http://tinyurl.com/C2CBRDCAP

Genomics of Bovine Respiratory Disease (BRD) : An Update

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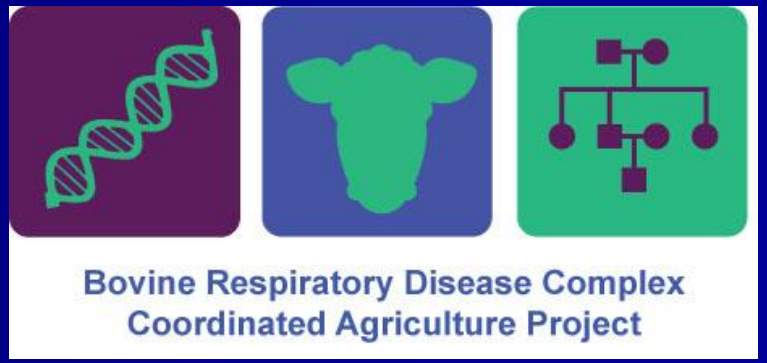
US Bovine Respiratory Disease
Coordinated Agricultural Project
http://www.brdcomplex.org



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.

Bovine Respiratory Disease Complex
Coordinated Agriculture Project

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
- Description of 2012 CA dairy calf study
- General outline of other research studies

Bovine Respiratory Disease Complex
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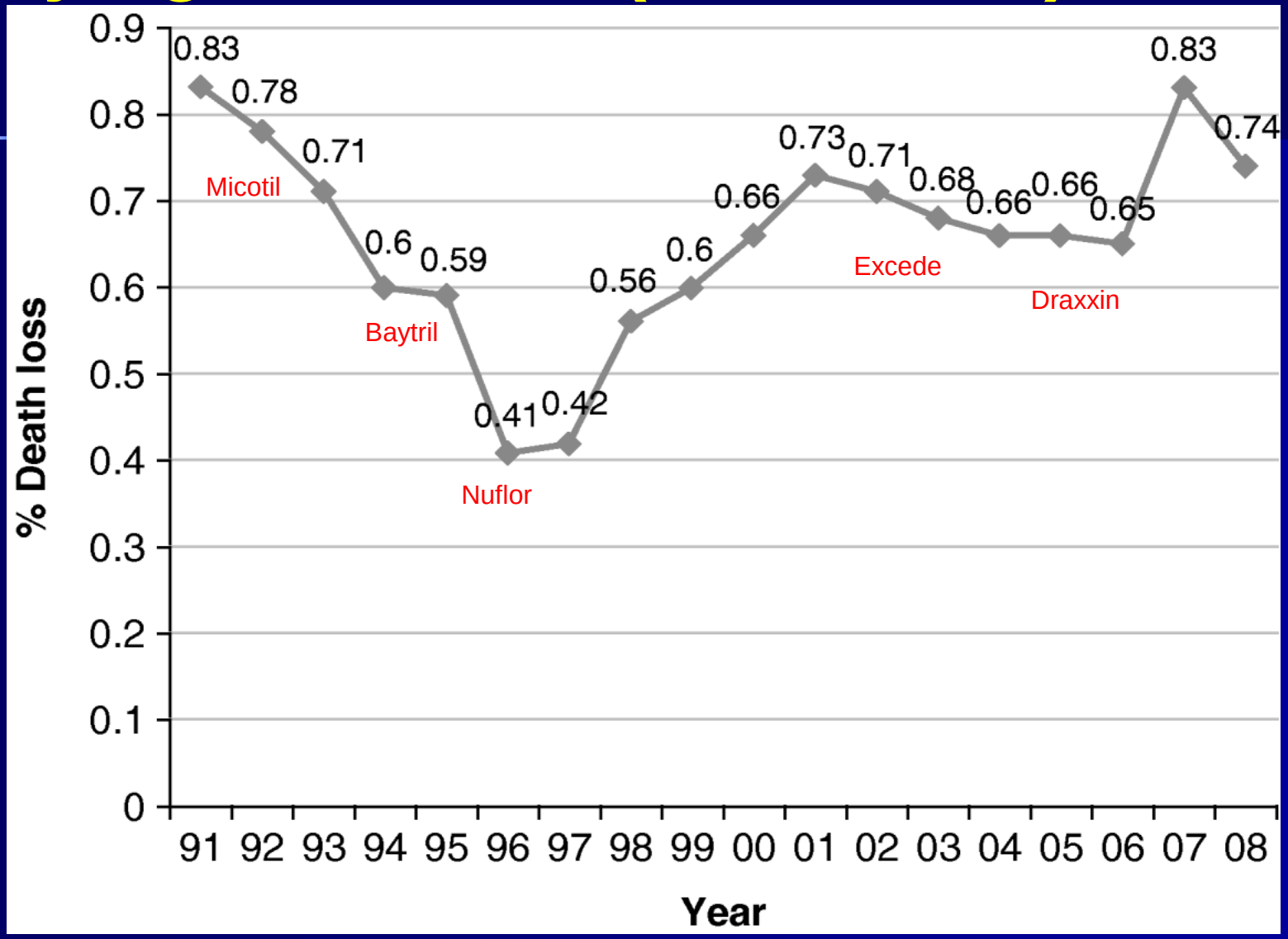
Bovine Respiratory Disease

- 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.

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Disease resistance is a very attractive target trait for genetic improvement

- 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.
- The non-permanent effectiveness of chemical agent (due to development of resistance by the pathogen) further contributes to this interest.

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

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Coordinated Agriculture Project

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

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

WASHINGTON STATE UNIVERSITY

- **Holly Neibergs**
- Shannon Neibergs

UC DAVIS UNIVERSITY OF CALIFORNIA

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

Colorado State University

- **Milt Thomas**
- Mark Enns

NEW MEXICO STATE AGGIES

- Robert Hagevoort
- Tim Ross

MISSOURI

- Jerry Taylor

United States Department Of Agriculture Agricultural Research Service

- Mike MacNeil
- Curt Van Tassell

OTHER COLLABORATORS

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

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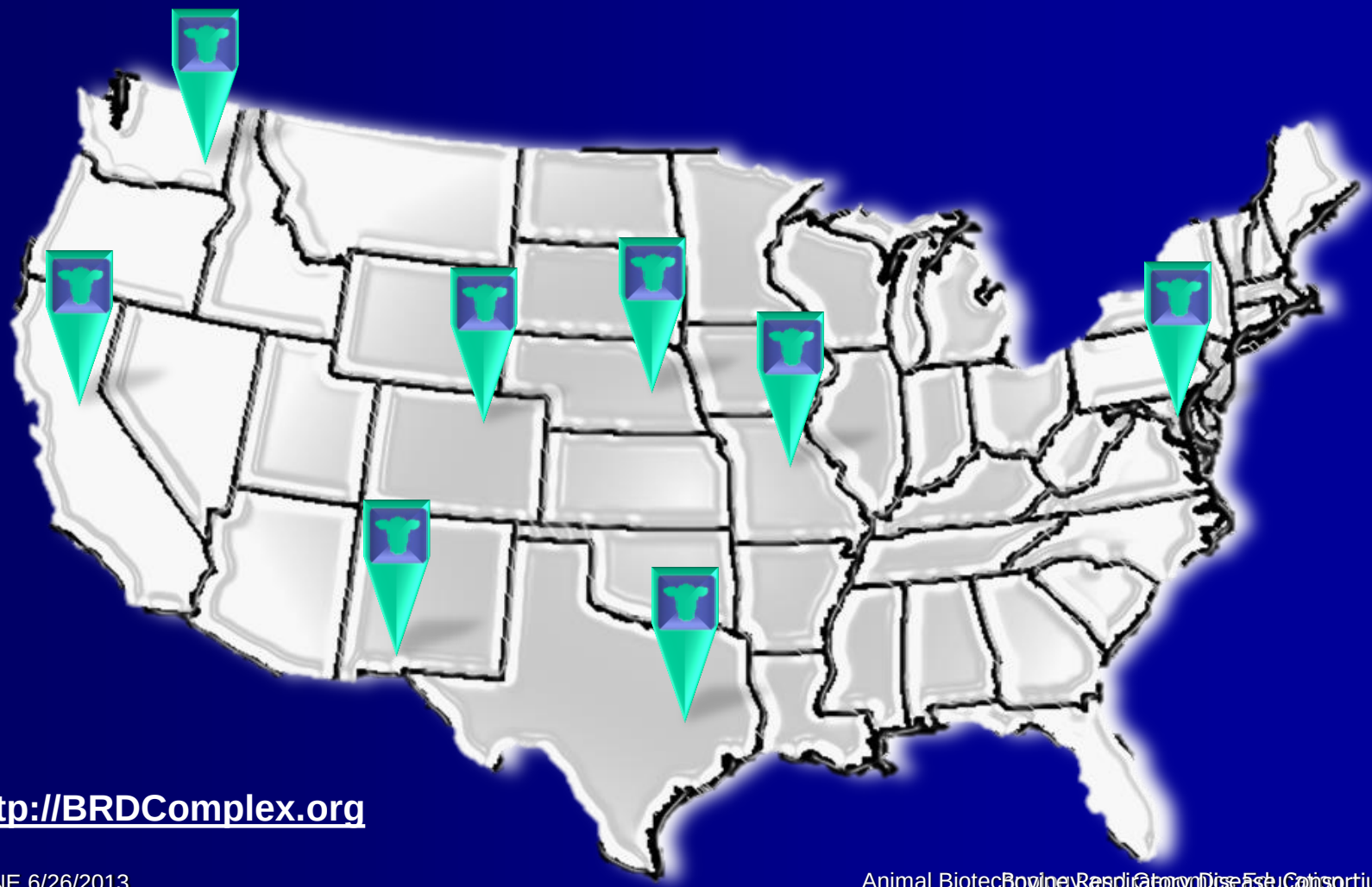
Location of US collaborators



http://BRDComplex.org

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Bovine Respiratory Disease Complex
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Home | For Students | For Producers | For Researchers | Prevention Risk Assessment

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United States Department of Agriculture
National Institute of Food and Agriculture

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http://BRDComplex.org

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Cattlemen to Cattlemen – Episode 1.

Shot on location at MARC in NE June 2012.
Aired week ***Tuesday October 16, 2012.***

"Six ten minute video vignettes be developed for viewing and distribution via various outlets including YouTube, eXtension, and the National Cattlemen's Beef Association (NCBA) TV show **"Cattlemen to Cattlemen"** (http://tinyurl.com/C2CBRDCAP)

Brad Bulla and Pete Kaiser
of Baxter Communications

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What is needed to develop DNA-tests for BRD susceptibility?

Large training/discovery populations with BRD observations and SNP genotypes = used to estimate the value of every chromosome fragment contributing variation BRD susceptibility. This allows for prediction of which chromosome segments regions are important for the trait.

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

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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.

RESEARCH OBJECTIVE 1

Objective 1. Identify genomic regions associated with BRD resistance/susceptibility in beef and dairy cattle.

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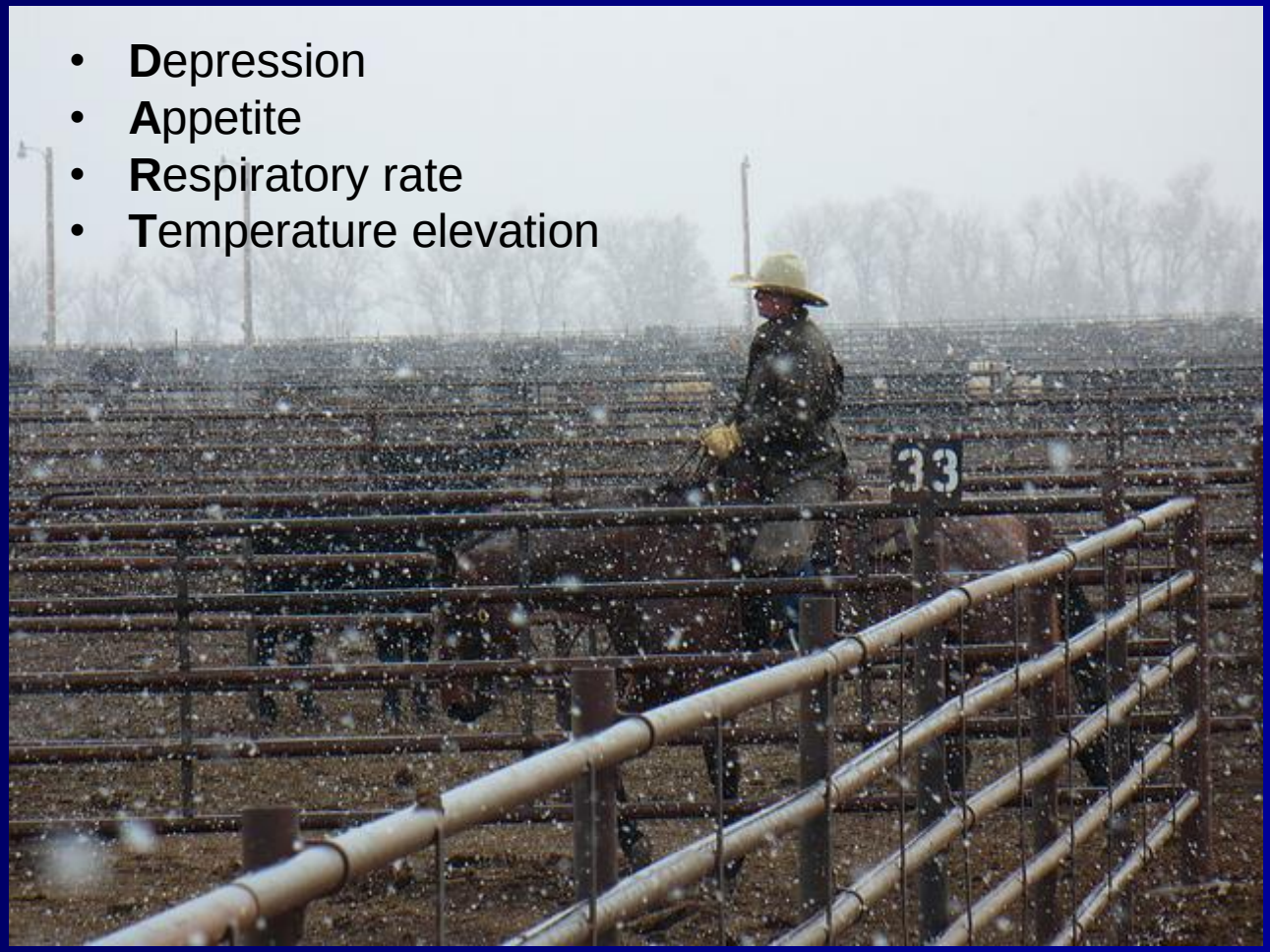
Accurate diagnosis (i.e. case definition) of BRD is critical for success of studies



- **D**epression
- **A**ppetite
- **R**espiratory rate
- **T**emperature elevation

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

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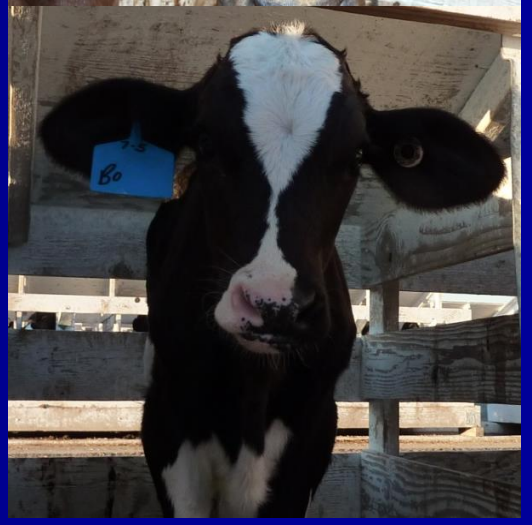
Accurate diagnosis (i.e. case definition) of BRD is critical for success of studies

- 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.
- 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
- All of these diagnostic systems are ***subjective in nature***.

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
			



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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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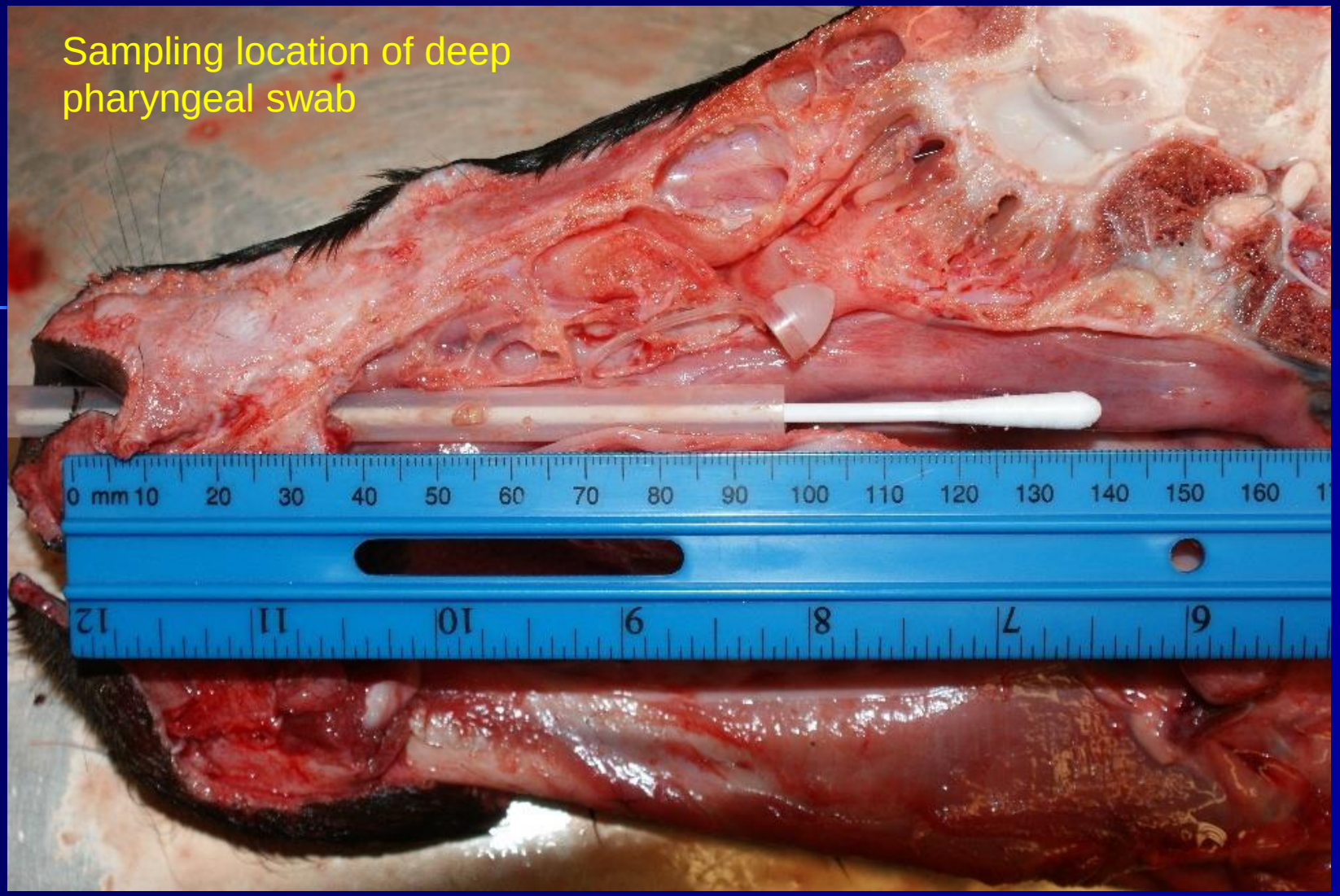
Standardization of BRD Diagnosis

- 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


Blood collection


Deep pharyngeal swab collection


Nasal 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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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

POPULATION A: DAIRY CALVES

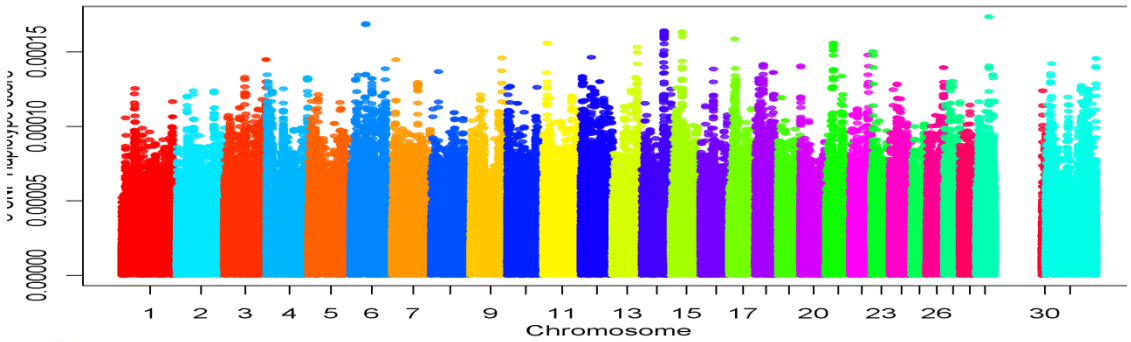
UC DAVIS, WSU

- Samples on 2013 calves collected and clinical scores obtained
- Diagnostics for Mycoplasma, *P. Multocida, M. Haemolytica, H. Somni,* bovine respiratory syncytial virus, bovine viral diarrhea virus, IBR completed
- DNA extracted, and genotyped for 778,000 SNPs

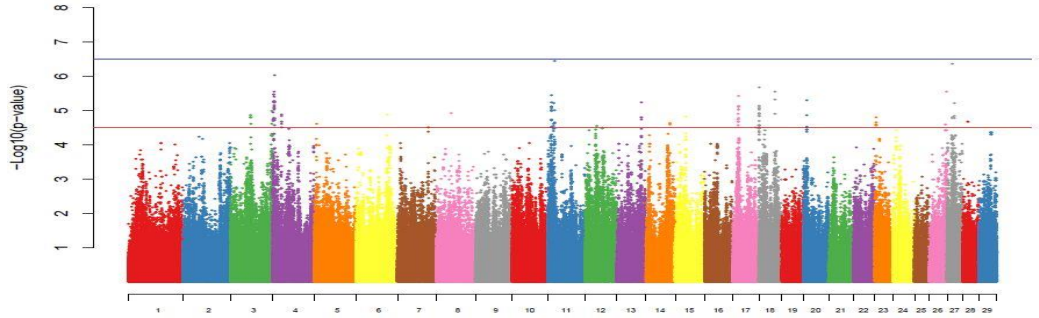
H. Neibergs *et al. Unpublished*

GBLUP, PLINK, SVS7
SIGNIFICANT SNPS CASE/CONTROL
MISSOURI, TAMU, WSU

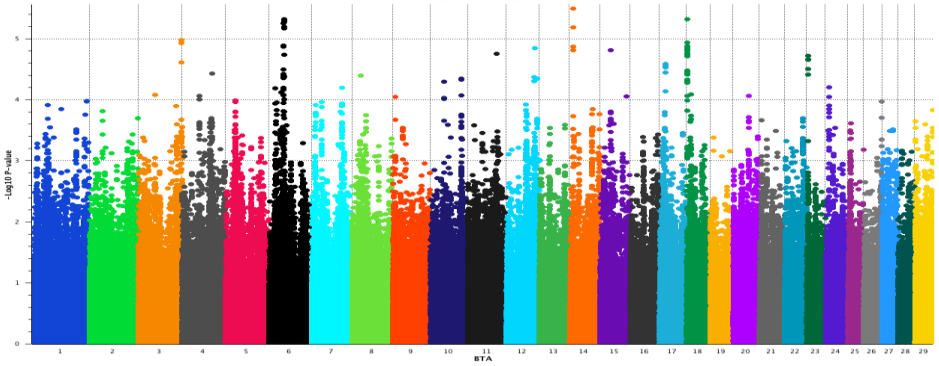
GBLUP



PLINK



SVS7



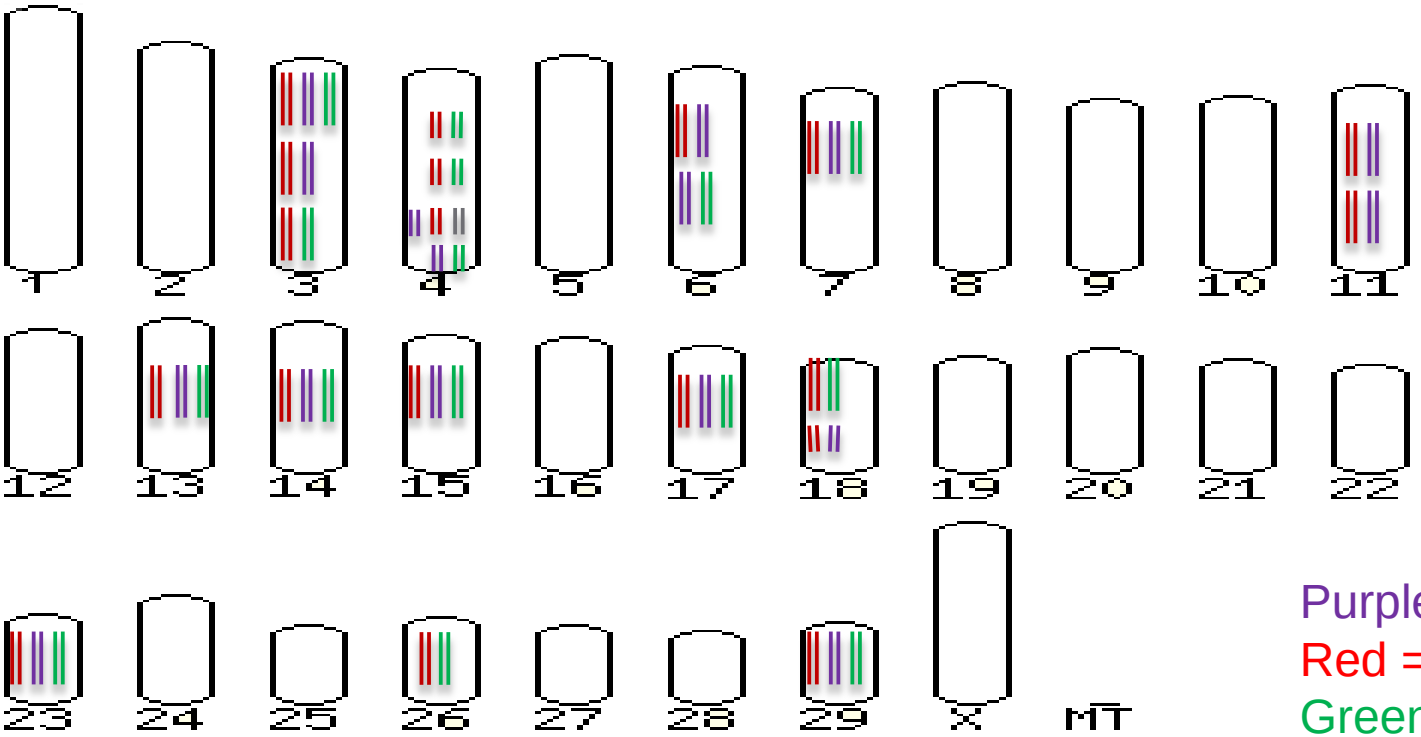
H. Neibergs *et al.* *Unpublished*

SHARED SIGNIFICANT SNPS

- **7 SNPs common to *all* analyses**
  - **BTA3, BTA15, BTA23 (5 SNPs)**
- **11 common to GBLUP and PLINK**
  - **BTA3, BTA11, BTA17 (8 SNPs)**
- **17 common to PLINK, SVS7**
  - **BTA13, BTA18 (15 SNPs), BTA26**
- **19 common to GBLUP, SVS7**
  - **BTA4, BTA6 (10 SNPs), BTA12, BTA14, BTA15 (3 SNPs), BTA22 (3 SNPs)**

H. Neibergs *et al.* *Unpublished*

REGIONS ASSOCIATED WITH BRD ACROSS ANALYSES



Purple = GBLUP
Red = PLINK
Green = SVS7

H. Neibergs *et al.* *Unpublished*

GBLUP SNP EFFECTS

- Explained the variation in incidence of:
  - Nasal discharge (9%)
  - Cough (19%)
  - Temperature (10%)
  - Ocular discharge/ear tilt (8%)
  - Total clinical score (18%)
  - BRD (20%)

H. Neibergs *et al.* *Unpublished*

Bovine Respiratory Disease Complex
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Year 2: CO Feedlot
Bos taurus beef cattle

Sample collection (1000 case and 1000 controls) scheduled to be completed by 12/31/2014

RESEARCH OBJECTIVE 2

Objective 2. Determine the transcription profiles of genes being expressed in animals challenged with individual specific pathogens

CHALLENGE STUDY
UC DAVIS, MISSOURI

- 300 kg Angus calves challenged with *Mycoplasma bovis*, *P. Multocida, M. Haemolytica, H. Somni,* bovine viral diarrhea virus (BVDV), and bovine respiratory syncytial virus (BRSV), and *IBR (bovine herpes virus).*
- Identify genes expressed with given pathogens via RNA-seq of various tissues
- Characterize immunological responses

ADMINISTRATION OF BACTERIAL INOCULUM

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

A foal size stomach tube with internal polyethylene tubing and 3 way stop-cock is passed through the ventral nasal meatus to posterior trachea where inoculum is deposited and followed by air to empty the tube.

AEROSOL ADMINISTRATION OF VIRUS

DeVilbis air compressor and nebulizer and hooked up mask. Open system requires that those close to the aerosol wear protective respirators to avoid inhalation of protein material in aerosol.

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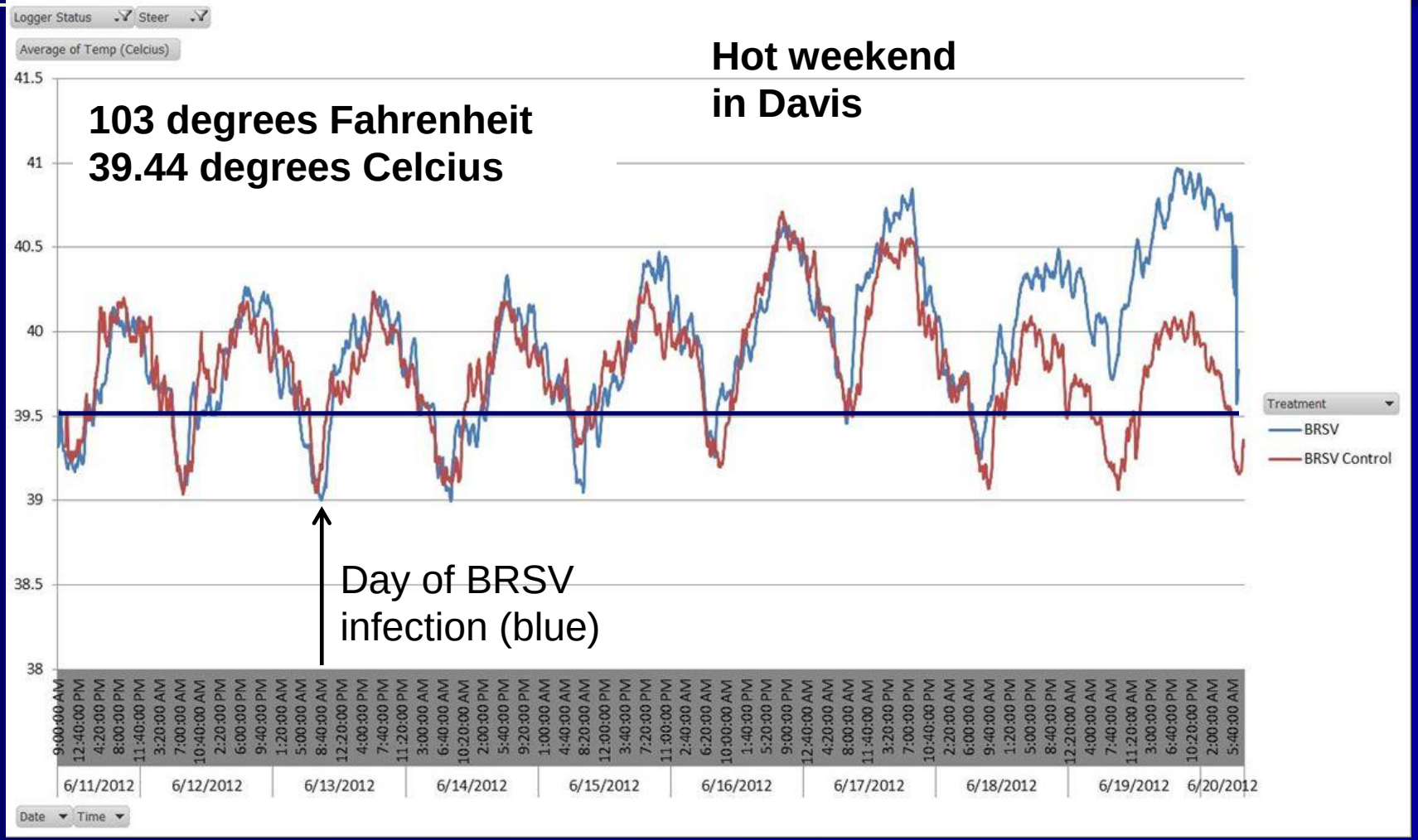
Symptomatic animals with a rectal temperature ≥ 103°F are usually considered morbid and given treatment.




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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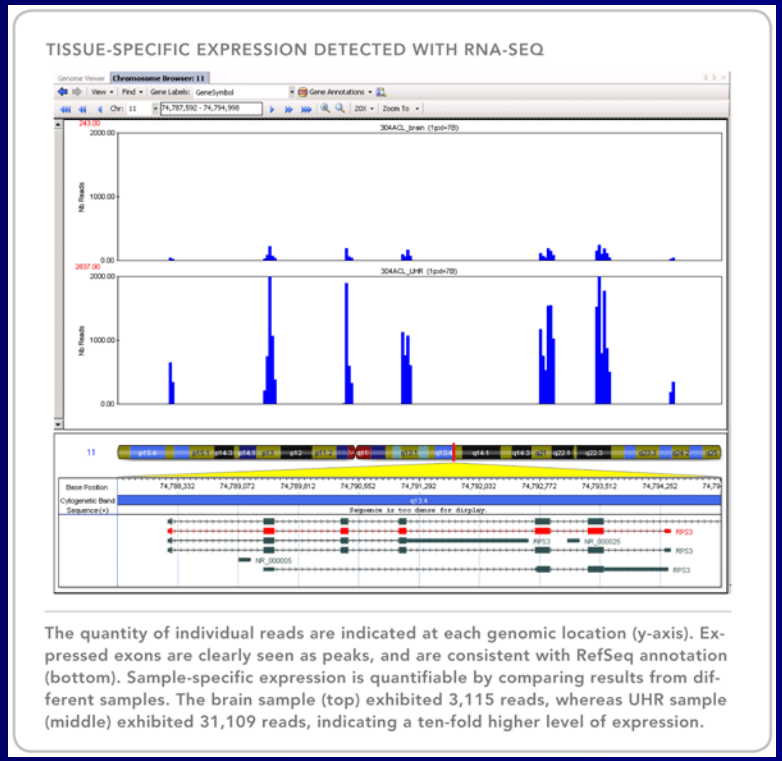
RNA-Sequencing and Metagenomics

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

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:

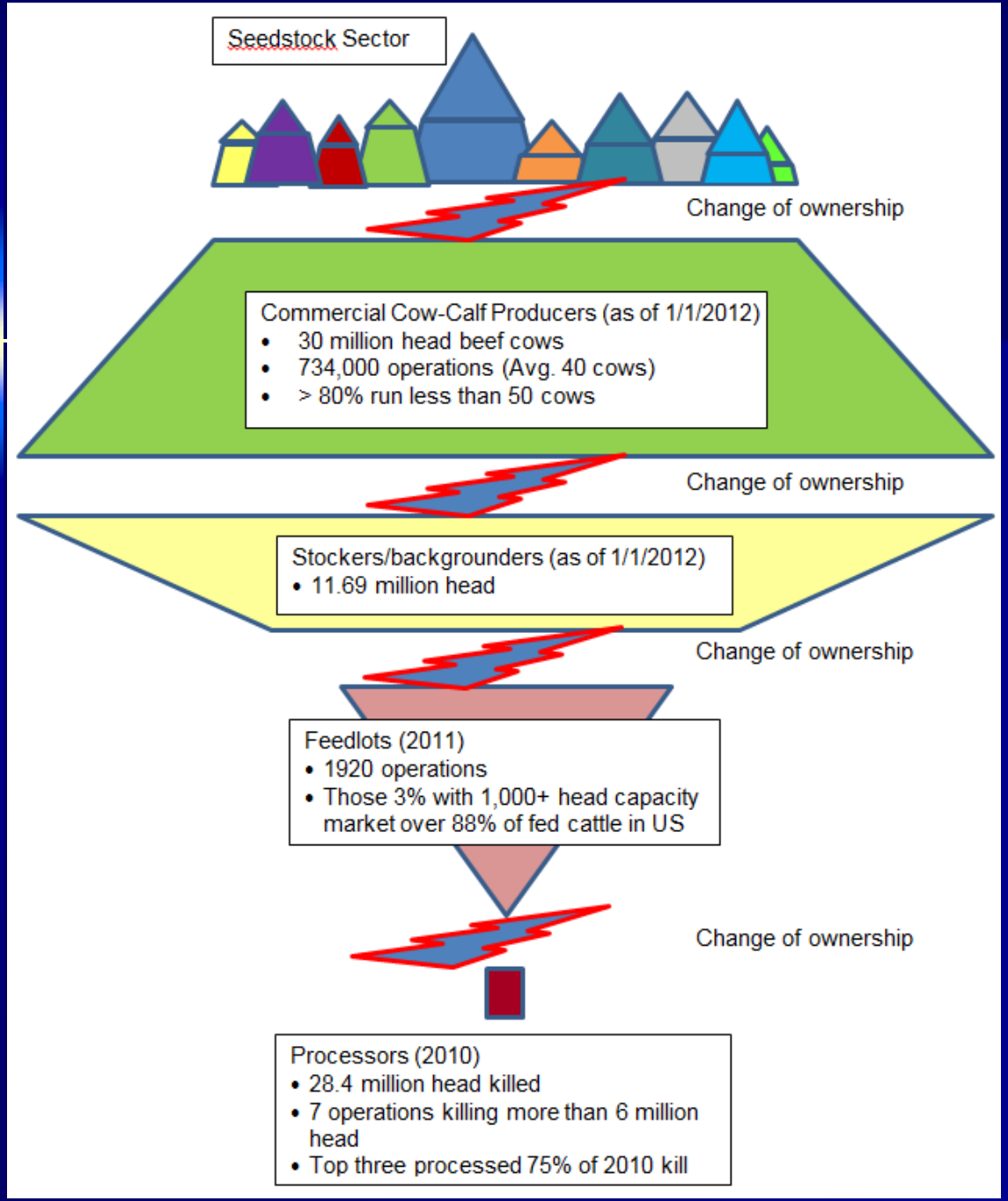
- Are difficult or expensive to measure
- Cannot be measured until late in life or after the animal is dead
- Are not currently selected for because they are not routinely measured
- Have low heritability

How can genomic tools be integrated to capture the economic value of project findings within the beef industry

Lots of hard to measure economically-important trait cattle grants

National Program for Genetic Improvement of Feed Efficiency in Beef Cattle **Taylor *et al*., MO**	5
Bovine Respiratory Disease Complex Coordinated Agricultural Project **Womack *et al*., TX**	10
Identification And Management Of Alleles Impairing Heifer Fertility While Optimizing Genetic Gain In Angus Cattle – Patterson *et al*., MO	3
Reproduction in dairy cattle – Spencer *et al*., WA	3

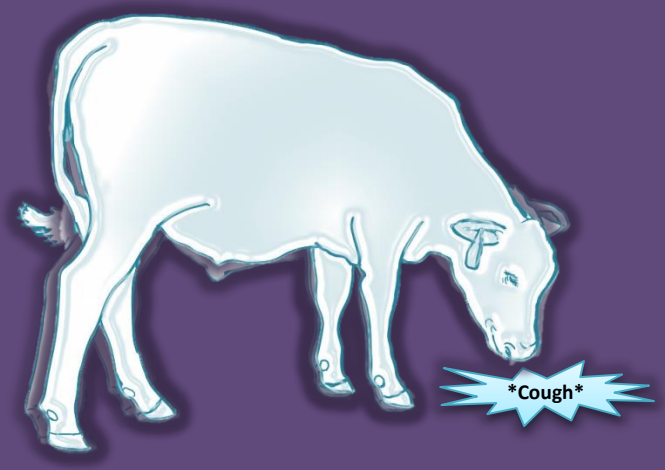
> $20 million in active AFRI grants – can these work together?



For widespread technology adoption, breeders need to be adequately rewarded for making DNA investments and selection decisions for traits that benefit the different sectors of the beef industry.

Van Eenennaam, A. L. *et al*. 2013. Applied Animal Genomics: Results from the Field. *Annual Review of Animal Biosciences. Submitted.*

Thanks for inviting me



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USDA United States Department of Agriculture | National Institute of Food and Agriculture

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