Genomate®

Second Opinion Report for

Test Patient

This report provides an expert second opinion from a qualified medical professional based on the molecular test results submitted by the patient.

This report does not replace, supersede, or substitute the care provided by the patient's treating physician. Rather, it is intended to support shared clinical decision-making by providing a second opinion from a qualified medical professional.

Report ID: 6453129370911899861

Report Date: 1/27/2026

Consulting Oncologist: Dr. John Smith

Dr. John Smith's clinical assessment*

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- 5508 genes
- 69797 mutations
- 24771 functional evidence

**The opinions and interpretations expressed in this report represent my independent medical judgment and are intended to inform discussion with the patient's treating healthcare team.*

Dr. John Smith, MD PhD

Date: **1/27/2026**

Signature:

Genomate®

Patient: **Test Patient**
DOB: **1/1/1960**
Sex: **Male**
Tumor type: **biliary tract adenocarcinoma**

Report ID: **6453129370911899861**
Report Date: **1/27/2026**
Consulting Oncologist: **Dr. John Smith**
State: **Florida**

Everything you shared about your diagnosis*

Tumor type: **biliary tract adenocarcinoma**
Disease stage: **IV**

Molecular highlights:

Drivers	***Biomarkers***
PD-L1 (CPS 2, CPS 1)	*MMR proficient*
BRAF-G469A (24%)	*TMB LOW*
PIK3CA-G1049R (35%)	*HER2 negative*
CLDN18 overexpression	*NTRK fusion not detected*
CTNNB1-S45F (27%)	*BRCA pathogenic mutation not detected*

Processed molecular pathology reports:

Exacta (NGS) - Blood - 4/15/2024
FoundationOne CDx - FFPE - 5/25/2025
PD-L1 IHC - FFPE - 4/10/2024

Treatment history:

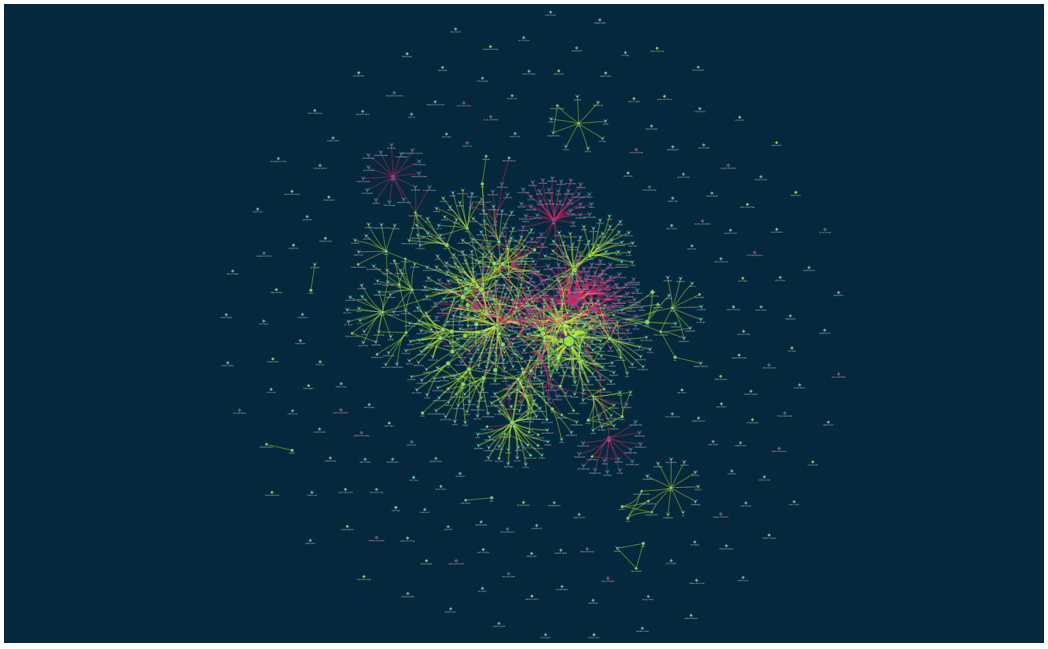
Neoadjuvant treatment: carboplatin + pemetrexed (2023)
Surgery: liver surgery (2023)
Adjuvant treatment: carboplatin + pemetrexed (01/02/2024 - 05/01/2024)
First-line treatment: Pembrolizumab (05/01/2024 - 02/01/2026)

***This is based solely on the information you have provided. The authors of this report do not independently verify the accuracy or completeness of this information. Inaccurate, incomplete, or outdated data may affect the analyses, interpretations, and conclusions presented in this report.*

What we have uncovered

The diagram is a visual representation* of the individualized evidence network generated by Genomate®. The process links tumor molecular features to potential treatment options. Each item represents either a molecular alteration that may influence tumor growth (a driver), a biological structure or process that can be targeted by treatment (a target), or a drug that has been studied in this context. Lines between items indicate the strength (line thickness) and direction (green = positive, pink = negative) of the evidence connecting them.

The diagram is meant to give an overview of the scientific relationships relevant to your specific tumor type and molecular profile. It does not, by itself, indicate which treatments should or should not be used; rather, it illustrates the biological rationale for therapies that medical experts may consider as part of the second-opinion evaluation.



Test Patient's cancer network, represented as a personalized knowledge graph

**This visualization is provided for informational purposes only and does not constitute medical advice or a treatment recommendation.*

Molecular Evidence

This section explains the scientific reasons behind the treatment options selected by the consulting oncologist. It summarizes research findings that connect the specific characteristics of your cancer, such as the tumor type and molecular changes identified, to the listed medications.

Alpelisib

Alpelisib is a phosphatidylinositol 3-kinase alpha (PI3Kα)–specific inhibitor designed to target tumors harboring activating PIK3CA mutations. Preclinical studies demonstrate that alpelisib effectively inhibits PI3K pathway signaling, reduces epithelial-to-mesenchymal transition, and limits invasiveness in squamous lung cancer cell lines with PIK3CA E545K mutations [1]. Functional profiling confirms potent activity against multiple PIK3CA hotspot mutations, including E545K, across tumor models [2]. Additional data show the drug's specificity for PI3Kα and its efficacy in variant-specific contexts, supporting a biomarker-driven treatment strategy [3].

The patient's PIK3CA E545K mutation is a well-characterized activating alteration with strong preclinical and translational support for alpelisib sensitivity. Evidence exists for therapy resistance for other rare PIK3CA variants not present in the patient's tumor and tumors with PTEN loss, which can also mediate resistance. Still, PTEN loss is absent in this patient [4][5].

Although alpelisib is not FDA-approved for bile duct carcinoma, it is approved for hormone receptor–positive breast cancer. Multiple studies in PIK3CA-altered solid tumors indicate consistent pathway inhibition and antitumor activity across different solid tumor types [6][7], supporting its use in off-label contexts where the oncogenic driver is the same.

Given the molecular match and absence of resistance mechanisms, alpelisib represents a rational, biomarker-directed therapeutic option.

References:

1. *Inhibition of PI3K Pathway Reduces Invasiveness and Epithelial-to-Mesenchymal Transition in Squamous Lung Cancer Cell Lines Harboring PIK3CA Gene Alterations. PubMed ID: 26013318.*
2. *Identification of Variant-Specific Functions of PIK3CA by Rapid Phenotyping of Rare Mutations. PubMed ID: 26627007.*

3. *Characterization of the novel and specific PI3Kα inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. PubMed ID: 24608574.*
4. *Allosteric PI3Kα Inhibition Overcomes On-target Resistance to Orthosteric Inhibitors Mediated by Secondary PIK3CA Mutations. PubMed ID: 37916958.*
5. *Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. PubMed ID: 25409150.*
6. *Phosphatidylinositol 3-kinase α–selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: results from the first-in-human study. PubMed ID: 29401002.*
7. *Phase I study of alpelisib (BYL719), an α-specific PI3K inhibitor, in Japanese patients with advanced solid tumors. PubMed ID: 30588709.*

Trastuzumab Deruxtecan

Trastuzumab deruxtecan is an antibody-drug conjugate (ADC) combining a HER2-targeted monoclonal antibody with a cytotoxic topoisomerase I inhibitor payload. It binds to HER2-expressing tumor cells, delivering targeted cytotoxic activity and promoting a bystander effect.

While T-DXd is not approved for HER2 low bile duct carcinoma, its efficacy has been demonstrated in HER2 low breast caner [1], and HER2 positive solid tumors including biliary tract caner [2]. T-DXd showed signal of efficacy in an early phase trial in HER2 low biliary tract cancer [3].

References:

1. *Modi S, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610-621.*
2. *Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. J Clin Oncol. 2024;42(1):47-58. doi:10.1200/JCO.23.02005*
3. *Ohba A, Morizane C, Kawamoto Y, et al. Trastuzumab Deruxtecan in Human Epidermal Growth Factor Receptor 2-Expressing Biliary Tract Cancer (HERB; NCCH1805): A Multicenter, Single-Arm, Phase II Trial. J Clin Oncol. 2024;42(27):3207-3217. doi:10.1200/JCO.23.02010*

Olaparib

Olaparib is a PARP inhibitor that exploits synthetic lethality in tumors with homologous recombination repair (HRR) deficiency. The patient's PALB2 frameshift variant impairs DNA repair, creating a vulnerability to PARP inhibition. Clinical studies in other solid tumors, including ovarian and breast cancers, have shown that olaparib improves outcomes in

patients with germline or somatic mutations in PALB2 or other HRR genes [1][2]. A phase II trial tested olaparib in HRR mutant biliary tract cancer patients, and it reached its primary endpoint of PFS [3]. Preclinical and early clinical trial data support the activity of olaparib in IDH1-mutated tumors [4][5]. However, in some tumor types, including cholangiocarcinoma, IDH mutations alone have not been sufficient as biomarkers of olaparib sensitivity [6].

While there is no direct phase III evidence in bile duct carcinoma, scientific data demonstrate antitumor activity of olaparib in diverse solid tumors harboring DNA repair defects. Given the patient's multiple repair pathway alterations, olaparib represents a rational targeted approach, despite off-label use.

References:

1. *Tung NM, Robson ME, Ventz S, et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol. 2020;38(36):4274-4282. doi:10.1200/JCO.20.02151*
2. *Hussain M, et al. PROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations. Annals of Oncology. 2019 Oct 1;30:v881-2.*
3. *Ahn D, et al. 261MO A phase II study of olaparib in patients (pts) with advanced biliary tract cancer (aBTC) with aberrant homologous recombinant repair (HRR) mutations. Annals of Oncology. 2025 Jul 1;36:S102-3.*
4. *Eder JP, Doroshow DB, Do KT, et al. Clinical Efficacy of Olaparib in IDH1/IDH2-Mutant Mesenchymal Sarcomas. JCO Precis Oncol. 2021;5:466-472. doi:10.1200/PO.20.00247*
5. *Sulkowski PL, et al. 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. Science Translational Medicine. 2017 Feb;9(375):eaal2463. DOI: 10.1126/scitranslmed.aal2463. PMID: 28148839; PMCID: PMC5435119.*
6. *Cecchini M, Pilat MJ, Uboha N, et al. Olaparib in treatment-refractory isocitrate dehydrogenase 1 (IDH1)- and IDH2-mutant cholangiocarcinoma: Safety and antitumor activity from the phase 2 National Cancer Institute 10129 trial. Cancer. 2025;131(4):e35755. doi:10.1002/cncr.35755*

Clinical Trials

The following section lists clinical trials that may be relevant to you. These trials use medications selected by the consulting oncologist based on your diagnosis and test results. Only clinical trials that are currently available in your state are shown. The information in this section is sourced from ClinicalTrials.gov, a publicly available database of clinical research studies.

Please note that inclusion of a clinical trial in this list is provided for informational purposes only and does not constitute a recommendation, referral, or guarantee of eligibility or enrollment. Participation in a clinical study may involve potential risks and benefits, which should be discussed with your treating physician or the clinical trial study team before making any decisions.

NCI number	Title of the trial
NCT05687136	Testing the Combination of Two Anti-cancer Drugs, Peposertib (M3814) and M1774 for Advanced Solid Tumors
NCT04068194	Testing the Combination of New Anti-cancer Drug Peposertib With Avelumab and Radiation Therapy for Advanced/Metastatic Solid Tumors and Hepatobiliary Malignancies
NCT04983810	A Study to Investigate Fadraciclib (CYC065), in Subjects With Advanced Solid Tumors and Lymphoma
NCT03682289	Ceralasertib (AZD6738) Alone and in Combination With Olaparib or Durvalumab in Patients With Solid Tumors
NCT06654037	Testing the Addition of an Anti-Cancer Drug, Abemaciclib, to the Usual Chemotherapy Treatment (5-Fluorouracil) for Metastatic, Refractory Colorectal Cancer

Glossary

Amplification: A genetic alteration in which cancer cells have extra copies of a gene, causing the gene to be overactivated.

Biomarker: A measurable molecular characteristic in the tumor or blood that can provide information about the cancer or help guide treatment decisions.

Driver: A molecular alteration that plays a central role in driving cancer cells to grow and survive.

FISH (Fluorescence In Situ Hybridization): A laboratory test that uses fluorescent markers to detect specific genetic alterations in tumor cells.

Gene: A segment of DNA that carries instructions controlling how cells function, grow, and divide.

Germline mutation: A genetic alteration that is inherited and present in all cells of the body.

HER2 low expression: A state in which the cancer cells have a small amount of the HER2 protein, but not enough to be classified as HER2-positive.

HRD (Homologous Recombination Deficiency): A condition in which cancer cells have an impaired ability to repair specific types of DNA damage. HRD can serve as a biomarker to help identify patients who may benefit from certain targeted therapies.

IHC (Immunohistochemistry): A laboratory test that uses specialized staining techniques to detect specific proteins in tumor tissue.

Immunotherapy: A treatment that stimulates or enhances the body's own immune system to recognize and attack cancer cells.

Lack of expression: A state in which a gene or protein is produced at lower levels, or not produced at all in cancer cells.

Molecular alteration: A change in a gene or protein within cancer cells that may affect how the cancer grows or responds to treatment.

Molecular profile: A comprehensive overview of the key genetic and molecular alterations found in the tumor.

MSI (Microsatellite Instability): A condition where cancer cells have impaired DNA repair mechanisms, leading to an increased number of genetic alterations. Tumors with MSI-High status may be more likely to benefit from immunotherapy.

Mutation: An alteration in a gene's DNA sequence that may alter the resulting protein and affect normal cell function.

NGS (Next-Generation Sequencing): A laboratory test that analyzes multiple genes simultaneously to identify clinically relevant molecular alterations in a tumor.

Overexpression: A state in which a gene or protein is produced at higher levels than normal in cancer cells.

Precision Oncology: An approach to cancer care that uses the unique molecular features of a person's tumor to help inform treatment options.

Protein: A molecule produced by cells that performs essential functions in the body, such as supporting cell growth, communication, and survival. Proteins are produced according to instructions encoded in genes.

Somatic mutation: A genetic alteration that arises in tumor cells during a person's lifetime and is not inherited.

Target: A specific molecule or pathway in cancer cells that a treatment is designed to interact with.

Targeted Therapy: A type of treatment that selectively targets specific molecular alterations in cancer cells, helping to reduce effects on healthy cells.

TMB (Tumor Mutational Burden): A measure of the number of genetic mutations present in a tumor. Tumors with high TMB may be more likely to respond to certain immunotherapy treatments.

Translocation: A genetic alteration where segments of two different chromosomes are rearranged, altering genes and potentially affecting protein function as well.

Disclaimer

This report represents the independent second medical opinion of the consulting healthcare professional. This report does not replace, supersede, or substitute the care provided by the patient's treating physician. Rather, it is intended to support shared clinical decision-making by providing a second opinion from a qualified medical professional. This opinion is based solely on the review of the information and materials provided and does not include a physical examination of the patient. This second opinion establishes a limited consulting physician–patient relationship solely for the purpose of preparing this report and does not include ongoing care, treatment, or follow-up obligations, unless otherwise expressly agreed in writing.

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This report is not intended for use in medical emergencies or urgent care situations, and patients should seek immediate medical attention from their treating physician or emergency services as appropriate.

This second opinion is rendered in accordance with applicable U.S. federal and state laws governing telemedicine and consultative medical services.

For more information, contact us at support@genomate.health.

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