NovoFocus™ NSCLC 2.0 Test Report

Patient Name : _____

Physician ID: _____

Report Date: _____

Content

Patient and Specimen Information

Patient	Specimen	Physician
Name: ******	**Specimen I.D.:** TKHS190003989-2A	**Ordering Physician:**
Patient NRIC/FIN/ID:	**Specimen Type/Size:** tissue	**Institution:**
	Specimen Collection Date:	
Gender: ******	**Specimen Received Date:**	
Data of Birth:		
Nationality:		
Diagnosis: ******		

About the Test

NovoFocus™ NSCLC 2.0

This is a next-generation sequencing (NGS)-based assay that detects genomic alterations (also known as "mutations") in 47 genes that are relevant for the diagnosis and treatment of non-small cell lung cancer (NSCLC) according to clinical guidelines and medical literature. This test interrogates 48 genes for mutations that may exist in the forms of single nucleotide variant (SNV), Insertion/Deletion (InDel), copy number variation (CNV) or Fusion. This report presents the mutations detected in the submitted patient sample and information on approved therapies, clinical trials and other scientific findings.

Disclaimer:

- Due to the technical limitations of NGS, not all genomic alterations in the targeted regions can be detected. Therefore, the test results should be interpreted in the context of the patient's clinical and pathological characteristics as well as other laboratory findings. In addition, information/suggestions provided in this report on the relevant treatment options, clinical trials and other scientific findings are based on the clinical guidelines, clinical trial registry and scientific literature which are continuously evolving. It is the user's responsibility to verify these information/suggestions against the most recent advancement in the aforementioned sources. The diagnostic and/or treatment implications of these information/suggestions should be interpreted only by licensed/certified medical professionals.

Accreditations

This test was conducted in a College of American Pathologists (CAP) accredited facility for next-generation sequencing (CAP Number: 9043632, AU-ID: 1759306). Its performance characteristics was determined in compliance to all applicable standards for the accreditation. This test has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Targeted Gene Detection

Targeted Therapy

In this sample, **1** mutations in **1** gene(s) were detected, which were related to targeted therapies. See "Detailed Results of Variant and the Relevance to Targeted Therapy" for more information.

Gene	Variant	VAF	Targeted Therapy with Potential Benefit			Information on Potential Drug Resistance
			Level A	Level B	Level C	
ERCC3	exon10 c.1720C>T p.R574*	1.14%	None	None	**Niraparib #**	None

Note:

1. Therapies associated with benefit or lack of benefits are **solely** based on the cancer-related genes sequenced (Refer to the Gene List in the Appendix) and genomic findings on patient tumor. Other clinicopathological factors will need to be taken into consideration when choosing appropriate therapy for the patient.
2. SNV: single nucleotide variant; InDel: Insertion/Deletion; CNV: copy number variation; VAF: variant allel fraction.
3. If the mutation is SNV, InDel or fusion, the VAF is the percentage of mutation variant reads among the total reads on that locus. If the mutation is CNV, the VAF is the relative copy number of the gene compared to the two normal copies.
4. N.D: Not Detected..
5. Targeted therapies with potential benefit:

   Level A: Therapies that have been approved by FDA/NMPA, or are included in the clinical guidelines.

   Level B: Therapies that have shown efficacy by published data from large-scale registered clinical trials (Phase II、Phase III、Phase IV).

   Level C: Therapies that that have been approved by FDA or NMPA for another tumor type, or have shown evidence of efficacy by published data from Phase I clinical trials or clinical case studies, or small-scale investigator-initiated clinical trials, or are being tested in large-scale registered clinical trials for which the patient may be eligible to enroll.
6. Information on potential drug resistance: patients with the detected mutations may have reduced sensitivity or resistance the listed drugs that have been approved by FDA/NMPA, or are recommended by the clinical guidelines for this patient's tumor type, which may reduce drug sensitivity or produce drug resistance.
7. The therapies labeled by * have been approved by NMPA.
8. The therapies in bold font have been approved by FDA/NMPA and others have not yet been approved by FDA/NMPA.
9. The therapies labeled by # are being tested in large-scale registered clinical trials for which the patient may be eligible to enroll.
10. Further details can be found in the “Detailed Results of Variant and the Relevance to Targeted Therapy”.

Detailed Results of Variant and the Relevance to Targeted Therapy

PIK3CA

<table>
<tr><td>Variant</td><td colspan="4">exon21 c.3140A>G p.H1047R</td></tr>
<tr><td>VAF</td><td colspan="4">32.56%</td></tr>
<tr><td rowspan="3">Targeted Therapy</td><td colspan="3">Potential Benefit</td><td rowspan="2">Potential Resistance</td></tr>
<tr><td>Level A</td><td>Level B</td><td>Level C</td></tr>
<tr><td>Alpelisib + Fulvestrant</td><td>None</td><td>Everolimus + Exemestane, Doxorubicin + Bevacizumab + Everolimus, Doxorubicin + Bevacizumab + Temsirolimus, Pazopanib + Everolimus</td><td>Pertuzumab + Trastuzumab, Trastuzumab</td></tr>
<tr><td>Evidence-based Medicine</td><td colspan="4">Gene description: PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) is a Protein Coding gene. Diseases associated with PIK3CA include Congenital Lipomatous Overgrowth, Vascular Malformations, And Epidermal Nevi and Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome. Among its related pathways are Glioma and Development Dopamine D2 receptor transactivation of EGFR. Gene Ontology (GO) annotations related to this gene include transferase activity, transferring phosphorus-containing groups and protein serine/threonine kinase activity. This gene was present in the common ancestor of animals.
Description of signaling pathway: None.
Variant description: PIK3CA H1047R is a hotspot mutation that lies within the kinase domain of the Pik3ca protein (UniProt.org). H1047R confers a gain of function on the Pik3ca protein as indicated by increased phosphorylation of Akt and Mek1/2, growth factor-independent cell survival, and transformation in cell culture [PMID: 26627007,PMID: 29533785].
Description of NCCN Guidelines: None.
Description of prognostic diagnosis: None.
Related biological and medical information: PIK3CA, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform, activates AKT/mTOR signaling to promote cell proliferation [PMID: 23411347]. PIK3CA activating mutations have been identified in a number of tumor types such as breast cancer, colon cancer and endometrial cancer [PMID: 20535651]. In a phase 3 trial, 572 patients with HR-positive, HER2-negative advanced breast cancer were randomised to alpelisib plus fulvestrant or placebo plus fulvestrant, including 341 patients with confirmed tumor-tissue PIK3CA mutations.In the cohort of patients with PIK3CA-mutated cancer, progression-free survival at a median follow-up of 20 months was 11.0 months(95% confidence interval [CI], 7.5 to 14.5) in the alpelisib fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo fulvestrant group (hazard ratio for progression or death, 0.65; 95%</td></tr>
</table>

	CI, 0.50 to 0.85; P<0.001) [PMID: 31091374]. In the BOLERO-2 trial, patients with HR+ , HER2- MBC were randomised to everolimus plus exemestane or placebo plus exemestane. Everolimus plus exemestane prolonged median PFS in patients with PIK3CA H1047R (7.59 vs 4.04 month; HR, 0.37) mutations [PMID: 28183140].In a phase 1 trial,fifty-two women with metaplastic TNBC were treated with liposomal doxorubicin, bevacizumab, and temsirolimus (N=39) or liposomal doxorubicin, bevacizumab, and everolimus (N=13). The objective response rate was 21% in overall patients or 31% in patients with PI3K pathway activation,respectively.Outcomes were similar if mutations in PIK3CA were located in the helical or kinase domain(ORR,22% vs 23%;P > .99; and CBR,33% vs 46%;P = .67,respectively)[PMID:27893038].In a phase 1 trial,fifty-seven patients treated with the combination of pazopanib and everolimus, among 52 patients evaluable for response, the clinical benefit rate (CBR) was 27% (14/52) including four partial responses (PR), and 10 stable disease (SD) ≥6 months, including one patient with ER+, PR+, HER2- breast cancer carrying PIK3CA H1047R mutation[PMID:25902899]. **Description of drug resistance:** In the phase III study of pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel as first-line treatment for patients with HER2-positive metastatic breast cancer.PIK3CA showed the greatest prognostic effect, with longer median PFS for patients whose tumors expressed wild-type versus mutated PIK3CA in both the control (13.8 v 8.6 months) and pertuzumab groups (21.8 v 12.5 months)[PMID: 25332247].A retrospective analysis of first trastuzumab-containing regimen treatment data showed that PI3K pathway activation correlated with a shorter median progression-free survival (4.5 versus 9.0 months, P = 0.013)[PMID: 21676217].In 80 HER2-positive patients treated with 1 year of trastuzumab,better disease-free survival (DFS) was observed in patients with PIK3CA wild-type compared with mutated tumours (P=0.0063)[PMID: 23612454].

Details of Drug Information

Drugs	Indications
Alpelisib	FDA approved Alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer.
Everolimus	FDA approved Everolimus in (1) postmenopausal women with advanced hormone receptor-positive, HER2 negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole; (2) adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic; (3) adults with advanced renal cell carcinoma (RCC) after failure of treatment with Sunitinib or Sorafenib; (4) adults with renal angiomyolipoma and tuberous sclerosis complex (TSC),not requiring immediate surgery
Bevacizumab	FDA approved bevacizumab for the treatment of (1) metastatic colorectal cancer, in combination with intravenous fluorouracil based chemotherapy for first- or second-line treatment; (2) metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan-or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.
Pazopanib	FDA approved pazopanib for the treatment of (1) advanced renal cell carcinoma; (2) advanced soft tissue sarcoma who have received prior chemotherapy
Temsirolimus	FDA approved temsirolimus for the treatment of advanced renal cell carcinoma (RCC).

ERBB2

Variant	exon19 c.2264T>C p.L755S			
VAF	29.44%			
Targeted Therapy	**Potential Bbenefit**			**Potential Resistance**
	Level A	**Level B**	**Level C**	
	None	None	Neratinib, Lapatinib, Afatinib	None
Evidence-based Medicine	**Gene description:** ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2) is a Protein Coding gene. Diseases associated with ERBB2 include Glioma Susceptibility 1 and Gastric Cancer. Among its related pathways are Development EGFR signaling via small GTPases and GPCR Pathway. Gene Ontology (GO) annotations related to this gene include identical protein binding and protein kinase activity. This gene was present in the common ancestor of animals. **Description of signaling pathway:** None. **Variant description:** ERBB2 (HER2) L755S lies within the protein kinase domain of the Erbb2 (Her2) protein (UniProt.org). L755S results in increased phosphorylation of Erbb2 (Her2), activation of downstream signaling, is transforming in cell culture [PMID: 29967253]. **Description of NCCN Guidelines:** None. **Description of prognostic diagnosis:** None. **Related biological and medical information:** ERBB2 (HER2), erb-b2 receptor tyrosine kinase 2, is an EGFR receptor tyrosine kinase that activates PI3K-AKT-mTOR and RAS-RAF-MEK-ERK pathways, therefore regulating growth and transformation [PMID: 17471238]. ERBB2 (HER2) amplification, overexpression, and activation has been implicated in several tumor types [PMID: 17471238]. A case report describes a young woman with metastatic breast cancer whose tumor was found to carry a HER2 L755S mutation. Treatment with the second-generation HER2/EGFR tyrosine kinase inhibitor neratinib resulted in partial response and dramatic improvement in the patient's functional status. Upon disease progression, she was treated with neratinib plus capecitabine and her cancer again responded [PMID: 26358790]. The clinical trials for HER2-mutated solid tumors are currently enrolling patients. **Description of drug resistance:** None. **The clinical trials shown in the table below are recommended.**			

Details of Drug Information

Drugs	Indications
Neratinib	FDA approved Neratinib for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

Information on Related Clinical Trials

Trial ID on ClinicalTrials.gov or chinadrugtrials.org.cn	Clinical Trial Name	Tumor Type	Phase	Drug Candidate(s)	Locations of Recruiting Sites

Trial ID on ClinicalTrials.gov or chinadrugtrials.org.cn	Clinical Trial Name	Tumor Type	Phase	Drug Candidate(s)	Locations of Recruiting Sites
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors	Malignant Solid Neoplasms	Phase 2	Lapatinib	France
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	Advanced Malignant Solid Neoplasm	Phase 2	Afatinib	United States

Note:

1. The above information is constantly evolving. Therefore, the health care providers are responsible for obtaining the most recent and appropriate information through proper resources.

Chemotherapy-related Gene Detection

Detailed Results of Variant and the Relevance to Chemotherapy

Potential Relevance to Chemotherapy Toxicity

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Toxicity	Evidence Level
Fluorouracil, Leucovorin and Oxaliplatin	MTHFR	rs1801131	GT	GT: Cancer patients with the GT genotype may have an increased risk of drug toxicities as compared to those with the TT genotype, and decreased survival times as compared to those with the GG genotype, when receiving capecitabine-based chemotherapy. Other genetic and clinical factors may also influence a patient's risk of drug toxicities. [PMID:20819423]	3
		rs1801133	GG	GG: Genotype AG is associated with increased risk of Drug Toxicity when treated with capecitabine, fluorouracil, leucovorin and oxaliplatin in people with Colorectal Neoplasms. [PMID:23314736]	3
	ERCC1	rs11615	AG	AG: Patients with the AG genotype and colon cancer may have a decreased risk of neutropenia when treated with FOLFOX (fluorouracil, leucovorin, oxaliplatin) as compared to patients with the AA genotype. Other genetic and clinical factors may also influence risk of neutropenia. [PMID:23314736]	3
Fluorouracil and Leucovorin	MTHFR	rs1801131	GT	GT: Genotype GG is associated with increased risk of Drug Toxicity when treated with capecitabine, fluorouracil, leucovorin and oxaliplatin in people with Colorectal Neoplasms. Other genetic and clinical factors may also influence a patient's risk of drug toxicities.[PMID:20819423]	3
		rs1801133	GG	GG: Cancer patients with the GG genotype may have a decreased risk of drug toxicities when treated with fluorouracil- or capecitabine-based therapy as compared to patients with the AA or	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Toxicity	Evidence Level
				AG genotype, however this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's risk of toxicities when taking these drugs. [PMID:19384296]	
Cyclophosphamide + Epirubicin	GSTP1	rs1695	AA	AA: Patients with the AA genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) increased drug response 2) decreased severity of toxicity as compared to patients with GG genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patient's response to cyclophosphamide, epirubicin and fluorouracil. [PMID:21362365]	2A
Carboplatin + PaclitaxelPlatinum compounds	GSTP1	rs1695	AA	AA:Genotype AA is associated with increased risk of hematological toxicity when treated with Platinum compounds and taxanes in people with Ovarian Neoplasms as compared to genotypes GG + AG. [PMID:19203783]	2A
Cisplatin + Cyclophosphamide	ERCC1	rs11615	AG	AG: Patients with the AG genotype and Ovarian Neoplasms who are treated with cisplatin and cyclophosphamide may have an increased risk of nephrotoxicity as compared to patients with the GG genotype. This association has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's risk for adverse events with cisplatin and cyclophosphamide treatment. [PMID:19786980]	3
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens.	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Toxicity	Evidence Level
				[PMID:22188361]	
Irinotecan	C8orf34	rs1517114	GG	GG: Patients with the GG genotype may have decreased severity of Diarrhea when treated with irinotecan in people with Non-Small-Cell Lung Carcinoma as compared to patients with the CC or CG genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity. [PMID:22664479]	2B
Cyclophosphamide	MTHFR	rs1801133	GG	GG: Patients with the GG genotype may have decreased likelihood of Drug Toxicity when treated with cisplatin, cyclophosphamide, dactinomycin, doxorubicin, methotrexate and vincristine in people with Osteosarcoma as compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of toxicity to cyclophosphamide. [PMID:19159907] [PMID:20638924]	3
Cyclophosphamide	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with cyclophosphamide-containing chemotherapy regimens as compared to patients with the CC genotype. However, all studies evaluated also included platinum drugs which may interact with this variant. Other genetic and clinical factors may also influence response to treatment. [PMID:19786980]	3
Fluorouracil	GSTP1	rs1695	AA	AA: Patients with the AA genotype and cancer who are treated with fluorouracil may have a higher risk of hematological toxicity as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's risk for hematological toxicity when exposed to fluorouracil. [PMID:18540691]	3
	MTHFR	rs1801131	GT	GT: Genotype GG is associated with increased likelihood of Drug Toxicity when treated with fluorouracil in people with Colorectal Neoplasms as compared to genotypes GT + TT. This has been contradicted in another study, and no association with drug toxicity found in a third study. Other genetic and clinical factors may influence a	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Toxicity	Evidence Level
				patient's response to fluorouracil-based chemotherapy. [PMID:17700593]	
		rs1801133	GG	GG: Cancer patients with the GG genotype may have a decreased risk of drug toxicities when treated with fluorouracil- or capecitabine-based therapy as compared to patients with the AA or AG genotype, however this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's risk of toxicities when taking these drugs. [PMID:23314736] [PMID:19384296] [PMID:20638924]	3
Capecitabine	MTHFR	rs1801131	GT	GT: Cancer patients with the GT genotype may have an increased risk of drug toxicities as compared to those with the TT genotype, and decreased survival times as compared to those with the GG genotype, when receiving capecitabine-based chemotherapy. Other genetic and clinical factors may also influence a patient's risk of drug toxicities. [PMID:18245544] [PMID:20819423]	3
		rs1801133	GG	GG: Cancer patients with the GG genotype may have a decreased risk of drug toxicities when treated with fluorouracil- or capecitabine-based therapy as compared to patients with the AA or AG genotype, however this has been contradicted in some studies. Other genetic and clinical factors may also influence a patient's risk of toxicities when taking these drugs. [PMID:20819423]	3
Carboplatin	GSTP1	rs1695	AA	AA: Allele G is associated with decreased risk of Neutropenia when treated with Platinum compounds in people with Carcinoma, Non-Small-Cell Lung as compared to allele A. [PMID:17409936]	3
Oxaliplatin	GSTP1	rs1695	AA	AA: Patients with the AA genotype and cancer who are treated with oxaliplatin or platinum compounds may have an increased risk for hematological toxicity, neurotoxicity, neutropenia, and discontinuation of treatment as compared to patients with the AG or GG genotype. Conflicting	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Toxicity	Evidence Level
				data exist for the neurotoxicity risk showing that patients with the AA might have a decreased, but not absent, risk. Other genetic and clinical factors may also influence a patient's risk for adverse events with oxaliplatin or platinum compounds treatment. [PMID:20530282][PMID:16707601]	
Cisplatin	XPC	rs2228001	TT	TT: Patients with the TT genotype may have a decreased but not non-existent risk for toxicity with cisplatin treatment as compared to patients with the GG or GT genotype. Other genetic and clinical factors may also influence a patient's risk for toxicity. [PMID:21047201][PMID:19434073]	1B
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:19786980]	2B
	GSTP1	rs1695	AA	AA: Allele G is associated with decreased risk of Neutropenia when treated with Platinum compounds in people with Carcinoma, Non-Small-Cell Lung as compared to allele A. [PMID:17409936]	3
	MTHFR	rs1801133	GG	Patients with the GG genotype may have:Genotype AA is associated with increased likelihood of Drug Toxicity when treated with cisplatin, cyclophosphamide, dactinomycin, doxorubicin, methotrexate and vincristine in people with Osteosarcoma as compared to genotypes GG + AG. [PMID:19159907]	3

Potential Relevance to Chemotherapy Efficacy

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
Fluorouracil+Leucovorin +Oxaliplatin	GSTP1	rs1695	AA	AA: Genotype GG is associated with increased progression free survival when treated with fluorouracil, leucovorin and oxaliplatin in people with Colorectal Neoplasms as compared to genotypes AA + AG. [PMID:20078613]	2A
	MTHFR	rs1801131	GT	GT:Patients with the GT genotype and colorectal cancer who are treated with FOLFOX therapy (includes fluorouracil, leucovorin, oxaliplatin) may have a better response to treatment as compared to patients with the TT genotype. Other genetic and clinical factors may influence a patient's response to chemotherapy. [PMID:20385995][PMID:20078613]	2A
		rs1801133	GG	GG: Patients with genotype GG and colonic neoplasms may have increased response to fluorouracil, leucovorin and oxaliplatin (FOLFOX therapy) as compared to patients with genotypes AA and AG. However, other studies showed decreased response to oxaliplatin. [PMID:24980946]	3
	ABCG2	rs2231142	GG	GG: Patients with the GG genotype and and colorectal cancer who are receiving FOLFOX/XELOX regimens may have a poorer response rate as compared to patients with the GT or TT genotype. Other genetic and clinical factors may also influence response to chemotherapy regimens. [PMID:24338217]	3
	ERCC1	rs11615	AG	AG: Patients with the AG genotype and colorectal cancer may have decreased overall and progression-free survival time when treated with FOLFOX (fluorouracil, leucovorin, oxaliplatin) as compared to patients with the GG genotype. Other genetic and clinical factors may also influence	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				overall and progression-free survival time. [PMID:21057378][PMID:15213713]	
	XRCC1	rs25487	CT	CT: Genotype CC is associated with increased overall survival progression-free survivaland when treated with fluorouracil, leucovorin and oxaliplatin in people with Colorectal Neoplasms as compared to genotypes CT + TT. Other genetic and clinical factors may also influence response to platinum-based regimens. Other genetic and clinical factors may also influence response to treatment.‖ [PMID:21057378][PMID:23314736]	3
Fluorouracil+Oxaliplatin	GSTP1	rs1695	AA	AA: Patients with the AA genotype and colorectal cancer who are treated with fluorouracil and oxaliplatin may have poorer treatment outcome (reduced responsiveness, lower overall survival time, increased risk of death) as compared to patients with the GG genotype. Other genetic and clinical factors may also influence a patient's response to fluorouracil and oxaliplatin treatment. [PMID:21449681]	2A
	ERCC1	rs11615	AG	AG: Genotype AA is associated with increased risk of dying when treated with Platinum compounds in people with Colorectal Neoplasms as compared to genotype GG. [PMID:15213713]	3
Capecitabine+Oxaliplatin	MTHFR	rs1801133	GG	GG: Patients with genotype GG and colonic neoplasms may have increased response to fluorouracil, leucovorin and oxaliplatin (FOLFOX therapy) as compared to patients with genotypes AA and AG. However, other studies showed decreased response to oxaliplatin. [PMID:24980946]	3
Carboplatin+Docetaxel	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA.	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004]	
Cisplatin+Docetaxel	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:24446315]	2B
	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004]	3
Cisplatin/Carboplatin+Gemcitabine	ERCC1	rs11615	AG	AG: Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or survival. Other genetic and clinical factors may also influence a patient's response to platinum-based chemotherapy. [PMID:25069034]	2B
	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased	3

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004]	
Cisplatin/Carboplatin+Pemetrexed	ERCC1	rs11615	AG	AG: Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or survival. Other genetic and clinical factors may also influence a patient's response to platinum-based chemotherapy. [PMID:25069034]	2B
Cisplatin/Carboplatin+Pemetrexed	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:24732178]	3
Cisplatin/Carboplatin+Paclitaxel	ERCC1	rs11615	AG	AG: Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				survival. Other genetic and clinical factors may also influence a patient's response to platinum-based chemotherapy. [PMID:25069034]	
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:24446315]	2B
	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004]	3
Cisplatin/Carboplatin+Vinorelbine	ERCC1	rs11615	AG	AG: Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or survival. Other genetic and clinical factors may also influence a patient's response to platinum-based chemotherapy. [PMID:25069034]	2B
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:24446315]	
	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004]	3
Cyclophosphamide+Epirubicin+Fluorouracil	GSTP1	rs1695	AA	AA: Patients with the AA genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) increased drug response 2) decreased severity of toxicity as compared to patients with GG genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patient's response to cyclophosphamide, epirubicin and fluorouracil. [PMID:20568049]	2A
Cyclophosphamide+Epirubicin	GSTP1	rs1695	AA	AA: Patients with the AA genotype and Breast Neoplasms who are treated with cyclophosphamide and epirubicin may have 1) increased drug response 2) decreased severity of toxicity as compared to patients with GG genotype. Some patients were additionally treated with fluorouracil. Other genetic and clinical factors may influence a patient's response to cyclophosphamide, epirubicin and fluorouracil. [PMID:21362365]	2A

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
carboplatin+Cyclophosphamide	ERCC1	rs11615	AG	AG: Genotype AA is associated with decreased response to Platinum compounds in women with Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of recurrence of disease when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of Death when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG. [PMID:22329723]	2B
Carboplatin+Paclitaxel	ERCC1	rs11615	AG	AG: Genotype AA is associated with decreased response to Platinum compounds in women with Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of recurrence of disease when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of Death when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG. [PMID:22329723]	2B
Cisplatin+Cyclophosphamide	ERCC1	rs11615	AG	AG: Genotype AA is associated with decreased response to Platinum compounds in women with Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of recurrence of disease when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of Death when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG. [PMID:22329723]	2B
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:19786980]	
	GSTP1	rs1695	AA	AA:Patients with the AA genotype and Ovarian Neoplasms who are treated with cisplatin and cyclophosphamide may have an increased likelihood of progression free survival as compared to patients with the AG and GG genotype. However, this association was contradicted in other studies. Other genetic and clinical factors may also influence a patient's response to cisplatin and cyclophosphamide treatment. [PMID:19786980]	3
Cisplatin+Paclitaxel	ERCC1	rs11615	AG	AG: Genotype AA is associated with decreased response to Platinum compounds in women with Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of recurrence of disease when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG.Genotype AA is associated with increased risk of Death when treated with Platinum compounds in women Ovarian Neoplasms as compared to genotype GG. [PMID:22329723]	2B
Cisplatin+Docetaxel+Gemcitabine+Capecitabine	ERCC1	rs11615	AG	AG: Genotypes AG + GG are associated with decreased overall survival when treated with capecitabine, cisplatin, docetaxel, epirubicin and gemcitabine in people with Pancreatic Neoplasms as compared to genotype AA. [PMID:22026922]	2B
	XRCC1	rs25487	CT	CT: Genotypes CT + TT are associated with decreased overall survival when treated with	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				capecitabine, cisplatin, docetaxel, epirubicin and gemcitabine in people with Pancreatic Neoplasms as compared to genotype CC. [PMID:22026922]	
Cisplatin+Epirubicin+Gemcitabine+Capecitabine	ERCC1	rs11615	AG	AG: Genotypes AG + GG are associated with decreased overall survival when treated with capecitabine, cisplatin, docetaxel, epirubicin and gemcitabine in people with Pancreatic Neoplasms as compared to genotype AA. [PMID:22026922]	2B
	XRCC1	rs25487	CT	CT: Genotypes CT + TT are associated with decreased overall survival when treated with capecitabine, cisplatin, docetaxel, epirubicin and gemcitabine in people with Pancreatic Neoplasms as compared to genotype CC. [PMID:22026922]	2B
Pemetrexed	MTHFR	rs1801133	GG	Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:24732178]	3
Cyclophosphamide	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with cyclophosphamide-containing chemotherapy regimens as compared to patients with the CC genotype. However, all studies evaluated also included platinum drugs which may interact with this variant. Other genetic and clinical factors may also influence response to treatment. [PMID:22188361]	3
Fluorouracil	NQO1	rs1800566	AG	Patients with AG genotype may have better OS and PFS than those with AA genotype. There were worse OS and PFS than GG genotypes	2A
Alkylating agents	NQO1	rs1800566	AG	Patients with AG genotype may have better OS and PFS than those with AA genotype. There were worse OS and PFS than GG	2A

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
				genotypes	
Anthracyclines	NQO1	rs1800566	AG	Patients with AG genotype may have better OS and PFS than those with AA genotype. There were worse OS and PFS than GG genotypes	2A
Carboplatin	MTHFR	rs1801133	GG	GG:Patients with GG genotype may have 1) decreased likelihood of response 2) decreased progression free survival to carboplatin in people with Non-Small-Cell Lung Carcinoma as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to carboplatin. [PMID:21605004][PMID:19307503]	2A
	ERCC1	rs11615	AG	AG: Patients with the AG genotype who are treated with platinum-based chemotherapy may have an increased risk for nephrotoxicity as compared to patients with the GG genotype. The findings for response and overall survival are inconclusive. Patients with the AG genotype may have an increased response compared to patients with the AA genotype. However, another study showed an increased response compared to patients with the GG genotype. Additionally, some studies find no association with drug toxicity or survival. Other genetic and clinical factors may also influence a patient's response to platinum-based chemotherapy. [PMID:25069034]	2B
	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:24446315]	2B

Chemotherapy	Gene	Mutation Site	Genotype	Potential Relevance to Efficacy	Evidence Level
Oxaliplatin	XRCC1	rs25487	CT	CT: Genotype CC is associated with increased overall survival progression-free survivaland when treated with fluorouracil, leucovorin and oxaliplatin in people with Colorectal Neoplasms as compared to genotypes CT + TT. Other genetic and clinical factors may also influence response to platinum-based regimens. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:21057378]	2B
Platinum	NQO1	rs1800566	AG	Patients with AG genotype may have better OS and PFS than those with AA genotype. There were worse OS and PFS than GG genotypes	2A
Cisplatin	XRCC1	rs25487	CT	CT: Patients with the CT genotype may have 1) decreased survival and 2) decreased risk of severe neutropenia when treated with platinum-based regimens as compared to patients with the CC genotype. However, one study found increased survival as compared to patients with the CC genotype. Conflicting results exist for the relationship between the CT genotype and response to platinum-based treatment. Other genetic and clinical factors may also influence response to platinum-based regimens. [PMID:25025378][PMID:22188361][PMID: 22026922][PMID:16875718]	2B
Cisplatin	MTHFR	rs1801133	GG	Patients with the GG genotype may have: 1) decreased likelihood of response to chemotherapy, 2) decreased likelihood of Drug Toxicity when treated with cisplatin in cancer patients as compared to patients with genotype AA. Other genetic and clinical factors may also influence a patient's response to cisplatin. [PMID:21605004]	3

Note:

* Description of the Levels of Evidence (PharmGKB)

Level 1A: Annotation for a variant-drug correlation in a CPIC or medical society-endorsed PGx guideline or implemented at a PGRN site or in another major health system.

Level 1B: Annotation for a variant-drug correlation where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.

Level 2A: Annotation for a variant-drug correlation that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenetics related genes, therefore the functional significance is more likely.

Level 2B: Annotation for a variant-drug combination with moderate evidence of association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.

Level 4: Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

* The toxicity and efficacy of chemotherapy drugs are often affected by multiple genetic polymorphisms. Due to the limitations of the current knowledge in pharmacogenomics, the conclusions based on genotypes alone may sometimes contradict to each other. In addition, other genetic or environmental factors could also influence the toxicity and efficacy of chemotherapy drugs.

Appendix

Gene List

ABCG2	AKT1	ALK	ATR	AXL	BRAF	C8orf34
CCND1	CDK4	CDK6	DDR2	EGFR	ERBB2	ERCC1
FGFR1	FGFR2	FGFR3	GNA11	GNAQ	GSTP1	HRAS
JAK1	JAK2	JAK3	KDR	KIT	KRAS	MAP2K1
MAP2K2	MET	MTHFR	NRAS	NTRK1	NTRK2	NTRK3
PDGFRA	PIK3CA	PTEN	RET	ROS1	SMO	STK11
TP53	TSC1	UGT1A1	XPC	XRCC1		