TECHNICAL BULLETIN

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INHERIT CONNECT TECHNICAL REPORT

INHERIT Connect Product Features for North America

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TECHNICAL SUMMARY

- INHERIT Connect is a genomic test for male and female cattle that delivers available sire and dam parentage discovery, genomic sex, genomic approximations of breed composition, genotypes for black/red/wild-type and silver color dilution and polled; optional genetic predictions for health traits as well as simple recessive genetic conditions, collectively for more informed selection, crossbreeding, and marketing decisions.
- INHERIT Connect parentage discovery requires candidate parents to have qualifying High Density (HD) genotypes included in the Zoetis parentage archive and is updated weekly to enable dynamic parentage authentication for progeny tested with INHERIT Select, INHERIT Optimize and INHERIT Progress.
- INHERIT Connect is intended for use in straight-bred and crossbred cattle comprising the following breeds, for which predicted genomic breed composition is reported: Angus, Red Angus, South Devon, Hereford, Shorthorn, Simmental, Gelbvieh, Limousin, Charolais, Wagyu, Akaushi, Brahman, Nelore, Holstein, Jersey, Brown Swiss, and Guernsey – although for straightbred dairy animals, parentage discovery is not supported by this product (CLARIFIDE Plus advised).
- While INHERIT Connect is not currently intended for cattle with theoretical breed composition other than the above prescribed breeds, INHERIT Connect can be used for parent discovery, color, and polled, and is an ordering and reporting pathway to simple recessive genetic conditions independent of breed composition.
- INHERIT Connect delivers genotypes for Polled (based on Celtic and Friesian variants), Color as determined by the Extension locus (black, red, and wild type variants) and Silver Color Dilution, the variant present in Hereford and Simmental (different from dilution in Charolais).
- INHERIT Connect is a conduit through which over 20 simple recessive inherited genetic conditions and myostatin variants may optionally be ordered and reported.
- Optional Genomic Expected Progeny Differences (GEPD) and percent ranks for Bovine Respiratory Disease Health (BRDH), Survival (BRDS), and the $BRD economic selection index.[4]
- Optional GEPD and percent ranks for Bovine Congestive Heart Failure (BCHF) score, provided via license agreement with Simplot Livestock Co.[1]
- Optional Bovine Viral Diarrhea Virus (BVDV) add-on.

INHERIT CONNECT PRODUCT FEATURES

PARENTAGE DISCOVERY

Sire and/or dam parentage discovery are included features of INHERIT Connect and are updated weekly. An essential prerequisite for parentage discovery, is that candidate parents must have HD50K® or qualifying High Density (HD) genotypes included in the **Zoetis** parentage HD archive. Since the evaluation is executed weekly, genotypes for parents or progeny may enter parentage discovery any time. Updated parentage results are reported via secured customer login to the Zoetis genetics reporting platform called SearchPoint® whether parents are submitted prior to, at the same time (with these two options recommended), or after parents or progeny are tested.

INHERIT Connect parentage determination is flexible, and both 1) verifies presumed sires and dams of record, as well as 2) identifies the specific sire and dam from tested bull batteries and cow inventories, without having to nominate defined groups of candidate parents. If sires and/or dams of record exist for specific animals, based on A.I. breeding and calving records, single sire breeding pastures, or observed services, the presumed parent registration number and breed association, or ZID numbers, may be included on the order form. Alternatively, if sire and/or dam of record are unknown, typically due to multiple sire breeding programs, the sire and/or dam identity of record should be left blank.

There are five possible Parentage Status outcomes – detailed separately for sire and dam – reported by INHERIT Connect. These outcomes apply to the reported Sire and Dam of Evaluation, and are reported in the Sire and Dam Status fields as follows:

1. **Genomically confirmed**
   The listed 'Sire or Dam of Evaluation' is genomically confirmed.
2. **Submitted sire | dam excluded, alternative sire | dam genomically confirmed**
   The alternative listed Sire or Dam was identified and genomically confirmed, while the submitted sire or dam was excluded.
3. **Submitted sire | dam excluded, no alternative sire | dam found**
   The 'Sire or Dam of Evaluation' field is blank, because the submitted sire or dam was excluded, and no qualifying alternative sire or dam was identified.
4. **Submitted sire | dam not genotyped, unable to genomically confirm**
   The 'Sire or Dam of Evaluation' field contains the recorded parent submitted on the order form, but since the sire or dam does not have genotypes available, the evaluation was unable to genomically confirm.
5. **No sire | dam found**
   The 'Sire or Dam of Evaluation' field is blank because such was not submitted on the order form and there was no sire or dam found by the evaluation.

INHERIT Connect parentage verification and discovery is not officially recognized by breed associations, as related to fulfilling requirements for registry. However, the expanded set of SNP markers used by Zoetis for parent discovery, includes the subsets of commonly recognized markers used to officially verify parentage by most domestic and international breed associations.

GENOMIC BREED COMPOSITION

An informative feature of INHERIT Connect are genomic estimates of breed composition. Using the percentage of DNA possessed by tested animals that originated from defined breeds and breed groups represented in the Zoetis reference populations breed composition percentages are derived. The current reference population supports approximations for 17 different breeds, reported individually and combined into breed categories defined as British, Continental, Indicus and Dairy. Table 1 below provides the list of included breeds and associated codes, while Table 2 provides an example report.

At the present time, if reported genomic breed composition is 25% or more for the combination of Nelore, Wagyu and Akaushi breed makeup, animals are not eligible for INHERIT Select, Optimize and Progress individual trait and index predictions. The reason is because currently these breed groups and related crosses are not adequately represented with performance data in the Zoetis Multi-Breed Genetic Evaluation (ZMBE), to yield predictions with documented accuracy.

Genomic approximations of breed composition have several useful purposes. Breed composition is indicative of potential individual, maternal, and paternal heterosis, the increase in production of crossbreds above

Table 1. INHERIT Connect genomic predicted breed composition population groups and associated codes.

Breeds & Codes for Genomic Predicted Breed Composition				
British (B)	**Continental (C)**	**Dairy (D)**	**Indicus (I)**	**Wagyu (WY)**
Angus (AN)	Simmental (SM)	Holstein (HO)	Brahman (BR)	Black Waygu (KB)
Red Angus (RA)	Gelbvieh (GV)	Jersey (JE)	Nelore (NE)	Akaushi (AK)
South Devon (SD)	Limousin (LM)	Brown Swiss (BS)		
Hereford (HE)	Charolais (CH)	Guernsey (GU)		
Shorthorn (SH)				

Table 2. Example INHERIT Connect genomic predicted breed composition.

Identification		British (%)					Continental (%)				Dairy (%)				Indicus (%)		Breed Summary (%)					
EID	TAG	AN	RA	HE	SD	SH	SM	GV	LM	CH	HO	JE	BS	GU	BR	NL	B	C	D	I	WG	AK
982000426445318	H1658	75	0	0	0	0	25	0	0	0	0	0	0	0	0	0	75	25	0	0	0	0
982000426445475	H1326	50	25	0	0	0	0	25	0	0	0	0	0	0	0	0	75	25	0	0	0	0
982000425779448	H2490	25	0	0	0	0	25	0	0	0	50	0	0	0	0	0	25	25	50	0	0	0
982000427585450	H1166	0	0	0	0	0	0	0	50	0	0	50	0	0	0	0	0	50	50	0	0	0
982000426445394	H1021	50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	50	0	0	0	50	0

[1]AN = Angus (black); RA = Red Angus; HE = Hereford; SD = South Devon; SH = Shorthorn; SM = Simmental; GV = Gelbvieh; LM = Limousin; CH = Charolais; HO = Holstein; JE = Jersey; BS = Brown Swiss; GU = Guernsey; BR = Brahman; NL = Nelore; B = sum of evaluated Bristish breeds; C = sum of evaluated Continental breeds; D = sum of evaulated Dairy breeds; I = sum of evaluated Indicus breeds; WG = Wagyu; AK = Akaushi.

that of the average of parent breeds. Thus, knowledge of genomic breed composition helps inform selection and crossbreeding decisions for desired levels of heterosis expressed by tested animals and future calf-crops, often with more precision than theoretical breed composition based on available pedigree information.

INHERIT Connect customers are advised against testing animals whose composition includes meaningful proportions of breeds other than those listed in Table 1. The algorithm used to predict genomic breed composition uses differences in allele frequencies among purebreds of included populations, with the sum of predictions across these breeds equaling 100%. If tested animals possess breed(s) that are not currently factored into the predictive algorithm – for example Salers - it will erroneously allocate such to the closest match among one or more of the included breeds.

As with all predictions, genomic breed composition is not perfect – possible error, or noise in the form of roughly 1% to 5% composition sometimes is allocated to sources other than what is thought to possibly be the true breed or breed-cross. At least partially, this may be due to “purebred and fullblood” resource populations - used to derive allele frequencies - that possess fractions of other breeds.

The Polled test determines whether phenotypically polled animals are heterozygous or homozygous polled. This innovation from Zoetis positively supports animal well-being by helping to identify animals that carry the allele for horned, which enables selective breeding to reduce or eliminate horned progeny. Possible outcomes of the test include:

- PP = Homozygous polled
- Ph = Heterozygous polled
- I = Indeterminate: The polled status of the animal was horned or not definitively determined
- N/R = No result: Sample failed testing

The Black Test is primarily used to identify if black animals are homozygous or heterozygous for black coat color at the Extension locus. Homozygous Black seedstock animals are often more valuable because they always transmit the black. More specifically, the test identifies the black (ED), red (e) and wild-type (E+) alleles present at the Extension (E) locus. The order of dominance for these alleles as related to expression of color translates into black as dominant to red, and both black and red as dominant to wild-type. Heterozygous black animals only transmit the black allele to one-half of their progeny. Importantly, additional genes exist that also affect color. Possible outcome of this test include:

- EDED: Homozygous Black
- ee: Red (Homozygous)
- EDe: Heterozygous Black
- E+E+: Homozygous Wild Type
- E+ED: Black - Wild Type Carrier
- E+e: Red - Wild Type carrier
- NR: No Result: Sample failed testing

Silver Color Dilution (CD) test results involve the variant most frequently found in Hereford and Simmental breeds, that results in grey or light red expression of color when combined with black (ED) or red color (e) at the Extension locus, respectively. This dilution variant is different than the variant most prevalent in Charolais. The allele for this variant of dilution is dominant to the corresponding allele for non-dilution, hence either one or two copies – heterozygous (CDC) or homozygous (CDA) for dilution - result in diluted expression of color. Reported results for SCD are as follows:

- CDF – Silver Color Dilution Free – homozygous free of CD
- CDC – Silver Color Dilution Carrier - heterozygous for CD
- CDA – Silver Color Dilution Affected – homozygous for CD

GENETIC CONDITIONS OPTIONS

INHERIT Connect can also be used as an ordering and reporting conduit for twenty-two optional simple recessive inherited genetic conditions, as well as for Myostatin variants - (Table 3). For more detailed information about included genetic defects, two informative references include Mississippi State University – Managing Genetic Defects in Beef Cattle Herds[2] – and the Australian Wagyu Association[3].

For simple recessive inherited genetic conditions, carrier animals are visually indistinguishable from animals that are free of the condition. Free versus carrier status are reported for animals using letter designations following the acronym associated with each genetic condition. Animals tested "Free" are designated with an "F." Carrier animals are identified with a "C" and possess one copy of the allele (gene pair) that causes the condition. Affected animals with two alleles for the genetic condition are designated with an "A". In isolated instances, an "NR" status representing "No Result" may be reported to indicate that it was not initially possible to derive a definitive test result for the submitted sample.

Table 3. Genetic conditions and myostatin variants[1] optionally available through INHERIT Connect.

General Genetic Conditions:
Arthrogryposis Multiplex (AM)
Contractural Arachnodactyly (CA)
Dwarfism PRKG2 (D2)
Developmental Duplication (DD)
Hypotrichosis (HY)
Idiopathic Epilepsy (IE)
Alpha-Mannosidosis (MA)
Maple Syrup Urine Disease (MSUD)
Myostatin in Piedmontese (MYO-PDM)
Neuropathic Hydrocephalus (OH)
Oculocutaneous Hypopigmmentation (OH)
Osteopetrosis (OS)
Pulmonary Hypoplasia with Anasarca (PHA)
Pompes Disease (E7)
Tibial Hemimelia (TH)
Wagyu Genetic Conditions:
Chediak-Higashi Syndrome (CH5)
Bovine Claudin- 16/paracellin-1 (CL 16_Type 1)
Factor XI Deficiency (F11)
Bovine Blood Coagulation Facor XIII Deficiency (F13)
Growth Hormone Exon-5 (GHE5)
Isoleucyl-tRNA Sythetase (IARS)
Stearoyl RoA Desaturase (SCD)
Myostatin 9 Variant Bundle, including:
Myostatin Belgian Blue (MYO-BB)
Myostatin in Limousin (MYO-F94L)
Myostatin M1 (MYO-M1)

[1] C313Y, nt419, E226X, nt821, E291X, Q204X, D182N, F94L, and S105C

OPTIONAL GENOMIC EXPECTED PROGENY DIFFERENCES (GEPD) AND ECONOMIC INDEX FOR BOVINE RESPIRATORY DISEASE (BRD)[4]

Bovine Respiratory Disease Health (BRDH) GEPD predict genetic differences in the probability of healthy progeny defined as not requiring pull and treatment for BRD during the post-weaning, growing and finishing phases of production to harvest, where higher BRDH GEPD values and lower related percent ranks are desirable. The estimated heritability for BRDH as defined above in the resource population of mostly *Bos taurus* crossbred feedlot cattle was .13.

Bovine Respiratory Disease Survival (BRDS) GEPD predict genetic differences in the probability of progeny survival from weaning to harvest – not dying from BRD regardless of treatment – where higher BRDS GEPD values and lower related percent ranks are desirable. The estimated heritability for BRDS as defined above in the resource population of mostly *Bos taurus* crossbred feedlot cattle was .16. The correlation between GEPD for BRDS and BRDH was .74.

Dollar Bovine Respiratory Disease Economic Index ($BRD) predicts differences in the direct and indirect impacts on revenue per progeny due to combined genetic merit for BRD Health (BRDH) and BRD Survival (BRDS), where higher $BRD values and lower ranks are desirable.

Importantly, $BRD includes four assumptions consistent with the moderate to high BRD risk reference populations from which the predictions were developed and that continue to contribute records to the ZMBE. Two of the assumptions were related to incidences, 1) of pull and related treatment (13.5%), and 2) of death due to BRD (3.8%). The other two assumptions were economic and included 3) the direct and indirect (reduced feedlot performance and carcass value) costs of treated versus untreated ($75), and 4) the average cost of dead, based on means for standardized feeder cattle purchase price, purchase weight, days on feed to death, and related costs ($2,500).

At present, relationships between these post-weaning to harvest trait definitions and GEPD for BRD versus similar or alternative birth to weaning trait definitions for BRD are unknown. For this reason, and because $BRD is also quite sensitive to the four assumptions discussed above, BRDH and BRDS are not yet included in other INHERIT indexes.

OPTIONAL GENOMIC EXPECTED PROGENY DIFFERENCES (GEPD) FOR BOVINE CONGESTIVE HEART FAILURE (BCHF) SCORE[1]

Thanks to an agreement with Simplot Livestock Co, Zoetis offers optional **Bovine Congestive Heart Failure (BCHF) Genomic Expected Progeny Differences (GEPD) and Percentile Rankings**. The BCHF GEPDs are expressed in units of differences in the probability of unhealthy heart scores of 4 and 5 in harvested progeny, with lower GEPDs and lower percent ranks being favorable. The reference population for percent ranks includes over 25,000 genotyped commercial crossbred animals with phenotypes for both BCHF and Lung Scores. The cattle primarily consist of Angus, Red Angus, Hereford, Charolais, and Simmental, along with beef-dairy crosses from Holstein or Jersey dams.

Heritability estimates for heart and lung scores were .36 and .29 respectively, and the genetic correlation between scores for these two traits was .90. Genetic correlations between heart score and growth traits and feed intake were moderate (higher growth associated with somewhat unfavorable heart scores) and positive (0.289–0.460). Genetic correlations between heart score and backfat and marbling score were −0.120 and −0.108 (higher marbling slightly associated with unfavorable heart scores), respectively[1].

OPIONAL BOVINE VIRAL DIARRHEA VIRUS (BVDV) TEST

Customers may optionally also request the add-on, Bovine Viral Diarrhea Virus (BVDV) test. There are added fees for this add-on, which must be requested at time of initial ordering. The BVDV test Uses an Erns Antigen Capture ELISA kit that detects BVDV Types 1 and 2 antigens from ear tissue (TSU) samples to help identify persistent infection (PI) status. Tissue samples – using either Allflex, Caisley or Datamars TSO (tissue sample only – are required for BVDV testing, and the same sample can be used for INHERIT Connect testing.

GENOMIC DETERMINED GENDER

INHERIT Connect uses SNP markers on the X and Y chromosomes to ascertain and report genomic sex. In addition to helping correct gender recording errors, genomic determined gender is used to qualify animals for various trait and index predictions related to INHERT Select and Optimize.

POTENTIAL INHERIT CONNECT TESTING STRATEGY

INHERIT Connect results provide foundational pedigree, breed composition, color, polled and gender information. The following is intended to illustrate possible strategies and general uses:

- Collect DNA using Allflex® Tissue Sampling Units (TSU), Caisley™ Tissue Sampling Ear Tags or Datamars™ Tissue Sampling Tags (TSO/TST) at first processing (roughly two to three months of age), pre-conditioning, weaning, when heifers are vaccinated for Brucellosis, when bulls receive breeding soundness exams, etc.
- SEEDSTOCK – INHERIT Connect test complete bull batteries and calf crops at an early age so that authenticated parentage gets matched with birth, weaning and later performance information for breed association genetic evaluations from the get-go, and for determining red, horned and dilution carriers.
- SEEDSTOCK & COMMERICAL - INHERIT Connect test the bull battery and new bulls (if not already tested) to enable future sire parentage determination of tested progeny, optional simple recessive genetic conditions, GEPD for BRDH, BRDS, $BRD, and/or BCHF to identify and cull or minimize use of sires with unfavorable genetic merit for respiratory disease, heart and lung health.
- SEEDSTOCK & COMMERCIAL – Estrous synchronization and fixed time A.I. with immediate turnout of cleanup bulls for added early conceptions – use INHERIT Connect to determine A.I. versus cleanup sire parentage.
- STOCKERS, FEEDERS, CALF RANCHES, DAIRY crossbreeding – INHERIT Connect results can be used to document or audit sire parentage and/or breed composition as related to branded beef end-product claims (i.e. Wagyu); to help inform feeder price discovery or fed cattle marketing (i.e. fraction Jersey vs other dairy and beef breeds in beef-dairy crosses); and to help inform genetic merit for BRD and BCHF health traits.

REFERENCES

[1] Buchanan JW, Flagel LE, MacNeil MD, Nilles AR, Hoff JL, Pickrell JK, Raymond RC. Variance component estimates, phenotypic characterization, and genetic evaluation of bovine congestive heart failure in commercial feeder cattle. Front Genet. 2023 Jun 8;14:1148301. doi: 10.3389/fgene.2023.1148301. PMID: 37359370; PMCID: PMC10285703.

[2] Mississippi State University – Managing Genetic Defects in Beef Cattle Herds - http://extension.msstate.edu/publications/publications/managing-genetic-defects-beef-cattle-herds.

[3] Australian Wagyu Association – www.wagyu.org.au

[4] Development of Genomic Predictions for Bovine Respiratory Disease in beef cattle. Genetics R&D Technical Report 7AGNN00000. Veterinary Medicine Research & Development Kalamazoo, Michigan 49007 United States. October 24, 2024.