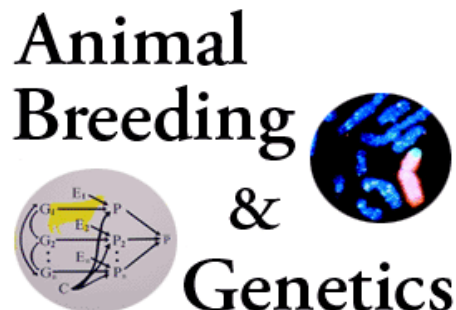


# Applied Animal Breeding in the Genomics Era

Jack Dekkers

Animal Breeding & Genetics  
Department of Animal Science  
Iowa State University

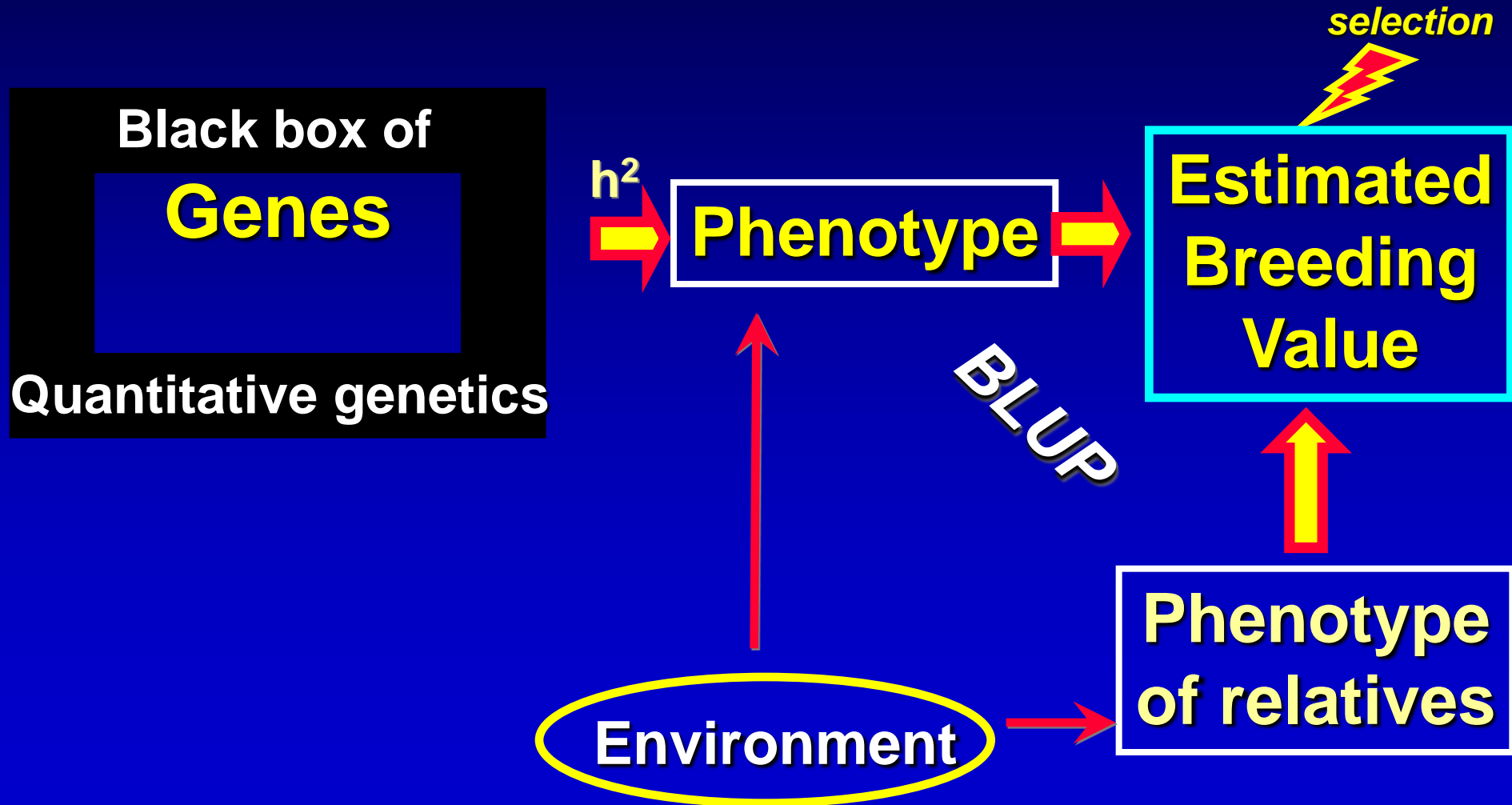
IOWA STATE  
UNIVERSITY



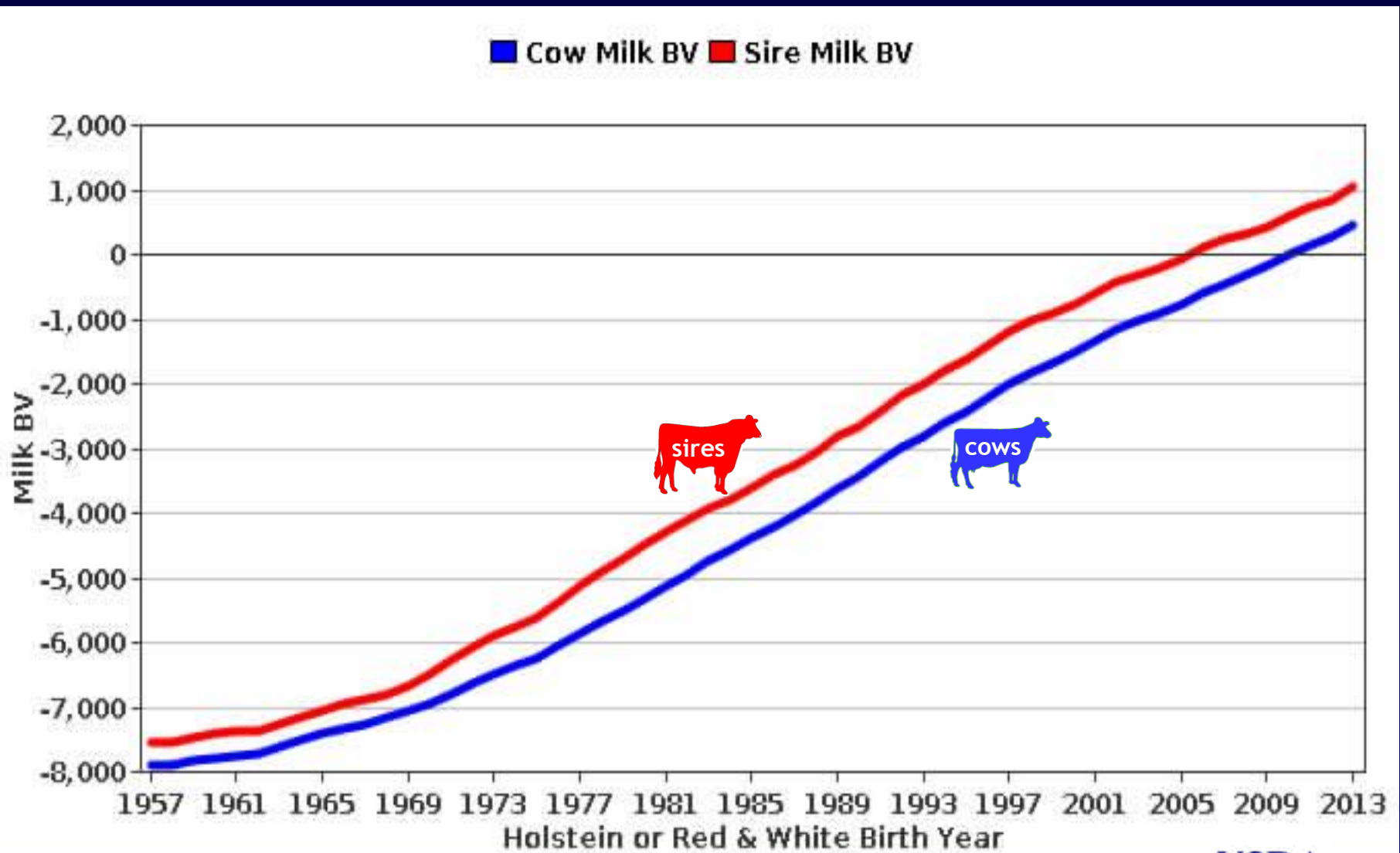
ANIMAL  
SCIENCE

# Phenotype-based BLUP

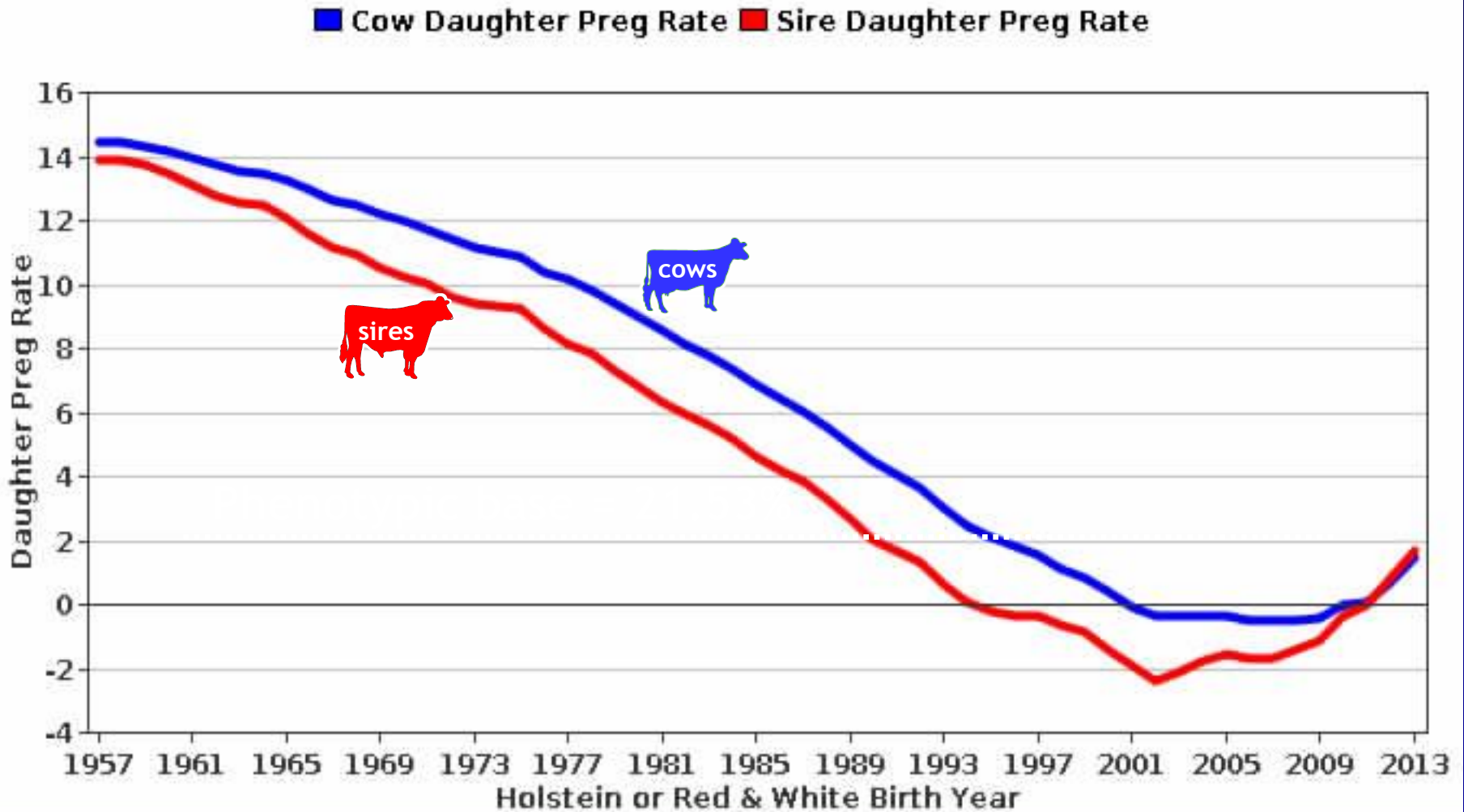
## Selection for Quantitative Traits



# This approach has been very successful for many traits



..... less for others .....





# and has important limitations

E.g. Need to select Bulls by Progeny Test



X  
Embryo  
Transfer



5 years and



\$\$\$\$ later

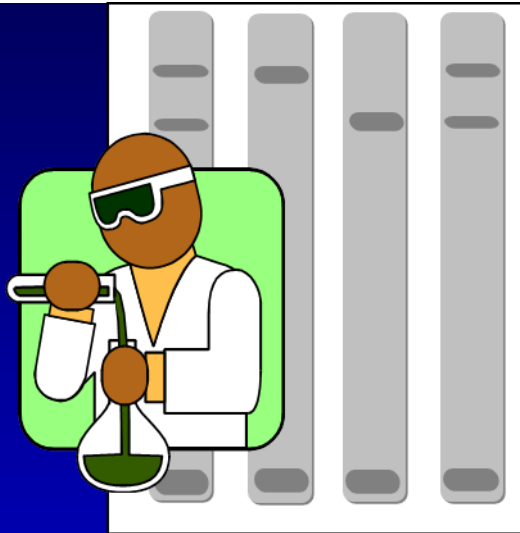
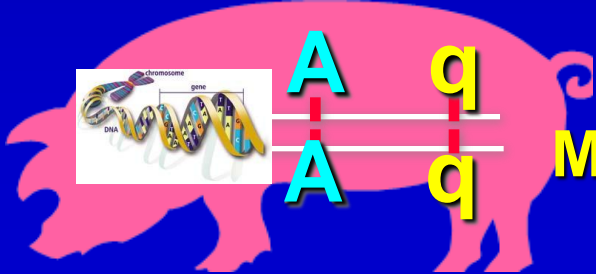
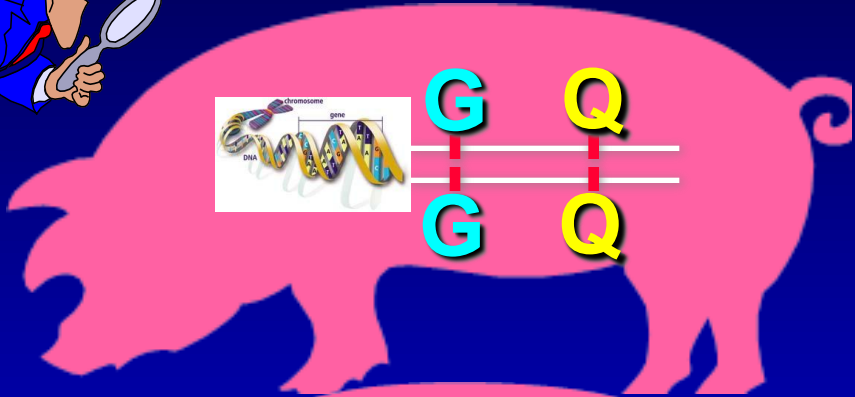
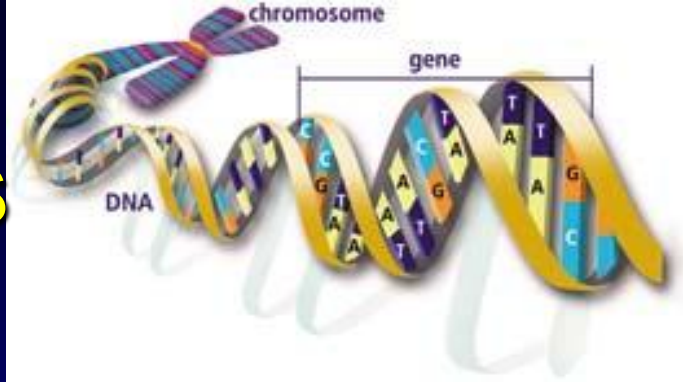


Superior progeny  
tested bull

Progeny-test  
evaluation



# '70 – '00: Promise of Molecular Genetics



Find major genes  
or  
markers linked to QTL

and use these for  
**Marker-Assisted Selection**

# Marker-Assisted Selection

**Genes**

Molec. genetics

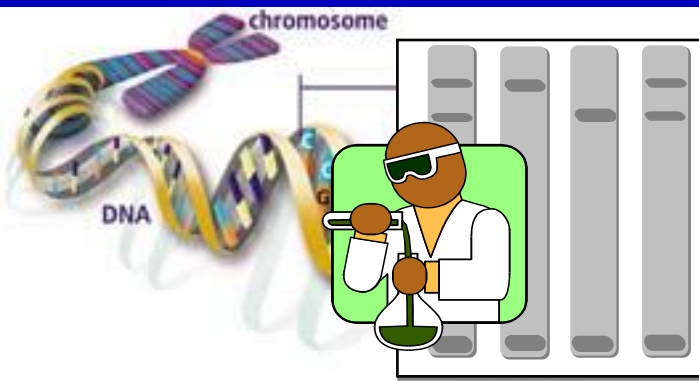
**Major genes  
Markers  
QTL**

**Phenotypic  
data**

**BLUP**

**Marker-Assisted  
Selection**

**Molecular  
data**



- Expressed in both sexes
- Expressed at early age
- Doesn't require phenotypes on animal itself or close relatives

# 2004: Limited use of MAS in livestock

- # markers available was limited
- Markers only explain limited % of genetic variance
  - Only QTL with moderate – large effects detected
- High genotyping costs
- Marker/QTL effects were not consistent / not transferable to commercial breeding populations
  - ‘Beavis’ effect – effects of ‘significant’ markers tend to be overestimated
  - Marker effects were estimated within families or in experimental crosses
  - Inconsistent marker-QTL LD across populations



# Since 2000: A Revolution in Molecular Technology



2.8 million SNPs  
**Nature 2004**

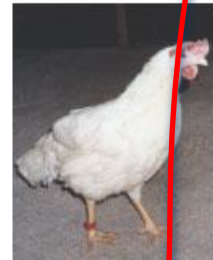
Single Nucleotide Polymorphisms



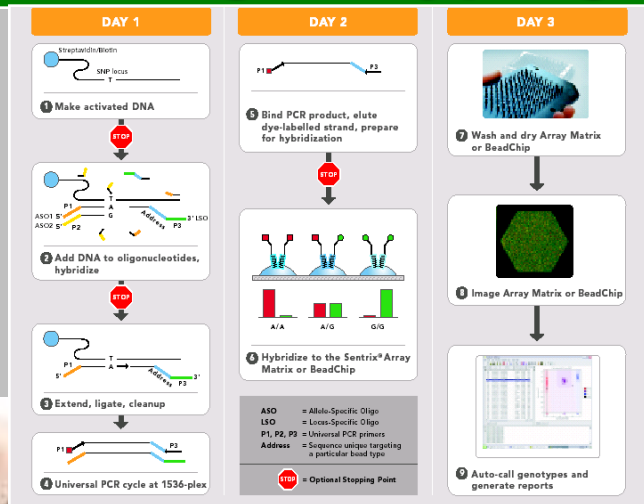
Broiler

Layer

Silkie



## High-throughput SNP genotyping



International Swine Genome Sequencing Consortium

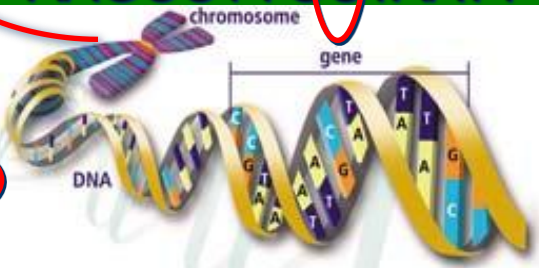
AAGCCTTGATAATT  
maternal  
paternal  
AAGCCTTGCTAATT

## Bovine Genome Project



+ discovery of many

Single Nucleotide Polymorphisms **SNPs**

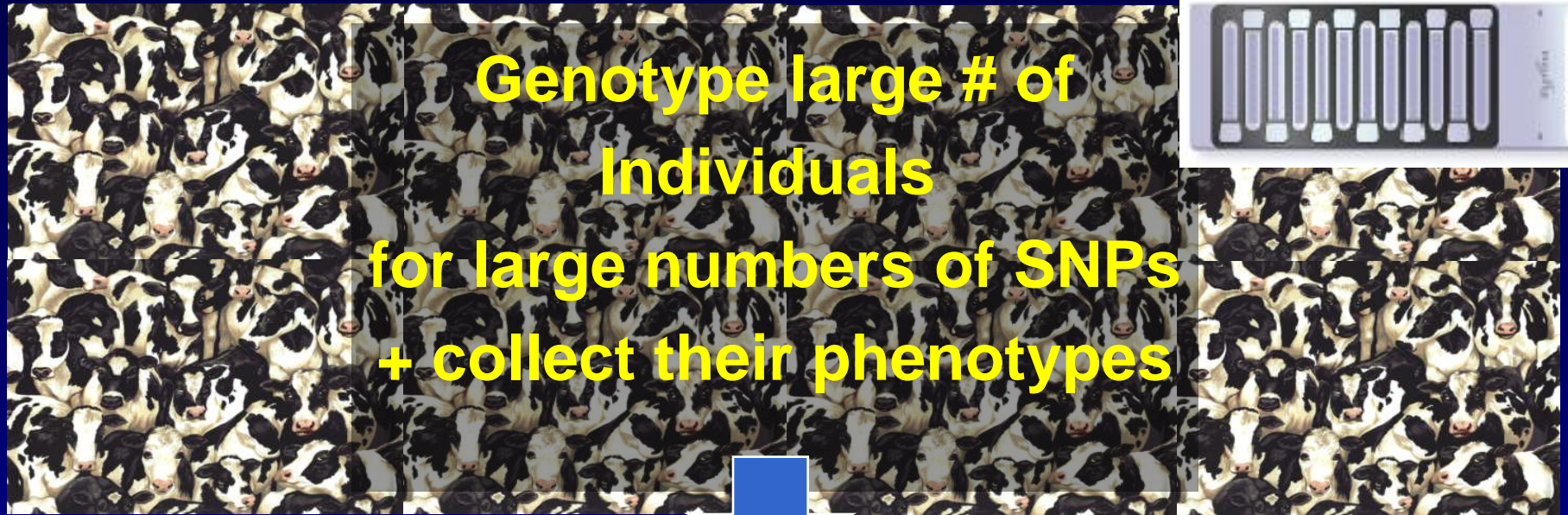


## NOW AVAILABLE: Illumina Bovine 50k Beadchip



50,000 DNA tests for <\$100

# How to use high-density SNP data?



Genotype large # of  
Individuals  
for large numbers of SNPs  
+ collect their phenotypes

**Conduct Association Analysis  
for each SNP - GWAS**



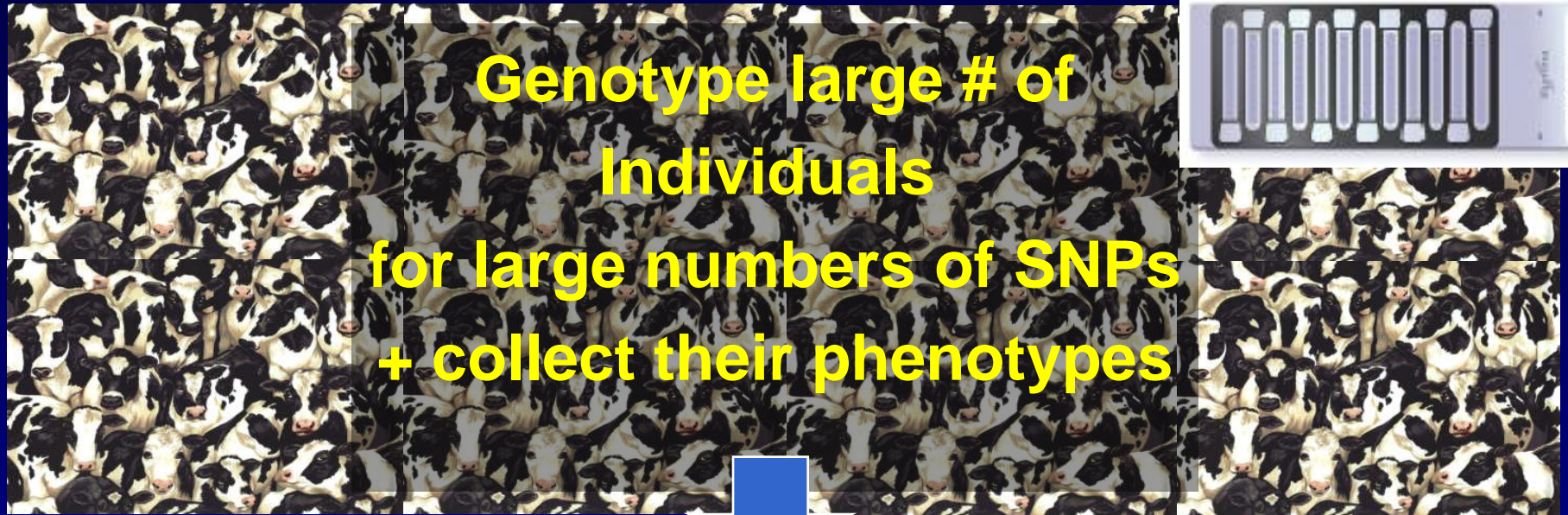
**Use only  
significant SNPs  
for MAS**

Allows more significant effects to  
be detected but:

- Small effects are missed



# How to use high-density SNP data?



**Conduct Association Analysis  
for each SNP - GWAS**

**Use only  
significant SNPs  
for MAS**

**Use ALL  
SNPs  
for MAS**

**Genomic  
selection**  
(Meuwissen et al. '01)

# Genomic Selection/Prediction

Meuwissen et al. 2001 Genetics

## Genetic Evaluation using high-density SNPs

- SNP effects are fitted as random vs. fixed effects
  - enables all SNPs to be fitted simultaneously
  - shrinks SNP effect estimates to 0 depending on evidence from data

$$y_i = \mu + \sum_{\text{SNP } k} \beta_k g_{ik} + e_i$$

SNP effect  
# 'A' alleles (0/1/2)

Estimates of SNP effects  $\hat{\beta}_k$

Implemented using a variety of Bayesian methods (Bayes-A, -B, -C, C- $\pi$ )  
Or by using genomic vs. pedigree relationships in animal model BLUP (GBLUP)

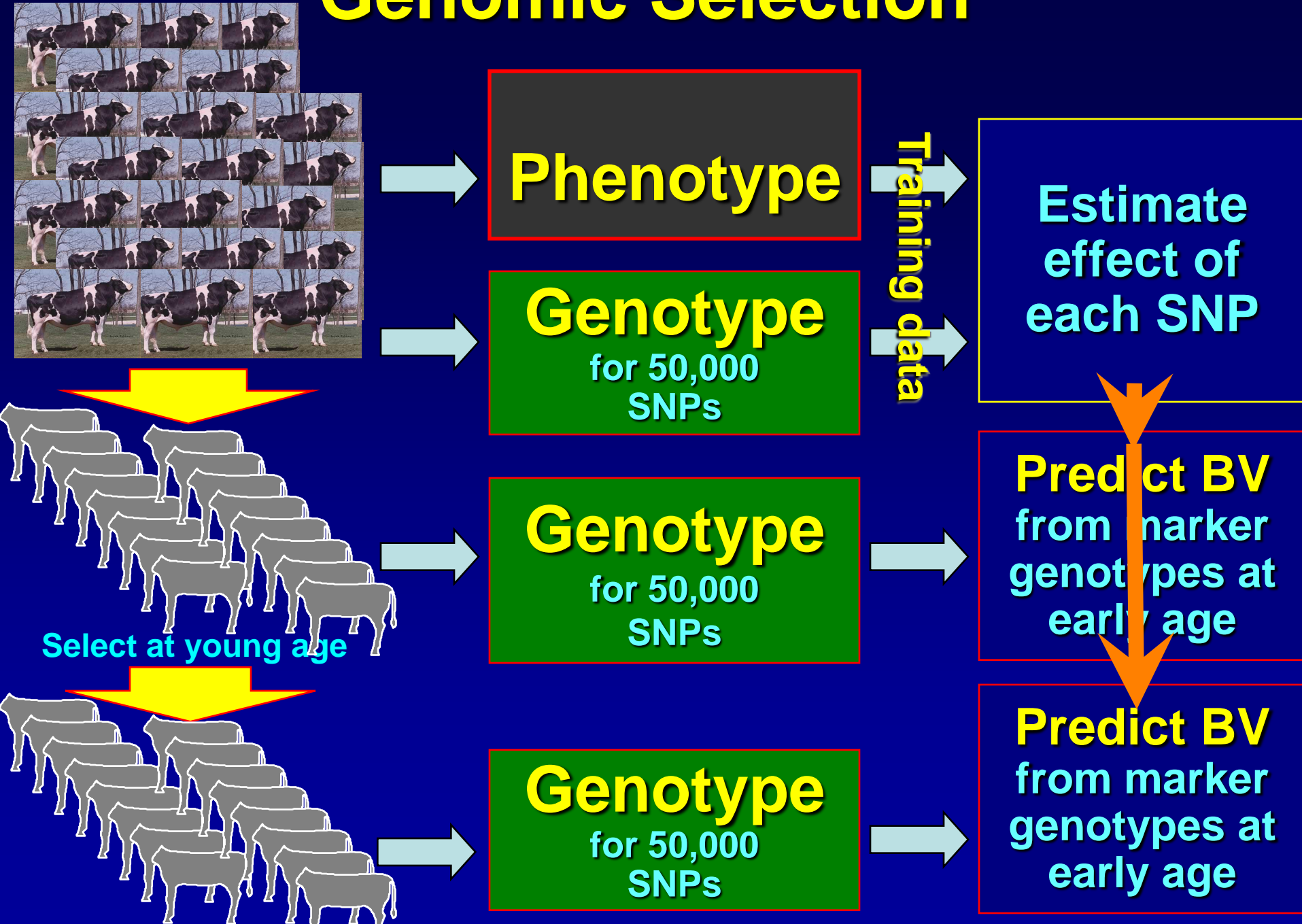
Use to estimate breeding value of new animals based on genotypes alone

$$\text{Genomic EBV} = \sum \hat{\beta}_k g_{ik}$$



# Genomic Selection

Meuwissen et al. 2001



# The Promise of Genomic Selection

- Increase accuracy of EBV at a young age
- Reduce need for costly phenotyping
- Reduce generation intervals
- Increase accuracy for 'difficult' traits
  - Reproduction, longevity, meat quality
  - Disease resistance
  - Crossbred performance in field
- Reduce rates of inbreeding / generation
  - Less emphasis on family information
  - Select on animal's 'own' genotypes (for markers)

# Applied Animal Breeding in the Genomics Era

## Outline

1. Implementation of GS in Dairy Cattle in the US
2. Implementation of GS in Pigs Breeding Programs
  - **GS for Crossbred Performance**
3. Implementation of GS in Poultry Breeding Programs
  - **Experimental evaluation of GS in Layers**
4. Genetic Improvement of Host Response to PRRS in Pigs

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# Holstein prediction accuracy

<b>Trait</b>	<b>Reliability (%)</b>	<b>Reliability gain (% points)</b>
Milk (kg)	69.2	30.3
Fat (kg)	68.4	29.5
Protein (kg)	60.9	22.6
Fat (%)	93.7	54.8
Protein (%)	86.3	48.0
Productive life (mo)	73.7	41.6
Somatic cell score	64.9	29.3
Daughter pregnancy rate (%)	53.5	20.9
Sire calving ease	45.8	19.6
Daughter calving ease	44.2	22.4
Sire stillbirth rate	28.2	5.9
Daughter stillbirth rate	37.6	17.9

\*2013 deregressed value – 2009 genomic evaluation

# Larry Schaeffer. 2006, J. Anim. Breed. Genet.

**Table 1** Schedule of progeny testing activities

Time (months)	Activity
0	Elite dams chosen and bred.
9	Bull calves born from elite dams
21	Test matings of young bulls made
30	Daughters of young bulls born
45	Daughters of young bulls bred
54	Daughters calve and begin first lactation
57	First estimated breeding values for young bulls from test day model
64	Daughters complete first lactations, keep or cull young bulls

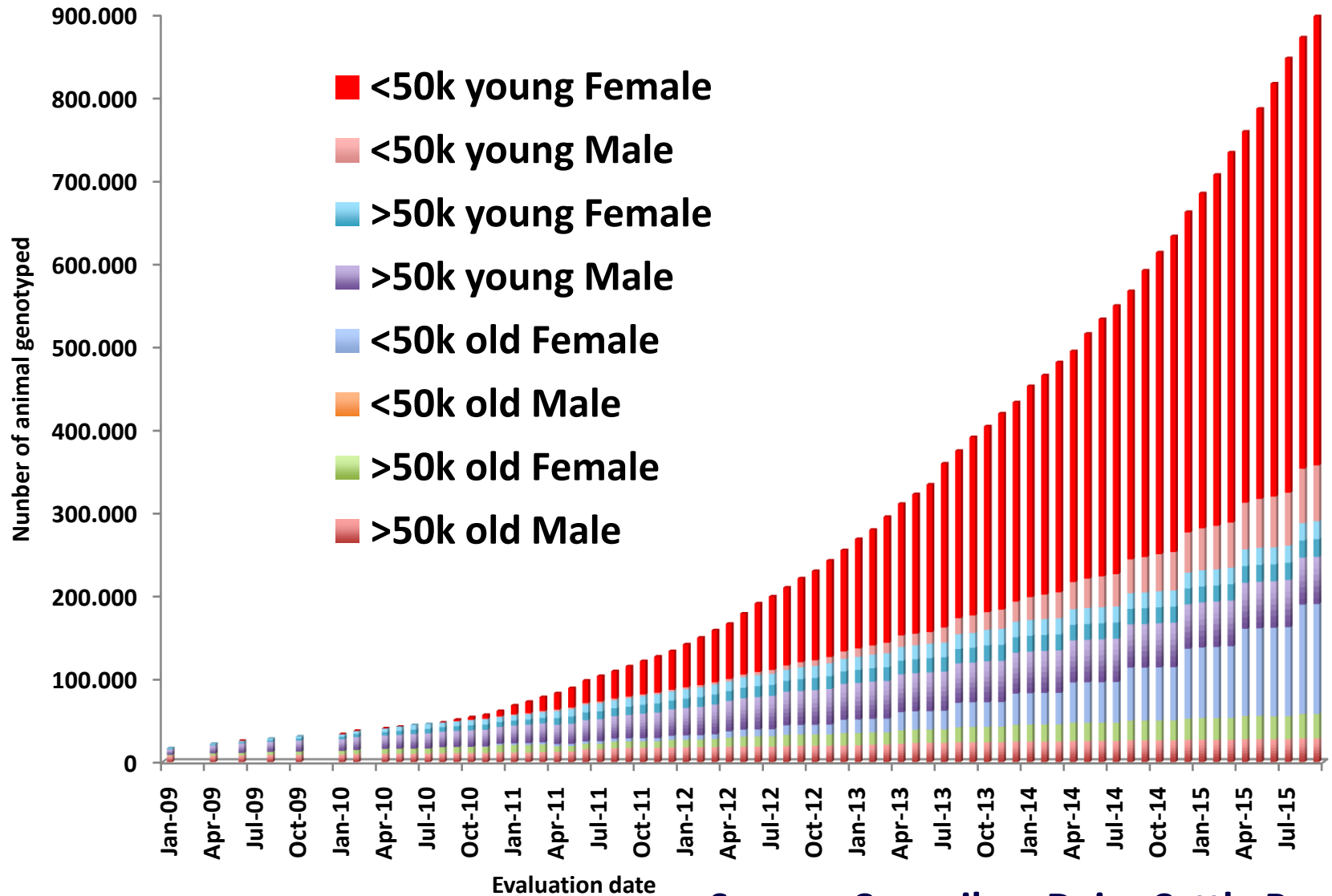
**Table 2** Four pathways of selection, progeny testing

		Accuracy		Generation	
		$i$	$r_{TI}$	Interval, $L$	$i \times r_{TI}$
<b><math>\Delta G = 4.68 / 21.75</math> <math>= 0.22 \sigma_g/\text{yr}</math></b>					
Pathway	Selection %				
Sire of bulls	5	2.06	0.99	6.5	2.04
Sire of cows	20	1.40	0.75	6	1.05
Dams of bulls	2	2.42	0.60	5	1.45
Dams of cows	85	0.27	0.50	4.25	0.14
Total				21.75	4.68

**Table 3** Four pathways of selection, genome-wide strategy

		Accuracy		Generation	
		$i$	$r_{TI}$	Interval, $L$	$i \times r_{TI}$
<b><math>\Delta G = 4.55 / 9.75</math> <math>= 0.47 \sigma_g/\text{yr}</math></b>					
Pathway	Selection %				
Sire of bulls	5	2.06	0.75	1.75	1.54
Sire of cows	20	1.40	0.75	1.75	1.05
Dams of bulls	2	2.42	0.75	2	1.82
Dams of cows	85	0.27	0.50	4.25	0.14
Total				9.75	4.55

# Holstein Genotypes evaluated



Source: Council on Dairy Cattle Breeding

# How is Genomic Selection changing Dairy Cattle Breeding?

- AI Studs market **young bulls / bull teams** selected on Genomic EBV
- These young bulls are from ET or JIVET of **heifers** mated to **young bulls** selected on Genomic EBV
- Use of progeny-testing is decreasing



x



# The Future of Dairy Cattle Breeding . . . .

**How can AI companies maintain  
market share?**

**When Everyone . . . .**

- **has access to superior genetics**
- **can identify such genetics using genomics**
- **and market that genetics using genomics**

**How to differentiate/protect your product?**



# The Future of Dairy Cattle Breeding . . . .

How can AI companies maintain market share?

**How to differentiate/protect your product?**

- **Protect elite germplasm**

- Elite nucleus herds with integration of genomic and reproductive technologies
- Delay release of young bulls
- Disseminate germplasm as crossbred embryos

- **Provide information on new traits?**

- Collected in information nucleus herds for genomic prediction
  - Feed efficiency
  - Disease resistance

# Summary/conclusions

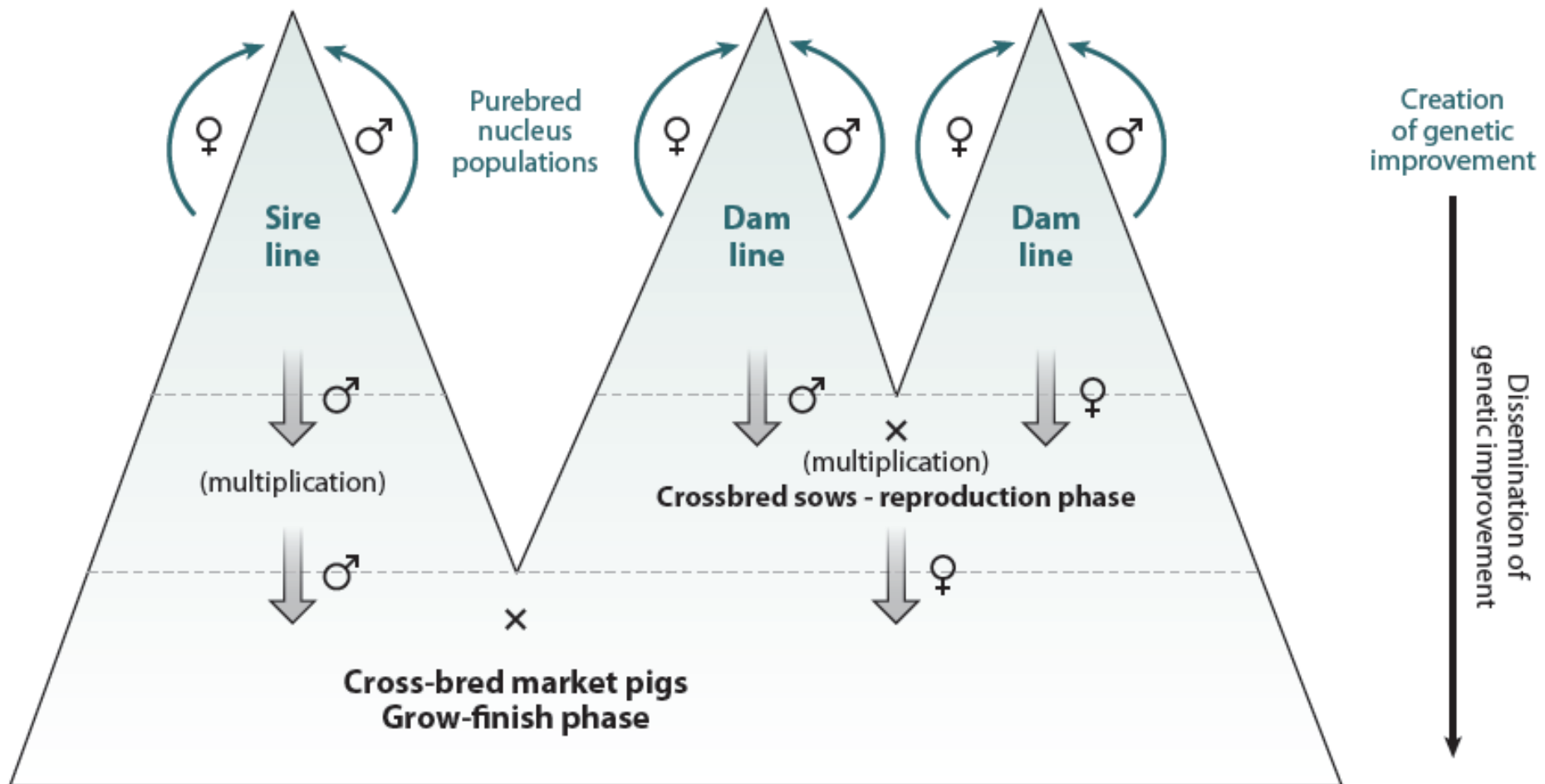
## Genomic Selection in Dairy Cattle

- **Genomic selection is revolutionizing dairy breeding**
- **Integration of genomic and reproductive technologies is reducing generation intervals**
- **Keys for the future:**
  - Maintain and further develop phenotype recording programs
  - Find ways to protect elite germplasm in order to develop a competitive advantage
  - Inbreeding?

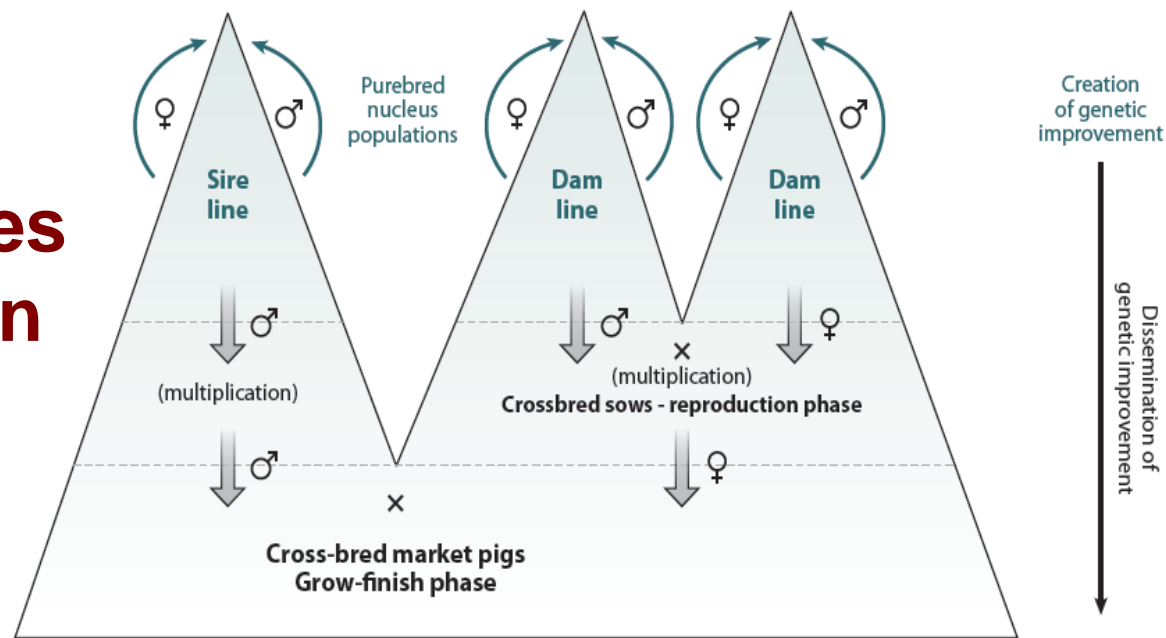
# **Implementation of Genomic Selection in Pig Breeding Programs**

- **Ongoing in some breeding companies**

# Typical Breeding Pyramid for Pigs



# Limited opportunities to reduce generation intervals



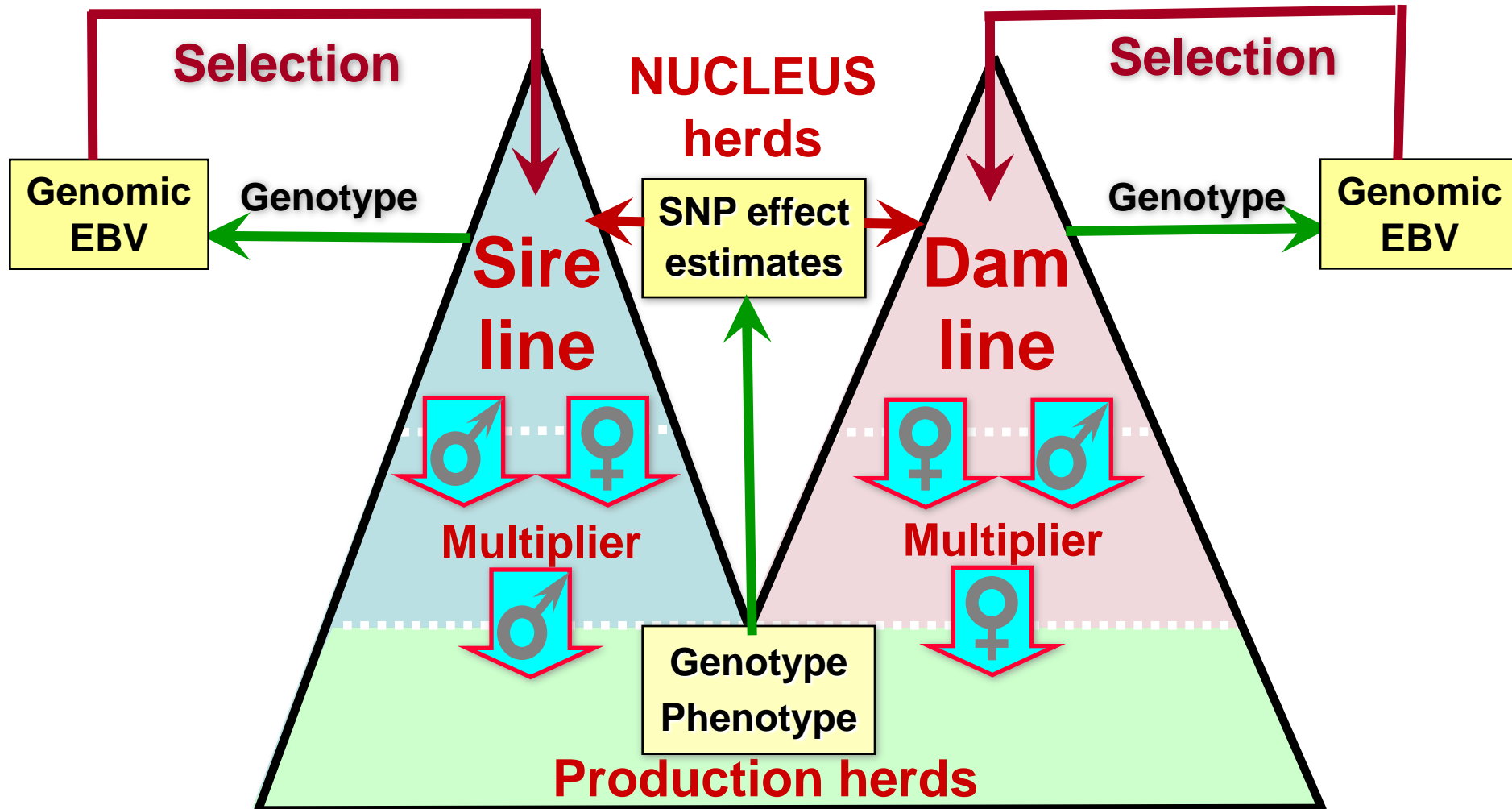
- Challenges:

- Preselection of candidates for further testing (eg feed intake)
- Selection for female reproduction and longevity
- Selection for feed efficiency
- Selection for carcass/meat quality traits
- Selection for commercial crossbred performance
- Selection for Disease resistance/resilience/robustness
- Limited size of individual nucleus populations

# Genomic Selection for Commercial Crossbred Performance

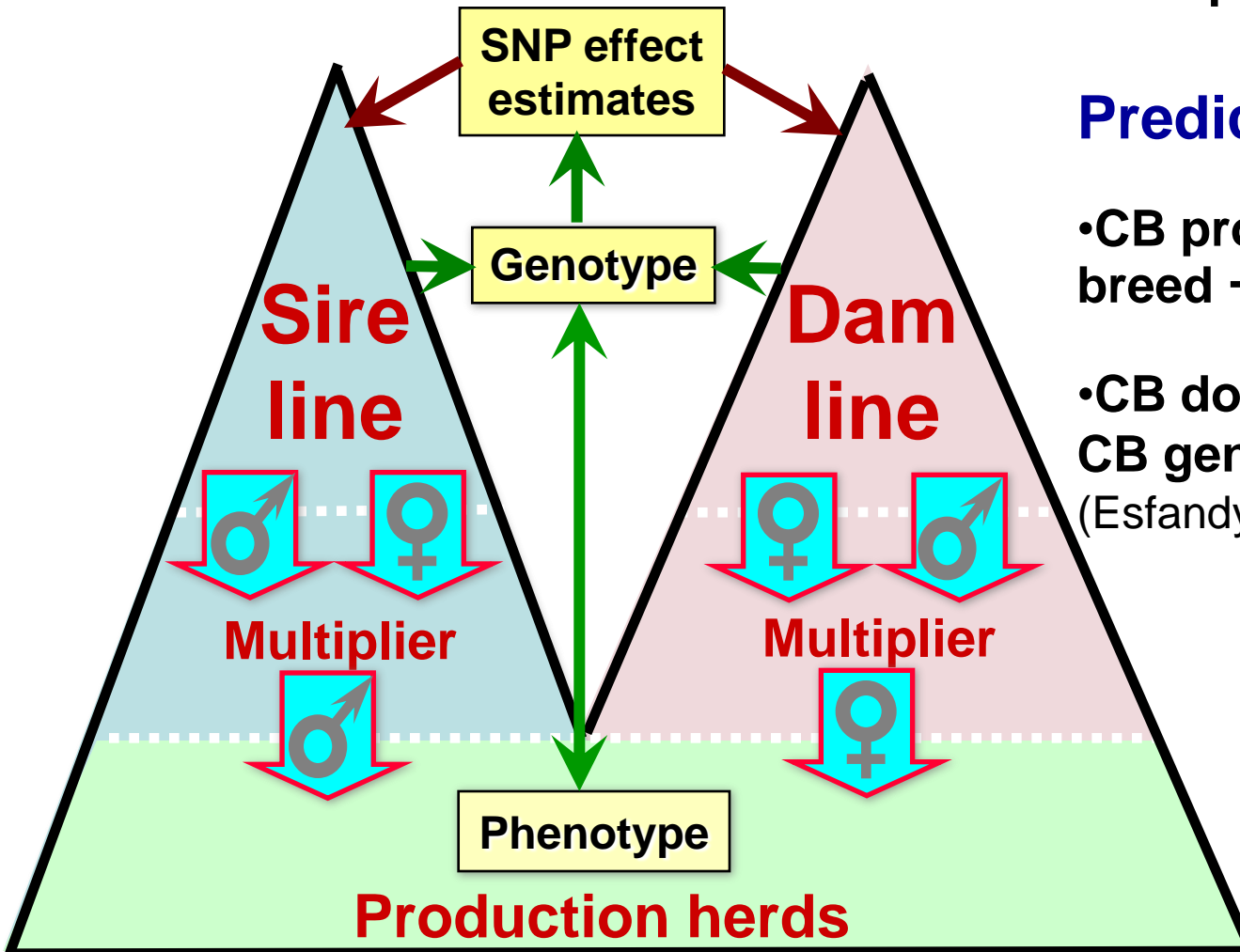
Training on Crossbred data

(Dekkers 2007 JAS)



# Possible GS training scenarios

1. Genotype phenotyped CB → train on own phenotype
  - does not require pedigree
2. Genotype PB and train on CB progeny performance
  - requires pedigree



## Prediction models

- CB progeny mean model by breed → breed-specific  $\alpha$
- CB dominance model using CB genotype probabilities (Esfandyari et al. 2014)

# Application of genomic selection in poultry

A. Wolc<sup>\*,†</sup>, A. Kranis<sup>‡,§</sup>, J. Arango<sup>†</sup>, P. Settar<sup>†</sup>, J.E. Fulton<sup>†</sup>,  
N. O'Sullivan<sup>†</sup>, S. Avendaño<sup>‡</sup>, K.A. Watson<sup>‡</sup>, R. Preisinger<sup>#</sup>,  
D. Habier<sup>\*</sup>, S.J. Lamont<sup>\*</sup>, R. Fernando<sup>\*</sup>,  
D.J. Garrick<sup>\*</sup>, J.C.M. Dekkers<sup>\*</sup>

\*Department of Animal Science, Iowa State University,

† Hy-Line International, Dallas Center, USA,

‡Aviagen Limited, Newbridge, UK,

§ Roslin Institute, R(D)SVS, Univ. Edinburgh, Scotlan

# Lohmann Tierzucht GmbH, Cuxhaven, Germany





- **Short generation interval**

- overlapping generations every 6 weeks in broilers
- non-overlapping generations every year in layers)

**GS has to be fast and accurate**

- **Very large # selection candidates and high selection intensity**

- **Low marginal revenue from a single individual**

- **No cryopreservation**

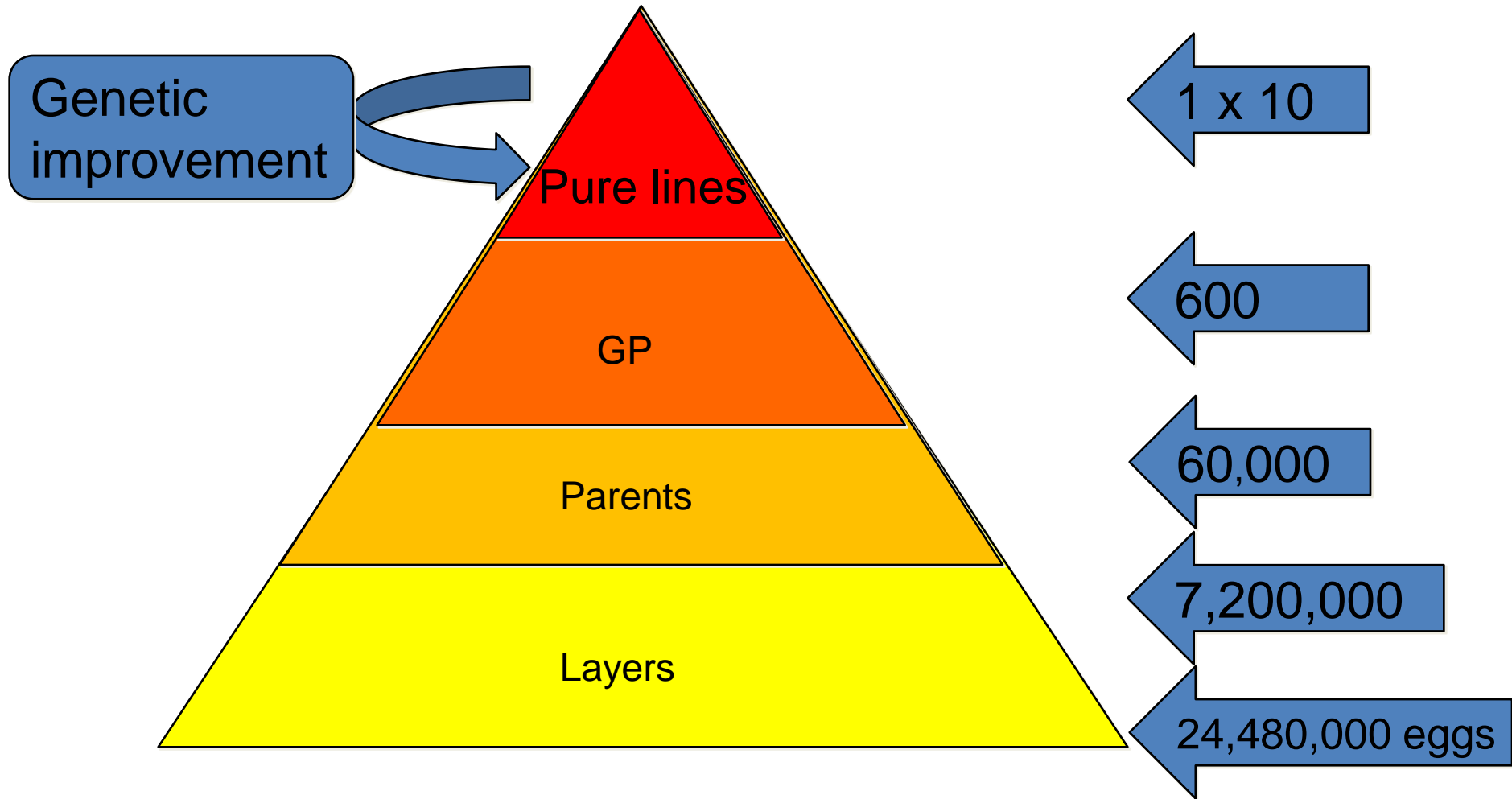
**GS has to be cheap  
Can't afford HD genotyping or sequencing**

- **Multiplication pyramid of the progress**

**Small changes have a big impact**

# Breeding pyramid

– small improvements have large impact



# Implementing GS in Pig/Poultry Programs

## Problem

High cost of genotyping  $\leftrightarrow$  value of an individual

Very large numbers of selection candidates



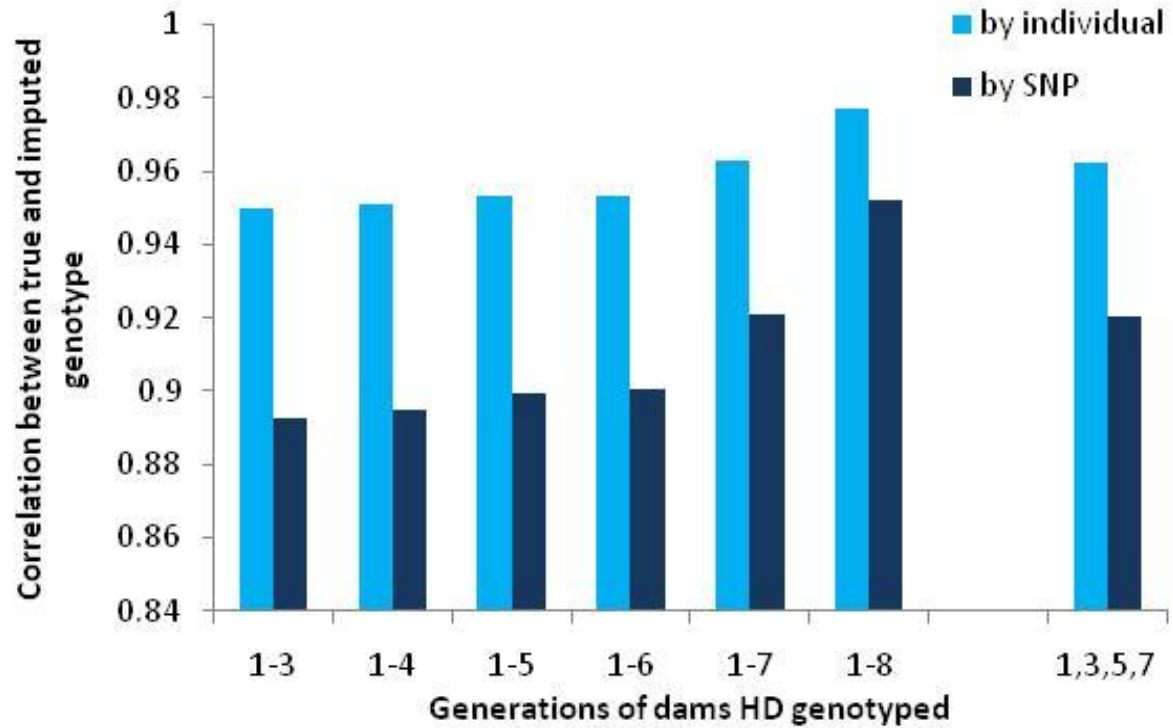
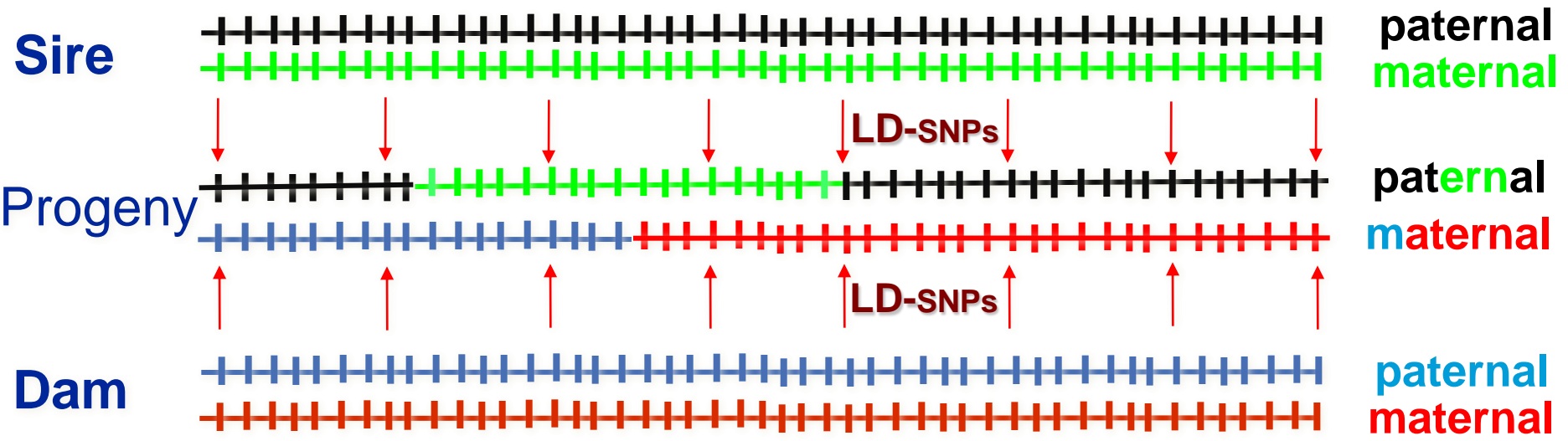
Impossible to implement genomic selection based on high density genotyping in cost efficient manner

## Solution

Combination of strategic genotyping and imputation

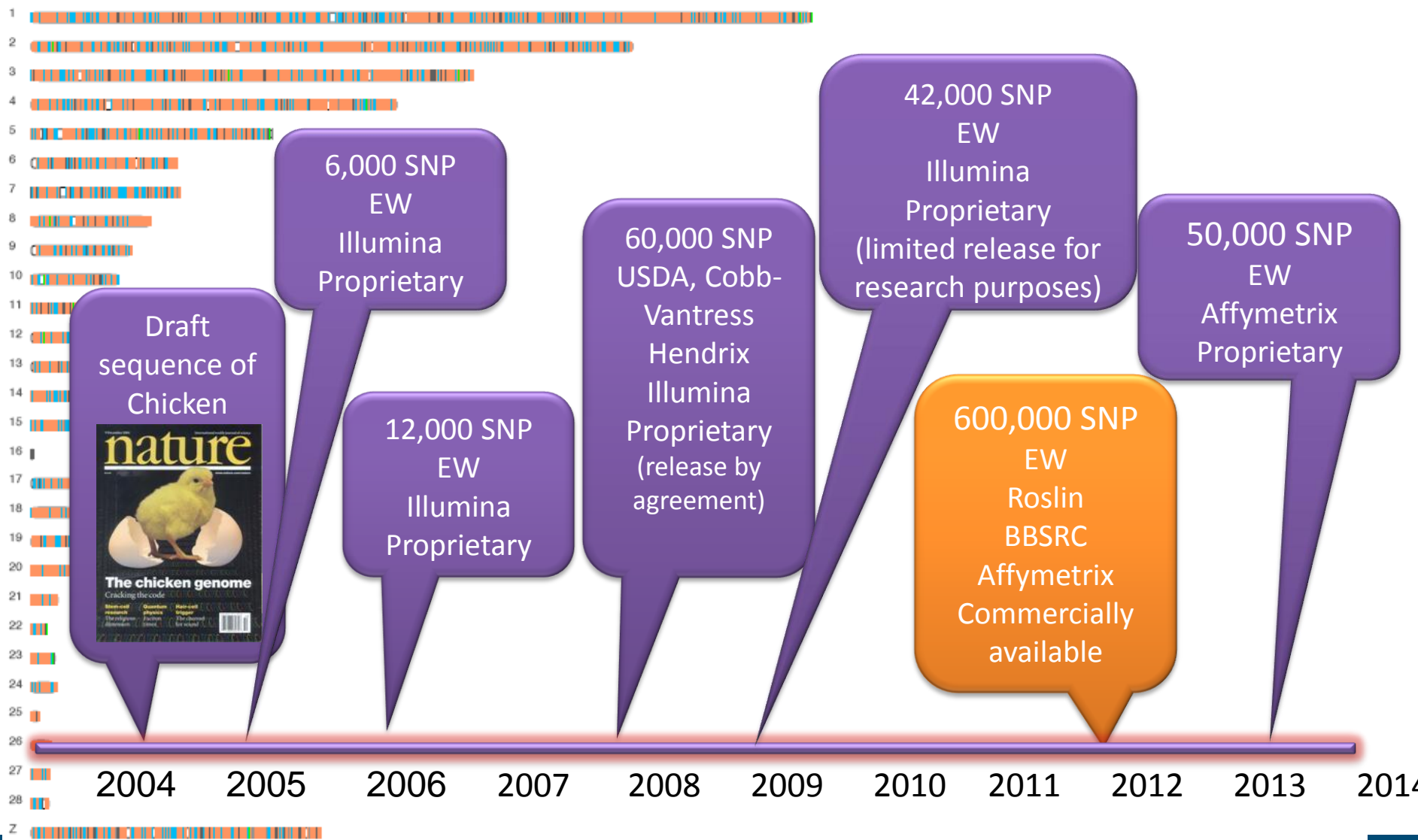
# Genomic Selection using Low-Density Panels

(Habier, Fernando, Dekkers, 2009, Genetics)



(Wolc, et al. 2013)





# Experimental Implementation of Genomic Selection in Layer Chickens

**Anna Wolc, Neil O' Sullivan, Janet Fulton, Petek Settar and Jesus Arango**

**HY-LINE INTERNATIONAL**

**Jack Dekkers, Chris Stricker, Nathan Bowerman,  
Rohan Fernando, Dorian Garrick, David Habier and Sue Lamont**

**IOWA STATE UNIVERSITY**

# Implementation of Genomic Selection in Layer Chickens

## Research Objective

Evaluate and demonstrate  
the advantages and pitfalls of Genomic Selection  
in a commercial breeding population

## Research Questions / Goals

In layer chickens, Genomic Selection can:

- increase response by halving the generation interval
- without increasing the rate of inbreeding per year
- in a breeding program comprising fewer individuals





# Breeding Program Design

## A Layer Chicken Example



Selection strategy	Traditional		Genomic	
Selection parameters	♂♂	♀♀	♂♂	♀♀
# candidates/gener.	1,000	3,000	300	300
# phenotyped <sup>a</sup>		3,000		300
# selected	60	360	50 <sup>b</sup>	50 <sup>b</sup>
Generation interval	12 mo <sup>c</sup>	12 mo <sup>c</sup>	6 mo <sup>d</sup>	6 mo <sup>d</sup>

<sup>a</sup> Complete phenotypes available at ~10 months of age

<sup>c</sup> Traditional selection is *after* ♀♀ are phenotyped → 12 mo.

Traditional selection is limited by cost to rear and phenotype

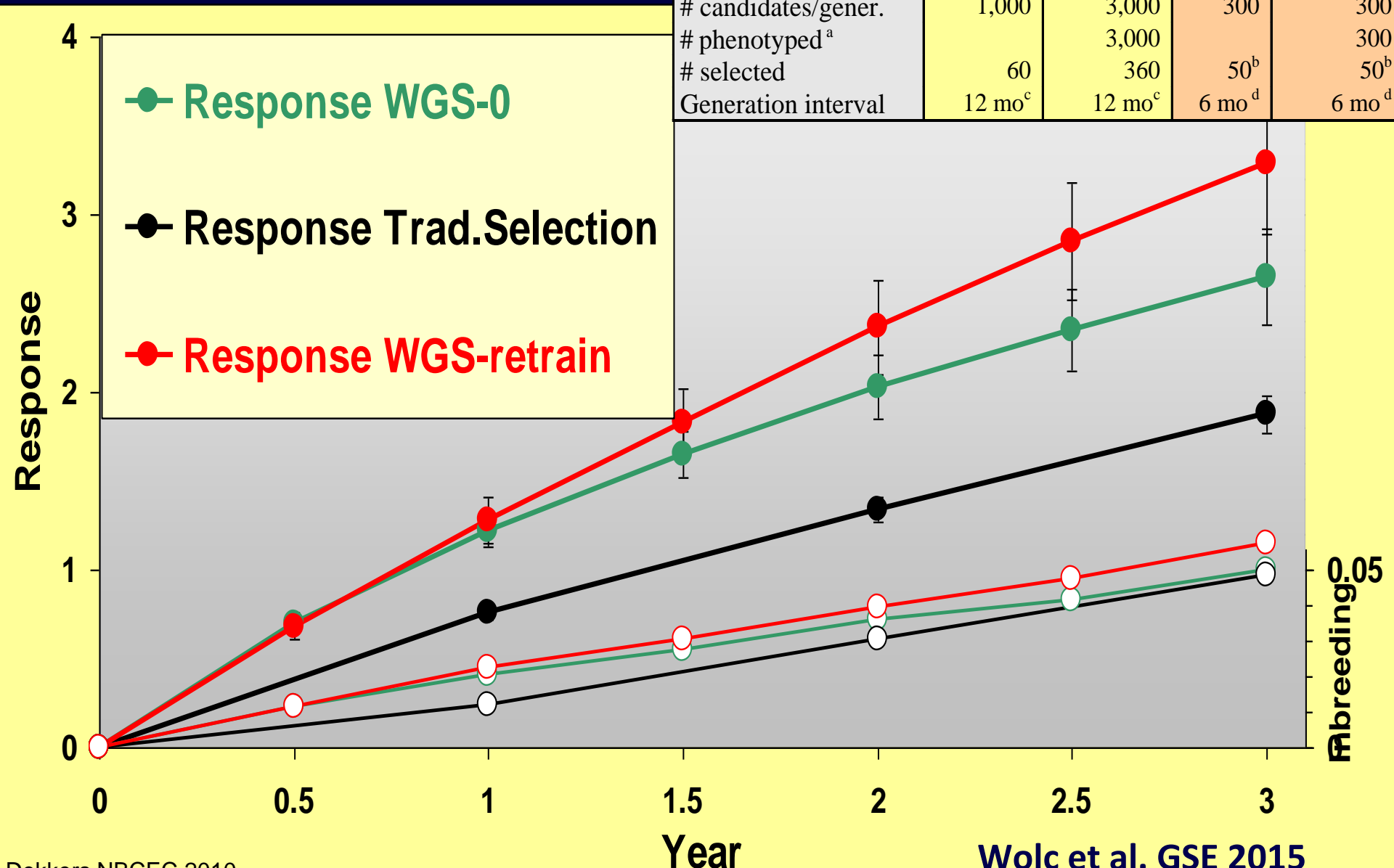
Male traditional selection is on sib data → low accuracy → high ΔF

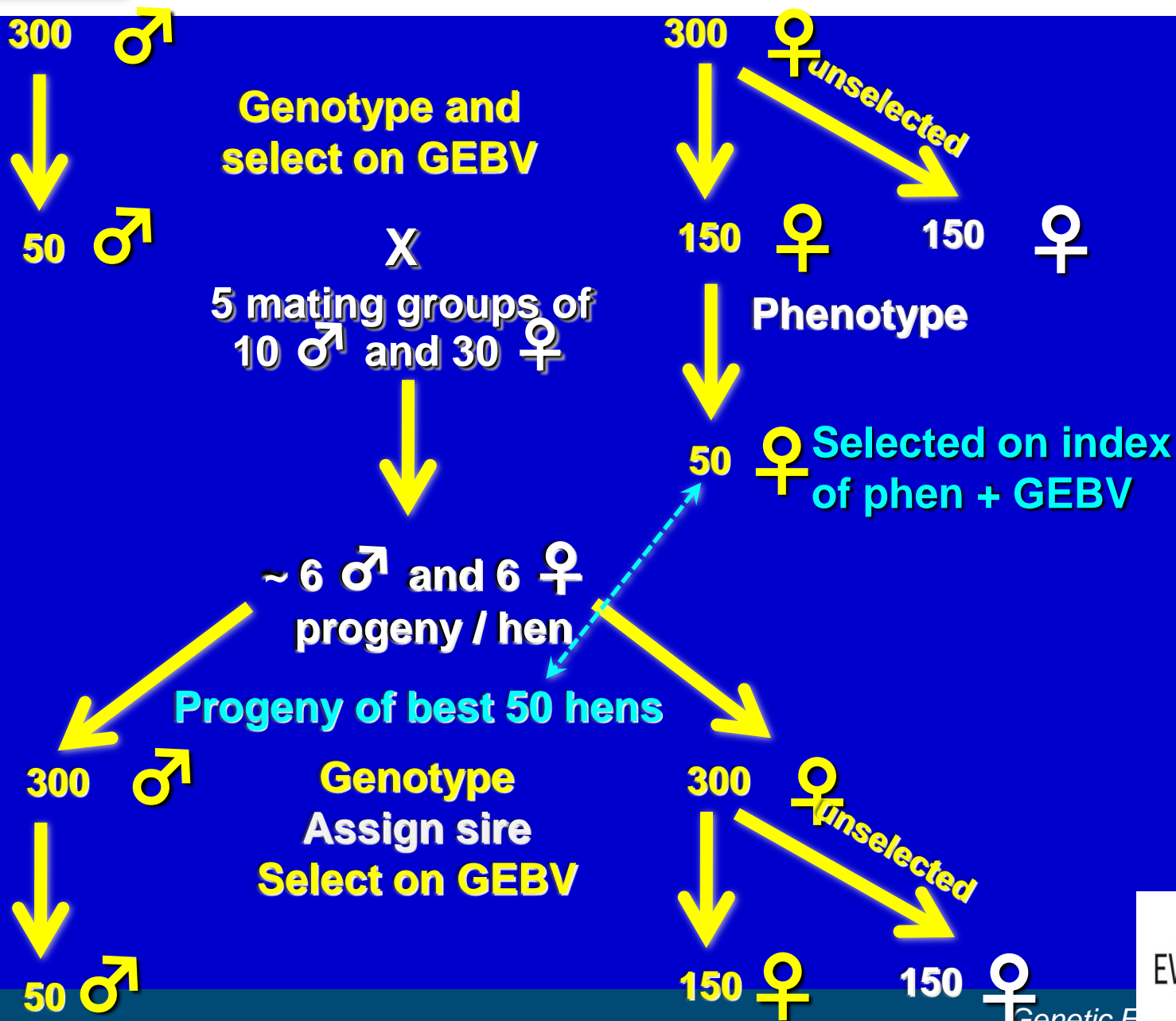


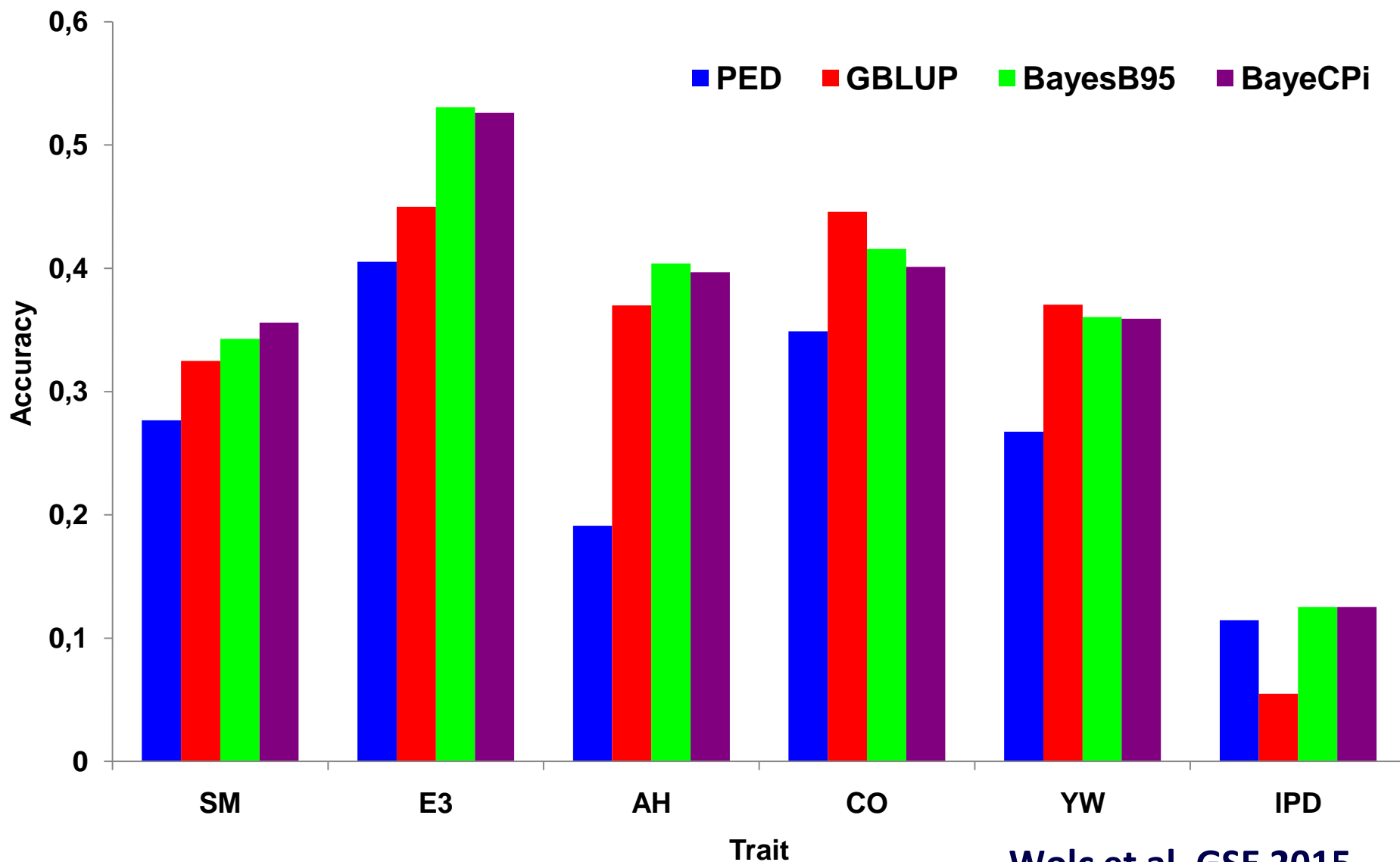
# Expected Response and Inbreeding

Based on simulation

Strategy	Traditional		WGS	
Parameters	♂♂	♀♀	♂♂	♀♀
# candidates/gener.	1,000	3,000	300	300
# phenotyped <sup>a</sup>		3,000		300
# selected	60	360	50 <sup>b</sup>	50 <sup>b</sup>
Generation interval	12 mo <sup>c</sup>	12 mo <sup>c</sup>	6 mo <sup>d</sup>	6 mo <sup>d</sup>





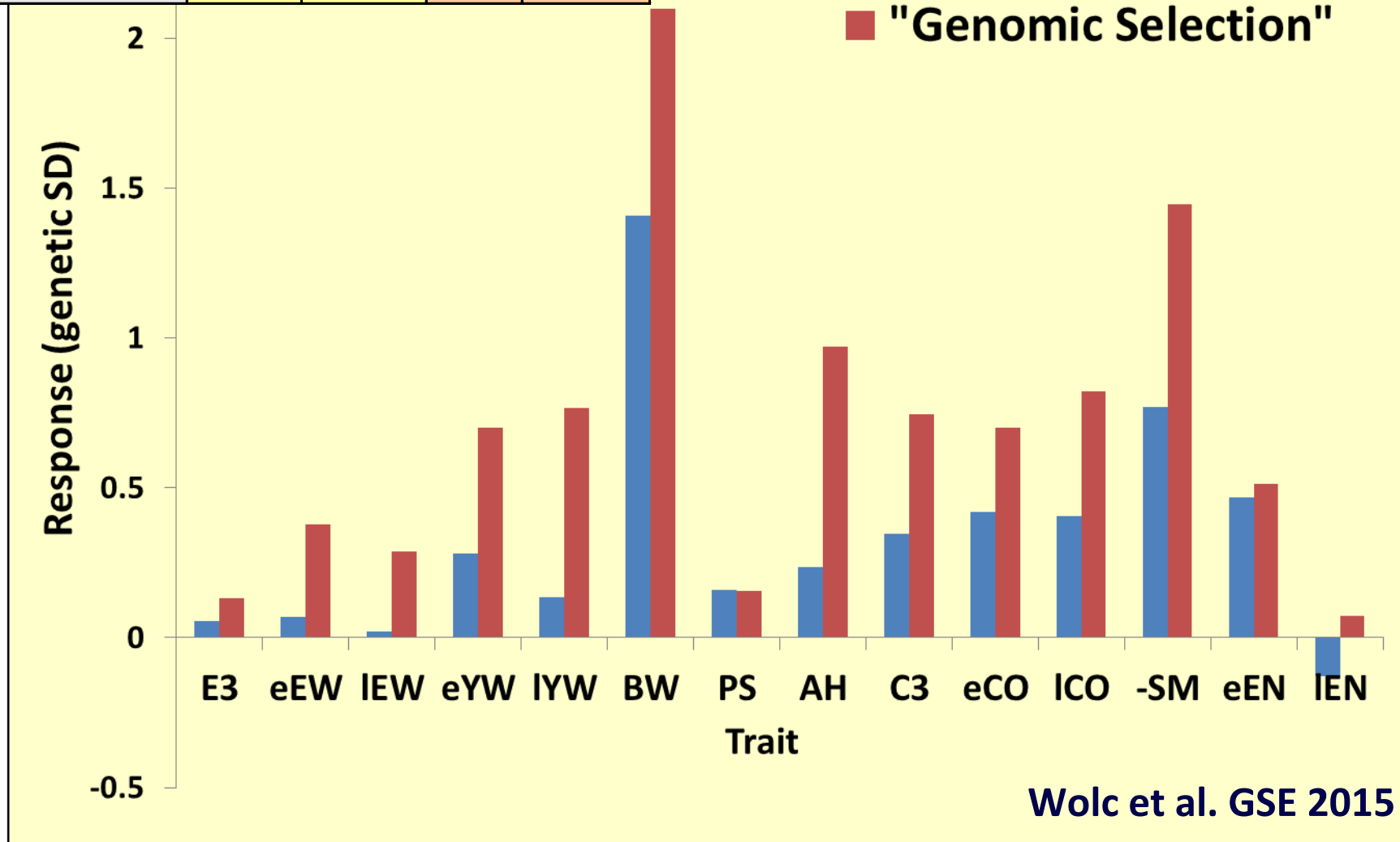


Wolc et al. GSE 2015

Strategy	Traditional		WGS	
	♂♂	♀♀	♂♂	♀♀
# candidates/gener.	1,000	3,000	300	300
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Generation interval	12 mo <sup>c</sup>	12 mo <sup>c</sup>	6 mo <sup>d</sup>	6 mo <sup>d</sup>

## Response to Selection

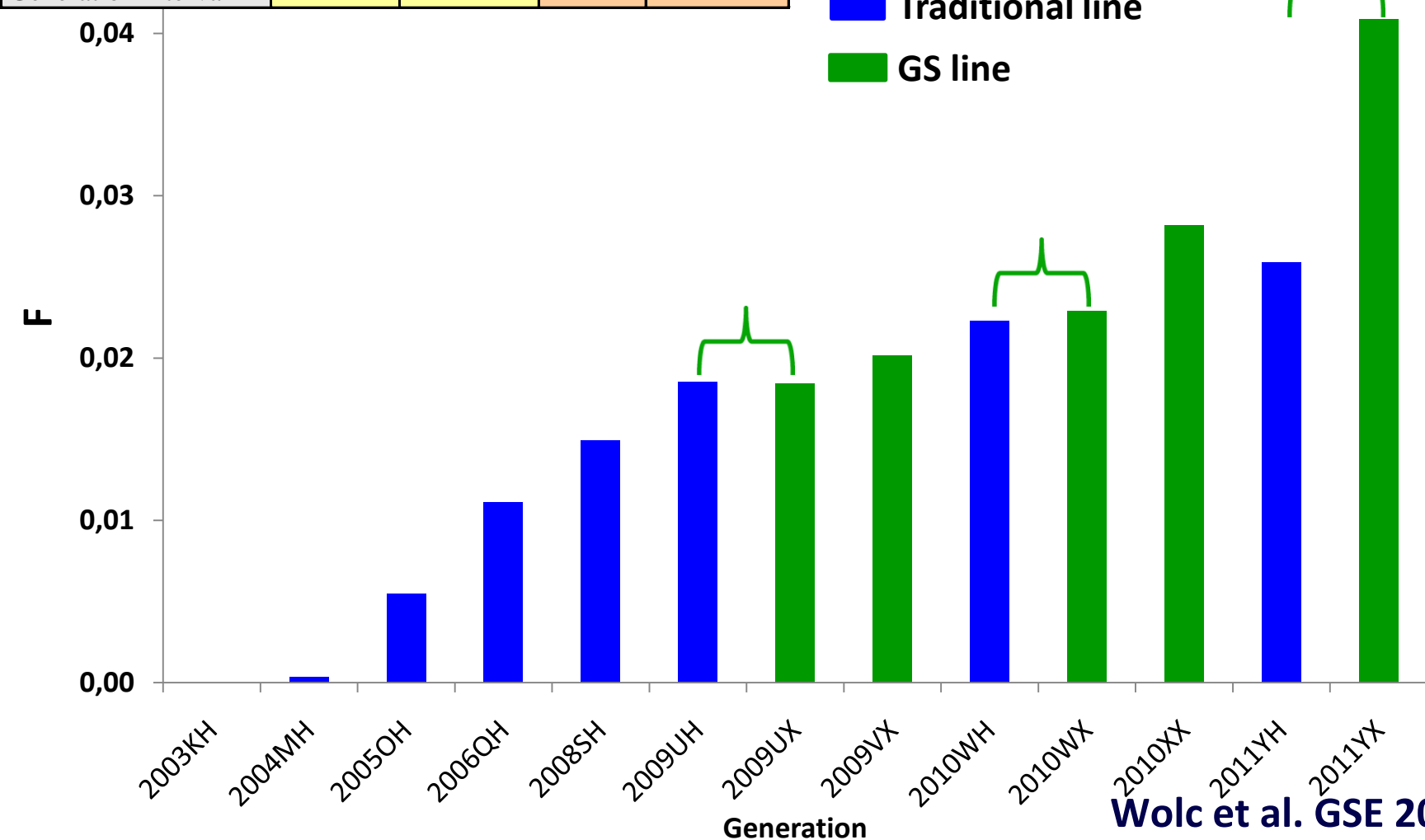
- "Traditional Selection"
- "Genomic Selection"



Strategy	Traditional		WGS	
	♂♂	♀♀	♂♂	♀♀
# candidates/gener.	1,000	3,000	300	300
# phenotyped <sup>a</sup>		3,000		300
# selected	60	360	50 <sup>b</sup>	50 <sup>b</sup>
Generation interval	12 mo <sup>c</sup>	12 mo <sup>c</sup>	6 mo <sup>d</sup>	6 mo <sup>d</sup>

## Inbreeding

- 2004MH
- Traditional line
- GS line



Wolc et al. GSE 2015

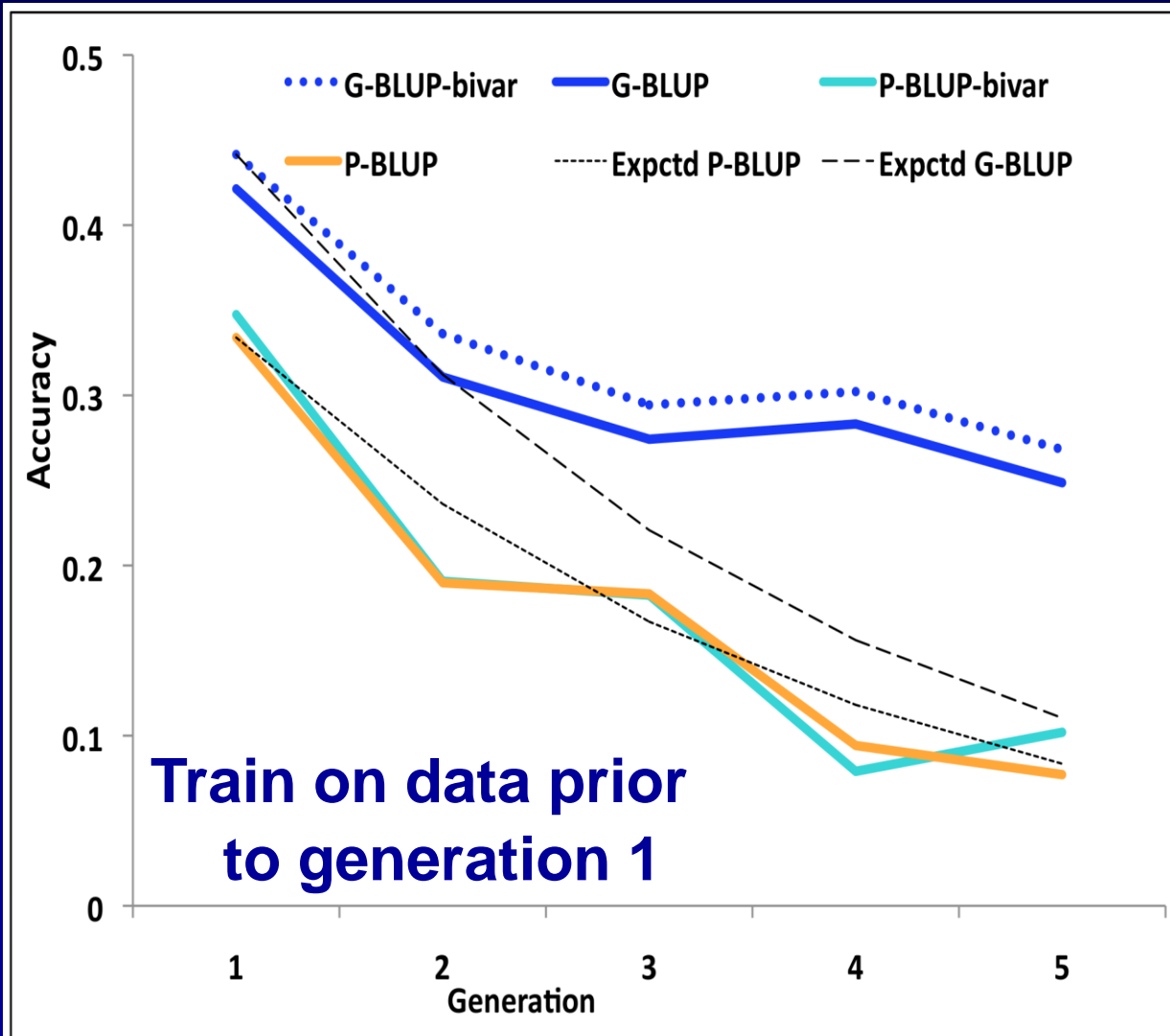


Hy-Line®



# Need for Retraining

Wolc et al. (GSE, 2012)



# Implementation of Genomic Selection in Pig/Poultry Breeding Programs

- **Requirements**

- **Large numbers of genotyped animals**
  - Focus on breeders with large amounts of data
  - Use of Genotype imputation
- **Computing resources**
- **Logistics of DNA collection, phenotype collection, genotyping, analysis**
- **Continued phenotype recording (retraining)**
- **Consider redesign of breeding program**

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## Outline

1. Implementation of GS in Dairy Cattle in the US
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# Porcine Reproductive and Respiratory Syndrome - PRRS

Large financial loss in both production settings

## Sows

- ▣ Abortions
- ▣ Stillborn/weak pigs
- ▣ Delayed estrus
- ▣ Respiratory problems



Respig.com

## Grower

- ▣ Increased mortality
- ▣ Decreased production
- ▣ Respiratory problems



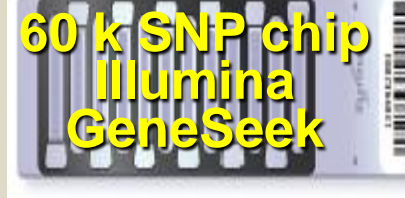
## Strategies to control PRRS

- ▣ Eradication
- ▣ Biosecurity
- ▣ Vaccination
- ▣ Host genetics

Respig.com



2007



## Objective

Use genomics to identify genes / genomic regions associated with resistance / susceptibility to PRRS virus infection

### Led by

- Joan Lunney – USDA – ARS Beltsville
- Bob Rowland – Kansas State University
- Jim Reecy – Iowa State University
- Jack Dekkers – Iowa State University



**Strong Industry Participation**

**PHGC Breeding Companies**

Fast

Genetics, Genesis, Genetiporc, Choi



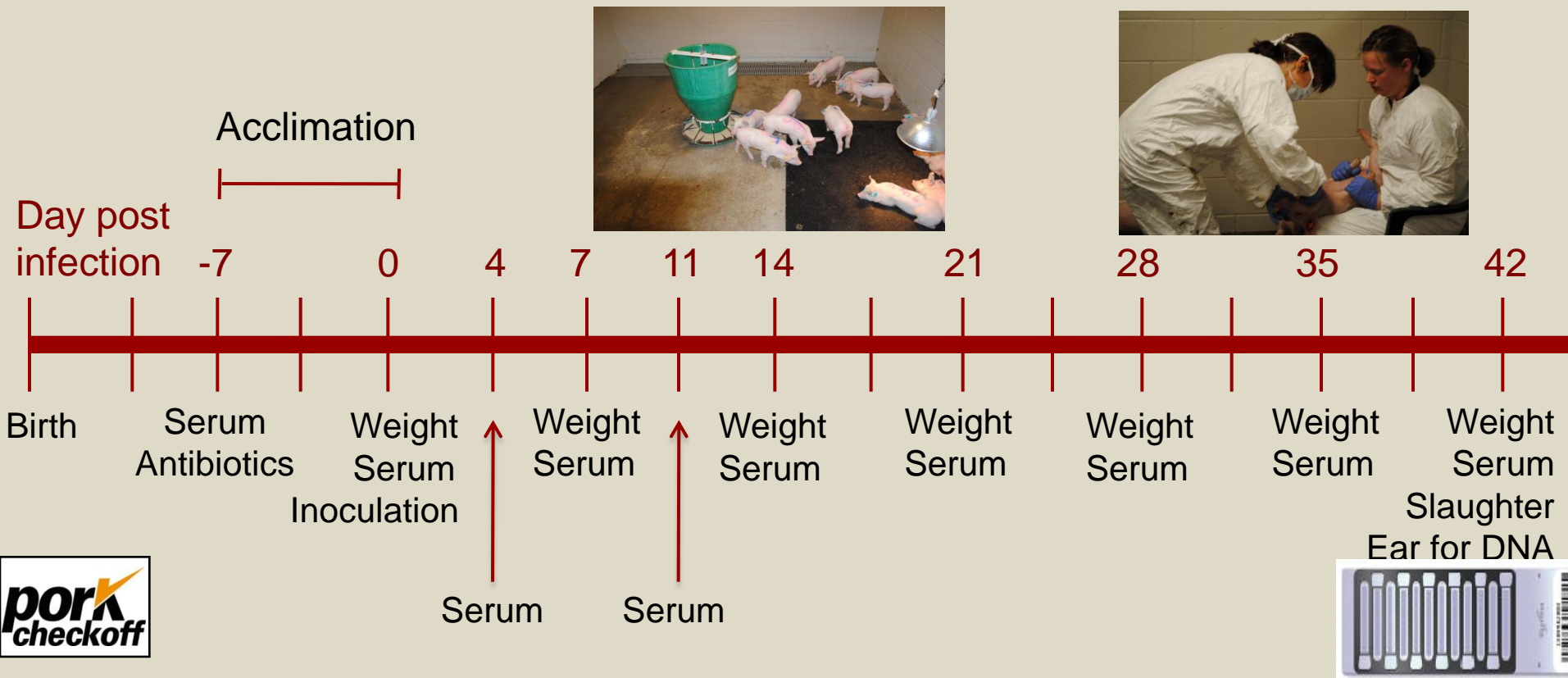


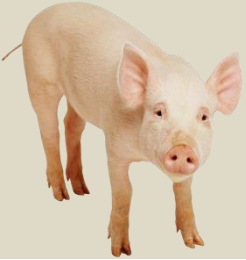
# Nursery Pig Challenge Model



R.R.R. Rowland et al., Kansas State University

Groups of ~200 commercial crossbred pigs infected with PRRS virus isolate NVSL97-7985 between 18 and 28 d of age





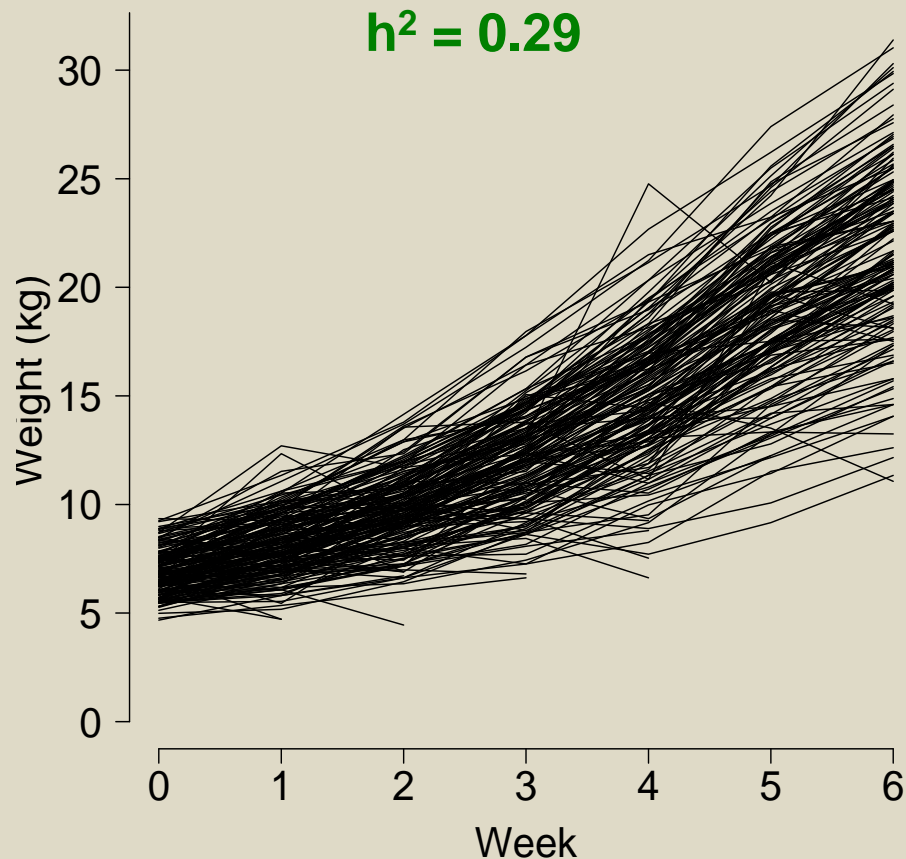
# Host Response Phenotypes



**Body weight**

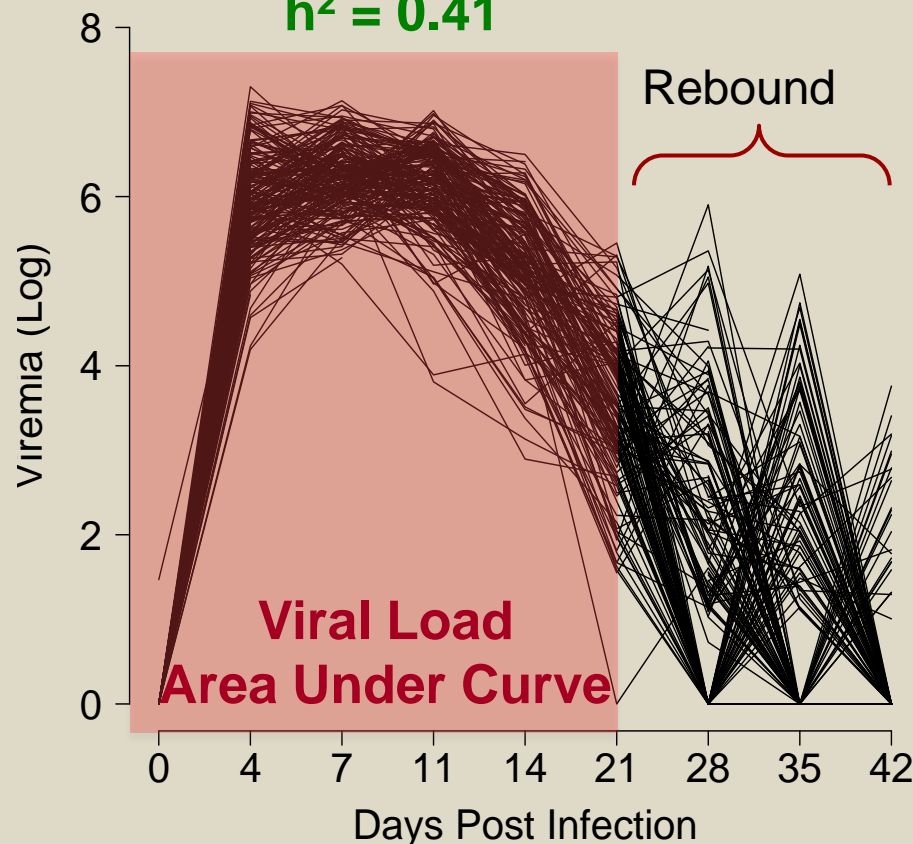
$$r_p = -0.25$$
$$r_g = -0.47$$

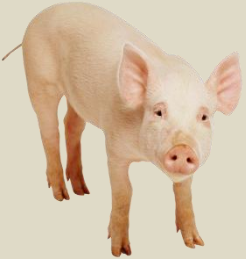
$$h^2 = 0.29$$



**Log(viremia)**

$$h^2 = 0.41$$



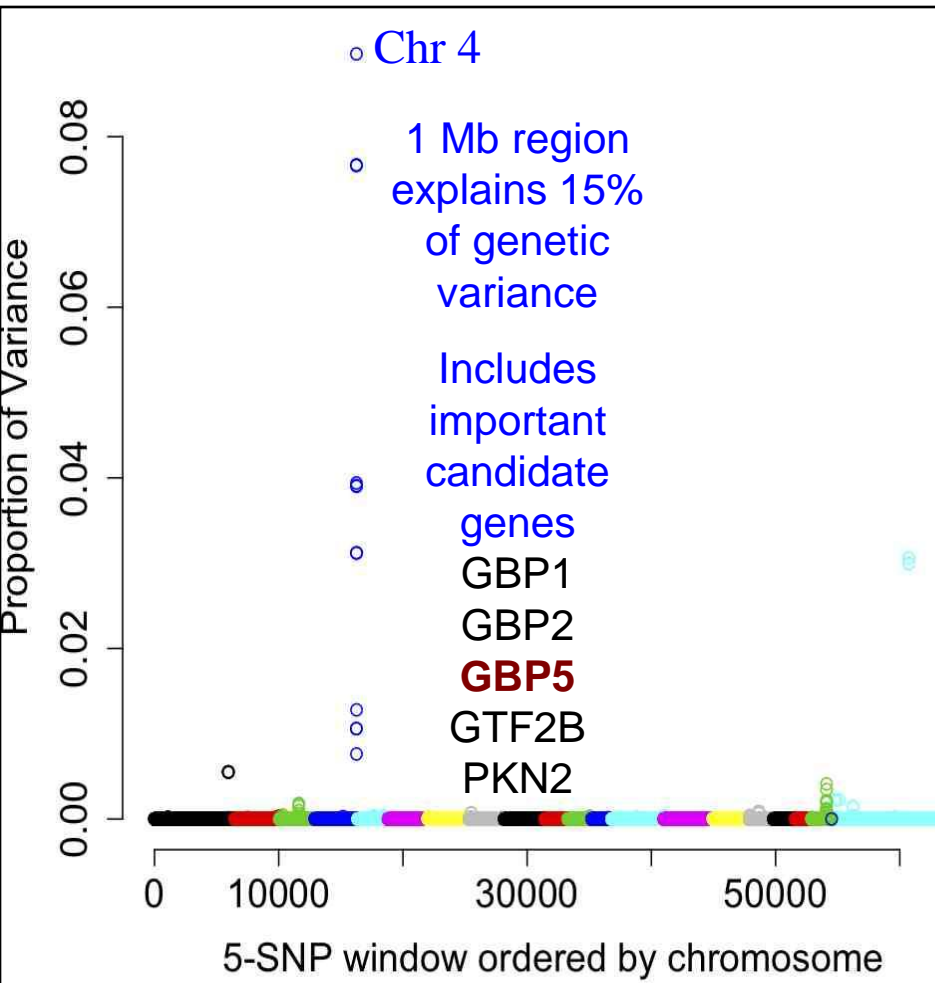


# Genome-wide Association Study

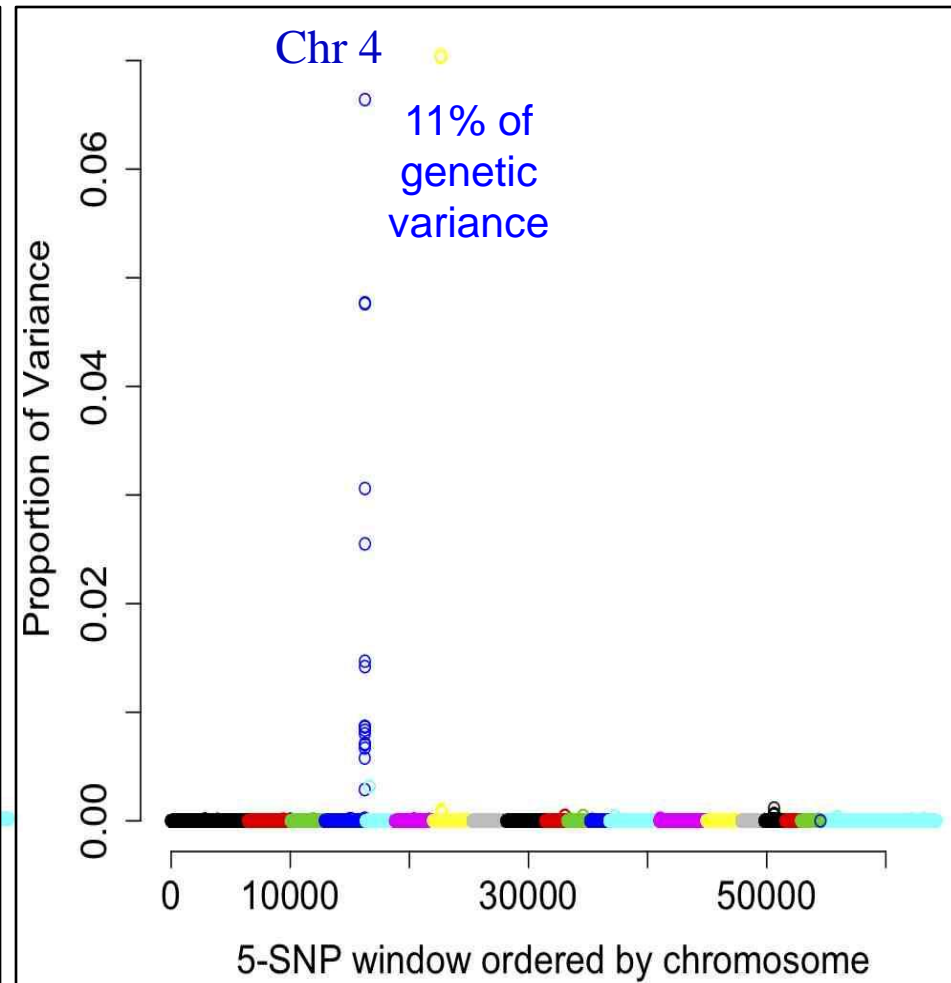
Boddicker et al. 2012, 2014a,b



## Viral Load



## Weight Gain

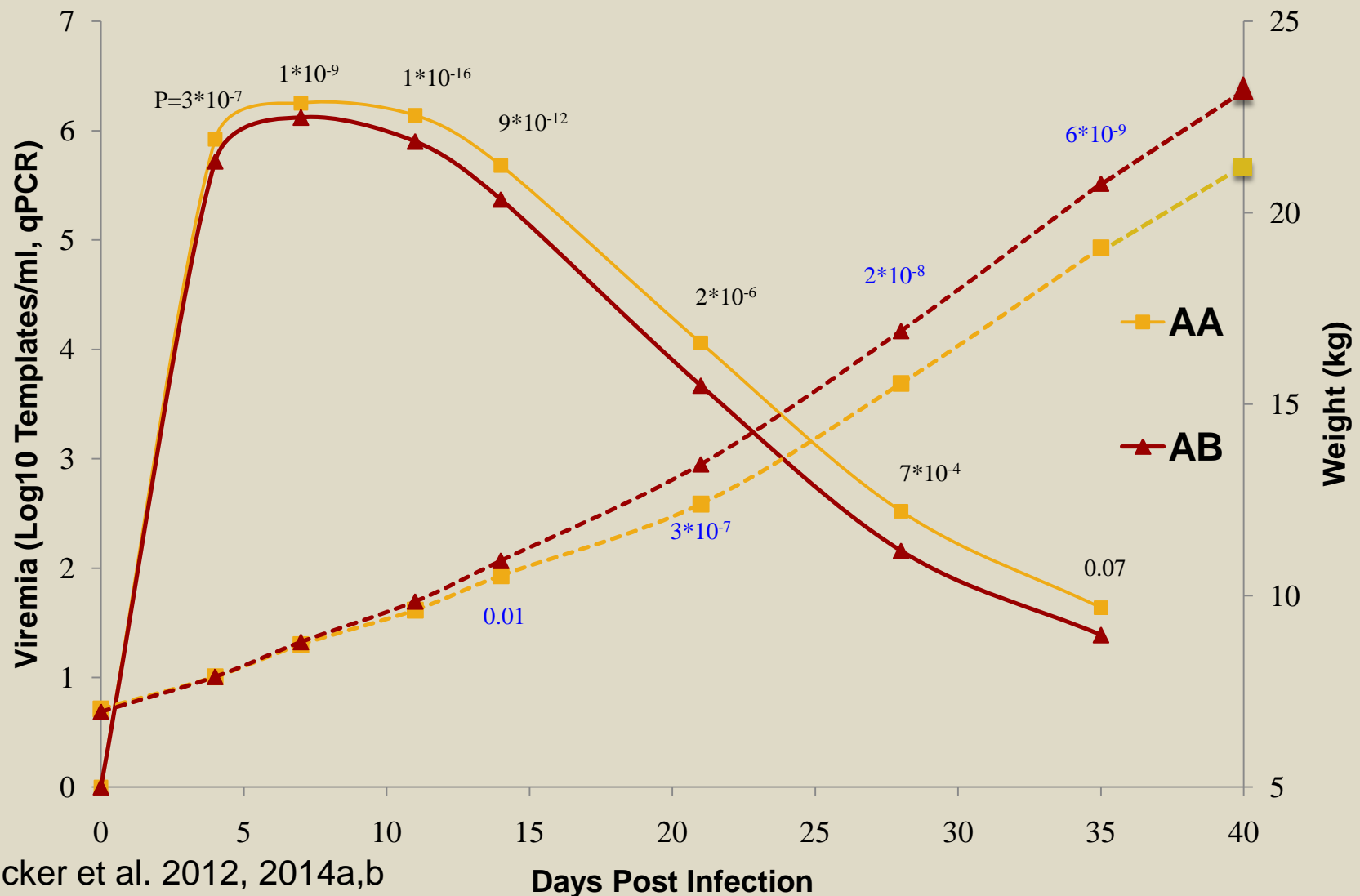






# Effects Chrom. 4 region over time

## PHGC1-7/8



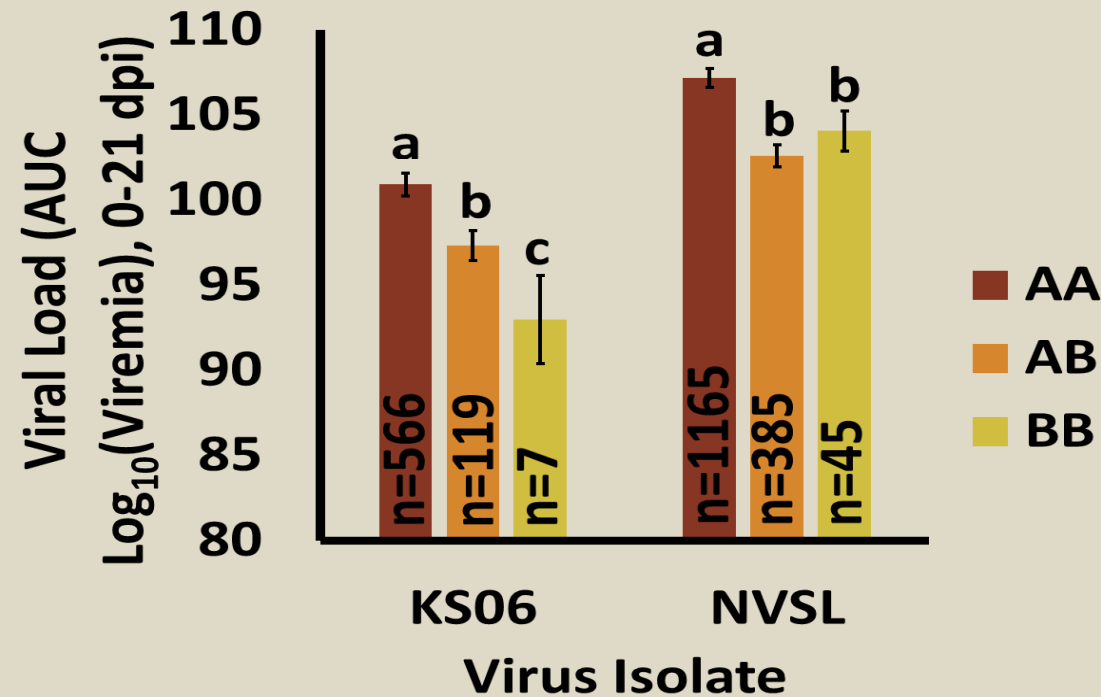


# Effects of SSC4 SNP WUR10000125

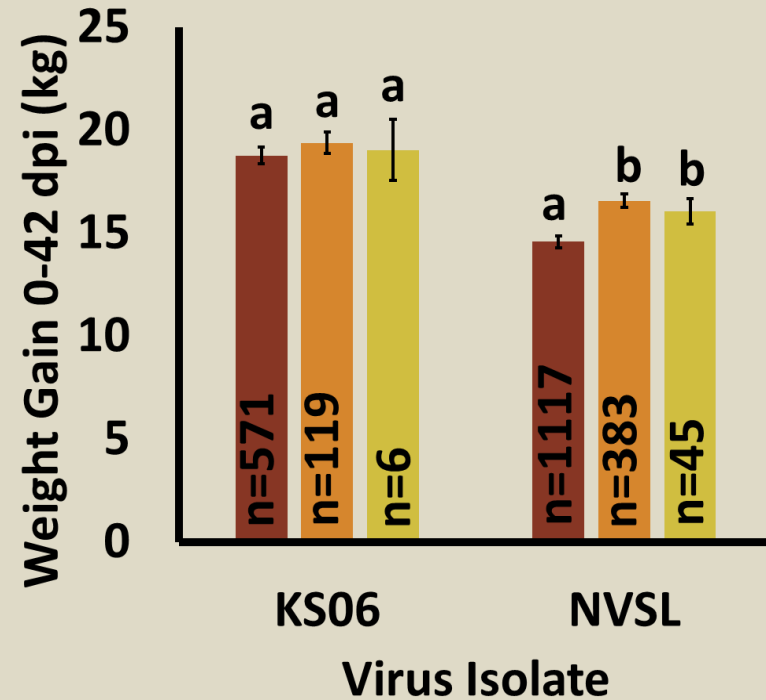


Hess et al. 2015

## VIRAL LOAD

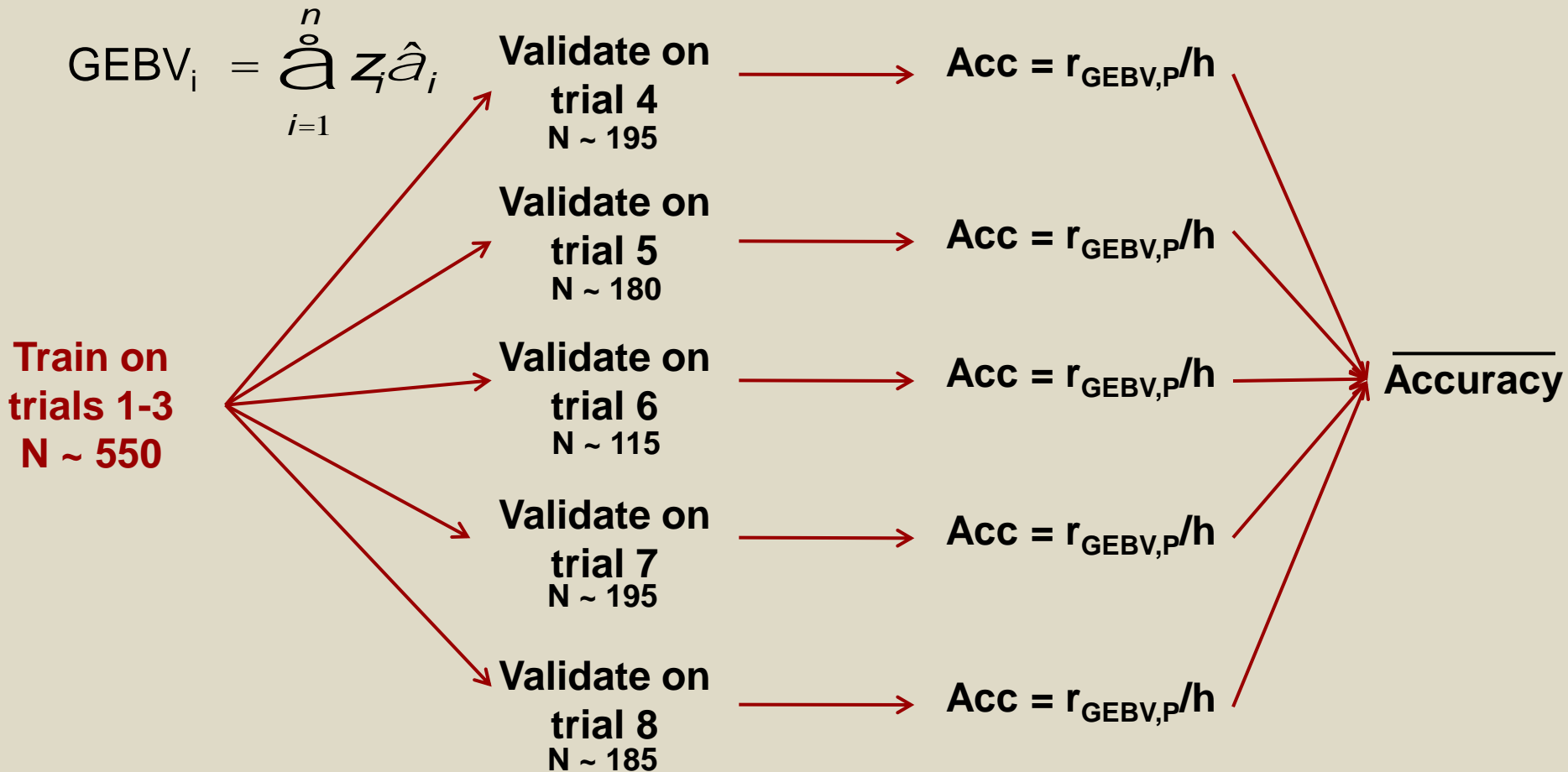


## WEIGHT GAIN



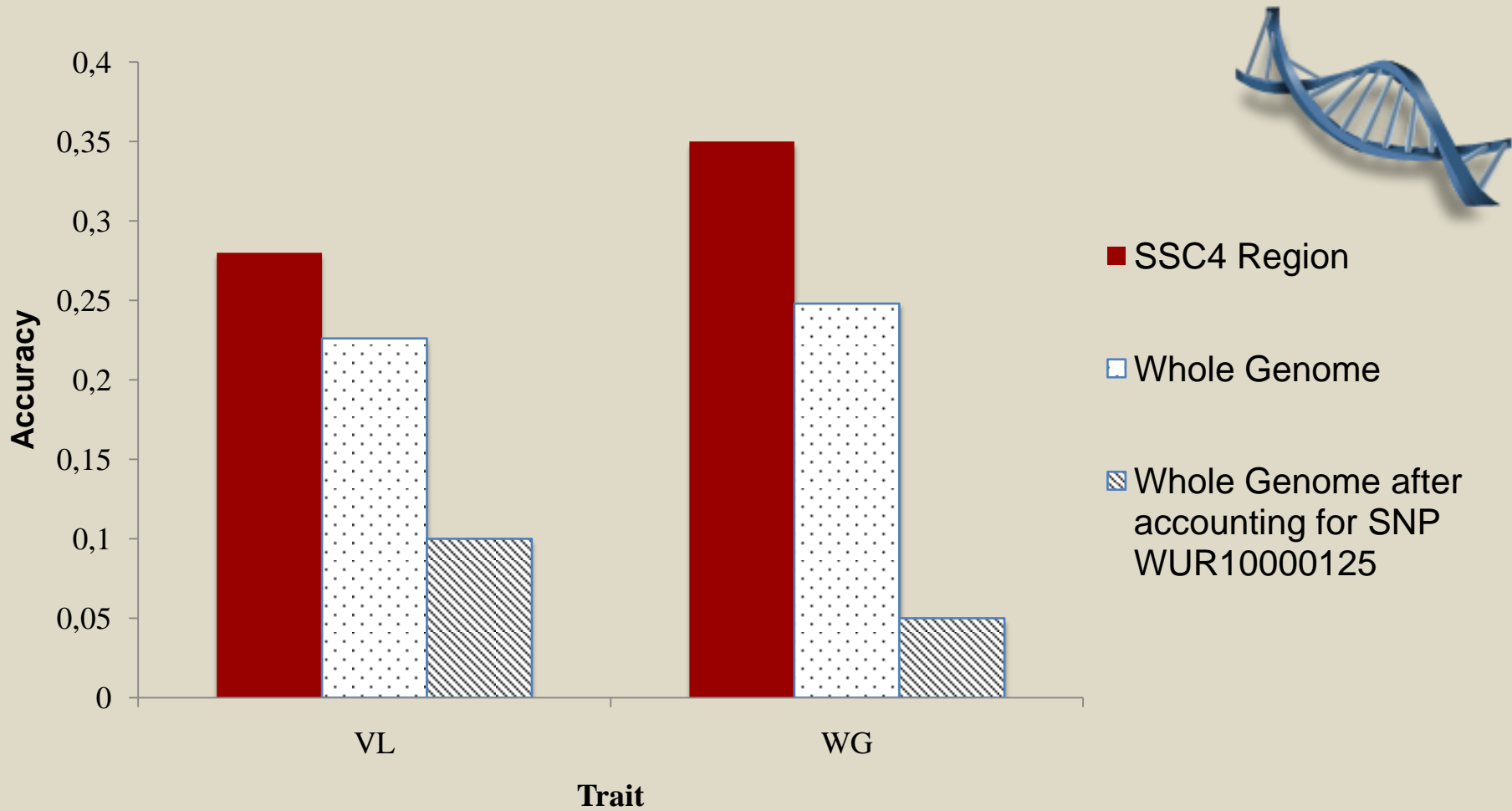
# Genomic Prediction of PRRS infection response

(Boddicker et al. 2014 GSE)



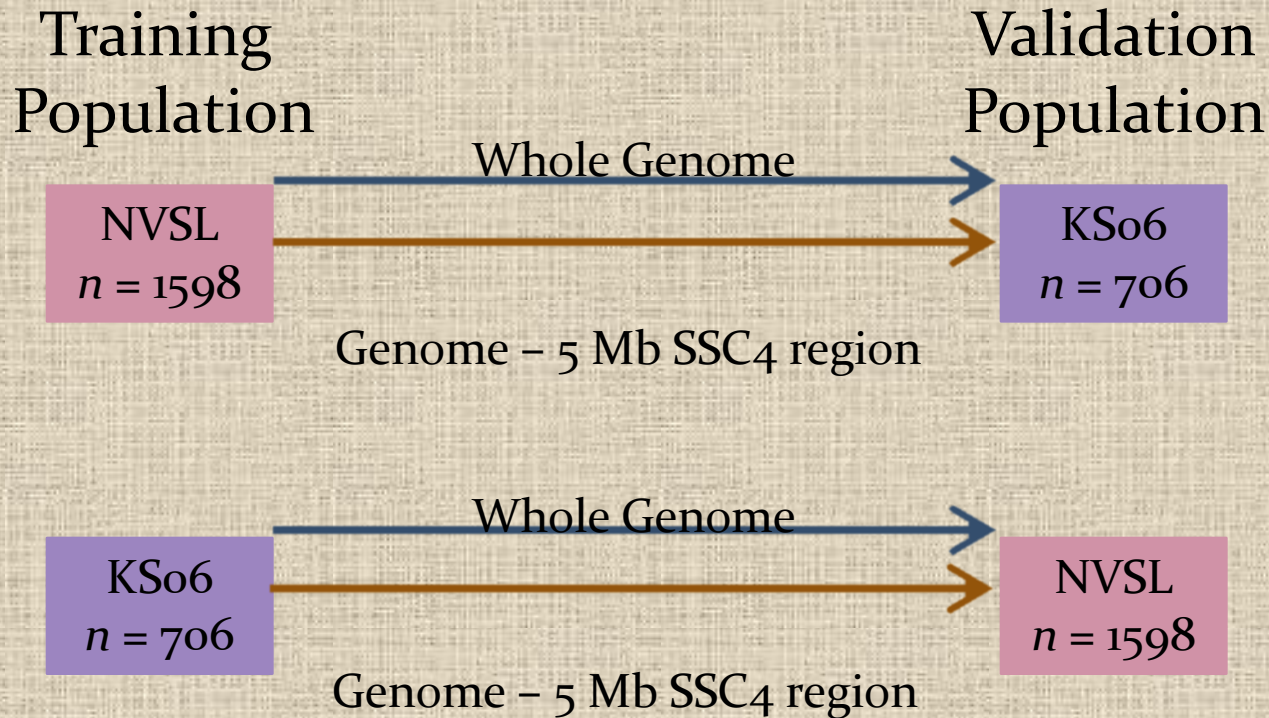


# Genomic Prediction Validation



# Genomic Prediction across Isolates

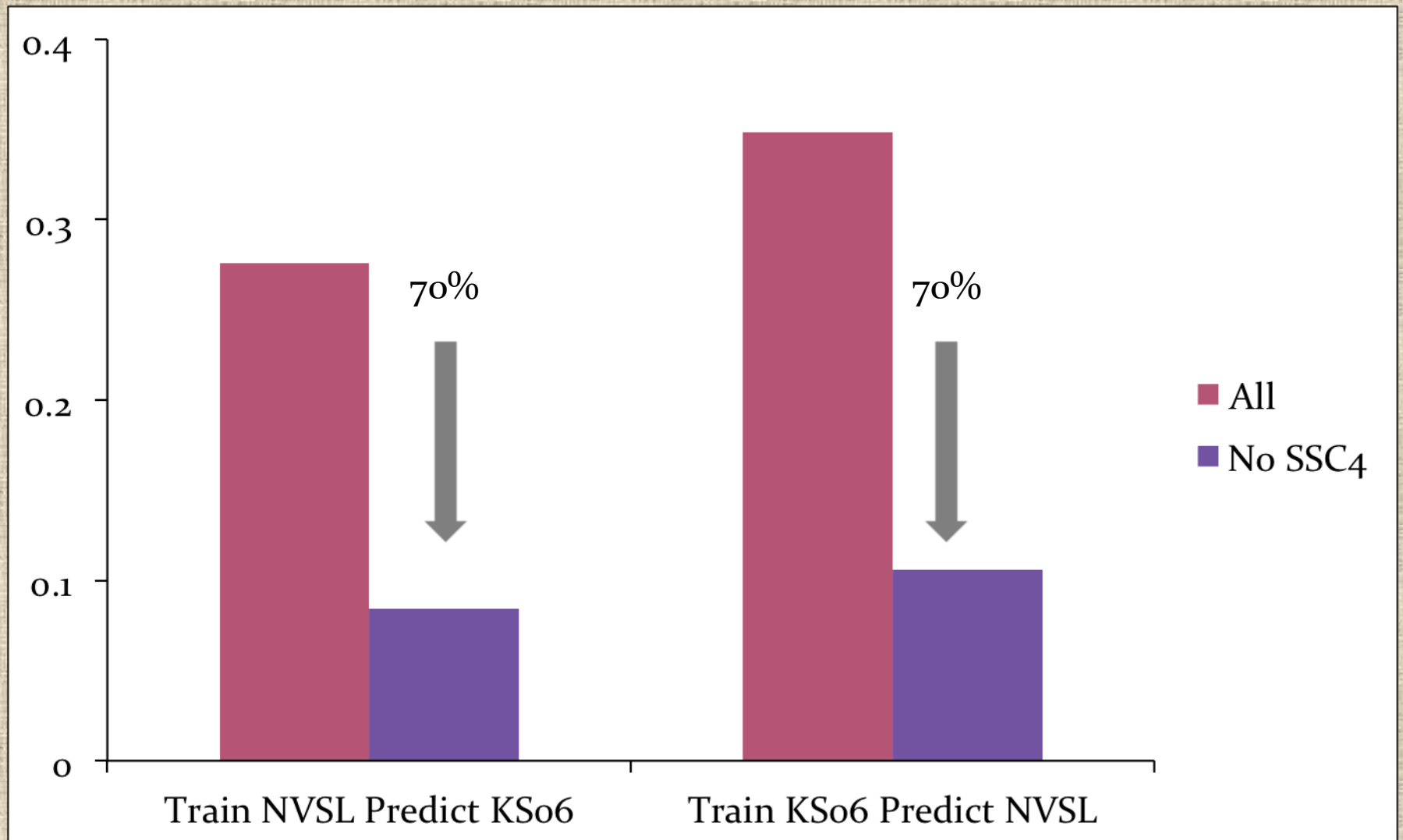
(Waide et al. 2015)



$$\text{Accuracy} = r_{P,EBV} / \sqrt{h^2_{\text{Validation}}}$$

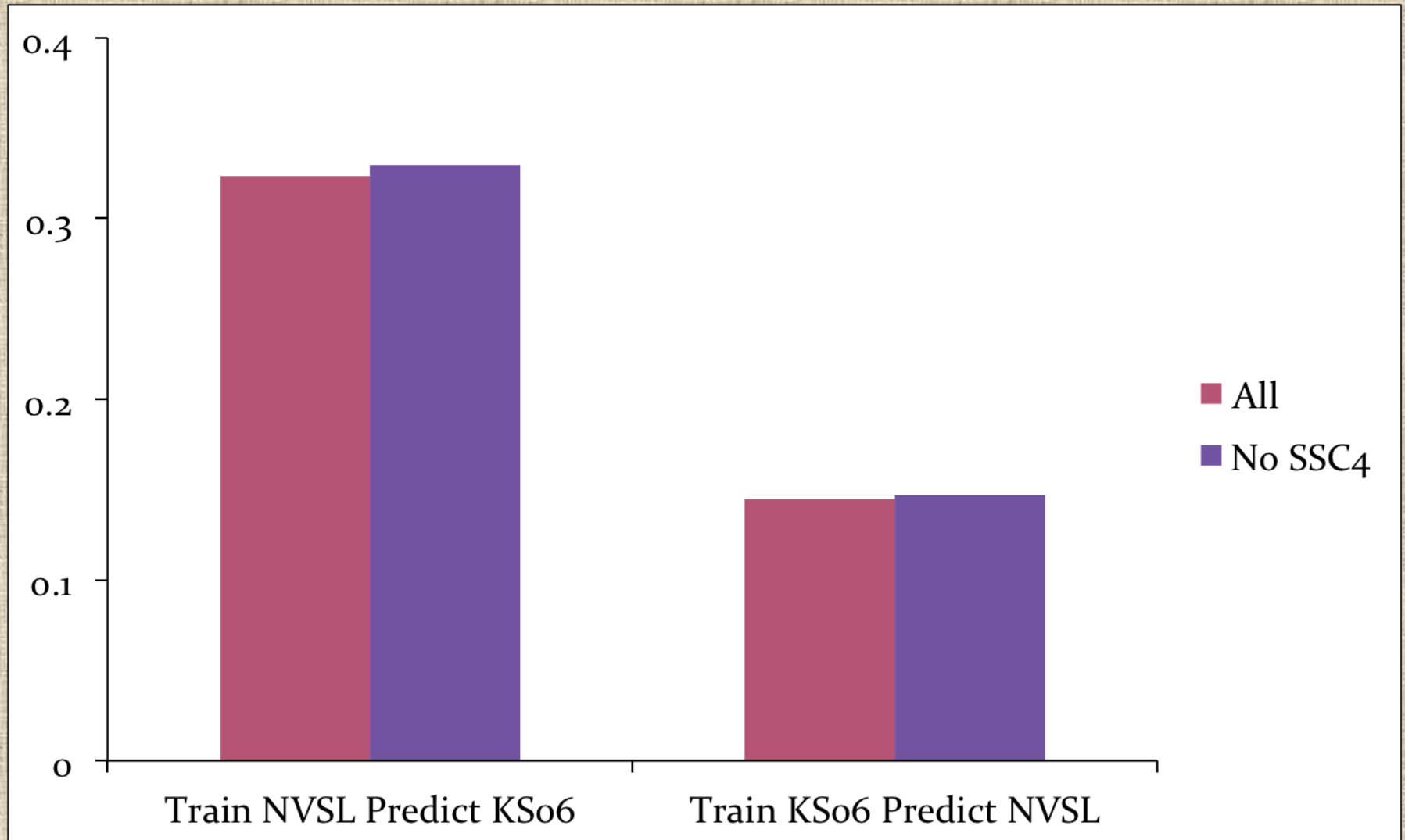
# Genomic Prediction Accuracies

## VL

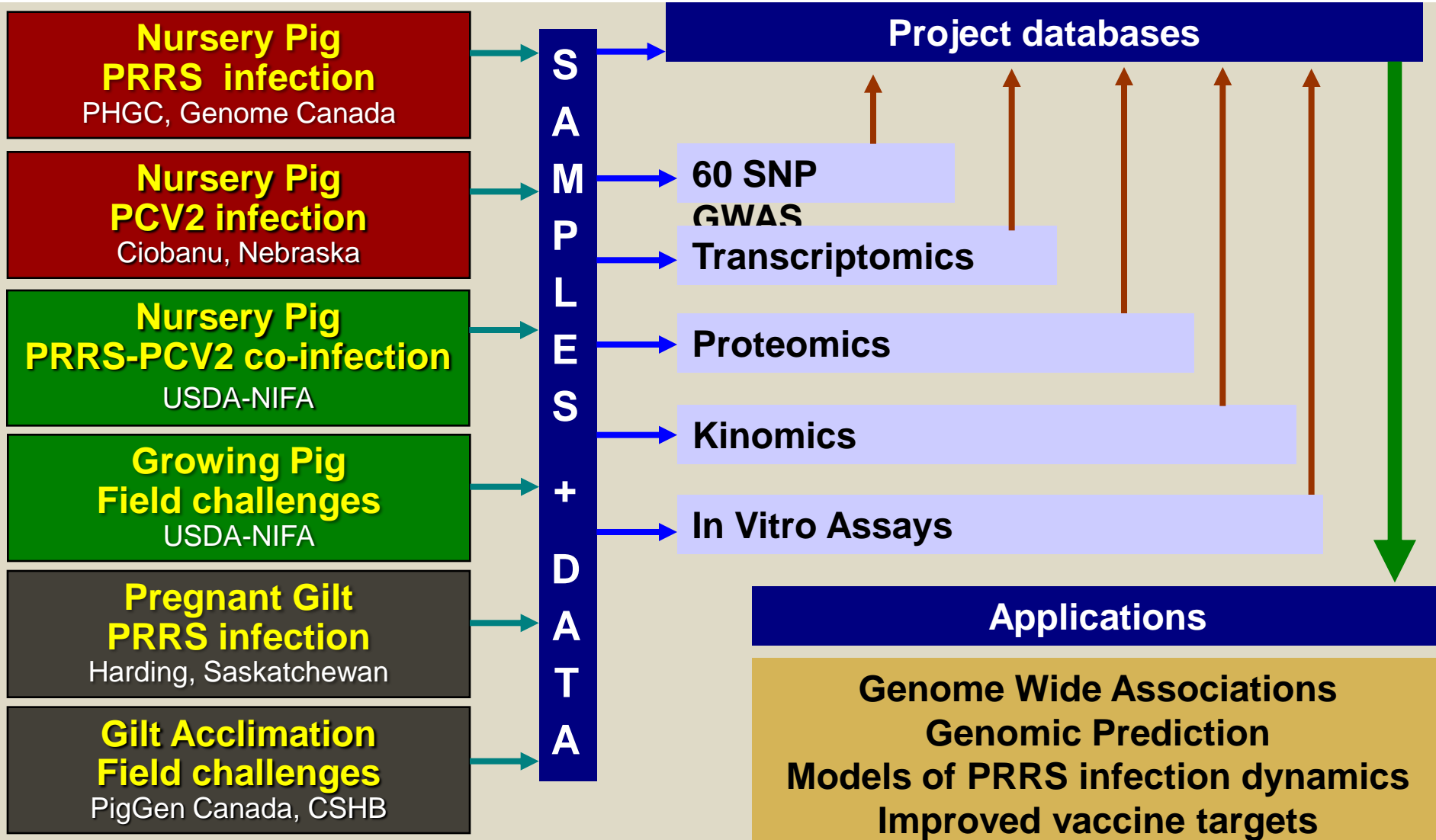


# Genomic Prediction Accuracies

## WG



# Integrated International Interdisciplinary Projects





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# Reproductive PRRS Outbreak Study

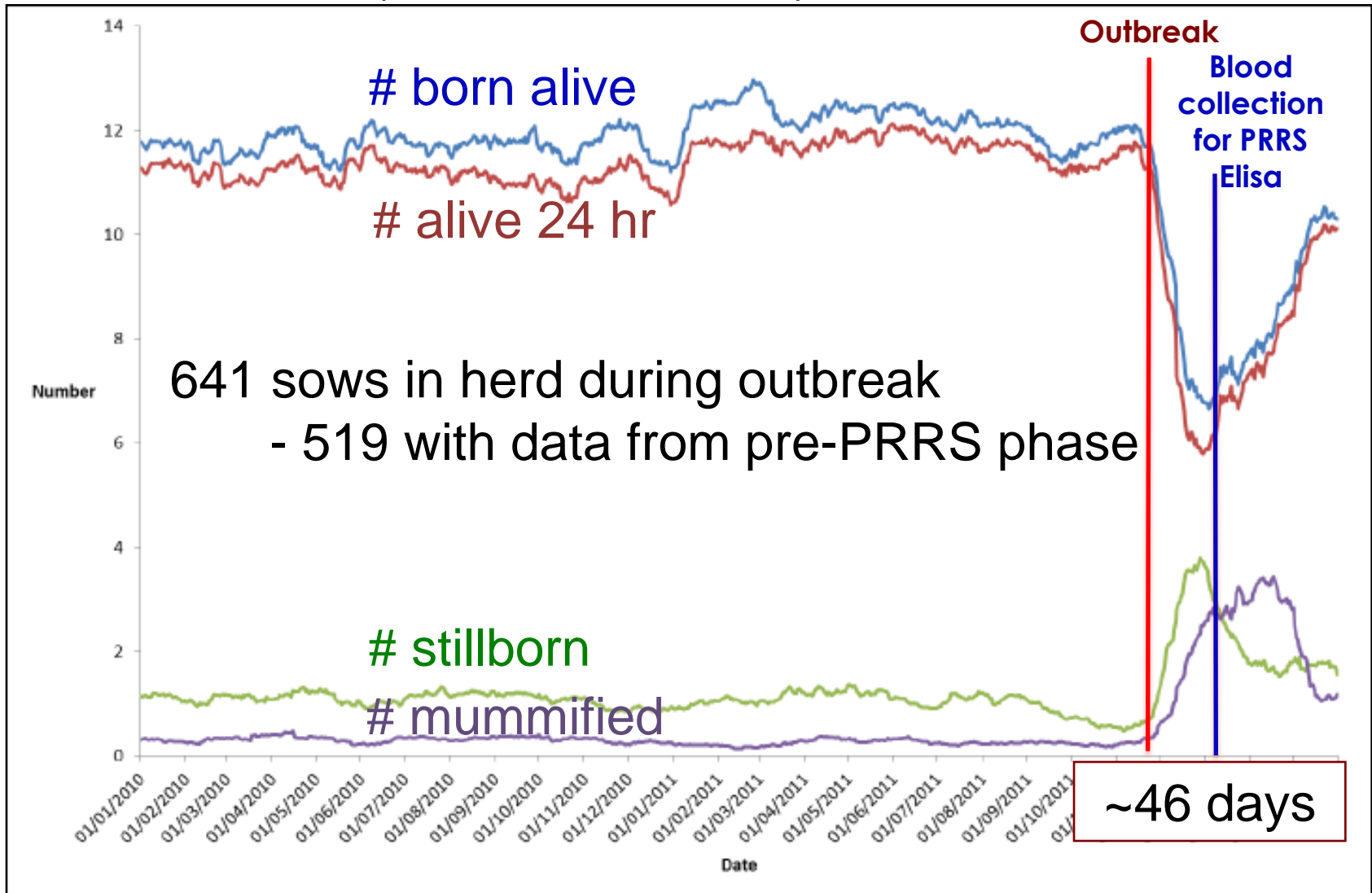
**Serão N.V.L., O. Matika, R.A. Kemp, J.C.S. Harding, S.C. Bishop, G.S. Plastow, J.C.M. Dekkers**

Genetic analysis of reproductive traits and antibody response  
in a PRRS outbreak herd

*Journal of Animal Science (2014) 92:2905-2921*

# Identification of PRRS outbreak

- PRRS Outbreak (Winter of 2011/12)

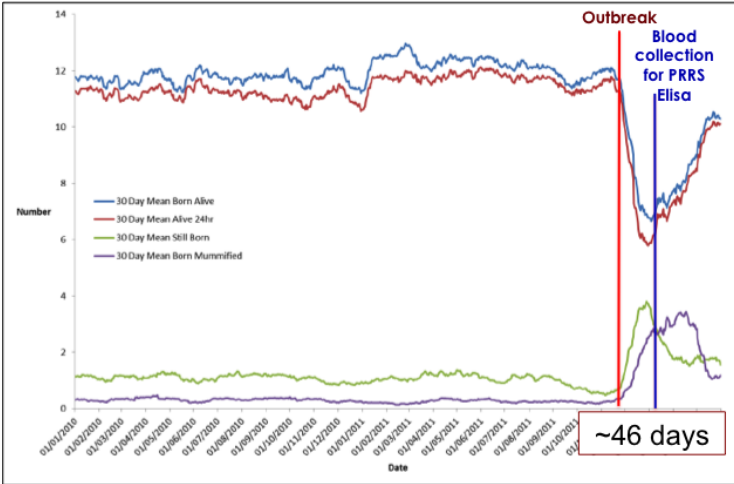




# Reproductive PRRS

## Outbreak Study

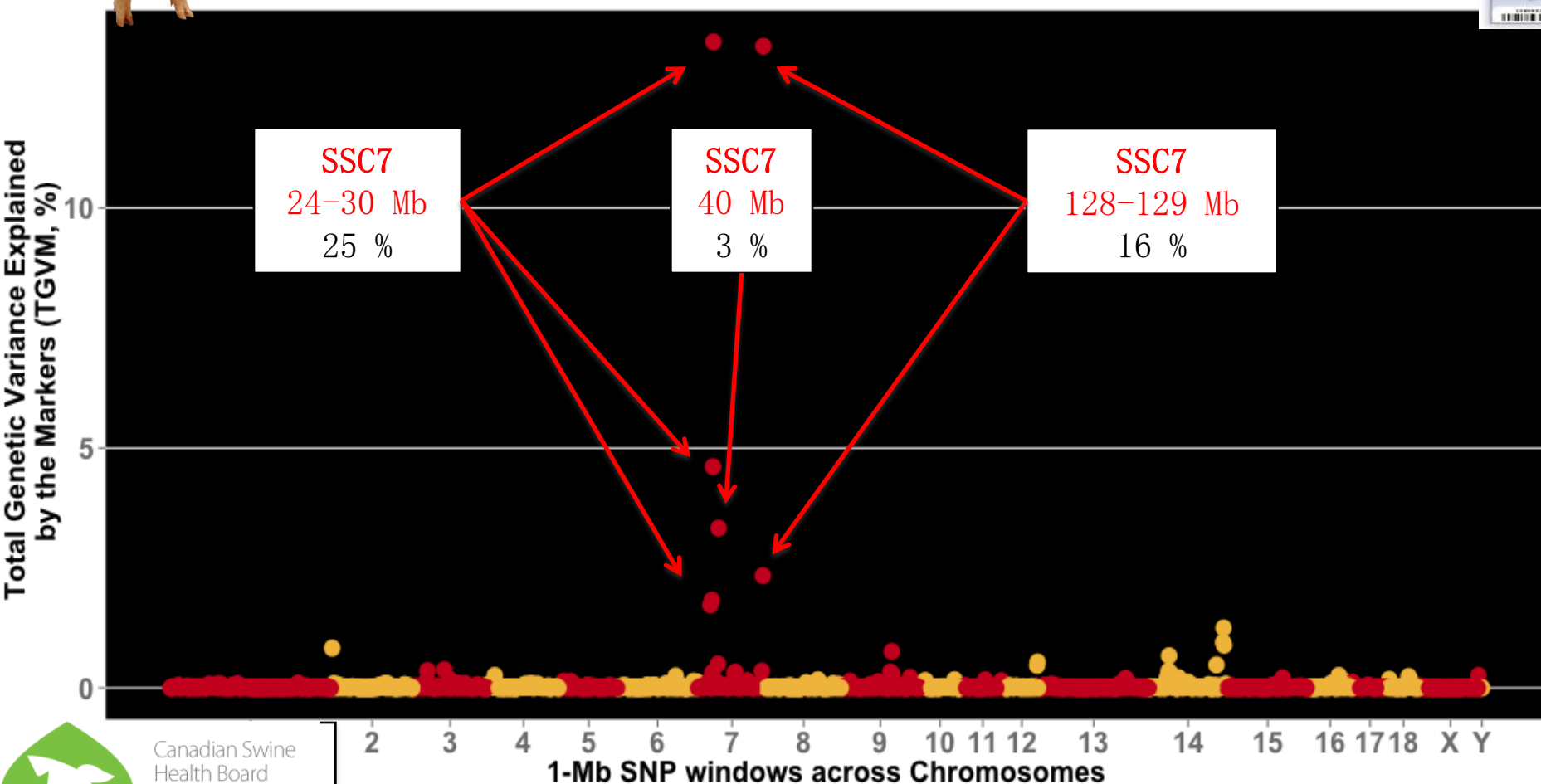
Correlations of S/P ratio with reproductive traits during PRRS phase



## Estimates of heritability (se)

Trait	Pre-PRRS phase		<i>Pheno- typic correl.</i>	<i>Genetic corre- lation</i>
		PRRS phase		
# born alive	0.08 (.03)	0.09 (.07)	0.06 (.05)	<b>0.73</b> (.24)
# stillborn	0.12 (.03)	0.06 (.07)	-0.07 (.05)	<b>-0.72</b> (.28)
# mummified	0.01 (.01)	0.08 (.07)	-0.04 (.05)	<b>-0.66</b> (.28)
% born dead	0.09 (.02)	0.07 (.06)	-0.04 (.05)	<b>-0.70</b> (.27)
# weaned	0.03 (.02)	0.09 (.07)	-0.04 (.05)	<b>-0.58</b> (.29)
S/P ratio	— —	<b>0.45</b> (0.13)		

# Genomic Regions affecting S/P ratio

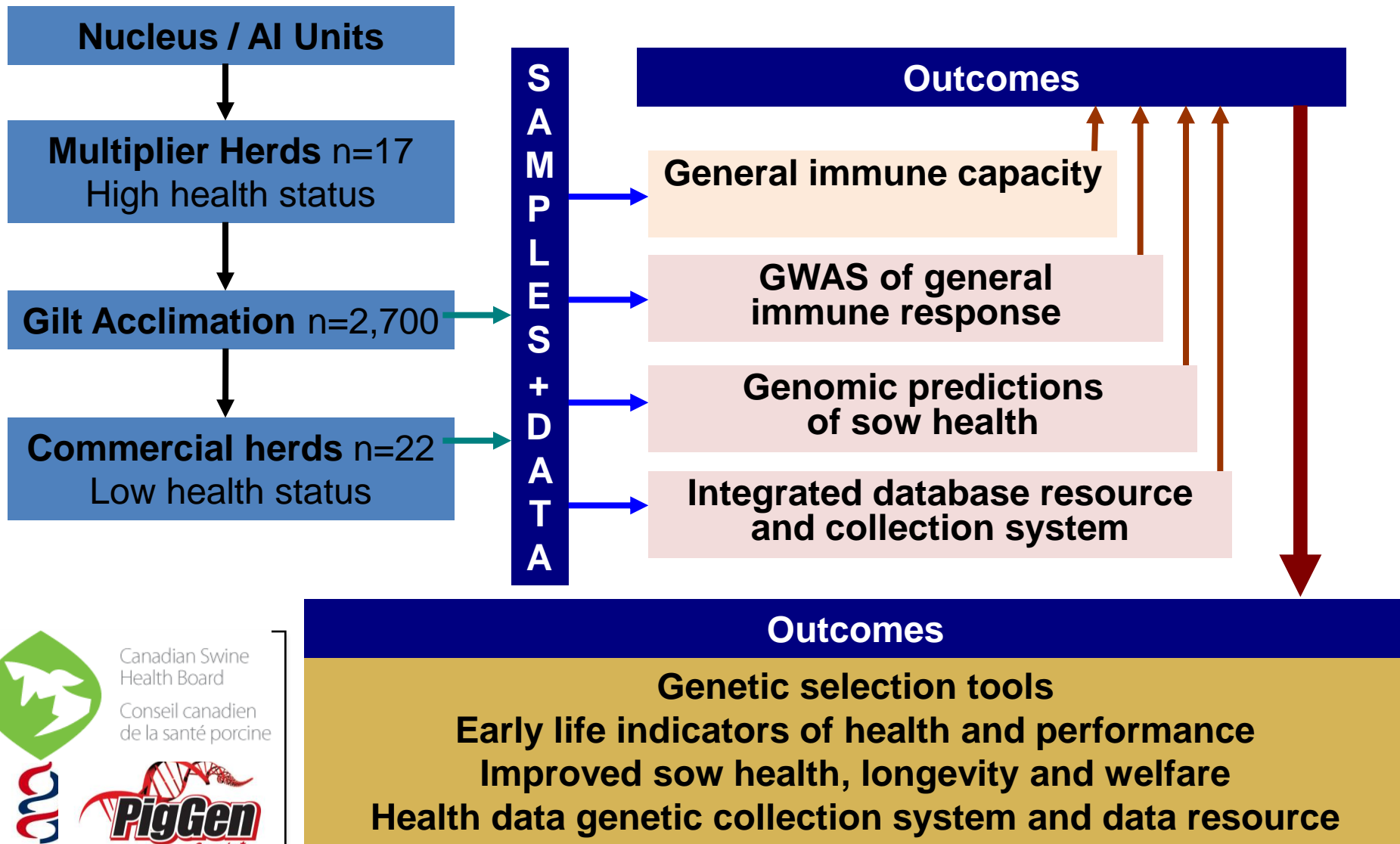


Serão N.V.L., O. Matika, R.A. Kemp, J.C.S. Harding,  
S.C. Bishop, G.S. Plastow, J.C.M. Dekkers  
*Journal of Animal Science* (2014) 92:2905-2921



# Gilt Acclimation Project

Groups of Clean Replacement Gilts → Health Challenged Herds



# Gilt Acclimation - Initial Results



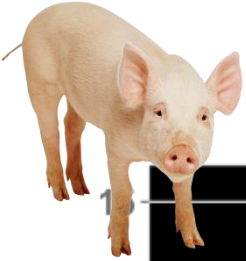
- **Heritabilities**

- **Average Daily Gain during acclimation** **0.09**
- **PRRSv S/P ratio**
  - On entry ( 3% PRRS+) **0.13**
  - During acclimation (~40 days after entry) **0.47**  
(83% PRRS+)
  - During first parity (67% PRRS+) **0.11**



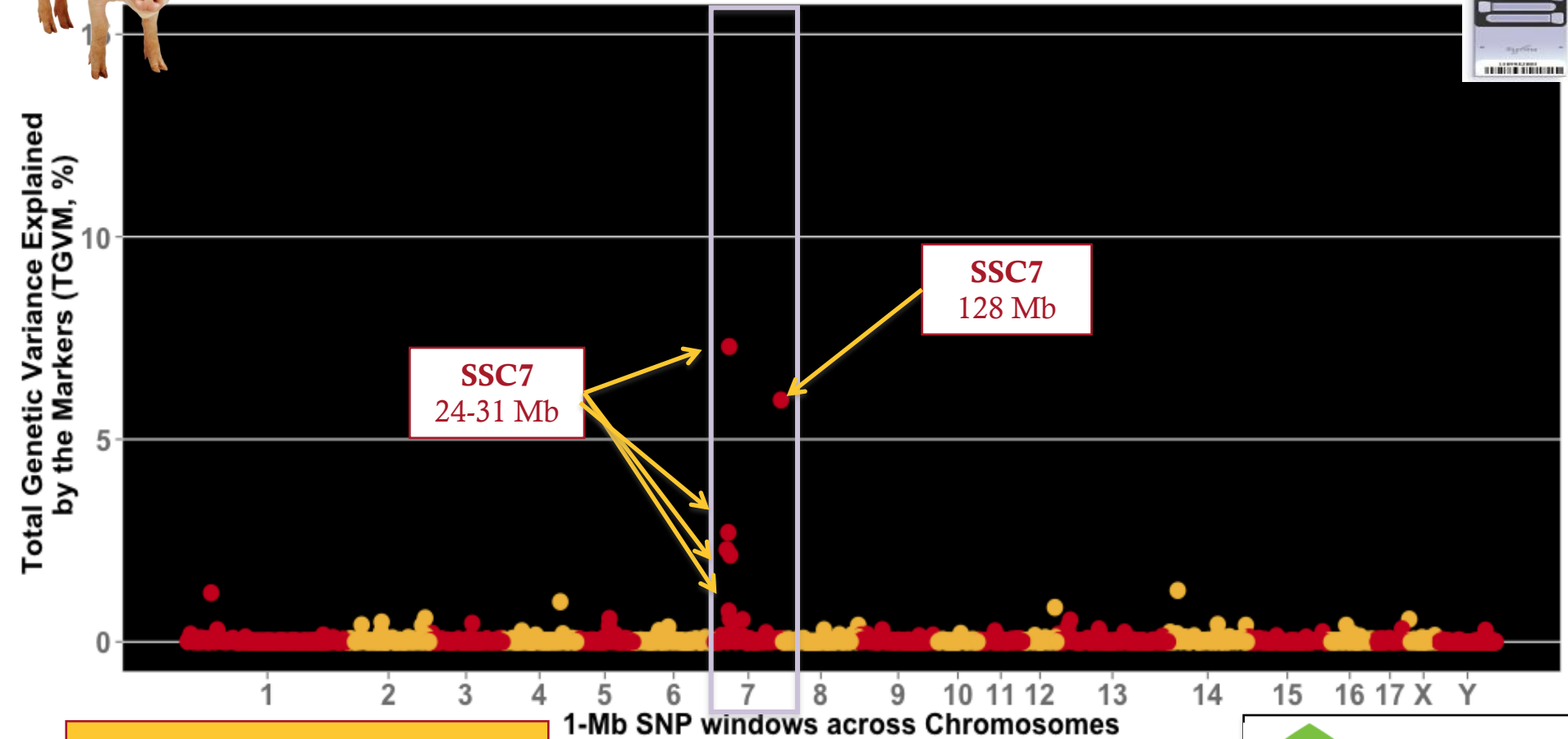
Serão N.V.L., R.A. Kemp, B.E. Mote, J.C.S. Harding,  
P. Wilson, S.C. Bishop, G.S. Plastow, J.C.M. Dekkers

10<sup>th</sup> World Congress Genetics Applied to Livestock Production (2014)



# Effects of MHC on S/P ratio validated

Post-Acclimation S/P ratio



Serão et al. (2014a)

S/P ratio @ ~42 days

24-30 Mb: 25%

128-129 Mb: 16%



Canadian Swine Health Board  
Conseil canadien de la santé porcine



GenomeCanada



# Accuracy of Genomic Prediction for PRRS S/P Ratio



Can we use genetic marker effects estimated in the gilt acclimation data to predict S/P ratio in the outbreak herd?

## Training (Gilt Acclimation)

**Day 0 S/P**

( $n = 2220$ ;  $h^2 = 0.42$ )

**Post-Acclimation S/P**

( $n = 2095$ ;  $h^2 = 0.31$ )

**Parity 1 S/P**

( $n = 919$ ;  $h^2 = 0.12$ )

Genomic  
prediction →

## Validation (Outbreak Herd)

(Serão et al., 2014a)

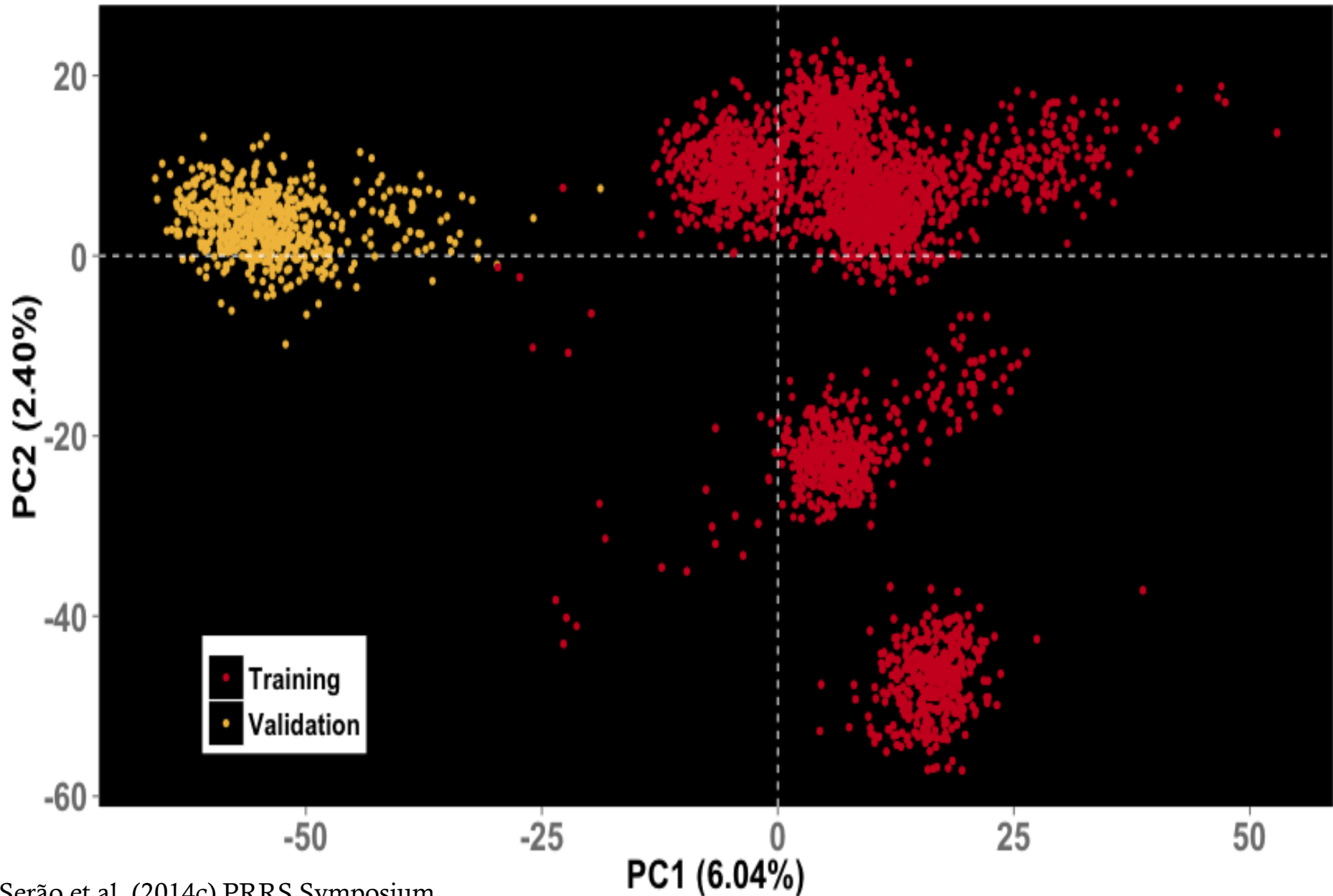
S/P ratio @ ~ 42 days

( $n = 629$ ;  $h^2 = 0.42$ )

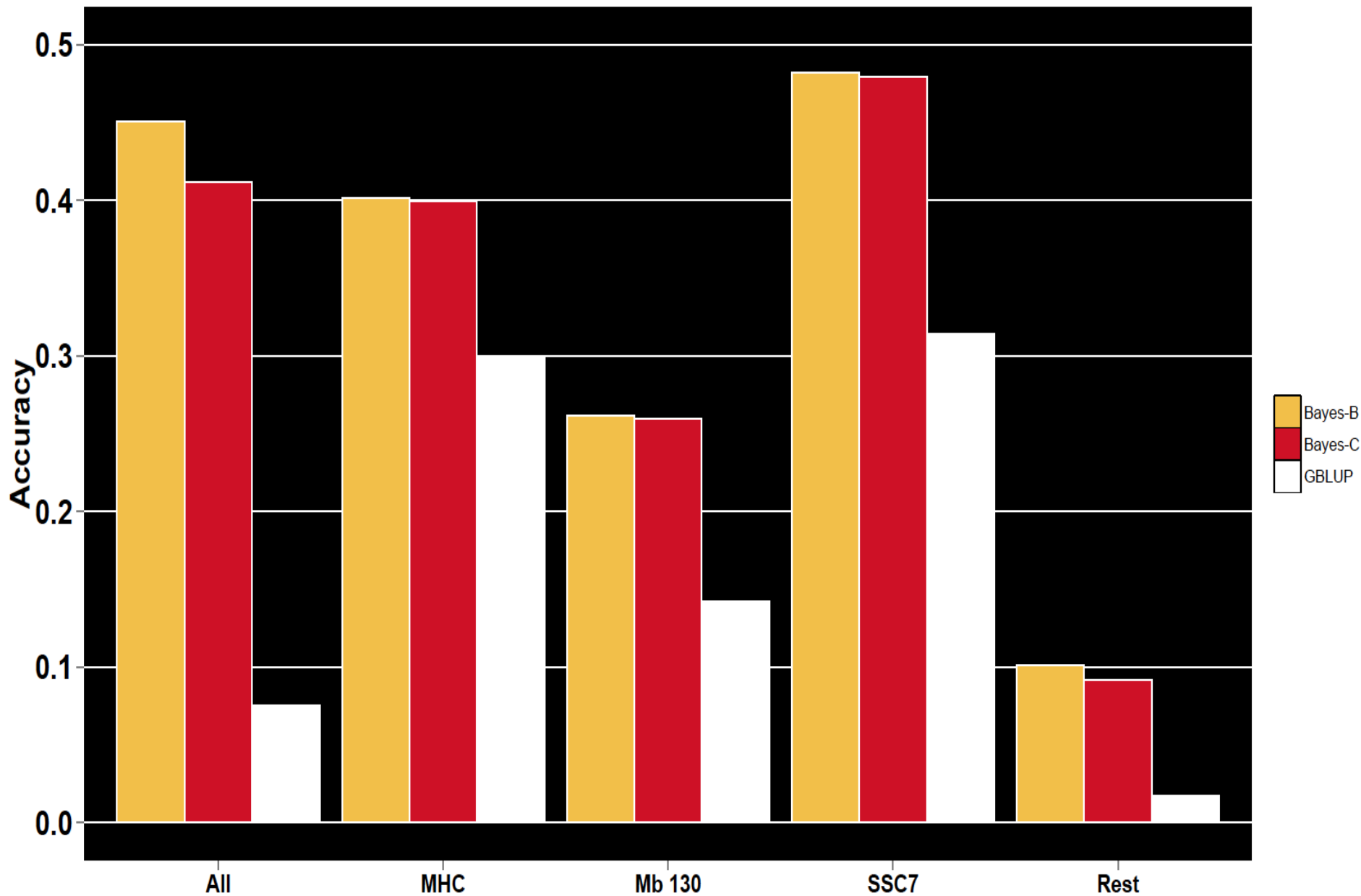
$$\text{Prediction Accuracy} = \frac{r_{(GEBV, Phenotype)}}{\sqrt{h^2}}$$



# Genomic Prediction of S/P ratio



# Genomic Prediction of S/P ratio Serão et al. (2015)





# Can we use genomic predictions for S/P ratio based on the gilt acclimation data to predict reproductive performance in the outbreak herd?



## Training (Gilt Acclimation)

Day 0 S/P

( $n = 2220$ ;  $h^2 = 0.42$ )

Post-Acclimation S/P

( $n = 2095$ ;  $h^2 = 0.31$ )

Parity 1 S/P

( $n = 919$ ;  $h^2 = 0.12$ )

Genomic prediction

Genomic prediction

$$\text{Prediction Accuracy} = \frac{r_{(GEBV, Phenotype)}}{\sqrt{h^2}}$$

## Validation (Outbreak Herd)

(Serão et al., 2014a)

S/P ratio @ ~ 42 days

( $n = 629$ ;  $h^2 = 0.42$ )

$r_g = 0.65-0.75$

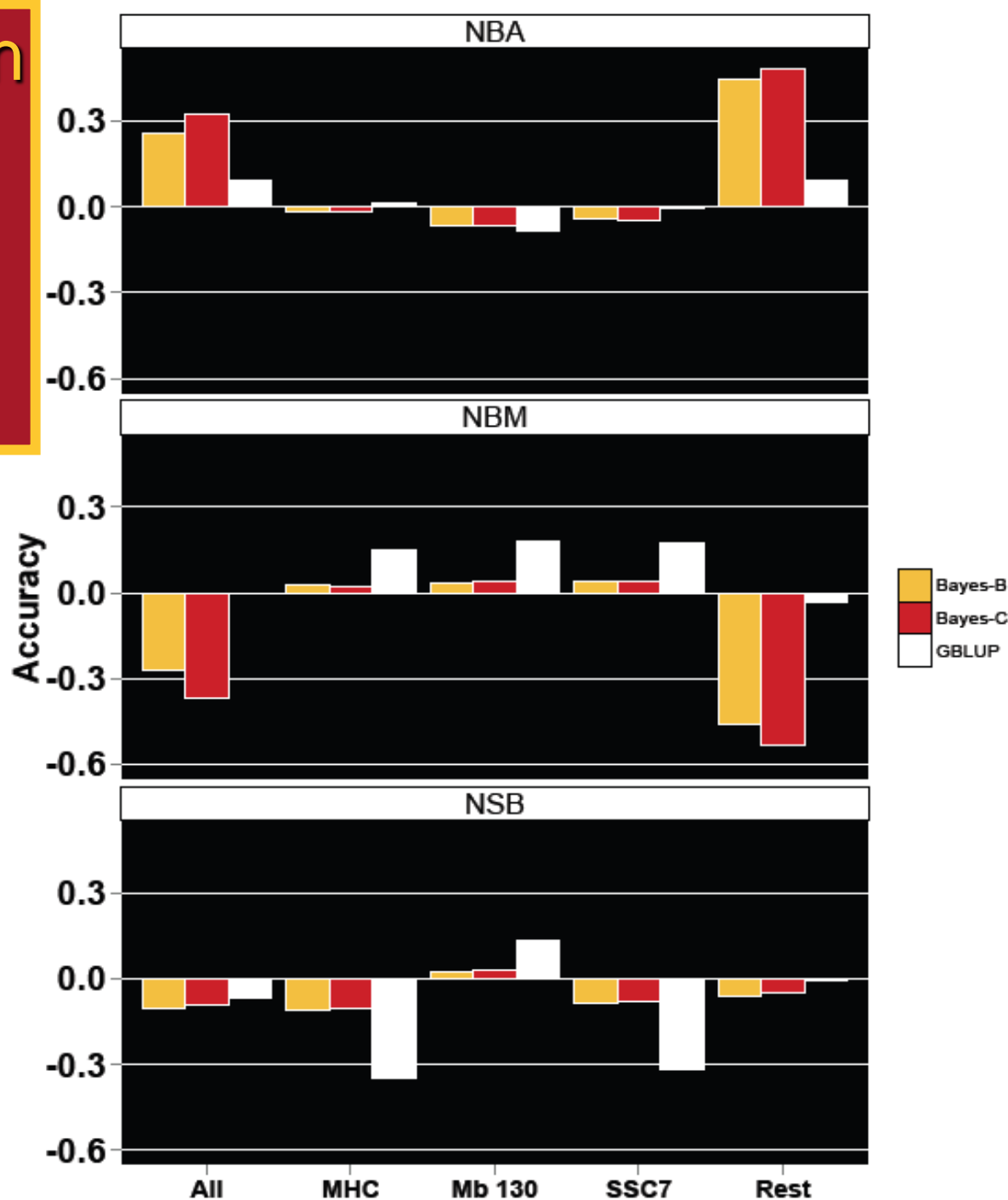
Reproductive Performance

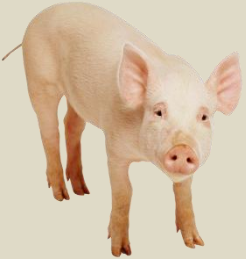
( $n = 402$ ;  $h^2 = 0.08$ )

# Genomic Prediction of Reproductive Performance based on S/P ratio

*Genetic correlation with S/P ratio in outbreak herd*

#born alive	<b>0.73</b> (.24)
#mummies	<b>-0.66</b> (.28)
#stillborn	<b>-0.72</b> (.28)





# Conclusions - PRRS



- Piglet response to experimental PRRSv challenge has a sizeable genetic component.
- A region on Chromosome 4 contains a major gene for host response to PRRSv in growing piglets.
- PRRS S/P ratio following PRRS challenge is heritable and may be a good genetic indicator of reproductive performance during PRRS.
- The MHC is a major contributor to differences in PRRS S/P ratio following challenge but not necessarily to reproductive performance during a PRRS outbreak.
- **Genetic selection for improved host response to PRRSv appears possible**
  - and can be an important component in the fight against PRRS

# Final Conclusions

- GS is revolutionizing dairy cattle breeding
- GS has promise also for other species
- **But requires:**
  - Large data sets, continuous re-training
  - Strategic use of low-density panels and genotype imputation to reduce cost
  - May require redesign of breeding programs
  - Initial implementation likely within breeds
    - Across-breed prediction problematic at present
  - **GWAS remains important for traits without routine phenotype**