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Scientific Overview

A Genomic Approach for Advancing Heart Healthy Cattle

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INTRODUCTION

Bovine Congestive Heart Failure (BCHF) stands as a significant threat to the health and productivity of feedlot cattle. With recent genomics advancements, the cattle industry can confidently select for heart-healthy herds that will uplift the industry overall and mitigate both herd health, and economic risks. In severely affected cattle pens, mortality rates have surged up to 7%, translating to staggering annual losses surpassing $250,000 for a single operation[1]. However, the causes of heart failure are often multifaceted and influenced by environmental stressors as well as management practices. BCHF is particularly challenging to address because it often manifests late in the production cycle when cattle are nearing market readiness. This timing exacerbates the economic impact, as it represents a significant loss of prior investments in feed, labor, and veterinary care. Altitude and temperature fluctuations can further complicate the issue, interacting with genetic predispositions and management practices for the onset of heart failure.

In broad terms, heart failure is best described as a syndrome, not a specific disease or diagnosis[2]. The true source of this syndrome is often difficult to determine because it may be caused by any cardiac abnormality resulting in the heart's inability to pump enough blood to meet animal maintenance requirements. Due to the absence of definitive clinical diagnoses, the terminology describing and characterizing heart failure symptoms remains unstandardized and continues to evolve as new research is published within the scientific community. Recent research has identified genetic markers associated with an increased susceptibility to BCHF[3]. The development of standardized diagnostic criteria and early warning systems for identifying cattle showing subclinical symptoms holds promise for more effective interventions. By leveraging genomic insights alongside improved management practices, the economic and animal welfare impacts of this multifactorial syndrome can be significantly reduced.

HEART DISEASE

Heart disease in cattle has historically received limited scientific attention, with most research focusing on specific forms of cardiac disorders and their clinical manifestations[5]. It can also progress to heart failure when the heart is unable to cope with increasing compensatory neurohumoral responses. The progression of heart failure depends on the severity and extent of myocardial and structural heart modifications. Clinical signs of heart failure in cattle include syncope, dyspnea, tachypnea, cyanosis, peripheral and pulmonary edema, jugular venous distension, and congested mucous membranes[4]. Common cardiac conditions in cattle encompass bacterial endocarditis, pericarditis, primary dilated cardiomyopathy, congenital heart diseases like ventricular septal defects, and conditions secondary to factors such as ionophore toxicity, vitamin E/selenium deficiency, or infections. More recently, idiopathic hemorrhagic pericarditis has also been reported[5].

Diagnosis of heart disease in cattle typically involves a combination of clinical examination and advanced techniques such as echocardiography, radiography, pulmonary arterial pressure assessment, electrocardiography, and blood culture, depending on the suspected etiology[5]. However, these methods are often challenging to implement in routine practice due to their cost, the need for specialized equipment, and the time-intensive nature of the procedures. Consequently, many cases of heart disease remain undiagnosed until advanced stages. As an alternative, genetic testing offers a promising solution by enabling the early identification of animals predisposed to this syndrome[6]. Genetic testing can be less invasive, more cost-effective in the long term, and applicable at a larger scale, potentially improved herd management strategies. Integrating genetic testing with traditional diagnostic methods may help address current limitations in the early detection and prognosis of heart disease in cattle.

HIGH ALTITUDE DISEASE

One of the more commonly known symptoms of heart failure has been termed high altitude disease (HAD), also referred to as dropsy, brisket disease, high-mountain disease, and right-sided heart failure throughout the literature. Cattle with symptoms like HAD were first documented over 100 years ago in high-altitude regions[7]. HAD is a non-infectious, heart-lung dysfunction impacting cattle at high elevations (≥ 1500 m), resulting in lethargy, edema of the neck and brisket, and jugular vein distention.

The prevailing understanding is that the reduced oxygen levels at higher elevations lead to hypoxic pulmonary vasoconstriction, resulting in cardiac failure as the heart and lung functions become compromised.

While there is no cure for HAD, current best management practices include removing affected animals from high elevations and measuring mean pulmonary arterial pressure (mPAP) as an indicator of potential vulnerability in that environment. It is recommended that animals with mPAP measurements exceeding 50 mmHg should be excluded from the breeding population as a practical strategy to reduce the prevalence of HAD within a herd[8]. Heritability estimates of mPAP are generally considered moderate, although variations have been seen across ages, sex, and breeds[9]. Due to the genetic variation captured in mPAP over the last several decades, breed associations have started publishing expected progeny differences (EPDs) to improve the genetics propagating the cattle industry[10]. However, one of the challenges with collection of mPAP phenotypes over multiple generations is that it involves significant cost, and a veterinarian trained in jugular catheterization for invasive blood pressure monitoring[8]. This has resulted in the collection of relatively few phenotypes in comparison to other traits in commercial cattle systems. In addition, research has shown that mPAP measurements must be taken at high elevations to be an accurate indicator and should not be replaced by the PAP EPD alone[8]. Rather, the two characterizations should be utilized in tandem for proper management and selection decisions.

BOVINE CONGESTIVE HEART FAILURE

A condition resembling HAD was first reported in feedlot cattle at lower altitudes (≤1524 m) during the 1970s and has been reported to be increasing in prevalence since then[11]. Now termed Bovine Congestive Heart Failure (BCHF), this syndrome has also been referred to as feedlot heart disease, bovine heart failure, and right sided congestive heart failure throughout the literature. The physical symptoms of live animals with BCHF are similar to that of HAD, specifically the swelling of the neck, brisket, and abdominal regions[12].

Physiologically, BCHF is characterized by a progression of cardiopulmonary changes, beginning with pulmonary hypertension, ventricular fibrosis and stiffening of the myocardium, diastolic dysfunction, and severe ventricular remodeling leading to heart failure and mortality[13].

BCHF is often associated with mPAP or, more precisely, these two conditions are frequently mentioned as having a common degree of risk in adverse environments, such as in cattle raised at high altitudes and/or other factors that contribute to hypoxic environments[12]. Over the last decade, research efforts have focused on the relationships between heart morphology, mPAP, animal performance, and carcass characteristics to better understand the differences exhibited between animals with HAD and BCHF symptoms. During this time, a heart score (HS) system was developed, which assigns a score post-harvest based on heart remodeling severity[14]. A significant positive relationship has been reported between HS and mPAP, with higher HS associated with deteriorated feed efficiency and reduced carcass quality[15]. Additional findings indicate that steers with low mPAP and lower HS have better feed efficiency and higher-quality carcasses, whereas those with elevated mPAP and HS exhibited compromised performance[16]. A HS heritability of 0.36 was reported, supporting the feasibility of an EPD as a selection tool[6]. Significant positive genetic correlations between HS and traits of high economic importance including growth traits and feed intake explain the increased rate of BCHF observed over time[6]. These findings support the use of HS in a selection tool to lower the genetic risk of BCHF without compromising genetic progress in other traits. However, further research is required to understand these associations better and develop targeted interventions for the cattle industry.

Identification of feedlot animals with higher genetic susceptibility to BCHF may allow for targeted care and management strategies to be implemented. By genetically testing groups of cattle to determine their heart health risk, producers can more effectively sort animals for ease of management, and then collaborate with their nutritionist to develop rations or feeding strategies at the pen level. To complement this, low-stress handling techniques could be employed to further help mitigate heart failure risk. These approaches may alleviate the significant financial impact of the condition by minimizing the substantial economic losses due to late days on feed mortality.

GENOMIC TESTING IMPLEMENTATION

Igenity BCHF is a revolutionary genomic test designed to assess an animal's genetic predisposition to heart failure, and accounts for the latest advances in research today. The test results (1-10 scores) directly correlate with the percentage of BCHF risk an animal has (and should pass on to their progeny), serving as a genetic indicator of the likelihood of disease development. A lower score on the scale is more favorable.

This chart provides a comparative assessment of genetic potential rather than predictive rates. It illustrates the genetic impact anticipated in progeny, offering a reference between Igenity scores and genetic effects for BCHF. These values predict the relative profile of an animal compared to the progeny of other reported animals, where minor scores indicate a lower risk in the development of Bovine Congestive Heart Failure.

Igenity Score	BCHF (%)
1	0.0
2	3.5
3	7.1
4	10.6
5	14.1
6	17.6
7	21.2
8	24.7
9	28.2
10	31.8

More Favorable

Less Favorable

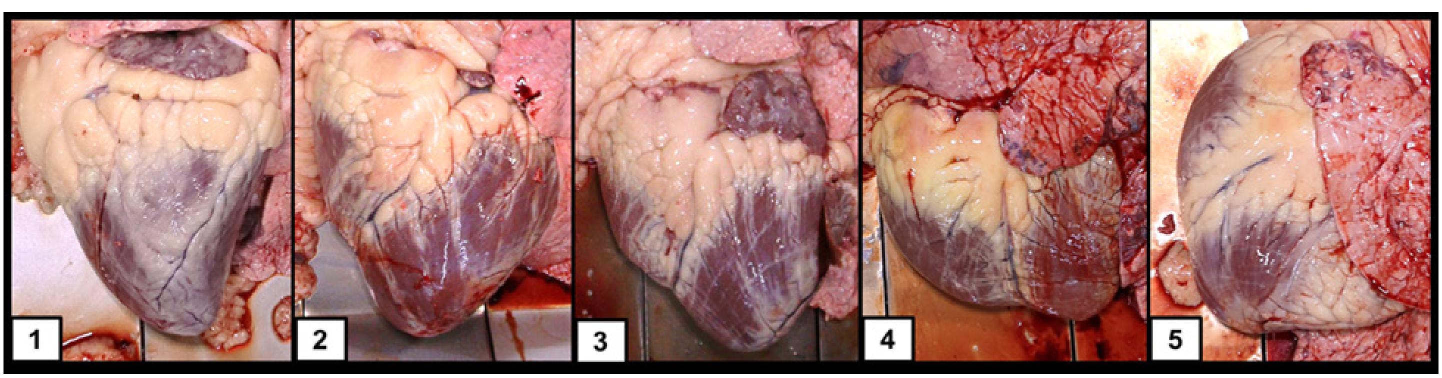
The table on the right demonstrates the relative percentage risk of BCHF for each Igenity BCHF score, allowing the ability to cross-reference the 1-10 scores with the correlated risk of BCHF. Each increase in Igenity Score represents a 3.5% increase in risk of BCHF with a score of 1 representing 0% risk and a score of 10 representing a 31.8% risk.

PHENOTYPIC AND GENOMIC ANALYSES

To create Igenity BCHF, a robust database of phenotypes (32,763) and genotypes (25,186) was assembled from animals fed at a single commercial feedlot and harvested at a single facility, which represents one of the largest single source commercial data sets of its kind[6]. A subset of this reference population was also selected for genomic sequencing to determine the heritabilities and genetic correlations of the phenotypes collected and complete a genome-wide association study (GWAS). Moderate heritability of heart score (0.36) was observed, reinforcing the genetic selection potential of this syndrome[6].

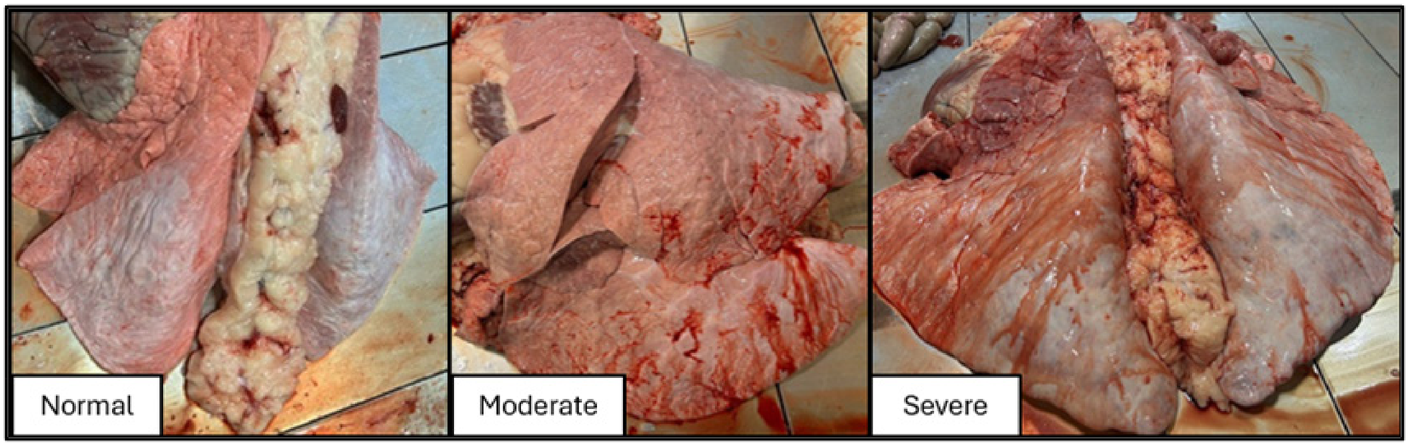
Because BCHF has been phenotypically characterized as a progression of cardio-pulmonary changes resulting in ventricular remodeling and leading to reduced performance or mortality, it was imperative that heart pathology was considered in a genomic solution. Congestive heart failure progression in feedlot cattle has been characterized in normal harvest groups by applying a post-mortem heart score scale with five categories describing cardio-pulmonary remodeling[14]. Phenotypes were collected on the reference population on a 1 to 5 scale and re-classified into categories of Normal (Scores 1 and 2) and BCHF Case (Scores 3, 4, and 5) for genomic prediction of BCHF risk.

Figure 1. Heart images taken at harvest representative of the five categories of heart scores[6]



In addition to capturing variation in heart morphology, a novel scoring system was developed describing pulmonary changes exhibited. A similar post-mortem collection methodology was applied to normal harvest groups, but instead of a heart score, a lung deflation score was assigned[17]. The lung deflation score is defined as a failure of the lungs to deflate. Phenotypes were classified into normal, mild (not shown), moderate, and severe failure to deflate categories as pulmonary tissue became increasingly more turgid **(Figure 2).**

Figure 2. Lung images taken at harvest representative of categories of lung deflation scores[17]



Since all breed types in the reference population were found to be susceptible to heart failure **(Table 1)**, genomic breed percentage was incorporated into Igenity BCHF to further strengthen the prediction equation. Breeds represented in the assembled reference population were a combination of crossbred commercial beef calves (Angus, Hereford, Charolais) and beef-on-dairy calves (beef sire on Holstein or Jersey dam) for a total of 13 unique breed types.

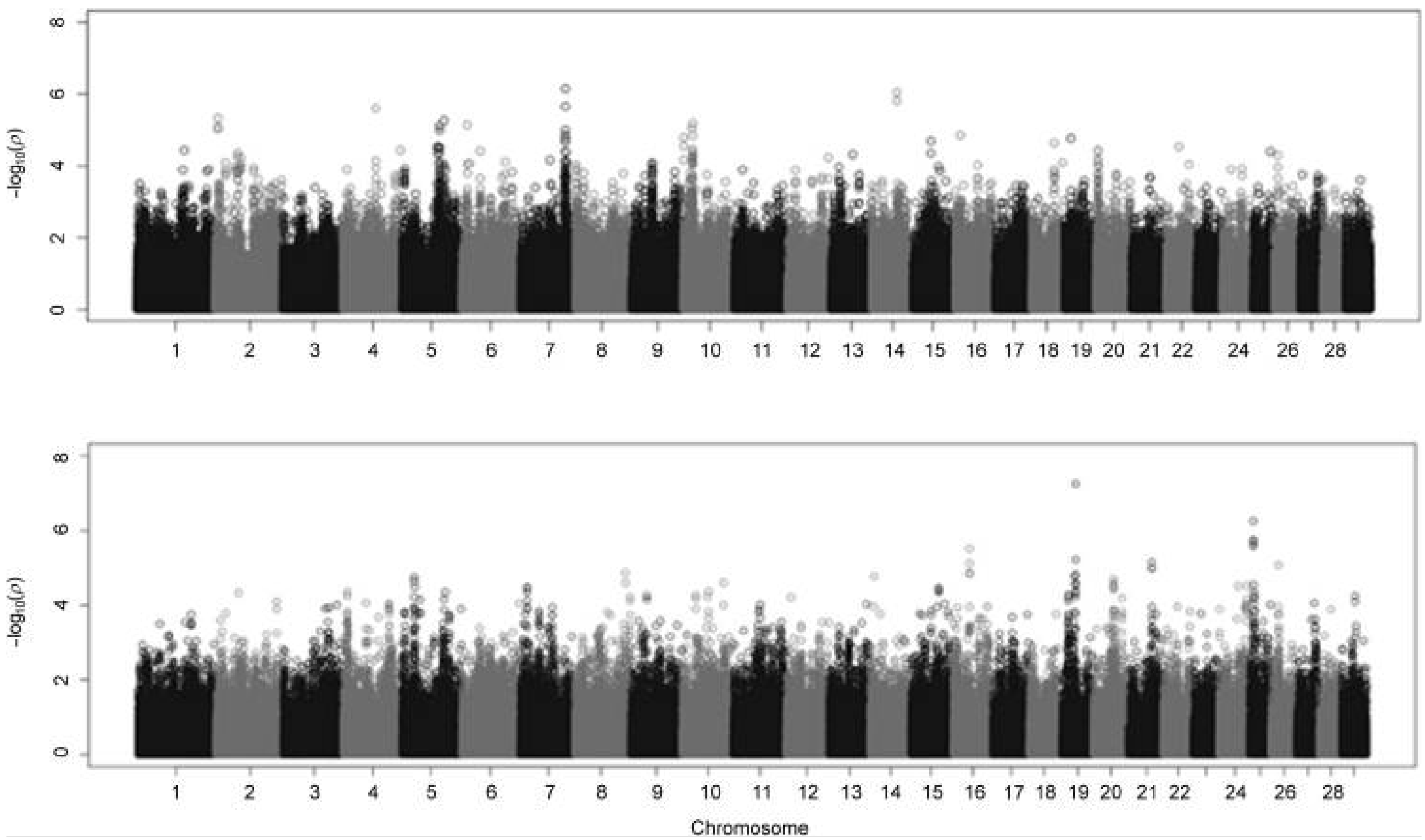
Table 1. Percent distribution (and head count) of heart score by breed type[6]

	Heart Score				
Observed Breed Type	**1**	**2**	**3**	**4**	**5**
Angus	56.71% (1,335)	27.70% (652)	11.09% (261)	3.31% (87)	1.19% (28)
Angus x Hereford	62.85% (1,308)	24.94% (519)	9.18% (191)	1.92% (40)	1.11% (23)
Angus x Dairy	71.83% (2,012)	20.56% (576)	5.96% (167)	1.21% (34)	0.43% (12)
Charolais x Dairy	63.99% (3,007)	36.45% (1,247)	7.83% (368)	1.43% (67)	0.21% (10)
Charolais x Angus x Hereford	68.05% (2,151)	21.92% (693)	8.54% (270)	1.20% (38)	0.22% (9)

PHENOTYPIC AND GENOMIC ANALYSES (CONT.)

Igenity BCHF represents additive polygenic effects across the entire genome rather than the single nucleotide polymorphism (SNP) markers initially discovered at USDA-ARS, which was based on the non-additive effects of two SNPs. Igenity BCHF captures more genetic effects along the entire genome instead of a few genomic regions. With more robust marker sets, the polygenic effects can be better characterized, resulting in a more precise test. **Figure 3** illustrates that no major quantitative trait loci (QTL) effects were observed for heart score in the reference population and support the understanding of a polygenic approach to Igenity BCHF.

Figure 3. Manhattan plot from genome-wide association study (GWAS)[6]



SUMMARY

Igenity BCHF employs the most robust reference population of commercial feedlot cattle, while also integrating significant phenotypic indicators of the cardiopulmonary system[6]. By employing DNA testing for BCHF in cattle, veterinarians and technicians can use genetic testing to identify animals predisposed to BCHF, enabling early intervention. By incorporating genetic insights, feedlots can better allocate resources and reduce the risk of BCHF-related losses. In addition, the selection of animals with superior genetic predispositions through Igenity BCHF testing promises to uplift bovine heart health standards. In herds grappling with a pronounced incidence of BCHF among finishing cattle, an accurate culling of breeding animals bearing higher Igenity BCHF scores emerges as a pivotal strategy. Curbing the prevalence of heart failure-associated genes within the breeding herd anticipates a subsequent decline in BCHF risk among calf crops. This proactive approach not only safeguards the health of cattle, but also mitigates economic losses attributed to BCHF.

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