Tempus HRD is a laboratory developed test available for ovarian and breast cancer. The Tempus HRD test provides a result based on DNA genome-wide loss-of-heterozygosity (GWLOH) or evidence of biallelic BRCA1 or BRCA2 loss from the analysis of sequencing data generated from tumor + normal match using xT.†

HRD-DNA

GWLOH is determined by the number of basepairs with LOH (excluding regions of aneuploidy with LOH that span > 80% of a chromosome arm) divided by the total number of basepairs among DNA segments across the genome inferred by the Tempus copy number calling algorithm (excluding X and Y chromosomes and filtered regions).

The HRD-DNA model was trained on a cohort that is representative of patients eligible for testing using an expanded logic for the HRR wild-type (WT) group than was described previously in Leibowitz et al[1] (see training labels for details) and performs in close alignment with population frequency in the literature.[2-6] The GWLOH threshold was established as the threshold determined to best distinguish the BRCA-biallelic loss samples from the HRR WT samples in addition to other clinically relevant metrics (as defined in Table 1). GWLOH is considered positive for HRD at > 8.5% for breast cancer and > 8.0% for ovarian cancer; all samples with BRCA biallelic loss are considered positive regardless of GWLOH. The sensitivity of the HRD-DNA method for breast and ovarian cancers at predicting BRCA biallelic loss are detailed in Table 1 below.

TABLE 1: HRD-DNA MODEL PERFORMANCE

	Breast Cancer	Ovarian Cancer
HRD score definition	Genome Wide LOH	Genome Wide LOH
Threshold values	8.5%	8.0%
Thresholds tuned on	Sensitivity, specificity, HRD prevalence among ovarian and breast cancers[2-6] and among CCNE1 amplified ovarian cancer[7-9]	
Sensitivity	83.3%	90.0%
Training labels **HRR WT:** Samples with no detected pathogenic mutations, fusions, or biallelic loss in BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L and no gene-level LOH + low gene expression in BRCA1 or RAD51C. **BRCA1/2 Biallelic loss:** Samples with (a) homozygous deletion, (b) a pathogenic germline or pathogenic somatic mutation with overlapping LOH of the other allele, or (c) a co-occurring pathogenic germline and pathogenic somatic mutation in BRCA1 or BRCA2.		

For more information regarding the HRD-DNA model please reach out to **support@tempus.com.**

1 Leibowitz BD, Dougherty BV, Bell JSK, et al. Validation of genomic and transcriptomic models of homologous recombination deficiency in a real-world pan-cancer cohort. *BMC Cancer*. 2022;22(1):587

2 Stires H, Zhang Z, McShane L, et al. Assessing variability across HRD assays: findings from the Friends' HRD Harmonization Project. Poster presented at: Association for Molecular Pathology; November 1-5, 2022; Phoenix, AZ.

3 Nguyen L, W. M. Martens J, Van Hoeck A, et al. Pan-cancer landscape of homologous recombination deficiency. *Nat Commun*. 2020;11(1).

4 Sokol ES, Pavlick D, Khiabanian H, et al., Pan-cancer analysis of BRCA1 and BRCA2 genomic alterations and their association with genomic instability as measured by genome-wide loss of heterozygosity. *JCO Precis Oncol*. 2020;(4):442-465.

5 Feng C, Zhang Y, Wu F, et al. Relationship between homologous recombination deficiency and clinical features of breast cancer based on genomic scar score. *Breast*. 2023;69:392-400.

6 Telli ML, Timms KM, Reid J, et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. *Clin Cancer Res*. 2016;22(15):3764–3773.

7 Etemadmoghadam D, Weir BA, Au-Yeung G, et al. Synthetic lethality between CCNE1 amplification and loss of BRCA1. *Proc Natl Acad Sci U S A*. 2013;110(48).

8 Perez-Villatoro F, Oikkonen J, Casado J, et al. Optimized detection of homologous recombination deficiency improves the prediction of clinical outcomes in cancer. *NPJ Precis Oncol*. 2022;6(1).

9 Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. *Nature*. 2015;521(7553):489-494.

† HRD is not included in the FDA-approved labeling for xT CDx and is not part of its FDA-approved intended use. HRD is provided as a laboratory-developed test (LDT).