Genomics Provides Clues for Fertility and Health

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USLGE
The One Source for Superior Livestock Genetics

About USLGE

- Nonprofit, nationwide trade association (established 1993) with 50 members
- Represents international marketing interests of dairy, beef, sheep, swine, horse, and sheep and goat breeding industries
- **Mission:** To better serve world markets with superior livestock genetics from leading, progressive U.S. livestock breeders

Bur-Wall Buckeye Gigi EX-94 5E
U.S. Record-Holder for Milk Production and 2013 Star of the Breed

Definitions

- **Genotype: The genetic constitution of an animal.**
- **Phenotype: Set of observable characteristics.**

Selz-Pralle Aftershock 3918

365 d 78,170 M 3,094 F 2,393 P

Is genomic testing of cattle popular?

> 3.8 million dairy cattle have been genotyped in the USA

(CDCB, 2020)

Sources of DNA for Genotyping

- Tissue
- Blood
- Hair
- Semen
- Nasal swab

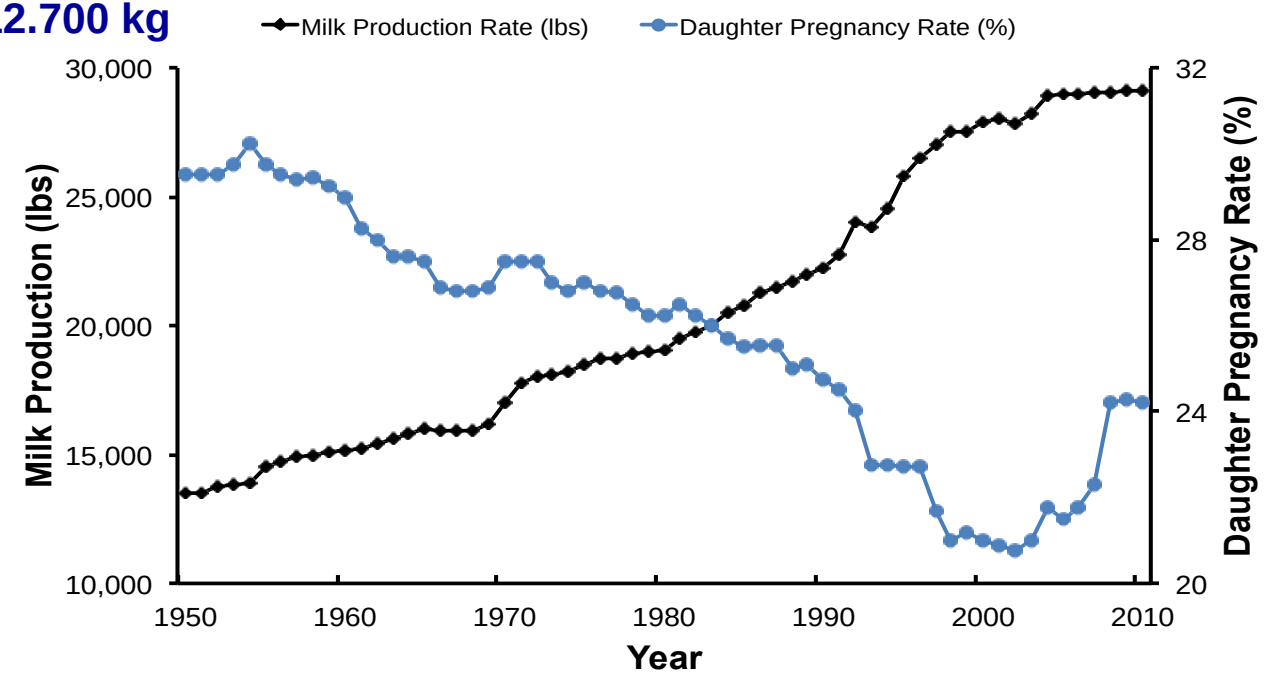
(Images courtesy of Allflex USA)

What has been the historical relationship between milk production and fertility?

Milk Production and Daughter Pregnancy Rate

1 lbs = 0,4535 kg

30,000 lbs = 12.700 kg



DPR is the percentage of a bull's nonpregnant daughters that become pregnant during each 21-day period.

Improving Dairy Cattle Fertility Using Translational Genomics

AFRI 2013-68004-20365

T. Spencer, H. Neibergs, J. Dalton, M. Chahine, D. Moore, P. Hansen, J. Cole, and A. De Vries

How do we increase fertility?

- Genomic Selection
  - Marker-assisted selection (using the whole genome)
  - Increased feasibility due to sequencing of bovine genome and new methods to efficiently genotype animals
  - Marker discovery requires carefully phenotyped populations

Illumina 777K BovineHD Beadchip

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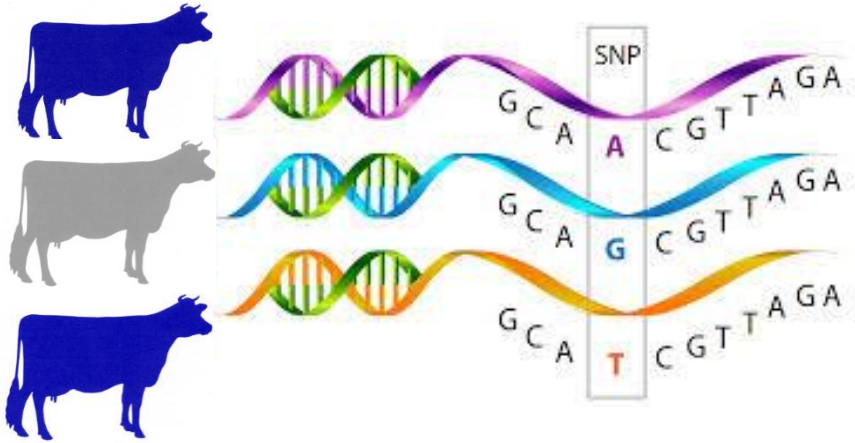
Single Nucleotide Polymorphisms



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(Courtesy of Neibergs, 2016)

Objective 1: Develop Novel Markers of Fertility

- **Approach:** Using records, Holstein heifers and primiparous cows were fertility classified based on pregnancy outcome to AI.
  - **Heifers:** normal reproductive tract, no record of diseases, and display standing estrus before AI.
  - **Cows:** normal reproductive tract, uncomplicated pregnancy, no record of diseases before or after AI, and display standing estrus before AI.

- **Fertility phenotypes:**
  - ***Highly fertile***
  - ***Sub-fertile***

USDA NIFA AFRI 2013-68004-20365

Kiser *et al. BMC Genomics* (2019) 20:576
https://doi.org/10.1186/s12864-019-5935-3

BMC Genomics

RESEARCH ARTICLE Open Access

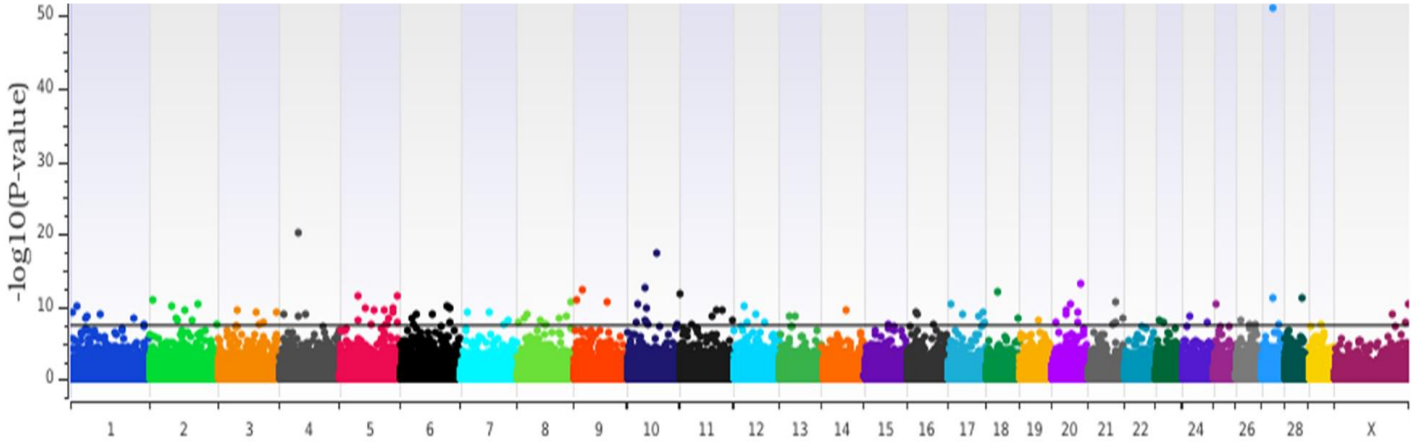
Validation of 46 loci associated with female fertility traits in cattle

Jennifer N. Kiser[1], Elizabeth M. Keuter[1], Christopher M. Seabury[2], Mahesh Neupane[1], Joao G. N. Moraes[3], Joseph Dalton[4], Gregory W. Burns[3], Thomas E. Spencer[3] and Holly L. Neibergs[1*]

USDA NIFA AFRI 2013-68004-20365

Genome-wide Association Analysis of Fertility in Holstein Heifers (HCR1)

- Fertility phenotyped by AI record analysis
  - 468 Highly fertile (pregnant upon first AI)
  - 371 Sub-fertile (did not conceive to first AI)
- 116 loci were associated ($P < 5 \times 10^{-8}$) with HCR1

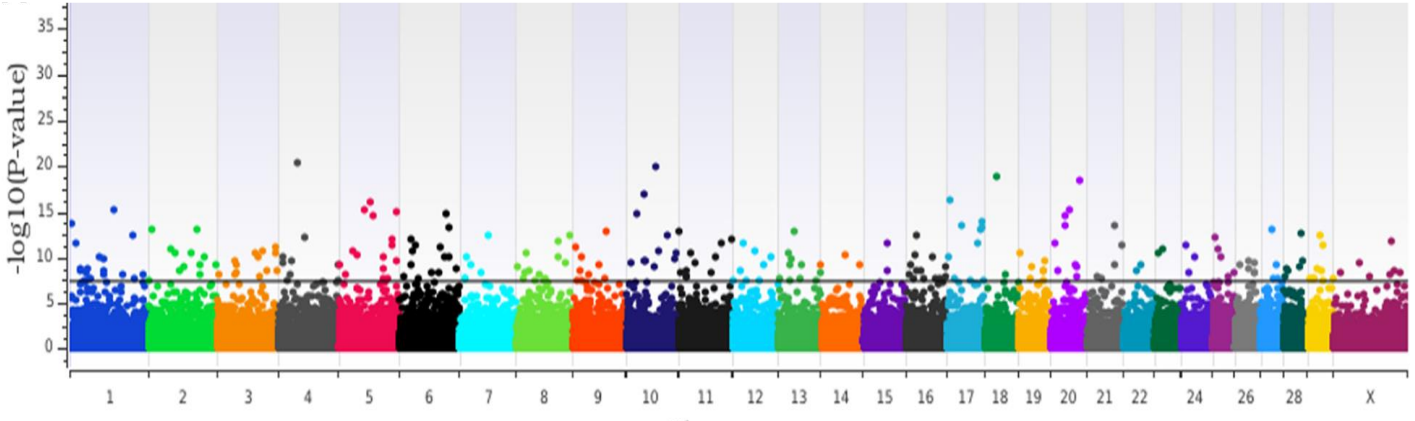


(Kiser et al., 2019)

USDA NIFA AFRI 2013-68004-20365

Genome-wide Association Analysis of Times Bred to Achieve Pregnancy in Holstein Heifers (TBRD)

- Fertility phenotyped by AI record analysis
  - 468 Highly fertile (pregnant upon first AI)
  - 203 Sub-fertile (pregnant ≥ 4^{th} AI)
- 235 loci were associated ($P < 5 \times 10^{-8}$) with TBRD



(Kiser et al., 2019)

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Summary: Heifers

- Number of loci previously associated with fertility:
  - shared with HCR1 and TBRD: 22
  - associated with HCR1 only: 5
  - associated with TBRD only: 19

46

- Loci previously reported were from Holstein, Angus, Brahman, Brangus, and Jersey.
- There appears to be ample opportunity to make gains in Holstein heifer fertility with genomic selection.

USDA NIFA AFRI 2013-68004-20365

(Kiser et al., 2019)

But wait, there's more……

Kiser et al. BMC Genomics (2019) 20:840
https://doi.org/10.1186/s12864-019-6203-2

BMC Genomics

RESEARCH ARTICLE Open Access

Identification of loci associated with conception rate in primiparous Holstein cows

Jennifer N. Kiser[1], Erin Clancey[1], Joao G. N. Moraes[2], Joseph Dalton[3], Gregory W. Burns[2], Thomas E. Spencer[2] and Holly L. Neibergs[1*]

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics
SHORT COMMUNICATION
doi: 10.1111/age.12792

Genome-wide association analysis and gene set enrichment analysis with SNP data identify genes associated with 305-day milk yield in Holstein dairy cows

E. Clancey*, J. N. Kiser*, J. G. N. Moraes†, J. C. Dalton‡, T. E. Spencer† and H. L. Neibergs*

genes
MDPI

Article

Genomic Analysis of Spontaneous Abortion in Holstein Heifers and Primiparous Cows

Kayleen F. Oliver [1], Alexandria M. Wahl [1], Mataya Dick [1], Jewel A. Toenges [1], Jennifer N. Kiser [1], Justine M. Galliou [1], Joao G. N. Moraes [2], Gregory W. Burns [2], Joseph Dalton [3], Thomas E. Spencer [2] and Holly L. Neibergs [1,*]

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Objective 2: Determine Effects of SNPs on DPR

Seagull-Bay Supersire

Pawnee Farm Arlinda Chief

Round Oak Rag Apple Elevation

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(Photos courtesy of Select Sires, Inc., and Curtiss Breeding Service)

Daughter Pregnancy Rate

Pregnancy rate of a bull's daughters

A 1% increase in DPR = ~ -4 days open

Welcome Super Petrone-ET
(December 2019)
+4.9 (-19 days open)
Milk +600 lb

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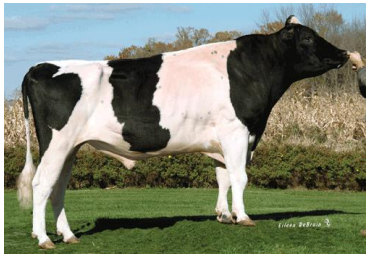
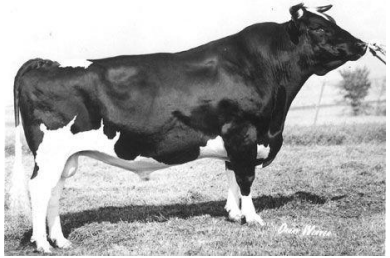
(Courtesy of Select Sires, Inc., and P.J. Hansen)

Bull Selection (n=550)

- Obtained semen from 550 bulls born between 1962 and 2010
- High DPR Bulls (>1.7) (n=288)
- Low DPR Bulls (<-2) (n=262)
- Varying reliabilities (46-99%)





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(Courtesy of P.J. Hansen; Cochrane et al., 2013; Photos courtesy of Select Sires, Inc., Genex, ABS Global)

SNPs in Genes Associated with DPR

- Bulls: (Cochran et al., 2013)
  - 39 SNPs were identified that were related to DPR.
  - 29/39 SNPs were not significantly related to production traits. Therefore, selection for fertility without negative selection for milk yield is possible.

- Cows: (Ortega et al., 2016)
  - Of the 39 SNPs found to be related to DPR by Cochran et al. (2013), 19 were significantly related to DPR.

- *Implications:*
  - SNPs associated with genetic estimates of fertility in Holstein bulls maintained their association in a separate population of cows.

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(Adapted from P.J. Hansen)

United States Department of Agriculture
National Institute of Food and Agriculture

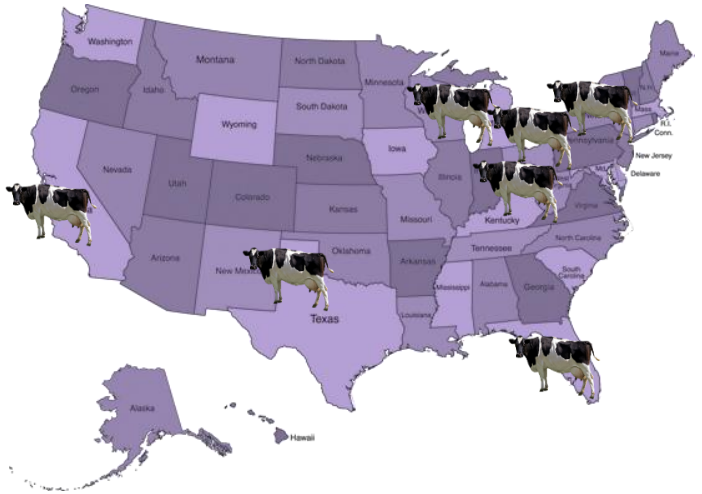
Award # 2013-02115
NIFA AFRI Translational Genomics for Improved Fertility of Animals

Genomic Selection for Improved Fertility of Dairy Cows With Emphasis on Cyclicity and Pregnancy

Pinedo PJ, Santos JE, Galvao K, Seabury C, Rosa JM, Bicalho RC, Gilbert RO, Schuenemann G, Chebel R, Thatcher W, Rodriguez-Zas S, Fetrow J

Study Population

- Cows calving from Nov 2012 to Oct 2014
- Warm season: May – July
- Cool season: Oct - Dec

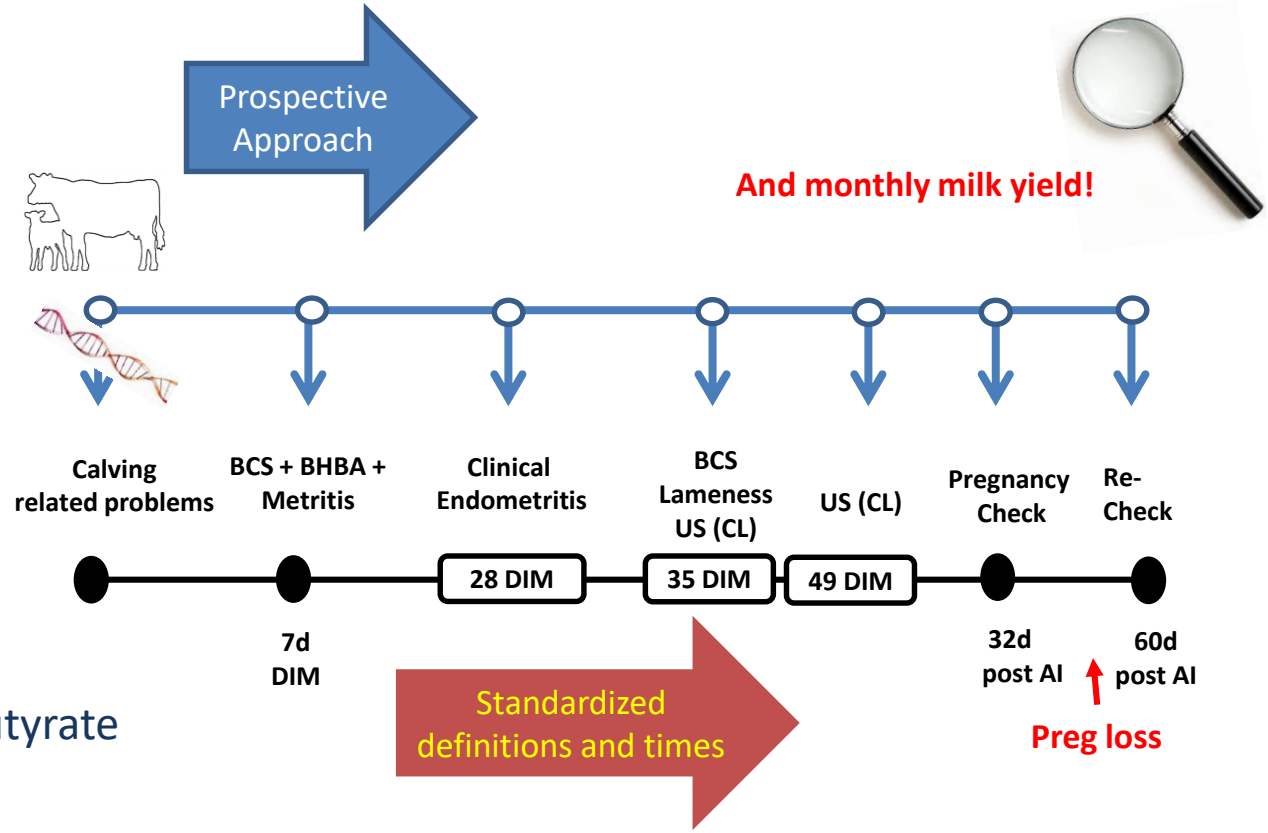


11,733 cows calving in 16 farms located in 4 regions

(Pinedo et al., 2018)

USDA NIFA AFRI 2013-02115

Monitoring Protocol



beta-hydroxybutyrate
BHBA

(Pinedo et al., 2018)

USDA NIFA AFRI 2013-02115

Frequencies of Health Events (<50 Dim)

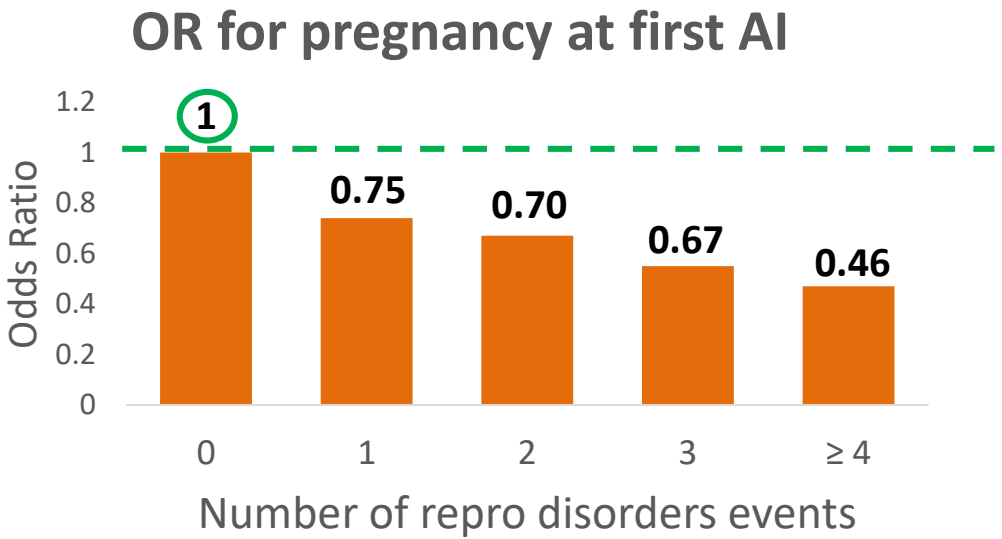
~45% of the dairy cows are diagnosed with a problem in the first 60 DIM

(Pinedo et al., 2018)

USDA NIFA AFRI 2013-2115

Reproductive Health and Pregnancy

Dystocia, twins, retained fetal membranes, metritis, and clinical endometritis



(Pinedo et al., 2018)

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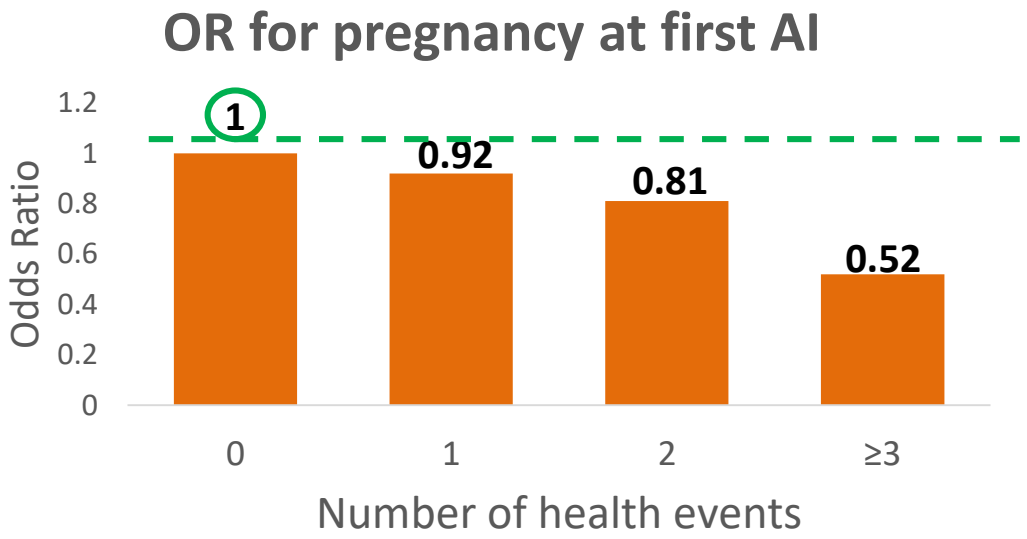
Other Health and Pregnancy

Subclinical ketosis, mastitis, displaced abomasum, and pneumonia



(Pinedo et al., 2018)

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Genomics, Health, and Fertility

Trait	Heritability
Retained placenta	9%
Metritis	6 - 10%
Clinical Endometritis	10%
Resumption of cyclicity	7 - 35%
Mastitis	5%
Days Open	10 - 14%
Pregnancy 60 d after first AI	11 - 20%
Reproductive index	12%

16 genes on bovine chromosomes 1, 3, 6, 10, 11, 12, 14, 15, 22, and 29 were associated with the traits of interest.

(Pinedo et al., 2018; Brito et al., 2018)

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Potential Management Strategies

- Use better AI bulls
- Genomic test
  - Which dairy calves to raise as herd replacements?
    - Health and fertility
  - Which cows (or heifers) to cull?
  - Which animals to breed with sexed semen?
  - Use of beef semen to create crossbred calves?

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Food for Thought

- Genomic testing of females can be profitable, depending on:
  - generation of surplus heifers
  - breeding decisions regarding the use of sexed and beef semen
- Better reproduction makes innovative breeding schemes more profitable.
- Seek professional help to implement and monitor management strategies.

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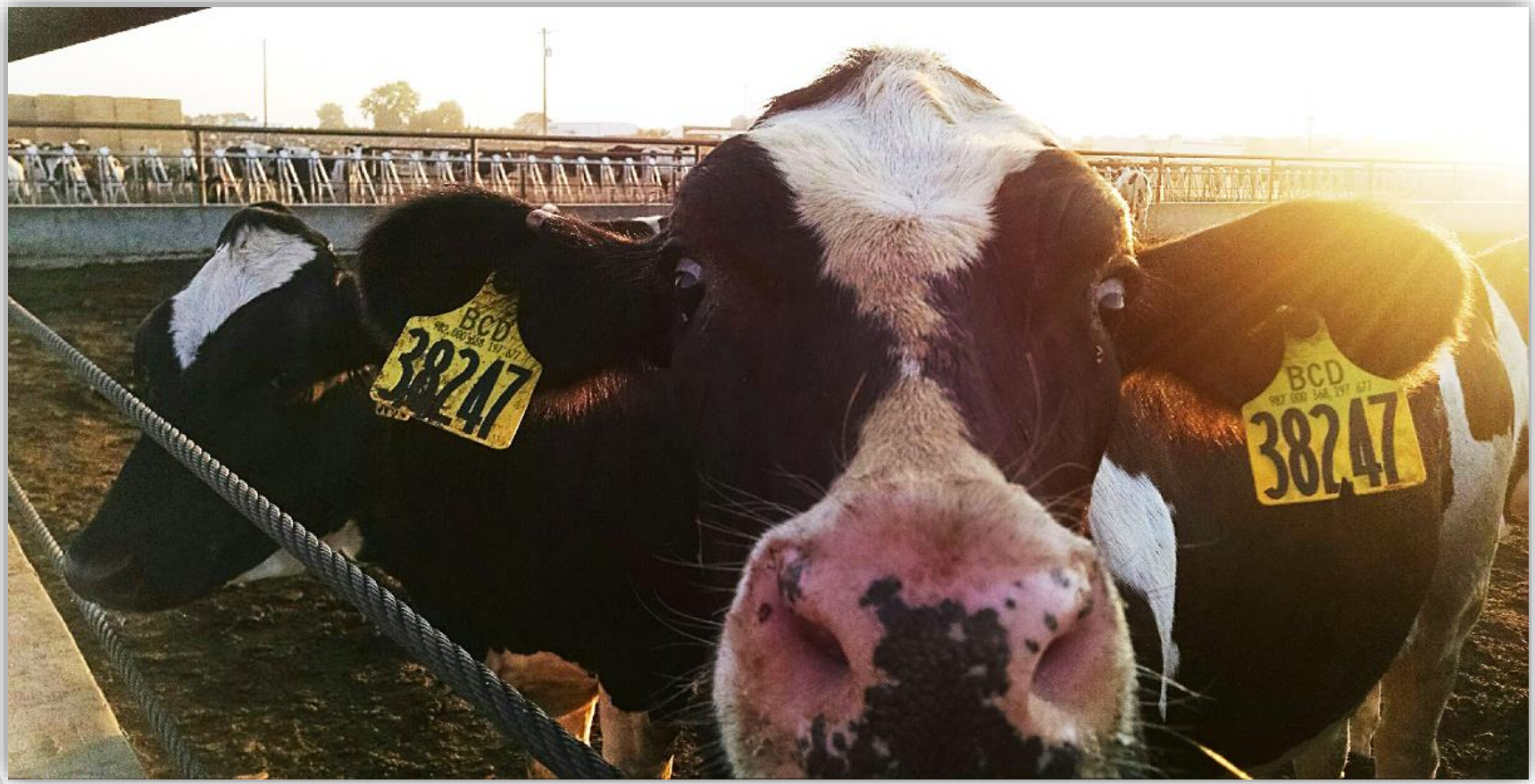
Questions?



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