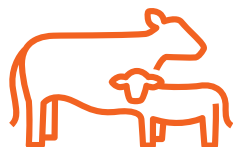


TECHNICAL BULLETIN

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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 males and females that delivers available sire and dam parentage discovery; genomic sex to help inform pedigree; genomic approximations of breed composition; genotypes for black/red/wild-type and silver color dilution, as well as for polled and optionally for 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 comprised of the following breeds, for which predicted genomic breed composition is reported: Angus, Red Angus, South Devon, Hereford, 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, polled status 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 (list provided herein).
- An optional add-on to INHERIT Connect are Genomic Expected Progeny Differences (GEPD) and percentile rankings for Bovine Congestive Heart Failure (BCHF) – expressed as differences in the probability of unfavorable heart scores of 4 or 5 – and as provided via license agreement with Simplot Livestock Co.¹
- Bovine Viral Diarrhea Virus (BVDV) is another optional INHERIT Connect 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 Zoetic 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. Breed percentages are derived from differences in allele frequencies across reference breed populations. The current reference population supports approximations for 15 different breeds, reported individually and combined into breed categories defined as British, Continental, Indicus, Dairy and Wagyu. Table 1 below provides the list of included breeds and associated codes, while table 2 provides an example report.

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)	Akaushi (AK)
Angus (AN)	Simmental (SM)	Holstein (HO)	Brahman (BR)		
Red Angus (RA)	Gelbvieh (GV)	Jersey (JE)	Nelore (NE)		
South Devon (SD)	Limousin (LM)	Brown Swiss (BS)			
Hereford (HE)	Charolais (CH)	Guernsey (GU)			

Table 2. Example INHERIT Connect genomic predicted breed composition.

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

At the present time, if reported genomic breed composition is 25% or more for the

¹AN = Angus (black); RA = Red Angus; HE = Hereford; SD = South Devon; 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 British breeds; C = sum of evaluated Continental breeds; D = sum of evaluated Dairy breeds; I = sum of evaluated Indicus breeds; WG = Wagyu; AK = Akaushi.

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 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 Shorthorn or 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 definitive
- 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 allele. 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

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 Herds² – and the Australian

Wagyu Association³.

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 variants¹ optionally available through INHERIT Connect.

General Genetic Conditions:
Arthrogryposis Multiplex (AM)
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)
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 Factor XIII Deficiency (F13)
Growth Hormone Exon-5 (GHE5)
Isoleucyl-tRNA Synthetase (IARS)
Stearoyl RoA Desaturase (SCD)
Myostatin 9 Variant Bundle, including:
Myostatin Belgian Blue (MYO-BB)
Myostatin in Limousin (MYO-F94L)
Myostatin M1 (MYO-M1)

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

OPTIONAL BCHF AND BVDV

ADD-ONS

Thanks to an agreement with Simplot Livestock Co, Zoetis offers optional **Bovine Congestive Heart Failure (BCHF) Genomic Expected Progeny Differences (GEPD) and Percentile Rankings.**¹ 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 (table 4). The reference population for percent ranks includes over 25,000 genotyped commercial crossbred animals

with phenotypes for both BCHF and Lung Scores. The cattle in the Simplot evaluation primarily consist of Angus, Red Angus, Hereford, Charolais, and Simmental, along with beef-dairy crosses from Holstein or Jersey dams.

Table 4. BCHF GEPD Descriptive Statistics

Min GEPD (Favorable)	-10.5%
Average GEPD	4.6%
Max GEPD (Unfavorable)	33.0%
Standard Deviation	5.7%

The weekly BCHF genetic evaluation includes over 15,000 progeny of over 800 genomic determined sires (remainder were not sire identified). 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), respectively¹.

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.

Bovine Viral Diarrhea Virus (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 or Caisley – 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 INHERIT Select and Optimize.

POTENTIAL INHERIT CONNECT TESTING STRATEGY

INHERIT Connect results provide and enable 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 or when heifers are vaccinated for Brucellosis.
- SEEDSTOCK – INHERIT Connect test the complete calf crop 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 & COMMERCIAL – 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, and GEPI for BCHF to identify and cull or minimize use of sires with unfavorable genetic merit for heart and lung health.
- SEEDSTOCK & COMMERCIAL – Estrous synchronization and fixed time A.I. with immediate turnout of cleanup bulls – 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 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), to help inform retained

ownership, sorting, management and grid marketing.

REFERENCES

- ¹Buchanan 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.
- ²Mississippi State University – Managing Genetic Defects in Beef Cattle Herds - <http://extension.msstate.edu/publications/publications/managing-genetic-defects-beef-cattle-herds>.
- ³Australian Wagyu Association – www.wagyu.org.au



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