NovoFocus™ PARPi CDx 1.0

Test Report

Patient Name:	XXX
Physician ID:	
Report Date:	2019/06/25

NovoFocus™ PARPi CDx 1.0 Report

Patient	Data of Birth	Diagnosis	Specimen I.D	Report Date	Ordering Physician
XXX	1981/04/02	Breast Cancer	MKHSxxxxxxxxx-2A	2019/06/25	XXX

Genomic Alterations - Clinical Actionable

Summary of genomic alterations found in patient specimen. Only variants of clinical relevance are listed.

SNV and InDel

Gene and Associated Alterations		VAF
TP53	NM_000546.5 exon10 c.1045G>T p.E349*	72.41%
NF1	NM_000267.3 exon5 c.499_502delTGTT p.C167Qfs*10	Heterozygote
ATM	NM_000051.3 exon 62 c.8814_8824del11 p.M2938Ifs*14	Heterozygote
MUTYH	NM_001128425.1 c.925-2A>G	Heterozygote

CNV

Gene and Associated Alterations		VAF
ERBB2	Amplification	12.1X

Note:

1. SNV: single nucleotide variant; InDel: Insertion/Deletion; CNV: copy number variation; VAF: variant allele fraction
2. If the mutation is SNV or InDel, 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.
3. /: Not Detected.

NovoFocus™ PARPi CDx 1.0 Report

Therapeutic Implications

Tier I - Strong Clinical Significance

Variant	Level	Clinical Impact
ERBB2 Amplification	B	May benefit from --- **Trastuzumab + Pertuzumab + Docetaxel***, **Ado-trastuzumab emtansine**, **Neratinib**

Tier II - Potential Clinical Significance

Variant	Level	Clinical Impact
ERBB2 Amplification	C	May benefit from --- Trastuzumab + Pyrotinib + Docetaxel#, A166#, Trastuzumab + Pertuzumab#
TP53 NM_000546.5 exon10 c.1045G>T p.E349*	C	May benefit from --- Adavosertib + Carboplatin#

Potential Resistance

Variant	Clinical Impact
/	/

Note:

1. Therapies associated with benefit or lack of benefits are **solely** based on the 45 genes (Ref to gene list) sequenced and genomic findings on patient tumor. Other clinicopathological factors will need to be taken into consideration when choosing appropriate therapy for the patient.
2. 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.
3. 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.
4. The therapies labeled by * have been approved by NMPA.
5. The therapies in **bold font** have been approved by FDA/NMPA and others have not yet been approved by FDA/NMPA.
6. The therapies labeled by # are being tested in large-scale registered clinical trials for which the patient may be eligible to enroll.
7. Further details can be found in the “Detected Mutations and Related Targeted Therapy”.

.

NovoFocus™ PARPi CDx 1.0 Report

Other Biomarker

HRD (Genomic instability status)

Positive

Note:

1. Homologous Recombination Deficiency (HRD) is defined by either a deleterious or suspected deleterious BRCA mutation, or the percentage of genomic loss of heterozygosity (LOH) high, or genomic instability in patients with disease progression greater than six months after response to the last platinum-based chemotherapy. The results of the test are used as an aid in identifying cancer patients with HRD-positive status for treatment with the targeted therapy in accordance with the approved therapeutic product labeling. For instance: on October 23, 2019, the Food and Drug Administration approved Niraparib (ZEJULA®, Tesaro, Inc.) for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD-positive status.

NovoFocus™ PARPi CDx 1.0 Report

Hereditary Cancer Risk Assessment

Gene	Variant	Zygosity	Classification
NF1	NM_000267.3 c.499_502delTGTT p.C167Qfs*10	Heterozygote	Pathogenic
ATM	NM_000051.3 c.8814_8824del11 p.M2938Ifs*14	Heterozygote	Pathogenic
MUTYH	NM_001128425.1 c.925-2A>G	Heterozygote	Likely pathogenic

The genetic test contains hereditary cancer risk genes, and it is found that NF1 pathogenic variant, ATM pathogenic variant and MUTYH likely pathogenic variant, so your risk of developing cancer is higher than the general population.

This individual is heterozygous for a pathogenic variant in the NF1 gene, consistent with Neurofibromatosis type 1(NF1) syndrome. NF1 syndrome is associated with an increased risk of pheochromocytoma (1-13%), malignant peripheral nerve sheath tumors (6-16%), optic nerve gliomas (15%), breast cancer in women, gastrointestinal stromal tumors (GIST) and childhood leukemias.

This individual is also heterozygous for a pathogenic variant in ATM. Associated risks include an increased risk for breast cancer in women, and for colon, pancreatic, prostate, and other cancers in both women and men.

Recommendations

- Genetic counseling is recommended to discuss the implications of these results.
- Surveillance and treatment recommendations for Neurofibromatosis type 1 are summarized in Evans et al. (2017) and the Neurofibromatosis 1 article in GeneReviews (Friedman 2018). In addition, the "NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian" include management recommendations for individuals with pathogenic variants in NF1.
- The "NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian" include management recommendations for individuals with pathogenic variants in ATM.
- First degree relatives have up to a 50% chance of also having the pathogenic variant(s) identified in this individual. Targeted testing for the pathogenic variant(s) is available for at-risk relatives.
- For individuals and family members of reproductive age, assessment of the reproductive risk associated with being a carrier of an ATM pathogenic variant is recommended.
- If you would like to discuss these results in further detail, please consult your healthcare provider or genetic counselor.

Analyzed and reported by: **Checked and approved by:**

NovoFocus™ PARPi CDx 1.0 Report

Patient and Order Details

Patient	Specimen	Physician
Name: XXX	**Specimen I.D.:** MKHSxxxxxxxxx-2A	**Ordering Physician:**
Patient NRIC/FIN/ID:	**Specimen Type/Size:** Tissue > 60% tumor cells*	**Institution:**
Gender: Female	**Specimen Collection Date:**	
Data of Birth: YY/MM/DD	**Specimen Received Date:**	
Nationality:		
Diagnosis: Breast Cancer		

Test Indication (Personal / Family History Summary)

Personal History & Family History: Unknown

*: A minimum of 10% tumor is required and at least 50 mm^2 of tissue is required.

Therapeutic Variant Details - Clinical Actionable

Variant	Interpretations
ERBB2 Amplification VAF: 12.1X	**Gene description:** The ERBB2/HER2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2) gene encodes a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases. It binds tightly to other ligand-bound EGF receptor family members to form a heterodimer, stabilizing ligand binding and enhancing kinase-mediated activation of downstream signalling pathways. Amplification and/or overexpression of this gene have been reported in breast cancer, non-small cell lung cancer, etc. **Description of signaling pathway:** Its related signaling pathways such as PI3K/AKT/mTOR and Ras/Raf/MEK/ERK are involved in the regulation of cell proliferation, survival and differentiation. HER2 amplification results in numerous downstream molecular cascades, leading to enhanced proliferative signals. **Variant description:** This variation is a gene amplification that may result in increased protein expression. **Description of NCCN Guidelines:** None. **Description of prognostic diagnosis:** None. **Related biological and medical information:** The randomized trial was a multicenter, double-blind, placebo-controlled, phase III trial of 808 patients with HER2-positive metastatic breast cancer (breast tumor specimens were required to show HER2 overexpression defined as 3+ IHC or FISH amplification ratio determined at a central laboratory). Patients were randomized 1:1 to receive placebo plus Trastuzumab and Docetaxel or Pertuzumab plus trastuzumab and docetaxel. The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the Pertuzumab-treated group compared with the placebo-treated group [hazard ratio (HR) = 0.62 (95% CI: 0.51, 0.75), p < 0.0001] and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the Pertuzumab-treated group vs. 12.4 months in the placebo-treated group) [FDA Reference ID:4198338]. In a phase III, randomized, multicenter, open-label trial that enrolled 991 patients, patients in the trial had to have breast tumor specimens that showed HER2 overexpression or amplification. Patients were randomly assigned (1:1) to receive Ado-trastuzumab emtansine, or Lapatinib plus Capecitabine. Patients who received Ado-trastuzumab emtansine lived statistically significantly longer without their disease getting worse (PFS) compared with those who received Lapatinib plus Capecitabine [HR of progression 0.65 (95 percent CI: 0.55, 0.77), p < 0.0001]. The median PFS was 9.6 months for patients who received Ado-trastuzumab emtansine and 6.4 months for patients who received Lapatinib plus Capecitabine. At the time of the second interim OS analysis, patients who received Ado-trastuzumab emtansine had a statistically significant improvement in OS compared with people who received Lapatinib and Capecitibine [HR of death 0.68 (95 percent CI: 0.55, 0.85), p = 0.0006]. The median OS was 30.9 months for patients who received Ado-trastuzumab emtansine and

NovoFocus™ PARPi CDx 1.0 Report

Variant	Interpretations
	25.1 months for patients who received Lapatinib plus Capecitabine [FDA reference ID: 4323855]. Based on results of ExteNET trial, which is a multicenter, randomized, double-blind, placebo-controlled trial, women (n = 2840) were randomized to receive either Neratinib (n = 1420) or placebo (n = 1420) for one year. The major efficacy outcome measure was invasive disease-free survival (iDFS) defined as the time between the randomization date to the first occurrence of invasive recurrence (local/regional, ipsilateral or contralateral breast cancer), distant recurrence, or death from any cause. iDFS was 94.2% in patients treated with Neratinib compared with 91.9% in those receiving placebo (HR 0.66; 95% CI: 0.49, 0.90, p = 0.008) [FDA Reference ID: 4284195]. **Description of drug resistance:** None.

Variant	Interpretations
TP53 NM_000546.5 exon10 c.1045G>T p.E349* VAF: 72.41%	**Gene description:** The TP53 (tumor protein p53) gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome, soft tissue and osteosarcoma, breast cancer, brain cancer, adrenal cortical cancer, etc. **Description of signaling pathway:** None. **Variant description:** This variation is an inactive mutation that may result in a loss of protein function. **Description of NCCN Guidelines:** None. **Description of prognostic diagnosis:** None. **Related biological and medical information:** Adavosertib is a WEE1 kinase inhibitor targeting G2 checkpoint control, preferentially sensitizing TP53-deficient tumor cells to DNA damage. A phase I study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of oral Adavosertib as monotherapy or in combination with chemotherapy in patients with refractory solid tumors. Of 176 patients evaluable for efficacy, 94 (53%) had stable disease as best response, and 17 (10%) achieved a partial response. The response rate in TP53-mutated patients (n = 19) was 21% compared with 12% in TP53 wild-type patients (n = 33). So Adavosertib was safe and tolerable as a single agent and in combination with chemotherapy at doses associated with target engagement [PMID: 27601554]. **Description of drug resistance:** None.

NovoFocus™ PARPi CDx 1.0 Report

Details of Approved Drug Information

Approved drugs associated with this patient's genomic profile and tumor type are displayed below.

Variant	Drugs	Indications
ERBB2 Amplification	Trastuzumab + Pertuzumab + Docetaxel*	FDA approved PERJETA (Pertuzumab) is a HER2/neu receptor antagonist indicated for use in combination with Trastuzumab and Docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. NMPA approved Pertuzumab in combination with Trastuzumab and chemotherapy for adjuvant treatment of patients with HER2-positive early breast cancer with a high risk of recurrence.
ERBB2 Amplification	Ado-trastuzumab emtansine	FDA approved KADCYLA (Ado-trastuzumab emtansine) is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for: 1. the treatment of patients with HER2-positive, metastatic breast cancer who previously received Trastuzumab and a Taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy; 2. the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant Taxane and Trastuzumab-based treatment.
ERBB2 Amplification	Neratinib	FDA approved NERLYNX (Neratinib) is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant Trastuzumab-based therapy.

Potential Clinical Trials

Clinical Trials associated with this patient's genomic profile and tumor type are displayed below.

Variant	Drug Candidates	Phase	Clinical Trial Name	Trial ID on ClinicalTrials.gov or chinadrugtrials.org.cn
ERBB2 Amplification	Trastuzumab + Pyrotinib + Docetaxel (Anti-HER2 + SHR1258 + RP56976)	III	Preoperative Treatment of HER2-Positive Breast Cancer with Pyrrolidine plus Herceptin/Docetaxel Versus Placebo plus Herceptin/Docetaxel	CTR20180941
ERBB2 Amplification	Trastuzumab + Pertuzumab (Anti-HER2 + 2C4 Antibody)	II	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	NCT02693535
ERBB2 Amplification	A166	I/II	A Phase I/II, FIH Study of A166 in Locally Advanced/Metastatic Solid Tumors Expressing Human Epidermal Growth Factor Receptor 2 (HER2) or Are HER2 Amplified That Did Not Respond or Stopped Responding to Approved Therapies	NCT03602079
TP53 NM_000546.5 exon10 c.1045G>T p.E349*	Adavosertib + Carboplatin (AZD1775 | MK1775 + CBDCA)	II	Molecular Profiling-Based Assignment of Cancer Therapy for Patients with Advanced Solid Tumors	NCT01827384

Note:

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

NovoFocus™ PARPi CDx 1.0 Report

Hereditary Cancer Risk Variant Details

Variant	Clinical and Variant Interpretation
NF1 NM_000267.3 c.499_502delTGTT p.C167Qfs*10 **Zygosity:** Heterozygote **Clinical Significance:** Pathogenic	**Variant description**: This deletion of 4 nucleotides in NF1 is denoted c.499_502delTGTT at the cDNA level and p.Cys167GlnfsX10 (C167Qfs*10) at the protein level. The normal sequence, with the deleted bases in brackets, is TGTT[delTGTT]CAGA. The deletion causes a frameshift which changes a Cysteine to a Glutamine at codon 167, and creates a premature stop codon at position 10 of the new reading frame. **Gene description**: Tumor suppressor gene NF1(neurofibromin 1) encoded protein appears to function as a negative regulator of the Ras signal transduction pathway, which promotes cell growth and differentiation. Defects in this gene are responsible for tumorigenesis as a result of the tumor inhibition function of NF1 protein is impaired and cell growth is uncontrolled. Mutations of NF1 gene are associated with many diseases including neurofibromatosis, monocytic leukemia, Watson syndrome, melanoma, lung cancer, colorectal cancer, etc. **Variant analysis:** This variant is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. This variant, previously published as NF1 495delTTGT, has been observed in multiple individuals with a clinical diagnosis of Neurofibromatosis Type 1 (Osborn 1999, Ars 2003, Lee 2006, Bendova 2007, Brinckmann 2007, Wimmer 2007, Sabbagh 2013, Schaefer 2013, Uusitalo 2014). Pasmant et al. (2011) identified this variant in an individual whose malignant peripheral nerve sheath tumor displayed loss of heterozygosity.Therefore, in view of the current research progress, we consider this variant to be a pathogenic variant.

Variant	Clinical and Variant Interpretation
ATM NM_000051.3 c.8814_8824del11 p.M2938Ifs*14 **Zygosity:** Heterozygote **Clinical Significance:** Pathogenic	**Variant description**: This deletion of 11 nucleotides in ATM is denoted c.8814_8824del11 at the cDNA level and p.Met2938IlefsX14(M2938Ifs*14) at the protein level. The surrounding sequence is TGAT[del11]AGGA. The deletion causes a frameshift, which changes a Methionine to an Isoleucine at codon 2938, and creates a premature stop codon at position 14 of the new reading frame. **Gene description**: The protein encoded by ATM(ATM serine/threonine kinase) gene belongs to the PI3/PI4-kinase family. This protein is an important cell cycle checkpoint kinase that phosphorylates many checkpoint proteins such as p53, CHK2, H2AX, MDM2, BRCA1 and so on, upon DNA stress. ATM encoded protein is an integration point of different signal transduction pathways which are crucial for cellular homeostasis. Mutations of ATM in cells bring about accumulation of DNA damage and genomic instability, leading to tumorigenesis. Mutations of ATM gene are associated with many cancers including endometrial cancer, bowel cancer, stomach cancer, etc. **Variant analysis:** This variant is predicted to cause loss of normal protein function through either protein truncation or nonsense-mediated mRNA decay. ATM c.8814_8824del11 has been observed in individuals with a personal history of Ataxia-Telangiectasia (Gilad 1998, Sandoval 1999, Cavalieri 2008, Prodosmo 2013). Therefore, in view of the current research progress, we consider this variant to be a pathogenic variant.

Variant	Clinical and Variant Interpretation
MUTYH NM_001128425.1 c.934-2A>G	**Variant description**: This variant is denoted MUTYH c.934-2A>G or IVS10-2A>G and consists of an A>G nucleotide substitution at the -2 position of intron 10 of the MUTYH gene. Using an alternate transcript, this variant has been reported as MUTYH c.892-2A>G. This variant destroys a

.

NovoFocus™ PARPi CDx 1.0 Report

Variant	Clinical and Variant Interpretation
Zygosity: Heterozygote **Clinical Significance:** Likely Pathogenic	canonical splice acceptor site and is predicted to cause abnormal gene splicing, leading to an abnormal message that is subject to nonsense-mediated mRNA decay or to an abnormal protein product.This variant is of a heterozygous type. **Gene description**: MUTYH is located at 1p34.1 and encodes 546 amino acids. Associated with hereditary polyposis, it is an autosomal recessive gene. The MUTYH protein is a specific adenine transglucosylase located in the nucleus and mitochondria and involved in base excision repair. If the MUTYH protein is inactivated, it will easily lead to the transversion of G:C-->A:T during replication, thereby promoting tumorigenesis. In patients with familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP), if no APC gene mutation was detected, MUTYH mutations were detected with a 33% and 57% chance, respectively. The two most common variants in 70%-86% of MAP patients are p.Y179C and p.G396D (originally named Y165C and G382D). MUTYH heterozygous variants increase the risk of breast cancer by 1.9 times. **Variant analysis:** The mutation is known as variation (rs77542170) and the frequency in the ExAC population is 0.00102. The mutation was recorded as a causative mutation in the ClinVar database (variation ID: 41766). It has been reported in the literature that mutations in this splice site produce abnormal mRNA transcripts, which in turn leads to truncation of the MUTYH protein and loss of nuclear localization of the protein [PMID: 15180946]. Since the wild-type MUTYH protein is mainly localized in the nucleus, this data indicates that this splicing variation disrupts protein function [PMID: 16199547]. The mutation has been reported to be a heterozygous mutation in several individuals with colorectal adenoma, colorectal cancer [PMID: 15890374, 17703316] and/or breast cancer [PMID: 15890374, 17703316, 26824983], but the mutation has not been determined. Whether it is the cause of the disease. Therefore, in view of the current research progress, we consider this variant to be an likely pathogenic variant. Since the variation is heterozygous, your first-degree relatives are 50% likely to carry the mutation. It is recommended that your relatives participate in further testing to determine genetic risk.

Risk of Developing Cancer

Note: Data from European and American people, for reference only.

In the light of having a likely pathogenic variant in the MUTYH gene, your risk of developing cancer is significantly higher than the general population and it needs to be taken seriously. However, you don't need to be overly nervous. You can check the disease regularly and take other appropriate measures to prevent it. At the same time, you can achieve three early clinical measures: early detection, early diagnosis, early treatment, then you will have a high chance to prevent cancer from developing or curing.

The list of disease risks caused by MUTYH mutations is as follows:

Homozygous mutation			
Cancer	**Age（year）**	**Risk of developing cancer**	**Risk of the general population**
Colorectal cancer	To 80	43%-100%	3.4%
Small Intestine Cancer	To 80	4%	0.2%
Heterozygous mutation			
Cancer	**Age（year）**	**Risk of developing cancer**	**Risk of the general population**
Colorectal cancer	To 80	3.4%-10%	3.4%

NovoFocus™ PARPi CDx 1.0 Report

Management Options for Risk Reduction

Cancer risk management measures related to MUTYH mutation

There are a few things you can do to reduce your cancer risk. Discuss with your health care provider or clinician before deciding on a suitable plan.

Homozygous mutation			
Cancer	**Measure**	**Age**	**Frequency**
Colorectal cancer	Colonoscopy	25-30 years	3-5/yeat
	Colorectal surgery assessment and consultation	Density and distribution according to adenoma	uncertain
Small Intestine Cancer	Upper gastrointestinal endoscopy	30-35 years	3-5/yeat

Heterozygous mutation			
Cancer	**Measure**	**Age**	**Frequency**
Colorectal cancer	Colorectal cancer screening	50 years	According to individual circumstances

Note:

The above risk management recommendations are derived from the NCCN guidelines and leading-edge scientific research. Specific risk management measures should be carefully selected in conjunction with their own quality of life requirements and family history.

What Does this Result Mean for Family Members?

Genetic variants are hereditary and the pathogenic variants are detected in your genes, so:

- Your family members (parents, children, brothers, and sisters) have a 50% chance of having the same variation.
- Your distant relatives (cousin, uncle, aunt etc.) may also have the same variation.
- In general, mutations will only be found in the parent (father or mother) with a family history of cancer.
- Relatives interested in genetic testing need to know your specific mutations. The cost of a single site detection is much less than the full cost of testing.
- If your relatives:
  - ★ The pathogenic variant is detected, his/her risk of developing cancer will increase and you can benefit from proper medical management.
  - ★ The pathogenic variant is not detected. His/her risk of developing cancer is the same as the general population. He/she can follow the general population screening guidelines.

.

NovoFocus™ PARPi CDx 1.0 Report

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.

Methodology

This sample was analyzed by next-generation sequencing of the coding regions and immediate flanking regions (20bp) of the 45 genes, which covers Single Nucleotide Variant (SNV), Insertion/Deletion (InDel) or Copy Number Variation (CNV). For negative results, the patients need to test for long genomic rearrangements (LGRs) in the *BRCA1/2* genes. This report presents the mutations detected in the submitted patient sample and information on approved therapies, clinical trials, risk assessment and other scientific findings. The result interpretation about germline variants, followed by in-house ACMG bioinformatics pipeline, is based on the current thinking of variant knowledge, and with the progress in genetic research, the interpreted results might change when more evidence published.

Gene list

Evidence level	NovoFocus PARPi CDx 1.0
NCCN guideline	*BRCA1, BRCA2*
From clinical trials of PARP inhibitors	*ATM, ATR, BARD1, BRIP1, CDK12, CHEK1, CHEK2, ERCC3, FAM175A, FANCA, FANCL, FANCM, GEN1, HDAC2, MRE11, MLH3, MSH2, MSH6, NBN, PALB2, PMS2, PPM1D, PPP2R2A, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RAD54L*
DNA damage repair pathway	*TP53*
NCCN guideline for genetic/Familial High-risk assessment: breast and ovarian cancer	*CDH1, EPCAM, MLH1, NF1, STK11*
NCCN guideline for genetic/Familial High-risk assessment: colon cancer	*APC, MUTYH*
Other gene targets in breast cancer or ovarian cancer	*AR, ERBB2, ESR1, PIK3CA, TSC1, TSC2*

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 and indication, clinical trials and other scientific findings are based on the clinical guidelines, clinical trial registry, ACMG variant classification 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 and/or risk assessment of these information/suggestions should be interpreted only by licensed/certified medical professionals.
- The detect result makes no promises or guarantees that PARP inhibitor therapy will be effective in the treatment of disease in any patient. It is the user's responsibility to verify these information/suggestions against the most recent advancement in the aforementioned sources. The information/suggestions should be interpreted only by licensed/certified medical professionals. Decision on patient care and treatment should be based on the independent

medical judgement and information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community.