



J. Dairy Sci. TBC

<https://doi.org/10.3168/jds.2023-23788>

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Genetic Parameters and Genetic Trends for Johne's Disease in U.S. Holsteins: An Updated Study

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ABSTRACT

Johne's disease (JD) is an infectious enteric disease in ruminants, causing substantial economic loss annually worldwide. This work aimed to estimate JD's genetic parameters and the phenotypic and genetic trends by incorporating recent data. It also explores the feasibility of a national genetic evaluation for JD susceptibility in Holstein cattle in the United States (US). The data were extracted from a Johne's disease data repository, maintained at the Council on Dairy Cattle Breeding (CDCB), and initially supplied by 2 dairy records processing centers. The data comprised 365,980 Holstein cows from 1,048 herds participating in a voluntary control program for JD. Two protocol kits, Idexx Paratuberculosis Screening Ab Test (IDX) and Parachek® 2 (PCK), were used to analyze milk samples with the Enzyme-Linked Immunosorbent Assay (ELISA) technique. Test results from the first 5 parities were considered. An animal was considered infected if it had at least one positive outcome. The overall average of JD incidence was 4.72% in these US Holstein cattle. Genotypes of 78,964 SNP markers were used for 25,000 animals randomly selected from the phenotyped population. Variance components and genetic parameters were estimated based on 3 models, namely, a pedigree-only threshold model (THR), a single-step threshold model (ssTHR), and a single-step linear model (ssLR). The posterior heritability estimates of JD susceptibility were low to moderate: 0.11 to 0.16 based on the 2 threshold models and 0.05 to 0.09 based on the linear model. The average reliability of estimated breeding values of JD susceptibility using single-step analysis for animals with or without phenotypes varied from 0.18 (THR) to 0.22 (ssLR) for IDX and from 0.14 (THR) to 0.18 (ssTHR and ssLR) for

PCK. Despite no prior direct genetic selection against JD, the estimated genetic trends of JD susceptibility were negative and highly significant (P-value <0.01). The correlations of bulls' predicted transmitting abilities with economically important traits such as milk yield, milk protein, milk fat, somatic cell score, and mastitis were low, indicating a non-overlapping genetic selection process with traits in current genetic evaluations. Our results suggest the feasibility of reducing the JD incidence rate by incorporating it into the national genetic evaluation programs.

Key words: animal model, infectious disease, heritability, genetic trend, reliabilities

INTRODUCTION

Paratuberculosis, also known as Johne's disease (JD), is a chronic infectious disease caused by *Mycobacterium avium* ssp. *paratuberculosis* (MAP) that affects cattle and other ruminants. After infection, the MAP resides in macrophages in the intestines and triggers a chronic immune response, resulting in inflammation of host intestine walls and potentially leading to death. Like tuberculosis in humans, infected animals silently carry the mycobacteria and spread the disease among herds (Whittington et al., 2017). Though the true herd prevalence of JD is challenging to assess, studies have reported up to 75% of herds with at least one positive case in the United States (US) (Garcia and Shalloo, 2015a). Johne's disease is commonly associated with increased premature culling, diminished production and reproduction, reduced feed efficiency, and increased veterinary costs and penalty payments due to reduced milk quality. The economic losses caused by JD in the US were estimated to be around \$198 million per year (Rasmussen et al., 2021).

The epidemiology of JD is complex and depends on many factors, such as herd management, age, infection dose, and disease prevalence. Clinically, this disease has a silent period lasting between 2 to 10 years, and test protocols have varying sensitivity levels, making JD-

Received May 24, 2023.

Accepted February 1, 2024.

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controlling programs arduous. A substantial research effort has been placed on the vaccination for JD in past decades, yet its effects are far from elucidated (e.g., Bannantine et al., 2014). Hence, the control for this disease currently relies on a voluntary program implemented by US dairy producers (Davis and Park, 2018). Although JD is a heritable trait, the genetics underlying host resistance remains not fully known, and while being actively studied, data collection aiming at genomic selection against JD susceptibility is challenging (Mallikarjunappa et al., 2021). As a result, indicator traits are often used to assist genetic programs in reducing JD incidence (Brito et al., 2018).

Throughout the last century, genetic evaluations in dairy cattle have heavily emphasized production over reproductive and health traits. Consequently, an antagonistic genetic relationship between production and health has become increasingly apparent (Pryce et al., 1998; Rauw et al., 1998). Meanwhile, the dairy industry has been shifting toward larger herd sizes and increasingly recognizing the importance of cows with strong disease resistance. Genetic improvement of disease resistance in dairy cattle has been an area of research for more than 50 years (Parker Gaddis et al., 2020). Still, official genetic evaluations on large populations began considering health traits in the mid-1990s through indirect selection and indicator traits. In the US, for example, somatic cell score and productive life were combined with yield traits into a total net merit selection index (NMS; VanRaden and Wiggans, 1995); both representing indirect selection and indicator traits. Somatic cell score was a convenient indicator trait for clinical mastitis (VanRaden, 2017). Productive life provides an indirect indicator of overall health by estimating the length of time a cow remains in the milking herd, and hence, it is a measurement related to the cow's health (VanRaden, 2017). However, direct recording and selecting for health traits are more appealing because they can add value and make progress toward breeding healthier dairy cattle (Parker Gaddis et al., 2020). Over the past 30 years, there has been a shift in the selection index from yield traits to fertility, health, and fitness traits (Cole et al., 2020). Health traits such as hoof health (Cole et al., 2020) and still-birth (e.g., Yao et al., 2014; Sigdel et al., 2022) are being considered. In the past decade, genetic evaluation and prediction of JD susceptibility have also been of great interest (e.g., Zare et al., 2014; Kirkpatrick et al., 2022).

In the past few decades, the search for genes involved in the genetic determination of JD susceptibility has continued through candidate gene studies (e.g., Pinedo et al., 2009a; b; Pant et al., 2011), QTL mapping (e.g., Gonda et al., 2007; Minozzi et al., 2010), and genome-

wide association studies (e.g., Settles et al., 2009; Kirkpatrick et al., 2011, 2022; van Hulzen et al., 2012; Zare et al., 2014; Sanchez et al., 2022a). These studies have linked JD with immune-mediated diseases, maturation of lymphocytes, mitochondrial health, and innate immune response that are also present in other infectious diseases in dairy cattle. However, genetic evaluations limited to significantly identified markers linked to functional genes or QTL are suboptimal in their prediction power. For example, Zare et al. (2014) reported an early study to predict JD in US Jersey cattle using estimated SNP effects from genome-wide association studies in a data set of approximately 5,000 mature cows. However, the accuracy measured by the receiver operating characteristic curve was low. Recently, Kirkpatrick et al. (Kirkpatrick et al., 2022) evaluated the efficacy of genomic prediction using a sire data set (897 sires with genotypes and daughters with phenotypes) in US Holstein cattle. The average accuracy, assessed by the correlation of genomic-estimated breeding values (GEBV) for the testing using sires and their daughter averages in 5-fold cross-validations, ranged between 0.43 and 0.53. Kirkpatrick et al. (2022) thus suggested that genomic predictions using genome-wide SNP markers for susceptibility to MAP infection could be used by producers in selecting AI service sires or replacement females as a means of producing a herd with lesser susceptibility to MAP infection. Still, the results were not representative of a full population genetic evaluation on JD resistance because genomic and proven sires tend to have higher prediction accuracies than other categories of animals (e.g., cows with/without genotypes and phenotypes or bulls without genotypes and daughters). Sanchez et al. (2022) reported genomic predictions with relatively higher reliability for JD resistance (reliability = 0.55). These predictions were estimated from a reduced reference population that included about 75% of cows with phenotypes in a large Holstein population consisting of 161,253 animals, which included 56,766 cows with ELISA serological phenotypes and 12,431 animals with genotypes raised in northwestern France.

Genetic evaluation of JD susceptibility (or resistance) depends on 2 factors. First, collecting phenotypic and genotypic data can take many years. Second, it remains crucial to determine how accurate or reliable the genetic evaluations will be. In the past 2 decades, the JD records collected in US Holstein cattle have accumulated substantially, thus providing a dedicated opportunity to assess a genetic evaluation on JD. As such, the primary objectives of this study were to characterize the available JD data repository in terms of incidence rate, variance components, and genetic parameters and to assess the reliability of estimated breeding values for JD susceptibility in US Holstein cattle. We anticipate

that the results will also help determine the feasibility of implementing official genetic evaluation programs for reducing the JD susceptibility in Holstein cattle in the US

MATERIALS AND METHODS

The data were extracted from the JD data repository maintained at the Council on Dairy Cattle Breeding (CDCB), initially supplied by 2 dairy records processing centers. This data repository contained a total of 973,652 ELISA scores. After removing redundant records, 713,395 ELISA scores were obtained, representing 413,255 unique animals from 17 pure breeds and crossbred animals. The majority (92.38%) of these records were collected from Holstein cattle, and approximately 3.90% of the ELISA scores were collected from crossbred cattle. The remaining records were compiled from Jersey (2.94%), Brown Swiss (0.36%), and other purebred cattle breeds (0.42%). The JD tests used 2 ELISA kits, with specificity greater than 98%, namely, Idexx Paratuberculosis Screening Ab Test (Idexx, Montpellier, France) (**IDX**) and Parachek® 2 (Prionics AG, Schlieren, Switzerland) (**PCK**). Individual JD records were primarily collected in the states of Wisconsin (50.28%), Michigan (29.6%), and Minnesota (18.48%), as well as 15 additional states (1.64%). Although both test kits aim to detect MAP-specific antibodies in bovine milk, the joint analysis of different JD ELISA-based tests is not recommended due to poor agreement between kits and consequent inaccurate interpretation (McKenna et al., 2006). Additionally, the tests were applied during distinct phases of genetic selection for health traits in the US. While PCK was mainly used before the visible impact of genomic evaluations, IDX was the primary test used in a period of great improvement in health traits trends (i.e., mastitis and milk fever). An animal described as positive for one test may not have the same diagnosis if tested with a different kit, considering that the cut-off values are conditioned to the manufacturer and current population status. Therefore, the subsequent analyses were performed considering the tests as different traits.

Considering the epidemiological profile of the disease, we kept only test results from the first 5 parities. Animals were classified as infected if they had at least one positive result, while animals without positive test results were deemed uninfected. The average number of tests per animal within the first 5 lactations was 1.68 ± 1.01 , with less than 7% of the animals with more than 3 tests. For animals with multiple positive (or negative) tests, only the first positive (or last negative) result was retained. The data were cleaned by removing animals with inconclusive or suspect JD results and herds

with less than 15 animals. Only herds with at least one positive result were considered. In total, ELISA scores for 365,980 animals from 1,048 herds participating in the voluntary control program for JD were retained, covering the period from 1992 to 2022 with 2 protocol kits: IDX and PCK. The PCK milk analysis results represented 94,639 samples analyzed between 1992 and 2017, while IDX results represented 271,341 samples analyzed between 2002 and 2022. Genotypes of 78,964 SNP markers were extracted for 35,420 animals with IDX and 170 animals with PCK test results. For cows with IDX tests, only 25,000 of the total genotyped animals were randomly selected and included in the present study due to a limitation of the free software version (Lourenco et al., 2020) used for variance component estimation. The same set of genotyped animals was used for all the subsequent analyses to maintain the consistency of their impact on the estimated variance components and breeding values. The pedigree consisted of 834,853 animals traced up to 5 generations.

The JD data were analyzed separately for the 2 JD diagnostic tests using the single-step approach implemented in the BLUPF90 suite of programs (Miszta et al., 2014) versions 3.16 and 2.47 for GIBBSF90+ and BLUPF90+, respectively. The PREGSF90 (version 1.4) program was used to obtain genomic and pedigree relationship matrices and to perform quality control of the genotype file. The quality control removed monomorphic markers, markers with a minor allele frequency of less than 0.05, animals and markers with a call rate of less than 0.90, and animals with parent-progeny conflicts. After the data quality control, the data set included 75,313 markers on 24,927 animals in the IDX-test category and 164 animals in the PCK-test category. The phenotypes of JD test results were coded as a binary (2 = infected, 1 = uninfected) trait.

Linear model

The linear model is described as the following:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}_1\mathbf{h} + \mathbf{Z}_2\mathbf{u} + \mathbf{e}$$

where $\boldsymbol{\beta}$ is a vector of fixed effects including age within lactation (15 levels) and stage of lactation (3 levels), $\mathbf{h}$ and $\mathbf{u}$ are the vectors of random effects for herd-year-season of the test (6,367 levels) and additive genetic, respectively, $\mathbf{X}$, $\mathbf{Z}_1$, and $\mathbf{Z}_2$ are the corresponding incidence matrices, and $\mathbf{e}$ is a vector of residuals. The random effects were assumed to follow a multivariate normal distribution with $\mathbf{h} \sim N(0, \mathbf{I}\sigma_h^2)$, $\mathbf{u} \sim N(0, \mathbf{H}\sigma_u^2)$, where $\mathbf{I}$ is an identity matrix and $\mathbf{H}$ is a matrix combining pedigree and genomic information. To correct the

age discrepancies of the test for each lactation within herds, the age categories equally divided the animals into 3 groups (younger, average, and older; 33% of total animals, each) for each lactation. The groups of lactation stages (s) were defined as early ($s < 150d$), peak ($150d \leq s < 300d$), and late ($s \geq 300d$) lactation when the tests were conducted.

Threshold model

The threshold model postulates a continuous and normally distributed variable, namely liability (η_i), that delimits the observable binary trait (y_i) according to a threshold κ (Gianola, 1982). That is,

$$y_i | \eta_i, \kappa = \begin{cases} 1 & \text{if } \eta_i > \kappa \\ 0 & \text{otherwise} \end{cases}. \quad (1)$$

The threshold κ is fixed arbitrarily to center the distribution, hence not an unknown parameter in a binary threshold model. The reliability variable is then modeled by the linear model as is shown in (1) but with the observable vector $\mathbf{y}$ replaced by the unobservable reliability vector $\boldsymbol{\eta}$. The conditional probability of observing a realization vector of $\boldsymbol{\eta}$, given a vector of observations ($\mathbf{y}$) for a population of n animals, and the threshold κ , is the following (Wu et al., 2008):

$$\begin{aligned} &Pr(\mathbf{y} | \boldsymbol{\eta}, \kappa) \\ &= \prod_{i=1}^n \{I(\eta_i \leq \kappa)Pr(y_i = 0) + I(\eta_i > \kappa)Pr(y_i = 1)\}, \end{aligned} \quad (2)$$

where $I(A)$ is an indicator function, which takes the value one if condition A is true and a zero otherwise. The threshold model was analyzed by Bayesian analysis implemented via Markov chain Monte Carlo simulation (Korsgaard et al., 2003).

Estimations of variance components

Variance components and genetic parameters (e.g., heritabilities) were estimated using 3 models: a pedigree-only threshold model (**THR**), a single-step threshold model (**ssTHR**), and a single-step linear model (**ssLR**). In single-step methodology, the pedigree relationship matrix ($\mathbf{A}$) is replaced by the realized relationship matrix (Legarra et al., 2009; Misztal et al., 2009; Christensen and Lund, 2010). However, $\mathbf{H}$ is challenging to calculate. Therefore, Aguilar et al. (2010) proposed the direct construction of the inverse of the realized relationship matrix ($\mathbf{H}^{-1}$) as:

$$\mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} 0 & 0 \\ 0 & \mathbf{G}^{-1} - \mathbf{A}_{22}^{-1} \end{bmatrix}, \quad (3)$$

Where $\mathbf{G}^{-1}$ is the inverse of the genomic relationship matrix for genotyped animals calculated based on the method of VanRaden (2008) and $\mathbf{A}_{22}^{-1}$ is the inverse of the pedigree relationship matrix for genotyped animals. The inbreeding coefficient is considered in the calculation of the $\mathbf{A}^{-1}$ and $\mathbf{A}_{22}^{-1}$ matrices by default by BLUPF90+. The heritabilities obtained via the threshold model were presented in the original liability scale and back transformed following the Dempster and Lerner (1950) formula: $h_o^2 = h_l^2 z^2 / K(1 - K)$, where h_o^2 and h_l^2 are the heritability estimates in the observed and liability scale, respectively, z is the value of the standard normal probability density function at the truncation threshold, and K is the proportion of cases in the population.

The GIBBSF90+ and BLUPF90+ programs (Misztal et al., 2014) were used to implement the Bayesian threshold and linear models, respectively. Convergence was determined by visual inspection of the trace plots and by the Geweke convergence diagnostic value (Geweke, 1992). The Geweke method assesses a convergence diagnostic for Markov chains based on a test for equality of the means of the first and last part of a Markov chain (by default, the first 10% and the last 50%). The test assumes that if the samples are drawn from the stationary distribution of the chain, then the 2 means are equal, and Geweke's statistic has an asymptotically standard normal distribution. The test statistic is a standard Z-score, the difference between the means of the 2 samples divided by its estimated standard error. The standard error is calculated from the spectral density at zero and thus considers any autocorrelation. The Markov chain Monte Carlo simulation consisted of 80,000 iterations after discarding a burn-in period of 15,000 iterations and thinned for every 100th sample for posterior inferences.

Breeding values and reliabilities

Breeding values, reliabilities, and genetic trends were obtained with univariate analysis for both JD tests and models using the BLUP90IOD2 and CBLUP90IOD2 programs (Tsuruta et al., 2001). The THR model calculated traditionally estimated breeding values (EBV), whereas the ssTHR and ssLR calculated genomic estimated breeding values (GEBV) as these 2 methods include genomic information. The reliabilities were obtained from ACCF90GS as in:

$$REL = 1 - \left(\frac{PEV}{\sigma_u^2} \right). \quad (4)$$

Here, $PEV = var(\hat{u}_i - u_i) = c^{ii}\sigma_e^2$ is the prediction error variance of $\hat{u}_i$, where c^{ii} is the diagonal elements in the subblock of the inverse matrix of the left-hand side of the mixed model equation (MME) corresponding to the random animal effect for individual i , and σ_e^2 is the residual variance, and $var(u_i) = \sigma_u^2$. While inbreeding is considered for the calculation of A^{-1} , ACCF90GS does not include an inbreeding coefficient for the estimation of PEV. The reliabilities had initially been manually calculated to consider inbreeding; however, as described by Aguilar et al. (2020), a considerable proportion of animals could not have their reliabilities calculated due to having PEVs larger than σ_u^2 , possibly as a result of low heritability of the traits that could not be avoided, despite having considered the inbreeding as suggested by the authors. Due to the large data set, an additional analysis for the threshold model, considering only the pedigree relationship, was performed as a benchmark model for comparison and is presented along with the results for the single-step models.

Estimation of genetic trends

Genetic trends were estimated with the breeding values of the JD incidence by adjusting the 2 diagnostic test results to a common base, assuming that the differences in the JD incidence rate between the 2 JD tests were essentially non-genetic. Hence, we fitted a temporal linear regression on the estimated JD breeding values, assuming heterogenous intercepts and a common regression coefficient for the 2 tests. That is,

$$\bar{u}_{kj} = a_k + b(t_{kj} - \bar{t}_k) + \epsilon_{kj}, \quad (5)$$

where $\bar{u}_{kj}$ is the mean of breeding values computed in year j for the k th test (i.e., $k = 1$ for PCK tests and $k = 2$ for IDX tests), t_{kj} is the year of the test (i.e., 1992 – 2017 for PCK tests and 2002 – 2020 for IDX) with $\bar{t}_k$ being the corresponding mean, a_k is the heterogenous intercept, b is the common coefficient pertaining to the 2 tests, and ϵ_{kj} is an error term. The model parameters were solved by least squares. In brief, the solutions of the model parameters are the following:

$$\begin{pmatrix} \hat{a}_1 \\ \hat{a}_2 \\ \hat{b} \end{pmatrix} = \begin{pmatrix} n_1 & 0 & \sum_{j=1}^{n_1} (t_{1j} - \bar{t}_1) \\ 0 & n_2 & \sum_{j=1}^{n_2} (t_{2j} - \bar{t}_2) \\ \sum_{j=1}^{n_1} (t_{1j} - \bar{t}_1) & \sum_{j=1}^{n_2} (t_{2j} - \bar{t}_2) & \sum_{j=1}^{n_1} (t_{1j} - \bar{t}_1)^2 + \sum_{j=1}^{n_2} (t_{2j} - \bar{t}_2)^2 \end{pmatrix}^{-1} \times \begin{pmatrix} \sum_{j=1}^{n_1} \bar{u}_{1j} \\ \sum_{j=1}^{n_2} \bar{u}_{2j} \\ \sum_{j=1}^{n_1} \bar{u}_{1j} (t_{1j} - \bar{t}_1) + \sum_{j=1}^{n_2} \bar{u}_{2j} (t_{2j} - \bar{t}_2) \end{pmatrix}, \quad (6)$$

where n_1 and n_2 are the numbers of years having IDX and PCK test results, respectively.

Approximated genetic correlations

Approximated genetic correlations between JD test kits and production and health traits included in the national genetic evaluation were obtained following the method proposed by Calo et al. (1973). The predicted transmitting abilities (PTAs) of 18,509 sires in the JD evaluation were obtained from CDCB's official genetic evaluation performed in August 2023. Of the bulls selected, 336 had less than 10 daughters, all genomically tested. The average reliability for the production and health traits varied from 78.96 for mastitis to 95.38 for SCS. Briefly, the method computed the genetic correlation (r_G) between 2 traits (denoted by A and B) as the Pearson correlations (r) between the estimated PTA for each trait adjusted for reliabilities. That is,

$$\hat{r}_G = \frac{\sqrt{\Sigma(REL_A) \times \Sigma(REL_B)}}{\Sigma(REL_A REL_B)} \times r, \quad (6)$$

where $\hat{r}_G$ is the approximate genetic correlation between traits, $\Sigma(REL_A)$ and $\Sigma(REL_B)$ are the sum of reliabilities for the trait A and B, respectively. The traits were chosen based on economic importance (e.g., milk yield, protein, and fat), and traits that could be impacted by or related to JD (e.g., SCS, mastitis, livability, and productive life).

RESULTS AND DISCUSSION

Data summarization and characterization of Johne's disease diagnostic tests

A major limitation in the development of direct genetic measures for health traits over the past decades has been the lack of a centralized system to collect health data at a national level (Parker Gaddis et al., 2020). Zwald et al. (2004) demonstrated that producer-recorded health event data were a viable source of phenotypes for genetic evaluation if collected into a national data set. In the US, the Animal Improvement Program Laboratory (now the Animal Genomics and Improvement Laboratory, AGIL; Beltsville, MD) has collaborated with industry partners and veterinary experts to develop a standardized health recording system since 2008 (Cole et al., 2008) and advance the development of health evaluations. On the other hand, the standardization of health traits may overlook the discrepancy between JD objective diagnosis and producer-reported occurrences of other traits such as ketosis, milk fever, and others. The CDCB JD data repository was established to accommodate phenotypes and genotypes that could be used for genetic evaluations for JD.

The CDCB JD data repository represented the world's largest one in Holstein cattle. After data quality control, ELISA records were retained for 365,980 animals from 1,048 herds participating in the voluntary control program for JD tests. Compared with the studies conducted a decade ago (e.g., Gonda et al., 2006), the JD data size has increased by over a hundred-fold. The data set used by Kirkpatrick et al. (2022b) partially overlapped with the data set used in this study, including only data collected up to 2016. Their data fell into 3 categories. The data in the first category represented the US commercial dairy cattle population from 2010 to 2016 with farm records for MAP infections (i.e., milk ELISA test results for US Holstein cows) provided by the Dairy Records Management System and AgSource Cooperative (Kirkpatrick and Lett, 2018). They retained JD records for 202,367 cows after the data editing. The other 2 categories included testing cows from commercial dairy herds developed as resource populations at the University of Minnesota and Michigan State University. In contrast, the data set used in this study contained twice as many animals. Recently, Sanchez et al. (2022) merged 2 JD data sets to evaluate the genetic resistance to paratuberculosis in French Holstein cattle. The first data set contained non-redundant MAP statuses (serum ELISA and fecal PCR results) for 4,100 cows, while the second data set included non-redundant MAP statuses of 243,274

cows from 15,476 herds, deduced from serological tests routinely recorded since 2015. After the data cleaning, the merged data set comprised 161,253 animals, including 56,766 cows with ELISA serological phenotypes and 12,431 animals with genotypes. Approximately 3-fourths of the serum samples were diagnosed with IDX, whereas around one-fourth were diagnosed with Idvet ID Screen[®] Paratuberculosis Indirect (Idvet, Montpellier, France).

Figure 1 shows the yearly distribution of these 2 tests reported through the voluntary program. The number of IDX tests increased substantially after 2012 due to the rising use of IDX as the primary test and the USDA's subsidies provided for testing. As previously mentioned, although the tests are designed to diagnose the same pathogen using the same technique, it is challenging to maintain good agreement of ELISA test kits for MAP detection between them, even when using the same antibodies in the same broad population (McKenna et al., 2006). Using the test outcomes as a trait, as exemplified in this work, instead of the ELISA score, can exacerbate the differences in diagnosis between tests. Meanwhile, PCK is not an authorized kit for the time being by the USDA for the diagnosis of MAP, and its future use remains uncertain (USDA, 2023). Additionally, the combination of 2 different tests will be subject to confirmed agreement in either genetic correlation or validation tests between them. A preliminary multi-trait variance component estimation based on a threshold model using the same parameters and the set of the same animals resulted in a 0.41 genetic correlation between PCK and IDX. Hence, our result supports the results of both tests as different traits for genetic evaluations.

The overall JD positive rate was 2.06% with IDX tests and 6.7% with PCK tests, reflecting the differences between the 2 tests. Still, such a difference might also be confounded by the nonzero yearly phenotypic or genetic trends due to the switch of JD tests over the years. This question is addressed in the latter section with estimated phenotypic and genetic trends. The average age of cows with positive results did not change considerably between the 2 tests (53.6 ± 16.24 mo for IDX vs. 52.65 ± 16.31 mo for PCK). Hence, we excluded the age of cows at testing as an influential factor for the different JD positive rates between the 2 tests. In fact, the testing methods based on ELISA and fecal PCR, for instance, are not able to detect the infection time, but instead, the response of the organism to MAP translated as an increase in antibody production and shedding into the environment, respectively. An infected animal, in this case, can pass undetected by the test until the organism has produced sufficient antibodies, often after years. As a milk-based ELISA

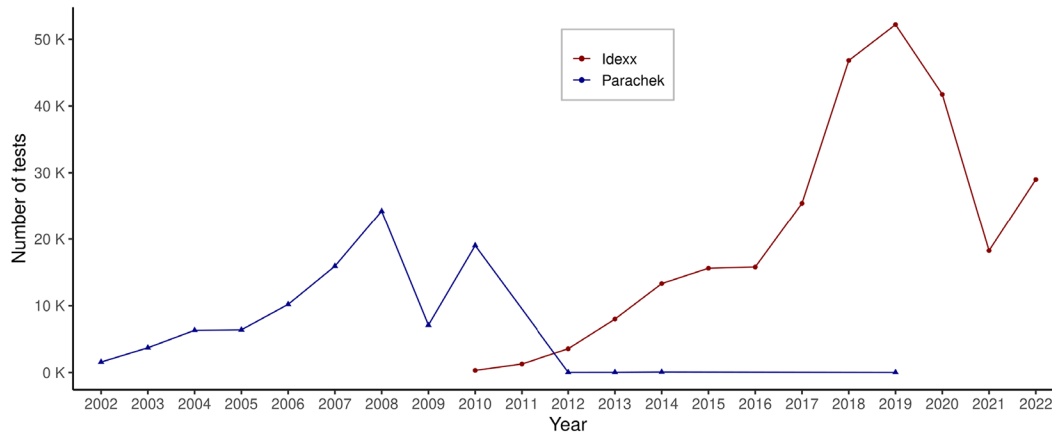


Figure 1. Yearly distributions of Johne's disease tests using 2 Enzyme-Linked Immunosorbent Assay (ELISA) kits, IDX (Idexx) and PCK (Parachek).

test, the incidence rate in a herd is tied to the onset of lactation, in which the age of animals can vary among farms.

Accordingly, the JD positive rates varied substantially in lactations (Table 1), which is expected if the epidemiological profile of the disease is considered (Whittington et al., 2017). For the PCK tests, the average JD-positive rate increased steadily from 4.8% at lactation 1 to 9.1% at lactation 3 and then declined afterward (6.3 – 7.9%). For the IDX tests, the average JD positive rate increased from 1.8% at lactation 1 to 3.8% at lactation 4 and declined afterward (3.4 – 4.3%). Overall, the JD positive rate per lactation was higher with PCK compared with IDX. The weighted average of JD-positive rates between the 2 tests increased drastically from lactation 1 (1.8%) to 4 (5.0%) and did not change substantially for lactation 5 and beyond. For either test, the overall positive rate at the fourth lactation was approximately twice as much as that at the first lactation. Also, due to the temporal switch of JD tests, the number of genotyped animals with PCK tests was far less than that with IDX tests because PCK kits were primarily used before 2010, when high-through genotyping was less popular.

Variance components and heritability estimates

Variance components and heritability estimates were obtained using 3 models: a pedigree-only threshold model (THR), a single-step threshold model (ssTHR), and a single-step linear model (ssLR) (Table 2). With ssLR, we estimated the genetic variance to be between 0.001 and 0.005, the herd-year-season variance between 0.001 and 0.003, and the residual variance between 0.02 and 0.05, respectively, for both tests. The estimated heritability was 0.05 for IDX and 0.09 for PCK. The 2 threshold models postulated a liability variable underlying the binary JD test outcomes (positives vs. negatives) when fixing the residual variance to 1.0. These 2 threshold models estimated the genetic variances to be between 0.16 and 0.25 and the herd-year-season variance between 0.18 and 0.25. The heritability estimates were 0.13 and 0.17 for IDX and PCK, respectively. While ssLR had lower variance components than the 2 threshold models, they had proportionally higher residual variances. Hence, the estimated JD heritability with ssLR was lower than those obtained with the 2 threshold models. Overall, our heritability estimates for JD susceptibility (or liability to JD susceptibility)

Table 1. Overall Johne's disease incidence rate (positive % versus negative %) and positive rate (%) by lactation observed in US Holstein cattle¹

Diagnostic test ²	N	Overall		Positive rate (%) by lactation (number of animals)				
		Negative %	Positive %	1	2	3	4	5+
PCK	94,639	93.35	6.64	4.83 (19495)	7.56 (4672)	9.11 (23452)	7.91 (16623)	6.30 (10397)
IDX	271,341	97.20	2.80	1.75 (116084)	2.80 (86543)	3.84 (42850)	4.32 (18175)	3.59 (7680)
Weighted average	—	96.18	3.82	1.76 (135579)	3.17 (111215)	4.48 (66302)	5.04 (34798)	5.17 (18086)

²PCK: Parachek tests; IDX: Idexx tests; Weighted average: average of results weighted by the number of records per diagnostic test.

are within the range (from 0.04 to 0.18) of previous heritability estimates for serum ELISA phenotypes measured in various Holstein populations in the literature (Gonda et al., 2006; Hinger et al., 2008; Berry et al., 2010; Shook et al., 2012). Note that the previous studies mainly reported within-herd heritabilities, whereas ours were cross-herd heritability estimates. If the herd-year-season variance component is removed from the denominator of the heritability formula, the within-herd heritability estimates would be slightly higher (i.e., 0.05 - 0.20).

The 2 threshold models gave similar heritability estimates, and adding genomic information did not significantly alter the posterior variance components. However, the estimated heritability for PCK test results was higher than that for IDX test results based on all 3 models. This difference could be the result of the intrinsic differences between the diagnostic tests that possibly captured genetic and environmental variations differently. Still, the impact of sampling sizes could also matter. In the present study, the number of animals with IDX tests was 2.87 times as many as those with PCK tests. Statistically, a large sample size leads to more precise estimates. Hence, the standard errors of heritability estimates for the IDX tests were significantly smaller than those for the PCK tests (Table 2). The heritability estimates obtained from the 2 threshold models were higher than those of the linear model for the reason explained before. Somewhat differently, Gonda et al. (2006) reported higher heritability estimates with linear models than with threshold models. This difference could arise from varied JD incidence rates between studies. The JD incidence rates in this study were 2.8% for IDX tests, 6.6% for PCK tests, and 3.8% as a weighted average, respectively, which were considerably lower than the JD incidence rates (7.7%, ranging from 4.7% to 12.4%) in the Holstein cows used by Gonda et al. (2006). For a ratio variable, the variance depends on its mean (i.e., average incidence rate)

such that the variance of a linear binary trait decreases substantially as the incidence rate drops. For example, let the phenotypic variance for a 50:50 (JD positives vs. negatives) incidence rate be 100%. Then, a 20% positive incidence rate would retain 64% of the phenotypic variance. When the positive incidence rate dropped to 7.7%, it could retain 28.4% of the phenotypic variance. However, when the positive incidence rate fell further to 2.9%, it could only retain 11.3% of the phenotypic variance. The smaller the JD incidence rate, the more the JD phenotypes deviate from the normal distributions. Possibly, a linear model did not effectively capture the variation of the phenotypes. Instead, our results showed that a threshold model could perform better than a linear model to effectively capture the variance components, particularly when the disease incidence rate was low. Hence, given the binary nature of these traits, a threshold model can be more appropriate when the incidence rate in the minor category is low (Lynch and Walsh, 1998).

Kirkpatrick and Lett (2018) also reported higher heritability estimates with threshold models (0.157 to 0.186) than linear models (0.041 to 0.062) using a data set that partially overlapped with ours. They showed that heritability estimates increased as data were restricted to herds with presumed higher MAP exposure for the linear model. In another study, van Hulzen et al. (2012) analyzed log-transformed ELISA test results (percentage S/P + 50) as the dependent variable in a linear mixed-effects model. They showed that the phenotypic variance increased concurrently with an increase in within-herd test prevalence. Additionally, they observed an increase in heritability due to increased genetic variance relative to phenotypic variance. Attalla et al. (2010) reported higher heritability estimates for milk ELISA test results with the linear model ($h^2 = 0.08$) than the threshold model ($h^2 = 0.065$) when ignoring the maternal genetic effects. Still, they found lowered heritability estimates with the linear model (h^2

Table 2. Variance components and heritability estimates³ (SD) for Johne's disease (JD) susceptibility (or liabilities to JD susceptibility) in US Holstein dairy cattle diagnosed by two different test kits: Idexx and Parachek.^{1,2}

	THR		ssTHR		ssLR	
	IDX	PCK	IDX	PCK	IDX	PCK
h^2	0.13 (0.01)	0.16 (0.12)	0.12 (0.003)	0.17 (0.01)	0.05 (0.003)	0.09 (0.008)
σ_g^2	0.17 (0.02)	0.23 (0.03)	0.16 (0.02)	0.25 (0.05)	0.001 (0.00–09)	0.005 (0.0002)
σ_{hys}^2	0.18 (0.01)	0.24 (0.01)	0.18 (0.009)	0.25 (0.02)	0.001 (0.0004)	0.003 (0.0005)
σ_e^2	1 (0.003)	1 (0.003)	1 (0.003)	1 (0.003)	0.02 (0.0009)	0.05 (0.0005)

¹PCK: Parachek tests; IDX: Idexx tests;

²Variance and covariance components were estimated using three statistical models: a pedigree-based threshold model (THR), a single-step threshold model (ssTHR), and a single-step linear model (ssLR).

³ h^2 = heritability; σ_g^2 = genetic variance; σ_{hys}^2 = herd-year-season variance; σ_e^2 = residual (error) variance.

= 0.075) than with the threshold model ($h^2 = 0.095$) when the genetic variance included the maternal genetic variance. Based on these results, Attalla et al. (2010) stated that there was no solid evidence to recommend a linear model over a threshold model for genetic evaluation. Note that the linear trait in their analysis is not binary scores per se but the natural log of the optical density results obtained with a PCK diagnostic test.

The herd-year-season variances are similar to the additive genetic variance for all models but can vary substantially depending on actual model settings. Factors such as herd size and distribution may interfere with its variance. For JD, grouping the animals by their herd-year-season combinations is conceptually different. The transmission of the disease is intrinsically linked to the environment and is known to be more active in larger herds (>200 cows; Wolf et al., 2014; Corbett et al., 2018). While most studies do not report herd or herd-year-season sizes, and when present, the effect is included in the model as fixed. Thus, direct comparisons between our study and previous ones may not be accurate. To our knowledge, our study utilized the largest JD data set that has been obtained so far to evaluate genetic parameters for this disease. The total number of herds was larger than those reported in the literature, but the average herd size in this study was 349 (max = 19,351 animals). As larger herds tend to have more active transmission, we believe the number of herds and herd size may display lower variance between groups. We also note that 97% of the animals originated from only 3 states with similar weather and management practices may contribute to less variable herd incidence. By adding year-season as a grouping factor, more variance is expected to be captured by the variable. For JD, however, changes in the prevalence of the disease across time are not common, and once infected, the herd tends to continue to be positive (Corbett et al., 2018).

Reliabilities of (genomic) estimated breeding values

The reliabilities of (genomic) estimated breeding values for JD susceptibility based on the linear model (or liability to JD based on the threshold models) were generally low to moderate, with standard errors varying from 0.07 to 0.18 (Table 3). Overall, the standard deviation (error) of the reliability of susceptibility to JD was relatively large, possibly suggesting a wide genetic diversity concerning the susceptibility to JD. Yet, it could also result from inconsistent data quality concerning the JD tests and diverse management practices affecting the JD incidences among herds over the past 2 decades. When considering all animals in the pedigree, the overall reliability means were 0.18

(THR), 0.21 (ssTHR), and 0.22 (ssLR) for IDX, and 0.14 (THR), 0.18 (ssTHR), and 0.18 (ssLR) for PCK. The average reliabilities of JD susceptibility in the present study were comparable to previously reported reliabilities for metabolic diseases (14.6 – 33.7%) but lower than the genomic reliabilities for mastitis (65.8 – 76.6%) (Parker Gaddis et al., 2020). Sanchez et al. (2022) reported high (0.55) genomic reliabilities for JD resistance in French Holstein cattle. However, their results are not directly comparable to ours because, conceptually, JD resistance is not precisely the same as JD susceptibility, as a low JD susceptibility indicates a high JD resistance. Besides that, Sanchez et al. (2022) used an approximation method to calculate reliabilities that differed from ours.

Including genomic information led to higher overall average reliabilities for IDX (0.21) with the single-step threshold model, compared with the pedigree-based threshold model (0.18). While the same effect was observed for PCK, the increase could not be attributed to the use of genotyped animals because only 164 were present in the final data set. These reliabilities were obtained based on animal models, which may differ from a sire or sire-maternal-grandsire model. Sire models were widely used in genetic evaluations. Still, they may underestimate or overestimate EBVs because assumptions such as no genetic relationships between sire and dam and random mating are usually not met in dairy cattle breeding. In contrast, an animal model can provide more consistent estimates (Sun et al., 2009).

The distributions of reliabilities of JD are shown in Figures 2 (IDX) and 3 (PCK). Based on the THR model, most animals had low to moderate (<0.5) reliabilities, yet there were 0.5% of animals with 0.50 reliability or higher. With the ssTHR model, including genomic information led to a slightly larger percentage (4.1%) of animals with reliabilities higher than 0.50. The ssLR model had a similar pattern of reliability group distributions except fewer animals with reliabilities greater than 0.50. For the PCK tests, a considerable percentage (55%) of the animals had low (<0.2) reliabilities. Again, including genomic information in the single-step models (ssTHR) led to more animals with reliabilities of 0.20 or more compared with THR. Around 0.31% of the animals had reliabilities of 0.50 or higher with ssTHR, whereas the same category only accounted for 0.001% (THR) of the animals.

Furthermore, the reliabilities were calculated by subgroups of animals, that is, cows with their own records, sires (dams) with records measured in their daughters, and sires of cows without phenotype (Table 3). Overall, the EBV of the liabilities to JD for sires were higher on average than those for cows or dams. As expected, sires of cows with phenotypes had higher reliabilities

Table 3. Reliability estimates (standard error) of genomic and pedigree-based estimated breeding values for Johne's disease susceptibility in US Holstein dairy cattle ^{1,2}

	N		THR		ssTHR		ssLR	
	IDX	PCK	IDX	PCK	IDX	PCK	IDX	PCK
Overall	638,316	247,031	0.18 (0.14)	0.14 (0.11)	0.21 (0.12)	0.18 (0.13)	0.22 (0.14)	0.18 (0.13)
Cows with phenotype	271,341	94,639	0.31 (0.07)	0.30 (0.08)	0.31 (0.11)	0.27 (0.08)	0.30 (0.11)	0.25 (0.10)
Sires of cows with phenotypes	13,000	8,658	0.41 (0.17)	0.35 (0.15)	0.38 (0.17)	0.32 (0.14)	0.41 (0.15)	0.36 (0.13)
Dams of cows with phenotypes	196,846	60,212	0.24 (0.10)	0.21 (0.11)	0.23 (0.11)	0.19 (0.11)	0.25 (0.12)	0.20 (0.12)
Sires of cows with no phenotype	25,693	14,927	0.18 (0.13)	0.18 (0.15)	0.20 (0.14)	0.17 (0.11)	0.22 (0.14)	0.21 (0.18)

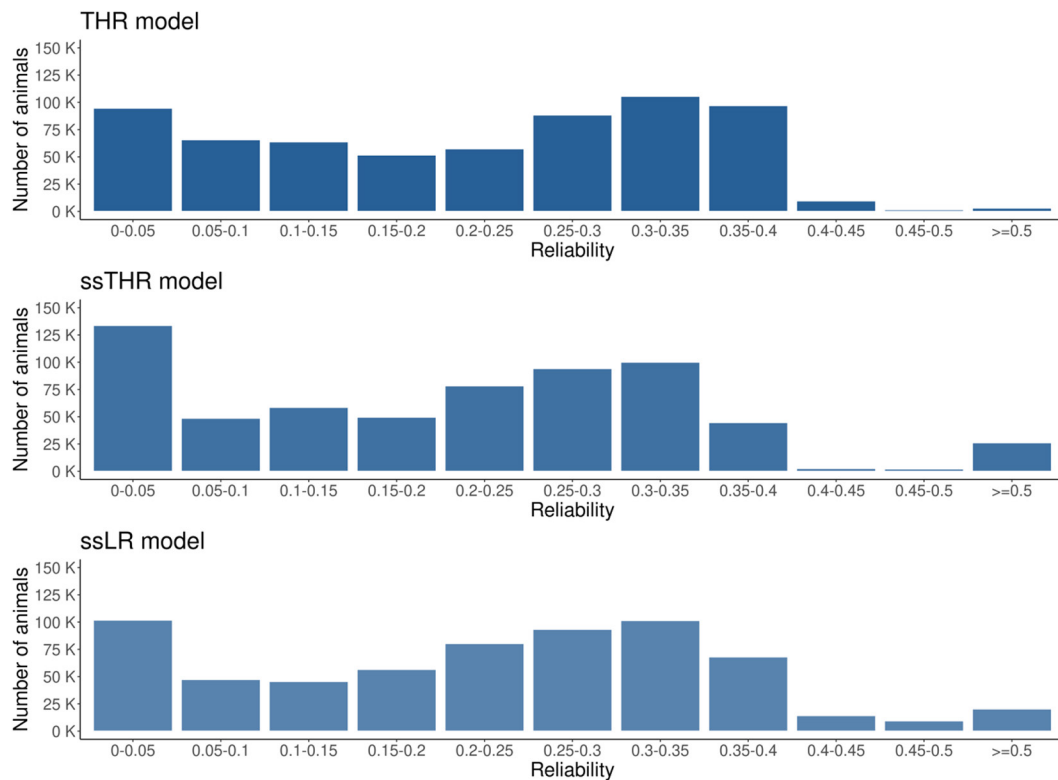
¹Johne's disease was diagnosed with two test kits: Parachek tests (PCK) and Idexx tests (IDX);.

²Reliabilities were calculated for (genomic) estimated breeding values based on three statistical models: a pedigree-based threshold model (THR), a single-step threshold model (ssTHR), and a single-step linear model (ssLR).

than sires of cows without phenotypes. Across models, sires of cows with no phenotypes for IDX seemed to be under the more significant impact (@ 4% of the change in reliability), suggesting that the shift in overall reliability observed in Figure 2 may be linked with this category. For PCK, on the other hand, only dams of cows with phenotypes appeared not to be influenced by the change in models. In contrast, other categories, especially cows with phenotypes, were sensitive to both different phenotype formats and the inclusion of genotypes in the evaluation. In other words, the shift of animals from the 0.05 to 0.1 category to the 0 to

0.05 category between THR and ssTHR models, for instance, could result from an impact on all subgroups collectively.

The addition of genomic information in a genetic analysis aims to better estimate breeding values for animals that lack genotypes through an improved relationship matrix. Although for some categories (i.e., sires of cows with phenotype) there was no significant change in reliability with the addition of genomic information, sires of cows without phenotype had considerably higher reliabilities. Conceptually, this category is the one that benefits from the single-step approach. As

**Figure 2.** Overall reliabilities of Idexx test for Johne's disease in US Holstein dairy cattle obtained using 3 models: pedigree-based threshold (THR), single-step threshold (ssTHR), and single-step linear (ssLR) models.

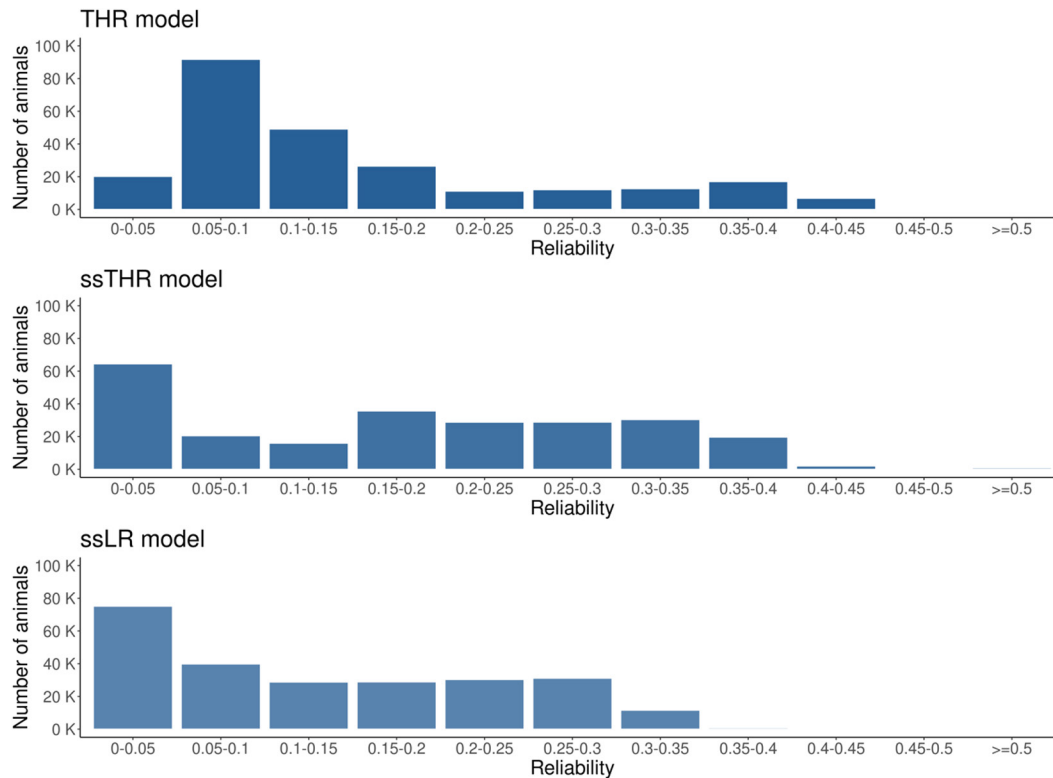


Figure 3. Overall reliabilities of Parachek test for Johne's disease in US Holstein dairy cattle obtained using 3 models: pedigree-based threshold (THR), single-step threshold (ssTHR), and single-step linear (ssLR) models.

sires of cows with no phenotypes have a more distant connection to the phenotypes per se and are connected to it only by the relationship matrix, the blending of genomic and pedigree led to more information utilized in the genetic evaluation for this category of sires, compared with other categories.

Between the 2 JD tests, the reliabilities of JD breeding values were higher with the IDX tests than those with the PCK tests because the sample sizes (and the family sizes) with the IDX tests were larger than those with the PCK tests. By adding genomic information in the single-step model (ssTHR), an increase in the reliability for all categories was expected. Yet, the single-step approach did not significantly change reliability values when the trait had many phenotypes. These results coincided with the observations on feed intake by Harder et al. (2020). For the IDX and PCK tests, the evaluations on JD susceptibility did not vary substantially, whether using pedigree information or including genomic information.

Reliability corresponds to the correlation between the estimated and actual breeding values of the animals. Consequently, models with higher heritability values are expected to yield higher reliabilities. However, the results presented in this work partially contradict

this assumption. Despite using the same data set, the threshold models presented higher heritabilities while higher reliabilities were derived from the linear model. It is important to note that regarding these 2 types of models, direct comparisons should be taken carefully as they are in different scales (liability and linear). The implication of different scales in comparing reliabilities of the same animals has been reported, suggesting higher values for linear models as a consequence (Tsuruta et al., 2017). When back transformed following Dempster and Lerner (1950), the heritabilities for threshold models were 0.04 and 0.05 for PCK using pedigree-based and single-step models, respectively, and 0.02 for IDX with both THR and ssTHR models. Considering the lower converted heritabilities and reliabilities given by the threshold model and also the computational convenience of a linear model, the latter would be practically preferred for the JD genetic evaluations.

Approximate genetic correlations

Approximate genetic correlations using sire PTAs for ssTHR, THR, and ssLR models are presented in Table 4. In this study, we evaluated the susceptibility to JD. Hence, a high PTA indicates a high JD risk

and vice versa. In view of genetic selection, negative genetic correlations with PTA for susceptibility to JD are beneficial to avoid unintended selection antagonism in which the selection of favorable traits also increases JD incidences. Overall, JD susceptibility had favorable genetic correlations, through low ($-0.01 \sim -0.11$), with milk yield, fat yield, protein yield, production life, livability, and resistance to mastitis, and a positive genetic correction with somatic cell account ($0 \sim 0.07$). Relatively speaking, the genetic correlations obtained for IDX were slightly higher than those obtained for PCK. Among the different models, the ssTHR model gave slightly higher genetic correlations for IDX than THR and ssLR. For PCK, however, THR gave higher genetic correlations than the other 2 models. These discrepancies may be intrinsic to the statistical methods or JD tests or random subjective to the samples used.

Concerning production traits (milk, fat, and protein), the genetic correlations indicate that higher susceptibility for JD is linked with lower milk yield, fat, and protein levels ($-0.09 \sim -0.11$ for IDX and $-0.02 \sim -0.10$ for PCK). Previous genetic correlation estimates of MAP with production traits ranged from -0.44 to 0.04 . For instance, Berry et al. (2010) estimated the genetic correlation between susceptibility to JD and first lactation performance and found values varying from -0.44 for milk yield to 0.06 for percentage of fat. On the other hand, Attalla et al. (2010), considering linear phenotypes for JD based on ELISA optical density, showed correlations ranging from -0.34 for NM to -0.18 for protein in kilograms, however, with no effect on protein or fat percentages or milk production. Similar results were reported when direct EBV correlations were used, with no significant correlations for milk yield (Brito et

al., 2018). While all these genetic correlation estimates were negative and low to modest, they were favorable because, genetically, animals with high average yield tended to be associated with a low risk of MAP infection.

Positive correlations between susceptibility to JD and production traits were also documented, e.g., by Shook et al. (2012). They estimated that the posterior means of genetic correlations for MAP with yield traits were 0.22 (MY), 0.16 – 0.20 (FY), and 0.15 (PY), respectively. However, none of these genetic corrections significantly differed from zero because their 95% highest posterior density (HPD) interval included zero. Two main differences exist between our study and Shook et al. (2012). First, the Israel Holstein population studied by Shook et al. (2012) is genetically different from the US Holstein population used in the present study, and the former had a considerably lower JD incidence rate (1.6%). They utilized a recursive model, which assumed direct, recursive effects from MAP infection to the production traits, but the feedback or simultaneous effects were non-existent. The latter assumption, however, may not be true. The weak positive genetic correlations of MAP with the 3 yield traits suggest that animals with high breeding values for yield may be genetically more susceptible to Johne's disease. Nevertheless, these genetic correlations, including ours, are not statistically significant. Therefore, all these genetic correlations between JD and production traits must be regarded with some uncertainty.

Coincidentally, Gonda et al. (2007) reported significantly lower milk production and fat and protein content per lactation for JD-susceptible cows. Their results also showed that infected animals would present a produc-

Table 4. Approximated genetic correlations between Johne's Disease susceptibility and production and health-related traits^{1,2}

Trait	AvRel (%) ⁴	THR		ssTHR		ssLR	
		IDX	PCK	IDX	PCK	IDX	PCK
		r_g^2	r_g^2	r_g^2	r_g^2	r_g^2	r_g^2
Milk yield	95.3	-0.08	-0.08	-0.09	-0.02	-0.05	-0.02
Fat	95.3	-0.10	-0.09	-0.10	-0.03	-0.06	-0.02
Protein	95.2	-0.10	-0.10	-0.11	-0.03	-0.06	-0.02
SCS	95.4	0.06	0.06	0.07	0.01	0.04	0.01
PL ³	90.9	-0.10	-0.09	-0.11	-0.02	-0.06	-0.02
Livability	81.9	-0.04	-0.04	-0.05	-0.01	-0.02	-0.004
Mastitis	79.0	-0.06	-0.05	-0.07	0.00	-0.05	0.003

¹Johne's disease was diagnosed with two test kits: PCK: Parachek and IDX: Idexx;.

²Correlations were calculated from the correlation of sires in Johne's Disease evaluation ($n = 18509$) obtained three statistical models: a pedigree-based threshold model (THR), a single-step threshold model (ssTHR), and a single-step linear model (ssLR).

³PL = Productive Life.

⁴AvRel = average reliability of bulls for production and health-related traits.

tive life 2.8 mo shorter than negative animals. Indeed, the genetic correlations in our study for productive life (-0.02 to -0.11) would indicate the same pattern. On the other hand, livability, a trait that represents the probability that a lactation does not end with the cow's death, presented a negative but more negligible correlation (-0.01 to -0.04). Similarly, Shook et al. (2012) also reported the adverse effects of MAP infection on production traits in the Israel Holstein population, though their genetic correlation estimates were positive. These adverse phenotypic effects of MAP infection on production traits were included as circumstantial evidence. It is noted that though many phenotypic and genetic correlations between 2 traits tend to be in the same direction, the opposite situation is also likely when opposite residual correlations dominate the phenotypic correlation. The latter situations, however, are fewer than the former situations.

Genetic correlations between JD and traits such as livability or productive life are limited in the literature, and the available findings, as the ones observed in the work of Brito et al. (2018), show a significant correlation between bulls' EBVs and livability (measured as direct herd life in days) from 0.12 to 0.19. Likewise, a significant and favorable correlation of -0.29 between productive life and antibody response for JD was estimated by Attalla et al. (2010), indicating that the selection of animals based on longevity in the herd also decreases the susceptibility for JD. For health-related traits such as SCS and mastitis resistance, correlations were favorable. As an infectious disease, it is expected that debilitated animals would have an immune response reflected by SCS directly or by a weakened system caused by JD that would facilitate infection of other diseases, such as mastitis (Martins et al., 2018).

The approximate correlation with mastitis resistance observed in this work supports this hypothesis.

Genetic trends

Annual averages of breeding values for JD susceptibility (ssLR) or liabilities to JD susceptibility (ssTHR) showed temporal decreasing trends. For example, with the IDX tests, the annual means of JD breeding values increased during 2002 and 2004, remained relatively stable from 2008 to 2009, and dropped after 2009 (Figure 4). Genetic trends of JD were estimated jointly for the 2 JD test results obtained from linear (ssLR) and threshold (ssTHR) single-step models, respectively (Table 5), assuming that the differences in observed JD incidences between the 2 JD tests were non-genetic. The genetic trends were relatively flat from 1994 to 2009 for PCK tests (Figure 6) and from 2002 to 2009 for IDX tests (Figure 5) and began to drop afterward (Figure 5). The extent of the decrease in genetic trend for IDX tests after 2009 was more significant with the single-step threshold model (ssTHR) than with the single-step linear model (ssLR). In contrast, PCK test results did not show apparent changes in the genetic trend over the years. The visual fluctuations in the genetic trends between 2009 and 2017 were attributable to the fact that fewer data were analyzed. There were between 5 and 124 PCK records per year for this period, which was insufficient to accurately estimate the yearly means of JD incidence rate, thus leading to inaccurately estimated genetic trends.

Although there is no official genetic evaluation or selection program implemented for Johne's disease in the US, this study observed significantly (P -value < 0.01) negative, favorable trends based on the GEBV obtained from the linear (ssLR) and the threshold

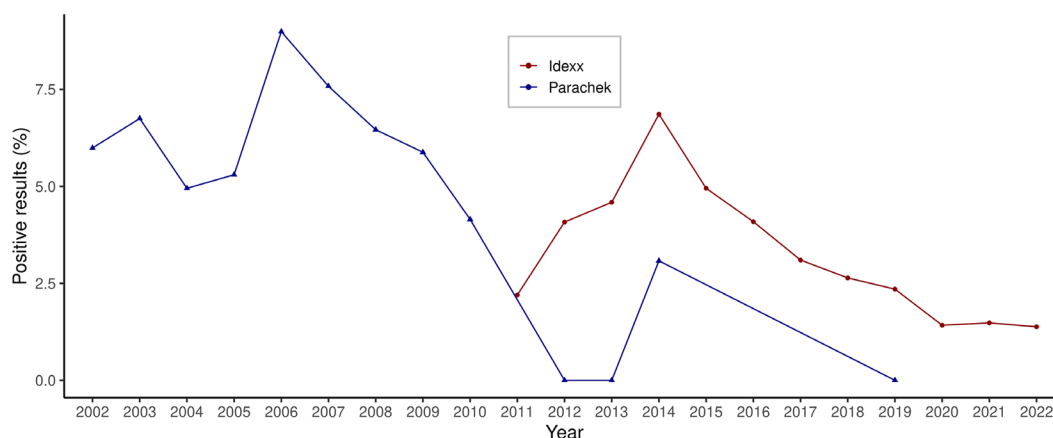


Figure 4. Phenotypic trend as the percentage of positive results relative to total tests with using 2 test kits for Johne's Disease, Idexx and Parachek, respectively.

Table 5. Estimated intercepts and slopes from linear regression of genetic trends for genomic breeding values of Johne's disease obtained from a threshold and a linear single-step models ^{1,2,3}

Model	Heterogeneous intercept		Genetic trend (slope)			
	IDX	PCK	Estimate	SE	t-value	Probability
ssTHR	-0.0918 (0.0190)	-0.1440 (0.0163)	-0.0091	0.0018	-5.226	<0.001
ssLR	-0.005 (0.0016)	-0.1149 (0.0014)	-0.0006	0.0001	-3.810	<0.001

¹Johne's disease was diagnosed with two test kits: PCK: Parachek and IDX: Idexx;.

²Genetic trends were estimated for annual means obtained from two statistical models: a single-step threshold model (ssTHR) and a single-step linear model (ssLR);.

³SE = standard error.

(ssTHR) models, respectively. The estimated genetic trends from the GEBV obtained from both models are not comparable because they were not assessed on the same scales. The threshold model estimated (genomic) EBV on the unobserved liability scale, whereas the linear model estimated (genomic) EBV on the observed binary scale. Still, the results from both models consistently suggested a negative, favorable trend on the IDX test results for JD, likely starting around 2004. Coincidentally, the genomic selection program in US Holstein cattle began in 2009 and accelerated after 2010 (Wiggins et al., 2017). The introduction of genomic selection in US dairy cattle improvement programs in 2008

has led to a significant increase in the rates of genetic gain, particularly for traits with low heritabilities, such as fertility, longevity, and udder health (García-Ruiz et al., 2016). Possibly, the negative, favorable trend can be attributed to indirect genetic gain from selecting highly genetically correlated traits, such as milk yield, somatic cell score, and lifespan. This postulation was supported by the results that the JD susceptibility was associated with milk yield, milk fat, and milk protein levels and also negatively correlated with productive life and livability in this US Holstein population. It is possible that the favorable, negative genetic trend was associated with NM\$ used in the US cattle genetic evalu-

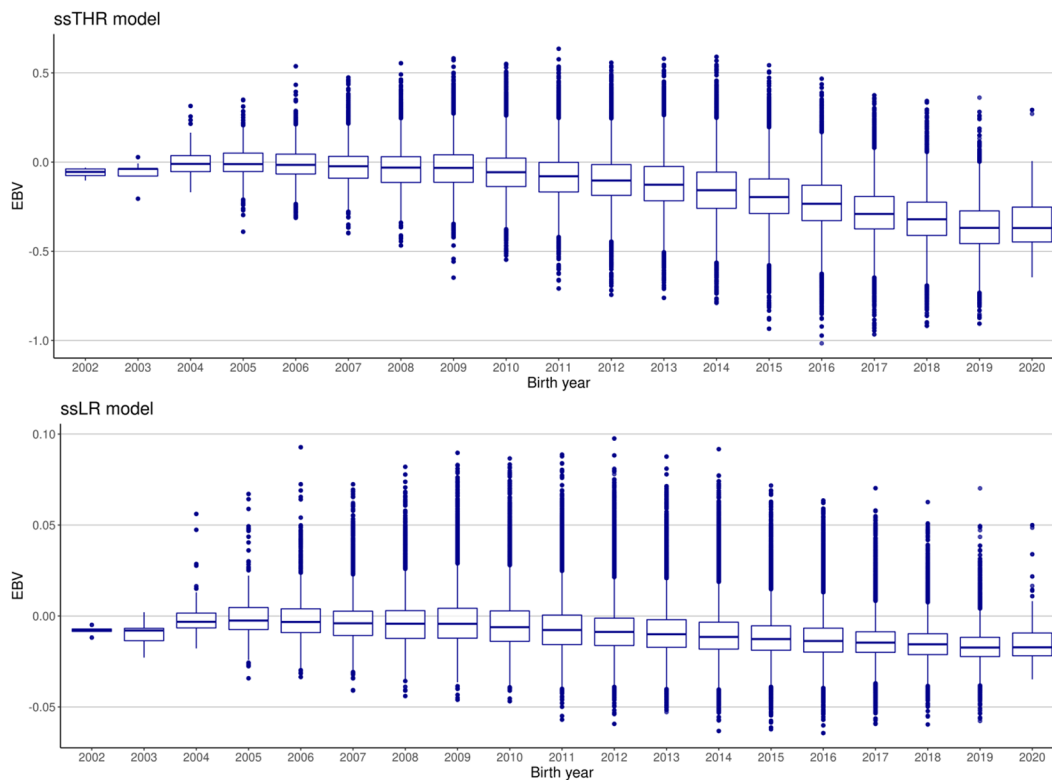


Figure 5. Genetic trend for the susceptibility to Johne's disease (JD) as diagnosed with the Idexx test in US Holstein cows. The JD susceptibilities were estimated using single-step threshold (ssTHR) and single-step linear (ssLR) models, respectively.

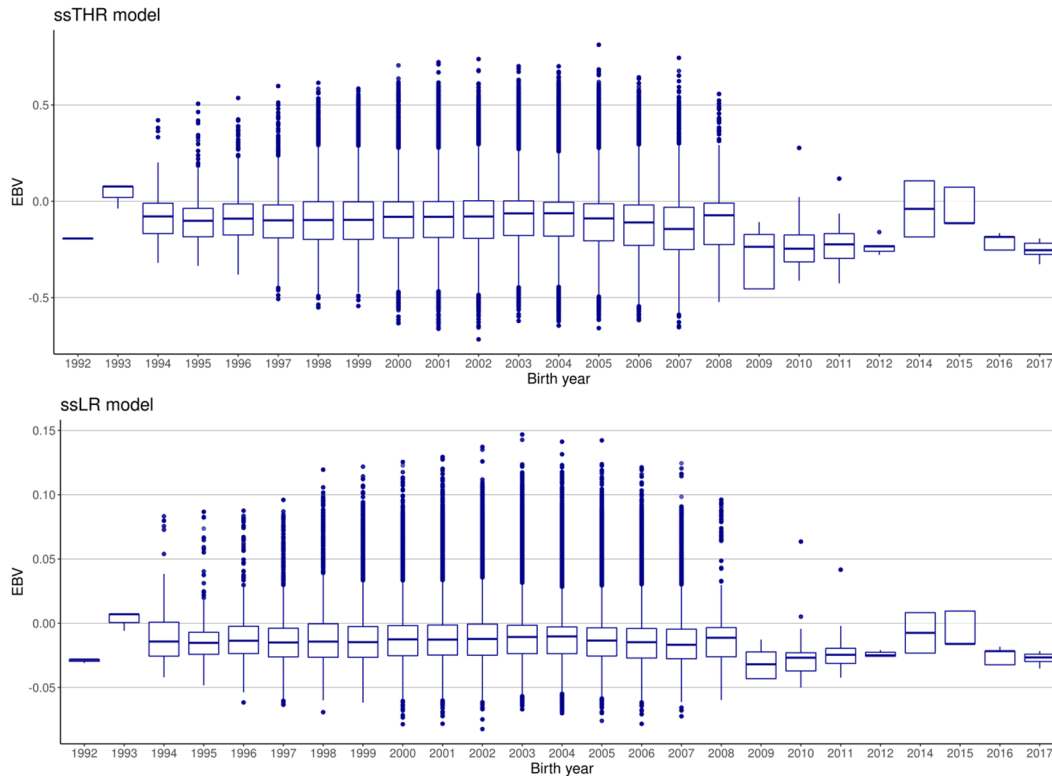


Figure 6. Genetic trend of the susceptibility to Johne's disease (JD) as diagnosed with the Parachek test in US Holstein cows. The JD susceptibilities were estimated using single-step threshold (ssTHR) and single-step linear (ssLR) models, respectively.

ations. Net merit is a selection index used to identify animals expected to have the greatest lifetime profit for a combination of economically important traits. It takes into account multiple traits, including milk yield, fat and protein yield, SCS, productive life, and daughter pregnancy rate, among others. The weights assigned to these traits in the calculation of NM\$ are determined based on their relative economic importance to the dairy industry.

Coincidentally, Neupane et al. (2021) showed that a moderate correlation with productive life helped decrease replacement heifer cost resulting from the correlated response in heifer livability and assisted in genetic improvement programs through added selection intensity resulting from beneficial genetic correlations. Recently, Sanchez et al. (2022) reported a slightly favorable genetic trend in resistance to JD in Holstein cattle raised in northwestern France over the last 2 decades, also possibly resulting from the indirect selection because of a low positive genetic correlation (0.06) between resistance to JD and total merit index. Besides that, ad hoc selection may also be one of the forces that have lowered the JD incidences since 2004 because culling animals with various diseases or disorders is a routine practice in many dairy farms ([https://](https://queries.uscdcb.com/publish/dhi/dhi09/cull1.htm)

queries.uscdcb.com/publish/dhi/dhi09/cull1.htm). We hold that the latter could be one of the reasons for the reduction of JD incidences. Although our results provided plausible evidence of indirect selection against the susceptibility to JD due to the selection for production and health traits throughout the years, the pace of improvement and magnitude of correlations indicate that the progress toward lower incidence of JD in US herds cannot rely solely on indirect selection. With an estimated prevalence of up to 75% of JD in dairy herds across the US (Garcia and Shalloo, 2015), the selection against JD susceptibility has the potential to expedite the process.

CONCLUSION

Johne's disease records have been collected in the US since 2002, consisting of test results with IDX and PCK kits. The records have accumulated substantially over the past 2 decades. The addition of genotypes has enabled the use of the single-step method to estimate genetic parameters and implement genetic evaluations to assess JD susceptibility. The overall positive rate of JD in the US Holstein cattle was 2.80% with IDX tests and 6.64% with PCK tests. Estimated heritabilities

were 0.05 to 0.09 for JD susceptibilities on the observed binary scale based on the single-step linear model and 0.12 to 0.17 for the liabilities to JD on the unobserved liability scale based on the 2 threshold models. Our results assert that Johne's disease has a genetic component upon which selection could operate to achieve the expected genetic improvement. The reliabilities of (genomic) breeding values for JD susceptibility (or liability to JD) were low to moderate. There were approximately 0.001 to 4.1% of the animals with >0.5 reliabilities. Another motivation of this preliminary study was to leverage the current data repositories toward the official implementation of genetic evaluation of Johne's disease in the Holstein dairy breed. The JD phenotypes and genotypes have accumulated substantially in the available data repositories. Yet, the protocol used for diagnosing JD should be considered because varied protocols led to systematic biases in the estimated JD incidence rate. Given the discrepancies between the tests and the low-to-moderate genetic correlations, treating different test results as different traits in a joint multi-trait analysis seems appropriate. The health status of animals can be modeled linearly as a binary variable or described by the underlying continuous liability variable. Adding genomic information resulted in elevated reliabilities of estimated genomic breeding values. The present study utilized animal models in 3 forms, allowing all relatives to contribute to the assessment of an animal and permitting a cow to be evaluated based on its own phenotypes. Follow-up studies are expected as more JD phenotypes and genotypes become available.

ACKNOWLEDGMENTS

LN was supported by the Fulbright Brazil Commission and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

REFERENCES

- Aguilar, I., E. N. Fernandez, A. Blasco, O. Ravagnolo, and A. Legarra. 2020. Effects of ignoring inbreeding in model-based accuracy for BLUP and SSGBLUP. *J. Anim. Breed. Genet.* 137:356–364. <https://doi.org/10.1111/jbg.12470>.
- Aguilar, I., I. Misztal, D. L. Johnson, A. Legarra, S. Tsuruta, and T. J. Lawlor. 2010. Hot topic: A unified approach to utilize phenotypic, full pedigree, and genomic information for genetic evaluation of Holstein final score. *J. Dairy Sci.* 93:743–752. <https://doi.org/10.3168/jds.2009-2730>.
- Attalla, S. A., A. J. Seykora, J. B. Cole, and B. J. Heins. 2010. Genetic parameters of milk ELISA scores for Johne's disease. *J. Dairy Sci.* 93:1729–1735. <https://doi.org/10.3168/jds.2009-2625>.
- Bannantine, J. P., M. E. Hines, L. E. Bermudez, A. M. Talaat, S. Sreevatsan, J. R. Stabel, Y. F. Chang, P. M. Coussens, R. G. Barletta, W. C. Davis, D. M. Collins, Y. T. Grohn, and V. Kapur. 2014. Rational framework for evaluating the next generation of vaccines against mycobacterium avium subspecies paratuberculosis. *Front. Cell. Infect. Microbiol.* 4:1–11. <https://doi.org/10.3389/fcimb.2014.00126>.
- Berry, D. P., M. Good, P. Mullooney, A. R. Cromie, and S. J. More. 2010. Genetic variation in serological response to Mycobacterium avium subspecies paratuberculosis and its association with performance in Irish Holstein-Friesian dairy cows. *Livest. Sci.* 131:102–107. <https://doi.org/10.1016/j.livsci.2010.03.007>.
- Brito, L. F., S. Mallikarjunappa, M. Sargolzaei, A. Koeck, J. Chesnais, F. S. Schenkel, K. G. Meade, F. Miglior, and N. A. Karrow. 2018. The genetic architecture of milk ELISA scores as an indicator of Johne's disease (paratuberculosis) in dairy cattle. *J. Dairy Sci.* 101:10062–10075. <https://doi.org/10.3168/jds.2017-14250>.
- Calo, L. L., R. E. McDowell, L. D. VanVleck, and P. D. Miller. 1973. Genetic Aspects of Beef Production among Holstein-Friesians Pedigree Selected for Milk Production. *J. Anim. Sci.* 37:676–682. <https://doi.org/10.2527/jas1973.373676x>.
- Christensen, O., and M. Lund. 2010. Genomic relationship matrix when some animals are not genotyped. *Genet. Sel. Evol.* 42:1–8. <https://doi.org/10.1186/1297-9686-42-2>.
- Cole, J. B., S. A. E. Eaglen, C. Maltecca, H. A. Mulder, and J. E. Pryce. 2020. The future of phenomics in dairy cattle breeding. *Anim. Front.* 10:37–44. <https://doi.org/10.1093/af/vfaa007>.
- Cole, J.B., D. Null, and L. Bacheller. 2008. A data exchange format and national database for producer-recorded health event data from on-farm management software. Pages 2–3 in *Journal of Dairy Science*.
- Corbett, C. S., S. A. Naqvi, J. De Buck, U. Kanevets, J. P. Kastelec, and H. W. Barkema. 2018. Environmental sample characteristics and herd size associated with decreased herd-level prevalence of Mycobacterium avium ssp. paratuberculosis. *J. Dairy Sci.* 101:8092–8099. <https://doi.org/10.3168/jds.2018-14661>.
- Davis, W. C., and K. T. Park. 2018. Progress Towards Control of a Mycobacterial Pathogen, Mycobacterium avium subsp. paratuberculosis, the Causative Agent of Johne's Disease in Cattle and Humans. *Hangug. Sigum Wisaeng Anjeonseong Haghoeji* 33:221–228. <https://doi.org/10.13103/JFHS.2018.33.4.221>.
- Dempster, E. R., and I. M. Lerner. 1950. Heritability of threshold characters. *Genetics* 35:212–236. <https://doi.org/10.1093/genetics/35.2.212>.
- Dempster, E. R., and I. M. Lerner. 1950. Heritability of threshold characters. *Genetics* 35:212–236. <https://doi.org/10.1093/genetics/35.2.212>.
- García, A. B., and L. Shalloo. 2015. Invited review: The economic impact and control of paratuberculosis in cattle. *J. Dairy Sci.* 98:5019–5039. <https://doi.org/10.3168/jds.2014-9241>.
- García-Ruiz, A., J. B. Cole, P. M. VanRaden, G. R. Wiggins, F. J. Ruiz-López, and C. P. Van Tassell. 2016. Changes in genetic selection differentials and generation intervals in US Holstein dairy cattle as a result of genomic selection. *Proc. Natl. Acad. Sci. USA* 113:E3995–E4004. <https://doi.org/10.1073/pnas.1519061113>.
- Geweke, J. 1992. Evaluating the Accuracy of Sampling-Based Approaches to the Calculation of Posterior Moments. *J.O. Berger, J.M. Bernardo, A.P. Dawid, and A.F.M. Smith, ed. Oxford University Press, Oxford, UK*.
- Gianola, D. 1982. Theory and Analysis of Threshold Characters. *J. Anim. Sci.* 54:1079–1096. <https://doi.org/10.2527/jas1982.5451079x>.
- Gonda, M. G., Y. M. Chang, G. E. Shook, M. T. Collins, and B. W. Kirkpatrick. 2006. Genetic variation of Mycobacterium avium ssp. paratuberculosis infection in US Holsteins. *J. Dairy Sci.* 89:1804–1812. [https://doi.org/10.3168/jds.S0022-0302\(06\)72249-4](https://doi.org/10.3168/jds.S0022-0302(06)72249-4).
- Gonda, M. G., Y. M. Chang, G. E. Shook, M. T. Collins, and B. W. Kirkpatrick. 2007. Effect of Mycobacterium paratuberculosis infection on production, reproduction, and health traits in US Holsteins. *Prev. Vet. Med.* 80:103–119. <https://doi.org/10.1016/j.prevetmed.2007.01.011>.
- Harder, I., E. Stamer, W. Junge, and G. Thaller. 2020. Estimation of genetic parameters and breeding values for feed intake and energy balance using pedigree relationships or single-step genomic evaluation in Holstein Friesian cows. *J. Dairy Sci.* 103:2498–2513. <https://doi.org/10.3168/jds.2019-16855>.

- Hinger, M., H. Brandt, and G. Erhardt. 2008. Heritability estimates for antibody response to *Mycobacterium avium* subspecies paratuberculosis in German Holstein cattle. *J. Dairy Sci.* 91:3237–3244. <https://doi.org/10.3168/jds.2008-1021>.
- Kirkpatrick, B. W., M. E. Cooke, M. Frie, K. R. B. Sporer, B. Lett, S. J. Wells, and P. M. Coussens. 2022. Genome-wide association analysis for susceptibility to infection by *Mycobacterium avium* ssp. paratuberculosis in US Holsteins. *J. Dairy Sci.* 105:4301–4313. <https://doi.org/10.3168/jds.2021-21276>.
- Kirkpatrick, B. W., and B. M. Lett. 2018. Short communication: Heritability of susceptibility to infection by *Mycobacterium avium* ssp. paratuberculosis in Holstein cattle. *J. Dairy Sci.* 101:11165–11169. <https://doi.org/10.3168/jds.2018-15021>.
- Kirkpatrick, B. W., X. Shi, G. E. Shook, and M. T. Collins. 2011. Whole-Genome association analysis of susceptibility to paratuberculosis in Holstein cattle. *Anim. Genet.* 42:149–160. <https://doi.org/10.1111/j.1365-2052.2010.02097.x>.
- Korsgaard, I. R., M. S. Lund, D. Sorensen, D. Gianola, P. Madsen, and J. Jensen. 2003. Multivariate Bayesian analysis of Gaussian, right censored Gaussian, ordered categorical and binary traits using Gibbs sampling. *Genet. Sel. Evol.* 35:159–183. <https://doi.org/10.1186/1297-9686-35-2-159>.
- Legarra, A., I. Aguilar, and I. Misztal. 2009. A relationship matrix including full pedigree and genomic information. *J. Dairy Sci.* 92:4656–4663. <https://doi.org/10.3168/jds.2009-2061>.
- Lourenco, D., A. Legarra, S. Tsuruta, Y. Masuda, I. Aguilar, and I. Misztal. 2020. Single-step genomic evaluations from theory to practice: using snp chips and sequence data in blupf90. *Genes (Basel)* 11:1–32. <https://doi.org/10.3390/genes11070790>.
- Lynch, M., and B. Walsh. 1998. *Genetics and Analysis of Quantitative Genetics*. Sinauer Associates Inc., Sunderland, MA.
- Mallikarjunappa, S., L. F. Brito, S. D. Pant, F. S. Schenkel, K. G. Meade, and N. A. Karrow. 2021. Johne's Disease in Dairy Cattle: An Immunogenetic Perspective. *Front. Vet. Sci.* 8:1–19. <https://doi.org/10.3389/fvets.2021.718987>.
- Martins, E. G., P. Oliveira, B. M. Oliveira, D. Mendonça, and J. Niza-Ribeiro. 2018. Association of paratuberculosis sero-status with milk production and somatic cell counts across 5 lactations, using multilevel mixed models, in dairy cows. *J. Dairy Sci.* 101:7638–7649. <https://doi.org/10.3168/jds.2017-13746>.
- McKenna, S. L. B., H. W. Barkema, G. P. Keefe, and D. C. Sockett. 2006. Agreement between three ELISAs for *Mycobacterium avium* subsp. paratuberculosis in dairy cattle. *Vet. Microbiol.* 114:285–291. <https://doi.org/10.1016/j.vetmic.2005.12.002>.
- Minozzi, G., L. Buggiotti, A. Stella, F. Strozzi, M. Luini, and J. L. Williams. 2010. Genetic loci involved in antibody response to *Mycobacterium avium* ssp. paratuberculosis in cattle. *PLoS One* 5. <https://doi.org/10.1371/journal.pone.0011117>.
- Misztal, I., A. Legarra, and I. Aguilar. 2009. Computing procedures for genetic evaluation including phenotypic, full pedigree, and genomic information. *J. Dairy Sci.* 92:4648–4655. <https://doi.org/10.3168/jds.2009-2064>.
- Misztal, I., S. Tsuruta, D. Lourenco, I. Aguilar, A. Legarra, and Z. Vitezica. 2014. Manual for BLUPF90 Family of Programs. Accessed. http://nce.ads.uga.edu/wiki/lib/exe/fetch.php?media=blupf90_all2.pdf.
- Neupane, M., J. L. Hutchison, C. P. Van Tassell, and P. M. VanRaden. 2021. Genomic evaluation of dairy heifer livability. *J. Dairy Sci.* 104:8959–8965. <https://doi.org/10.3168/jds.2020-19687>.
- Pant, S. D., C. P. Verschoor, F. S. Schenkel, Q. You, D. F. Kelton, and N. A. Karrow. 2011. Bovine PGLYRP1 polymorphisms and their association with resistance to *Mycobacterium avium* ssp. Paratuberculosis. *Anim. Genet.* 42:354–360. <https://doi.org/10.1111/j.1365-2052.2010.02153.x>.
- Parker Gaddis, K. L., P. M. VanRaden, J. B. Cole, H. D. Norman, E. Nicolazzi, and J. W. Dürr. 2020. Symposium review: Development, implementation, and perspectives of health evaluations in the United States. *J. Dairy Sci.* 103:5354–5365. <https://doi.org/10.3168/jds.2019-17687>.
- Pinedo, P. J., C. D. Buergelt, G. A. Donovan, P. Melendez, L. Morel, R. Wu, T. Y. Langae, and D. O. Rae. 2009a. Association between CARD15/NOD2 gene polymorphisms and paratuberculosis infection in cattle. *Vet. Microbiol.* 134:346–352. <https://doi.org/10.1016/j.vetmic.2008.09.052>.
- Pinedo, P. J., C. D. Buergelt, G. A. Donovan, P. Melendez, L. Morel, R. Wu, T. Y. Langae, and D. O. Rae. 2009b. Candidate gene polymorphisms (BoIFNG, TLR4, SLC11A1) as risk factors for paratuberculosis infection in cattle. *Prev. Vet. Med.* 91:189–196. <https://doi.org/10.1016/j.prevetmed.2009.05.020>.
- Pryce, J. E., R. J. Esslemont, R. Thompson, R. F. Veerkamp, M. A. Kossabati, and G. Simm. 1998. Estimation of genetic parameters using health, fertility and production data from a management recording system for dairy cattle. *Anim. Sci.* 66:577–584. <https://doi.org/10.1017/S1357729800009152>.
- Rasmussen, P., H. W. Barkema, S. Mason, E. Beaulieu, and D. C. Hall. 2021. Economic losses due to Johne's disease (paratuberculosis) in dairy cattle. *J. Dairy Sci.* 104:3123–3143. <https://doi.org/10.3168/jds.2020-19381>.
- Rauw, W. M., E. Kanis, E. N. Noordhuizen-Stassen, and F. J. Grommers. 1998. Undesirable side effects of selection for high production efficiency in farm animals: A review. *Livest. Prod. Sci.* 56:15–33. [https://doi.org/10.1016/S0301-6226\(98\)00147-X](https://doi.org/10.1016/S0301-6226(98)00147-X).
- Sanchez, M. P., T. Tribout, S. Fritz, R. Guatteo, C. Fourichon, L. Schibler, A. Delafosse, and D. Boichard. 2022. A single step genetic evaluation including causal candidate SNPs for resistance to paratuberculosis in Holstein cattle. Pages 1–4 in *World Congress of Genetics Applied to Livestock Production*, Rotterdam, Netherlands.
- Settles, M., R. Zanella, S. D. McKay, R. D. Schnabel, J. F. Taylor, R. Whitlock, Y. Schukken, J. S. Van Kessel, J. M. Smith, and H. Neibergs. 2009. A whole genome association analysis identifies loci associated with *Mycobacterium avium* subsp. paratuberculosis infection status in US holstein cattle. *Anim. Genet.* 40:655–662. <https://doi.org/10.1111/j.1365-2052.2009.01896.x>.
- Shook, G. E., M. Chaffer, X. L. Wu, and E. Ezra. 2012. Genetic parameters for paratuberculosis infection and effect of infection on production traits in Israeli Holsteins. *Anim. Genet.* 43(s1):56–64. <https://doi.org/10.1111/j.1365-2052.2012.02349.x>.
- Sigdel, A., X. L. Wu, K. L. Parker Gaddis, H. D. Norman, J. A. Carrillo, J. Burchard, F. Peñagaricano, and J. Dürr. 2022. Genetic Evaluations of Stillbirth for Five United States Dairy Breeds: A Data-Resource Feasibility Study. *Front. Genet.* 13:1–12. <https://doi.org/10.3389/fgene.2022.819678>.
- Sun, C., P. Madsen, U. S. Nielsen, Y. Zhang, M. S. Lund, and G. Su. 2009. Comparison between a sire model and an animal model for genetic evaluation of fertility traits in Danish Holstein population. *J. Dairy Sci.* 92:4063–4071. <https://doi.org/10.3168/jds.2008-1918>.
- Tsuruta, S., D. A. L. Lourenco, I. Misztal, and T. J. Lawlor. 2017. Genomic analysis of cow mortality and milk production using a threshold-linear model. *J. Dairy Sci.* 100:7295–7305. <https://doi.org/10.3168/jds.2017-12665>.
- Tsuruta, S., I. Misztal, and I. Strandén. 2001. Use of the preconditioned conjugate gradient algorithm as a generic solver for mixed-model equations in animal breeding applications. *J. Anim. Sci.* 79:1166–1172. <https://doi.org/10.2527/2001.7951166x>.
- USDA. 2023. Veterinary Biological Products Licensees and Permittees. Ames, IA.
- van Hulzen, K. J. E., G. C. B. Schopen, J. A. M. van Arendonk, M. Nielen, A. P. Koets, C. Schrooten, and H. C. M. Heuven. 2012. Genome-wide association study to identify chromosomal regions associated with antibody response to *Mycobacterium avium* subspecies paratuberculosis in milk of Dutch Holstein-Friesians. *J. Dairy Sci.* 95:2740–2748. <https://doi.org/10.3168/jds.2011-5005>.
- VanRaden, P. M. 2008. Efficient methods to compute genomic predictions. *J. Dairy Sci.* 91:4414–4423. <https://doi.org/10.3168/jds.2007-0980>.
- VanRaden, P. M. 2017. Net Merit as a Measure of Lifetime Profit: 2017 Revision. Accessed. <https://aipl.arsusda.gov/reference/nmcalc-2014.htm>.

- VanRaden, P. M., and G. R. Wiggans. 1995. Productive Life Evaluations: Calculation, Accuracy, and Economic Value. *J. Dairy Sci.* 78:631–638. [https://doi.org/10.3168/jds.S0022-0302\(95\)76674-7](https://doi.org/10.3168/jds.S0022-0302(95)76674-7).
- Whittington, R. J., D. J. Begg, K. de Silva, A. C. Purdie, N. K. Dhand, and K. M. Plain. 2017. Case definition terminology for paratuberculosis (Johne's disease). *BMC Vet. Res.* 13:1–13. <https://doi.org/10.1186/s12917-017-1254-6>.
- Wiggans, G. R., J. B. Cole, S. M. Hubbard, and T. S. Sonstegard. 2017. Genomic Selection in Dairy Cattle: The USDA Experience. *Annu. Rev. Anim. Biosci.* 5:309–327. <https://doi.org/10.1146/annurev-animal-021815-111422>.
- Wolf, R., H. W. Barkema, J. De Buck, M. Slomp, J. Flaig, D. Hauptstein, C. Pickel, and K. Orsel. 2014. High herd-level prevalence of *Mycobacterium avium* subspecies paratuberculosis in Western Canadian dairy farms, based on environmental sampling. *J. Dairy Sci.* 97:6250–6259. <https://doi.org/10.3168/jds.2014-8101>.
- Wu, X. L., B. Heringstad, and D. Gianola. 2008. Exploration of lagged relationships between mastitis and milk yield in dairy cows using a Bayesian structural equation Gaussian-threshold model. *Genet. Sel. Evol.* 40:333–357. <https://doi.org/10.1051/gse:2008009>.
- Yao, C., K. A. Weigel, and J. B. Cole. 2014. Short communication: Genetic evaluation of stillbirth in US Brown Swiss and Jersey cattle. *J. Dairy Sci.* 97:2474–2480. <https://doi.org/10.3168/jds.2013-7320>.
- Zare, Y., G. E. Shook, M. T. Collins, and B. W. Kirkpatrick. 2014. Genome-wide association analysis and genomic prediction of *Mycobacterium avium* subspecies paratuberculosis infection in US Jersey cattle. *PLoS One* 9:e88380. <https://doi.org/10.1371/journal.pone.0088380>.
- Zwald, N. R., K. A. Weigel, Y. M. Chang, R. D. Welper, and J. S. Clay. 2004. Genetic selection for health traits using producer-recorded data. I. Incidence rates, heritability estimates, and sire breeding values. *J. Dairy Sci.* 87:4287–4294. [https://doi.org/10.3168/jds.S0022-0302\(04\)73573-0](https://doi.org/10.3168/jds.S0022-0302(04)73573-0).

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