Factsheet (Update: April 2022)

Genetic testing for bovine congestive heart failure (BCHF) in feedlot cattle

What's new? A scientific report describing the discoveries is now publicly available[1]. Additional DNA sequence variants (markers) in the *NFIA* gene have been identified as having increased association with disease when two copies are present. Additional linked markers for *ARRDC3* have also been identified and provide flexiblity for chosing genotyping platforms and test designs.

1. **What is bovine congestive heart failure (BCHF)?** BCHF is a significant cause of death in feedlot cattle in the Western Great Plains of North America. Mortality from BCHF has reached 7% in severely affected pens of cattle, with annual losses exceeding $250,000 at a single operation[2].

2. **What are genetic risk factors?** Genetic risk factors are specific DNA sequence variants associated with disease. Examples in people include DNA variants associated with breast cancer, lung cancer, or heart disease. However, an individual that has a genetic risk factor for a disease is not guaranteed the disease will occur. There are many important non-genetic factors such as lifestyle and environment that may be needed for disease to develop. In cattle, research has identified two significant bovine genetic risk factors that predispose feedlot cattle to BCHF at moderate altitudes [1].

3. **How were these genetic risk factors for BCHF discovered?** Beginning in 2017, more than 140,000 Western Plains feedlot cattle were screened by experienced pen riders for signs of BCHF. A set of 102 matched pairs of BCHF-affected and unaffected (normal) pen mates were chosen for genetic evaluation[2]. Pairs from 30 ranch sources were matched for their breed type (appearance), arrival date, sex, and origin. Matching the cattle pairwise helped standardize their genetic background and exposure to similar environments.

4. **How can only 102 diseased cattle be used to identify genetic risk factors?** Cases were screened from a group of 140,000 feedlot cattle. A well-defined veterinary case definition, together with meticulous evaluation at necropsy by trained veterinarians and researchers provided additional power. The genetic information from 560,000 DNA markers for each BCHF case was compared to that of its matched unaffected pen mate in a genome-wide study to discover chromosomal regions associated with BCHF. The results from all 102 pairs of animals were combined in a computer analysis to identify two distinct chromosomal regions that had statistically outstanding associations with BCHF. Each of the two associated regions spanned a different gene (*ARRDC3* and *NFIA,* respectively). Two copies of specific markers at **each** gene are associated with risk for BCHF in feedlot cattle in this study[1]. This result is a refinement of preliminary findings.

5. **How does a BCHF genetic test work?** A test for predisposition to BCHF detects the animal's genetic information (genotype) for at least one specific DNA marker at each of the two implicated genes. The animal's genotypes for BCHF markers identifies the genetic risk factors present in that animal. Research showed that feedlot animals with risk factors from one of either gene, died from BCHF at a rate 8-times higher than animals with neither risk factor present. Animals with risk factors at both genes died from BCHF at a rate 28-times higher than animals with neither risk factor present. Cattle

with both genetic risk factors for BCHF represented 29% of the disease cases compared to only 2% of unaffected cattle.

6. **What does the outcome of a genetic test for BCHF really indicate?** Cases are expected to arise in animals with both risk factors at a rate 28-fold higher than those with no risk factors in pens of Western Plains feedlot cattle affected with BCHF.

7. **How well do these two BCHF risk factors predict if a feedlot animal <u>will not</u> die from BCHF?** The two-gene BCHF test was the most accurate at identifying animals that were not likely to become BCHF cases in the affected feedlots. If an animal had neither of the two risk factors for BCHF, there was only a 1% chance that they became a BCHF case in this study. Knowing which animals have minimal BCHF risk BCHF may be particularly useful in selective breeding.

8. **How well do these two BCHF risk factors predict if a feedlot animal <u>will</u> die from BCHF?** Not all cattle with both risk factors developed BCHF in the study. However, 29% of BCHF cases had both risk factors compared to only2% of the matched unaffected pen mates. These results illustrate the likelihood of other genetic and environmental factors contributing to the development of BCHF. Thus, the positive predictive value of the two-gene test is relatively low[1]. Regardless, identifying which feedlot cattle have both risk factors may be useful in future research aimed at interventions.

9. **Is a two-gene BCHF test similar to Genomically-Enhanced-EPDs?** No. Genomically-enhanced expected progeny differences (GE-EPDs) estimate an animal's genetic merit through prediction equations based on pedigree, performance information, and genetic information from 50 to 778k+ DNA markers. The two-gene BCHF test here estimates an animal's genetic risk for heart failure without prediction equations, pedigree, performance information, or the use of other DNA markers.

10. **Are these two gene markers genetic defects?** Genetic defects or otherwise known causes of BCHF have not been identified yet. Although its plausible that one of the linked *ARRDC3* markers represents a loss of function, it is not known which specific DNA sequences are causing the increased risk for disease. Thus, the causes and mechanisms of BCHF have yet to be determined.

11. **Are these two gene markers predictive of heart failure in all cattle breeds?** The study population consisted of 140,000 feedlot cattle without regard for breed. However, the 102 BCHF cases that met the study criteria were 93% solid black, 5% solid red, and 2% red/white face. Most of the affected animals in the study were likely from Angus or Angus-influenced germplasm based on breed prevalence and coat color in these feedlots. The predictive value of these two BCHF risk factors in other breeds is completely unknown.

12. **How can feedlot operators benefit from using a two-gene BCHF test?** DNA testing was developed from BCHF research in Western Plains feedlots. Operators of affected feedlots in similar environments may benefit from testing. Once high-risk animals are identified, options are available for selectively managing animals grouped by genetic predisposition to BCHF. Research on beneficial management options is ongoing.

13. **How can cattle breeders benefit from a two-gene test?** Cattle producers affected by BCHF can benefit by selecting animals that do not carry risk factors in *ARRDC3* and *NFIA* genes. Reducing these risk factors in breeding herds is predicted to reduce the impact of disease in subsequent calf crops. The percentage of sires without both risk factors varies by breed and has been estimated[1].

14. **Who will not likely gain benefits from a two-gene BCHF test?** Producers not experiencing BCHF problems with their cattle will gain little from this test, unless they are selling breeding animals to other producers affected by or concerned about BCHF.

15. **Should I be culling all my animals with high BCHF risk?** This decision depends on the cost of BCHF in your operation. In most situations, reducing the frequency of these two risk factors in the breeding herd is predicted to reduce BCHF risk in the calf crop over time while maintaining desirable production characteristics. In herds with a known high prevalence of BCHF in finishing cattle, aggressive culling of breeding animals with the highest potential for transmitting risk to their offspring is predicted to reduce the frequency of future BCHF cases.

16. **Is the problem of BCHF now solved?** Not yet. It is unknown whether these discoveries are generalizable to other cattle and other environments. However, a two-gene BCHF test provides a tool for affected producers to begin reducing disease impact now. As new research results are obtained, DNA tests with better predictive values are anticipated, along with information about applicability to breeds, management systems, environments, and conditions.

17. **When will better genetic tests for BCHF risk be available?** The most useful genetic tests for disease risk require knowledge of the causal variants. The search is underway to identify and confirm causal variants for BCHF risk. A mechanistic understanding of their mode action is also being sought.

18. **How do I test my cattle?** Producers are encouraged to reach out to contact Dr. Vander Ley or their genotype provider for additional information on the most current options for genetic testing.

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