An Integrated Program for Reducing Bovine Respiratory Disease Complex in Beef and Dairy Cattle

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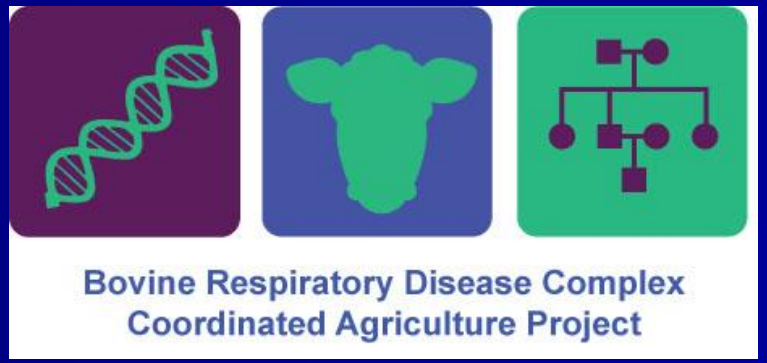
US Bovine Respiratory Disease
Coordinated Agricultural Project
http://www.brdcomplex.org



The "Integrated Program for Reducing Bovine Respiratory Disease Complex (BRDC) in Beef and Dairy Cattle" Coordinated Agricultural Project is supported by Agriculture and Food Research Initiative Competitive Grant no. 2011-68004-30367 from the USDA National Institute of Food and Agriculture.

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Overview

- Review Bovine Respiratory Disease (BRD)
- What is the BRD CAP?
- Research overview of BRD CAP
  - Advantage of selecting for disease traits
  - Challenges of selecting for disease traits
  - "Genomics Primer"
- Summary of education and extension aims
- Future plans

Steer # 77

Steer # 77 BRSV damage to lung

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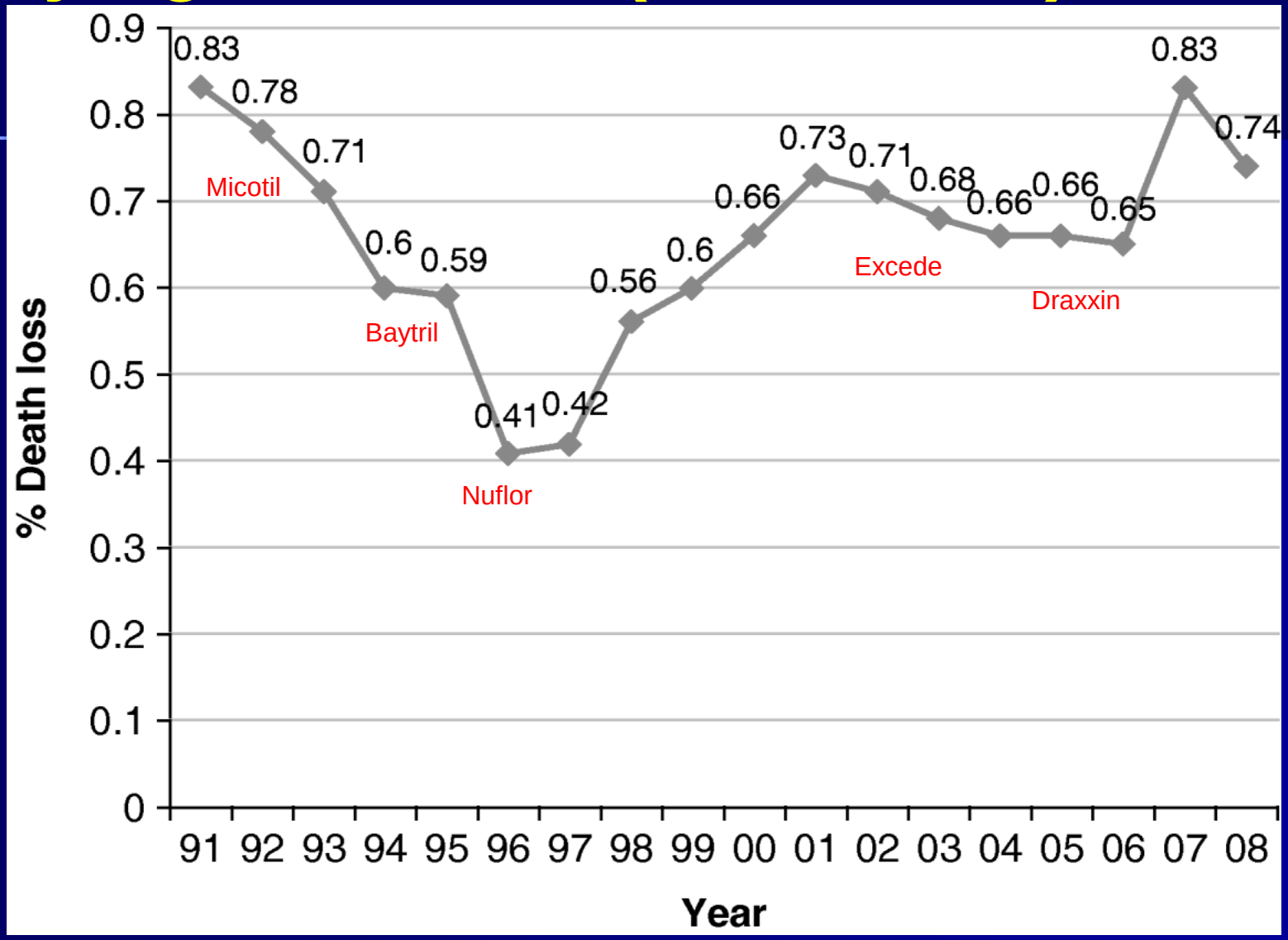
What is Bovine Respiratory Disease?

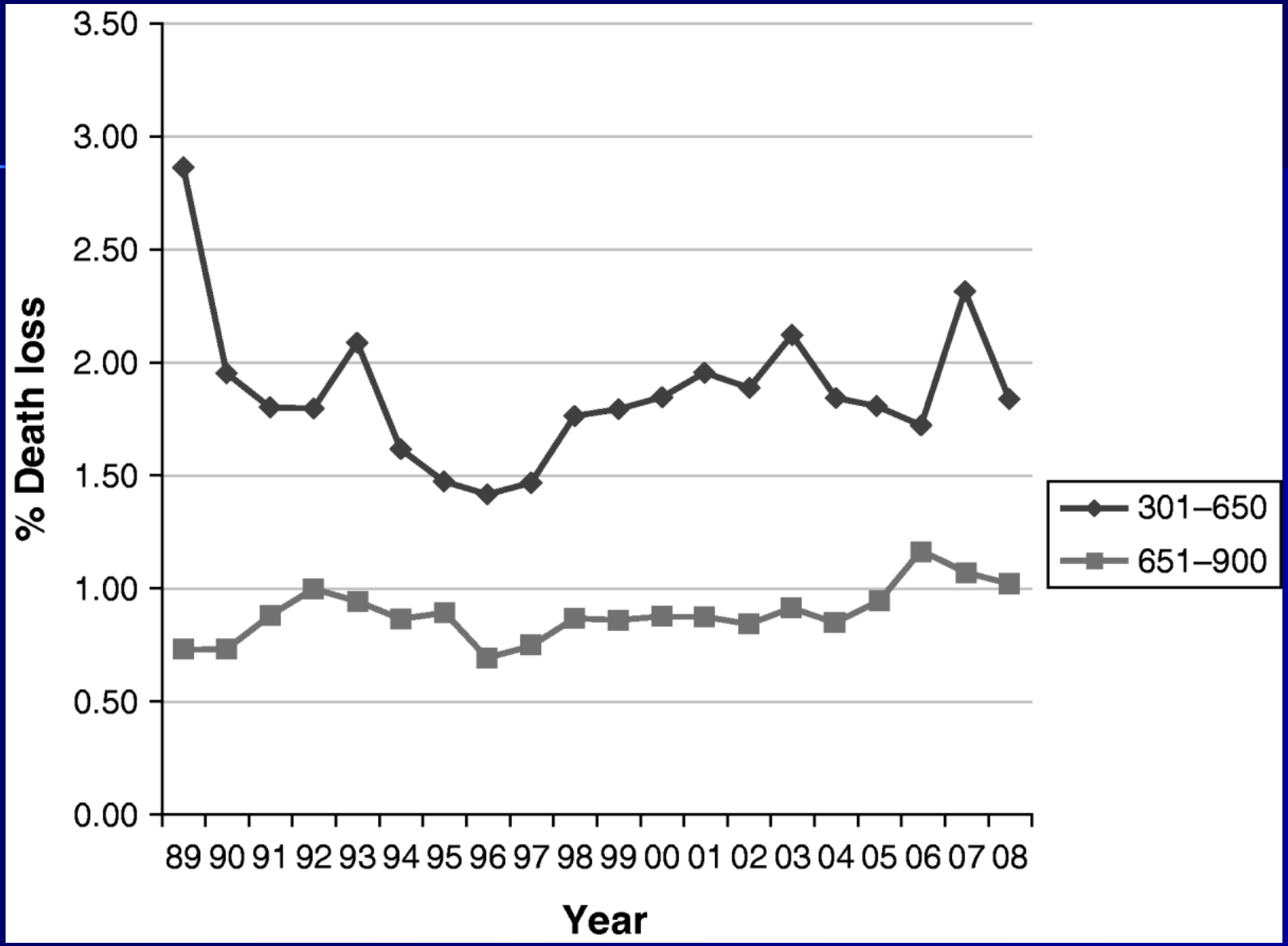
- Leading cause of death in both dairy and beef cattle
- Economic losses to industry—estimated > US$1 billion/year
- Responsible for 22.5% of mortalities in unweaned dairy heifers, 46.5% in weaned dairy heifers, and 28% of non-predator losses in cattle and calves
- Disease associated with many pathogens, both viral and bacterial
- Exacerbated in times of stress

Percent of cattle placed in feedlots dying from BRD (1991–2008).



Miles, D. 2009. Overview of the North American beef cattle industry and the incidence of bovine respiratory disease (BRD). Animal Health Research Reviews. 10:101-103.

Death loss in feeder cattle (1989–2008) in relation to two weight categories (301–650 and 651–900 lbs).



Miles, D. 2009. Overview of the North American beef cattle industry and the incidence of bovine respiratory disease (BRD). Animal Health Research Reviews. 10:101-103.

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Background and Rationale

"Year in and year out, diseases of the respiratory system are a major cause of illness and death in cattle from 6 weeks to two years of age. Sadly, this is as true today as it was 30 years ago despite development of new and improved vaccines, new broad spectrum antibiotics, and increased fundamental knowledge as to the cause of disease "

- Bovine Respiratory Disease (BRD) has been extensively studied since the 1800s, and yet it remains prevalent
- More effective vaccines have not decreased the morbidity or mortality of BRD
- Mortality has increased as vaccine efficiency has increased
- 1.4% of all US feedlot cattle perish before reaching harvest weight
- **Need to develop new approaches to tackle BRD**

Montgomery, D. 2009. Bovine Respiratory Disease & Diagnostic Veterinary Medicine. Proceedings, The Range Beef Cow Symposium XXI. December 1, 2 and 3 2009, Casper, WY. Pages 1-6.

United States Department of Agriculture

National Institute of Food and Agriculture

USDA Awards Grants to Improve Cattle Production and Health

COLUMBIA, Mo., April 15, 2011 – Roger Beachy, director of the U.S. Department of Agriculture's National Institute of Food and Agriculture (NIFA), today announced two grant awards to the University of Missouri and Texas A&M University to support research, education and outreach on cattle production to increase global food security.

"The United States is the world's largest producer of beef and milk and has the largest fed-cattle industry in the world," Beachy said. "As the demand for food rises due to a growing global population, it will be critically important to develop methods to produce more food with greater efficiency, while lowering the prevalence of bovine respiratory disease that inflicts significant losses each year."

NIFA also awarded a **$9.75 million grant** to Texas A&M University to support research led by Dr. James Womack to reduce the prevalence of bovine respiratory disease (BRD) in beef and dairy cattle. BRD is the leading natural cause of death in beef and dairy cattle, causing annual losses of more than 1 million animals valued at nearly $700 million.

Womack and colleagues will use a DNA-based approach to identify cattle that are resistant to disease-causing pathogens. In addition to studying known pathogens, they will identify novel pathogens responsible for BRD. The data will be used to develop BRD diagnostic tests and genetic selection tools to identify BRD-resistant animals, while also assessing the welfare of cattle with BRD. The researchers intend to share their results with producers and develop undergraduate courses and related educational materials and instruction for 4-H youth.

Womack's team includes scientists from the University of California-Davis, Colorado State University, the University of Missouri, New Mexico State University, Washington State University and USDA's Agricultural Research Service.

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BRD Coordinated Agricultural Project (BRD CAP)

Long-term goal is to reduce the incidence of BRD in beef and dairy cattle by capitalizing on recent advances in genomics to enable novel genetic approaches to select for cattle that are less susceptible to disease

Agriculture and Food Research Initiative Competitive Grant no. 2011-68004-30367

BRD Coordinated Agricultural Project

TEXAS A&M UNIVERSITY

- **Jim Womack, PD**
- Alan Dabney
- Scott Dindot
- Noah Cohen
- Chris Seabury
- Lawrence Falconer
- Lauren Skow
- Gary Snowder

UC DAVIS UNIVERSITY OF CALIFORNIA

- Laurel Gershwin
- Terry Lehenbauer
- Cassandra Tucker
- **Alison Van Eenennaam**

MISSOURI

- Jerry Taylor

Colorado State University

- Mark Enns

United States Department Of Agriculture Agricultural Research Service

- Mike MacNeil
- Curt Van Tassell

WASHINGTON STATE UNIVERSITY

- **Holly Neibergs**
- Shannon Neibergs

AGGIES NEW MEXICO STATE

- **Milt Thomas**
- Robert Hagevoort
- Tim Ross

OTHER COLLABORATORS

- Daniel Pomp (NC)
- Shiela McGuirk (WI)
- Adroaldo Zanella (Norway)

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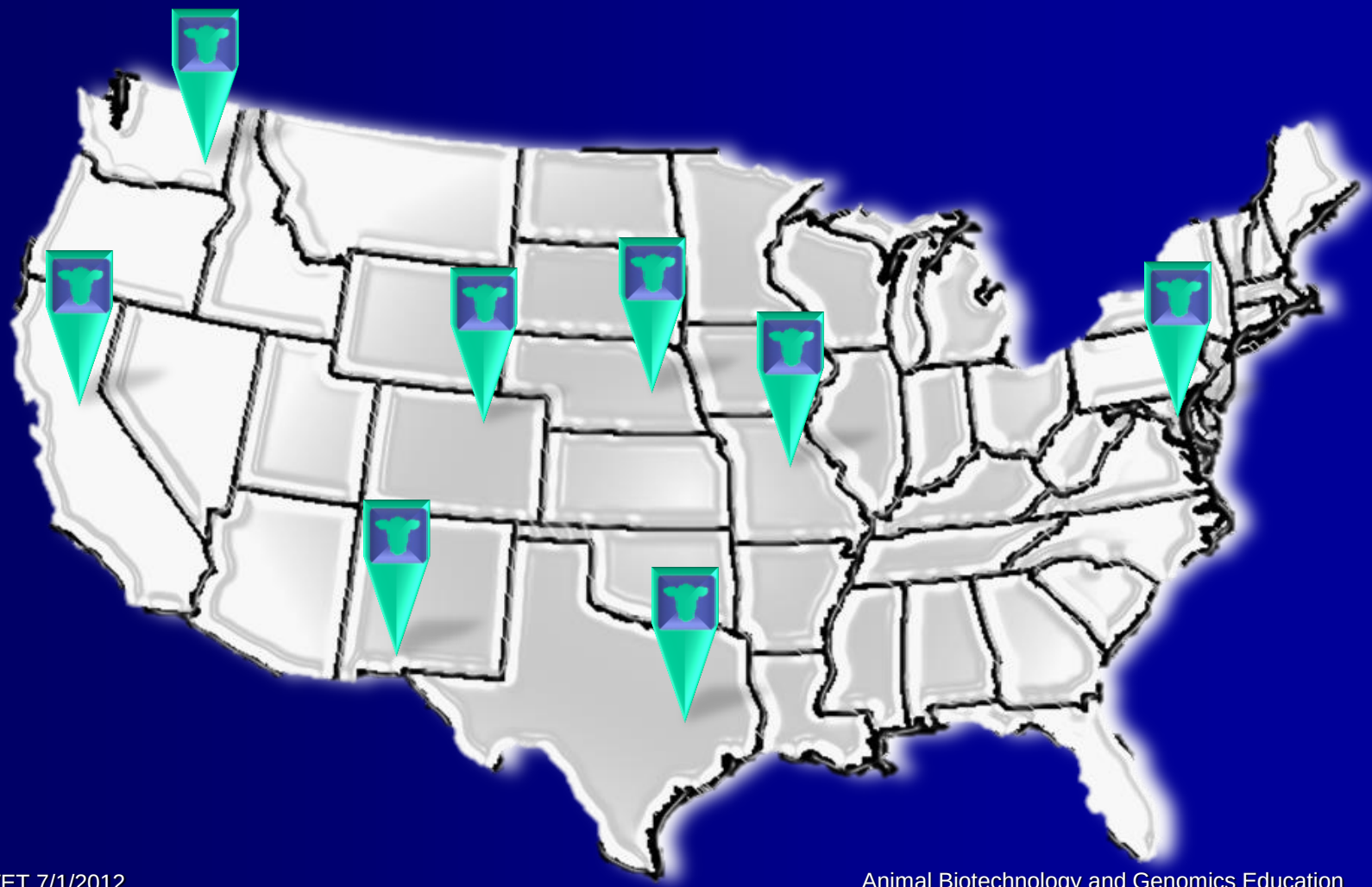
Location of US collaborators



Our goal is to integrate research, education, and extension activities to develop cost-effective genomic and management approaches to reduce the incidence of BRD in beef and dairy cattle

Dr. Jim Womack, Texas A&M University, College Station, TX

The objective of this multi-institutional project is to reduce the incidence of bovine respiratory disease by:

- Capitalizing on recent advances in genomics to enable novel genetic approaches to select for disease-resistant cattle
- Developing improved DNA-based tests for disease diagnosis
- Providing educational opportunities for undergraduate, graduate and veterinary students to generate a future human resource for the continued reduction in bovine respiratory disease incidence
- Producing and delivering a variety of educational materials for beef and dairy cattle producers, and feedlot personnel on best management practices to reduce disease incidence

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Potential benefits of genomics are greatest for economically-important traits that:

- Are difficult or expensive to measure
- Cannot be measured until late in life or after the animal is dead
- Are not currently selected for because they are not routinely measured
- Have low heritability

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Issues in the development of genetic approaches to select for disease resistance.

- Disease resistance heritabilities tend to be low, especially under field conditions
  - suboptimal diagnosis (e.g. not all sick animals are identified and healthy animals may be incorrectly diagnosed as ill),
  - some susceptible animals will appear resistant to a disease when in fact they have not been exposed to the disease agent.

Bishop, S. C., and J. A. Woolliams. 2010. On the genetic interpretation of disease data. Plos One 5: e8940.

- In feedlot calves, BRD resistance heritability estimates were low and ranged from 0.04 to 0.08 (Snowder et al., 2006). When the observed heritability estimate was transformed to an underlying continuous scale, the estimate increased to 0.18

Snowder, G. D., L. D. Van Vleck, L. V. Cundiff, and G. L. Bennett. 2006. Bovine respiratory disease in feedlot cattle: environmental, genetic, and economic factors. J Anim Sci 84: 1999-2008.

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Other animal industries have successfully targeted selection for disease resistance

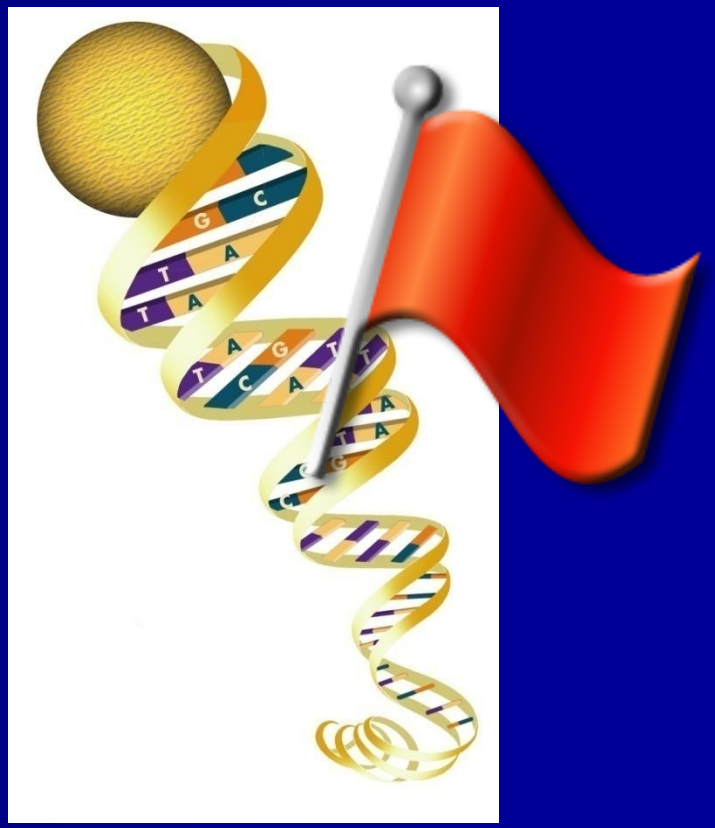
- In dairy cattle, selection programs have been developed to take advantage of genetic variability in mastitis resistance, despite the fact that the heritability of clinical mastitis is low and mastitis resistance has an adverse correlation with production traits
- Likewise chicken breeders have long used breeding to improve resistance to avian lymphoid leucosis complex and Marek's disease

Stear, M. J., S. C. Bishop, B. A. Mallard, and H. Raadsma. 2001. The sustainability, feasibility and desirability of breeding livestock for disease resistance. Res Vet Sci 71: 1-7

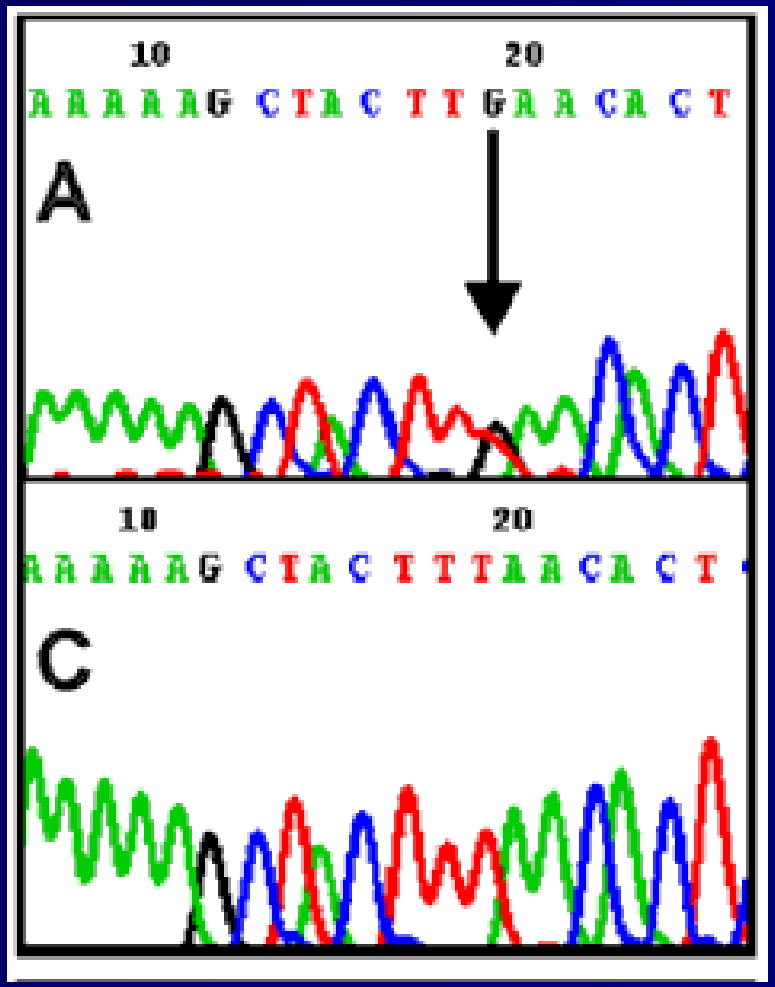
Genomics primer

SNP (Single Nucleotide Polymorphism)

A DNA sequence variation that varies sufficiently between individuals that its inheritance can be tracked through families

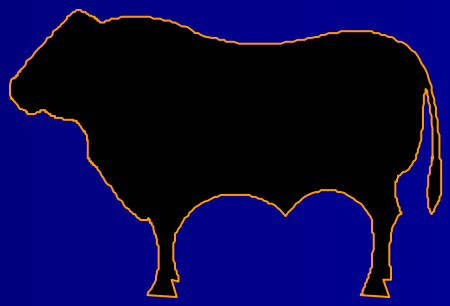


Genotyping identifies genetic variation (SNPs)

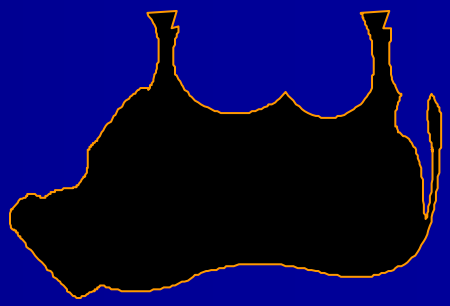


Heterozygous bull

TTGAA



TTTAA



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Genomic development: High Density SNP Chip

- The ready availability of dense single nucleotide polymorphism arrays (i.e. SNP chips) has given rise to hitherto unforeseen opportunities to dissect between-host variation and identify possible genes contributing to this variation using genome wide association studies (GWAS)

Bishop, S. C., and J. A. Woolliams. 2010. On the genetic interpretation of disease data. Plos One 5: e8940.

770,000 SNPs evenly distributed throughout the genome

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What is needed to develop DNA-tests for selection against BRD?

Large training/discovery populations with BRD case:control (BRD:healthy) and SNP genotypes used to estimate the value of every chromosome fragment contributing variation to BRD susceptibility. This allows for prediction of which chromosome segments or regions are important to confer resistance/susceptibility.

Prediction equation = the results of training can then be used to predict the genetic merit of new animals not contained in the training data set based on their genotype alone.

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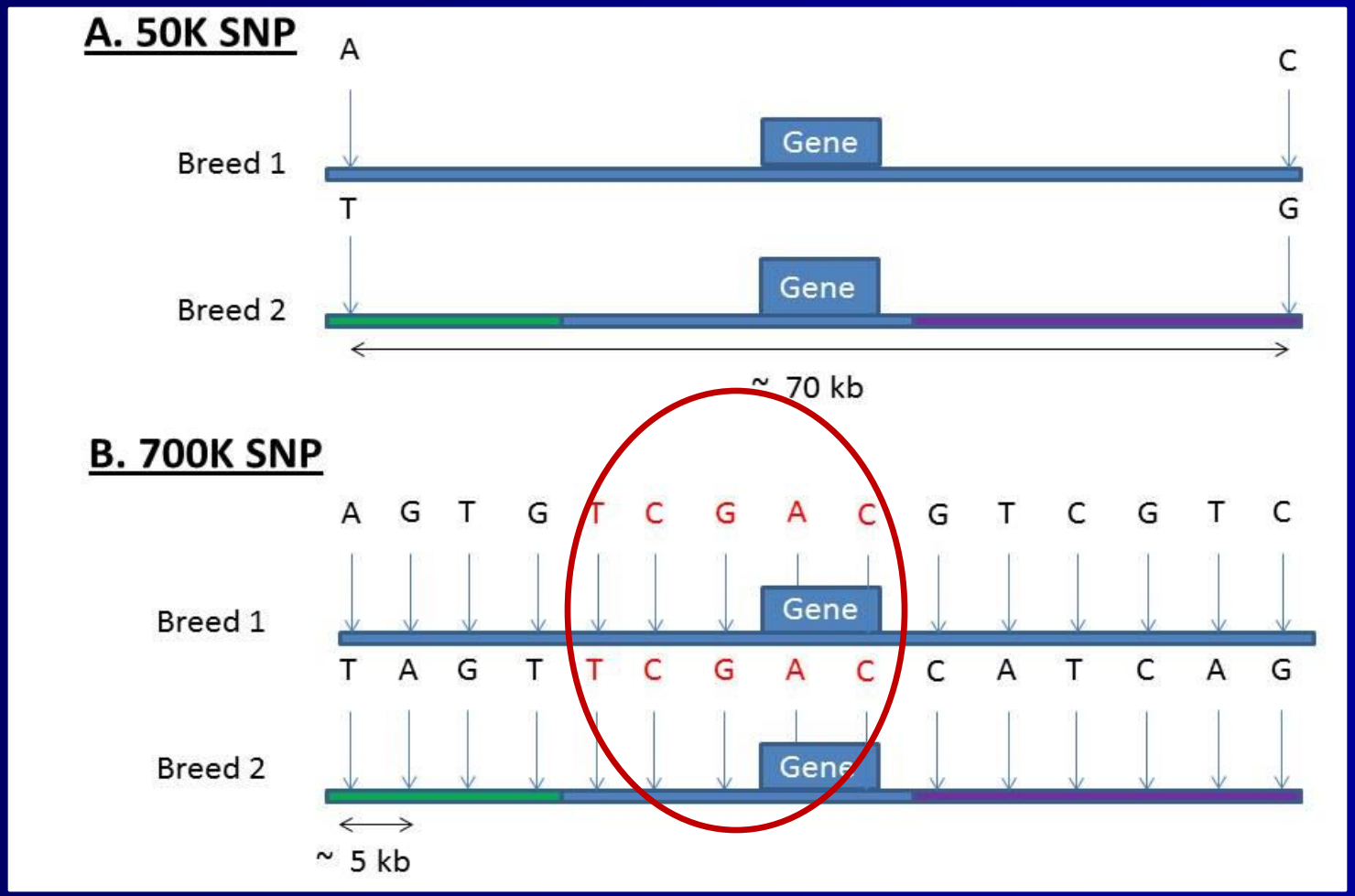
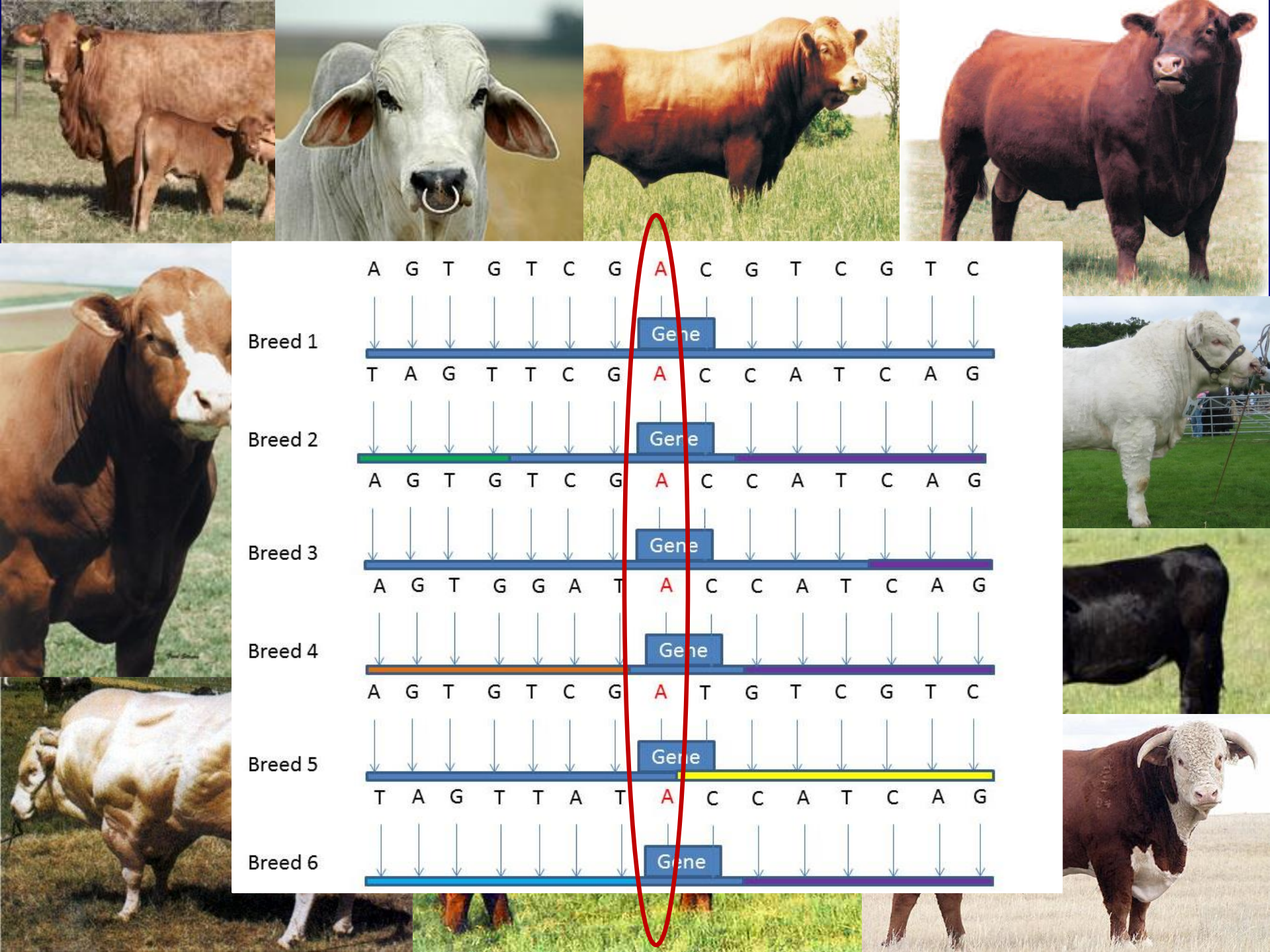
High density SNP chips may enable DNA tests to be predictive across breeds




A G T G T C G A C G T C G T C
Breed 1
Gene
T A G T T C G A C C A T C A G
Breed 2
Gene
A G T G T C G A C C A T C A G
Breed 3
Gene
A G T G G A T A C C A T C A G
Breed 4
Gene
A G T G T C G A T G T C G T C
Breed 5
Gene
T A G T T A T A C C A T C A G
Breed 6
Gene

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Need for large commercial training populations

- To have the power to meaningfully quantify genetic variation or perform a genome scan using a dense SNP chip it is necessary to have datasets comprising observations **on several thousands of individuals**.

- For studies of infectious diseases this usually necessitates utilizing field data because challenge experiments of a sufficient scale will not be possible.

Bishop, S. C., and J. A. Woolliams. 2010. On the genetic interpretation of disease data. Plos One 5: e8940.

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Accurate diagnosis (i.e. case definition) of BRD is critical for success of studies

- Traditional methods for detecting morbid cattle include visual appraisal once or twice daily.
- Animals displaying nose or eye discharge, depression, lethargy, emaciated body condition, labored breathing or a combination of these, should be further examined
- Symptomatic animals with a rectal temperature ≥ 103°F are usually considered morbid and given treatment.
- All of these diagnostic systems are ***subjective in nature***.
- Confounding factors include the diligence and astuteness of those checking the animals, the variability and severity of the symptoms the animals experience with chronic and acute BRD, and the disposition of the animals

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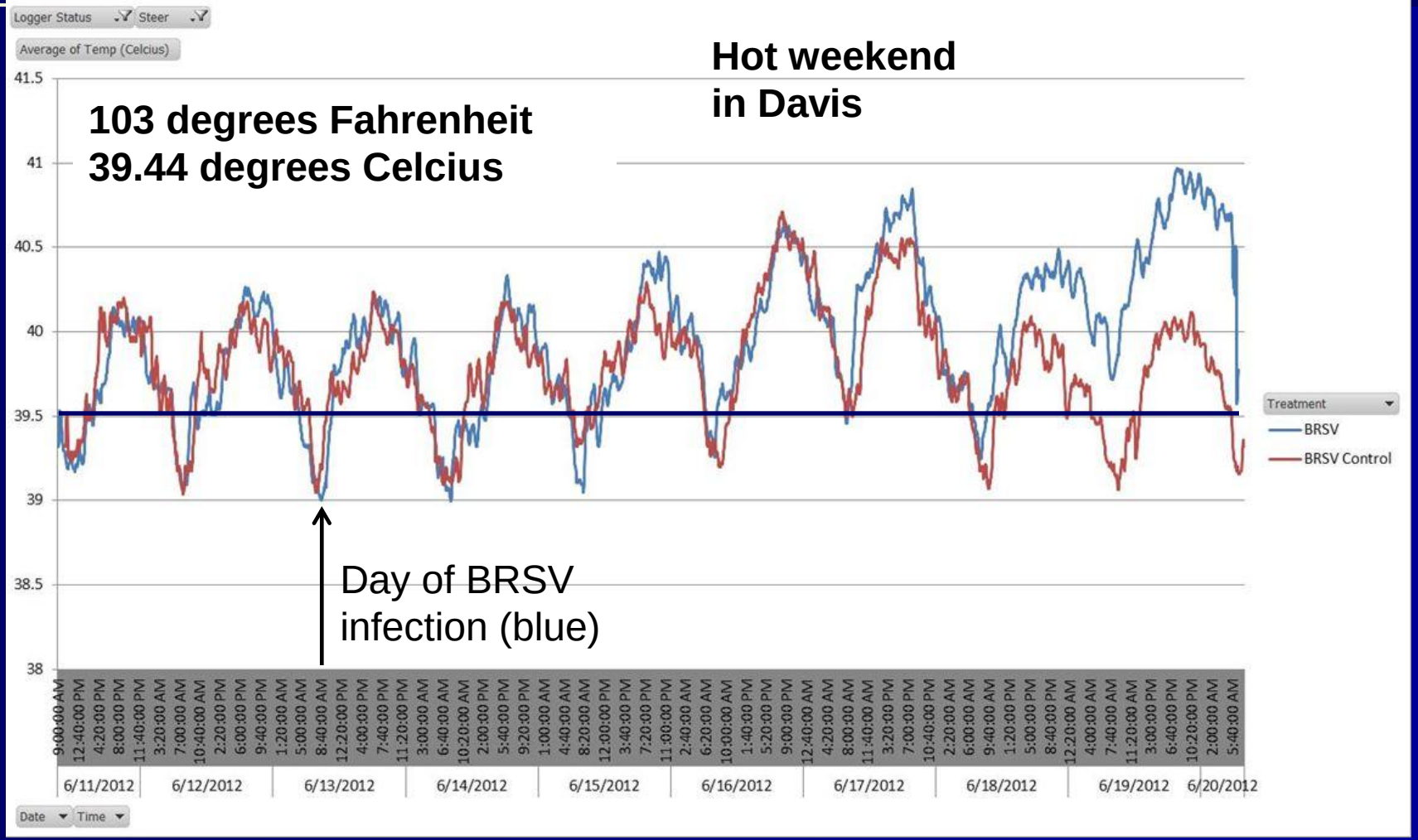

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No one said we are targeting the low hanging fruit

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However, BRD resistance is a very valuable target

- The presence of genetic variation in resistance to disease, coupled with the increased consumer pressure against the use of drugs, is making genetic solutions to animal health problems increasingly attractive.

Newman, S. and Ponzoni, R.W. 1994. Experience with economic weights. Proc. 5th World Congress on Genetics Applied to Livestock Production. 18:217-223.

- Considerable weighting (6X growth traits) was given to decreasing the feedlot incidence of BRD in a terminal beef sire selection index simulation.

Van Eenennaam, A. L. and M. D. MacNeil. 2011. What weighting should be given bovine respiratory disease (BRD) resistance in selection decisions? Pages 61-68 in Proceedings of the Beef Improvement Federation 43rd Annual Research Symposium and Annual Meeting.

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BRD CAP: BRD field datasets

Case:control field datasets being developed for BRD Genome Wide Association Studies (GWAS)

- 6000 animals – case:control design
  - 2000 dairy calves diagnosed on a collaborating dairy calf rearing ranch (CA)
  - 2000 feedlot cattle diagnosed on a collaborating feedlot (CO)
  - 1000 dairy (NM) and 1000 beef (NV) case:control animals will be used to validate loci associated with BRD in the discovery populations
- All will be genotyped on 770K high density SNP chip
- Pathogens are being characterized using bacteriology and virology
  - Genotype x pathogen interactions

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Year 1: CA Dairy Calf Ranch 70,000 head capacity

Dr. Terry Lehenbauer, DVM, University of California, Davis, CA

Sharif Aly, DVM
Pat Blanchard, DVM
Jessica Davis, DVM

Veterinary Medicine Teaching and Research Center, Tulare

Photo credit: Jessica Davis

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Standardization of BRD Diagnosis

- 1000 case and 1000 control 30-60 day old calves
- Use Dr. Sheila McGuirk's calf respiratory scoring chart
  - Temperature, eyes, ears, nose, +/- cough
  - Additional clinical signs: tachypnea, dyspnea, position of head, appetite
  - Give score and either enroll or not (5 or greater to enroll as case)
- Sample collection
  - Blood for DNA
  - Nasal swab and deep pharyngeal swab to identify viruses (PCR: IBR, BVD, BRSV, and Corona) and bacteria (*Manheimia haemolytica, Pasteurella multocida*, and *Histophilus somni*, and Mycoplasma spp.) present in the nasopharyngeal and pharyngeal recesses

SCHOOL OF VETERINARY MEDICINE
University of Wisconsin-Madison

http://www.vetmed.wisc.edu/dms/fapm/fapmtools/8calf/calf_health_scoring_chart.pdf

Calf Health Scoring Criteria			
0	**1**	**2**	**3**
Rectal temperature			
100-100.9	101-101.9	102-102.9	≥103
Cough			
None	Induce single cough	Induced repeated coughs or occasional spontaneous cough	Repeated spontaneous coughs
Nasal discharge			
Normal serous discharge	Small amount of unilateral cloudy discharge	Bilateral, cloudy or excessive mucus discharge	Copious bilateral mucopurulent discharge
			
Eye scores			
Normal	Small amount of ocular discharge	Moderate amount of bilateral discharge	Heavy ocular discharge
			
Ear scores			
Normal	Ear flick or head shake	Slight unilateral droop	Head tilt or bilateral droop
			

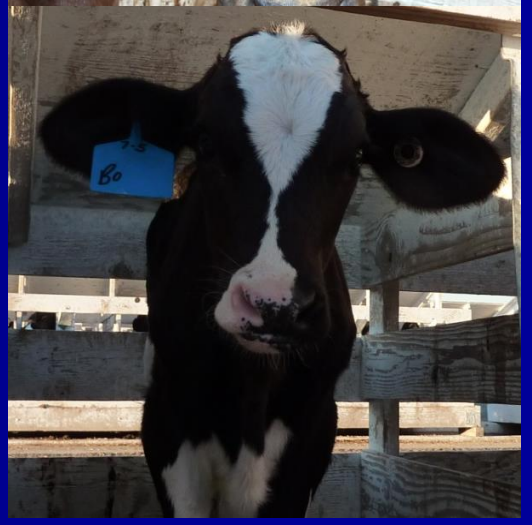

Photo credit: Jessica Davis

Sampling location of deep pharyngeal swab

To culture organisms associated with BRD, pharyngeal swabs offer a less invasive, less stressful and more rapid alternative to broncheoalveolor lavage.

Photo credit: Jessica Davis

Control Calves

- Score control in same way as cases (score of 4 or less)
- Try to select animals in the adjacent hutch, same dairy of origin, and same sex
- Collect samples for control animals in same was as case

Try to identify cases and controls in a relatively constant environment, subjected to the same exposure and stresses, to decrease the environmental "noise" of these field BRD datasets

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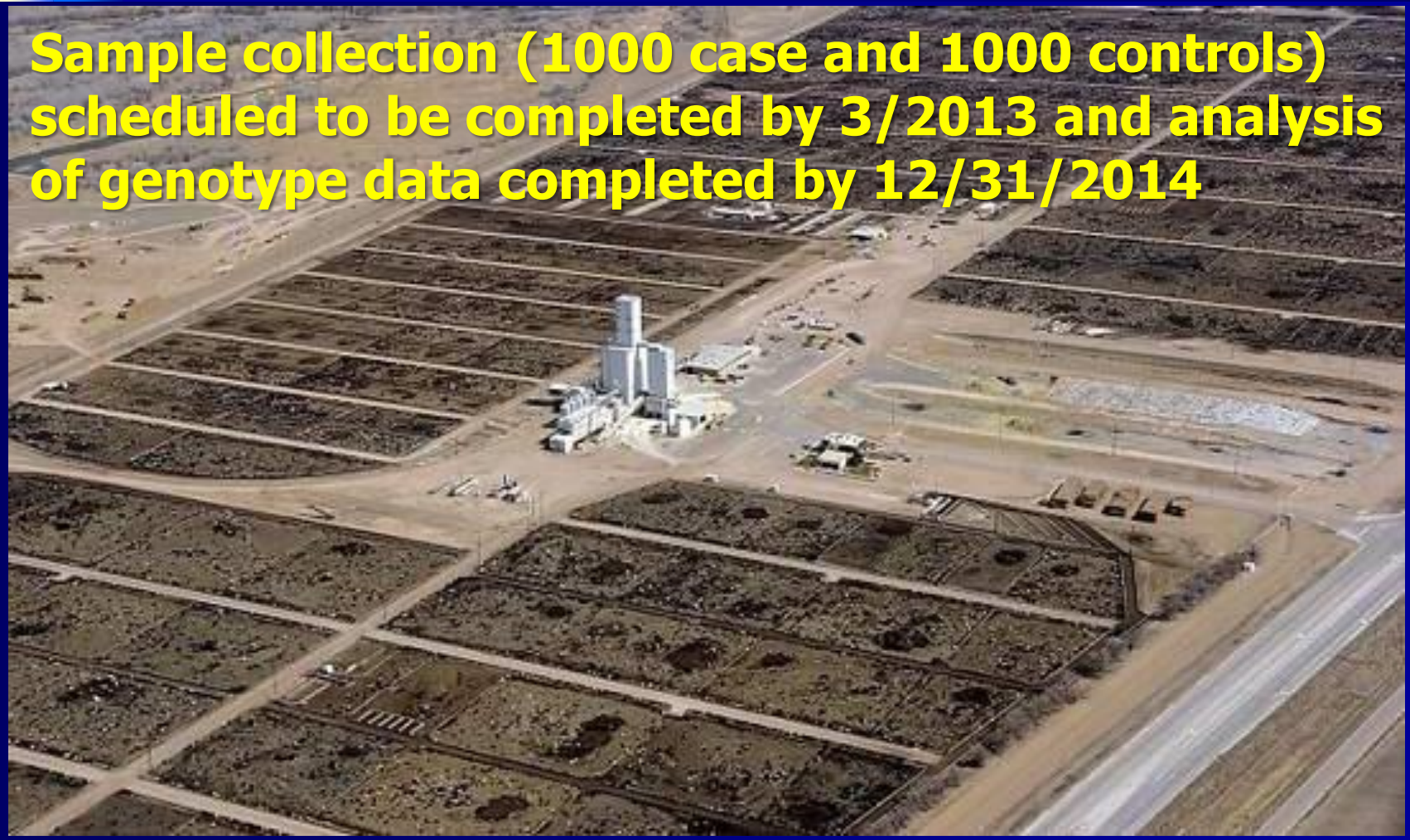
Year 2: CO Feedlot
Bos taurus beef cattle



1000 BRD case:control dairy heifers will be used as validation population

Dr. Robert Hagevoort, New Mexico State University, NM

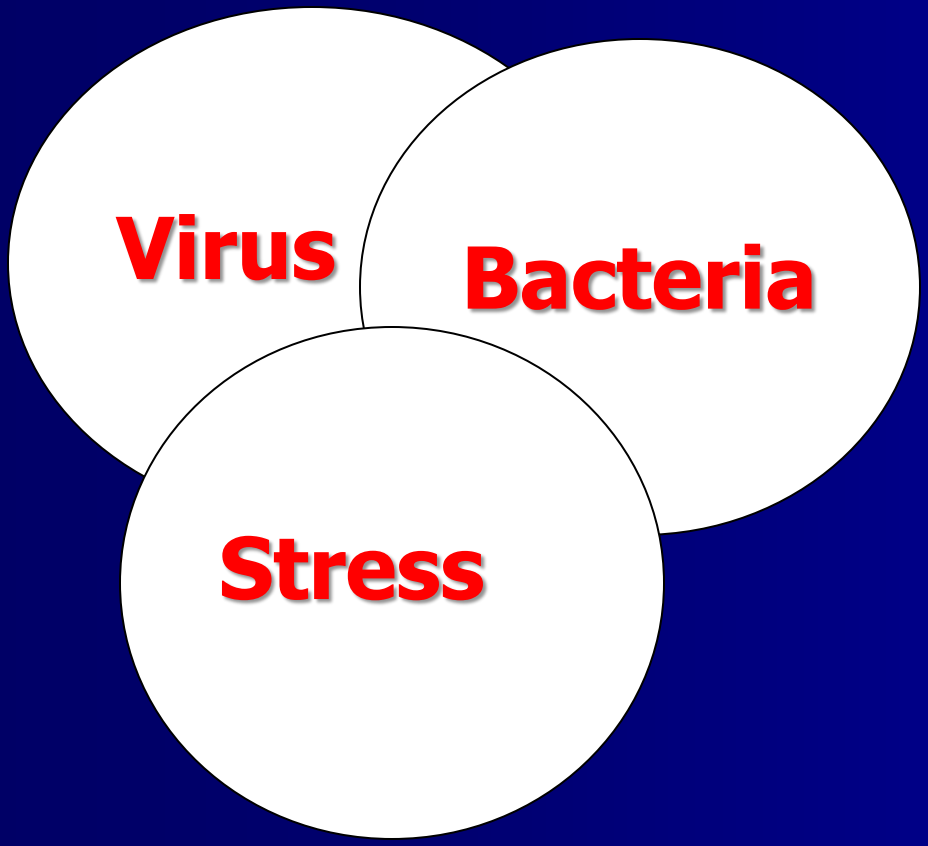
1000 case:control purebred beef bulls Will be used as validation population (NV)

Dr. Holly Neibergs, Washington State University, WA

Challenge Study

ne Respiratory Disease Complex
oordinated Agriculture Project

Dr. Laurel Gershwin, DVM, University of California, Davis, CA



Objective: To determine the transcription profiles of genes being expressed in animals challenged with individual specific pathogens

Seven pathogens are being used to challenge animals

1. *BRSV*
2. *BVDV*
3. *IBR (bovine herpes virus)*
4. *Histophilus somni*
5. *Manheimnia hemolytica*
6. *Pasteurella multocida*
7. *Mycoplasma bovis*


9251

Tissues collected from animals at necropsy – typically 5-7 post infection depending upon pathogen – and snap frozen for RNA extraction

- Healthy lung
- Representative samples of lesions if present
- Whole lung lavage
- Retropharyngeal nodes
- Pharyngeal tonsil
- Nasal pharynx
- Bronchial node
- Mesenteric nodes
- Liver
- Spleen
- Blood

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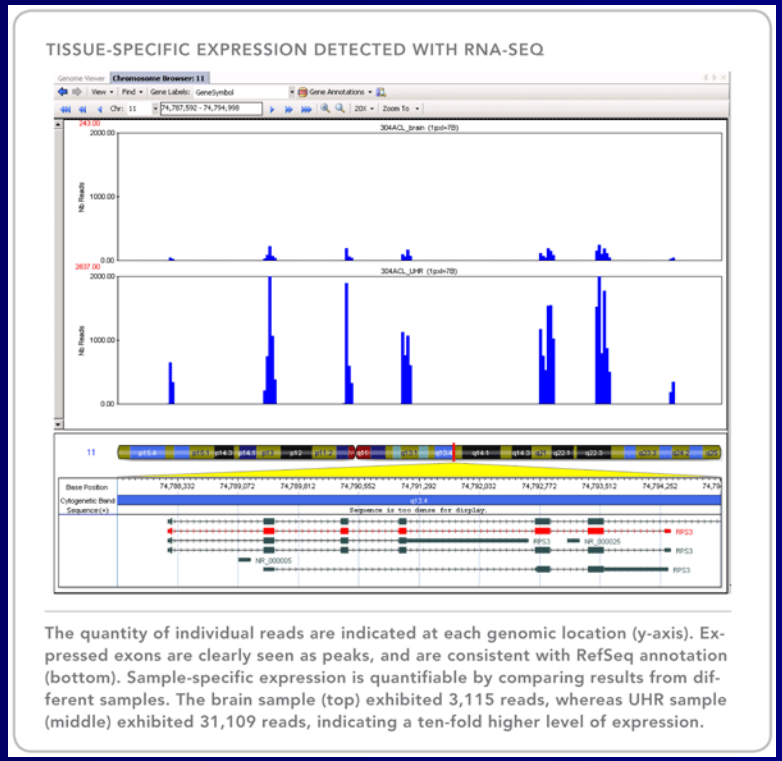
RNA-Sequencing and Metagenomics

Dr. Jerry Taylor, University of Missouri, Columbia, MO

Transcriptional profiles of host response to the specific pathogens responsible for BRD.



Can look at millions of transcripts in a single run and determine relative expression levels of individual genes

Metagenomics: is defined as the study of the collective genomes of microorganisms (as opposed to clonal cultures) that are present in a given environment (e.g. the pharynx).

- Sequence the "metagenome" of the microorganisms that are present in the respiratory tract of animals that are diagnosed with BRD (before treatment with antibiotics).
- Geographical sampling to determine what microorganisms (including those that cannot be grown using traditional culturing techniques) are found in the deep pharynx in animals experiencing BRD in both dairy and beef cattle in different regions of the US.
- Identify and sequence the genome(s) of previously uncultured organisms associated with BRD with objective of identifying new and emerging pathogens.

Assess how animal welfare and behavior is affected by BRD in cattle

Dr. Cassandra Tucker, University of California, Davis, CA

Two studies looking at 1) the use if NSAID; and 2) use of behavioral measures (use of brushes in pens) to identify animals that are becoming sick with BRD.

Age and weight matched
With and without NSAID administration

BRD+ meloxicam

BRD

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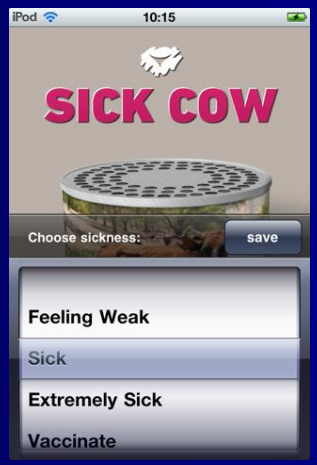
Employ genomics to develop improved diagnostic tests

- Development of rapid, cost-effective BRD molecular diagnostic tool for Veterinary Diagnostic labs
- Rapidly developing field



Potential uses and value of genomic information for different sectors of the cattle industry

Use	Seedstock	Commercial	Feedlot	Processor
DNA-assisted selection	XXXX	X	XXXX	XXXX
Parentage	XX	X		
Recessive allele testing	XX	X		
Control of Inbreeding	XX	X		
Mate selection	XX	X		
DNA-assisted management/purchasing		X	XX	XX
Product differentiation				XXXX
Traceability				XX
Vet med. diagnostics - the "diagnomics" age?	X	X	XX	X

Our goal is to integrate research, education, and extension activities to develop cost-effective genomic and management approaches to reduce the incidence of BRD in beef and dairy cattle

The objective of this multi-institutional project is to reduce the incidence of bovine respiratory disease by:

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- Developing improved DNA-based tests for disease diagnosis
- Producing and delivering a variety of educational materials for beef and dairy cattle producers, and feedlot personnel on best management practices to reduce disease incidence
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www.brdcomplex.org

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