J. Dairy Sci. 108:3045–3067
https://doi.org/10.3168/jds.2024-26035

Invited review: Management of genetic defects in dairy cattle populations

John B. Cole,[1,2,3]* Christine F. Baes,[4,5] Sophie A. E. Eaglen,[6] Thomas J. Lawlor,[7] Christian Maltecca,[3] M. Sofía Ortega,[8] and Paul M. VanRaden[9]
[1]Council on Dairy Cattle Breeding, Bowie, MD 20716
[2]Department of Animal Sciences, Donald Henry Barron Reproductive and Perinatal Biology Research Program, and the Genetics Institute, University of Florida, Gainesville, FL 32611
[3]Department of Animal Science, North Carolina State University, Raleigh, NC 27695
[4]Centre for Genetic Improvement of Livestock, University of Guelph, Guelph, ON N1G 2W1, Canada
[5]Institute of Genetics Vetsuisse, University of Bern, Bern 3012, Switzerland
[6]National Association of Animal Breeders, Madison, WI 53717
[7]Holstein Association USA Inc., Brattleboro, VT 05302
[8]Department of Animal and Dairy Sciences, University of Wisconsin–Madison, Madison, WI 53706
[9]Animal Genomics and Improvement Laboratory, Henry A. Wallace Beltsville Agricultural Research Center, USDA Agricultural Research Service, Beltsville, MD 20705

ABSTRACT

When related animals are mated to one another, genetic defects may become apparent if recessive mutations are inherited from both sides of the pedigree. The widespread availability of high-density DNA genotypes for millions of animals has made it possible to identify and track known defects as well as to identify and track previously unknown defects that cause early embryonic losses. Although the number of known defects has increased over time, the availability of carrier information has been used to dramatically reduce the frequency of many disorders. The economic impact of known genetic defects in the US dairy cattle population has decreased by ~2/3 since 2016, due largely to the avoidance of carrier-to-carrier matings. Effective population management requires robust systems for reporting new defects, identification of causal mechanisms, and development of commercially available tests. The United States and Canada depend on informal cooperation among many groups, including farmers, purebred cattle associations, genetics companies, and researchers, to identify emerging and causal defects. The structure of a collaborative system including all key sectors of the dairy cattle industry to support long-term population management is described. This review provides a comprehensive overview of the landscape surrounding genetic defects in dairy cattle. Topics covered include current defects of relevance to commercial dairy producers, trends in carrier frequencies over time, how best to manage these defects, strategies for detecting emerging diseases, and marketing and trade considerations.
Key words: genetic defects, lethal recessives, population management

INTRODUCTION

Genetic defects are an inevitable consequence of mammalian biology and the imperfect mechanisms that underlie DNA replication (e.g., Caldecott, 2022). Some defects can result in embryonic loss, whereas others result in abortions, stillbirths, and the birth of calves that must be euthanized or that do not survive their first year. These losses result in impaired animal welfare, reputational harm, emotional distress, and economic damage to livestock producers. The problem is especially pronounced in animals with long generation intervals, such as cattle, where artificial insemination (**AI**) is used heavily. In these populations, new defects can spread quickly before they are detected, and the loss of a calf represents the loss of several months of opportunity.

The understanding of genetic defects in livestock has come a long way since the early 20th century, with early publications showing limited but increasing, awareness of the issue. The more recent advent of genomics and the use of high-throughput genotyping technologies has dramatically improved our ability to identify and manage genetic defects in dairy cattle populations.

Genetic defects in dairy cattle can have profound effects on the health, productivity, and economic sustainability of dairy farms. Most genetic defects follow an autosomal recessive mode of inheritance, and this review will focus on that class of traits. In North America, the Council on Dairy Cattle Breeding (Bowie, MD), purebred dairy cattle associations, and genetics companies

Received November 19, 2024.
Accepted January 20, 2025.
*Corresponding author: john.cole@ucsdsb.com

The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-25. Nonstandard abbreviations are available in the Notes.

publish test results for genetic defects for bulls used in AI. Although this promotes transparency and allows for effective population management, it also produces a large amount of highly technical data that can be difficult for farmers and government officials to interpret. As the number of identified genetic defects and diagnostic methods grows, so does the responsibility to communicate this information clearly. Using overly technical jargon risks creating confusion among nonexpert stakeholders, who often play a crucial role in making decisions about the use of germplasm. In this review, we provide a comprehensive overview of the current landscape around genetic defects in dairy cattle. We outline known defects currently affecting the dairy industry, examine how carrier frequencies for various defects have changed over time, discuss current best practices for management of defects and strategies for identifying and managing new defects, and make recommendations for proper communication of carrier data.

GENETIC DEFECTS IN DAIRY CATTLE POPULATIONS

Historical Background

The 18th-century UK livestock breeder Robert Bakewell may have been the first person to systematically practice animal breeding as we recognize it today (Ernle, 1962), but he did so without knowledge of the nature of inheritance or of Mendel's principles. Although the transmission of genetic defects in livestock families was not well known until linebreeding and inbreeding became common in cattle breeding, the astute breeder might have learned from the lessons of European royalty, which were entering the public consciousness in the early 20th century (e.g., Guyer, 1927, p. 4). As noted by Lush (1945, p. 270), "The undesired recessive genes are there all the time, but homozygous recessive individuals appear more frequently when inbreeding begins." A survey of general agricultural genetics texts found that some awareness of genetic defects was present in the early 1900s (Shaw, 1902, pp. 66–70; Babcock and Clausen, 1918, pp. 264–268; Cole, 1925, pp. 44-46), but detailed examples were scarce. As an example, Jones (1925, pp. 397–399) discussed a case of embryonic loss in mice as an example of a genetic defect. Although the biological understanding of genetics increased through the 20th century, many textbooks remained frustratingly vague on the topic of recessive defects. Rice (1934, p. 204) mentioned polling as an example of a mutation in cattle that follows a Mendelian mode of inheritance, although polled is dominant to horned and not generally considered to be harmful); Lush (1945, p.128) mentioned that many are known, but did not elaborate further; and Lasley (1978, pp. 411–413) provided only a handful of examples. The notable exception to this trend was Bogart (1959, pp. 81–97), who provided an extensive list of genetic disorders with accompanying photographs, which was later referenced by Legates and Warwick (1990, pp. 63–76) in their discussion. More recent texts (e.g., Bourdon, 1999; Isik et al., 2017) have not markedly improved in this area. Most purebred dairy cattle associations (breed societies) around the world established population monitoring programs in the 20th century to identify genetic defects, but practices are not uniform, and coordination among industry groups is sometimes poor.

Cole (2017) launched an initiative in the United States that provided modest infrastructure for defect reporting, biological sample collection, and causal variant identification, but it had little success. This is largely due to the project being limited to a single laboratory in one institution, rather than representing a collaboration of all the key stakeholders in the US industry. Personnel and funding also were limited, resulting in slow progress with no major successes to report. In retrospect, more time should have been spent recruiting collaborators before sample collection began.

Rate at Which Defects Are Identified

A perception exists among many dairy producers and industry professionals that genetic defects are being discovered more frequently than in the past, and some make the error of concluding these defects must be occurring at a higher rate. The first of these is true, but the second might not be. The number of Mendelian defects reported annually in taurine (*Bos taurus taurus*) cattle between 1893 and 2024 is shown in Figure 1 and is based on 168 unique entries in the Online Mendelian Inheritance in Animals database (Nicholas et al., 1995). The rate of reporting for defects identified in the field is fairly consistent over time, with about 1 (0.947) new defect reported each year before the widespread adoption of genomic testing. The increase in genotyping following the introduction of genomic selection (Wiggans and Carrillo, 2022) permitted the identification of previously unobserved haplotypes affecting fertility using a deficiency-of-homozygotes approach (VanRaden et al., 2011). These haplotypes resulted in embryonic loss, rather than developmental defects, and were not detectable without a combination of fertility data, pedigree information, and genotypes. Many breeds were screened as genotype data accumulated around the world, resulting in the *annus mirabilis* of 2013, in which 31 new haplotypes affecting fertility were published. After this initial surge in reports, the rate of discovery has slowed dramatically and returned to the historical baseline.

Known Defects in Contemporary Cattle Populations

As discussed above, there are many Mendelian defects known in taurine cattle (e.g., Nicholas et al., 1995; VanRaden et al., 2011; Gentile and Testoni, 2006; Gozdek et al., 2024; van den Berg et al., 2024). The most important of these in the major US dairy breeds are described in Table 1. Although haplotypes affecting fertility have received much attention in recent years, several new defects affecting calves have also been reported, including cholesterol deficiency (Kipp et al., 2015; Charlier, 2016; Menzi et al., 2016; Schütz et al., 2016) and early-onset muscle weakness (Dechow et al., 2022; Al-Khudhair et al., 2024b) in Holsteins and neuropathy with splayed forelimbs (Al-Khudhair et al., 2022) in Jerseys. The recessives with the greatest impact are those that result in the birth of calves that die or must be euthanized (e.g., Ayrshire Haplotype I, Brown Swiss Haplotype 2, Holstein cholesterol deficiency and early-onset muscle weakness, Jersey neuropathy with splayed forelimbs, Montbéliarde haplotype 2; Fritz et al., 2013; Besnard et al., 2024), and those with the lowest impact result in embryonic loss (e.g., Holstein Haplotypes 1–5, **HH1–HH5**; Jersey Haplotype 1, **JH1**).

A second broad category of loci exists, which we might refer to as "conditions" rather than "defects" because, although they are Mendelian in nature, they do not have unfavorable effects. Examples include polled (more properly, horned; Medugorac et al., 2012), slick (Littlejohn et al., 2014), coat color (e.g., Joerg et al., 1996), and milk protein variants (e.g., Sebastiani et al., 2022). Animal genotypes based on causal variants and haplotype tests are often reported together for the sake of convenience (e.g., Al-Khudhair et al., 2024a).

Trends in Carrier Frequencies

The rapid and widespread adoption of genomic selection in the United States has enabled the detection of previously unknown genetic defects affecting fertility (e.g., VanRaden et al., 2011), as well tracking of other causal variants. Publication of these haplotypes (Al-Khudhair et al., 2024a) has allowed AI companies, breeders, and dairy producers to make informed decisions when selecting mates. In the decade of 2012 to 2022, carrier frequencies in the United States have decreased by 1/3 in Holsteins and 1/2 in Jerseys, while cumulative effects of these alleles on conception and death losses decreased by almost 1/2 in Holsteins and 7/8 in Jerseys. (Table 2). As a result, hundreds or thousands of other markers now have larger additive genetic effects than the haplotypes associated with fertility losses, which no longer have any measurable effects on fertility traits. By any reasonable measure this is a success story that has increased animal welfare and improved farm profitability.

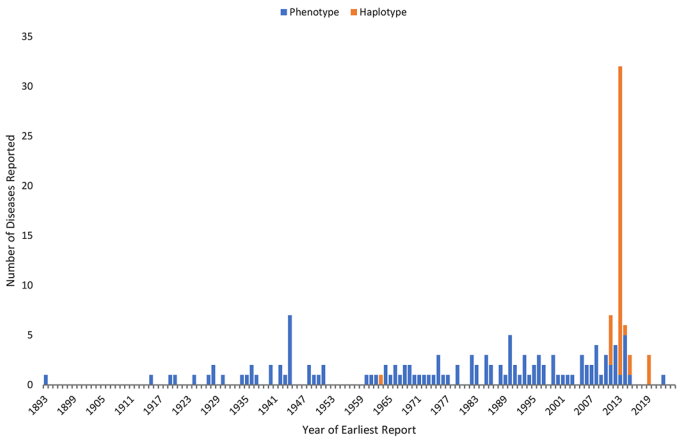

Figure 1. The number of Mendelian diseases of taurine (*Bos taurus taurus*) cattle reported by year from 1893 to 2024. Defects were identified based on phenotypes ("phenotypes," blue bars) reported from the field or using a deficiency-of-homozygotes approach ("haplotypes," orange bars). Data were taken from the Online Mendelian Inheritance in Animals database (Nicholas et al., 1995).

Ayrshire, Brown Swiss, and Jersey carrier frequencies in the United States are shown in Figure 2, and Holstein haplotypes are shown in Figure 3. Ayrshire breeders are somewhat limited in the portfolio of bulls from which they can select, but Ayrshire Haplotypes 1 and 2 (AH1, AH2) have decreased slightly over time, and Ayrshire Haplotype C (AHC) may be trending down. Brown Swiss breeders are doing very well, with frequencies decreasing for all known unfavorable haplotypes. The frequency of JH1 has decreased substantially since its discovery, whereas Jersey neuropathy with splayed forelimbs (JNS) is, unfortunately, increasing in frequency. Trends in Holsteins are favorable in most cases, although HH5 remains essentially unchanged and HH6 and early-onset muscle weakness (HMW) have increased in frequency. Because the Holstein breed is so large, it is often possible to find bulls with desirable genetic values that are free of recessive defects.

Biological Complexity

The genetic defects of greatest historical interest to cattle breeders follow a Mendelian mode of inheritance and have a clear expression of the phenotype (e.g., embryonic loss, macroscopic congenital malformation). However, some conditions affect the health of animals while still permitting them to function normally for some or all of their lifespan. For example, Holsteins affected by bovine lymphocyte intestinal retention defect (**BLIRD**; Besnard et al., 2024) grow more slowly than unaffected calves and have higher mortality and premature culling rates,

Table 1. Genetic defects in US dairy cattle and their characteristics, including breed of origin, Online Mendelian Inheritance in Animals database identification number (OMIA ID), year of initial reporting, haplotype ID, gene associated with the defect (if known), haplotype frequency, chromosome on which the gene is found, and coordinates on the 2018 ARS-UCD1.2 assembly of the *Bos taurus* genome (after Al-Khudhair et al., 2024a)[1,2]

				Haplotype					
Breed[3]	Defect	OMIA ID[4]	Year	Identifier[5]	Gene name	Frequency (%)	Chromosome	Location (bp)	Reference
AY	AH1	001934	2014	AH1	*PIRM/UBE3B*	8.23	17	63,668,380	Cooper et al. (2014); Venhoranta et al. (2014)
	AH2	002134	2017	AH1	*RPAP2*	6.58	3	51,086,099–51,119,146	Null et al. (2017)
	Arthrogryposis multiplex congenita	002022	2016	AHC	*CHRNB1*	5.81	19	27,121,939–27,131,139	Agerholm et al. (2016)
BS	Brown Swiss Haplotype 2	001939	2011	BH2	*TUBD1*	2.11	19	10,833,921	Schwarzenbacher et al. (2016)
	Brown Swiss Haplotype 14	002518	2021	BH14	*MRPL55*	—	7	2,996,436	Häfliger et al. (2021)
	Spinal dysmyelination	001247	1993	BHD	*SDM/SPAST*	0.71	11	13,246,972–14,736,876	Hafner et al. (1993); Thomsen et al. (2010)
	Spinal muscular atrophy	000939	1989	BHM	*SMA/KDSR(FVT1)*	0.33	24	61,620,374	el-Hamidi et al. (1989); Krebs et al. (2007)
	Syndrome of arachnomelia and arthrogryposis	000059	1975	—	*SUOX*	—	5	57,316,723–57,316,724	Testoni and Gentile (2004); Drögemüller et al. (2010)
	Weaver	000827	1973	BHW	*PNPLA8*	0.08	4	49,339,002–49,461,342	McClure et al. (2013); Kunz et al. (2016)
HO	Bovine leukocyte adhesion deficiency (BLAD)	000595	1983	HHB	*ITGB2*	0.03	1	144,770,078	Shuster et al. (1992)
	Bovine lymphocyte intestinal retention defect (BLIRD)	002872	2023	—	*ITGB7*	—	5	26,807,079	Besnard et al. (2023)
	Brachyspina	000151	2006	HH0	*FANCI*	0.28	21	20,775,563	Agerholm et al. (2006); Charlier et al. (2012)
	Cholesterol deficiency	001965	2015	HCD	*APOB*	0.34	11	77,872,709	Kipp et al. (2015); Charlier et al. (2016); Menzi et al. (2016); Schütz et al. (2016)
	Complex vertebral malformation	001340	2000	HHC	*SLC35A3*	0.25	3	43,261,946	Agerholm et al. (2001)
	Deficiency of uridine monophposphate synthase (DUMPS)	000262	1983	HHD	*UMPS*	<0.01	1	69,151,931	Shanks et al. (1984)
	Early-onset muscle weakness syndrome	002819	2022	HMW	*CACNA1S*[6]	2.04	16	79,613,592	Dechow et al. (2022); Al-Khudhair et al. (2024b)
	Holstein Haplotype 1	000001	2011	HH1	*APAF1*	0.40	5	62,810,245	Adams et al. (2016)
	Holstein Haplotype 2	001823	2011	HH2	*IFT80*	0.68	1	107,172,615	McClure et al. (2014); Ortega et al. (2022)
	Holstein Haplotype 3	001824	2011	HH3	*SMC2*	0.65	8	93,753,358	Daetwyler et al. (2014); McClure et al. (2014)
	Holstein Haplotype 4	001826	2013	HH4	*GART*	0.09	1	1,997,582	Fritz et al. (2013)
	Holstein Haplotype 5	001941	2013	HH5	*TFB1M*	2.50	9	91,847,117–91,937,003	Cooper et al. (2013); Schütz et al. (2016)
	Holstein Haplotype 6	002149	2018	HH6	*SDE2*	1.14	16	29,015,336–29,059,673	Fritz et al. (2018)
	Holstein Haplotype 7	001830	2020	—	*CENPU*	0.80	27	14,168,130–14,168,133	Hozé et al. (2020)
	Holstein Haplotype 8	001831	2013	—	—	2.10	7	78,800,000–80,100,000	Fritz et al. (2013)
	Mulefoot (syndactylism)	000963	1949	HHM	*LRP4*	<0.01	15	76,807,960	Eldridge et al. (1951); Duchesne et al. (2006)
JE	Jersey Haplotype 1	001697	2013	JH1	*CWC15*	3.47	15	15,449,431	Sonstegard et al. (2013)
	Jersey neuropathy with splayed forelimbs	002298	2022	JNS	*UCHL1*	4.08	6	60,158,901	Al-Khudhair et al. (2022)
	Limber legs	—	1971	—	—	—	—	—	Lamb et al. (1971, 1976)
	Rectovaginal constriction	000850	1975	—	—	—	—	—	Leipold and Saperstein (1975)

[1]Although genetic conditions have been observed in the Guernsey (e.g., Kendrick et al., 1957) and Milking Shorthorn (e.g., Schild et al., 1993) breeds, no genetic conditions or genomic haplotypes are under active management in either breed at this time.

[2]A table entry of "—" indicates an unknown or missing value.

[3]AY = Ayrshire, BS = Brown Swiss, HO = Holstein, and JE = Jersey.

[4]Online Mendelian Inheritance in Animals (OMIA) identification number for *Bos taurus* (National Center for Biotechnology Information species code 9913).

[5]A value of "—" in the "Identifier" column indicates that there is not currently a haplotype test for a defect in the United States.

[6]The causal variant for early-onset muscle weakness syndrome appears to be incompletely penetrant, so carrier status for *CACNA1S* alone is not sufficient to predict an animal's phenotype.

Table 2. Changes in carrier frequencies and effects on conception and death losses between 2012 and 2022 for haplotypes tracking deleterious mutations in US Holstein and Jersey cattle[1,2]

		Data used for tracking			Carrier frequency (%)		Conception or death loss (%)	
Breed	Haplotype name	Haplotype	Causal variant	Both	2012	2022	2012	2022
Holstein	HH0			X	4.3	0.7	0.046	0.001
	HH1			X	3.7	1.0	0.034	0.002
	HH2	X			3.6	1.4	0.032	0.005
	HH3			X	6.2	1.7	0.096	0.007
	HH4			X	0.8	0.2	0.002	0.000
	HH5	X			3.7	6.0	0.034	0.091
	HH6			X	1.1	1.8	0.003	0.008
	HHB			X	0.5	0.1	0.001	0.000
	HHC			X	2.4	0.6	0.014	0.001
	HHD			X	<0.1	<0.1	0.000	0.000
	HHM			X	0.2	<0.1	0.000	0.000
	HCD	X			6.2	0.8	0.090	0.006
	HMW	X			0.3	3.2	0.000	0.031
Jersey	JH1			X	24.8	7.7	1.538	0.147
	JNS	X			4.2	5.7	0.044	0.082

[1]Carrier frequencies are based on all animals (bulls and cows) in the US National Cooperator Database.

[2]HH0 = Holstein Haplotype 0 (brachyspina/*FANCI*), HH1 = Holstein Haplotype 1 (*APAF1*), HH2 = Holstein Haplotype 2 (*IFT80*), HH3 = Holstein Haplotype 3 (*SMC2*), HH4 = Holstein Haplotype 4 (*GART*), HH5 = Holstein Haplotype 5 (*TFB1M*), HH6 = Holstein Haplotype 6 (*SDE2*), HHB = bovine leukocyte adhesion deficiency (*ITGB2*), HHC = complex vertebral malformation (*SLC35A3*), HHD = deficiency of uridine monophosphate synthase (*UMPS*), HHM = mulefoot (syndactyly; *LRP4*), HCD = cholesterol deficiency (*APOB*), HMW = early-onset muscle weakness (*CACNA1S*), JH1 = Jersey haplotype 1 (*CWC15*), and JNS = Jersey neuropathy with splayed forelimbs (*UCHL1*).

and Normande cattle carrying a frameshift in the *RP1* gene lose their vision as they age (Michot et al., 2016). The early onset of muscle weakness defect in Holsteins (Dechow et al., 2022; Al-Khudhair et al., 2024b) appears to be incompletely penetrant, as is BLIRD (Besnard et al., 2024), meaning the gene test or haplotype status alone is insufficient to predict an individual's phenotype. Cattle of several breeds are affected by progressive posterior paralysis (commonly referred to as "crampy"; Becker et al., 1961), which results in premature culling. Its mode of inheritance remains unclear after many years of research, with support for both monogenic (possibly with incomplete penetrance) and polygenic (Condello, 2024) models. Recent results suggest that the *CACNA1A* gene is associated with the crampy phenotype (Neustaeter et al., 2023), whereas a related gene, *CACNA1S*, is associated with early-onset muscle weakness (Dechow et al., 2022; Al-Khudhair et al., 2024b).

Economic Impact

The economic impact of genetic load in the US dairy cattle population using haplotype data was estimated by Cole et al. (2016) to be ~$11 million, but new defects have been discovered since then, and selection pressure has been applied against known loci. The current value of genetic load is ~$4.1 million (Supplemental Table S1; see Notes), a substantial reduction that is due principally to the rapid decrease in frequency for many haplotypes. However, these estimates do not account for indirect costs to producers or potential effects on social license to operate (e.g., Wolf et al., 2016).

INDUSTRY PARTICIPANTS AND CURRENT PRACTICES

There are many different participants in the US dairy industry, and many of them play roles in the genetics sector. Some of these organizations are described in Cole et al. (2021), but operational details relevant to each group's involvement in the management of genetic defects are provided herein. Each of these entities plays a specific role in the reporting, identification, and testing of genetic defects, although roles are often poorly defined and frequently overlap.

New genetic defects are typically reported when a dairy producer reports 1 or more cases to a breed association or their AI representative, but reports are sometimes made directly to veterinarians, university researchers, or USDA scientists. Notably, there is currently no single organization that serves as a universal point of contact or shared protocol for responding to these reports.

After a potential defect is reported, research is needed to determine whether the cause is genetic or environmental, and to identify causal mechanisms for genetic diseases. Although many defects follow the classical Mendelian model, not all do, and mechanisms such as incomplete penetrance can complicate this task. Parties involved in the identification process can include purebred cattle associations, university and USDA research-

ers, and veterinary diagnostic laboratories. The lack of a standardized reporting process is also felt in this stage, because a wide variety of biological samples may be provided, and phenotyping can range from a short description to a detailed report that includes a veterinary diagnosis, as well as photographs and video recordings. Biological samples and other information are also sometimes provided without a proper animal identification number, meaning that pedigree information may be missing, incomplete, or incorrect.

After the cause of a defect has been identified, tools for testing must be developed and information about the disorder shared with allied industry groups. Commercial genotyping laboratories provide both genotypes used for haplotype carrier determination and results from individual gene tests for putative causal variants. The Council on Dairy Cattle Breeding computes haplotypes for genetic conditions, which are distributed to genetics companies and purebred cattle associations. International organizations and standards bodies are sometimes involved in this process, and National Association of Animal Breeders members are affected by trade policies related to the importation of germplasm from known carriers of genetic conditions.

National Association of Animal Breeders

The National Association of Animal Breeders (**NAAB**; Madison, WI; https://www.naab-css.org/) is the official trade organization for the US bovine AI industry and represents US tax-paying organizations engaged in the artificial insemination of cattle and other livestock. Under the NAAB umbrella, member organizations come together to provide a unified approach to cattle improvement. Together, NAAB's membership accounts for about 95% of the US dairy cattle semen produced, sold in, and exported by the United States. Their Inherited Biochemical Defects Committee reviews reports of new genetic disorders and makes recommendations to NAAB members about nomenclature and publication. In their position as the official trade association, NAAB resolves international trade barriers that arise from concern or misunderstanding of genetic disorders.

Purebred Dairy Cattle Associations

As the official herd book registrars, dairy cattle breed associations were the first organizations to develop procedures for the identification and reporting of genetic defects (breed-specific information is discussed subsequently). In addition to providing guidelines for reporting of defects, these policies ensure that pedigrees include accurate information about carrier status. National organizations for each breed exist in many countries, sometimes operating under international umbrella groups. In the United States, the breed associations are the authorities for naming and labeling genetic defects, and farmers are asked to report calf abnormalities to these organizations. However, participation in reporting programs is voluntary.

Some genotyping laboratories have elected, for their own legal protection, to report genetic test results only to the owner or controller of the animal. Forwarding genetic test results to a third party, such as a breed association, requires the owner to opt in (i.e., check a box on the submission form, requesting that the genetic test result be sent to the respective breed association). This can result in selective reporting; however, it is our experience that most animal owners and controllers realize that the legal and financial consequences of not disclosing a genetic test result when it is known would exceed short-term profits from the sale of a genetic product. We know of no legal cases of a buyer suing a seller over an undisclosed genetic test result.

Ayrshire Cattle. No mention of a genetic defects policy currently appears in the Ayrshire Breeders Association Rules (https://web.archive.org/web/20240721155943/http://www.usayrshire.com/PDF/abarules.pdf) or on the website of the World Ayrshire Federation (https://www.worldayrshirefederation.com/).

Brown Swiss Cattle. The Brown Swiss Cattle Breeders' Association of the USA publishes a pamphlet, "Genetic Conditions in Brown Swiss Cattle," that provides information about known genetic defects in the breed and includes procedures for reporting defects, designating carrier status, and interpreting test results (Brown Swiss Association, 2021; A. Horn, Brown Swiss Association, Beloit, WI, personal communication). In addition, the European Brown Swiss Federation has as one of its goals the development of a "Common system of declaration of hereditary defects and common data bank" (https://www.brown-swiss.org/about-us).

Guernsey Cattle. No formal policies are presently listed on the American Guernsey Association (Columbus, OH; https://www.usguernsey.com/) or World Guernsey Cattle Federation (Myrtleford, Victoria, Australia; https://www.worldguernseys.com/) websites. However, Article IV, Section D, of the American Guernsey Association Bylaws includes the following provision:

> The Executive Secretary or the Executive Board shall make such investigations of genetic factors occurring in Guernsey animals as they believe necessary or advisable and shall report the results of their investigations to the Board of Directors. Each member and non-member of the Association shall cooperate fully in any such investigation. *The Board of Directors shall determine what genetic*

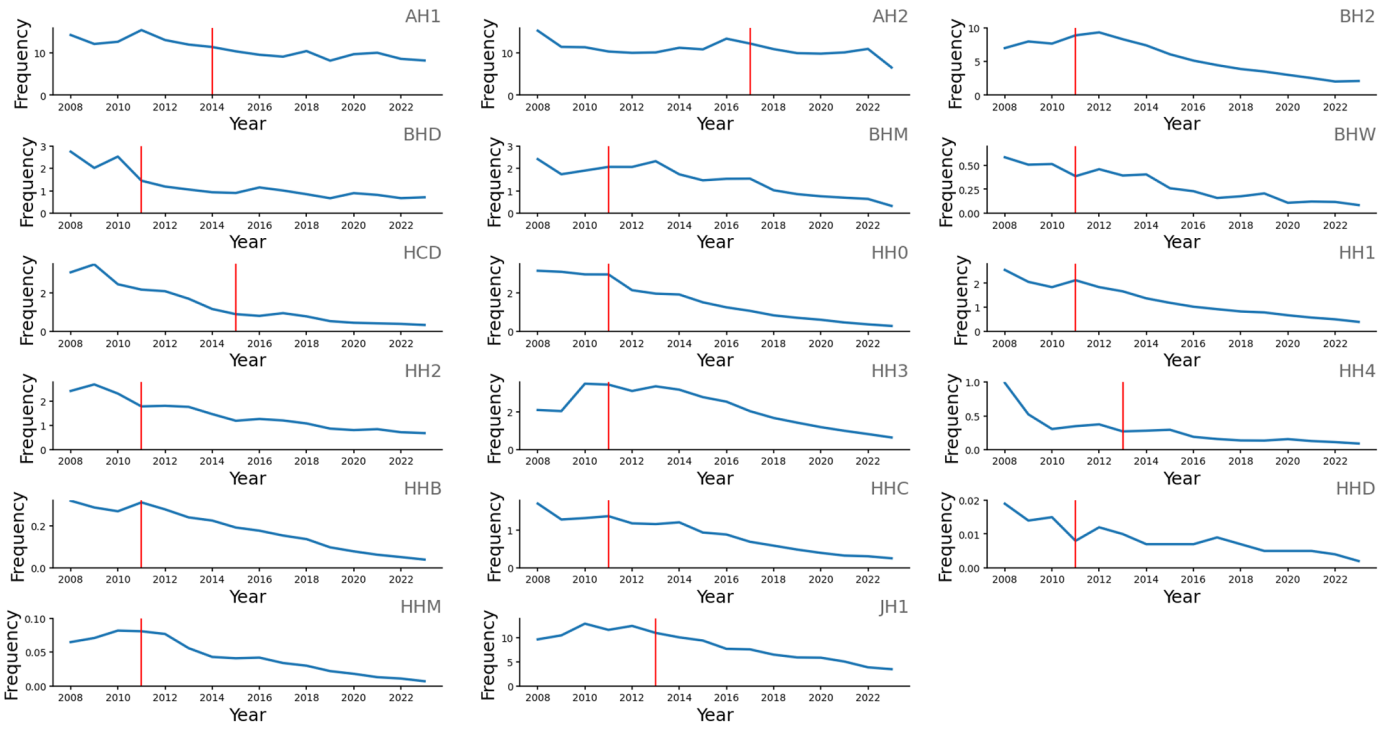

Figure 2. Haplotype frequencies by year (2008–2023) for recessive genetic defects in US Ayrshire, Brown Swiss, Holstein, and Jersey cattle, tracked by the Council on Dairy Cattle Breeding, that are under control (Al-Khudhair et al., 2024a). Vertical red lines indicate the year each haplotype was first published. AH1 = Ayrshire Haplotype 1 (PIRM/*UBE3B*), AH2 = Ayrshire Haplotype 2 (*RPAP2*), BH2 = Brown Swiss Haplotype 2 (*TUBD1*), BHD = spinal dysmyelination (SDM; *SPAST*), BHM = spinal muscular atrophy (SMA; *KDSR/FVT1*), BHW = Weaver (*PNPLA8*), HCD = cholesterol deficiency (*APOB*), HH0 = Holstein Haplotype 0 (brachyspina/*FANCI*), HH1 = Holstein Haplotype 1 (*APAF1*), HH2 = Holstein Haplotype 2 (*IFT80*), HH3 = Holstein Haplotype 3 (*SMC2*), HH4 = Holstein Haplotype 4 (*GART*), HHB = bovine leukocyte adhesion deficiency (*ITGB2*), HHC = complex vertebral malformation (*SLC35A3*), HHD = deficiency of uridine monophosphate synthase (*UMPS*), HHM = mulefoot (syndactyly; *LRP4*), and JH1 = Jersey haplotype 1 (*CWC15*). The year the haplotype test was introduced is not the time of initial discovery of a genetic defect; some defects were discovered decades before haplotype tests became available.

information is considered to be undesirable in the Guernsey breed and shall take whatever action it may consider appropriate to control and limit such undesirable genetics.

(R. Alden, American Guernsey Association, Columbus, OH, personal communication; emphasis added.)

Holstein Cattle. Holstein Association USA (Brattleboro, VT) provides information about recessives and other Mendelian traits in its "Genetic Conditions in the Holstein Breed" (https://www.holsteinusa.com/programs_services/genomics.html?tab=1) document, as well as guidance for use of haplotype information ("Interpreting and Utilizing Haplotype Information"; https://www.holsteinusa.com/pdf/Interpreting_and_Utilizing_Haplotype_Information_1218.pdf). The World Holstein Friesian Federation (**WHFF**; Rickmansworth, Hertfordshire, UK) has guidelines covering "Genetic Traits" (https://whff.info/genetic-traits/), which refers to "verified or suspected [monogenic] conditions in the Holstein breed, not quantitative traits such as milk yield or productive life." These guidelines are more nuanced than those provided for other breeds, and recognize that some monogenic traits are undesirable, some have small or no apparent phenotypic effects, and others are desirable. Criteria for inclusion of genetic conditions on the WHFF Master List include the frequency of the variant (>5% in 2 or more countries), identification of the causal variant, availability of diagnostic SNP, proportion of phenotypic variance explained (≥5%), independence from environmental effects, monogenic inheritance free from epistasis, high penetrance, and publicly available peer-reviewed documentation. These criteria provide an evidence-based framework for both listing and delisting genetic defects as population management programs are successful.

Jersey Cattle. The American Jersey Cattle Association (Reynoldsburg, OH) describes its approach to genetic defects in "Policies Regarding Undesirable Genetic Factors" (https://www.usjersey.com/AJCA-NAJ-JMS/AJCA/FromTheExecutiveSecretary/PolicyUndesirableGeneticFactors.aspx), and the section "Statement of Policy" very clearly outlines the Association's goals: "Every effort should be made within the

breed to identify those animals that carry undesirable genetic factors." Similarly, the World Jersey Cattle Bureau (Beganne, Brittany, France; http://www.worldjerseycattle.com/Pedigree-Registration) recommends that "Member organisations require owners of genomic test results to declare the lethal recessive and genetic defect status of males and females for publication on pedigree certificates, proof lists and marketing information."

Milking Shorthorn Cattle. No written policy for genetic defects is currently provided on the American Milking Shorthorn Society website (https://milkingshorthorn.com/). However, the Society does monitor the cholesterol deficiency (HCD) and complex vertebral malformation (**CVM**) haplotypes in the breed, and carrier status is provided on the registration form (S. Lee, American Milking Shorthorn Society, Beloit, WI, personal communication).

United States Department of Agriculture

The Agricultural Research Service, USDA's in-house research arm, has a nationwide team of scientists dedicated to addressing production agriculture challenges, including genetic diseases. The team at the National Animal Disease Center in Ames, Iowa, identified the *CD18* causal variant linked to bovine leukocyte adhesion deficiency (Shuster et al., 1992). Researchers at the US Meat Animal Research Center (Clay Center, NE) and the Animal Genomics and Improvement Laboratory (**AGIL**; Beltsville, MD) are involved in all aspects of livestock genomics, including the construction of reference genomes for cattle (Bovine Genome Sequencing and Analysis Consortium, 2009), sheep (Davenport et al., 2022), and goats (Bickhart et al., 2017), and were key contributors to the original bovine SNP chip (Matukumalli et al., 2009). Additionally, AGIL created the deficiency-of-homozygotes method to identify haplotypes affecting fertility (VanRaden et al., 2011) and several causal variants (Cooper et al., 2013, 2014; McClure et al., 2013; Sonstegard et al., 2013; Lawlor et al., 2014; Adams et al., 2016; Null et al., 2017; Al-Khudhair et al., 2022, 2024a; Ortega et al., 2022). Staff at AGIL also manage the Collaborative Dairy DNA Repository, an important storehouse for DNA from dairy animals.

University Research Groups and State Veterinary Diagnostic Laboratories

Historically, researchers at universities and veterinary schools have played important roles in the identification and characterization of genetic defects. For many years, Dr. Horst W. Leipold of the Department of Pathology, Kansas State University College of Veterinary Medicine, was the leading authority on congenital defects of cattle in the United States (e.g., Leipold et al., 1972; Cotton, 1989). Scientists at the University of Illinois were responsible for identifying the deficiency of uridine monophosphate synthase (**DUMPS**) defect in Holsteins (Shanks et al., 1984). More recently, a team at Penn State led the effort to characterize early-onset muscle weakness and develop a gene test (Dechow et al., 2022). Universities and research centers could serve as contacts for producers to report abnormalities, due to their often-expansive networks of scientists, extension personnel, and dairy producers. Collaborations with private industry to secure data are common, and intellectual property generated by university teams is often used to develop gene tests (e.g., Dechow et al., 2022).

Although most discussion has focused on North American institutions, important work is also being done in several European countries. One of the oldest national programs is the Danish Bovine Genetic Disease Programme (Agerholm et al., 1993), which was organized in 1988. Their successes include the identification of several diseases in Danish cattle, including epitheliogenesis imperfecta, spinal muscular atrophy, and syndrome of arthrogryposis and palatoschisis. In France, L'Observatoire National des Anomalies Bovines (**l'ONAB**; Grohs et al., 2016) was established in 2002 as a national center for population monitoring. The partnership includes representatives from government, university, and industry organizations, and covers both dairy and beef cattle. Many causal variants associated with recessive genetic defects have been identified by l'ONAB and its collaborators. Although more limited in scope, the Belgian Blue cattle breed (Sartelet, 2013) also has a population surveillance and causal variant identification that have been used to notably reduce carrier frequencies. The Irish Cattle Breeding Federation (Ballincollig, County Cork, Ireland) launched a program for the reporting of genetic diseases that includes comprehensive educational materials (McClure and McClure, 2016) which could serve as a model for others to follow. It is clear from the success of these programs that having a single organization to coordinate surveillance, discovery, and reporting is a great advantage.

Commercial Genotyping and Genetic Testing Laboratories

Several commercial laboratories in North America provide SNP genotyping and genetic testing services. The genotypes are used to predict breeding values and haplotype carrier status, and specific gene tests also can be included on arrays when the causal variants are known. In some cases, testing laboratories play an essential role in translating discovery science into practice. Labeling of tests and haplotypes across organizations is

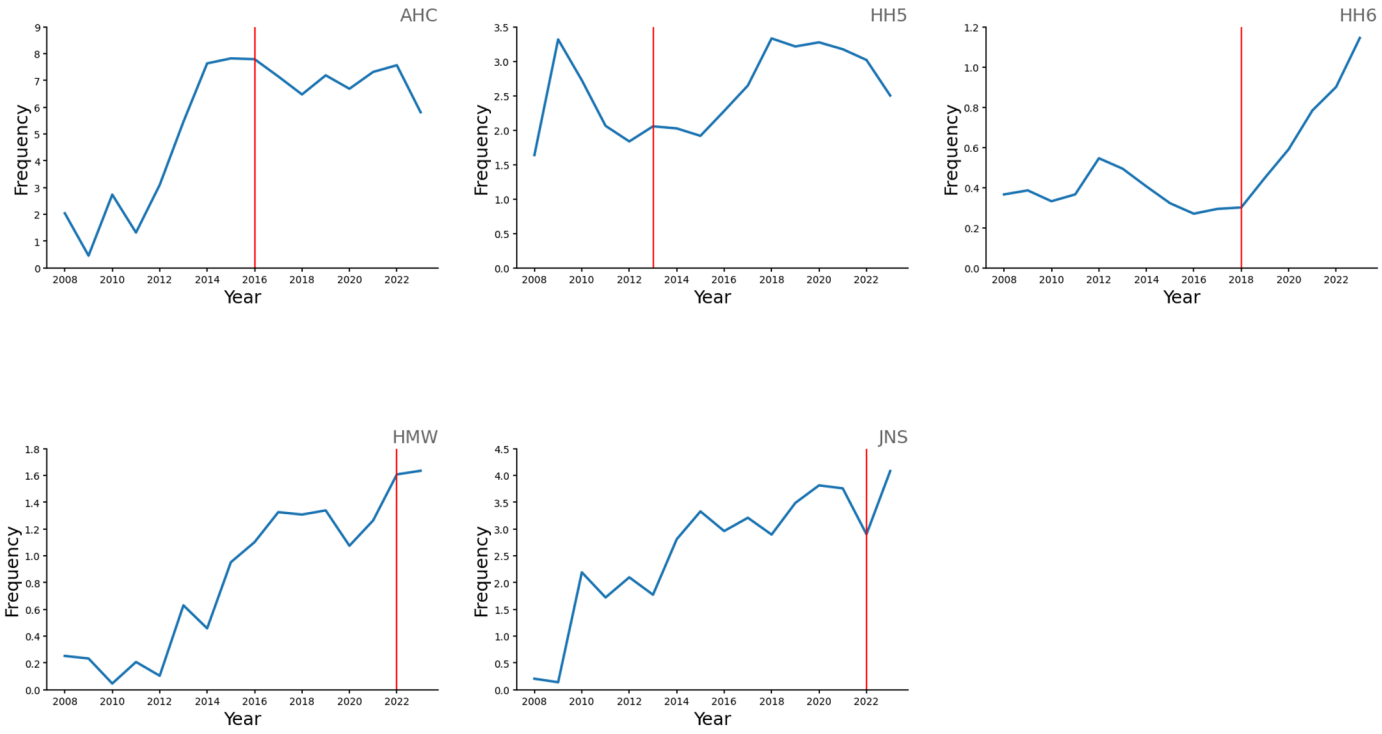

Figure 3. Haplotype frequencies by year (2008–2023) for recessive genetic defects in US Ayrshire, Holstein, and Jersey cattle, tracked by the Council on Dairy Cattle Breeding, which have unfavorable trends (Al-Khudhair et al., 2024a). Vertical red lines indicate the year the haplotype test associated with each defect was first published. AHC = Ayrshire Haplotype C (*CHRNB1*), HH5 = Holstein Haplotype 5 (*TFB1M*), HH6 = Holstein Haplotype 6 (*SDE2*), HMW = early-onset muscle weakness (*CACNA1S*), and JNS = Jersey neuropathy with splayed forelimbs (*UCHL1*). The year the haplotype test was introduced is not the time of initial discovery of a genetic defect; some defects were discovered decades before haplotype tests became available.

not consistent today, causing substantial confusion, particularly internationally.

International Organizations and Standards Bodies

Interbull. The International Committee for Animal Recording (**ICAR**; Utrecht, the Netherlands) is a global provider of guidelines, standards, and certification for animal identification, recording, and evaluation. The International Bull Evaluation Service (**Interbull**; Uppsala, Sweden) is a permanent subcommittee of ICAR focused on the conversion of international genetic evaluations for economically important traits of dairy cattle to support valid comparisons of genetic predictions across countries. Interbull collaborates with WHFF and uses their codes and nomenclature for genetic tests when sharing Holstein information (World Holstein Friesian Federation, 2024). This is an excellent example of how cooperation among organizations can promote beneficial uniformity and avoid unnecessary duplication of effort.

DNA Working Group. In addition to genetic evaluation services, ICAR also certifies laboratories that provide microsatellite- and SNP-based genotyping services for cattle through its DNA Working Group. This group has as one of its priorities for 2024 to continue work on guidelines for standardization of causal mutation SNP for genetic defects. This is straightforward when the causal variant can be tracked by a single SNP (e.g., is the result of a transition or transversion) but is more challenging when a causal variant is an insertion, deletion, copy number variant, or other structural change that can be difficult to track with a SNP. In the absence of standardization multiple approaches could be used to call the same variant, resulting in potential confusion across testing laboratories and genetic evaluation centers.

MANAGING GENETIC DEFECTS AT THE POPULATION LEVEL

Historical Management of Genetic Defects

Our knowledge of genetics has increased significantly in recent years, primarily due to advancements in whole-genome sequencing and access to genomic testing, which allows us to make early and accurate genomic predictions for quantitative traits and test for known causative variants for various genetic diseases (e.g., VanRaden et al., 2011; Liu et al., 2022; Guinan et al., 2023). Purebred

dairy cattle associations and genetics companies have long-standing interests in the management of undesirable recessive defects, consistent with their mission of breed stewardship. The Holstein Association USA launched a program in 1957 to record carriers of defects, and additional policies were established in 1961 and 1977 to discourage the use of carrier bulls and routinely publish carrier lists (Mansfield, 1985, pp. 113–114). At their 1958 annual convention, NAAB adopted a resolution encouraging breed associations to "report inherited defects of a deleterious nature" (Herman, 1981, p. 170). These long-term efforts to improve breeding programs have ushered in an era in which it is generally agreed that identifying and reporting defects is a good thing. Opportunity exists to further strengthen breeding programs through a formal surveillance program for emerging genetic defects, as discussed later in this paper.

Historically, genetic defects were investigated by evaluating patterns of nonaffected versus affected animals. Different patterns of segregation for a single genetic variant are often referred to as Mendelian ratios, in honor of the early scientist Gregor Mendel. These ratios provide evidence of different modes of inheritance, such as dominant, recessive, sex-linked, or mitochondrial inheritance (Smith, 1971). Livestock industries have benefited from the significant amount of research into heritable human diseases because of biological similarities among disparate-seeming species. The first step for many agricultural scientists when investigating a new disorder is to search databases funded by the National Human Genome Research Institute, such as Online Mendelian Inheritance in Man (**OMIM**; https://omim.org/) and the Gene Ontology Resource (https://geneontology.org/). The number of Mendelian disorders in humans where the causative variant has been identified has steadily increased in the genomic era, from approximately 800 in the year 2000 to about 4,900 today (https://omim.org/statistics/paceGraph).

Currently, there are approximately 5,000 known Mendelian disorders in OMIM for which the causative variant has been identified. Knowledge of causal variants provides valuable information on the biological mechanisms involved, understanding of relevant pathways, and lifestyle changes that might reduce harmful effects, and can aid in the development of targeted treatments. As technology evolves, some genetic diseases are now treatable. For example, the Medicus Genomics "Treatments for Genetic Disorders" database (https://rx-genes.com; Bick et al., 2021) provides information about the treatment of genetic disorders. At the time of its most recent update (Aug. 20, 2024), the database includes comprehensive entries for 800 diseases. Although the focus of these treatments is on human disease, treatments for important livestock diseases could become available in the future.

In the pre-genomics era, genetic disorders were mostly rare and catastrophic (e.g., bovine leukocyte adhesion deficiency [**BLAD**], CVM, DUMPS). The common practice of the time was to eliminate defects by removing suspected family members from the herd. Although breed associations understand the financial hardship that this can impose on an individual breeder, most of them have rules and bylaws that require disclosure. For example, Holstein Association USA states, "It is the duty of all persons who are subject to the Bylaws, rules, and regulations of the Association to report promptly to the Executive Secretary any manifestation of one or more declared recessive genes" (Holstein Association USA, 2024). Breeders feared the discovery of a new genetic defect in their breed and, more importantly, in their own herd. The culling of afflicted animals was often a small part of the financial burden compared with the reputational loss. Without the aid of genetic testing, a whole family or perhaps the whole herd would be shunned by others. As a result, some breeders preferred to quietly remove the affected animal and perhaps some of its relatives from their herd. Although producer concerns remain about negative consequences of reporting new defects, the growing use of genomic testing means that it is increasingly difficult to conceal such problems. Confusion about to whom reports should be made remains common.

Contemporary Management of Genetic Defects

A population's breeding structure, practices, and size can have a significant influence on the ability to detect genetic defects. Before widespread use of AI and genomics, the discovery of genetic defects relied on a pedigree analysis of observational data on closely related family members. As the use of AI has grown, and DNA technologies improve, the search for genetic defects has moved from an observational science of within-herd family members to population-based analysis of molecular information. Heavy use of prominent bulls creates large subpopulations of related animals (Steyn et al., 2023). The US Holstein population is also often used in modern-day studies, as researchers look for data sets that will give them the statistical power to prove the inheritance of a defect (e.g., Besnard et al., 2023; Kelson et al., 2024).

The challenge for modern cattle breeders is how to manage genetic information in an open and transparent way to reduce the frequency of undesirable genetic defects and minimize financial hardship to individual owners. Proper management of genetic defects can increase the frequency of the desirable alleles, reduce the frequency of undesirable alleles, and preserve genetic diversity. A good example of the positive economic effects

of a carrier bull with high genetic merit is Pawnee Farm Arlinda Chief (040HO02025; HOUSA000001427381); the positive global contribution of extra milk production from this bull is 70 times higher than the financial losses attributable to HH1, of which he was a carrier (P. M. VanRaden, USDA Agricultural Research Service, Beltsville, MD; personal communication). Genomic testing and embryo transfer provide ways to screen many full- and half-sib animals, cull carriers at a young age before a large financial investment has been made in them, and retain noncarriers for breeding purposes.

Figure 2 shows haplotype frequency trends for 17 recessive genetic defects in US Ayrshire, Brown Swiss, Holstein, and Jersey cattle, which demonstrate successful population management. In all cases, carrier frequencies have decreased substantially over time, in some cases to as close to zero as is feasible. This demonstrates the ability of the dairy cattle community to reduce the frequency of harmful defects and emphasizes the value of strong surveillance programs that identify emerging problems before they have an opportunity to spread through the population. The availability of precision mating tools (discussed in the next section), continuous growth in the number of cows genotyped, and widespread availability of genetic testing allow us to manage genetic diseases without automatically culling carriers. This increases the likelihood that new defects will be reported, because being a carrier no longer automatically eliminates an elite animal's marketability.

The precise way in which carrier status for new defects will be reported is still evolving, and more nuanced approaches to categorizing emerging defects may be needed. The World Holstein Friesian Federation recently published its "WHFF Guidelines for Interpreting New Evidence on Potential Monogenic Traits" (World Holstein Friesian Federation, 2024), which classifies monogenic variants into 5 categories, based on the phenotypic effects of a trait. For purposes of this discussion, classes 1 ("Traits with Distinctive Characteristics"), 2 ("Haplotypes Impacting Fertility"), and 4 ("Reduced Fitness and Health") are most relevant. The distinction between classes 1, 2, and 4 are particularly important. Class 1 includes "physical deformities," such as those caused by CVM and HH0. Class 2 includes the haplotypes affecting fertility, which generally cause early embryonic losses but which can also have effects late in gestation or following birth. Class 4 covers undesirable conditions, such as BLIRD, which can result in reduced animal health or fitness but often have times of onset beyond typical working lifespans. These categories recognize that genetic conditions can have different effects on health, welfare, and profitability. Figure 3 shows some recent examples of conditions in classes 1 and 2; in each case, the frequency of the undesirable haplotype is expected to decrease rapidly. This is an appealing model for classification because nothing about it is inherently breed-specific and it provides nuance that is currently lacking from this discussion.

Class 1 also includes physical characteristics of animals, which follow a Mendelian mode of inheritance but which are not detrimental to animal performance. As can be seen in Figure 4, some of these conditions are selected against (for example, red coat color), whereas others are desirable (such as polledness), but the effectiveness of this selection is often limited because of limited sire availability due to low frequency of the desirable haplotype.

One critique of this classification system is that it does not account for the potential economic losses from defects in different classes that farmers in different production systems may face. The costs of defects in class 4 have the potential to be much larger than those in class 1 or 2, particularly when culling rates are low and average cow ages are high. Cole (2015) proposed a simple method for managing recessive defects by deducting the expected cost of genetic load from parent averages when allocating mates. Haplotype frequencies decreased at rates similar to those found using the approach of Pryce et al. (2012), which penalized parent averages for increases in genomic inbreeding, and some loss of cumulative genetic gain was observed. Other schemes that consider genetic merit and harmful defects exist (e.g., Van Eenennaam and Kinghorn, 2014; Segelke et al., 2016), but the principal challenges to their adoption in the United States are increasing herd sizes, rising labor costs, and reproductive management programs that preclude the routine use of individual mate allocation in favor of portfolios of bulls used at random.

The Path Forward

The scientific community now has the tools to identify many putative genetic defects. Confirmed genetic defects, especially those with a known causative genetic variant, should be provided to the curators of the Online Mendelian Inheritance in Animals (https://omia.org/home/) database so this information will be available to others. Individual defects should be managed using a local surveillance and reduction program, because a defect that is present in one population may be absent from another. For example, within the international Holstein breed, 38 haplotypes affecting fertility have been identified, but only 7 of them possess the characteristics determined by the WHFF (discussed previously) to warrant routine testing (e.g., Häfliger et al., 2022). It is important for both breed stewardship and genetic progress that these conditions be monitored and managed when necessary, but not used as an excuse to establish barriers to trade.

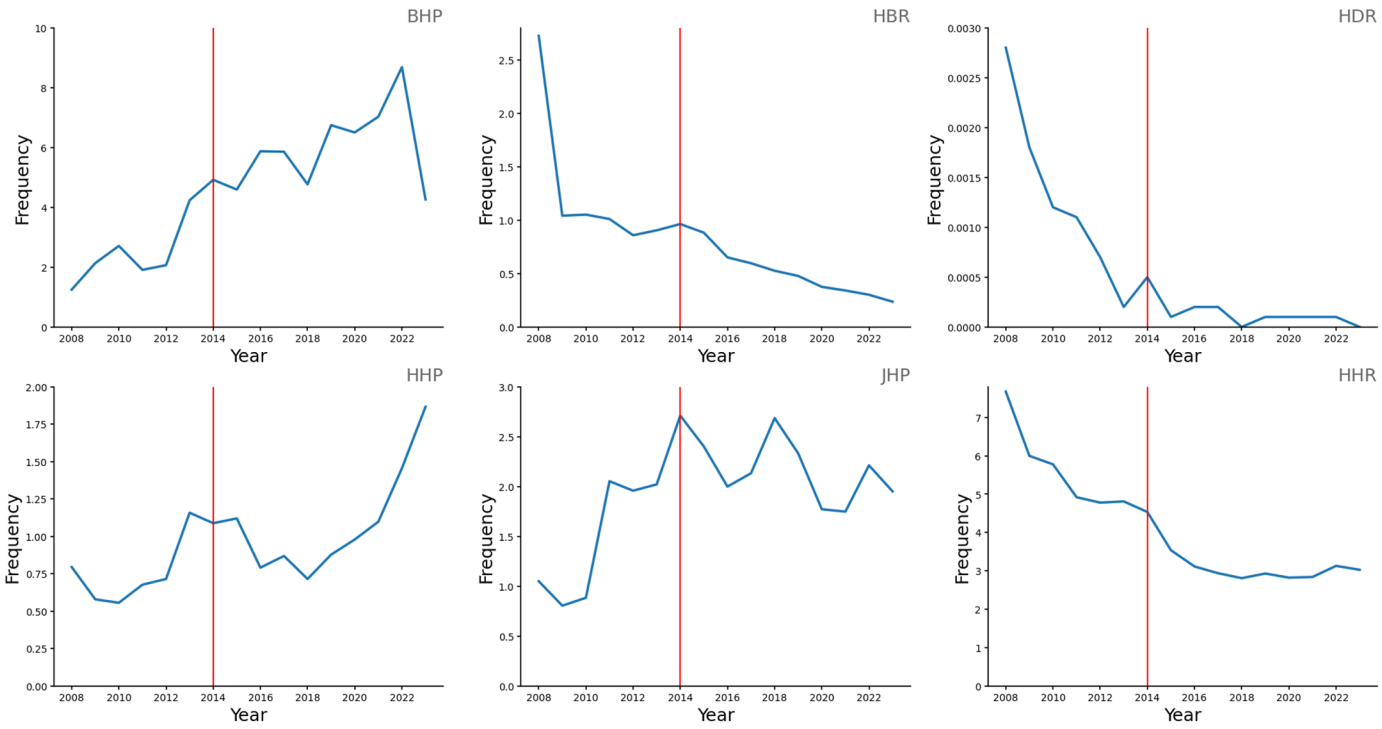

Figure 4. Haplotype frequencies by year (2008–2023) for physical characteristics in US Brown Swiss, Holstein, and Jersey cattle, tracked by the Council on Dairy Cattle Breeding (Al-Khudhair et al., 2024a). Vertical red lines indicate the year each haplotype was first published. BHP = polledness (*POLLED*) in the Brown Swiss breed, HBR = black/red coat color (*MC1R*/*MSHR*), HDR = dominant red coat color, HHP = polledness (*POLLED*) in the Holstein breed, HHR = red coat color (*MC1R*/*MSHR*), and JHP = polledness (*POLLED*) in the Jersey breed. The BHP, HHP, and JHP haplotypes are different from the others included in this figure because the desirable allele (polled) is dominant to the undesirable allele (horned). The year the haplotype test was introduced is not the time of initial discovery of a genetic defect; some defects were discovered decades before haplotype tests became available.

MANAGING GENETIC DEFECTS AT THE FARM LEVEL

A key challenge faced by breeders is that we know inbreeding is increasing, and at a faster rate than ever before, but we do not know when—or whether—that might become a problem (Cole, 2024). The continuous culling on performance practiced by dairy producers may help eliminate the sublethal alleles that are thought to account for much inbreeding depression (e.g., Maltecca et al., 2020). Cole (2024) recently showed that inbreeding depression in US Holsteins is modest, which is consistent with an earlier study of Bjelland et al. (2013), and that annual rates of gain exceed losses from inbreeding in almost all cases. However, hoping that rates of genetic gain continue to exceed losses from inbreeding depression is not a viable strategy for long-term population management. The rule of thumb that inbreeding should not increase by more than 6.25% each generation appears to trace back to Jay L. Lush, who wrote, "Fragmentary evidence of various kinds indicates that inbreeding rates as high as six percent per generation under favorable circumstances may be pursued for many generations without noticeably harmful consequences" (Lush, 1937, p. 224). Regardless of the recommendation given, inbreeding will continue to increase, with a concomitant increase in the frequency of undesirable alleles in the population. These alleles must be managed to avoid unacceptable welfare, economic, and social costs, and it is important to remember that "One of the potent features of the curse of the lethal recessive is that the number of cases (offspring homozygous for the lethal recessive) can give a misleading impression of the number of carriers" (Oldenbroek, 2017, p. 34). A situation may appear okay when it really is not.

Mating Programs

Every cow in a herd must be bred, and the use of computerized mating programs can ensure that each animal is matched with the bull that produces the best possible offspring. The mating program combines information from many sources, including parental PTA for dozens of traits, carrier status for recessive genetic defects, and genomic or pedigree inbreeding resulting from a mating. Additional constraints can be imposed, such as limits on the number of matings permitted per

sire, a maximum threshold for (genomic) inbreeding, or the allocation of complex portfolios, including sexed, conventional, and beef semen. A comprehensive review of mate allocation tools is beyond the scope of this paper, so the following discussion will focus on tools that explicitly support management of deleterious alleles as part of the process.

Although not presented as a formal scheme, Charlier et al. (2008) were perhaps the first to demonstrate that SNP genotypes can be used to identify many recessive defects. They proposed the avoidance of carrier-to-carrier matings, rather than culling of all carriers, and discussed the use of such a strategy to virtually eliminate 2 defects—congenital muscular dystony types 1 and 2—from the Belgian Blue breed. They also recommended the establishment of surveillance centers to detect emerging defects, centralize collection of samples from affected animals, and identify causal variants, which will be discussed further herein.

Gebreyesus et al. (2020) computed the total risk of calf mortality from polygenic and lethal allele components, allowing consideration of information about both recessive defects and polygenic traits such as calf livability. Accuracies were higher when both were considered, as were correlations of predicted with observed calf mortality. Although this is not an example of a mating program as such, integrating the effect of each defect into the breeding value for a particular trait accounts for both the polygenic and the recessive lethal allele components, and the resulting values can be included in a selection index with no need to assign weights for each lethal.

Linear programming can also be used to optimize the economic value of matings within a herd. Bengtsson et al. (2023) developed such a model, which included genetic merit, pedigree and genomic relationships, semen cost, economic impact of genetic defects, polledness, and β-casein. They concluded that it is possible to both reduce genetic relationships and dramatically reduce the number of offspring affected by genetic defects, with minimal effects on genetic merit. They did note that A2A2 bulls were less likely to carry the polled allele, which can be overcome by providing economic weights for both traits. This could be problematic in situations where farmers want to proactively select for a trait for which they are not currently being paid.

As the size of dairies in the United States increases, fewer farms are using individual mate allocation approaches because of the labor needed to identify a cow, select and thaw the matching semen, load the AI gun, and breed the cow. Instead, herds that use timed AI typically select one or a few bulls that are bred to the cows in estrous on a given day. In such situations, the use of bulls free of known genetic defects is the simplest strategy to adopt, but it may not produce the highest rates of genetic gain.

Selection Indices

Although the selection index is intended for ranking animals for selection, not for managing genetic defects in a population, its ubiquity has led some authors to investigate how it might be adapted to that purpose. Pryce et al. (2012) showed that the use of a sequential mate allocation scheme in which parent averages were penalized for inbreeding in the offspring was effective at reducing pedigree and genomic inbreeding, as well as the proportion of shared runs of homozygosity. They also demonstrated that controlling inbreeding reduced the frequency of homozygous minor alleles.

Building on this work, Cole (2015) proposed a sequential mate allocation scheme in which the parent average of each potential mate pair was penalized for inbreeding effects and the potential embryonic losses from carrier-to-carrier matings. Simulation showed that this approach successfully reduced undesirable allele frequencies, although cumulative genetic gains were slightly lower when using this adjustment, and effects on inbreeding rates were minimal. Bérodier et al. (2021) applied this approach to data from Montbéliarde herds in France and found that the use of genomic information in place of pedigree data maximized genetic gain and reduced the risk of producing affected offspring.

Segelke et al. (2016) also investigated ways to account for monogenic traits in breeding programs using a "genetic index" constructed using the major and minor allele frequencies and economic value of each trait. In the baseline scenario all animals were selected on their breeding values, and in the alternative scenario females were ranked for selection on their genetic index whereas mates were ranked on their breeding values. They concluded that the use of this genetic index in the female path of selection successfully reduced undesirable allele frequencies while sacrificing only a modest amount of genetic gain.

A tool that predicts the probability that offspring of a mating will be affected by at least one known genetic defect, called pANO, has been used by Montbéliarde breeders working with the GEN'IAtest AI company (Roulans, France) to reduce the risk of genetic defects. Brochard et al. (2018) reported that the rate of affected progeny was reduced by 25% when used on ~97,000 planned matings, with potential for much larger reductions if stricter criteria are used.

Culling of Carriers

Dairy cattle populations differ from many others in that a relatively small number of males are sires of the next generation through AI. Although this increases risk of spreading genetic defects before they have been

identified, it also provides a relatively easy way to avoid propagation of undesirable alleles once they have been identified through the culling of carriers. However, it is important to recognize that avoidance of carrier-to-carrier matings does not reduce the frequency of undesirable alleles in the population, but it is a short-term strategy to avoid undesirable outcomes while making long-term changes to population management. More sophisticated strategies that balance the desire to maintain high rates of genetic gain against the interest in reducing frequencies of harmful alleles are available, if not widely adopted. Van Eenennaam and Kinghorn (2014) showed that selection of mates that minimized the number of homozygous progeny, rather than selection against carrier offspring, maximized genetic gain (~94% of unconstrained progress) and minimized the number of affected offspring. Similarly, Upperman et al. (2019) concluded that the most profitable breeding strategy was always simultaneous selection and mate allocation to avoid homozygous offspring, rather than the complete avoidance of carriers as parents. Hjortø et al. (2021) recommended a pre-selection step for lethal recessive alleles that cause animal suffering, in which carriers were excluded. When used in conjunction with optimal contribution selection schemes, inbreeding was controlled, and minimal loss of genetic gain occurred, along with substantial reductions in the frequency of lethal recessives in subsequent generations. Genetics companies are understandably reluctant to adopt a blanket policy of culling all carriers, and the ubiquity of on-farm computers makes it feasible to make routine use of more complex mate allocation strategies.

Crossing Within Large Populations

Steyn et al. (2023) used US national data to identify clusters of Holstein bulls that were genetically similar. They identified 7 groups of males that may be present in the population. In a follow-up study, k-means clustering was used to group animals into 5 "families" that were shown to have different allele frequency distributions, reflecting group-specific selective sweeps, polygenic changes, hitchhiking, and epistasis. When SNP effects were computed separately for each family and applied to other families reranking of genomic PTA occurred, and genetic correlations differed across groups. These results suggest that unrecognized pools of variation exist within large breeds, which can be used to reduce within-family homozygosity while maintaining rates of genetic gain. Crossing breeds, rather than distinct lines within breeds, is not a solution to the problem of genetic diseases. The risk of carrier-to-carrier matings may be lower in rotational crossing programs, but purebred lines must still be maintained.

Crossbreeding has not been adopted in dairy cattle to the extent that it has been in beef, poultry, and swine production (e.g., McAllister, 2002). Notably, there are no terminal dairy populations that need to be supplied from multiplier herds, estimates of dominance variance are stubbornly low for most traits, and maternal and paternal lines for crossing have not been developed. This leaves us with rotational crossbreeding systems as the only viable path forward, and crossbred cows accounted for only 6.2% of the animals enrolled in US milk recording programs in 2023 (Council on Dairy Cattle Breeding, 2024; https://webconnect.uscdcb.com/#/national-performance-metrics). Even if crossbreeding were an attractive tool for managing genetic defects, that is unlikely to drive higher rates of adoption.

Germplasm Exchange

As the North American AI market has consolidated into a small group of large companies and breeders have been able to better leverage the value of their elite cow families through genomics and advanced reproductive technologies, AI company portfolios increasingly resemble distinct subpopulations. Recent work by Steyn et al. (2023) supports this latter idea, and they identified 5 distinct clusters of families within the US Holstein breed that have different allele frequency distributions, opposing directions of SNP effects, and fixation of different quantitative trait loci. The within-family selection strongly favored by the animal model (Verrier et al., 1993) interacts with commercial incentives that result in the creation of dozens or even hundreds of full-sib progeny of successful AI bulls. Due to limited capacity for producing, genomically testing, and rearing young bulls, this often results in portfolios with very narrow genetic bases.

Lozada-Soto et al. (2024) recently used simulation to study the effects of exchanging germplasm across AI companies on population diversity and rates of genetic gain. Across many scenarios some general patterns emerged: germplasm exchange across programs does increase cumulative genetic gain, but several rounds of exchange are needed. The larger the group of bulls exchanged, the greater the effects on long-term genetic diversity. One-time exchanges are unlikely to make a notable difference in either genetic gain or accumulation of homozygosity. Although the exchange of germplasm between programs is desirable in principle, real-world effects of such exchanges are likely small.

Gene Editing

Because many recessive defects are caused by single-base mutations, gene editing has been proposed as a

potential solution to the increased risks associated with greater genetic homozygosity (Johnsson et al., 2019). However, the use of gene editing introduces a time lag between the original genotype and the edited genotype because of the time it takes to establish a cell line, perform the edits, screen for outcomes, and create a cloned individual that carries the edits. Because the current genetic trend is so high, it is difficult to close resulting gaps using conventional or genomic selection. Conceptually, a more intensive program that uses gene editing to both eliminate defects and introduce desirable alleles for economically important traits could overcome these problems (e.g., Hickey et al., 2016), although regulatory and technical challenges make commercialization challenging at this time. However, there is reason for optimism: it is now feasible to "stack" multiple edits in the same animal, and marketing approval has been granted for gene-edited cattle in several countries (Sonstegard et al., 2024). If the technology needed to enable in vitro breeding schemes (Goszczynski et al., 2019) comes to fruition, it would be more feasible to make routine use of gene editing in livestock breeding programs.

THE FUTURE OF POPULATION MONITORING AND MANAGEMENT

In the following discussion, "population monitoring" refers to the process of surveilling a population to quickly identify emerging genetic defects and developing haplotypes and gene tests to track them. "Population management" covers genetic testing capacity, designation and publication of carriers, and trade-related issues. Management of individual animals is the responsibility of dairy producers and AI companies and is discussed above.

Population Monitoring

We Need a Coordinated System. The current system for identifying and managing genetic defects in the United States, such as it is, is largely ad hoc and loosely coupled. A conceptual model of the existing framework shown in Figure 5, and its most notable features are the lack of a central point of contact for dairy producers and the absence of accountability. Each of the participants shown has a role on the identification and management of genetic defects, as described earlier, but there is no central coordination of these activities. This is problematic for several reasons: farmers do not know who to contact to report new defects, provide, and share biological samples with clear provenance and assignment of rights; researchers do not always know who to contact to request access to resources such as the Collaborative Dairy DNA Repository; industry personnel do not know who can speak with authority about defect names, haplotypes, or gene tests; nobody is responsible for protecting the freedom to operate of all participants in the system; and no party is accountable to dairy producers. This system has undeniably been functional, but it lacks the flexibility and responsiveness to meet today's needs. Farmers and breeders have also have to pay high prices for tests for putative causal variants, which they helped develop by providing phenotypes and biological samples. Charlier et al. (2008) were perhaps the first to propose that national programs be established for population monitoring and variant discovery, and such systems could avoid many problems of the current status quo.

One solution to this problem is shown in Figure 6, which outlines a potential national program for defect identification and management. Key features of this approach include a single point of contact, which simplifies reporting for dairy producers; shared governance, which protects the interests of all parties involved; structured access to scientific and data resources; properly managed agreements; and coordinated communications. This national program would operate in a precompetitive space and protect the freedom to operate of all participants by documenting samples, managing agreements, and ensuring that predatory institutions do not claim ownership of tools developed using community resources. It would also coordinate naming of genetic defects and communications with industry participants about the status of haplotypes and gene tests. In addition to these activities, this would be the logical place to locate a population surveillance program, which would involve routine sequencing of important animals in the population and reverse-screening (as will be discussed shortly) to monitor for emerging new defects before they have a chance to spread, functional validation of putative new recessive defects, and automated monitoring for detection and management of genetic risks. The goal is not to exclude historical participants—they are critical to the success of any system for identifying and tracking genetic defects—but to develop a framework that is accountable to dairy producers. It is critical that any new system is easy to use, that the system is not perceived as blaming individuals for biological processes over which they have no control, and that all stakeholders actively help disseminate accurate information.

In Canada, a large project on monitoring systems for rapidly identifying, understanding, and managing detrimental haplotypes in the dairy population has been funded, and a comprehensive system is under development. In addition to ongoing surveillance, this program will allow for monitoring of genomic diversity in the population. The project aims to develop a rapid-response feedback system in which detrimental haplotypes are identified before their frequency in the population increases. This feedback system will be implemented with the help of a

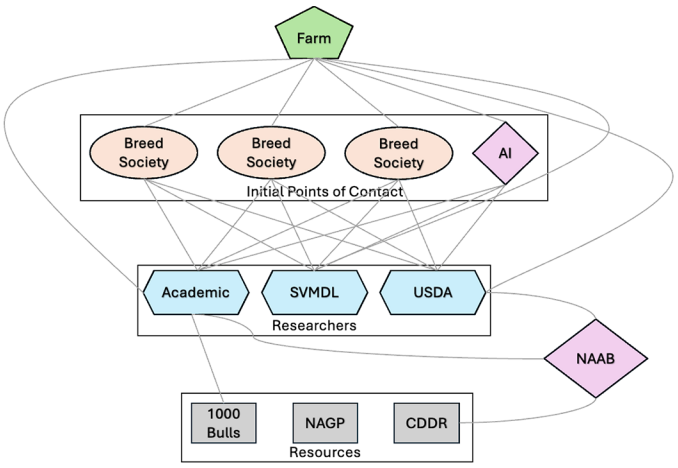

Figure 5. Current contact points and data flows for reports of genetic defects in the US dairy cattle population. Reports flow from farms to initial points of contact, who then may engage with researchers, who have access to resources needed for variant identification and haplotype development. 1000 Bulls = 1000 Bull Genomes Project, AI = genetics companies, CDDR = Collaborative Dairy DNA Repository, NAAB = National Association of Animal Breeders, NAGP = National Animal Germplasm Program, SVMDL = state veterinary medical diagnostic laboratories, and USDA = US Department of Agriculture.

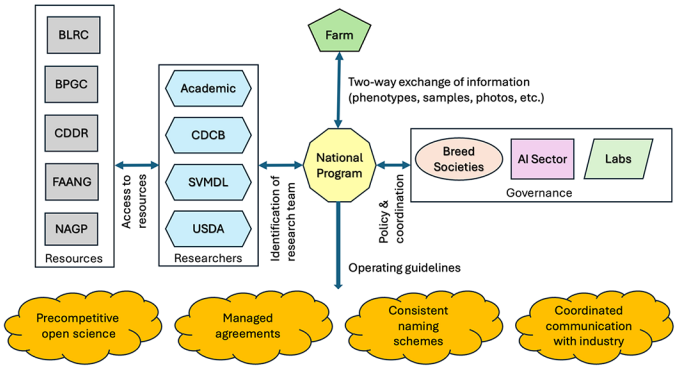

Figure 6. An alternative system for reporting of genetic defects in the United States that is centered on a national program, with governance from breed societies, the AI sector, and genotyping laboratories. This organization would operate in a precompetitive manner to ensure that the financial and intellectual property interests of all participants are protected. Providing a single point of contact for farmers encourages participation in the system and allows for uniform procedures. AI = genetics companies, BLRC = Bovine Long-Reads Consortium, BPGC = Bovine Pangenome Consortium, CDCB = Council on Dairy Cattle Breeding, CDDR = Collaborative Dairy DNA Repository, FAANG = Functional Annotation of Animal Genomes, NAGP = National Animal Germplasm Program, SVMDL = state veterinary medical diagnostic laboratories, and USDA = US Department of Agriculture.

centralized independent database, into which various organizations input data using application programming interface calls or similar methods. Simultaneously, patterns of inheritance (chromosomal segments inherited more frequently than others, as well as common recombination points within the genomes of the dairy population) using both actual and simulated data sets will be explored. Bulls used most frequently in the population and trios in which potential detrimental alleles are suspected will be sequenced using long-read technology on a routine basis. These results will be integrated to develop educational and extension materials for training of those involved in dairy production, stakeholders, and potentially the wider public. Lessons learned during the implementation of the Canadian monitoring system also can be incorporated into a US program.

Historical DNA Resources. The Collaborative Dairy DNA Repository (Ashwell and Van Tassell, 1999), which now includes materials originally deposited in the Dairy Bull DNA Repository (Da et al., 1994), was an essential resource for the development of genomic selection in the United States (e.g., VanRaden et al., 2009) because it provided DNA for high-reliability, progeny-tested bulls. It has also served as a valuable source of genetic material for use in causal variant discovery (McClure et al., 2013, 2014; Sonstegard et al., 2013; Adams et al., 2016; Null et al., 2017; Al-Khudhair et al., 2022, 2024b). The National Animal Germplasm Program, operated by USDA's Agricultural Research Service, maintains a collection of viable animal germplasm that includes 310,871 samples from 8,585 dairy animals. The 1000 Bull Genomes Project (Hayes and Daetwyler, 2019) and the Bovine Pangenome Consortium (https://bovinepangenome.github.io/) also use a community-based model to assemble data resources that are used to support many different projects.

Reverse Genetic Screening. As whole-genome DNA sequence databases grow, they can be used for population-wide screening to detect previously unknown defects. Reverse screens work by scanning the genomes of sequenced animals to identify differences between these individuals and the reference genome. The effects of these variants on gene function are assessed using a tool such as the SIFT ("sorting intolerant from tolerant") score (Ng and Henikoff, 2003), with which changes likely to produce changes in phenotypes associated with a gene are flagged. Several such studies have been reported in cattle (Charlier et al., 2016; Michot et al., 2016; Bourneuf et al., 2017; F. Besnard, Université Paris-Saclay, INRAE, Jouy-en-Josas, France, unpublished data), and their value is likely to grow as annotation of the bovine genome improves. These screens can be automated and run periodically as part of a national population monitoring program; their value increases as the database size grows. However, guidelines for the interpretation of genetic variants are needed to ensure that appropriate methods and standard terminology are used (e.g., Richards et al., 2015), to minimize the likelihood of false positives.

Routine Sequencing of Genetically Important Animals. In addition to reverse screens of the population in general, genetically important animals, such as AI bulls

that are being used as sires of sons, should be sequenced to identify potential harmful mutations before they are spread throughout the cow population. This is not a hypothetical situation; the Holstein bull Pawnee Farm Arlinda Chief (040HO02025; HOUSA000001427381) is the founder for HH1, an embryonic lethal mutation in the gene *APAF1* (Adams et al., 2016). Chief produced 16,000 daughters, 500,000 granddaughters, and more than 2 million great-granddaughters. The high rates of embryo transfer from genetically elite females in current commercial breeding programs means that screening of bulls alone is not sufficient to protect the health of the population, and influential embryo donors should also be sequenced. Information about new putative deleterious mutations will be shared back to the animal owners so they can make appropriate management decisions. However, the likelihood of false positive results is high, and sequencing efforts should be part of an integrated system that includes functional validation of putative causal variants.

Functional Validation. A notable challenge to effective population management is the lack of functional validation of putative causal variants, which are typically identified using a combination of statistical and bioinformatics approaches. In some cases, a clear biological relationship exists between the variant identified and the phenotype (e.g., Shanks et al., 1984; Schwenger et al., 1993), but in others, such as haplotypes affecting fertility, mechanisms are sometimes only statistical associations, with limited biological evidence underlying the correlation. This is driven in part by the relatively low quality of the annotation of the bovine genome (Rosen et al., 2020), and in part by the high cost of performing functional genomics studies in large ruminants (e.g., Liu et al., 2022). The functions of most genes in the bovine are known by homology with other species, such as the mouse, but cows are not large mice. Ortega et al. (2022) recently demonstrated that gene editing can be used to confirm the functional effects of putative causal variants associated with haplotypes affecting fertility. A similar approach should be used in concert with organoids (e.g., Lee et al., 2021; H. Tinning, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK, unpublished data) or other tissue culture systems to validate putative variants that act later in life, and is much less expensive than working with live animals. Such research could be supported as part of the "precompetitive open science" process shown in Figure 6, and considered in both the "identification of research team" and "access to resources" stages of project development. In the absence of functional validation, putative causal variants are just that—speculation.

Automated Reporting of Genetic Risks. The cost of whole-genome sequencing means that it will likely be used routinely only for high-valued animals, such as top-ranking young bulls or elite heifers used as embryo donors. However, the number of genotyped animals in North America continues to increase, and haplotypes can be monitored in an automated fashion, raising a signal when specific genomic regions are associated with lower conception rates, higher abortion rates, or increased calf mortality rates. In the United States, the Council on Dairy Cattle Breeding automatically screens haplotypes to identify genomic regions showing a deficiency of homozygotes using the method of VanRaden et al. (2011). However, a more comprehensive system that routinely estimates haplotype effects for embryonic loss, abortion, and stillbirth or early calf mortality could detect additional loci with important effects, such as incompletely penetrant alleles, so that they can be investigated.

Population Management

Availability of Genetic Tests. Although laboratory tests are available for many genetic disorders, not every test is available at every facility. This reflects both operational costs and business relationships of laboratories and associated companies. The adoption of timely genetic testing is affected when licensing costs are high because of encumbrance with intellectual property, particularly in low- and middle-income countries. Research findings on genetic defects also are sometimes kept intentionally secret to provide some countries with competitive advantages over others when it comes to testing. As a result, farmers and AI organizations are often reluctant to cooperate in research efforts because they feel they are expected to provide the materials needed to develop tests for free, only to be charged for them later. Although there are real costs to laboratory testing, the growing number of available tests makes comprehensive screening prohibitively expensive. Laboratories also may be pressured to exclusively license intellectual property to differentiate their services from competitors, and novel defects can be promoted as essential management tools even when associated risks are minimal.

There is a clear need for a policy, with which all industry participants comply, about the communication and publication of genetic information. The advertisement of genetic tests before official national or international recognition of a novel genetic defect causes considerable problems for the export market by causing confusion and anxiety on the part of policymakers. Widespread promotion of new tests gives the impression that a defect is more widespread or severe than it is, particularly in places where genetic defects are poorly understood. Heightened concern attracts the attention of trade authorities, which can lead to the swift inclusion of new defects in import regulations and genetic requirements.

Ideally, the advertisement of new testing services would follow the publication of information about prevalence, phenotypes, and structure of defects by reputable national or international organizations.

Defects Identified Using Only Genomic Data. Newly discovered defects for which no gene tests yet exist can be tracked using only genomic data, although such tests may not be accepted as valid when exporting semen or embryos. Cole et al. (2009) showed that approximate location of causal variants for Mendelian traits (BLAD, CVM, and red coat color) can be identified using only genotypes and phenotypes. The deficiency-of-homozygotes approach (VanRaden et al., 2011) described earlier identifies defects using only genotype information, and requires no phenotypes, although phenotypes are useful for validation. Biscarini et al. (2016) showed that SNP genotypes may be used to track defects with high accuracy and low misclassification rates.

How Are Haplotypes Different from Gene Tests? The critical difference between haplotype and gene tests is that haplotypes track segments of DNA presumed to contain the causal variant, whereas the gene test interrogates the genotype at the causal location directly. This means that the gene test should have higher sensitivity and specificity than a corresponding haplotype test. For example, the haplotype used by AGIL and the Council on Dairy Cattle Breeding to track the HH2 haplotype has changed over time (Ortega et al., 2022), and 2 cholesterol deficiency haplotypes have identical SNP fingerprints, but only 1 carries the causal variant. A related source of confusion is that original haplotype names, such as HH2, often are retained even after a gene test is available and a diagnostic SNP is widely available on genotyping arrays. This is problematic because haplotype calls can sometimes change, whereas gene test results should not, and it can be difficult for farmers and international authorities to understand when an animal has only a haplotype call and when they have an actual gene test. As a result, test results are sometimes interpreted and used inappropriately.

Designation and Publication of Carrier Status. In the past, genetic information was primarily distributed through bull catalogs, certified pedigrees, and other trusted sources. With the rise of on-farm genomic testing, however, laboratories now play a much more prominent role in the communication of genomic values. Through sheer volume of product, they have effectively become the primary voice in the dissemination and interpretation of genomic information, especially regarding genetic defects. There is currently no national or international body responsible for the standardization and coordination of genetic defect carrier statuses. As discussed previously, purebred dairy cattle associations do coordinate some harmonization across countries within breeds, but a notable lack of standardization exists across breeds and different sectors of the industry. The fragmented nature of data delivery and lack of standardization have serious consequences; different companies present the same data in different ways, creating confusion for both producers and global authorities. This inconsistency, combined with the complexity of the information, often leads to anxiety and misunderstandings, especially when critical decisions about genetic defects are involved. This, in turn, often leads to a blanket approach where carrier animals are not managed but culled, and germplasm of carrier animals is restricted from export.

An additional complication is the varying prevalence status of genetic defects. Genetic defects can linger in official trade regulations long after they have been effectively eradicated from a population. These regulations often serve as barriers to trade, but governments are often reluctant to change them because populations in other countries can act as reservoirs for defects that have been eliminated locally. The importation of germplasm or live cattle also can bring defects into countries where genomic testing is not routinely available, and testing requirements help to protect local populations. It can be difficult to prove that a defect is not segregating in a particular population, particularly as its frequency decreases, which increases the temptation to use ever-growing lists of genetic defects as trade barriers. For example, some countries require that imported animals and germplasm have negative tests for factor XI deficiency (Gentry and Black, 1980), even when it has effectively been eliminated from most populations and few laboratories even offer a test for the condition. In practice, this requirement limits access to high-quality genetics without clear evidence that it protects local cattle against genetic diseases.

CONCLUSIONS

Congenital defects, whether genetic in nature or the result of errors in development, have been an unfortunate fact of life since cattle were domesticated. The development of the first generation of effective genetic rankings in the 1960s laid the foundation for today's extremely efficient genomic selection programs and produced bulls such as Carlin-M Ivanhoe Bell (007HO00543; HOUSA000001667366) that drove the Holstein breed forward and, unfortunately, spread many undesirable alleles through the population. The global dissemination of these genes, and others, poses a challenge to all dairy cattle breeds. Consumers and the public are increasingly concerned about the welfare of the animals used to produce their food, and social license to operate depends on acceptance of industry practices. The new generation of genomic tools, paired with computerized mating programs, provide the tools needed to avoid carrier-to-

carrier matings, but, as Jay Lush presciently noted, "Selection is abundantly able to make an undesired gene rare but is almost powerless to eliminate it entirely from the population" (Lush, 1945, p. 124). Perhaps gene editing tools will one day allow for the elimination of all known deleterious alleles in a single generation of selection, but that may be far in the future. In the interim, the North American dairy industry needs to build systems that help manage the risks posed by intensive within-family selection in populations with small effective population sizes.

NOTES

Christine F. Baes gratefully acknowledges financial support by NSERC (Ottawa, Canada) and Agriculture and Agri-Food Canada (Ottawa, Canada), and by additional contributions from Dairy Farmers of Canada (Ottawa, Canada), Lactanet (Guelph, Canada), and the Canadian Dairy Commission (Ottawa, Canada) under the Agri-Science Clusters Initiative DC4. Christian Maltecca acknowledges support from Select Sires Inc. (Plain City, OH) and Holstein Association USA Inc. (Brattleboro, VT) for this work. Paul M. VanRaden was supported by appropriated project 8042-31000-002-00-D, "Improving Dairy Animals by Increasing Accuracy of Genomic Prediction, Evaluating New Traits, and Redefining Selection Goals" of the USDA Agricultural Research Service (Beltsville, MD). Figure 1 is based on information from the Online Mendelian Inheritance in Animals database (https://omia.org/home/); those data were made available by software support from the Sydney Informatics Hub (Newtown, Australia), funded by the Ronald Bruce Anstee bequest to the Sydney School of Veterinary Science (Camperdown, Australia) for the Anstee Hub for Inherited Diseases in Animals (AHIDA). Supplemental material for this article is available at https://doi.org/10.17605/OSF.IO/A8DPH. Supplemental Table S2 includes the most recent version of web pages stored in the Internet Archive as of November 20, 2024 (the date of submission of the manuscript). Because no human or animal subjects were used, this analysis did not require approval by an Institutional Animal Care and Use Committee or Institutional Review Board. Mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the US Department of Agriculture. The USDA is an equal opportunity provider and employer. The authors have not stated any conflicts of interest.

Nonstandard abbreviations used: AGIL = Animal Genomics and Improvement Laboratory; AI = artificial insemination; BLAD = bovine leukocyte adhesion deficiency; BLIRD = bovine lymphocyte intestinal retention defect; CVM = complex vertebral malformation; DUMPS = deficiency of uridine monophosphate synthase; HH1–HH5 = Holstein Haplotypes 1–5; ICAR = International Committee for Animal Recording; Interbull = International Bull Evaluation Service; JH1 = Jersey Haplotype 1; l'ONAB = L'Observatoire National des Anomalies Bovines; NAAB = National Association of Animal Breeders; OMIM = Online Mendelian Inheritance in Man; WHFF = World Holstein Friesian Federation.

REFERENCES

Adams, H. A., T. S. Sonstegard, P. M. VanRaden, D. J. Null, C. P. VanTassell, D. M. Larkin, and H. A. Lewin. 2016. Identification of a nonsense mutation in *APAF1* that is likely causal for a decrease in reproductive efficiency in Holstein dairy cattle. J. Dairy Sci. 99:6693–6701. https://doi.org/10.3168/jds.2015-10517.

Agerholm, J. S., A. Basse, and K. Christensen. 1993. Investigations on the occurrence of hereditary diseases in the Danish cattle population 1989–1991. Acta Vet. Scand. 34:245–253. https://doi.org/10.1186/BF03548188.

Agerholm, J. S., C. Bendixen, O. Andersen, and J. Arnbjerg. 2001. Complex vertebral malformation in Holstein calves. J. Vet. Diagn. Invest. 13:283–289. https://doi.org/10.1177/104063870101300401.

Agerholm, J. S., F. McEvoy, and J. Arnbjerg. 2006. Brachyspina syndrome in a Holstein calf. J. Vet. Diagn. Invest. 18:418–422. https://doi.org/10.1177/104063870601800421.

Agerholm, J. S., F. J. McEvoy, F. Menzi, V. Jagannathan, and C. Drögemüller. 2016. A *CHRNB1* frameshift mutation is associated with familial arthrogryposis multiplex congenita in Red dairy cattle. BMC Genomics 17:479. https://doi.org/10.1186/s12864-016-2832-x.

Al-Khudhair, A., D. J. Null, J. B. Cole, C. W. Wolfe, D. J. Steffen, and P. M. VanRaden. 2022. Inheritance of a mutation causing neuropathy with splayed forelimbs in Jersey cattle. J. Dairy Sci. 105:1338–1345. https://doi.org/10.3168/jds.2021-20600.

Al-Khudhair, A., P. M. VanRaden, D. J. Null, M. Neupane, M. C. McClure, and C. D. Dechow. 2024b. New mutation within a common haplotype is associated with calf muscle weakness in Holsteins. J. Dairy Sci. 107:3768–3779. https://doi.org/10.3168/jds.2023-24121.

Al-Khudhair, A. S., J. B. Cole, P. M. VanRaden, D. J. Null, J. L. Hutchison, and S. M. Hubbard. 2024a. AIP Research Report Genomic5 (8–24): Haplotype tests for economically important traits of dairy cattle. Accessed Sep. 4, 2024. https://www.ars.usda.gov/ARSUserFiles/80420530/Publications/ARR/AIP%20RESEARCH%20REPORT%20GENOMIC6%20(8-24).pdf.

Ashwell, M. S., and C. P. Van Tassell. 1999. The cooperative dairy DNA repository: A new resource for quantitative trait loci detection and verification. J. Dairy Sci. 82(Suppl. 1):360 (Abstr.).

Babcock, E. B., and R. E. Clausen. 1918. Genetics in Relation to Agriculture. McGraw-Hill Book Company Inc., New York, NY.

Becker, R. B., C. J. Wilcox, and W. R. Pritchard. 1961. Crampy or progressive posterior paralysis in mature cattle. J. Dairy Sci. 44:542–547. https://doi.org/10.3168/jds.S0022-0302(61)89774-9.

Bengtsson, C., H. Stålhammar, J. R. Thomasen, W. F. Fikse, E. Strandberg, and S. Eriksson. 2023. Mating allocations in Holstein combining genomic information and linear programming optimization at the herd level. J. Dairy Sci. 106:3359–3375. https://doi.org/10.3168/jds.2022-22926.

Bérodier, M., P. Berg, T. Meuwissen, D. Boichard, M. Brochard, and V. Ducrocq. 2021. Improved dairy cattle mating plans at herd level using genomic information. Animal 15:100016. https://doi.org/10.1016/j.animal.2020.100016.

Besnard, F., A. Guintard, C. Grohs, L. Guzylack-Piriou, M. Cano, C. Escouflaire, C. Hozé, H. Leclerc, T. Buronfosse, L. Dutheil, J. Jourdain, A. Barbat, S. Fritz, M.-C. Deloche, A. Remot, B. Gaussères, A. Clément, M. Bouchier, E. Contat, A. Relun, V. Plassard, J. Rivière, C. Péchoux, M. Vilotte, C. Eche, C. Kuchly, M. Charles, A. Boulling, G. Viard, S. Minéry, S. Barbey, C. Birbes, C. Danchin-Burge,

F. Launay, S. Mattalia, A. Allais-Bonnet, B. Ravary, Y. Millemann, R. Guatteo, C. Klopp, C. Gaspin, C. Iampietro, C. Donnadieu, D. Milan, M.-A. Arcangioli, M. Boussaha, G. Foucras, D. Boichard, and A. Capitan. 2024. Massive detection of cryptic recessive genetic defects in dairy cattle mining millions of life histories. Genome Biol. 25:248. https://doi.org/10.1186/s13059-024-03384-7.

Besnard, F., H. Leclerc, M. Boussaha, C. Grohs, N. Jewell, A. Pinton, H. Barasc, J. Jourdain, M. Femenia, L. Dorso, B. Strugnell, T. Floyd, C. Danchin, R. Guatteo, D. Cassart, X. Hubin, S. Mattalia, D. Boichard, and A. Capitan. 2023. Detailed analysis of mortality rates in the female progeny of 1,001 Holstein bulls allows the discovery of new dominant genetic defects. J. Dairy Sci. 106:439–451. https://doi.org/10.3168/jds.2022-22365.

Bick, D., S. L. Bick, D. P. Dimmock, T. A. Fowler, M. J. Caulfield, and R. H. Scott. 2021. An online compendium of treatable genetic disorders. Am. J. Med. Genet. C. Semin. Med. Genet. 187:48–54. https://doi.org/10.1002/ajmg.c.31874.

Bickhart, D. M., B. D. Rosen, S. Koren, B. L. Sayre, A. R. Hastie, S. Chan, J. Lee, E. T. Lam, I. Liachko, S. T. Sullivan, J. N. Burton, H. J. Huson, J. C. Nystrom, C. M. Kelley, J. L. Hutchison, Y. Zhou, J. Sun, A. Crisà, F. A. Ponce de León, J. C. Schwartz, J. A. Hammond, G. C. Waldbieser, S. G. Schroeder, G. E. Liu, M. J. Dunham, J. Shendure, T. S. Sonstegard, A. M. Phillippy, C. P. Van Tassell, and T. P. L. Smith. 2017. Single-molecule sequencing and chromatin conformation capture enable de novo reference assembly of the domestic goat genome. Nat. Genet. 49:643–650. https://doi.org/10.1038/ng.3802.

Biscarini, F., H. Schwarzenbacher, H. Pausch, E. L. Nicolazzi, Y. Pirola, and S. Biffani. 2016. Use of SNP genotypes to identify carriers of harmful recessive mutations in cattle populations. BMC Genomics 17:857. https://doi.org/10.1186/s12864-016-3218-9.

Bjelland, D. W., K. A. Weigel, N. Vukasinovic, and J. D. Nkrumah. 2013. Evaluation of inbreeding depression in Holstein cattle using whole-genome SNP markers and alternative measures of genomic inbreeding. J. Dairy Sci. 96:4697–4706. https://doi.org/10.3168/jds.2012-6435.

Bogart, R. 1959. Improvement of Livestock. The Macmillan Company, New York, NY.

Bourdon, R. M. 1999. Understanding Animal Breeding. 2nd ed. Prentice Hall, Englewood Cliffs, NJ.

Bourneuf, E., P. Otz, H. Pausch, V. Jagannathan, P. Michot, C. Grohs, G. Piton, S. Ammermüller, M.-C. Deloche, S. Fritz, H. Leclerc, C. Péchoux, A. Boukadiri, C. Hozé, R. Saintilan, F. Créchet, M. Mosca, D. Segelke, F. Guillaume, S. Bouet, A. Baur, A. Vasilescu, L. Genestout, A. Thomas, A. Allais-Bonnet, D. Rocha, M.-A. Colle, C. Klopp, D. Esquerré, C. Wurmser, K. Flisikowski, H. Schwarzenbacher, J. Burgstaller, M. Brügmann, E. Dietschi, N. Rudolph, M. Freick, S. Barbey, G. Fayolle, C. Danchin-Burge, L. Schibler, B. Bed'Hom, B. J. Hayes, H. D. Daetwyler, R. Fries, D. Boichard, D. Pin, C. Drögemüller, and A. Capitan. 2017. Rapid discovery of *de novo* deleterious mutations in cattle enhances the value of livestock as model species. Sci. Rep. 7:11466. https://doi.org/10.1038/s41598-017-11523-3.

Bovine Genome Sequencing and Analysis Consortium. 2009. The genome sequence of taurine cattle: A window to ruminant biology and evolution. Science 324:522–528. https://doi.org/10.1126/science.1169588.

Brochard, M., D. Boichard, A. Capitan, G. Fayolle, S. Fritz, L. Nicod, and J. M. Vacelet. 2018. pANO, le risque d'anomalie létale pour les produits d'accouplements: Principe et utilisation en race Montbéliarde sur la zone GEN'IAtest. Renc. Rech. Ruminants. 24:114–117.

Brown Swiss Association. 2021. Genetic Conditions in Brown Swiss Cattle. Accessed Sep. 3, 2024. https://www.brownswissusa.com/Portals/0/Documents/Breed/abnormality%20pamphlet%202021.pdf.

Caldecott, K. W. 2022. DNA single-strand break repair and human genetic disease. Trends Cell Biol. 32:733–745. https://doi.org/10.1016/j.tcb.2022.04.010.

Charlier, C. 2016. The role of mobile genetic elements in the bovine genome. Plant Anim. Genome XXIV Conf. Abstr. W636.

Charlier, C., J. S. Agerholm, W. Coppieters, P. Karlskov-Mortensen, W. Li, G. de Jong, C. Fasquelle, L. Karim, S. Cirera, N. Cambisano, N. Ahariz, E. Mullaart, M. Georges, and M. Fredholm. 2012. A deletion in the bovine *FANCI* gene compromises fertility by causing fetal death and brachyspina. PLoS One 7:e43085. https://doi.org/10.1371/journal.pone.0043085.

Charlier, C., W. Coppieters, F. Rollin, D. Desmecht, J. S. Agerholm, N. Cambisano, E. Carta, S. Dardano, M. Dive, C. Fasquelle, and J. C. Frennet. 2008. Highly effective SNP-based association mapping and management of recessive defects in livestock. Nat. Genet. 40:449–454. https://doi.org/10.1038/ng.96.

Charlier, C., W. Li, C. Harland, M. Littlejohn, W. Coppieters, F. Creagh, S. Davis, T. Druet, P. Faux, F. Guillaume, L. Karim, M. Keehan, N. K. Kadri, N. Tamma, R. Spelman, and M. Georges. 2016. NGS-based reverse genetic screen for common embryonic lethal mutations compromising fertility in livestock. Genome Res. 26:1333–1341. https://doi.org/10.1101/gr.207076.116.

Cole, J. B. 2015. A simple strategy for managing many recessive disorders in a dairy cattle breeding program. Genet. Sel. Evol. 47:94. https://doi.org/10.1186/s12711-015-0174-9.

Cole, J. B. 2017. A dairy calf DNA biobank for the discovery of new recessive genetic disorders. J. Anim. Sci. 95(Suppl. 4):83(Abstr. 169).

Cole, J. B. 2024. Perspective: Can we actually do anything about inbreeding? J. Dairy Sci. 107:643–648. https://doi.org/10.3168/jds.2023-23958.

Cole, J. B., D. J. Null, and P. M. VanRaden. 2016. Phenotypic and genetic effects of recessive haplotypes on yield, longevity, and fertility. J. Dairy Sci. 99:7274–7288. https://doi.org/10.3168/jds.2015-10777.

Cole, J. B., J. W. Dürr, and E. L. Nicolazzi. 2021. Invited review: The future of selection decisions and breeding programs: What are we breeding for, and who decides? J. Dairy Sci. 104:5111–5124. https://doi.org/10.3168/jds.2020-19777.

Cole, J. B., P. M. VanRaden, J. R. O'Connell, C. P. Van Tassell, T. S. Sonstegard, R. D. Schnabel, J. F. Taylor, and G. R. Wiggans. 2009. Distribution and location of genetic effects for dairy traits. J. Dairy Sci. 92:2931–2946. https://doi.org/10.3168/jds.2008-1762.

Cole, L. J. 1925. Chapter III: Inheritance in cattle. In Cattle Breeding: Proceedings of the Scottish Cattle Breeding Conference. G. F. Finlay, ed. Oliver and Boyd, Edinburgh, UK.

Condello, G. 2024. Investigating the genetics of bovine spastic syndrome (crampy) in Canadian Holstein dairy cattle. MS thesis. Department of Animal Biosciences, University of Guelph, Ontario, Canada. https://hdl.handle.net/10214/28650.

Cooper, T. A., G. R. Wiggans, D. J. Null, J. L. Hutchison, and J. B. Cole. 2014. Genomic evaluation, breed identification, and discovery of a haplotype affecting fertility for Ayrshire dairy cattle. J. Dairy Sci. 97:3878–3882. https://doi.org/10.3168/jds.2013-7427.

Cooper, T. A., G. R. Wiggans, P. M. VanRaden, J. L. Hutchison, J. B. Cole, and D. J. Null. 2013. Genomic evaluation of Ayrshire dairy cattle and new haplotypes affecting fertility and stillbirth in Holstein, Brown Swiss and Ayrshire breeds. J. Dairy Sci. 96(E-Suppl. 1):74(Poster T206).

Cotton, J. 1989. Some guidelines should you find a defective calf. Angus J. 10:166–168.

Da, Y., M. Ron, A. Yanai, M. Band, R. E. Everts, D. W. Heyen, J. I. Weller, G. R. Wiggans, and H. A. Lewin. 1994. The dairy bull DNA repository: A resource for mapping quantitative trait loci. Proc. 5th World Congress on Genetics Applied to Livestock Production, Guelph, Ontario, Canada, Aug. 7–12, 1994. 21:229–232.

Daetwyler, H. D., A. Capitan, H. Pausch, P. Stothard, R. van Binsbergen, R. F. Brøndum, X. Liao, A. Djari, S. C. Rodriguez, C. Grohs, D. Esquerré, O. Bouchez, M.-N. Rossignol, C. Klopp, D. Rocha, S. Fritz, A. Eggen, P. J. Bowman, D. Coote, A. J. Chamberlain, C. Anderson, C. P. VanTassell, I. Hulsegge, M. E. Goddard, B. Guldbrandtsen, M. S. Lund, R. F. Veerkamp, D. A. Boichard, R. Fries, and B. J. Hayes. 2014. Whole-genome sequencing of 234 bulls facilitates mapping of monogenic and complex traits in cattle. Nat. Genet. 46:858–865. https://doi.org/10.1038/ng.3034.

Davenport, K. M., D. M. Bickhart, K. Worley, S. C. Murali, M. Salavati, E. L. Clark, N. E. Cockett, M. P. Heaton, T. P. L. Smith, B. M. Murdoch, and B. D. Rosen. 2022. An improved ovine reference genome assembly to facilitate in-depth functional annotation of the sheep genome. Gigascience 11:giab096. https://doi.org/10.1093/gigascience/giab096.

Dechow, C. D., E. Frye, and F. P. Maunsell. 2022. Identification of a putative haplotype associated with recumbency in Holstein calves. JDS Commun. 3:412–415. https://doi.org/10.3168/jdsc.2022-0224.

Drögemüller, C., J. Tetens, S. Sigurdsson, A. Gentile, S. Testoni, K. Lindblad-Toh, and T. Leeb. 2010. Identification of the bovine arachnomelia mutation by massively parallel sequencing implicates sulfite oxidase (*SUOX*) in bone development. PLoS Genet. 6:e1001079. https://doi.org/10.1371/journal.pgen.1001079.

Duchesne, A., M. Gautier, S. Chadi, C. Grohs, S. Floriot, Y. Gallard, G. Caste, A. Ducos, and A. Eggen. 2006. Identification of a doublet missense substitution in the bovine *LRP4* gene as a candidate causal mutation for syndactyly in Holstein cattle. Genomics 88:610–621. https://doi.org/10.1016/j.ygeno.2006.05.007.

el-Hamidi, M., H. W. Leipold, J. G. E. Vestweber, and G. Saperstein. 1989. Spinal muscular atrophy in Brown Swiss calves. Zentralbl. Veterinarmed. A 36:731–738. https://doi.org/10.1111/j.1439-0442.1989.tb00786.x.

Eldridge, F. E., W. H. Smith, and W. M. McLeod. 1951. Syndactylism in Holstein-Friesian cattle. J. Hered. 42:241–250. https://doi.org/10.1093/oxfordjournals.jhered.a106217.

Ernle, R. E. 1962. English Farming, Past and Present. New (6th) ed. Quadrangle Books, Chicago, IL.

Fritz, S., A. Capitan, A. Djari, S. C. Rodriguez, A. Barbat, A. Baur, C. Grohs, B. Weiss, M. Boussaha, D. Esquerré, C. Klopp, D. Rocha, and D. Boichard. 2013. Detection of haplotypes associated with prenatal death in dairy cattle and identification of deleterious mutations in *GART, SHBG* and *SLC37A2*. PLoS One 8:e65550. https://doi.org/10.1371/journal.pone.0065550.

Fritz, S., C. Hoze, E. Rebours, A. Barbat, M. Bizard, A. Chamberlain, C. Escouflaire, C. Vander Jagt, M. Boussaha, C. Grohs, A. Allais-Bonnet, M. Philippe, A. Vallée, Y. Amigues, B. J. Hayes, D. Boichard, and A. Capitan. 2018. An initiator codon mutation in *SDE2* causes recessive embryonic lethality in Holstein cattle. J. Dairy Sci. 101:6220–6231. https://doi.org/10.3168/jds.2017-14119.

Gebreyesus, G., G. Sahana, A. Christian Sørensen, M. S. Lund, and G. Su. 2020. Novel approach to incorporate information about recessive lethal genes increases the accuracy of genomic prediction for mortality traits. Heredity 125:155–166. https://doi.org/10.1038/s41437-020-0329-5.

Gentile, A., and S. Testoni. 2006. Inherited disorders of cattle: A selected review. Slov. Vet. Res. 43:17–29.

Gentry, P. A., and W. D. Black. 1980. Prevalence and inheritance of Factor XI (plasma thromboplastin antecedent) deficiency in cattle. J. Dairy Sci. 63:616–620. https://doi.org/10.3168/jds.S0022-0302(80)82980-8.

Goszczynski, D. E., H. Cheng, S. Demyda-Peyrás, J. F. Medrano, J. Wu, and P. J. Ross. 2019. *In vitro* breeding: Application of embryonic stem cells to animal production. Biol. Reprod. 100:885–895. https://doi.org/10.1093/biolre/ioy256.

Gozdek, M., S. Mucha, A. Prostek, and T. Sadkowski. 2024. Selected monogenic genetic diseases in Holstein cattle—A review. Genes (Basel) 15:1052. https://doi.org/10.3390/genes15081052.

Grohs, C., A. Duchesne, S. Floriot, M. C. Deloche, D. Boichard, A. Ducos, and C. Danchin-Burge. 2016. L'Observatoire National des Anomalies Bovines, son action et ses résultats pour une aide efficace à la gestion des anomalies génétiques. INRA Prod. Anim. 29:307–318. https://doi.org/10.20870/productions-animales.2016.29.5.2998.

Guinan, F. L., G. R. Wiggans, H. D. Norman, J. W. Dürr, J. B. Cole, C. P. Van Tassell, I. Misztal, and D. Lourenço. 2023. Changes in genetic trends in US dairy cattle since the implementation of genomic selection. J. Dairy Sci. 106:1110–1129. https://doi.org/10.3168/jds.2022-22205.

Guyer, M. F. 1927. Being Well-Born: An Introduction to Heredity and Eugenics. 2nd ed. The Bobbs-Merrill Company, Indianapolis, IN.

Häfliger, I. M., F. R. Seefried, M. Spengeler, and C. Drögemüller. 2021. Mining massive genomic data of two Swiss Braunvieh cattle populations reveals six novel candidate variants that impair reproductive success. Genet. Sel. Evol. 53:95. https://doi.org/10.1186/s12711-021-00686-3.

Häfliger, I. M., M. Spengeler, F. R. Seefried, and C. Drögemüller. 2022. Four novel candidate causal variants for deficient homozygous haplotypes in Holstein cattle. Sci. Rep. 12:5435. https://doi.org/10.1038/s41598-022-09403-6.

Hafner, A., E. Dahme, G. Obermaier, P. Schmidt, and G. Dirksen. 1993. Spinal dysmyelination in new-born Brown Swiss × Braunvieh calves. Zentralbl. Veterinarmed. B 40:413–422. https://doi.org/10.1111/j.1439-0450.1993.tb00158.x.

Hayes, B. J., and H. D. Daetwyler. 2019. 1000 Bull Genomes Project to map simple and complex genetic traits in cattle: applications and outcomes. Annu. Rev. Anim. Biosci. 7:89–102. https://doi.org/10.1146/annurev-animal-020518-115024.

Herman, H. A. 1981. Improving Cattle by the Millions: NAAB and the Development and Worldwide Application of Artificial Insemination. University of Missouri Press, Columbia, MO.

Hickey, J. M., C. Bruce, A. Whitelaw, and G. Gorjanc. 2016. Promotion of alleles by genome editing in livestock breeding programmes. J. Anim. Breed. Genet. 133:83–84. https://doi.org/10.1111/jbg.12206.

Hjortø, L., M. Henryon, H. Liu, P. Berg, J. R. Thomasen, and A. C. Sørensen. 2021. Pre-selection against a lethal recessive allele in breeding schemes with optimum-contribution selection or truncation selection. Genet. Sel. Evol. 53:75. https://doi.org/10.1186/s12711-021-00669-4.

Holstein Association USA. 2024. Constitution and By-Laws as of June 27, 2024. Holstein Association USA, Brattleboro, VT. Accessed Nov. 14, 2024. https://www.holsteinusa.com/pdf/print_material/bylaws.pdf.

Hozé, C., C. Escouflaire, M. Mesbah-Uddin, A. Barbat, M. Boussaha, M. C. Deloche, D. Boichard, S. Fritz, and A. Capitan. 2020. Short communication: A splice site mutation in *CENPU* is associated with recessive embryonic lethality in Holstein cattle. J. Dairy Sci. 103:607–612. https://doi.org/10.3168/jds.2019-17056.

Isik, F., J. Holland, and C. Maltecca. 2017. Genetic Data Analysis for Plant and Animal Breeding. Springer International Publishing AG, Cham, Switzerland.

Joerg, H., H. R. Fries, E. Meijerink, and G. F. Stranzinger. 1996. Red coat color in Holstein cattle is associated with a deletion in the *MSHR* gene. Mamm. Genome 7:317–318. https://doi.org/10.1007/s003359900090.

Johnsson, M., R. C. Gaynor, J. Jenko, G. Gorjanc, D.-J. de Koning, and J. M. Hickey. 2019. Removal of alleles by genome editing (RAGE) against deleterious load. Genet. Sel. Evol. 51:14. https://doi.org/10.1186/s12711-019-0456-8.

Jones, D. F. 1925. Genetics in Plant and Animal Improvement. John Wiley & Sons Inc., New York, NY.

Kelson, V. C., J. N. Kiser, K. M. Davenport, E. M. Suarez, B. M. Murdoch, and H. L. Neibergs. 2024. Genomic regions associated with embryonic loss in primiparous Holstein cows. Front. Anim. Sci. 5:1458088. https://doi.org/10.3389/fanim.2024.1458088.

Kendrick, J. W., P. C. Kennedy, and C. Stormont. 1957. Adenohypophyseal aplasia, an inherited defect associated with abnormal gestation in Guernsey cattle. Cornell Vet. 47:160–178.

Kipp, S., D. Segelke, F. Reinhardt, R. Reents, S. Schierenbeck, C. Wurmser, H. Pausch, R. Fries, G. Thaller, J. Tetens, J. Pott, M. Piechotta, and W. Grünberg. 2015. A new Holstein haplotype affecting calf survival. Interbull Bull. 49:49–53.

Krebs, S., I. Medugorac, S. Röther, K. Strässer, and M. Förster. 2007. A missense mutation in the 3-ketodihydrosphingosine reductase *FVT1* as candidate causal mutation for bovine spinal muscular atrophy. Proc. Natl. Acad. Sci. USA 104:6746–6751. https://doi.org/10.1073/pnas.0607721104.

Kunz, E., S. Rothammer, H. Pausch, H. Schwarzenbacher, F. R. Seefried, K. Matiasek, D. Seichter, I. Russ, R. Fries, and I. Medugorac. 2016. Confirmation of a non-synonymous SNP in *PNPLA8* as a candidate causal mutation for Weaver syndrome in Brown Swiss cattle. Genet. Sel. Evol. 48:21. https://doi.org/10.1186/s12711-016-0201-5.

Lamb, R. C., C. W. Arave, and J. L. Shupe. 1971. Semi-lethal abnormality of limbs in Jersey cattle. J. Dairy Sci. 54:544–546. https://doi.org/10.3168/jds.S0022-0302(71)85884-8.

Lamb, R. C., C. W. Arave, and J. L. Shupe. 1976. Inheritance of limber legs in Jersey cattle. J. Hered. 67:241–244. https://doi.org/10.1093/oxfordjournals.jhered.a108718.

Lasley, J. F. 1978. Genetics of Livestock Improvement. 3rd ed. Prentice-Hall Inc., Englewood Cliffs, NJ.

Lawlor, T. J., P. M. VanRaden, D. Null, J. Levisee, and B. Dorhorst. 2014. Using haplotypes to unravel the inheritance of Holstein coat color. Abstract 289 in Proc. 10th World Congr. Genet. Appl. Livest. Prod., Vancouver, BC, Canada.

Lee, B.-R., H. Yang, S.-I. Lee, I. Haq, S.-A. Ock, H. Wi, H.-C. Lee, P. Lee, and J.-G. Yoo. 2021. Robust three-dimensional (3D) expansion of bovine intestinal organoids: An *in vitro* model as a potential alternative to an *in vivo* system. Animals (Basel) 11:2115. https://doi.org/10.3390/ani11072115.

Legates, J. E., and E. J. Warwick. 1990. Breeding and Improvement of Farm Animals. 8th ed. McGraw-Hill Inc., New York, NY.

Leipold, H. W., S. M. Dennis, and K. Huston. 1972. Congenital defects of cattle: Nature, cause, and effect. Adv. Vet. Sci. Comp. Med. 16:103–150.

Leipold, H. W., and G. Saperstein. 1975. Rectal and vaginal constriction in Jersey cattle. J. Am. Vet. Med. Assoc. 166:231–232.

Littlejohn, M. D., K. M. Henty, K. Tiplady, T. Johnson, C. Harland, T. Lopdell, R. G. Sherlock, W. Li, S. D. Lukefahr, B. C. Shanks, D. J. Garrick, R. G. Snell, R. J. Spelman, and S. R. Davis. 2014. Functionally reciprocal mutations of the prolactin signalling pathway define hairy and slick cattle. Nat. Commun. 5:5861. https://doi.org/10.1038/ncomms6861.

Liu, S., Y. Gao, O. Canela-Xandri, S. Wang, Y. Yu, W. Cai, B. Li, R. Xiang, A. J. Chamberlain, E. Pairo-Castineira, K. D'Mellow, K. Rawlik, C. Xia, Y. Yao, P. Navarro, D. Rocha, X. Li, Z. Yan, C. Li, B. D. Rosen, C. P. Van Tassell, P. M. Vanraden, S. Zhang, L. Ma, J. B. Cole, G. E. Liu, A. Tenesa, and L. Fang. 2022. A multi-tissue atlas of regulatory variants in cattle. Nat. Genet. 54:1438–1447. https://doi.org/10.1038/s41588-022-01153-5.

Lozada-Soto, E., C. Maltecca, J. Jiang, J. Cole, P. VanRaden, and F. Tiezzi. 2024. Effect of germplasm exchange strategies on genetic gain, homozygosity, and genetic diversity in dairy stud populations: A simulation study. J. Dairy Sci. 107:11149–11163. https://doi.org/10.3168/jds.2024-24992.

Lush, J. L. 1937. Animal Breeding Plans. Collegiate Press Inc., Ames, IA.

Lush, J. L. 1945. Animal Breeding Plans. 3rd ed. Iowa State College Press, Ames, IA.

Maltecca, C., F. Tiezzi, J. Cole, and C. Baes. 2020. Symposium review: Exploiting homozygosity in the era of genomics—Selection, inbreeding, and mating programs. J. Dairy Sci. 103:5302–5313. https://doi.org/10.3168/jds.2019-17846.

Mansfield, R. H. 1985. Progress of the Breed: The History of U.S. Holsteins. Holstein-Friesian World Inc., Sandy Creek, NY.

Matukumalli, L. K., C. T. Lawley, R. D. Schnabel, J. F. Taylor, M. F. Allan, M. P. Heaton, J. O'Connell, S. S. Moore, T. P. Smith, T. S. Sonstegard, and C. P. Van Tassell. 2009. Development and characterization of a high density SNP genotyping assay for cattle. PLoS One 4:e5350. https://doi.org/10.1371/journal.pone.0005350.

McAllister, A. J. 2002. Is crossbreeding the answer to questions of dairy breed utilization? J. Dairy Sci. 85:2352–2357. https://doi.org/10.3168/jds.S0022-0302(02)74315-4.

McClure, M., E. Kim, D. Bickhart, D. Null, T. Cooper, J. Cole, G. Wiggans, P. Ajmone-Marsan, L. Colli, E. Santus, G. E. Liu, S. Schroeder, L. Matukumalli, C. Van Tassell, and T. Sonstegard. 2013. Fine mapping for Weaver syndrome in Brown Swiss cattle and the identification of 41 concordant mutations across *NRCAM, PNPLA8* and *CTTNBP2*. PLoS One 8:e59251. https://doi.org/10.1371/journal.pone.0059251.

McClure, M. C., D. Bickhart, D. Null, P. VanRaden, L. Xu, G. Wiggans, G. Liu, S. Schroeder, J. Glasscock, J. Armstrong, J. B. Cole, C. P. Van Tassell, and T. S. Sonstegard. 2014. Bovine exome sequence analysis and targeted SNP genotyping of recessive fertility defects BH1, HH2, and HH3 reveal a putative causative mutation in *SMC2* for HH3. PLoS One 9:e92769. https://doi.org/10.1371/journal.pone.0092769.

McClure, M. C., and J. C. McClure. 2016. Understanding Genetics and Complete Genetic Disease and Trait Definition. Expanded ed. Irish Cattle Breeding Federation, Bandon, Co. Cork, Ireland.

Medugorac, I., D. Seichter, A. Graf, I. Russ, H. Blum, K. H. Göpel, S. Rothammer, M. Förster, and S. Krebs. 2012. Bovine polledness—An autosomal dominant trait with allelic heterogeneity. PLoS One 7:e39477. https://doi.org/10.1371/journal.pone.0039477.

Menzi, F., N. Besuchet-Schmutz, M. Fragnière, S. Hofstetter, V. Jagannathan, T. Mock, A. Raemy, E. Studer, K. Mehinagic, N. Regenscheit, M. Meylan, F. Schmitz-Hsu, and C. Drögemüller. 2016. A transposable element insertion in *APOB* causes cholesterol deficiency in Holstein cattle. Anim. Genet. 47:253–257. https://doi.org/10.1111/age.12410.

Michot, P., S. Chahory, A. Marete, C. Grohs, D. Dagios, E. Donzel, A. Aboukadiri, M.-C. Deloche, A. Allais-Bonnet, M. Chambrial, S. Barbey, L. Genestout, M. Boussaha, C. Danchin-Burge, S. Fritz, D. Boichard, and A. Capitan. 2016. A reverse genetic approach identifies an ancestral frameshift mutation in *RP1* causing recessive progressive retinal degeneration in European cattle breeds. Genet. Sel. Evol. 48:56. https://doi.org/10.1186/s12711-016-0232-y.

Neustaeter, A., L. F. Brito, W. J. B. Hanna, J. D. Baird, and F. S. Schenkel. 2023. Investigating the genetic background of spastic syndrome in North American Holstein cattle based on heritability, genome-wide association, and functional genomic analyses. Genes (Basel) 14:1479. https://doi.org/10.3390/genes14071479.

Ng, P. C., and S. Henikoff. 2003. SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Res. 31:3812–3814. https://doi.org/10.1093/nar/gkg509.

Nicholas, F. W., I. Tammen, and Sydney Informatics Hub. 1995. Online Mendelian Inheritance in Animals (OMIA). Accessed Jul. 16, 2024. https://omia.org/. https://doi.org/10.25910/2AMR-PV70.

Null, D. J., J. L. Hutchison, D. M. Bickhart, P. M. VanRaden, and J. B. Cole. 2017. Discovery of a haplotype affecting fertility in Ayrshire dairy cattle and identification of a putative causal variant. J Dairy Sci 100(Suppl. 2):199 (Abstr. 205).

Oldenbroek, J. K. 2017. Genomic Management of Animal Genetic Diversity. Wageningen Academic Publishers, Wageningen, the Netherlands. https://doi.org/10.3920/978-90-8686-850-6.

Ortega, M. S., D. M. Bickhart, K. N. Lockhart, D. J. Null, J. L. Hutchison, J. C. McClure, and J. B. Cole. 2022. Truncation of *IFT80* causes early embryonic loss in Holstein cattle associated with Holstein haplotype 2. J. Dairy Sci. 105:9001–9011. https://doi.org/10.3168/jds.2022-21853.

Pryce, J. E., B. J. Hayes, and M. E. Goddard. 2012. Novel strategies to minimize progeny inbreeding while maximizing genetic gain using genomic information. J. Dairy Sci. 95:377–388. https://doi.org/10.3168/jds.2011-4254.

Rice, V. A. 1934. Breeding and Improvement of Farm Animals. 2nd ed. McGraw-Hill Book Company Inc., New York, NY.

Richards, S., N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, and H. L. Rehm. 2015. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. 17:405–424. https://doi.org/10.1038/gim.2015.30.

Rosen, B. D., D. M. Bickhart, R. D. Schnabel, S. Koren, C. G. Elsik, E. Tseng, T. N. Rowan, W. Y. Low, A. Zimin, C. Couldrey, R. Hall, W. Li, A. Rhie, J. Ghurye, S. D. McKay, F. Thibaud-Nissen, J. Hoffman, B. M. Murdoch, W. M. Snelling, T. G. McDaneld, J. A. Hammond, J. C. Schwartz, W. Nandolo, D. E. Hagen, C. Dreischer, S. J. Schultheiss, S. G. Schroeder, A. M. Phillippy, J. B. Cole, C. P. Van Tassell, G. Liu, T. P. L. Smith, and J. F. Medrano. 2020. *De novo* assembly of the cattle reference genome with single-molecule sequencing. Gigascience 9:giaa021. https://doi.org/10.1093/gigascience/giaa021.

Sartelet, A. 2013. Management of inherited disorders in Belgian Blue cattle breed. Eur. Coll. Bov. Hlth. Mgmt., Nantes, France. Accessed Feb. 6, 2025. https://orbi.uliege.be/bitstream/2268/147826/1/Inherited_disorders_BBCB_Workshop_Nantes_2013.pdf.

Schild, A. L., F. Riet-Correa, M. C. Mkndez, and S. S. Barros. 1993. Hereditary hypermetria in Shorthorn cattle. J. Vet. Diagn. Invest. 5:640–642. https://doi.org/10.1177/104063879300500429.

Schütz, E., C. Wehrhahn, M. Wanjek, R. Bortfeld, W. E. Wemheuer, J. Beck, and B. Brenig. 2016. The Holstein Friesian lethal haplotype 5 (HH5) results from a complete deletion of *TFB1M* and cholesterol deficiency (CDH) from an ERV-(LTR) insertion into the coding region of *APOB*. PLoS One 11:e0154602. https://doi.org/10.1371/journal.pone.0154602.

Schwarzenbacher, H., J. Burgstaller, F. R. Seefried, C. Wurmser, M. Hilbe, S. Jung, C. Fuerst, N. Dinhopl, H. Weissenböck, B. Fuerst-Waltl, M. Dolezal, R. Winkler, O. Grueter, U. Bleul, T. Wittek, R. Fries, and H. Pausch. 2016. A missense mutation in *TUBD1* is associated with high juvenile mortality in Braunvieh and Fleckvieh cattle. BMC Genomics 17:400. https://doi.org/10.1186/s12864-016-2742-y.

Schwenger, B., S. Schober, and D. Simon. 1993. DUMPS cattle carry a point mutation in the uridine monophosphate synthase gene. Genomics 16:241–244. https://doi.org/10.1006/geno.1993.1165.

Sebastiani, C., C. Arcangeli, M. Torricelli, M. Ciullo, N. D'avino, G. Cinti, S. Fisichella, and M. Biagetti. 2022. Marker-assisted selection of dairy cows for β-casein gene A2 variant. Ital. J. Food Sci. 34:21–27. https://doi.org/10.15586/ijfs.v34i2.2178.

Segelke, D., H. Täubert, F. Reinhardt, and G. Thaller. 2016. Considering genetic characteristics in German Holstein breeding programs. J. Dairy Sci. 99:458–467. https://doi.org/10.3168/jds.2015-9764.

Shanks, R. D., D. B. Dombrowski, G. W. Harpestad, and J. L. Robinson. 1984. Inheritance of UMP synthase in dairy cattle. J. Hered. 75:337–340. https://doi.org/10.1093/oxfordjournals.jhered.a109951.

Shaw, T. 1902. Animal Breeding. Orange Judd Company, New York, NY.

Shuster, D. E., M. E. Kehrli Jr., M. R. Ackermann, and R. O. Gilbert. 1992. Identification and prevalence of a genetic defect that causes leukocyte adhesion deficiency in Holstein cattle. Proc. Natl. Acad. Sci. USA 89:9225–9229. https://doi.org/10.1073/pnas.89.19.9225.

Smith, C. 1971. Discriminating between different modes of inheritance in genetic disease. Clin. Genet. 2:303–314. https://doi.org/10.1111/j.1399-0004.1971.tb00291.x.

Sonstegard, T. S., J. B. Cole, P. M. VanRaden, C. P. Van Tassell, D. J. Null, S. G. Schroeder, D. Bickhart, and M. C. McClure. 2013. Identification of a nonsense mutation in *CWC15* associated with decreased reproductive efficiency in Jersey cattle. PLoS One 8:e54872. https://doi.org/10.1371/journal.pone.0054872.

Sonstegard, T. S., J. M. Flórez, and J. F. Garcia. 2024. Commercial perspectives: Genome editing as a breeding tool for health and well-being in dairy cattle. JDS Commun. 5:767–771. https://doi.org/10.3168/jdsc.2023-0481.

Steyn, Y., T. Lawlor, Y. Masuda, S. Tsuruta, A. Legarra, D. Lourenco, and I. Misztal. 2023. Nonparallel genome changes within subpopulations over time contributed to genetic diversity within the US Holstein population. J. Dairy Sci. 106:2551–2572. https://doi.org/10.3168/jds.2022-21914.

Testoni, S., and A. Gentile. 2004. Arachnomelia in four Italian Brown calves. Vet. Rec. 155:372. https://doi.org/10.1136/vr.155.12.372.

Thomsen, B., P. H. Nissen, J. S. Agerholm, and C. Bendixen. 2010. Congenital bovine spinal dysmyelination is caused by a missense mutation in the *SPAST* gene. Neurogenetics 11:175–183. https://doi.org/10.1007/s10048-009-0214-0.

Upperman, L. R., B. P. Kinghorn, M. D. MacNeil, and A. L. Van Eenennaam. 2019. Management of lethal recessive alleles in beef cattle through the use of mate selection software. Genet. Sel. Evol. 51:36. https://doi.org/10.1186/s12711-019-0477-3.

van den Berg, I., T. V. Nguyen, T. T. T. Nguyen, J. E. Pryce, G. J. Nieuwhof, and I. M. MacLeod. 2024. Imputation accuracy and carrier frequency of deleterious recessive defects in Australian dairy cattle. J. Dairy Sci. 107:9591–9601. https://doi.org/10.3168/jds.2024-24780.

Van Eenennaam, A. L., and B. P. Kinghorn. 2014. Use of mate selection software to manage lethal recessive conditions in livestock populations. Abstract 408 in Proc. 10th World Congr. Genet. Appl. Livest. Prod., Vancouver, BC, Canada.

VanRaden, P. M., K. M. Olson, D. J. Null, and J. L. Hutchison. 2011. Harmful recessive effects on fertility detected by absence of homozygous haplotypes. J. Dairy Sci. 94:6153–6161. https://doi.org/10.3168/jds.2011-4624.

VanRaden, P. M., C. P. Van Tassell, G. R. Wiggans, T. S. Sonstegard, R. D. Schnabel, J. F. Taylor, and F. S. Schenkel. 2009. Invited review: Reliability of genomic predictions for North American Holstein bulls. J. Dairy Sci. 92:16–24. https://doi.org/10.3168/jds.2008-1514.

Venhoranta, H., H. Pausch, K. Flisikowski, C. Wurmser, J. Taponen, H. Rautala, A. Kind, A. Schnieke, R. Fries, H. Lohi, and M. Andersson. 2014. In frame exon skipping in *UBE3B* is associated with developmental disorders and increased mortality in cattle. BMC Genomics 15:890. https://doi.org/10.1186/1471-2164-15-890.

Verrier, E., J. J. Colleau, and J. L. Foulley. 1993. Long-term effects of selection based on the animal model BLUP in a finite population. Theor. Appl. Genet. 87:446–454. https://doi.org/10.1007/BF00215090.

Wiggans, G. R., and J. A. Carrillo. 2022. Genomic selection in United States dairy cattle. Front. Genet. 13:994466. https://doi.org/10.3389/fgene.2022.994466.

Wolf, C. A., G. T. Tonsor, M. G. S. McKendree, D. U. Thomson, and J. C. Swanson. 2016. Public and farmer perceptions of dairy cattle welfare in the United States. J. Dairy Sci. 99:5892–5903. https://doi.org/10.3168/jds.2015-10619.

World Holstein Friesian Federation. 2024. WHFF Guidelines for Interpreting New Evidence on Potential Monogenic Traits. Accessed Feb. 2, 2025. https://whff.info/wp-content/uploads/2024/01/Guidelines-for-Interpreting-New-Evidence-on-Potential-Monogenic-Traits.pdf.

ORCIDS

John B. Cole, https://orcid.org/0000-0003-1242-4401
Christine F. Baes, https://orcid.org/0000-0001-6614-8890
Sophie A. E. Eaglen, https://orcid.org/0009-0007-5281-1330
Thomas J. Lawlor, https://orcid.org/0000-0002-4458-1025
Christian Maltecca, https://orcid.org/0000-0002-9996-4680
M. Sofía Ortega, https://orcid.org/0000-0003-4027-7314
Paul M. VanRaden https://orcid.org/0000-0002-9123-7278