Factsheet

Genetic risk factor testing for bovine congestive heart failure in feedlot cattle

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. **What are genetic risk factors?** Genetic risk factors are specific DNA sequence variants known to play a significant role in causing disease. In humans for example, a woman's risk of developing breast cancer is greatly increased if she inherits a harmful mutation in the BRCA1 or BRCA2 genes. In cattle, research presented at an International meeting in 2020[1,2] described new bovine genetic risk factors associated with BCHF in feedlot cattle at moderate altitudes.

3. **How were these genetic risk factors for BCHF discovered?** Beginning in 2017, more than 140,000 Western Plains feedlot cattle were screened by pen riders with experience in recognizing the signs of BCHF. From these cattle, a set of 102 matched pairs of BCHF-affected and unaffected (normal) penmates were chosen for genetic evaluation[3]. Matching the cattle into pairs effectively standardized their genetic background and exposure to similar environments. Pairs were matched for their place of origin, breed type (appearance), arrival date, and sex. The 102 pairs represented more than 30 different ranch sources.

4. **How can only 102 diseased cattle be used to identify genetic risk factors?** A well-defined veterinary case definition, together with careful and thorough evaluation at necropsy by trained veterinarians and scientists, provided extraordinary power to this approach. The DNA from each BCHF case was compared to a similar, but unaffected, penmate in a genome wide study to discover differences associated with BCHF (i.e., genetic risk factors). The results from all 102 pair-wise comparisons were combined in an analysis that identified 21 distinct genomic regions harboring risk factors that met the cutoff criteria: odds ratio >3.0, 1% significance level, and 95% power. Of these 21 regions, two were statistically outstanding with regards to their association with BCHF.

5. **How does the current BCHF genetic test work?** The current test detects a single nucleotide polymorphism (SNP) in each of the two best associated regions. The animal's genotype for these two most informative SNPs determines how many BCHF risk factors it has: zero, one, or two.

6. **Why not use all 21 genetic risk factors for BCHF in the test?** Evaluation of the remaining 19 risk factors is ongoing. The two best BCHF risk factors (with the largest effects) are being used now in an effort to provide relief for producers with severely affected cattle.

7. **How much disease risk is conferred by the two best BCHF genetic factors?** In this study, cattle with one or two of the best BCHF risk factors, respectively, were approximately 7.5- and 15-fold more likely to die of heart failure compared to those that inherited neither of the two risk factors. Of the 102 diseased cattle enrolled in the study, 63% had both BCHF genetic risk factors while only 1% of the diseased cattle had neither risk factor (Fig. 1). An additional set of 100 similar BCHF cases confirmed this difference. These results are the basis for using these two risk factor markers for BCHF risk testing.

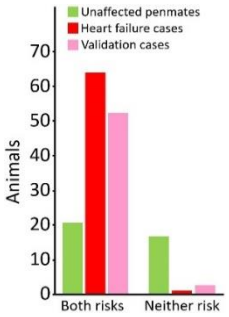

Fig. 1. Impact of BCHF risk factors

8. **What does the outcome of this two-SNP BCHF test really indicate?** For pens of Western Plains feedlot cattle affected with BCHF, cases are expected to arise in animals with both risk factors at a rate 15-fold higher than those with no risk factors.

9. **How well do these two BCHF risk factors predict if a feedlot animal <u>will not</u> die from BCHF?** The two-SNP BCHF test was the most accurate at identifying animals that did not become BCHF cases. If an animal had neither of the two risk factors for BCHF, there was only a 1% chance that they became a BCHF case. This feature of this two-SNP BCHF test may be useful in selective breeding.

10. **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, 63% of BCHF cases did have both risk factors. Other BCHF cases (36%) had only one risk factor. These results illustrate the reality that other genetic and environmental factors contribute to the development of BCHF. Regardless, identifying which feedlot cattle have both risk factor may be useful in identifying the smallest group of animals that will benefit from alternative management to limit BCHF development.

11. **Is this two-SNP 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 genotypes from 50k-770k SNP markers. The two-SNP BCHF test estimates an animal's *genetic risk for heart failure* without prediction equations, pedigree, performance information, or the use of other SNP markers.

12. **Are these two BCHF SNPs genetic defects?** No genetic defects or known causes of BCHF have been identified yet. Thus, it is not known which specific DNA sequences are causing the increased risk for disease. The causes and mechanisms of BCHF have yet to be determined.

13. **Are these two BCHF SNPs 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. Thus, most of the affected animals in the study were from Angus or Angus-influenced germplasm. The predictive value of these two BCHF risk factors in other breeds is unknown.

14. **How can feedlot operators benefit from using this two-SNP BCHF test?** The current test was developed from Western Plains feedlot research to identify animals at highest risk for BCHF and may benefit affected producers in similar environments. Once identified, options are available for selectively managing these animals. Research on beneficial management options is ongoing.

15. **How can cattle breeders benefit from this two-SNP test?** Cattle producers affected by BCHF can benefit by selecting animals that do not carry the two BCHF risk factors. Reducing the BCHF 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. Tables of risk frequencies by breed are provided at the end of this factsheet.

Breeding rank	Potential risk transmission to calves
1	0%
2	25%
3	50%
4	75%
5	100%

Fig. 2. Breeding rank based on risk factor transmission to calves

16. **Who will not likely gain benefits from this two-SNP 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 BCHF.

17. **Should I be culling all my animals with high BCHF risk?** Probably not, although this decision depends on the cost of clinical 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 individuals with the highest potential for transmitting risk to their offspring is predicted to reduce the frequency of future BCHF cases.

18. **Is the problem of BCHF now solved?** Not yet. It is unknown whether these discoveries are generalizable to other cattle and conditions. However, the purpose of releasing DNA marker information now is to facilitate ongoing BCHF research in environments and conditions outside the scope of this study. This first version of a two-SNP 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.

19. **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.

20. **How do I test my cattle now?** The two-SNP BCHF test is currently available as either a commercial stand-alone genetic test or as part of commercial bead microarray “chip” technologies. Please contact your genotyping providers for additional information. For reference, the gene names, marker names, SNP IDs, risk alleles, and risk configuration for the two SNPs are:

NF1A-AS2, BCHF2, chr3, BovineHD0300024366, A, 1 or 2 copies;
ARRDC3, BCHF5, chr7, BovineHD0700027239, A, 2-copies.

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Material cited:

1. International Plant and Animal Genome meeting XXVIII January 11-15, 2020, San Diego, CA, USA. Poster PE0326: Association of *ARRDC3* and *NFIA* Genes with Bovine Congestive Heart Failure

2. International Plant and Animal Genome meeting XXVIII January 11-15, 2020, San Diego, CA, USA. Slide presentation: Genetic Association with Bovine Congestive Heart Failure in Feedlot Cattle

3. Heaton MP, Bassett AS, Whitman KJ *et al.* Evaluation of *EPAS1* variants for association with bovine congestive heart failure. *F1000Research* 2019, 8:1189 (https://doi.org/10.12688/f1000research.19951.1)

4. Neary JM, Booker CW, Wildman BK, Morley PS. Right-Sided Congestive Heart Failure in North American Feedlot Cattle. Journal of Veterinary Internal Medicine. 20:1, 2016. https://doi.org/10.1111/jvim.13789

A link to this document and additional information can be found on the USMARC BCHF landing page: Bovine Congestive Heart Failure (BCHF) in Feedlot Cattle

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Questions about Tables 1 – 3.

1. **What is the difference between a genetic risk factor and a risk allele?** A risk *allele* is the DNA sequence associated with the disease. A *genetic risk factor* includes information about the mode of inheritance, such as the requirement for having two copies of the risk allele to have the disease risk.

2. **Are genetic risk factors "portable" between breeds?** It depends. Causal DNA variants, like the myostatin double muscle mutations in cattle tend to have similar effects, regardless of breed and thus are considered "portable" between breeds. However, DNA markers that are only linked to causal mutations (i.e., nearby) aren't as useful in other cattle populations or breeds. The BCHF SNPs listed in tables 1 and 2 are *not* known to be causal and thus, their utility outside the study population has yet to be determined.

How to use Tables 1 and 2. The "Risk allele freq." (columns 3 and 4) provide an estimate for the risk allele prevalence within each breed. However, the relevance of the BCHF2 and BCHF5 risk alleles is unknown in breeds other than Angus. This is because the risk alleles are not known to be causal (see "portable" question 2 above), and the study population consisted primarily of solid black cattle. The "Disease risk" for feedlot cattle (columns 5 through 7) may help identify the proportion of cattle at highest risk within breed, while the "Breeding rank" (columns 8 through 12) may help identify the proportion of animals not able to pass on either risk allele to their progeny. This may be helpful in reducing BCHF by selective breeding.

Table 1. BCHF allele frequencies in US cattle by breed.

		Risk allele freq.		Animals in each group							
				Disease risk[c]			Breeding rank[d]				
Breed group[a]	No.	BCHF2 (A)[b]	BCHF5 (A)[b]	1x	7.5x	15x	1	2	3	4	5
Angus	30	0.93	0.50	1	15	14	0	3	7	15	5
Ankole-Watusi	20	0.25	0.00	15	5	0	15	4	1	0	0
Ayrshire	24	0.71	0.00	7	17	0	7	9	8	0	0
Beefmaster	29	0.86	0.07	3	25	1	1	6	14	8	0
Belgian Blue	24	1.00	0.00	0	24	0	0	7	8	9	0
Blonde d'Aquitaine	24	0.63	0.00	9	15	0	9	8	6	1	0
Brahman	29	0.10	0.00	26	3	0	26	3	0	0	0
Brahmousin	24	0.50	0.00	12	12	0	12	10	2	0	0
Brangus	29	0.86	0.24	4	18	7	2	8	9	8	2
Braunvieh	28	0.75	0.00	7	21	0	7	14	7	0	0
Brown Swiss	24	0.75	0.00	6	18	0	6	12	6	0	0
Charolais	30	0.77	0.00	7	23	0	7	15	7	1	0
Chianina	28	0.75	0.11	6	20	2	5	10	10	2	1
Corriente	27	0.85	0.00	4	23	0	4	14	9	0	0
Devon	23	0.43	0.22	9	13	1	5	9	6	3	0
Dexter	24	0.58	0.00	10	14	0	10	13	1	0	0
Gelbveih	29	0.66	0.00	10	19	0	9	11	8	1	0
Guernsey	24	0.92	0.00	2	22	0	2	17	5	0	0
Hereford	30	0.80	0.37	3	19	8	2	2	15	11	0
Highland	24	0.50	0.00	12	12	0	12	11	1	0	0
Holstein	23	0.96	0.00	1	22	0	1	12	9	1	0
Indu-Brazil	24	0.00	0.00	24	0	0	24	0	0	0	0
Jersey	38	0.79	0.00	8	30	0	8	16	14	0	0
Limousin	30	0.63	0.07	10	19	1	7	17	5	0	1
Maine-Anjou	29	1.00	0.07	0	27	2	0	7	16	5	1
Marchgianna	23	0.70	0.00	7	16	0	7	4	12	0	0
Mini Hereford	24	0.96	0.42	1	13	10	0	5	4	10	5
Mini Zebu	24	0.08	0.00	22	2	0	22	2	0	0	0
Montbeliard	24	0.71	0.00	7	17	0	7	11	5	1	0
Murray Gray	24	0.67	0.46	6	9	9	1	5	7	9	2
Nelore	24	0.58	0.00	10	14	0	10	13	1	0	0
Piedmontese	24	0.79	0.00	5	19	0	5	15	4	0	0
Pinzgauer	24	0.67	0.00	8	16	0	8	11	5	0	0
Red Angus	30	0.73	0.57	2	17	11	0	5	13	10	2
Red Poll	24	0.71	0.21	6	14	4	5	2	10	4	3
Romagnola	24	0.83	0.00	4	20	0	4	17	3	0	0
Salers	29	0.52	0.00	14	15	0	12	8	9	0	0
Santa Gertrudis	28	0.75	0.07	7	19	2	4	18	3	2	1
Senepol	24	0.92	0.00	2	22	0	2	12	10	0	0
Shorthorn	29	0.76	0.03	7	21	1	2	12	10	5	0
Simmental	30	0.63	0.07	11	17	2	9	13	5	2	1
Tarentaise	28	0.36	0.00	18	10	0	14	12	2	0	0
T. Longhorn, MARC	28	0.64	0.00	10	18	0	10	13	4	1	0
T. Longhorn, CTLR	37	0.51	0.00	14	37	0	3	10	10	0	0
Tuli	23	0.35	0.00	15	8	0	15	8	0	0	0
Wagyu	24	0.92	0.04	2	21	1	2	8	12	2	0

Table 2. BCHF allele frequencies in US cattle by BCHF5/BCHF2 risk.

		Risk allele freq.		Animals in each group							
				Disease risk[c]			Breeding rank[d]				
Breed group[a]	No.	BCHF2 (A)[b]	BCHF5 (A)[b]	1x	7.5x	15x	1	2	3	4	5
Red Angus	30	0.73	0.57	2	17	11	0	5	13	10	2
Angus	30	0.93	0.50	1	15	14	0	3	7	15	5
Murray Gray	24	0.67	0.46	6	9	9	1	5	7	9	2
Mini Hereford	24	0.96	0.42	1	13	10	0	5	4	10	5
Hereford	30	0.80	0.37	3	19	8	2	2	15	11	0
Brangus	29	0.86	0.24	4	18	7	2	8	9	8	2
Devon	23	0.43	0.22	9	13	1	5	9	6	3	0
Red Poll	24	0.71	0.21	6	14	4	5	2	10	4	3
Chianina	28	0.75	0.11	6	20	2	5	10	10	2	1
Santa Gertrudis	28	0.75	0.07	7	19	2	4	18	3	2	1
Maine-Anjou	29	1.00	0.07	0	27	2	0	7	16	5	1
Beefmaster	29	0.86	0.07	3	25	1	1	6	14	8	0
Limousin	30	0.63	0.07	10	19	1	7	17	5	0	1
Simmental	30	0.63	0.07	11	17	2	9	13	5	2	1
Wagyu	24	0.92	0.04	2	21	1	2	8	12	2	0
Shorthorn	29	0.76	0.03	7	21	1	2	12	10	5	0
Belgian Blue	24	1.00	0.00	0	24	0	0	7	8	9	0
Holstein	23	0.96	0.00	1	22	0	1	12	9	1	0
Guernsey	24	0.92	0.00	2	22	0	2	17	5	0	0
Senepol	24	0.92	0.00	2	22	0	2	12	10	0	0
Corriente	27	0.85	0.00	4	23	0	4	14	9	0	0
Romagnola	24	0.83	0.00	4	20	0	4	17	3	0	0
Piedmontese	24	0.79	0.00	5	19	0	5	15	4	0	0
Jersey	38	0.79	0.00	8	30	0	8	16	14	0	0
Charolais	30	0.77	0.00	7	23	0	7	15	7	1	0
Braunvieh	28	0.75	0.00	7	21	0	7	14	7	0	0
Brown Swiss	24	0.75	0.00	6	18	0	6	12	6	0	0
Ayrshire	24	0.71	0.00	7	17	0	7	9	8	0	0
Montbeliard	24	0.71	0.00	7	17	0	7	11	5	1	0
Marchgianna	23	0.70	0.00	7	16	0	7	4	12	0	0
Pinzgauer	24	0.67	0.00	8	16	0	8	11	5	0	0
Gelbveih	29	0.66	0.00	10	19	0	9	11	8	1	0
T. Longhorn, MARC	28	0.64	0.00	10	18	0	10	13	4	1	0
Blonde d'Aquitaine	24	0.63	0.00	9	15	0	9	8	6	1	0
Dexter	24	0.58	0.00	10	14	0	10	13	1	0	0
Nelore	24	0.58	0.00	10	14	0	10	13	1	0	0
Salers	29	0.52	0.00	14	15	0	12	8	9	0	0
T. Longhorn, CTLR	37	0.51	0.00	14	37	0	3	10	10	0	0
Brahmousin	24	0.50	0.00	12	12	0	12	10	2	0	0
Highland	24	0.50	0.00	12	12	0	12	11	1	0	0
Tarentaise	28	0.36	0.00	18	10	0	14	12	2	0	0
Tuli	23	0.35	0.00	15	8	0	15	8	0	0	0
Ankole-Watusi	20	0.25	0.00	15	5	0	15	4	1	0	0
Brahman	29	0.10	0.00	26	3	0	26	3	0	0	0
Mini Zebu	24	0.08	0.00	22	2	0	22	2	0	0	0
Indu-Brazil	24	0.00	0.00	24	0	0	24	0	0	0	0

[a] Registered cattle chosen for minimal pedigree relationships. Heaton MP, Smith TPL, Carnahan JK, et al. Using diverse U.S. beef cattle genomes to identify missense mutations in EPAS1, a gene associated with high-altitude pulmonary hypertension. F1000Research 2016, 5:2003

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[b] The nucleotide base representing risk allele is shown in parentheses. The BCHF2 risk allele is on the antisense strand and the BCHF5 risk allele is on the sense strand. Both the BCHF2 and BCHF5 risk alleles are coded as the "A" genotype in the Illumina-based "A/B" calls on their beadarray platforms.

[c] The number of genetic risk factors are 0, 1, and 2 respectively for animals predicted to have 1x, 7.5x, and 15x disease risk.

[d] Animals with breeding rank 1 through 5 have progressively more risk alleles, with up to four possible. In other words, animals with breeding rank 1 have zero risk alleles while animals with breeding rank 5 are homozygous for both risk alleles.

How to use Table 3. This table converts all possible BCHF2 and BCHF5 genotypes into relative breeding ranks and disease risk. It can be used by genotype service providers to generate producer-oriented reports on cattle tested. Alternatively, it can be used by producers to translate an animal's genotypes into relative BCHF breeding rank and disease risk.

Table 3. BCHF2 and BCHF5 genotype configurations for relative breeding rank and disease risk.

Concatenated genotypes (BCHF2, BCHF5)[a]	Concatenated 1-letter codes (BCHF2, BCHF5)[b]	Breeding rank[c]	Potential risk for transmitting BCHF risk alleles to offspring (0 to 100% possible)	Risk for acquiring BCHF (1 to 15 scale)
GG,GG	G,G	1	0%	1x
GG,AG	G,R	2	25%	1x
AG,GG	R,G	2	25%	7.5x
AG,AG	R,R	3	50%	7.5x
AA,GG	A,G	3	50%	7.5x
GG,AA	G,A	3	50%	7.5x
AA,AG	A,R	4	75%	7.5x
AG,AA	R,A	4	75%	15x
AA,AA	A,A	5	100%	15x

[a] Nucleotide genotypes for BCHF2 (*NFIA-AS2*) and BCHF5 (*ARRDC3*). The respective SNP identifiers are BovineHD0300024366 and BovineHD0700027239.

[b] Key to 1-letter codes: A= AA; G = GG; R = AG or GA;

[c] The relative rank of an animal is based on BCHF2 and BCHF5 genotypes from best (1) to worst (5).

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