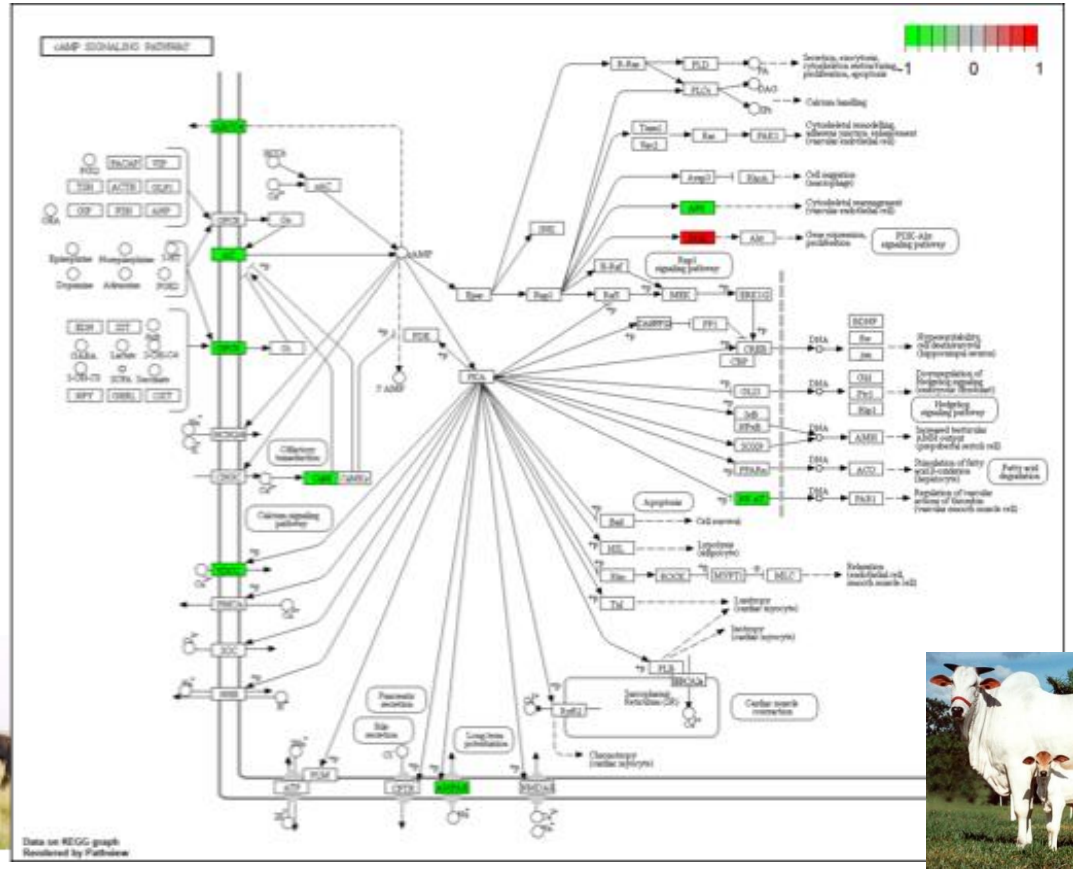
Mario Barbato[1*], Frank Hailer[2], Maulik Upadhyay[3,4], Marcello Del Corvo[1], Licia Colli[1], Riccardo Negrini[1], Eui-Soo Kim[5], Richard P. M. A. Crooijmans[3], Tad Sonstegard[5] & Paolo Ajmone-Marsan[1*]

Four candidate genes
KLHL36 → unknown function
USP10 → gluconeogenesis
***KIAA0513* e *FAM92B* → residual feed intake**

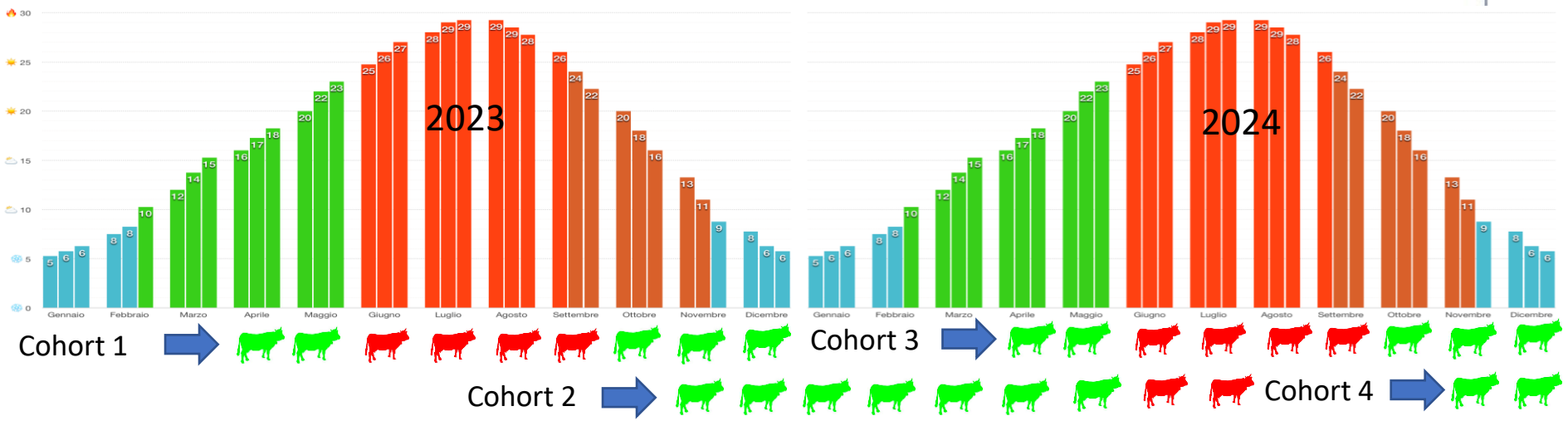


cAMP signalling pathway



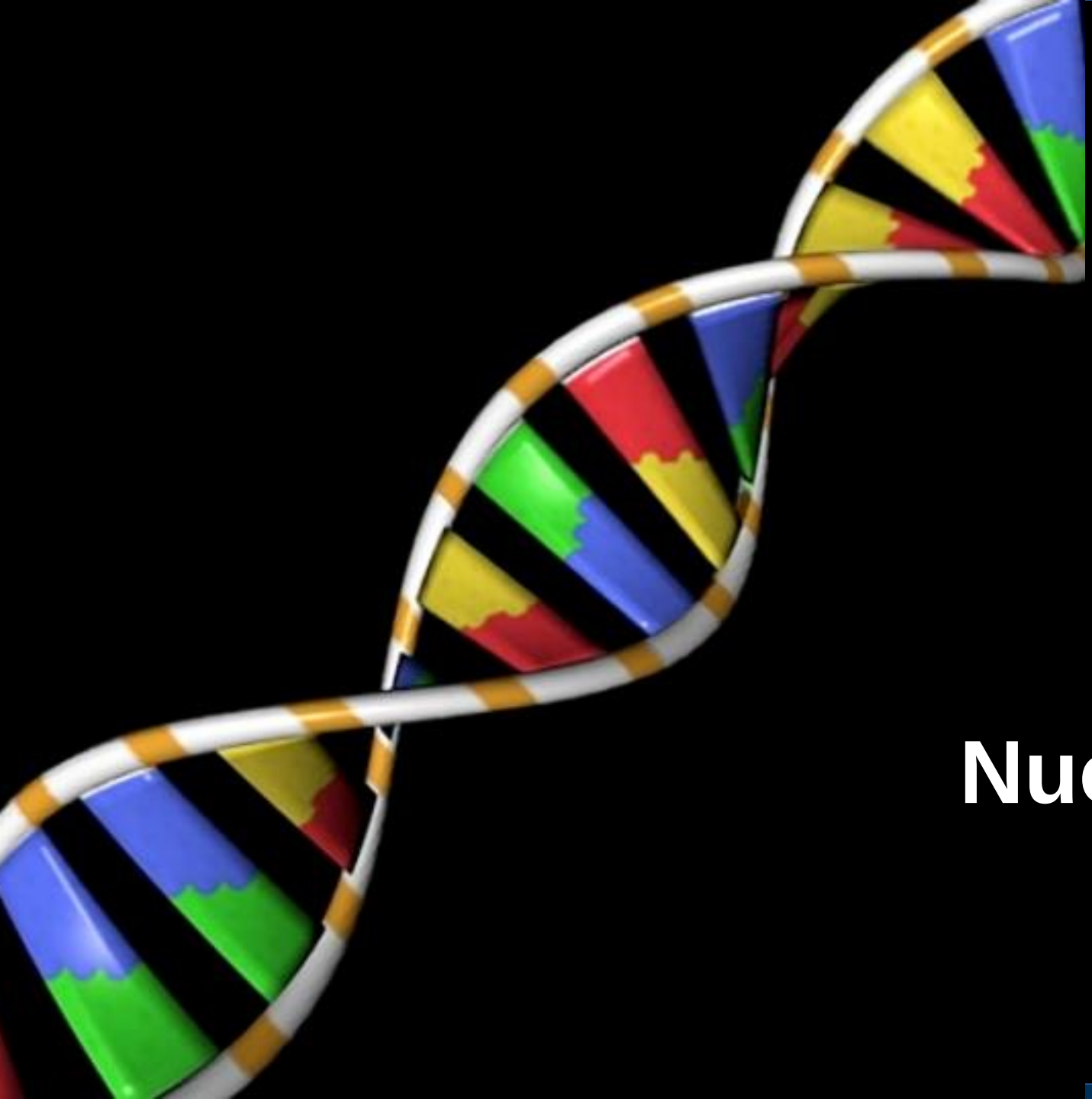


System biology



- Primiparous and secondiparous cows
- Similar stage of lactation (30-60 DIM) at experiment start
- Same diet
- All data from sensors, greenfeed etc. collected as frequently as possible
- In stable environmental data collected every hour
- Blood, milk, rumen and feces samples collected every other weak and if possile at peak temperature (19 sampling times per cohort).

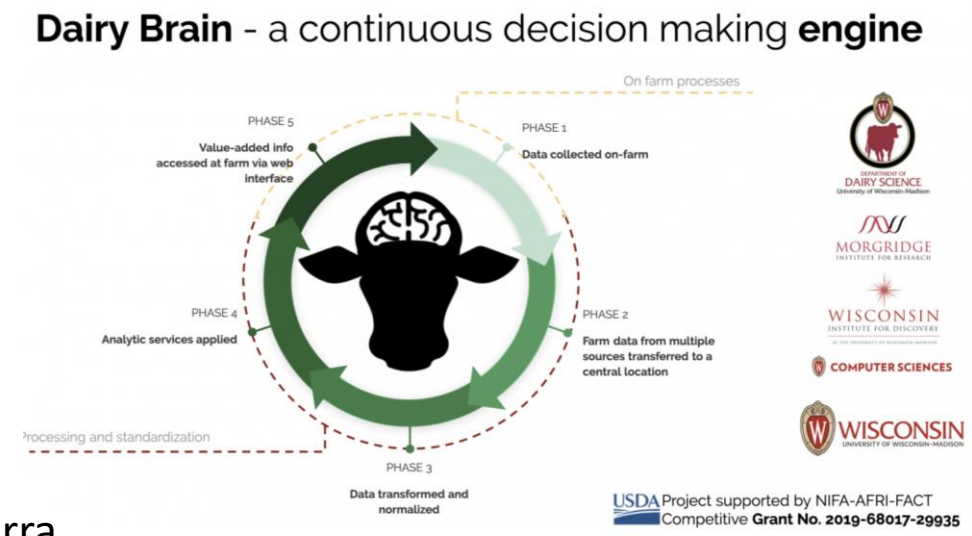
CREI
Centro di ricerca
Romeo ed Enrica Invernizzi
per le produzioni lattiero-casearie sostenibili



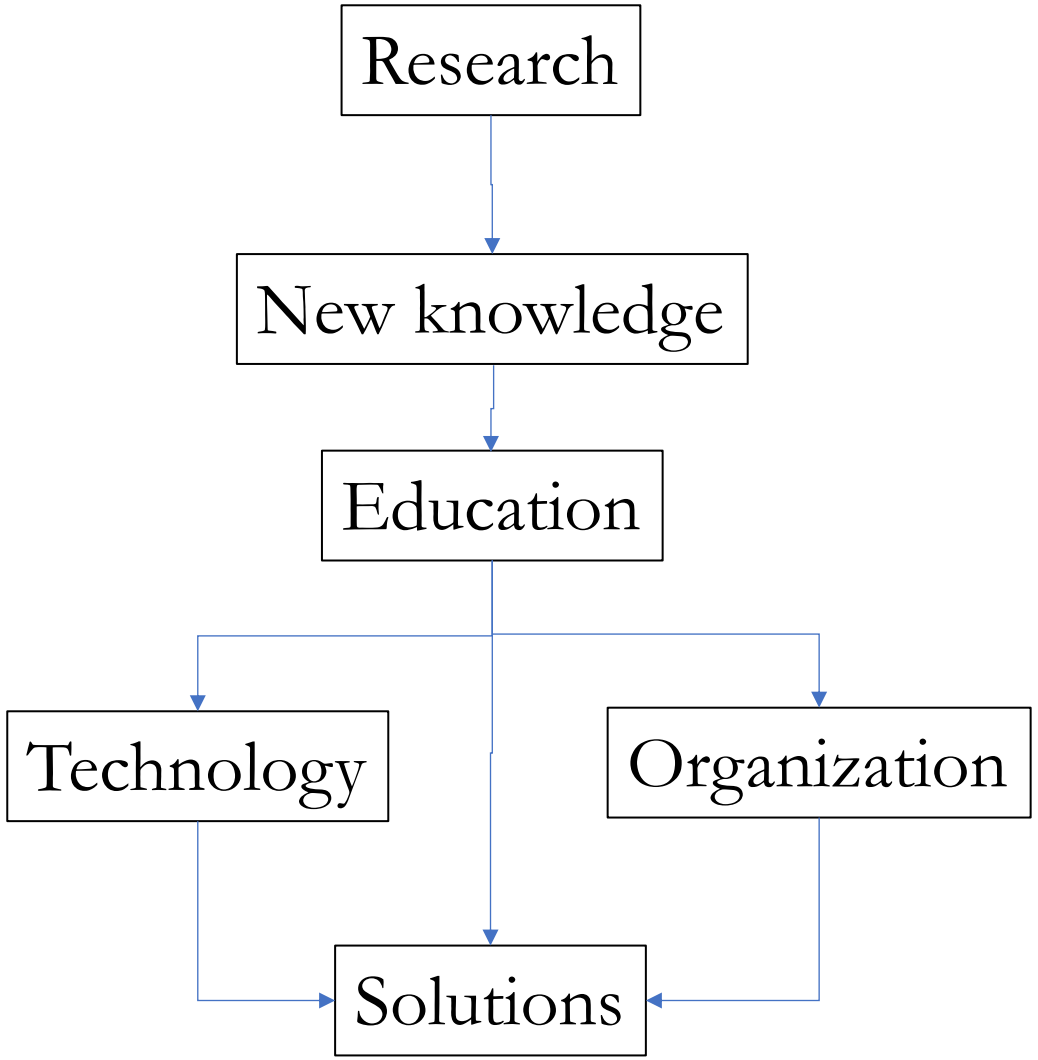
Nuovi modelli

Nuovi modelli

- Dieta personalizzata
- Monitoraggio del benessere
- Prevenzione malattie
- Riduzione sprechi
- Riduzione produzione di gas serra
- Management delle deiezioni



Le via da percorrere



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Grazie per l'attenzione