

## Clinical Research Report

### PATIENT & PHYSICIAN

**Patient Name:** LAST, FIRST  
**Patient sex assigned at birth:** SEX  
**Patient DOB:** YYYY-MM-DD  
**Requisitioner Email:** [NAME@domain.com](mailto:NAME@domain.com)  
**Physician Licence #:** nnnnnnnn  
**Physician:** LAST, FIRST  
**Physician Phone #:** nnn-nnn-nnnn  
**Physician Hospital:** HOSPITAL NAME AND ADDRESS

### CASE OVERVIEW

**Assay:** Whole genome sequencing (WGS)-80X Tumour, 30X Normal (v5.0)  
**Primary cancer:** Metastatic melanoma  
**Site of biopsy/surgery:** Skin  
**Study:** PLACEHOLDER **Patient Study ID:** None  
**Patient LIMS ID:** PLACEHOLDER **Tumour Sample ID:** PLACEHOLDER  
**Requisition Approved:** 2025-04-01 **Blood Sample ID:** PLACEHOLDER  
**Date of Report:** 2025-04-24 **Report ID:** PLACEHOLDER-v1

### TREATMENT OPTIONS

Review identified **1** option(s) indicating an FDA-approved and/or NCCN-compendium listed treatment, **2** option(s) indicating investigational therapies, and **0** option(s) indicating NCCN-listed biomarkers.

#### FDA-approved and/or NCCN-recommended Biomarker:

OncoKB	Treatment(s)	Gene(s)	Alteration
1	Dabrafenib, Dabrafenib+Trametinib, Vemurafenib+Atezolizumab+Cobimetinib, Trametinib, Vemurafenib, Vemurafenib+Cobimetinib, Encorafenib+Binimetinib	<i>BRAF</i>	p.V600E

#### Investigational Therapies:

OncoKB	Treatment(s)	Gene(s)	Alteration
3B	Encorafenib+Cetuximab, Encorafenib+Cetuximab+FOLFOX Regimen, Selumetinib, Tovorafenib, Encorafenib+Panitumumab	<i>BRAF</i>	p.V600E
4	Palbociclib, Ribociclib, Abemaciclib	<i>CDKN2A</i>	p.A68Gfs*51

### RESULTS SUMMARY

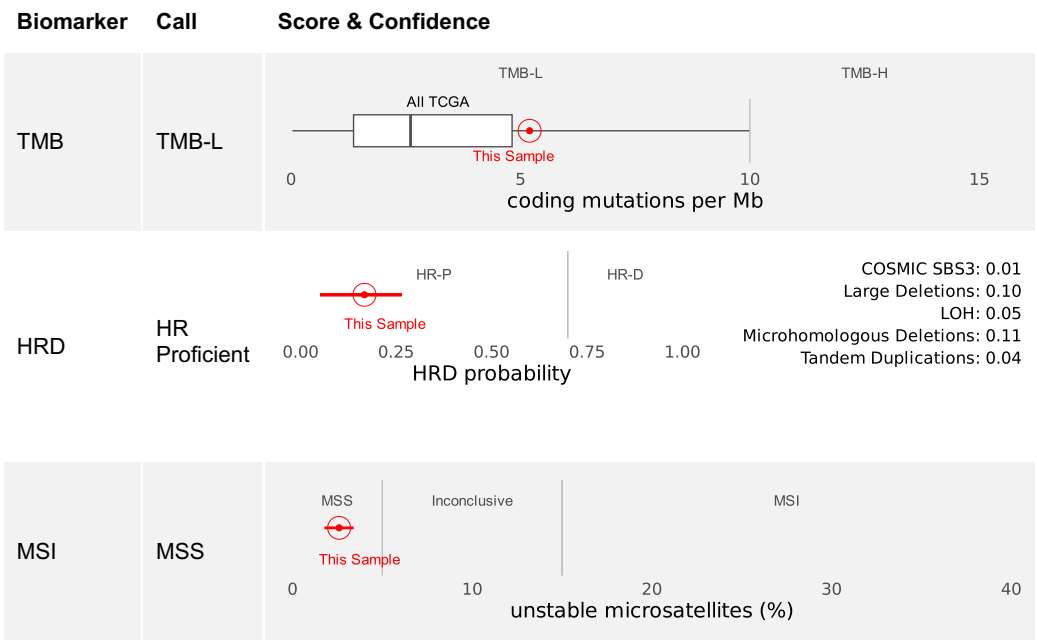
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.

### SAMPLE INFORMATION

**OncoTree code:** SKCM **Sample Type:** PLACEHOLDER  
**Callability (%):** 92 **Coverage (mean):** 101  
**Estimated Cancer Cell Content (%):** 99 **Estimated Ploidy:** 3.1

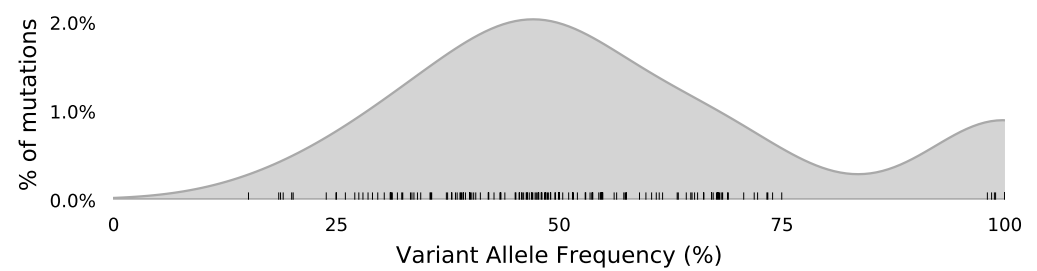
GENOMIC  
LANDSCAPE

Tumour Mutation Burden (TMB) was **5.2** coding mutations per Mb (194 mutations) which corresponds to the 72nd percentile of the pan-cancer cohort and classified it as **Tumour Mutational Burden Low (TMB-L, < 10 coding mutations / Mb)**. The microsatellite status was **Microsatellite Stable (MSS)**. This tumour had **37,517** candidate somatic SNVs genome-wide, making the sample **eligible** for OICR's plasma WGS cfDNA assay (minimum of 4,000 SNVs required). This sample shows signatures consistent with **Homologous Recombination Proficiency**.



SNVS AND  
IN/DELS

**322** somatic mutation(s) were detected in exonic or splice regions, of which **194** impacted a coding sequence, and **4** corresponded to an oncogenic mutation, as defined by OncoKB.



Gene	Chr.	Protein	Type	VAF	Depth	LOH	OncoKB
BRAF	7q34	p.V600E	Missense Mutation	67	105/156	False	1
CDKN2A	9p21.3	p.A68Gfs*51	Frame Shift Del	100	44/44	True	4
MYH11	16p13.11	p.?(c.5613+1G>A)	Splice Site	39	31/79	False	N2
MED12	Xq13.1	p.?(c.3210-6C>T)	Splice Region	100	44/44	NA	N2

**Chr.:** Chromosome and cytoband                      **LOH:** Loss of heterozygosity

COPY NUMBER  
VARIATION

The percent genome altered (PGA) was **55%**. **0** cancer gene(s) were subject to copy number variation, of which **0** corresponded to an oncogenic alteration, as defined by OncoKB. Regions with large copy number gains ( $\geq 6$  CN) marked as **▲** in plot below.



## ASSAY DESCRIPTION

This assay is a comprehensive next generation sequencing assay, specifically DNA-based whole genome sequencing (WGS). Whole Genome libraries were prepared using the KAPA Hyper Prep kit with DNA extracted from FFPE or fresh frozen tissue (for tumour samples) or buffy coat blood specimens (for matched normal blood samples). Paired-end sequencing was performed using the Illumina NovaSeq X Plus v1.2 technology. Reads were aligned using [bwa mem](#) (0.7.12) against reference genome [GRCh38.p12](#) and processed according to GATK best practices, including duplicate marking with [Picard](#) (2.21.2), realignment around small insertions and deletions (in/dels), and base recalibration with [GATK](#) (v.4.1.6.0). SNVs and in/dels were called using [MuTect2](#) (GATK v.4.2.6.1) and annotated with [VariantEffectPredictor](#) (v.105.0) using MANE transcripts (MANE Clinical version 1.0 when available, [MANE Select](#) version 1.0 for all other transcripts). Variants were further annotated for oncogenicity and actionability by [OncoKB](#). In cases where OncoKB did not use MANE Select, links in annotation have used the corresponding alteration in OncoKB. Copy number variations were called using [Purple](#) (3.8.1). Microsatellite (MS) Instability status was called using [msisensor-pro](#) (1.2.0) and a custom list of 1,900,495 MS sites created by msisensor-pro for the current reference genome. Homologous recombination deficiency (HRD) status was called using HRDetect ([Davies et al. 2017](#)), a weighted logistic regression model, using the signature.tools.lib R package ([Degasperi et al. 2020](#)). HRDetect takes SNVs and in/dels from MuTect2. The proportion of deletions occurring at microhomologous sites has been summarized as "Microhomologous Deletions". The counts of SNVs were categorized into exposures based on their trinucleotide context using [DeconstructSigs](#) (v. 1.8.0) and SBS signatures as defined in [COSMIC version 1](#). HRDetect also takes in LOH and structural variants. Structural variants were first called by [GRIDSS](#) (v.2.13.2) and then passed to PURPLE (v.3.8.1) for integrated LOH calling. Structural variants were then categorized into exposures based on break-end characteristics using [signature.tools.lib](#) (v. 2.1.2) and the rearrangement signature set defined in [Nik-Zainal et al. \(2016\)](#). Germline HLA analysis and HLA allele calls were performed using the [T1K tool](#) (v1.0.2). Assay results were collated into the report document by [Djerba](#) (1.8.4) using pipeline 5.0. Djerba component versions were: case\_overview (1.0.0), [core](#) (1.8.4), genomic\_landscape (2.0.0), input\_params\_helper (1.0.0), patient\_info (1.0.0), provenance\_helper (1.0.0), report\_title (1.0.0), sample (1.0.0), summary (0.1), [supplement.body](#) (0.1), wgts.cnv\_purple (0.1.0), wgts.snv\_indel (1.0.0).

## DISCLAIMER

Based on a minimum tumour purity of 30%, the sensitivity for SNVs and in/dels is 96% and 89%, respectively. The sensitivity for CNVs and RNA fusions is 100% and 32%, respectively. The limit of detection is 10% VAF for SNVs and 20% for in/dels. The limit of detection for MSI is cellularity  $\geq 50\%$ . For HRD, the sensitivity is 83% and the specificity is 90%. The lower limit of detection is  $\geq 50\%$  cellularity in FFPE samples and  $\geq 30\%$  cellularity in fresh frozen samples. For LOH, the sensitivity and specificity are both 100%. LOH is currently reported for autosomes; LOH on the X chromosome is not reported. Germline HLA allele calling sensitivity is above 95%. Although whole genome sequencing encompasses all genes in a specimen, this report is restricted to cancer genes defined by OncoKB as of the date the report is issued. The test was validated for somatic variant detection and it does not detect germline variants. Therefore, we cannot rule out the possibility that a germline variant exists that was not detectable using these methodologies. This test does not replace the need for germline testing in the context of hereditary cancer suspicion. Laboratory results are subject to approximately 0.5% error in any of the pre-analytical, analytical or post-analytical phases of the test ([Bonini et al. 2002](#)). This test was developed and its performance characteristics determined by OICR Genomics. It has not been cleared or approved by the US Food and Drug Administration.

## REPORT SIGN-OFFS

Report drafted by The Reporter on 2025-04-24

Report electronically signed out by PLACEHOLDER (ABMS #XXXXXXX) on yyyy-mm-dd

# APPENDIX

## Actionability Definitions

Variant prioritization is based on OncoKB actionability tiers:

Level	Definition
1	FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication
2	Standard care biomarker recommended by the NCCN or other expert panels predictive of response to an FDA-approved drug in this indication
3A	Compelling clinical evidence supports the biomarker as being predictive of response to a drug in this indication
3B	Standard care or investigational biomarker predictive of response to an FDA-approved or investigational drug in another indication
4	Compelling biological evidence supports the biomarker as being predictive of response to a drug
R1	Standard care biomarker predictive of resistance to an FDA-approved drug in this indication
R2	Compelling clinical evidence supports the biomarker as being predictive of resistance to a drug
N1	The biomarker is listed as "Oncogenic" by OncoKB, but is not in an actionable tier
N2	The biomarker is listed as "Likely Oncogenic" by OncoKB, but is not in an actionable tier
N3	The biomarker is listed as "Predicted Oncogenic" by OncoKB, but is not in an actionable tier
N4	The biomarker is listed as "Likely Neutral" or "Inconclusive" by OncoKB
P	The biomarker is listed as "Prognostic" by OncoKB

When provided, results and interpretations are consistent with available knowledge for the given tumour type as defined in [OncoTree](#). OncoKB tiers are tumour-specific and dependent on OncoTree definitions.

## Definitions

**Callability:** The percentage of bases above 30x in tumour sample. Callability above 75% is considered a pass.

**Coverage:** Mean number of bases covering each sequenced base.

**Estimated Cancer Cell Content (%):** The inferred tumour purity as determined bioinformatically.

**Estimated Ploidy:** The inferred tumour ploidy as determined bioinformatically. This value is not clinically validated.

**Tumor Mutation Burden (TMB):** The number of somatic, coding, non-synonymous base substitutions and short insertions and deletions (indels) per megabase of tumour genome.

**Microsatellite stability score (MSI)** represents the percentage of the genome's short repeats (microsatellites) with insertions or deletions in the tumour. Instability in microsatellite repeat regions is often caused by genetic or epigenetic alterations to genes in the mismatch repair (MMR) pathway (including *MLH1*, *MSH2*, and *MSH6*). Confidence intervals are based on 100 sets of 500 randomly sampled microsatellite sites. Tumours with an MSI score greater than 15.0% are considered microsatellite unstable (MSI).

**Homologous Recombination Deficiency (HRD)** is the loss of a key DNA damage repair pathway in cancer, canonically associated with loss-of-function mutations in *BRCA1/2*. HRD manifests as a composite genomic signature that includes somatic mutations (SNVs and in/dels), Loss-Of-Heterozygosity (LOH), copy number alterations and other structural variants, summed as an HRD score.

**Percent Genome Altered (PGA):** The fraction of the genome with evidence of copy number change, for a given sample.

**Cohort:** If available, the name of an external dataset used to calculate TMB percentile. Percentiles for tumour mutation burden (TMB) are plotted and reported against the corresponding cohort(s).

**TCGA Percentile:** Percentile of TMB scores are plotted relative to [all TCGA samples](#) or closest cohort.

**Loss of Heterozygosity:** A genetic event where there is loss of allelic variation for a given gene, ex. by loss of a wild-type allele. The calculation for LOH is a modification of the calculation described in the [PURPLE documentation](#). First, the variant copy number (VCN) is computed by adjusting the variant allele frequency (VAF) of a particular alteration by the purity and multiplying by the copy number (CN) for that gene. Then, based on the minor allele copy number (MACN) for that gene, the logic for the classification of LOH is as follows:

If  $MACN \leq 0.5$  and  $VCN > CN - 0.5$ , LOH = True.

If  $MACN \leq 0.5$  and  $VCN < CN - 0.5$ , LOH = False.

If  $MACN > 0.5$ , LOH = False.

**Copy Number Variants:** Calls at the gene-scale represent levels derived from copy-number analysis as used for annotation by OncoKB:

Deletion      a deep loss, possibly a homozygous deletion, defined by less than 0.5 copies

Amplification   a high-level amplification (more copies, often focal), defined as greater than 2.4Xploidy copies

## Gene Descriptions

Gene	Summary
<a href="#">BRAF</a>	<i>BRAF</i> , an intracellular kinase, is frequently mutated in melanoma, thyroid and lung cancers among others.
<a href="#">CDKN2A</a>	The <i>CDKN2A</i> gene encodes two proteins, p16INK4A and p14ARF, that regulate the cell growth and survival. <i>CDKN2A</i> is altered by mutation and/or deletion in a broad range of solid and hematologic cancers.
<a href="#">MED12</a>	<i>MED12</i> is a component of CDK8, a subcomplex involved in transcription initiation. <i>MED12</i> plays a role in the genesis of benign tumors such as uterine leiomyoma and breast fibroadenoma and is altered in a variety of estrogen-dependent tumors.
<a href="#">MYH11</a>	<i>MYH11</i> , a smooth muscle myosin protein, is altered at low frequencies in various cancer types.