TEMPUS | ONCOLOGY

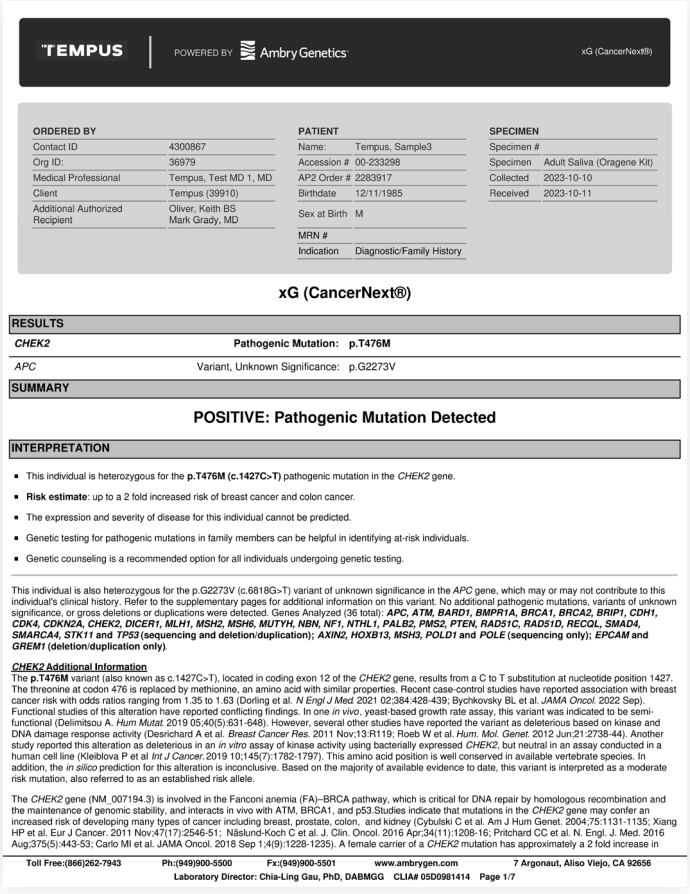
Tempus xG Hereditary Cancer Panels

A complete picture of your patient's disease includes their hereditary risk.

Tempus offers both somatic and germline testing through one platform

Tempus xG, powered by Ambry Genetics®, is a validated germline test offered in addition to Tempus somatic testing, providing a more comprehensive view of your patient's molecular profile.

These results can be used to specifically identify germline variants associated with hereditary cancer syndromes. Through one platform, you can order somatic, germline, and algorithmic testing with reports delivered through the Tempus HUB.



TEMPUS | POWERED BY Ambry Genetics xG (CancerNext®)

ORDERED BY	
Contact ID	4300867
Org ID:	36979
Medical Professional	Tempus, Test MD 1, MD
Client	Tempus (39910)
Additional Authorized Recipient	Oliver, Keith BS Mark Grady, MD

PATIENT	
Name:	Tempus, Sample3
Accession #	00-233298
AP2 Order #	2283917
Birthdate	12/11/1985
Sex at Birth	M
MRN #	
Indication	Diagnostic/Family History

SPECIMEN	
Specimen #	
Specimen	Adult Saliva (Oragene Kit)
Collected	2023-10-10
Received	2023-10-11

xG (CancerNext®)

RESULTS

CHEK2	**Pathogenic Mutation:**	**p.T476M**
APC	Variant, Unknown Significance:	p.G2273V

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.T476M (c.1427C>T)** pathogenic mutation in the *CHEK2* gene.
- **Risk estimate**: up to a 2 fold increased risk of breast cancer and colon cancer.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

This individual is also heterozygous for the p.G2273V (c.6818G>T) variant of unknown significance in the *APC* gene, which may or may not contribute to this individual's clinical history. Refer to the supplementary pages for additional information on this variant. No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (36 total): ***APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, PTEN, RAD51C, RAD51D, RECQL, SMAD4, SMARCA4, STK11*** **and** ***TP53*** **(sequencing and deletion/duplication);** ***AXIN2, HOXB13, MSH3, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only).**

CHEK2 **Additional Information**

The **p.T476M** variant (also known as c.1427C>T), located in coding exon 12 of the *CHEK2* gene, results from a C to T substitution at nucleotide position 1427. The threonine at codon 476 is replaced by methionine, an amino acid with similar properties. Recent case-control studies have reported association with breast cancer risk with odds ratios ranging from 1.35 to 1.63 (Dorling et al. *N Engl J Med.* 2021 02;384:428-439; Bychkovsky BL et al. *JAMA Oncol.* 2022 Sep). Functional studies of this alteration have reported conflicting findings. In one *in vivo*, yeast-based growth rate assay, this variant was indicated to be semi-functional (Delimitsou A. *Hum Mutat.* 2019 05;40(5):631-648). However, several other studies have reported the variant as deleterious based on kinase and DNA damage response activity (Desrichard A et al. *Breast Cancer Res.* 2011 Nov;13:R119; Roeb W et al. *Hum. Mol. Genet.* 2012 Jun;21:2738-44). Another study reported this alteration as deleterious in an *in vitro* assay of kinase activity using bacterially expressed *CHEK2*, but neutral in an assay conducted in a human cell line (Kleiblova P et al *Int J Cancer.* 2019 10;145(7):1782-1797). This amino acid position is well conserved in available vertebrate species. In addition, the *in silico* prediction for this alteration is inconclusive. Based on the majority of available evidence to date, this variant is interpreted as a moderate risk mutation, also referred to as an established risk allele.

The *CHEK2* gene (NM_007194.3) is involved in the Fanconi anemia (FA)–BRCA pathway, which is critical for DNA repair by homologous recombination and the maintenance of genomic stability, and interacts in vivo with ATM, BRCA1, and p53.Studies indicate that mutations in the *CHEK2* gene may confer an increased risk of developing many types of cancer including breast, prostate, colon, and kidney (Cybulski C et al. Am J Hum Genet. 2004;75:1131-1135; Xiang HP et al. Eur J Cancer. 2011 Nov;47(17):2546-51; Näslund-Koch C et al. J. Clin. Oncol. 2016 Apr;34(11):1208-16; Pritchard CC et al. N. Engl. J. Med. 2016 Aug;375(5):443-53; Carlo MI et al. JAMA Oncol. 2018 Sep 1;4(9):1228-1235). A female carrier of a *CHEK2* mutation has approximately a 2 fold increase in

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GERMLINE OFFERINGS

- xG+ (CancerNext-*Expanded*®): 77 genes associated with both common and rare hereditary cancer types analyzed by DNA sequencing, powered by Ambry Genetics® **(more comprehensive).**
- xG (CancerNext®): 36 genes associated with common hereditary cancer types analyzed by DNA sequencing, powered by Ambry Genetics®.
- Reports pathogenic, likely pathogenic, and variants of uncertain significance. Amended reports are provided for variant reclassifications when available.
- Available to order as confirmatory testing of potential germline findings reported on xT, allowing for possible identification of more patients with hereditary cancer risk.
- Familial variant/cascade testing is available for at-risk family members at no additional cost if ordered within 90 days of original xG+ or xG report (out to third degree relatives).

TECHNICAL SPECIFICATIONS

- Specimen type(s): peripheral blood (EDTA tube), saliva (Oragene®), or skin punch biopsy (cultured fibroblasts).
- Single nucleotide variants, indels, large deletions/duplications, rearrangements/inversions.
- Alternative sequencing or copy number detection methods, such as Sanger sequencing, MLPA, and/or targeted chromosomal microarray are used to analyze or confirm regions with inadequate sequence or copy number data by NGS.

Gene Lists

xG+ (CancerNext-*Expanded*®) — 77 Genes:

AIP	*ALK*	*APC*	*ATM*	*AXIN2*	*BAP1*	*BARD1*	*BLM*
BMPR1A	*BRCA1*	*BRCA2*	*BRIP1*	*CDC73*	*CDH1*	*CDK4*	*CDKN1B*
CDKN2A	*CHEK2*	*CTNNA1*	*DICER1*	*EGFR*	*EGLN1*	*EPCAM*	*FANCC*
FH	*FLCN*	*GALNT12*	*GREM1*	*HOXB13*	*KIF1B*	*KIT*	*LZTR1*
MAX	*MEN1*	*MET*	*MITF*	*MLH1*	*MSH2*	*MSH3*	*MSH6*
MUTYH	*NBN*	*NF1*	*NF2*	*NTHL1*	*PALB2*	*PDGFRA*	*PHOX2B*
PMS2	*POLD1*	*POLE*	*POT1*	*PRKAR1A*	*PTCH1*	*PTEN*	*RAD51C*
RAD51D	*RB1*	*RECQL*	*RET*	*SDHA*	*SDHAF2*	*SDHB*	*SDHC*
SDHD	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMARCE1*	*STK11*	*SUFU*	*TMEM127*
TP53	*TSC1*	*TSC2*	*VHL*	*XRCC2*			

xG (CancerNext®) — 36 Genes:

APC	*ATM*	*AXIN2*	*BARD1*	*BMPR1A*	*BRCA1*	*BRCA2*	*BRIP1*
CDH1	*CDK4*	*CDKN2A*	*CHEK2*	*DICER1*	*EPCAM*	*GREM1*	*HOXB13*
MLH1	*MSH2*	*MSH3*	*MSH6*	*MUTYH*	*NBN*	*NF1*	*NTHL1*
PALB2	*PMS2*	*POLD1*	*POLE*	*PTEN*	*RAD51C*	*RAD51D*	*RECQL*
SMAD4	*SMARCA4*	*STK11*	*TP53*				

xG (CancerNext®) and xG+ (CancerNext-Expanded®) powered by Ambry Genetics® is available to select providers.

Financial Assistance Program

We help provide access to our tests for patients in financial need. All Tempus tests, including xG/xG+, are eligible under the program. Patients can complete the application online at **access.tempus.com** or call **800.739.4137** to speak to a member of our team.

Please reach out to your local Tempus representative for more details on this offering.