Researching Genetic Conditions in Wagyu Cattle

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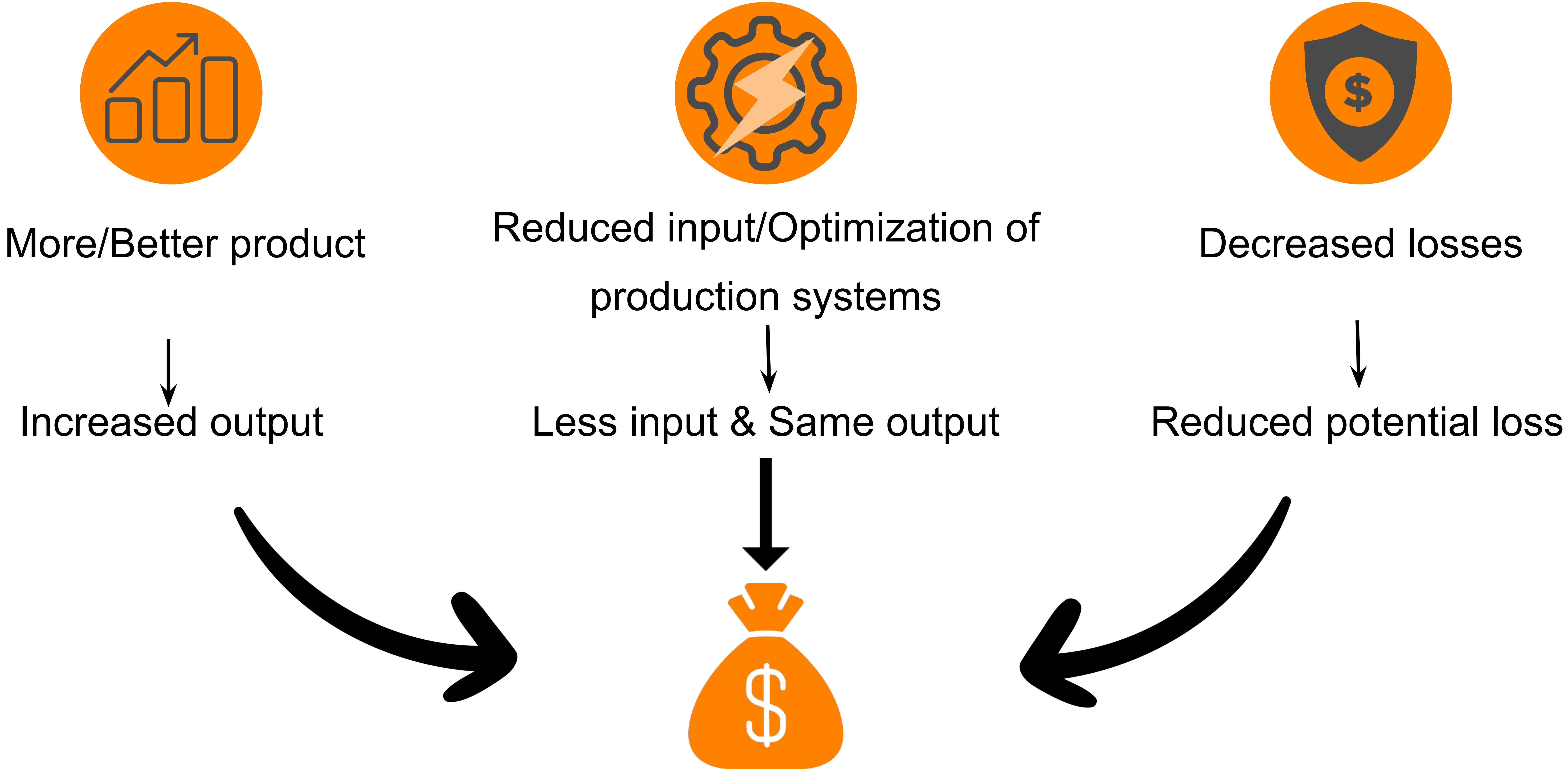
Where do genetic abnormalities fit in the economics of production?



More/Better product

↓

Increased output

Reduced input/Optimization of production systems

↓

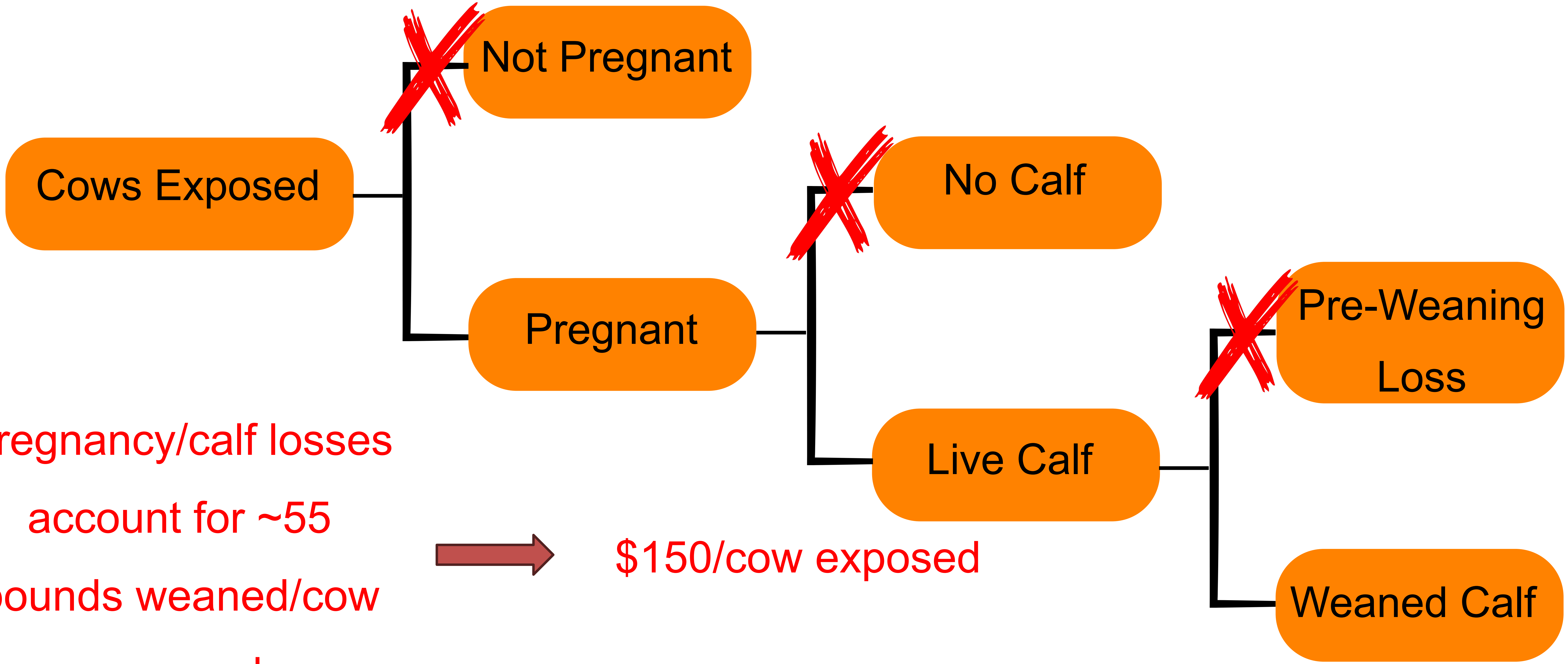
Less input & Same output

Decreased losses

↓

Reduced potential loss

Efficiency of Production



Pregnancy/calf losses account for ~55 pounds weaned/cow exposed → $150/cow exposed

Challenges in Wagyu

Small effective population size

- Limited foundation germplasm
- 222 foundation animals
    - ○ Potential of 444 “genomes”
    - ○ Likely closer to 10-30

Challenges in Wagyu

Small effective population size

- Limited foundation germplasm
- 222 foundation sires
  - Potential of 444 “genomes”
  - Likely closer to 10-30

Increased Potential for Inbreeding

- Inbreeding depression
- Deleterious combinations of alleles
  - Homozygosity of recessives
  - Epistatic interactions - genotype combinations

Solutions

Active Surveillance of Emerging Research

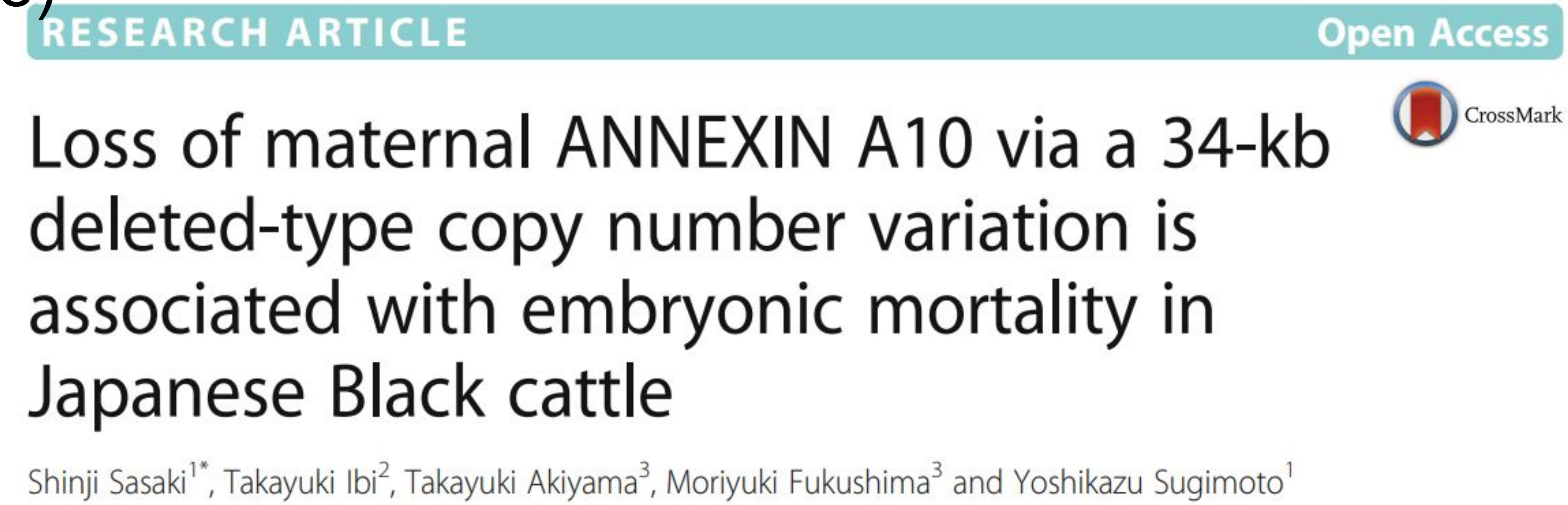
- Implement what is known

Proactive Investigation of Phenotypes

- Identification of concerning phenotypes and make a plan
- Genomic tools for discovery of potential deleterious variants

ANXA10

- Research initiated due to 11% decline in first service AI success over a 20 year period (1992-2012)
  - Analysis of ~800,000 breeding records from ~80,000 cows
  - Cows classified by timing of return to estrus following first AI (2nd AI service)



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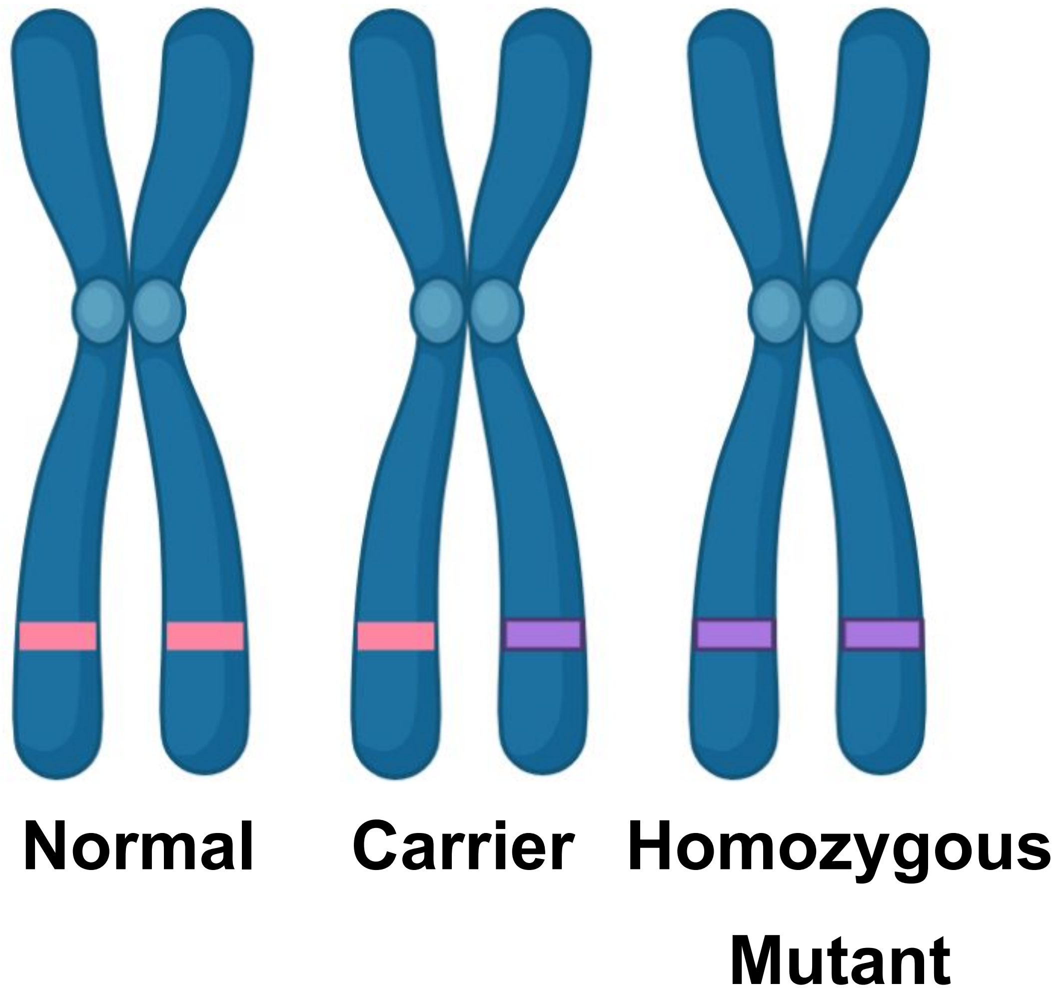
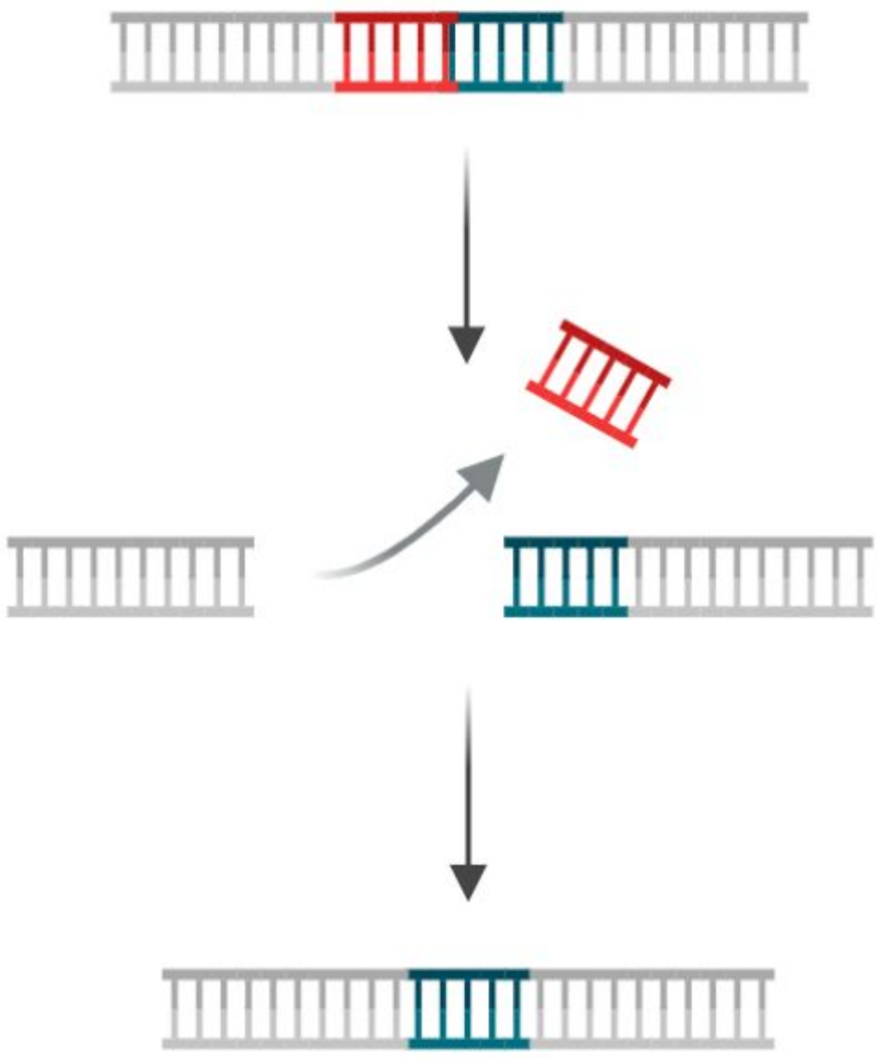
Loss of maternal ANNEXIN A10 via a 34-kb deleted-type copy number variation is associated with embryonic mortality in Japanese Black cattle

Shinji Sasaki[1*], Takayuki Ibi[2], Takayuki Akiyama[3], Moriyuki Fukushima[3] and Yoshikazu Sugimoto[1]

Association found between Copy Number Variant and 2nd AI service between 30 and 60 days

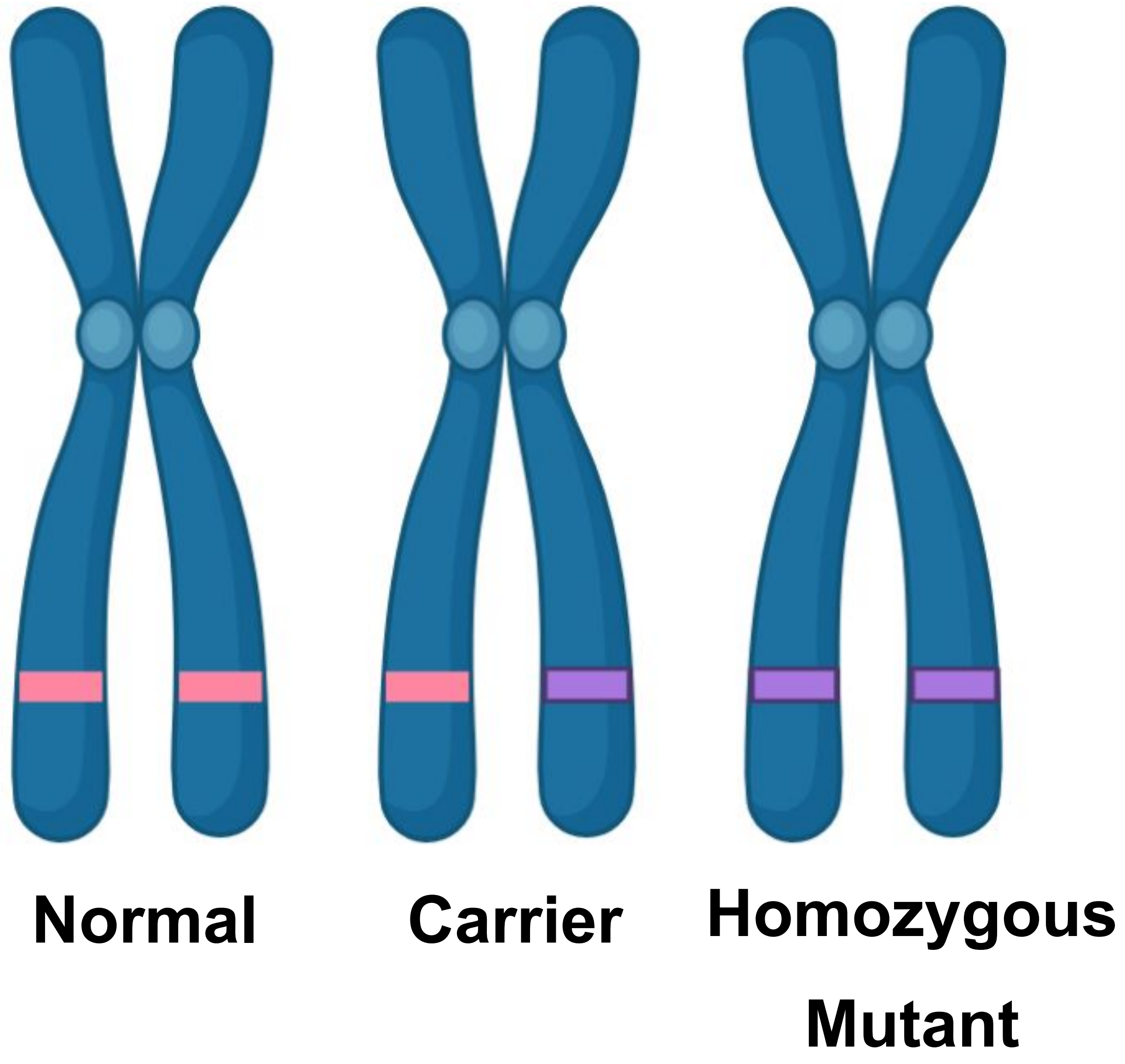
- Copy Number Variant (CNV)
    - Insertion or deletion of a DNA segment





Association found between Copy Number Variant and 2nd AI service between 30 and 60 days

- One deletion (carrier or heterozygote) is sufficient to affect embryonic mortality
- Dependent on maternal genotype
- Not associated with progeny genotype
- Maternal failure to establish pregnancy



Is this variant present in the Australian population?

ANXA10 in Australian Wagyu

Use stillborn calf DNA as proxy for the at large population

Carrier frequency of ~6% among 230 calves

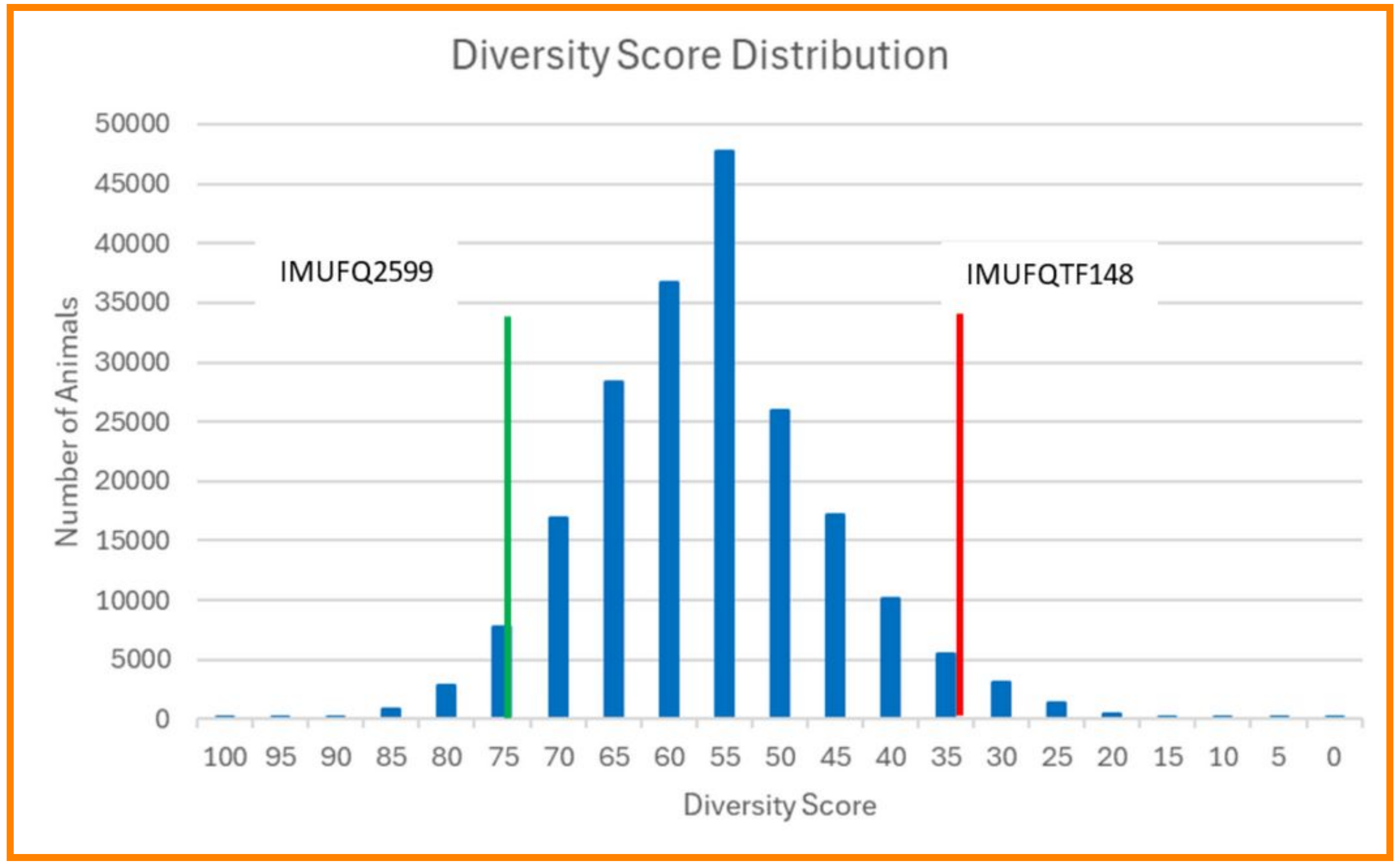
Recommendation is to screen representative sire population to confirm frequency and implement GENEPROB analysis and move to testing, etc. if warranted

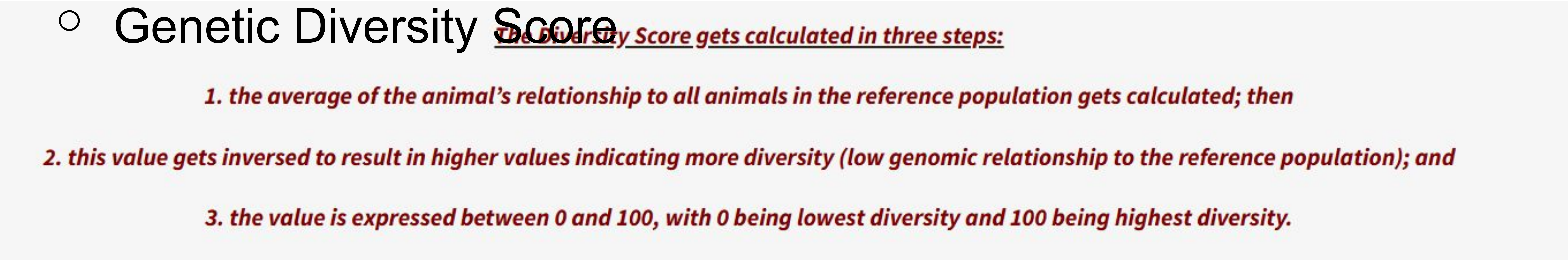
Solutions

MateSel

Manage genetic relationships between potential parents

- Minimize genomic relationship (new AuWA)
    - ○ MateSel
    - ○ Genetic Diversity Score




The Diversity Score gets calculated in three steps:

1. the average of the animal's relationship to all animals in the reference population gets calculated; then

2. this value gets inversed to result in higher values indicating more diversity (low genomic relationship to the reference population); and

3. the value is expressed between 0 and 100, with 0 being lowest diversity and 100 being highest diversity.

AuWA Stillborn Calf Project

- Collection of samples from stillborn calves over multiple calving seasons
    - Approximately 230 collected to date
    - Accompanied by mating data if available
    - Some phenotypic descriptors
- TSUs sent to the University of Tennessee for analyses
    - Very successful DNA isolation for both quantity and quality

Stillborn Calf Project

Could it be genetic?

- Accidents/abnormal phenotypes can happen

How much evidence is needed to define whether a phenotype is heritable?

- Specificity of phenotype
- Pedigree evidence
- Genomic analysis - a posteriori

Specificity of Phenotype

Specificity of Phenotype

Specificity of Phenotype

Disparities between phenotypic descriptions

Majority of affected calves are not diagnosed with "intensive" phenotypic descriptions

- "Academic" vs "field" examination
- Level of detail - gross vs exhaustive examination

Specificity of Phenotype

<u>Failure to distinguish suble differences in phenotype results in improper genetic grouping</u>

Examples:

- FXI deficiency vs hydrocephalus
- Tibial hemimelia
- Fetal hydrops vs pulmonary hypoplasia with anasarca

Challenges

How can you tell if a stillborn is due to environmental vs genetic causes?

- Creates disparities in potential associations between phenotype and genotype

How can you distinguish between benign or deleterious homozygosity within the genome?

- False associations due to common genome-wide regions of homozygosity (ROH)

Approach

Prioritization of calves with higher potential for genetic etiology

- Focus on groups of calves with distinguishing characteristics (specificity of phenotype)
- Ex: Stillborn without distinguishing characteristic vs. stillborn with parrot mouth/undershot jaw (brachygnathia)

Approach

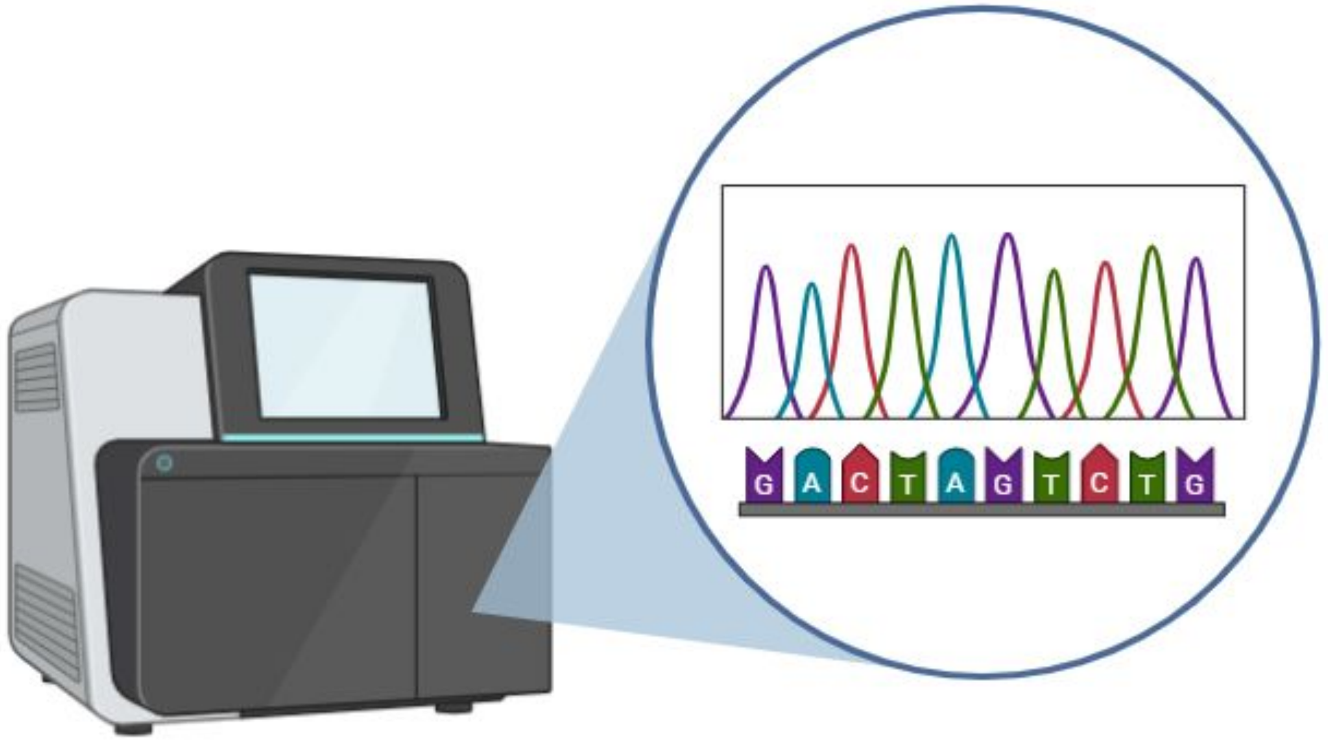
Parentage verified calves with common ancestry and high potential inbreeding coefficients

- 2nd or 3rd generation common ancestors on both sides of the pedigree

Technical Methods

Whole-genome sequencing

- Identify “all variants” that are present
- SNP chip (50K to 100K or 800K) vs. millions of variants (5M+)
- Detection of other mutations
    - Copy number variation
    - Structural rearrangements

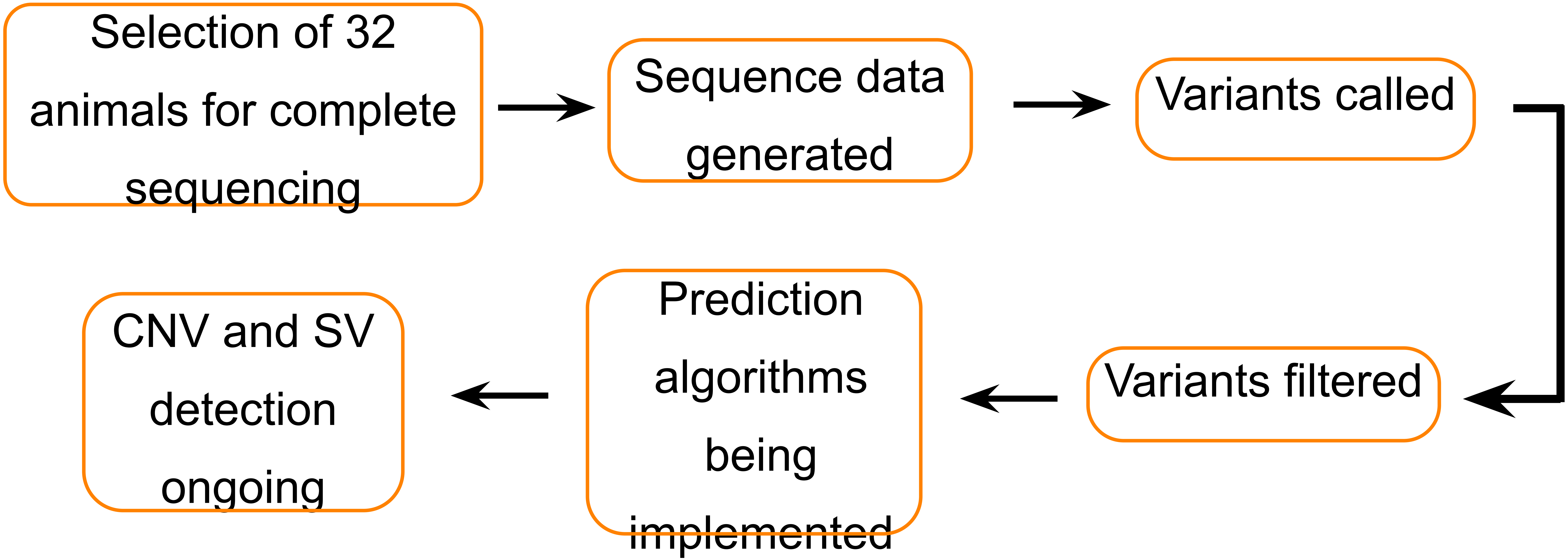


Technical Methods

Existing algorithms to identify variants with high potential impacts

- Based on multispecies conservation of gene sequence and function

Progress



Selection of 32 animals for complete sequencing

Sequence data generated

Variants called

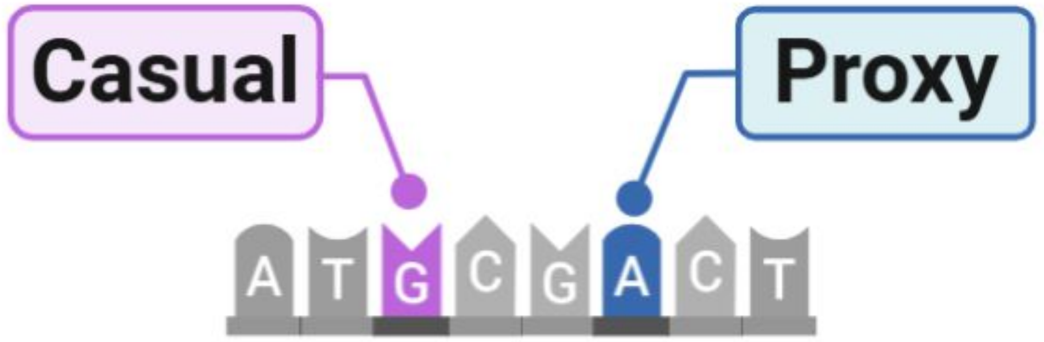
Variants filtered

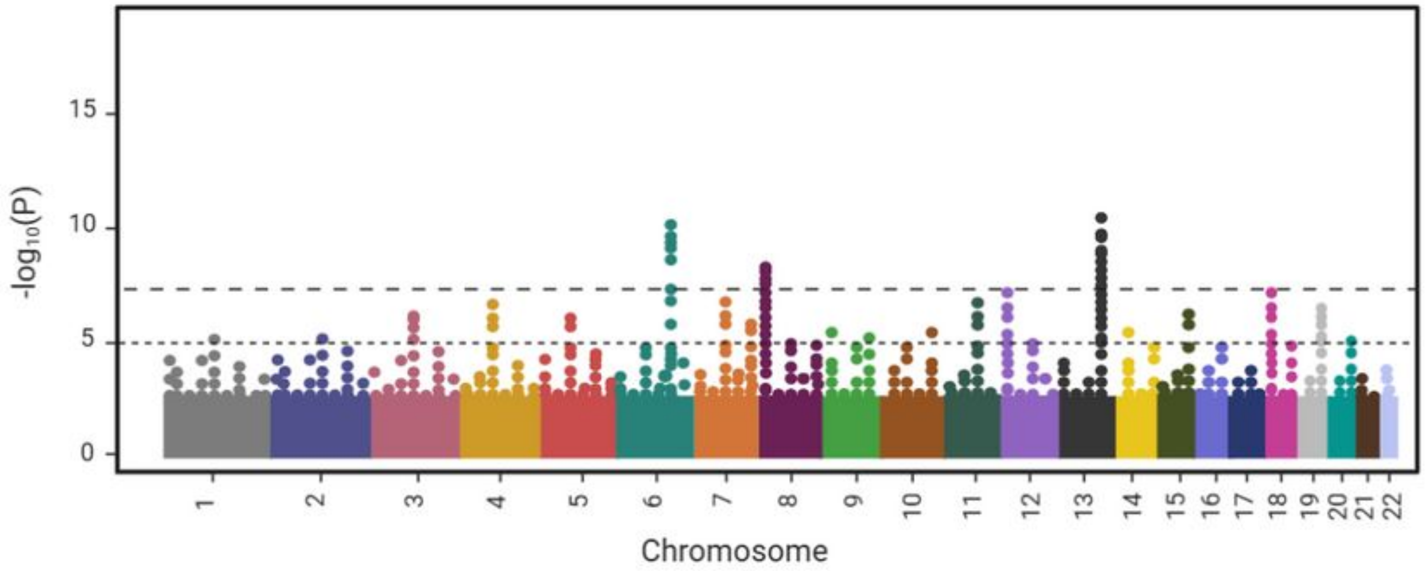
Prediction algorithms being implemented

CNV and SV detection ongoing

Downsampling

- Reducing sequencing data to mimic a SNP chip
    - Aligns sequence data with SNP-genotyped animals
- Enables GWAS
    - Removes noise from WGS data
- Focuses on common genetic markers





Future Prospects

- Continued collection of calf data
- Collection and sequencing of AuWA sires as a reference population
    - Based on progeny representation, e.g., >500 progeny)
    - Preemptive screening for variants to be surveilled
    - Resource for improving accuracy of genome-level imputation

Summary

- Genetic screenings play an important role in optimizing Wagyu beef production
- AuWA offers tools to reduce risk of genetic abnormalities and manage inbreeding
- AuWA Stillborn Calf Project
- Proactive surveillance and documentation of concerning phenotypes

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