MI PROFILE™
MOLECULAR INTELLIGENCE TUMOR REPORT

CARIS® LIFE SCIENCES

# FINAL REPORT

## PATIENT

**Name:** Patient, Test
**Date of Birth:** XX-Mon-19XX
**Sex:** Female
**Case Number:** TN16-XXXXXX
**Diagnosis:** Carcinosarcoma, NOS

## SPECIMEN INFORMATION

**Primary Tumor Site:** Ovary
**Specimen Site:** Pelvis, NOS
**Specimen ID:** ABC-1234-XY
**Specimen Collected:** XX-Mon-2016
**Testing Completed:** XX-Mon-2016

## ORDERED BY

**Ordring Physician, MD**
**The Cancer Center**
123 Main Street
Springfield, XY 12345
(123) 456-7890

**Bold Therapies** = On NCCN Compendium® Therapies

## ✔ THERAPIES WITH **POTENTIAL BENEFIT** (PAGE 4)

| | |
|---|---|
| **carboplatin**, **cisplatin**, **oxaliplatin** | ERCC1, BRCA2★ |
| **docetaxel**, **nab-paclitaxel**, **paclitaxel** | TUBB3★ |
| **doxorubicin**, **liposomal-doxorubicin** | TOP2A |
| **gemcitabine** | RRM1★ |
| **olaparib** | BRCA2★ |
| Mitomycin-C | BRCA2★ |
| epirubicin | TOP2A |

★ **Indicates Clinical Trial Opportunity • 224 Chemotherapy Trials • 55 Targeted Therapy Trials** *(See Clinical Trials Connector™ on page 7 for details.)*

## ✘ THERAPIES WITH **POTENTIAL LACK OF BENEFIT** (PAGE 5)

| | |
|---|---|
| **anastrozole**, **exemestane**, **letrozole**, **leuprolide**, **megestrol acetate**, **tamoxifen** | PR, ER |
| **capecitabine**, **pemetrexed** | TS |
| **irinotecan**, **topotecan** | TOPO1 |
| ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab | Her2/Neu |
| dabrafenib, vemurafenib | BRAF |
| fluorouracil | TS |
| fulvestrant, goserelin, toremifene | PR, ER |

## ? THERAPIES WITH **INDETERMINATE BENEFIT** (PAGE 6)

| | | |
|---|---|---|
| everolimus, temsirolimus | imatinib | |



Therapies associated with potential benefit or lack of benefit, as indicated above, are based on biomarker results provided in this report and are based on published medical evidence. This evidence may have been obtained from studies performed in the cancer type present in the tested patient's sample or derived from another tumor type. The selection of any, all, or none of the matched therapies resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information in addition to this report concerning the patient's condition in accordance with the applicable standard of care.

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## SUMMARY OF RESULTS (SEE APPENDIX FOR FULL DETAILS)

| Biomarker | Method | Result |
|---|---|---|
| ABL1 | NGS | Mutation Not Detected |
| AKT1 | NGS | Mutation Not Detected |
| ALK | NGS | Mutation Not Detected |
| APC | NGS | Mutation Not Detected |
| ATM | NGS | Mutation Not Detected |
| BRAF | NGS | Mutation Not Detected |
| BRCA1 | NGS | Mutation Not Detected |
| BRCA2 | NGS | Mutated, Pathogenic |
| | | Exon 11 \| E1953X |
| c-KIT | NGS | Mutation Not Detected |
| CDH1 | NGS | Mutation Not Detected |
| cMET | NGS | Mutation Not Detected |
| CSF1R | NGS | Mutation Not Detected |
| CTNNB1 | NGS | Mutation Not Detected |
| EGFR | IHC (H-Score) | Positive \| 200 |
| | NGS | Mutation Not Detected |
| ER | IHC | Negative \| 1+, 1% |
| ERBB4 | NGS | Mutation Not Detected |
| ERCC1 | IHC | Negative \| 2+, 10% |
| FBXW7 | NGS | Mutation Not Detected |
| FGFR1 | NGS | Mutation Not Detected |
| FGFR2 | NGS | Mutation Not Detected |
| FLT3 | NGS | Mutation Not Detected |
| GNA11 | NGS | Mutation Not Detected |
| GNAQ | NGS | Mutation Not Detected |
| GNAS | NGS | Mutation Not Detected |
| Her2/Neu | CISH | Not Amplified |
| | IHC | Negative \| 1+, 20% |
| Her2/Neu (ERBB2) | NGS | Mutation Not Detected |
| HRAS | NGS | Mutation Not Detected |

| Biomarker | Method | Result |
|---|---|---|
| IDH1 | NGS | Mutation Not Detected |
| JAK2 | NGS | Mutation Not Detected |
| JAK3 | NGS | Mutation Not Detected |
| KDR (VEGFR2) | NGS | Mutation Not Detected |
| KRAS | NGS | Mutation Not Detected |
| MPL | NGS | Mutation Not Detected |
| NOTCH1 | NGS | Mutation Not Detected |
| NPM1 | NGS | Mutation Not Detected |
| NRAS | NGS | Mutation Not Detected |
| PD-L1 | IHC | Negative \| 0, 100% |
| PDGFRA | NGS | Mutation Not Detected |
| PIK3CA | NGS | Mutation Not Detected |
| PR | IHC | Negative \| 0, 100% |
| PTEN | IHC | Positive \| 2+, 80% |
| | NGS | Mutation Not Detected |
| PTPN11 | NGS | Mutation Not Detected |
| RB1 | NGS | Mutation Not Detected |
| RET | NGS | Mutation Not Detected |
| RRM1 | IHC | Negative \| 2+, 30% |
| SMAD4 | NGS | Mutation Not Detected |
| SMARCB1 | NGS | Mutation Not Detected |
| SMO | NGS | Mutation Not Detected |
| STK11 | NGS | Mutation Not Detected |
| TOP2A | IHC | Positive \| 1+, 10% |
| TOPO1 | IHC | Negative \| 0, 100% |
| TP53 | NGS | Mutated, Pathogenic |
| | | Exon 5 \| H178fs |
| TS | IHC | Positive \| 1+, 20% |
| TUBB3 | IHC | Negative \| 2+, 2% |
| VHL | NGS | Mutation Not Detected |

**IHC:** Immunohistochemistry **CISH:** Chromogenic *in situ* hybridization **NGS:** Next-Generation Sequencing

**The Next-Generation Sequencing results above include only the genes most commonly associated with cancer. See summary below and for full Next-Generation Sequencing results, see Appendix page 1.**

**See the Appendix section for a detailed overview of the biomarker test results for each technology.**



*Biomarker Results continued on the next page. >*



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## NOTES OF SIGNIFICANCE

**SEE APPENDIX FOR FULL DETAILS**

Mutation analysis of BRCA1 and BRCA2 identified a E1953X (Mutated, Pathogenic) mutation in BRCA2.

**Next-Generation Sequencing:**

Genes tested: 45 | Genes with actionable mutations: 2 | Genes with unclassified mutations: 0 | Genes with no mutations detected: 43

**Note:** The Caris Molecular Intelligence NGS test is not intended to identify or diagnose a hereditary condition. Mutations detected in this assay may be somatic or germline in origin and are used primarily for theranostic purposes. Appropriate genetic counseling and testing may be considered.

**Immunohistochemistry:**

Inflammatory PD-L1 cells expression is seen in approximately 5% of the tumor volume.

**Chromogenic in situ Hybridization:**

Her2/Neu by CISH also reviewed by another Pathologist who agrees with the above entered results.





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## ✔ THERAPIES WITH **POTENTIAL BENEFIT**

| Therapies | Test | Method | Result | Value† | Clinical Association | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Potential Benefit | Decreased Potential Benefit | Lack of Potential Benefit | Highest Level of Evidence* | Reference |
| Mitomycin-C | BRCA1 | NGS | Mutation Not Detected | | | | | II-3 / Good | 1#, 2, 3 |
| | BRCA2 | NGS | Mutated, Pathogenic | E1953X | ✔ | | | II-3 / Good | 1#, 2, 3 |
| carboplatin, cisplatin, oxaliplatin | ATM | NGS | Mutation Not Detected | | | | | II-2 / Good | 32, 33#, 34 |
| | BRCA1 | NGS | Mutation Not Detected | | | | | II-2 / Good | 29#, 30#, 31 |
| | BRCA2 | NGS | Mutated, Pathogenic | E1953X | ✔ | | | II-2 / Good | 29#, 30#, 31 |
| | ERCC1 | IHC | Negative | 2+ 10% | ✔ | | | II-3 / Good | 27#, 28# |
| docetaxel, nab-paclitaxel, paclitaxel | TUBB3 | IHC | Negative | 2+ 2% | ✔ | | | II-3 / Good | 39#, 40#, 41 |
| doxorubicin, epirubicin, liposomal-doxorubicin | TOP2A | IHC | Positive | 1+ 10% | ✔ | | | I / Good | 42, 43 |
| gemcitabine | RRM1 | IHC | Negative | 2+ 30% | ✔ | | | I / Good | 47 |
| olaparib | BRCA1 | NGS | Mutation Not Detected | | | | | I / Good | 56#, 57#, 58#, 59 |
| | BRCA2 | NGS | Mutated, Pathogenic | E1953X | ✔ | | | I / Good | 56#, 57#, 58#, 59 |

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

# Evidence reference includes data from the same lineage as the tested specimen.

**†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.**





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## ✘ THERAPIES WITH **POTENTIAL LACK OF BENEFIT**

| Therapies | Test | Method | Result | Value† | Clinical Association | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Potential Benefit | Decreased Potential Benefit | Lack of Potential Benefit | Highest Level of Evidence* | Reference |
| ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab | Her2/Neu | CISH | Not Amplified | 1.39 | | | ✔ | I / Good | 4#, 5, 6, 7, 9, 10, 11, 12 |
| | Her2/Neu | IHC | Negative | 1+ 20% | | | ✔ | I / Good | 4#, 5, 6, 7, 8#, 9, 10, 11 |
| anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, megestrol acetate, tamoxifen, toremifene | ER | IHC | Negative | 1+ 1% | | | ✔ | I / Good | 13, 16, 17, 18, 19, 20, 21, 22, 23 |
| | PR | IHC | Negative | 0+ 100% | | | ✔ | I / Good | 13, 14, 15, 16, 17, 18, 19, 20, 21 |
| capecitabine, fluorouracil, pemetrexed | TS | IHC | Positive | 1+ 20% | | | ✔ | II-1 / Good | 24, 25, 26 |
| dabrafenib, vemurafenib | BRAF | NGS | Mutation Not Detected | | | | ✔ | I / Good | 35, 36, 37, 38 |
| irinotecan, topotecan | TOPO1 | IHC | Negative | 0+ 100% | | | ✔ | II-1 / Good | 53, 54#, 55# |

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

# Evidence reference includes data from the same lineage as the tested specimen.

**†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.**





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## ? THERAPIES WITH **INDETERMINATE BENEFIT**

(Biomarker results do not impact potential benefit or lack of potential benefit)

| Therapies | Test | Method | Result | Value† | Clinical Association | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Potential Benefit | Decreased Potential Benefit | Lack of Potential Benefit | Highest Level of Evidence* | Reference |
| everolimus, temsirolimus | PIK3CA | NGS | Mutation Not Detected | | | ✔ | | II-2 / Good | 44#, 45#, 46# |
| imatinib | c-KIT | NGS | Mutation Not Detected | | | | ✔ | II-2 / Good | 51, 52 |
| | PDGFRA | NGS | Mutation Not Detected | | | | ✔ | II-3 / Good | 48, 49, 50 |

* The level of evidence for all references is assigned according to the Literature Level of Evidence Framework consistent with the US Preventive Services Task Force described further in the Appendix of this report. The data level of each biomarker-drug interaction is the highest level of evidence based on the body of evidence, overall clinical utility, competing biomarker interactions and tumor type from which the evidence was gathered.

# Evidence reference includes data from the same lineage as the tested specimen.

**†Refer to Appendix for detailed Result and Value information for each biomarker, including appropriate cutoffs, unit of measure, etc.**





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## CLINICAL TRIALS CONNECTOR™

For a complete list of open, enrolling clinical trials visit MI Portal to access the **Clinical Trials Connector** . This personalized, real-time web-based service provides additional clinical trial information and enhanced searching capabilities, including, but not limited to:

- Location: filter by geographic area
- Biomarker(s): identify specific biomarkers associated with open clinical trials to choose from
- Drug(s): search for specific therapies
- Trial Sponsor: locate trials based on the organization supporting the trial(s)

**Visit www.CarisMolecularIntelligence.com to view all matched trials.**

### CHEMOTHERAPY CLINICAL TRIALS (224)

| Drug Class | Biomarker | Method | Investigational Agent(s) |
|---|---|---|---|
| DNA minor groove binding agents (8) | BRCA2 | NGS | PM01183 (lurbinectedin), trabectedin |
| Nucleoside analog (37) | RRM1 | IHC | gemcitabine |
| Platinum compounds (92) | BRCA2 | NGS | carboplatin, cisplatin, oxaliplatin |
| Taxanes (87) | TUBB3 | IHC | cabazitaxel, docetaxel, paclitaxel |

### TARGETED THERAPY CLINICAL TRIALS (55)

| Drug Class | Biomarker | Method | Investigational Agent(s) |
|---|---|---|---|
| Cell cycle inhibitors (6) | TP53 | NGS | LY2606368, MK-1775 |
| EGFR monoclonal antibody (8) | EGFR | IHC | cetuximab |
| p53 activators (1) | TP53 | NGS | PRIMA |
| p53-targeted biological agents (2) | TP53 | NGS | modified vaccinia virus ankara vaccine expressing p53 |
| PARP inhibitors (38) | BRCA2 | NGS | BMN-673, olaparib, rucaparib, veliparib |

( ) = represents the total number of clinical trials identified by the Clinical Trials Connector for the provided drug class or table.





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## REFERENCES

| SOURCE | LEVEL OF EVIDENCE* |
|---|---|
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| 2. Vyas, O., M.W. Saif, et al. (2015). "Clinical outcomes in pancreatic adenocarcinoma associated with BRCA-2 mutation." Anti-Cancer Drugs 26:224-226. View Citation Online | III / Good |
| 3. Chalasani, P., T. Dragovich, et al. (2008). "Response to a Third-Line Mitomycin C (MMC)-Based Chemotherapy in a Patient with Metastatic Pancreatic Adenocarcinoma Carrying Germline BRCA2 Mutation." JOP 9(3): 305-308. View Citation Online | III / Good |
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| 5. Baselga, J., S.M. Swain, et. al. (2012). "Pertuzumab plus trastumab plus docetaxel for metastatic breast cancer". N. Engl. J. Med. 36:109-119. View Citation Online | I / Good |
| 6. Yin, W., J. Lu, et. al. (2011). "Trastuzumab in adjuvant treatment HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials." PLoS ONE 6(6): e21030. doi:10.1371/journal.pone.0021030. View Citation Online | I / Good |
| 7. Cortes, J., J. Baselga, et. al. (2012). "Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor-2-positive breast cancer." J. Clin. Oncol. 30. DOI: 10.1200/JCO.2011.37.4207. View Citation Online | II-1 / Good |
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| 9. Hurvitz, S.A., E.A. Perez, et. al. (2013) "Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer." J Clin Oncol.31(9):1157-63 View Citation Online | I / Good |
| 10. Slamon, D., M. Buyse, et. al. (2011). "Adjuvant trastuzumab in HER2-positive breast cancer." N. Engl. J. Med. 365:1273-83. View Citation Online | I / Good |
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| 13. Bartlett, J.M.S., D. Rea, et al. (2011). "Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial." J Clin Oncol 29 (12):1531-1538. View Citation Online | I / Good |
| 14. Stendahl, M., L. Ryden, et al. (2006). "High progesterone receptor expression correlates to the effect of adjuvant tamoxifen in premenopausal breast cancer patients." Clin Cancer Res 12(15): 4614-8. View Citation Online | I / Good |
| 15. Yamashita, H., Y. Yando, et al. (2006). "Immunohistochemical evaluation of hormone receptor status for predicting response to endocrine therapy in metastatic breast cancer." Breast Cancer 13(1): 74-83. View Citation Online | II-3 / Good |
| 16. Stuart, N.S.A., H. Earl, et. al. (1996). "A randomized phase III cross-over study of tamoxifen versus megestrol acetate in advanced and recurrent breast cancer." European Journal of Cancer. 32(11):1888-1892. View Citation Online | II-2 / Fair |
| 17. Coombes, R.C., J.M. Bliss, et al. (2007). "Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial." The Lancet 369:559-570. View Citation Online | I / Good |



** See Appendix page 6 for Level of Evidence description.*



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## REFERENCES


| SOURCE | LEVEL OF EVIDENCE* |
|---|---|
| 18. Thurlimann, B., A. Goldhirsch, et al. (1997). "Formestane versus Megestrol Acetate in Postmenopausal Breast Cancer Patients After Failure of Tamoxifen: A Phase III Prospective Randomised Cross Over Trial of Second-line Hormonal Treatment (SAKK 20/90). E J Cancer 33 (7): 1017-1024. View Citation Online | II-2 / Fair |
| 19. Lewis, J.D., M.J. Edwards, et al. (2010). "Excellent outcomes with adjuvant toremifene or tamoxifen in early stage breast cancer." Cancer116:2307-15. View Citation Online | I / Good |
| 20. Dowsett, M., C. Allred, et al. (2008). "Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial." J Clin Oncol 26(7): 1059-65. View Citation Online | II-2 / Fair |
| 21. Cuzick J,LHRH-agonists in Early Breast Cancer Overview group. (2007). "Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials." The Lancet 369: 1711-1723. View Citation Online | I / Good |
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| 26. Lee, S.J., Y.H. Im, et. al. (2010). "Thymidylate synthase and thymidine phosphorylase as predictive markers of capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer." Cancer Chemother. Pharmacol. DOI 10.1007/s00280-010-1545-0. View Citation Online | II-3 / Good |
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| 34. Plimack, E.R., E.A. Ross, et al. (2015). "Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer". Eur Urol. 68:959-967. | II-2 / Good |


** See Appendix page 6 for Level of Evidence description.*





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## REFERENCES


| | SOURCE | LEVEL OF EVIDENCE* |
|---|---|---|
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** See Appendix page 6 for Level of Evidence description.*





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## REFERENCES

| SOURCE | LEVEL OF EVIDENCE* |
|---|---|
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** See Appendix page 6 for Level of Evidence description.*



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## SPECIMEN INFORMATION

**Specimen ID:** ABC-123-XY

**Specimen Collected:** XX-Mon-2016

**Specimen Received:** XX-Mon-2016

**Testing Initiated:** XX-Mon-2016

**Gross description:** 1 (A) Paraffin Block, site: Pelvis, NOS - Client ID (ABC-123-XY).

**Clinical History:** Per the submitted documents, the patient is a XX year-old female with adenocarcinoma in ovary. Per the physician's office this tumor is of pelvis origin.

**Pathologic Diagnosis:** Pelvic mass, resection: Carcinosarcoma with heterologous elements.

**Interpretation (Caris Life Sciences Microscopic Diagnosis):**

Interpretation (Caris Life Sciences Microscopic Diagnosis)

**Please Note:**

Electronic Signature

By my electronic signature, I as the attending pathologist affirm that I have personally reviewed and examined microscopically the prepared slide(s) and that the above diagnosis has been made or confirmed by me.





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## Disclaimer

All of the individual assays that are available through Caris Molecular Intelligence™ were developed and validated by Caris MPI, Inc. d/b/a Caris Life Sciences® and their test performance characteristics were determined and validated by Caris Life Sciences pursuant to the Clinical Laboratory Improvements Amendments and accompanying regulations ("CLIA"). Some of the assays that are part of Caris Molecular Intelligence have been approved by the U.S. Food and Drug Administration (FDA). For any remaining assays, Caris MPI, Inc. is certified under CLIA to perform high complexity testing, including all of the assays that comprise the Caris Molecular Intelligence.

The CLIA certification number of Caris MPI, Inc. laboratory performing testing in connection with Caris Molecular Intelligence can be found at the bottom of each page. This report includes information about therapies that appear to be associated with clinical benefit based on NCCN Compendium® guidelines, relevance of tumor lineage, level of published evidence and strength of biomarker results. This report, neither ranks biomarkers listed nor therapies associated with such biomarkers, in order of potential or predicted efficacy, and such therapies may or may not be suitable for administration to a particular patient. A determination of biomarker results do not necessarily indicate pharmacologic effectiveness or lack thereof. This report does not guarantee or suggest that any particular agent will be effective with the treatment of any particular condition. Caris Life Sciences expressly disclaims and makes no representation or warranty whatsoever relating, directly or indirectly, to review of identified scientific literature, the conclusions drawn from such review or any of the information set forth in this report that is derived from such review, including information and conclusions relating to therapies that are included or omitted from this report.

Decisions regarding care and treatment should not be based on a single test such as this test or the information contained in this report. The decision to select any, all or none of the listed therapies resides solely within the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including but not limited to, patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the applicable standard of care.

The information presented in the Clinical Trials Connector™ section of this report (if applicable) is compiled from sources believed to be reliable and current. We have used our best efforts to make this information as accurate as possible. However, the accuracy and completeness of this information cannot be guaranteed. The contents are to be used for clinical trial guidance and may not include all relevant trials. Current enrollment status for these trials is unknown. The clinical trials information present in the biomarker description was compiled from www.clinicaltrials.gov. The contents are to be used only as a guide, and health care providers should employ their judgment in interpreting this information for a particular patient. Specific eligibility criteria for each clinical trial should be reviewed as additional inclusion criteria may apply. Caris Life Sciences makes no promises or guarantees that a healthcare provider, insurer or other third party private or government payor, will provide reimbursement for any of the tests performed.

The next-generation sequencing assay performed by Caris Life Sciences examines nucleic acids obtained from tumor tissue only and does not examine normal tissue such as tumor adjacent tissue or whole or peripheral blood. As such, the origin of any mutation detected may be a somatic mutation (not inherited) or a germline mutation (inherited) and will not be distinguishable by this assay. It is recommended that results be considered within the patient's clinical and health history. If a germline inheritance pattern is suspected then counseling by a board certified genetic counselor is recommended.

A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope. The areas marked and extracted were microscopically reexamined on post-scraped slides and adequacy of scraping was verified by a board certified Pathologist.

Electronic Signature

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## MUTATIONAL ANALYSIS BY **NEXT-GENERATION SEQUENCING (NGS)**

### GENES TESTED WITH ALTERATIONS

| Gene | Alteration | Frequency (%) | Exon | Result |
|---|---|---|---|---|
| TP53 | H178fs | 90 | 5 | Mutated, Pathogenic |

**Interpretation:** A pathogenic frameshift mutation was detected in TP53

TP53, or p53, plays a central role in modulating response to cellular stress through transcriptional regulation of genes involved in cell-cycle arrest, DNA repair, apoptosis, and senescence. Inactivation of the p53 pathway is essential for the formation of the majority of human tumors. Mutation in p53 (TP53) remains one of the most commonly described genetic events in human neoplasia, estimated to occur in 30-50% of all cancers. Generally, presence of a disruptive p53 mutation is associated with a poor prognosis in all types of cancers, and diminished sensitivity to radiation and chemotherapy. Germline p53 mutations are associated with the Li-Fraumeni syndrome (LFS) which may lead to early-onset of several forms of cancer currently known to occur in the syndrome, including sarcomas of the bone and soft tissues, carcinomas of the breast and adrenal cortex (hereditary adrenocortical carcinoma), brain tumors and acute leukemias.

### GENES TESTED WITH NO MUTATIONS DETECTED

| | | | | | |
|---|---|---|---|---|---|
| ABL1 | CDH1 | FBXW7 | HRAS | NOTCH1 | RB1 |
| AKT1 | cMET | FGFR1 | IDH1 | NPM1 | RET |
| ALK | CSF1R | FGFR2 | JAK2 | NRAS | SMAD4 |
| APC | CTNNB1 | FLT3 | JAK3 | PDGFRA | SMARCB1 |
| ATM | EGFR | GNA11 | KDR | PIK3CA | SMO |
| BRAF | ERBB2 | GNAQ | KRAS | PTEN | STK11 |
| c-KIT | ERBB4 | GNAS | MPL | PTPN11 | VHL |

**For Next-Generation Sequencing, a total of 45 genes were analyzed. The results above include genes most commonly associated with cancer and any additional mutations identified. No alterations were identified in 43 genes. For a complete list of genes tested, visit www.CarisMolecularIntelligence.com/profilemenu.**

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### NGS Methods

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of the genome were amplified using the Illumina TruSeq Amplicon Cancer Hotspot panel. This panel only sequences selected regions of 44 genes and the amino acids sequenced by this assay can be found at www.carislifesciences.com. All variants reported by this are detected with >99% confidence based on the frequency of the mutation present and the amplicon coverage. This test is not designed to distinguish between germ line inheritance of a variant or acquired somatic mutation. This test has a sensitivity to detect as low as approximately 10% population of cells containing a mutation a sequenced amplicon. This test has not been cleared or approved by the United States Food and Drug Administration (FDA) as such approval is not necessary. All performance characteristics were determined by Caris Life Sciences. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.





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## MUTATIONAL ANALYSIS BY **NEXT-GENERATION SEQUENCING (NGS)**

### GENES TESTED WITH ALTERATIONS

| Gene | Alteration | Frequency (%) | Exon | Result |
|---|---|---|---|---|
| BRCA2 | E1953X | 95 | 11 | Mutated, Pathogenic |

**Interpretation:** A pathogenic nonsense mutation was detected in BRCA2. This mutation (also known as c.5857G>T; 6085G>T) has been reported as a frequent germline mutation, causal for hereditary breast and ovarian cancer (Serova-Sinilnikova 1997 Am J Hum Genet 60:1236).

### GENES TESTED WITH NO MUTATIONS DETECTED

BRCA1

Electronic Signature

**BRCA1 Sequencing Methods**

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of BRCA1 were amplified using primers flanking coding regions of this gene. All variants reported by this are detected with >99% confidence based on the frequency of the mutation present and the amplicon coverage. This test is not designed to distinguish between germ line inheritance of a variant or acquired somatic mutation. This test has a sensitivity to detect as low as approximately 20% population of cells containing a mutation a sequenced amplicon. This test has not been cleared or approved by the United States Food and Drug Administration (FDA) as such approval is not necessary. All performance characteristics were determined by Caris Life Sciences. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.

**BRCA2 Sequencing Methods**

Direct sequence analysis was performed on genomic DNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina MiSeq platform. Specific regions of BRCA2 were amplified using primers flanking coding regions of this gene. All variants reported by this are detected with >99% confidence based on the frequency of the mutation present and the amplicon coverage. This test is not designed to distinguish between germ line inheritance of a variant or acquired somatic mutation. This test has a sensitivity to detect as low as approximately 20% population of cells containing a mutation a sequenced amplicon. This test has not been cleared or approved by the United States Food and Drug Administration (FDA) as such approval is not necessary. All performance characteristics were determined by Caris Life Sciences. Insertions or deletions larger than 27 bp will not be detected by this assay. Benign and non-coding variants are not included in this report but are available upon request.





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## PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

| Biomarker | Patient Tumor | | | Thresholds* |
|---|---|---|---|---|
| | Staining Intensity (0, 1+, 2+, 3+) | Percent of cells | Result | Conditions for a Positive Result: |
| ER | 1 + | 1 | Negative | Intensity of ≥3+ with ≥50% or ≥2+ with ≥75% of cells stained |
| ERCC1 | 2 + | 10 | Negative | Intensity of ≥3+ with ≥10% or ≥2+ with ≥50% of cells stained |
| Her2/Neu | 1 + | 20 | Negative | Intensity ≥3+ and >10% of cells stained |
| PD-L1 | 0 | 100 | Negative | Intensity ≥2+ and ≥5% of cells stained |
| PR | 0 | 100 | Negative | Intensity ≥1+ and ≥10% of cells stained |
| PTEN | 2 + | 80 | Positive | Intensity ≥1+ and >50% of cells stained |
| RRM1 | 2 + | 30 | Negative | Intensity ≥2+ and ≥50% of cells stained |
| TOP2A | 1 + | 10 | Positive | Intensity ≥1+ and ≥10% of cells stained |
| TOPO1 | 0 | 100 | Negative | Intensity ≥2+ and ≥30% of cells stained |
| TS | 1 + | 20 | Positive | Intensity ≥1+ and ≥10% of cells stained |
| TUBB3 | 2 + | 2 | Negative | Intensity ≥2+ and ≥30% of cells stained |

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**IHC Methods**

These tests were developed and their performance characteristics determined by Caris MPI, Inc. d/b/a Caris Life Sciences®

* Caris Life Sciences has defined threshold levels of reactivity of IHC to establish cutoff points based on published evidence. Polymer detection systems are used for each IHC.

* HER2 results and interpretation follow the ASCO/CAP scoring criteria. See reference section for more information.

* Please note that PD-L1 staining is read from the membrane staining of cancer cells.

Clones used: ER(SP1), PR(1E2), TOPO1(1D6), TOP2A(3F6), TUBB3(Polyclonal), Her2/Neu(4B5), ERCC1(8F1), PD-L1(SP142), PTEN(6H2.1), RRM1(Polyclonal), TS(TS106/4H4B1).



*Additional IHC results continued on the next page. >*



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## PROTEIN EXPRESSION BY **IMMUNOHISTOCHEMISTRY (IHC)**

| Biomarker | H-Score | Result | Threshold (Condition for a Positive Result) |
|---|---|---|---|
| EGFR | 200 | Positive | H-Score ≥200 |

Electronic Signature

**IHC Methods**

These tests were developed and their performance characteristics determined by Caris MPI, Inc. d/b/a Caris Life Sciences®

* Caris Life Sciences has defined threshold levels of reactivity of IHC to establish cutoff points based on published evidence. Polymer detection systems are used for each IHC.

Clones used: EGFR(2-18C9).

**Comments on IHC Analysis**

Inflammatory PD-L1 cells expression is seen in approximately 5% of the tumor volume.





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## AMPLIFICATION BY **CHROMOGENIC *IN SITU* HYBRIDIZATION (CISH)**

| Gene / ISCN | Cells Counted | Result | Total/Avg Gene Copy Number | Total/Avg Control Copy Number | Cells with ≥4 Copies | Cells with ≥15 Copies | Ratio Calculation | Ratio |
|---|---|---|---|---|---|---|---|---|
| **Her2/Neu** nuc ish (D17Z1x1-2,HER2x1-2)[/30] | 20 | Not Amplified | 2.85 | 2.05 | N/A | N/A | Her2/neu/ Chromosome 17 | 1.39 |
| | *Reference Range:* Her2/Neu:CEP 17 signal ratio of >= 2.0; and non-amplification as <2.0 per Ventana INFORM HER2 CISH Package insert. | | | | | | | |

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**Comments on CISH Analysis**

Her2/Neu by CISH also reviewed by another Pathologist who agrees with the above entered results.

**CISH Methods**

HER2 CISH test was carried out using the INFORM DUAL HER2 ISH Assay (Ventana Medical Systems, Inc.), which has been cleared by the US Food and Drug Administration (FDA) for enumerating the ratio of HER2/Chr 17 in Breast Cancer samples. The HER2 CISH testing for cancer lineages other than breast has been developed and their performance characteristics determined by Caris MPI, Inc. (d/b/a Caris Life Sciences), and have not been cleared or approved by the FDA.

cMET CISH was carried out using a probe specific for cMET and a probe for the pericentromeric region of chromosome 7 (Ventana). The cMET CISH testing for cancer lineages has been developed and its performance characteristics determined by Caris MPI, Inc. (d/b/a Caris Life Sciences), and has not been cleared or approved by the FDA.

TOP2A CISH was carried out using a probe specific for TOP2 and a probe for the pericentromeric region of chromosome 17 (Ventana). The TOP2A CISH testing for cancer lineages has been developed and its performance characteristics determined by Caris MPI, Inc. (d/b/a Caris Life Sciences), and has not been cleared or approved by the FDA.

The FDA has determined that such clearance or approval is not currently necessary. These tests should not be regarded as investigational or research as they are used for clinical purpose and determined to be medically necessary by the ordering physician, who is not employed by Caris MPI, Inc. or its affiliates. This laboratory is certified under Clinical Laboratory Improvement Amendment of 1988 (CLIA-88) and is qualified to perform high complexity testing. CLIA 03D1019490





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## LITERATURE LEVEL OF EVIDENCE ASSESSMENT FRAMEWORK*

| STUDY DESIGN | |
|---|---|
| **Hierarchy of Design** | **Criteria** |
| **I** | Evidence obtained from at least one properly designed **randomized controlled trial**. |
| **II-1** | Evidence obtained from well-designed controlled trials **without randomization**. |
| **II-2** | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. |
| **II-3** | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence. |
| **III** | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence. |

| STUDY VALIDITY | |
|---|---|
| **Grade** | **Criteria** |
| **Good** | The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions and shows no significant flaws. |
| **Fair** | The study is judged to be valid and relevant as regards results, statistical analysis, and conclusions, but contains at least one significant but not fatal flaw. |
| **Poor** | The study is judged to have a fatal flaw such that the conclusions are not valid for the purposes of this test. |

* Adapted from Harris, T., D. Atkins, et al. (2001). "Current Methods of the U.S. Preventive Services Task Force." Am J Prev Med 20(3S)





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