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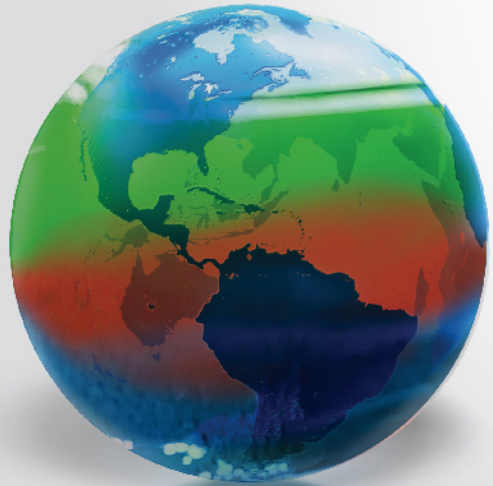


Why vaccines feed the world?

Will genomics spell the end of vaccines?

John Harding
Professor, Swine Production Medicine
University of Saskatchewan

PREVENTION WORKS
Shaping the future of swine health

Boehringer Ingelheim

Traditional health management approaches

PAST / PRESENT

- Antimicrobials
- Vaccines
- Herd elimination
- Regional control
- Biosecurity

CURRENT THREATS

- Antimicrobial usage / resistance
- Cost / time of vaccine development
- Elimination / regional re-breaks
- Biosecurity: implementation & lack of scientific assessment

Traditional vaccine strategies (pork industry)

PAST / PRESENT

- Whole cell killed
- Attenuated
- Multivalent
- Subunits
- Autogenous

STRATEGIES

- Identify risk / reward
- Identify target population
- Delivery parenteral, oral, transdermal
- Follow up / monitoring (clinical, diagnostic)

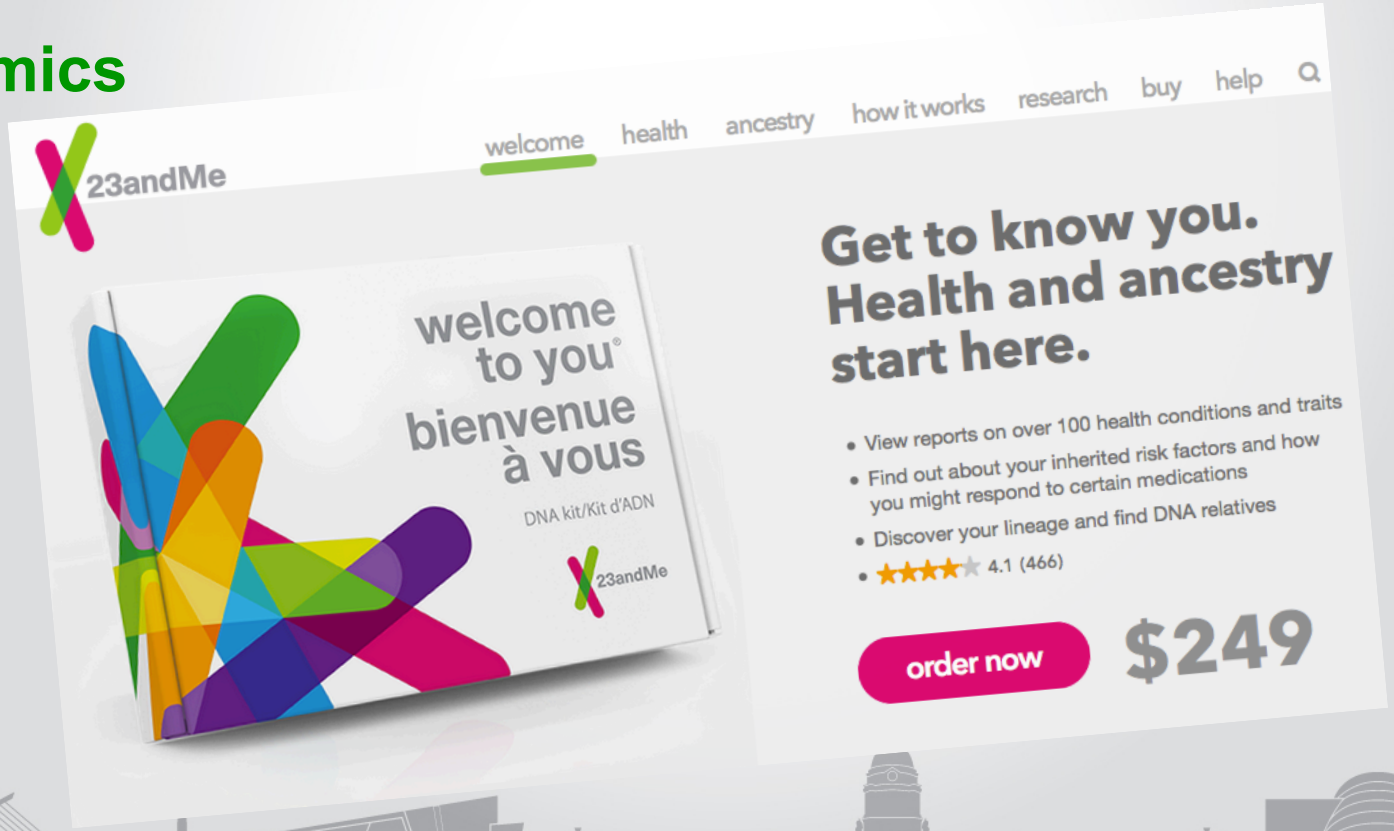
Need for improved health management strategies?

- New diseases
- Pathogen evolution
- Reduced antimicrobials
- Intensified production
- Zoonotic threats
- Animal welfare
- Public scrutiny

WILL VACCINES BE ENOUGH?

- Identify risk / reward
- Identify target population
- Delivery parenteral, oral, transdermal
- Follow up / monitoring (clinical, diagnostic)

Genomics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www.23andme.com

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Inherited Conditions

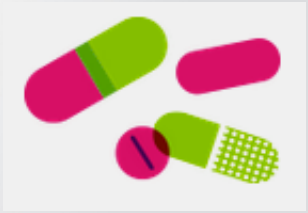
Cystic fibrosis
Sickle cell anemia
Tay-Sach's Disease
41 more…

Traits

Alcohol flush reaction
Asparagus metabolic detection
Breast morphology
Caffeine metabolism
Earwax type
Pain sensitivity
Male baldness
37 others…

Genetic risk factors

Alzheimer's
Caeliac disease
Parkinson's
Hereditary breast & ovarian cancers
8 others…



Drug response

Hep C treatment response
Warfarin sensitivity
Proton pump inhibitor metab
8 others…

NEOGEN

Animals Tested: 22

Choose Herd:

Tools

HOUSA000072390982 | NE17379

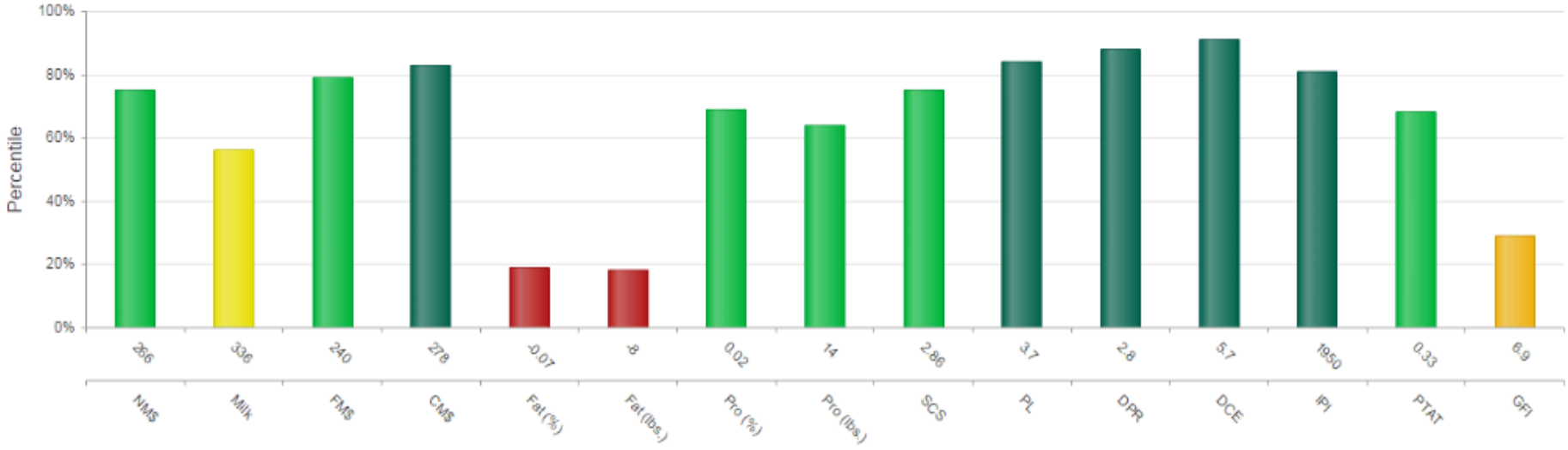
Sire HOUSA000062253367
Dam HOUSA000072390933

F - HO - DOB 05/08/15
Categories:

Key Traits

Compare To My Herd Only

Viewing: Key Traits Compared To All Herds



Health Yield Fertility

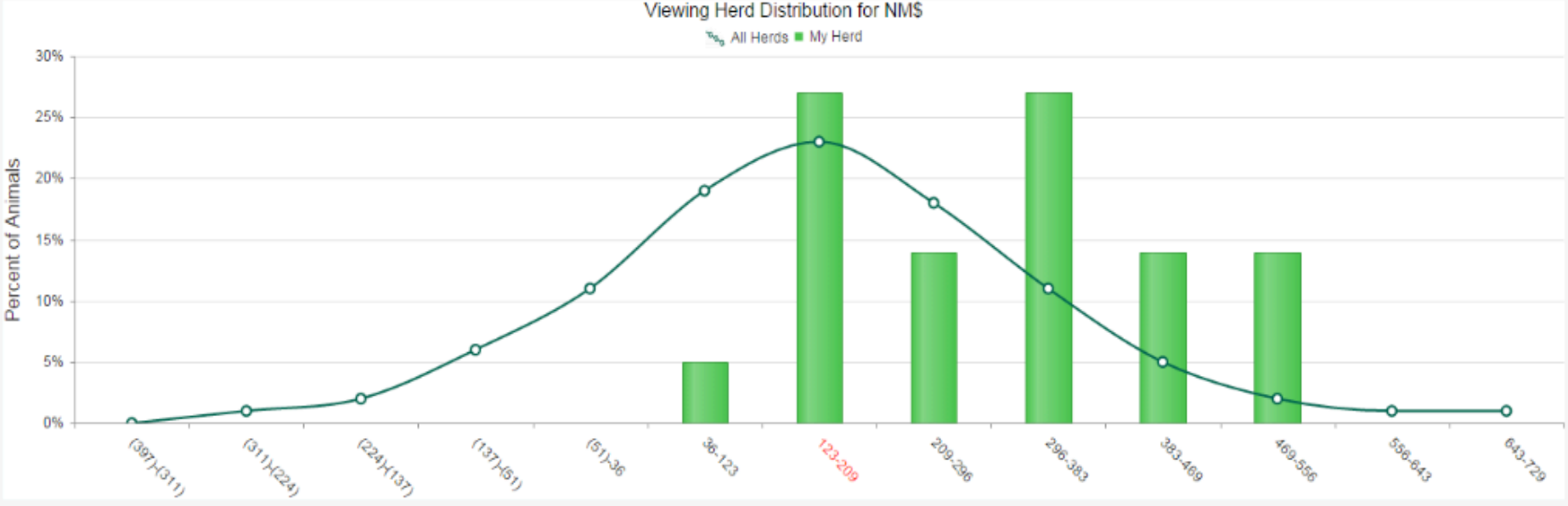
Genetic Conditions

NEOGEN

Animals Tested: 22

Choose Herd:

NM$ | HO | USDA



123-209

Farm ID	Official ID	Sex	Breed	Birth	NM$	NM Gen REL %	NM$ USA %	Milk	FM$	CM$	Fat (%)	Fat (lbs.)	Pro (%)	Pro (lbs.)	SCS	PL	DPR	DCE	IPI	PTAT	GFI
NE25...	074436066	F	HO	01/07/15	201	73	86	1015	238	185	-0.06	23	-0.03	23	3.08	1.1	-1.1	7.5	1826	0.82	8.3

Genomics: opportunity for swine health management?

Litter size
- Estrogen receptor
- Erythropoeitin receptor

Growth, feed intake & efficiency

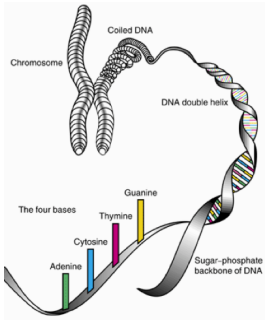
Fat content

Meat quality
- Porcine stress syndrome (HAL)
- Rendement Napole (RN)

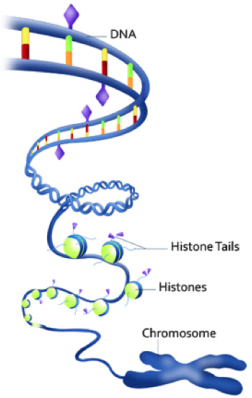
Disease
- *E. coli* resistance (F4 ab/ac)
- PRRSV resilience
- PCV2

Use of “functional genomics” to improve swine health

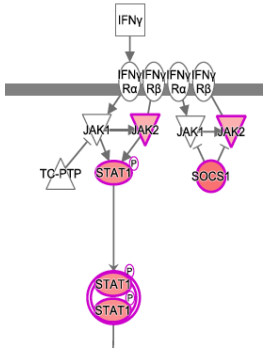
Genome



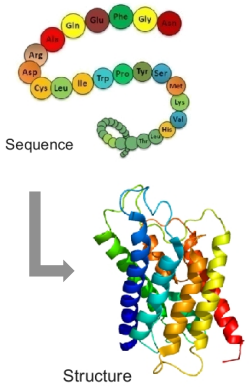
Epigenome



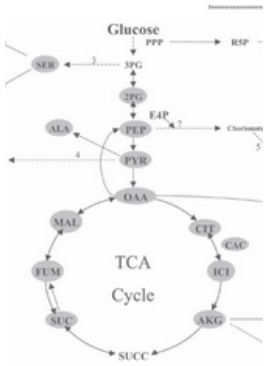
Transcriptome



Proteome



Metabolome



Phenome

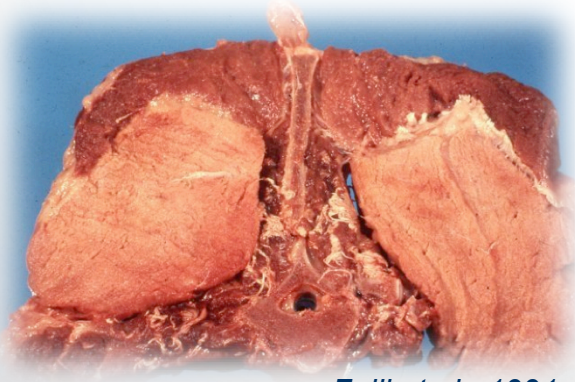
Genomic application for improved health phenotypes

a) Single markers

FUT1

Miejerink et al., 2000

HAL 1843



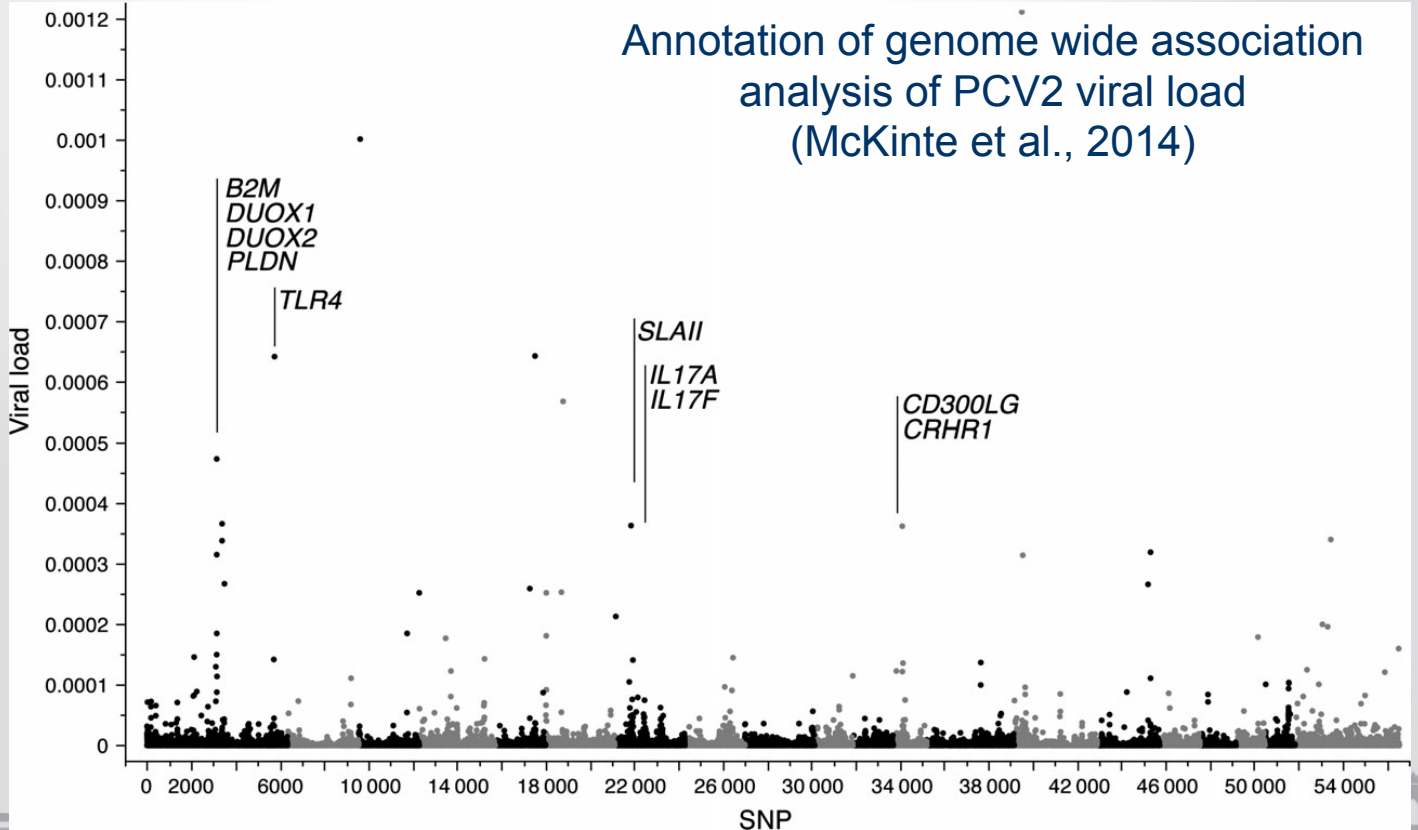
Fujii et al., 1991

RN

de Vries et al., 1997

Genomic application for improved health phenotypes

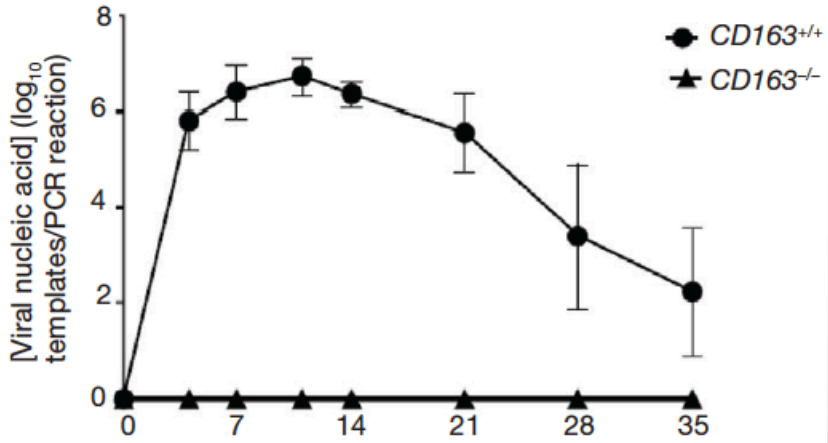
b) Polygenic traits



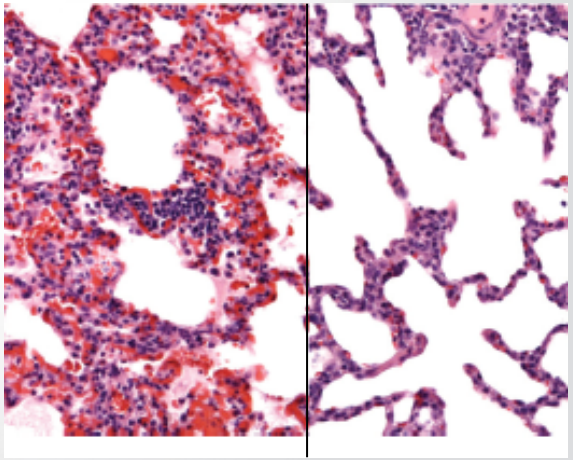
Genomic application for improved health phenotypes

c) Gene editing (CRISPR/Cas9)

PRRSV RNA concentration



Lung histopathology



CD163$^{+/+}$ CD163$^{-/-}$

Whitworth et al., 2016

Will genomics be sufficient to control all diseases?

Doubtful

- Cost
- Polygenic traits
- Interaction with other valuable traits
- Involvement with MHC genes (SSC 7)
- Resistance versus tolerance versus resilience
- Complex logistics from discovery to application
- Consumer and regulatory acceptance (editing)

Application of genomics to improve vaccines / strategies

Vaccine development / manufacturing

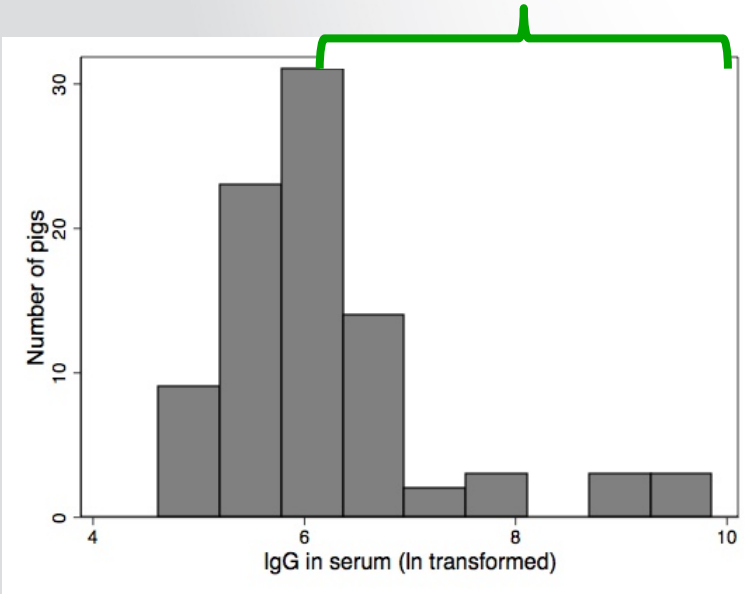
1. "Reverse vaccinology" – development of protein-based vaccines by using sequence data without bacterial propagation

"Vaccinomics" (genetics + epidemiology + genomics)

1. Selection of animals with improved vaccine response
2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring
3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes

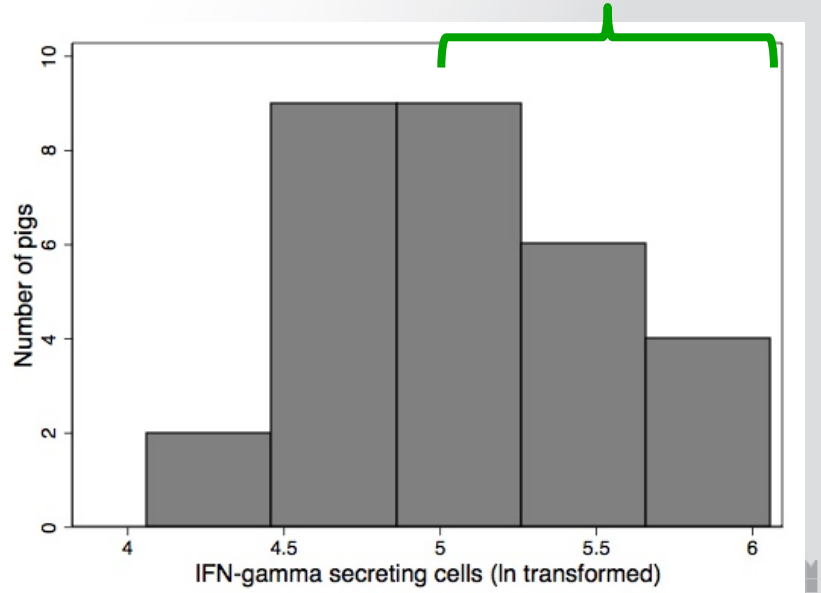
1. Selection of animals with improved vaccine response

M. hyopneumoniae IgG levels in serum following vaccination (n=100)



Harding et al., unpublished

M. hyopneumoniae IFNg secreting cells in blood following vaccination (n=66)



Harding et al., unpublished

Mechanisms of genetically-mediated vaccinal responses (human)

- ✓ HLA (MHC) class I and II polymorphisms
  - Measles, mumps, rubella
    - Antibody & cellular immune responses
    - IFN-gamma responses following vaccination
- ✓ Cytokine genes
  - IL-2, IL-4, IL-10, IL-12 responses (measles, mumps, hep B)
- ✓ Innate immunity
  - TLR2, TLR3, TLR4 responses (measles, rubella)

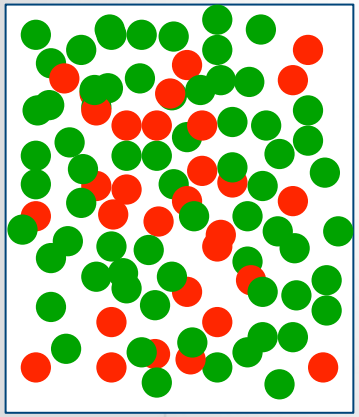
Reviewed by: Castiblanco & Anaya, Current Genomics, 2015

1. Selection of animals with improved vaccine response

- ✓ Relevant “test” of immune response following vaccination
- ✓ Could be antigen-specific response or generic immune response
- ✓ Test has moderate to high heritability and genetic correlation

  Humans: 40-70% heritability; high genetic correlation (40-90% of variability related to genetic factors)
- ✓ Initially – best to eliminate “low or non”-responders, versus selection of “high” responders?
- ✓ Feasibility: at laboratory and use in seedstock (nucleus) farms

2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring



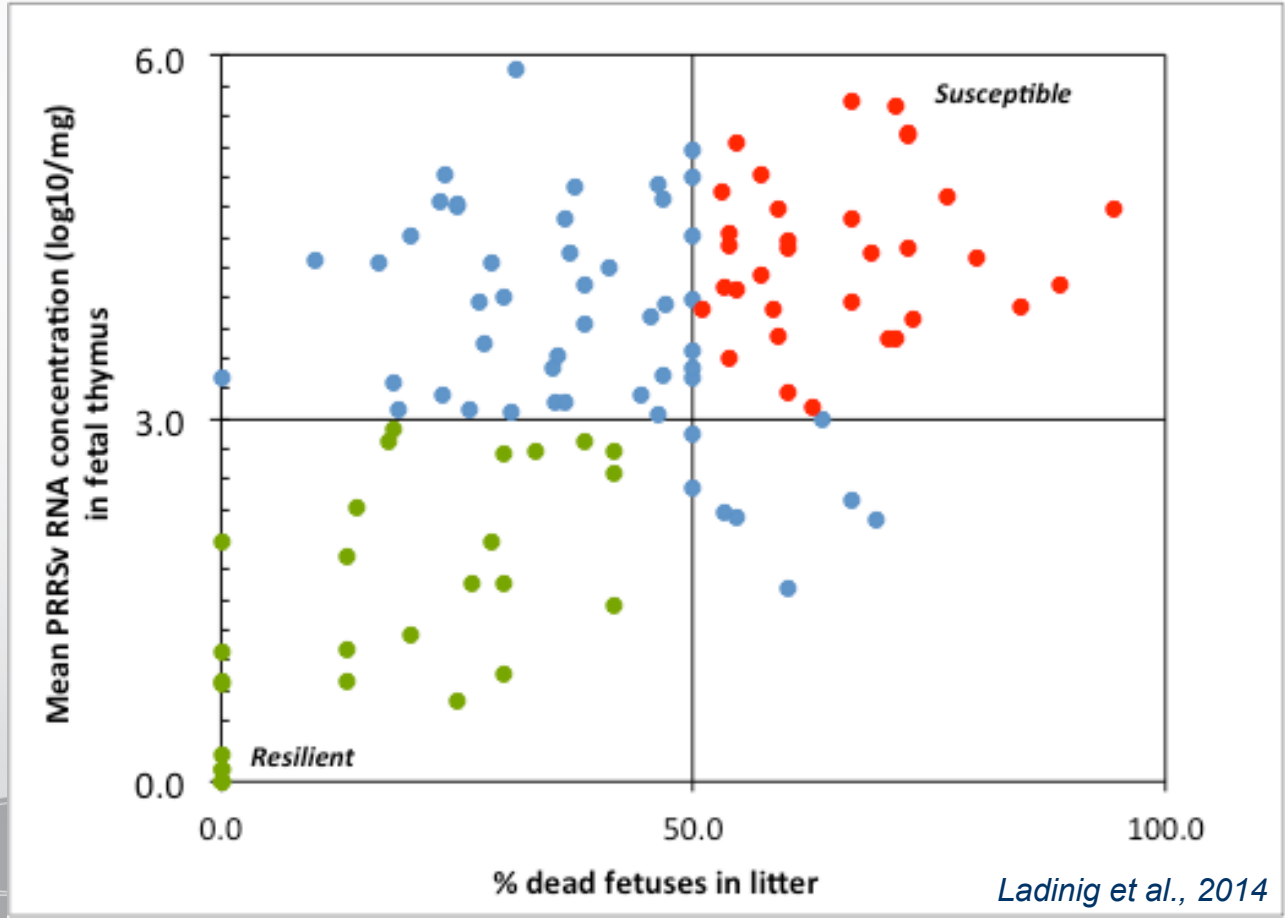
Genetic diversity within a heterogeneous population

Low risk population

high risk population

Differential vaccine strategies based based on predicted phenotypic responses (health phenotype)

Phenotypic variation following type 2 PRRSV challenge in pregnant gilts

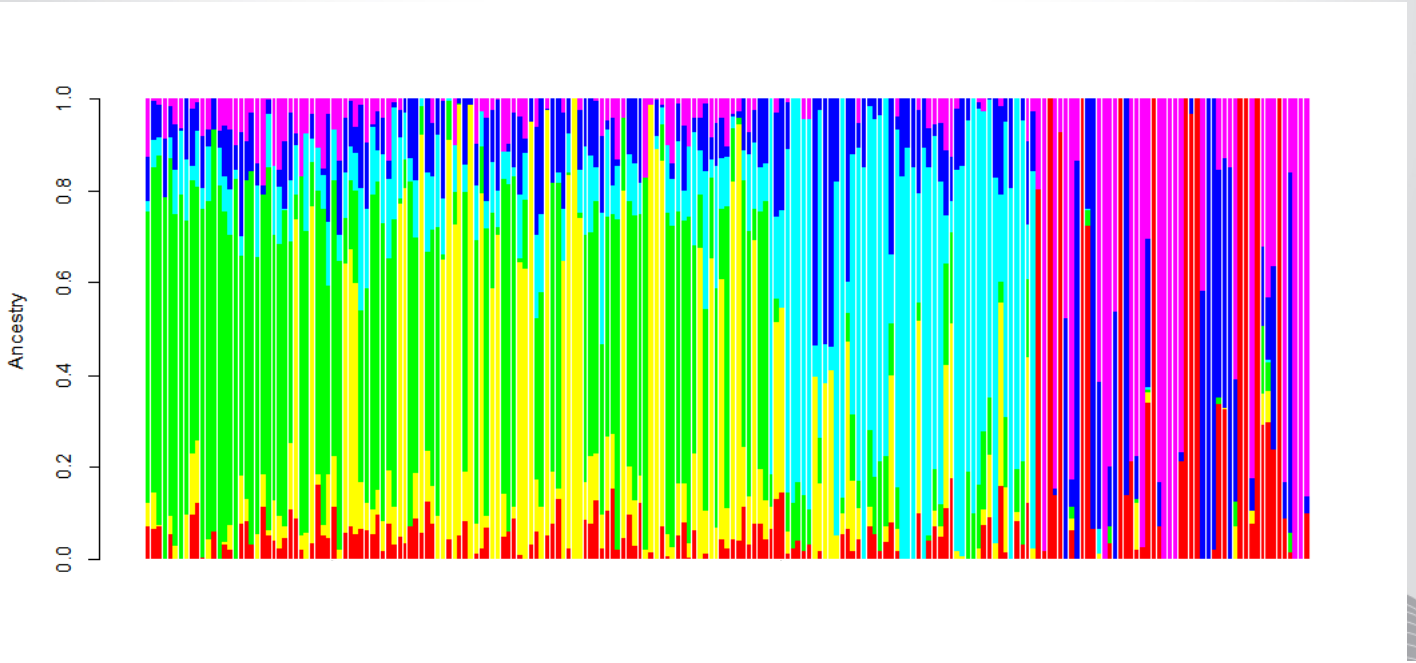


Ladinig et al., 2014

2. Identification of higher risk animals to justify high-end vaccine strategies and/or intensive monitoring

- ✓ Requires accurate assessment of phenotypes
  - Identification of extreme populations
- ✓ Requires a modified vaccination or intensive monitoring strategy
  - Superior product
  - 2 versus 1 dose strategy
  - Vaccination response monitoring
- ✓ Easily implemented at farm if functional genomic testing available to identify high risk populations

3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes



Bertolini & Rothschild, unpublished

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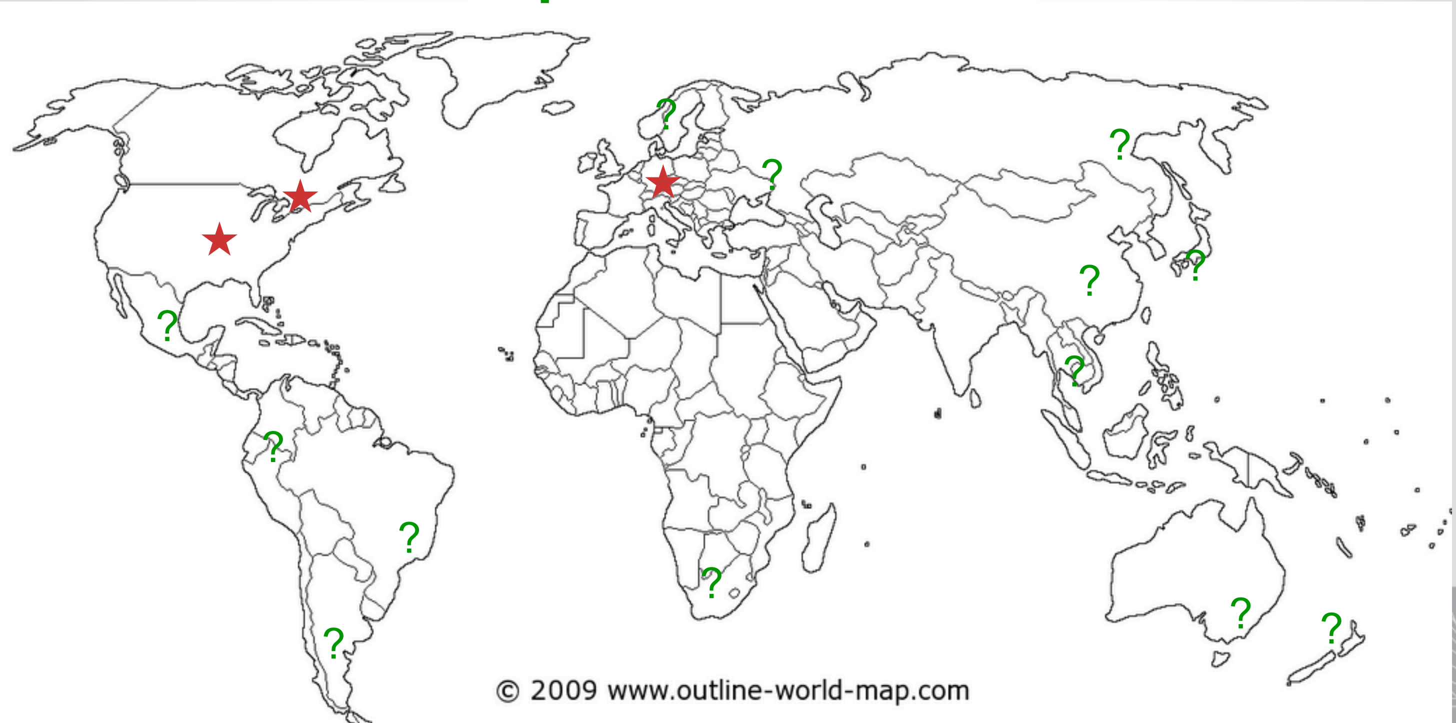
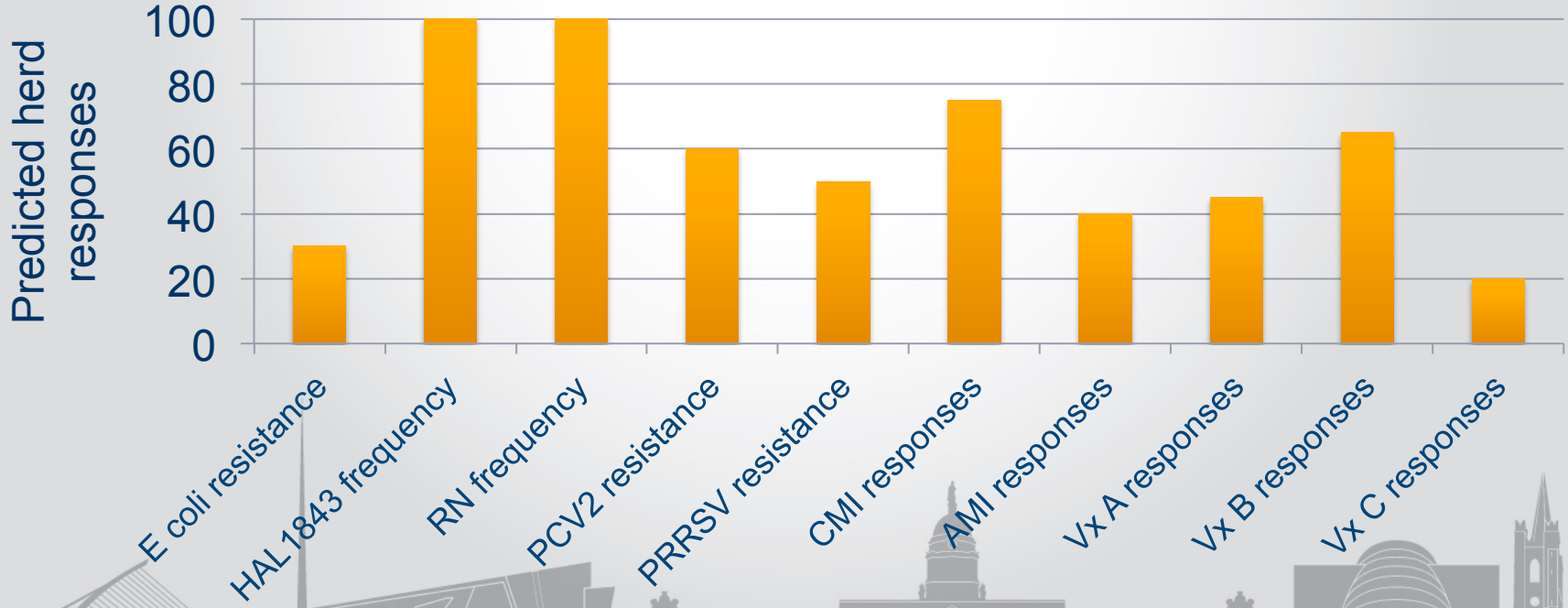
Given vast genomic heterogeneity, should vaccines be better targeted towards homogeneous populations or genetic lines with defined immune responses?



3. Development of novel vaccines for targeted populations based on anticipated immune response genotypes

- ✓ Requires understanding of global genotypic variability and its potential impact on vaccine response and disease susceptibility
- ✓ Could be streamlined by understanding variability amongst major genetics companies
- ✓ Requires large enough market to stimulate novel products specific to anticipated genotypic responses (global / niche)
  - Antigen, antigen load, novel adjuvants, formulation?
  - Development costs?
  - Critical evaluation of efficacy across many genetic populations and regions

Swine health dashboard



Conclusions

1. Excellent products available today; some of the most effective vaccines ever produced; excellent technical support
2. Swine health management founded on 20th century technology
3. Exponential advance of genomic technologies advancing will revolutionize health care over next 20 years
4. Solving the complex swine health issues of the 21st century will require more than vaccines

Conclusions

5. Application of “vaccinomics” (merger of functional genomics with innovative vaccine design) offer great potential to improve swine health in next 2 decades
6. Moving towards an era of “personlized and predictive vaccinology instead of a one-size fits all approach”

Personalized medicine for pig populations