

Towards high-quality clinical trials and  
implementation of genomic medicine

# ATLAS Training Program

Cancer Genome-based Medicine Course

Lecture Title : Procedures and Interpretation of Next Generation Sequencing Results

Speaker : Kuniko Sunami

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## Kuniko Sunami, M.D., Ph.D.

Department of Laboratory Medicine, National Cancer Center Hospital



### EDUCATION

Yokohama City University School of Medicine, Japan (2001–2007)

Juntendo University Graduated School of Medicine, Japan (2013–2016)

### WORK EXPERIENCE

Senior Resident, Respiratory Medicine and Medical Oncology, Tokyo Metropolitan Komagome Hospital (2009–2013)

Chief Resident, Thoracic Oncology, National Cancer Center (2013–2015)

Postdoctoral Fellow, Division of Genome Biology, National Cancer Center Research Institute (2014–2015)

Medical Staff, Division of Clinical Laboratory, National Cancer Center (2015–present)

Medical Staff, Genetic Medicine and Services, National Cancer Center (2015–present)

### BOARD CERTIFICATION

Diplomate, Subspecialty Board of Medical Oncology, JSMO (2014)

Fellow of the Japanese Society of Internal Medicine (2015)

Board Certified Member of the Japanese Respiratory Society (2015)

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## Goal

- Looking at a gene panel test report...
  - You can determine the recommended treatment
  - You can determine whether there are secondary findings (→Dr. Hirata)

Therefore...



- You can determine the pathogenic significance of the detected mutation
- You can extract mutations associated with therapeutic agents
- You can determine candidate drugs and the evidence level of these drugs

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## Q: What is the biological significance of the variants detected in Cases 1 and 2, and what are the candidate drugs?

### Case 1

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	
Tumor Mutational Burden - TMB-Low (5 Muts/Mb)	No therapies or clinical trials. see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
PALB2 - L9F	Niraparib Olaparib Rucaparib	Talazoparib
10 Trials see p. 16		
PIK3CA - H1047R	none	Alpelisib Everolimus Temozolimumus
10 Trials see p. 19		

### Case 2

### Simulated cases

RG summary report draft							
Test information							
Test name		NCC Oncopanel Test					
System name		OncoGuide TM NCC Oncopanel System					
Gene mutation							
Gene name	Variant allele frequency	CDS variant	Amino acid variant	COSMIC ID (No. of registrations)			
APC	72.1 (782/1,084)	exon10:c.1312+1G>A		4166472 (1)			
ATM	14.3 (51/350)	exon3:c.103C>T	R35*	922965 (2)			
Number of somatic cell mutations							
Region division		SNV		InDel		Total	
		Number of mutation	Mutation appearance	Number of mutation	Mutation appearance	Number of mutation appearances	Mutation appearance
Exon	nonsyn	0	0.0/Mb	0	0.0/Mb	0	0.0/Mb
	syn	0	0.0/Mb				
Non-exon		2	2.1/Mb	1	1.1/Mb	3	3.2/Mb
Entire region		2	1.6/Mb	1	0.8/Mb	3	2.3/Mb

\*2 Mutation appearance rate = number of mutations per 1 Mbp

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## Overview

- Understand the characteristics of gene panel tests and know how to interpret the results
- Determining the pathogenic significance of the detected mutation
- Extracting the mutation associated with therapeutic agents
- Selecting candidate drugs accompanied by their evidence levels

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## Gene panel tests covered by nation-wide insurance in Japan

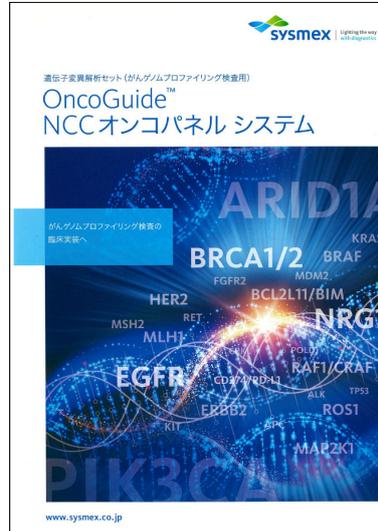


**FoundationOne® CDx**  
がんゲノムプロファイル  
総合製品ガイド

FoundationOne® CDx がんゲノムプロファイル

【重要】  
本製品による検査を実施する際には、関連するガイドラインに適合される施設要件を満たすことを確認するとともに、関連学会が作成したガイドライン等の最新の情報も参照してください。

中外製薬



遺伝子変異解析セット (がんゲノムプロファイリング検査用)  
**OncoGuide™**  
NCC オンコパネル システム

がんゲノムプロファイリング検査の  
臨床実用へ

ARID1A  
BRCA1/2  
KRAS  
BRAF  
MDM2  
FGFR2  
BCL2L1/BIM  
HER2  
RET  
MSH2  
MLH1  
EGFR  
CD3/AND11  
ERBB2  
K11  
POU3F1  
RAF1/RAF  
ALK  
TP53  
ROS1  
MARCKI

www.sysmex.co.jp

All oncogene panel tests are based on the same basic concepts.

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## Characteristics of each Cancer Genome Profiling Test

Test Name	FoundationOne® CDx Cancer Genome Profile	OncoGuide™ *As of September 2020 NCC Oncopanel System
Tested sample	Tumor (FFPE) Analyzes tumor only	Tumor (FFPE) + Normal (peripheral blood) Matched pair analysis
Number of genes (Number of genes targeted for fusion detection)	324 (36)	114 (12)
Role of companion diagnosis	Non-small cell lung cancer: <i>EGFR</i> (exon19del, L858R, T790M), <i>ALK</i> fusion, <i>ROS1</i> fusion, MET skipping Malignant melanoma: <i>BRAF</i> V600E/K Breast cancer: <i>ERBB2</i> copy number variation Colorectal cancer: <i>KRAS/NRAS</i> wild-type Solid cancer: <i>NTRK1/2/3</i> fusion Ovarian cancer/prostate cancer: <i>BRCA1/2</i>	-
Tumor mutational burden (/Mb)	○	○
Microsatellite instability	○	-
Germline pathogenic variants of hereditary tumor-causing genes (reportable genes)	-	○ ( <i>APC</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>MLH1</i> , <i>MSH2</i> , <i>PTEN</i> , <i>RB1</i> , <i>RET</i> , <i>STK11</i> , <i>SMAD4</i> , <i>TP53</i> , <i>TSC1</i> , <i>VHL</i> )

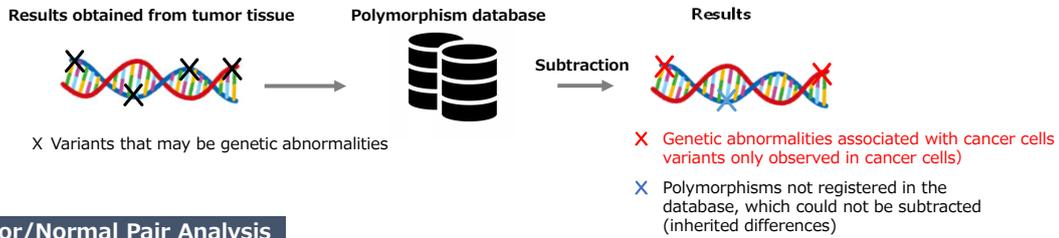
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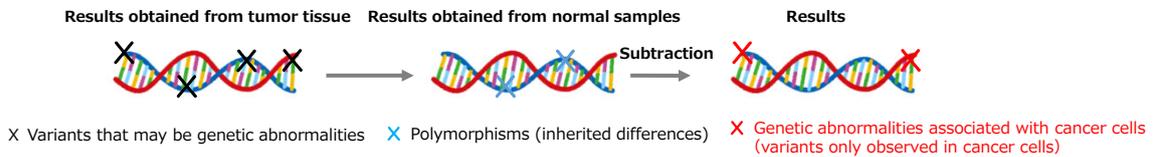
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# Tumor Tissue Only and Tumor/Normal Tissue Pair Analysis Somatic Mutations

## Tumor Tissue Only Analysis



## Tumor/Normal Pair Analysis

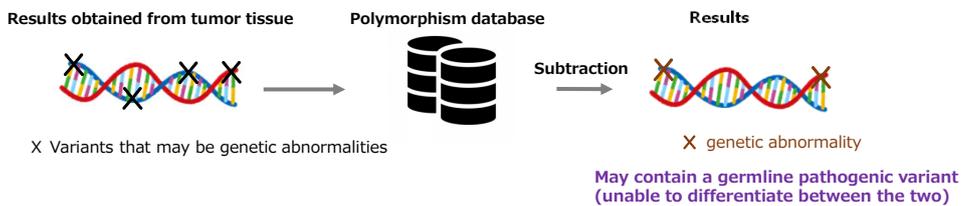


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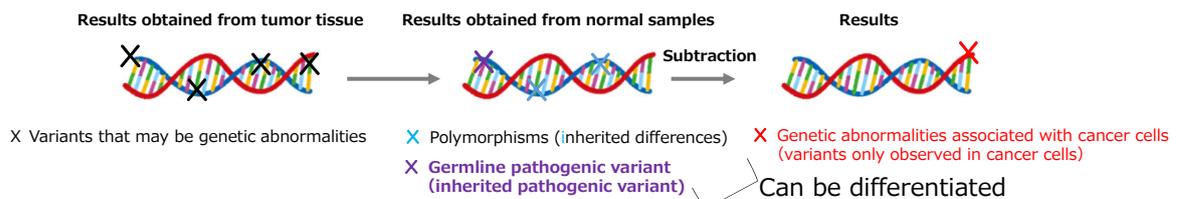
ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

# Tumor Tissue Only and Tumor/Normal Tissue Pair Analysis Germline Changes

## Tumor Tissue Only Analysis



## Tumor/Normal Pair Analysis



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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

## Overview

- Understand the characteristics of gene panel tests and know how to interpret the results
- Determining the pathogenic significance of the detected mutation
- Extracting the mutation associated with therapeutic agents
- Selecting candidate drugs accompanied by their evidence levels

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

## Public Databases Related to Assessment of Biological Significance

Type	Name	URL
Polymorphism DB	gnomAD (formerly ExAC)	<a href="https://gnomad.broadinstitute.org/">https://gnomad.broadinstitute.org/</a>
Somatic mutation DB	COSMIC	<a href="https://cancer.sanger.ac.uk/cosmic/">https://cancer.sanger.ac.uk/cosmic/</a>
Pathogenic variant DB	ClinVar	<a href="https://www.ncbi.nlm.nih.gov/clinvar/">https://www.ncbi.nlm.nih.gov/clinvar/</a>

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

## COSMIC

### Catalogue of Somatic Mutations In Cancer

- A somatic gene mutation database
- Human genome assembly version is also available (GRCh37 or GRCh38)
- Operated by the UK Wellcome Sanger Institute
- Regularly updated
- Possible to check whether each variant has been detected more than once in other cases

In case of oncogenes, variants with multiple cases listed may be pathogenic  
Often, truncating mutations in tumor suppressor genes are not registered, even if they are pathogenic

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

## How to use COSMIC

<http://cancer.sanger.ac.uk/cosmic/>

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

National Cancer Center Japan

## Searching "EGFR" in COSMIC

Pathogenic variant

The GRCh version can be changed here (GRCh37/hg19 can be used with the current tests)

GRCh38 · COSMIC v92

**Gene view**

Select each item

Number of registrations for each variant

**EGFR**

Gene view histogram is a graphical view of mutations across EGFR. These mutations are displayed at the amino acid level across the full length of the gene by default. Restrict the view to a region of the gene by dragging across the histogram to highlight the filters panel to the left. [Show more](#)

Substitutions

Plan

Complex

Insertions

Deletions

**Variants**

Mutations | Fusions | CNV & Exression | Methylation

This tab displays a table of mutations for the selected gene. You can see more information in our [help pages](#).

Show 10 entries

Export: CSV | TSV Search: L858

Position (AA)	Mutation (CDS)	Mutation (Amino Acid)	Legacy Mutation ID	Count	Mutation Type
858	c.2572C>A	p.L858M	COSM12366	5	Substitution - Missense
858	c.2572C>T	p.L858I	COSM26129	4	Substitution - coding silent
858	c.2572_2573delinsAA	p.L858K	COSM24268	1	Substitution - Missense
858	c.2572_2573insV	p.L858R	COSM13553	1	Substitution - Missense
858	c.2573T>A	p.L858Q	COSM29578	1	Substitution - Missense
858	c.2573T>G	p.L858R	COSM6224	2592	Substitution - Missense
858	c.2573_2574delinsGA	p.L858E	COSM133630	1	Substitution - Missense
858	c.2573_2574delinsGT	p.L858R	COSM12429	8	Substitution - Missense
858	c.2574G>A	p.L858I	COSM133590	1	Substitution - coding silent
858	c.2	p.L858I	COSM41667	1	Substitution - coding silent

Showing 1 to 10 of 3,442 entries

First Previous 1 2 3 4 5 ... 345 Next Last

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

National Cancer Center Japan

## Searching "EGFR L858R" in COSMIC

Pathogenic variant

Information for each variant

GRCh38 · COSMIC v92

**Mutation**

COSV51765161

**Overview**

This section shows a general overview of the selected mutation. It describes the source of the mutation i.e a gene name/sample name/tissue name with unique ID, and also shows the mutation syntax at the amino acid and nucleotide sequence level. You can see more information on our [help pages](#).

**Genomic Mutation ID** COSV51765161

**Legacy Identifier** COSM6224

**Gene name** EGFR

**AA mutation** p.L858R (Substitution - Missense, position 858, L→R)

**CDS mutation** c.2573T>G (Substitution, position 2573, T→G)

**SNP** No

**Nucleotides inserted** n/a

**Genomic coordinates** GRCh38, 7:55191822..55191822, view [Ensembl contig](#)

**CDD** n/a

**HomoloGene** n/a

**Ever confirmed somatic?** Yes

**FATHMM prediction** Pathogenic (score 0.98)

**Remark** n/a

**Recurrent** n/a

**Drug resistance** n/a

**Alternative Ids** 125918314(EGFR\_ENST00000454757), 126533041(EGFR\_ENST00000455089), 164416757(EGFR\_ENST00000638463)

**Tissue distribution**

This section displays the distribution of mutated samples and tissue types (top 5). You can see more information on our [help pages](#).

**Tissue Distribution**

Tissue

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

National Cancer Center Japan

## Searching "EGFR L858R" in COSMIC

Pathogenic variant

**Gene**  
EGFR

- Gene view
- Overview
- External links
- Drug resistance
- Tissue distribution
- Genome browser
- Mutation distribution
- Variants
- References

Search

Filters

Coordinate system

Tissue distribution

The tissue distribution histogram shows the distribution of mutations across the primary tissue types that are curated by COSMIC. Histograms show the percentage of mutated samples for point mutations, CNV data and gene expression data. Moving your mouse over the histograms will show additional data. The number of samples tested on this page include samples from the targeted and whole genomes/exome resequencing where all the protein coding genes have been screened for mutations.

You can see additional information about the data presented here in the [help pages](#).

Show All entries

Tissue	Point Mutations		Copy Number Variation		Gene Expression		Methylation	
	% Mutated	Tested	Variant %	Tested	% Regulated	Tested	% Diff. Methylated	Tested
Adrenal gland		1112		287		79		-
Autonomic ganglia		1556		-		-		-
Biliary tract		2323		-		-		-
Bone		1032		-		-		-
Breast		10708		1492		1104		707
Central nervous system		6021		1035		697		-
Cervix		1038		299		307		-
Endometrium		1432		586		602		398
Eye		384		-		-		-
Fallopian tube		6		-		-		-
Female genital tract (site indeterminate)		22		-		-		-
Gastrointestinal tract (site indeterminate)		3		-		-		-
Genital tract		218		-		-		-
Haematopoietic and lymphoid		8438		661		221		-
Kidney				995		600		513
Large intestine				718		610		-
Liver				663		373		-
Lung				1006		1019		717
Mediastinum		1		-		-		-

**Lung**

Total Samples tested: **99694**

Total Mutated samples: **26499**

Total Percentage of samples mutated: **26.58**

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ICRweb: [https://www.icrweb.jp/icr\\_index.php?lang=en](https://www.icrweb.jp/icr_index.php?lang=en)

National Cancer Center Japan

## Searching "BRAF A762V" in COSMIC

VUS

**Gene**

- Gene view
- Overview
- External links
- Drug resistance
- Tissue distribution
- Genome browser
- Mutation distribution
- Variants
- References

Search

Filters

Coordinate system

**Gene view**

The gene view histogram is a graphical view of mutations across BRAF. These mutations are displayed at the amino acid level across the full length of the gene by default. Restrict the view to a region of the gene by dragging across the histogram to highlight the region of interest, or by

Number of registrations for each variant

V600 mutations

**Variants**

This tab displays a table of mutations for the selected gene. You can see more information in our [help pages](#).

Show 35 entries

Position (AA)	Mutation (CDS)	Mutation (Amino Acid)	Legacy Mutation ID	Count	Mutation Type
758	c.2275G>T	p.G758E	COSM7896651	1	Substitution - coding silent
758	c.2275G>T	p.G758E	COSM9278976	1	Deletion - Frameshift
759	c.2275G>A	p.G759S	COSM9490493	1	Substitution - Missense
759	c.2275G>A	p.G759S	COSM9395142	1	Substitution - Missense
760	c.2275A>G	p.L760C	COSM9625372	1	Substitution - Missense
762	c.2285G>C	p.L762R	COSM9251928	1	Substitution - Missense
762	c.2285A>G	p.L762V	COSM9751833	1	Insertion - Frameshift
762	c.2285G>A	p.L762Q	COSM9188893	1	Substitution - Missense
762	c.2285G>T	p.L762Y	COSM9478757	7	Substitution - Missense
765	c.2295C>T	p.L765I	COSM9405537	1	Substitution - Missense

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## Searching "BRAF A762V" in COSMIC

VUS

**Gene**  
BRAF

**Variants**

Mutations | Fusions | CNV & Expression | Methylation

This tab displays a table of mutations for the selected gene. You can see more information in our [help pages](#).

Show 10 entries

Position (AA)	Mutation (CDS)	Mutation (Amino Acid)	Legacy Mutation ID	Count	Mutation Type
258	c.2274G>T	p.G758E	COSM7089651	1	Substitution - coding silent
758	c.2	p.G758Sfs*30	COSM9278976	1	Deletion - Frameshift
759	c.2275G>A	p.G759R	COSM4992903	1	Substitution - Missense
759	c.2276G>A	p.G759E	COSM9395542	1	Substitution - Missense
760	c.2279A>G	p.Y760C	COSM5625572	1	Substitution - Missense
762	c.2284G>C	p.A762P	COSM9251928	1	Substitution - Missense
762	c.2284_2285insA	p.A762Dfs*33	COSM5751833	1	Insertion - Frameshift
762	c.2285C>A	p.A762E	COSM6108893	1	Substitution - Missense
762	c.2285C>T	p.A762V	COSM3878757	7	Substitution - Missense

Number of registrations: 7

Annotated Mutation Distribution in MSK-IMPACT Clinical Sequencing Cohort (Zehir et al., Nature Medicine, 2017)

Y-Axis Max: 313

OncoKB <https://www.oncokb.org/gene/BRAF>

Legend

- Only a small number of registrations (7)
- The produced mutant protein is 766-aa long and encompasses the kinase domain
- Judged to be a mutation of unknown significance

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## gnomAD

### The Genome Aggregation Database

- Database containing whole-exon / whole-genome sequence data
- v.2 data set with GRCh37/hg19 as the reference genome and v.3 data set with GRCh38 as the reference genome, have been released
- Variant registration frequency can be checked by ethnicity

This database is useful for determining whether the variant of interest is a polymorphism, based on the registration frequency in the concerned ethnicity

gnomAD v2.1.1 | Search

gnomAD v3.1 released!

**gnomAD**  
genome aggregation database

gnomAD v2.1.1 | Search by gene, region, or variant

Please note that gnomAD v2.1.1 and v3.1 have substantially different but overlapping sample compositions and are on different genome builds. For more information, see the FAQ "Should I switch to the latest version of gnomAD?".

Examples - Gene: PCSK9, Variant: 1-55516888-G-GA

The Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community.

The v2 data set (GRCh37/hg19) provided on this website spans 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals sequenced as part of various disease-specific and population genetic studies. The v3.1 data set (GRCh38) spans 76,156 genomes, selected as in v2. The gnomAD Principal Investigators and groups that have contributed data to the current release are listed [here](#).

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# How to use gnomAD

gnomAD browser gnomAD v2.1.1 | Search

gnomAD v3.1 released!

## gnomAD

genome aggregation database

gnomAD v2.1.1 | Search by gene, region, or variant

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?

Search by variant or gene name or position in the genome

For example) TP53 E11Q, or TP53, or ch17: 7579882

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# Searching for "TP53 E11Q" in gnomAD

gnomAD browser gnomAD v2.1.1 | Search

gnomAD v3.1 released!

17-7579862-7579902 gnomAD v2.1.1 | Search

Gene: TP53 GRCh37/hg19  
Region chr: 17 BP  
Reference: VCF Browser

gnomAD v2.1.1 | Search by gene, region, or variant

Examples - Gene: PCSK9, Variant: 1-55516888-G-GA

The Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community.

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Enlarged

[https://gnomad.broadinstitute.org/variant/17-7579882-C-G/datasets/gnomad\\_v2\\_1](https://gnomad.broadinstitute.org/variant/17-7579882-C-G/datasets/gnomad_v2_1)

Variant ID	Gene	Consequence	Allele Frequency	Allele Frequency	Allele Frequency	Allele Frequency
17-7579862-A-C	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-C-G	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-T-C	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-G-A	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-G-C	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-G-T	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-G-G	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-A-G	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-A-T	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
17-7579862-T-G	TP53	p.Val158Leu	0.000000	0.000000	0.000000	0.000000
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17-7						

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## Searching for "TP53 E11Q" in gnomAD

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## Searching for "TP53 E11Q" in gnomAD

**Single nucleotide variant: 17-7579882-C-G (GRCh37)**

**Population Frequencies**

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
East Asian	13	19906	0	0.0006531
European (non-Finnish)	1	128800	0	0.000007764
African	0	24820	0	0.000
Latino	0	35384	0	0.000
Ashkenazi Jewish	0	10336	0	0.000
European (Finnish)	0	25112	0	0.000
Other	0	7180	0	0.000
South Asian	0	30558	0	0.000
Female	7	128884	0	0.00005431
Male	7	153212	0	0.00004569
<b>Total</b>	<b>14</b>	<b>282096</b>	<b>0</b>	<b>0.00004963</b>

**Age Distribution**

13 alleles are registered in individuals of East Asian descent  
 → highly likely to be a rare SNP unique to East Asians

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## Overview

- Understand the characteristics of gene panel tests and know how to interpret the results
- Determining the pathogenic significance of the detected mutation
- Extracting the mutation associated with therapeutic agents
- Selecting candidate drugs accompanied by their evidence levels

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## Databases Providing Therapeutic Options Accompanied by Evidence Level

Type	Name	URL
Knowledge database	CIViC	<a href="https://civicdb.org/home">https://civicdb.org/home</a>
Knowledge database	OncoKB	<a href="https://www.oncokb.org/">https://www.oncokb.org/</a>

These databases can be used to search for the [currently available therapeutic options that can be expected to be effective](#) based on the detected genetic abnormality and the [rationale for the efficacy \(evidence level\)](#)

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## CIViC

### Overview

- Knowledge database based on expert crowd sourcing
- Operating organization: Washington University School of Medicine
- Five levels of evidence (A to E) are presented, depending on clinical usefulness.

### Features

- Cleaned up by experts
- Provides evidence level and type



Griffith et al., *Nat Genet* 2017

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## How to use CIViC



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**Brief overview of the gene**

EGFR is widely recognized for its importance in cancer. Amplification and mutations have been shown to be driving events in many cancer types. Its role in non-small cell lung cancer, glioblastoma and basal-like breast cancers has spurred many research and drug development efforts. Tyrosine kinase inhibitors have shown efficacy in EGFR amplified tumors, most notably gefitinib and erlotinib. Mutations in EGFR have been shown to confer resistance to these drugs, particularly the variant T790M, which has been functionally characterized as a resistance marker for both of these drugs. The later generation TKI's have seen some success in treating these resistant cases, and targeted sequencing of the EGFR locus has become a common practice in treatment of non-small cell lung cancer. Overproduction of ligands is another possible mechanism of activation of EGFR. ERBB ligands include EGF, TGF- $\alpha$ , AREG, EFS, BTC, HB-EGF, EPR and NRG1-4 (for detailed information please refer to the respective ligand section). In ligand-activated cancers, Cetuximab appears to be more effective than tyrosine-kinase inhibitors (Artega et al.).

**Links to each variant**

**Select T790M**

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## Civic Evidence Level Classifications

Level	Definition	Examples and further comments
<b>A</b> Validated association	Proven/consensus association in human medicine.	"AML with mutated NPM1" is a provisional entity in WHO classification of acute myeloid leukemia (AML). This mutation should be tested for in clinical trials and is recommended for testing in patients with cytogenetically normal AML. Validated associations are often in routine clinical practice already or are the subject of major clinical trial efforts.
<b>B</b> Clinical evidence	Clinical trial or other primary patient data supports association.	BRAF V600E is correlated with poor prognosis in papillary thyroid cancer in a study of 187 patients with PTC and other thyroid diseases. The evidence should be supported by observations in multiple patients. Additional support from functional data is desirable but not required.
<b>C</b> Case study	Individual case reports from clinical journals.	A single patient with FLT3 over-expression responded to the FLT3 inhibitor sunitinib. The study may have involved a large number of patients, but the statement was supported by only a single patient. In some cases, observations from just a handful of patients (e.g. 2-3) or a single family may also be considered a case study/report.
<b>D</b> Preclinical evidence	In vivo or in vitro models support association.	Experiments showed that AG1296 is effective in triggering apoptosis in cells with the FLT3 internal tandem duplication. The study may have involved some patient data, but support for this statement was limited to in vivo or in vitro models (e.g. mouse studies, cell lines, molecular assays, etc.).
<b>E</b> Inferential association	Indirect evidence.	CD33 and CD123 expression were significantly increased in patients with NPM1 mutation with FLT3-ITD, indicating these patients may respond to combined anti-CD33 and anti-CD123 therapy. The assertion is at least one step removed from a direct association between a variant and clinical relevance.

Nature Genetics 49, 170–174 (2017)

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### Brief overview of the variant

**VARIANT T790M**

Aliases: RS121434569 and THR790MET

EGFR T790M was one of the very first mutations recognize therapies in non-small cell lung cancer. While successful in first and second generation TKIs (erlotinib, gefitinib, neratinib) in treating patients harboring this mutation before treatment is notably lower. This lack of efficacy can likely be to blame for the poorer prognosis for patients with this mutation as compared to patients with wildtype EGFR or other types of EGFR mutations. Approximately half of EGFR mutant tumors with acquired resistance to TKI inhibition have been shown to harbor this mutation, implicating it as a mechanism of acquired therapy resistance. A third generation TKI (osimertinib) has been approved for the treatment of EGFR T790M mutant NSCLC. Patients positive for T790M in a plasma-based test have similar outcomes like those with tumor biopsy testing.

Variant Type: Missense Variant

HGVS Expressions: ENST00000275493.2:c.2369G>T, NM\_005219.4:c.2369G>T, NP\_005219.2:p.Thr790Met, and NC\_000007.13:g.55249071C>T

ClinVar ID: 16613

Evidence for T790M 39 total items

EID	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
238	The T790M mutation in EGFR...	Non-small Cell Lung Carcinoma	Erlotinib	A	Predictive				5★
1592	Osimertinib has been approve...	Non-small Cell Lung Carcinoma	Osimertinib	A	Predictive				5★
1867	Randomized, international, op...	Non-small Cell Lung Carcinoma	Osimertinib	A	Predictive				5★
646	In a phase1-2 study, patients ...	Non-small Cell Lung Carcinoma	Rociletinib	B	Predictive				4★

**Resistant** (Erlotinib)  
**Sensitive** (Osimertinib)

Can be output as a CSV file

T790M mutation in non-small cell lung cancer is resistant to erlotinib and responsive to osimertinib.

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ClinVar ID: 16613

Evidence for T790M 39 total items

EID	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
238	The T790M mutation in EGFR...	Non-small Cell Lung Carcinoma	Erlotinib	A	Predictive				5★
1	Osimertinib has been approve...	Non-small Cell Lung Carcinoma	Osimertinib	A	Predictive				5★
1	Randomized, international, op...	Non-small Cell Lung Carcinoma	Osimertinib	A	Predictive				5★
1	In a phase1-2 study, patients ...	Non-small Cell Lung Carcinoma	Rociletinib	B	Predictive				4★

**EVIDENCE EID238**

Submitted by NickSpies Accepted by Morysiak

**Article summary**

The T790M mutation in EGFR has been shown to confer resistance to the tyrosine kinase inhibitor erlotinib, and patients harboring this mutation that are placed on the drug are likely to relapse.

Evidence Level: A - Validated  
Evidence Type: Predictive  
Evidence Direction: Supports  
Clinical Significance: Resistance or Non-Response  
Variant Origin: Somatic Mutation

Disease: Non-small Cell Lung Carcinoma  
Drug: Erlotinib  
Citation: Denis et al., 2015, Clin. Chim. Acta  
PubMed ID: 25468228  
Trust Rating: ★★★★★

Disclaimer: This resource is intended for purely research purposes. It should not be used for emergencies or medical or professional advice.

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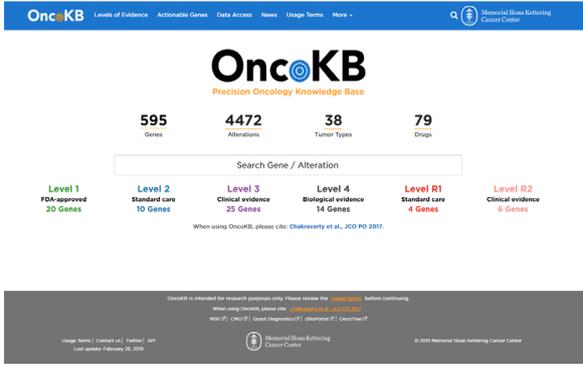
MEMBER OF THE **Global Alliance** HOSTED BY **Washington University in St. Louis** SCHOOL OF MEDICINE

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# OncoKB

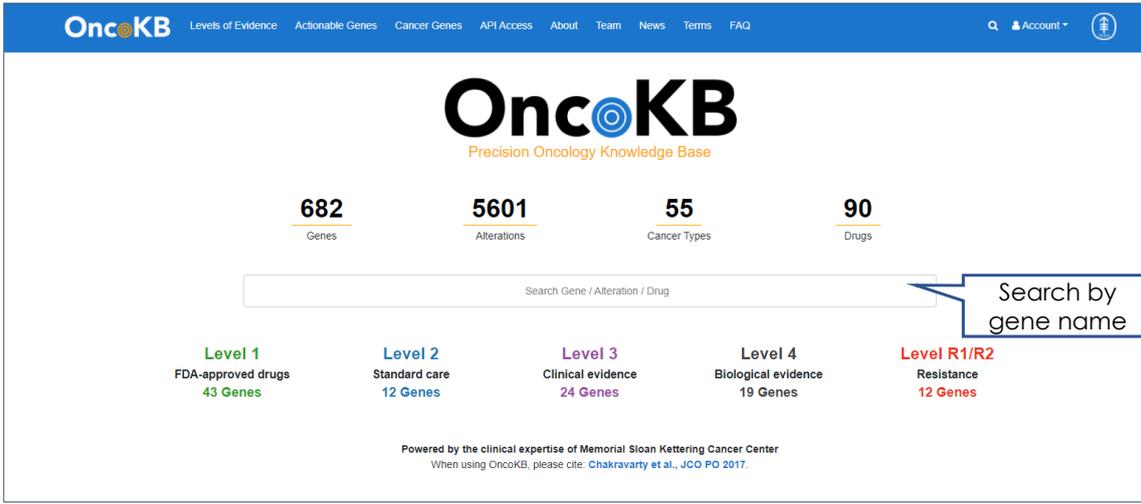
- Knowledge database curated by MSKCC clinical fellows and research fellows
- Operating organization: Memorial Sloan Kettering Cancer Center (MSKCC)
- Four evidence levels regarding clinical usefulness (1 to 4) and two evidence levels regarding resistance (R1 and R2) are presented



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# How to use OncoKB



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## How to use OncoKB

**OncoKB** Levels of Evidence Actionable Genes Cancer Genes API Access About Team News Terms

**Variants and drugs are listed for each evidence level**

Annotated Alterations Clinically Actionable Alterations

A list of the cancer type-specific EGFR alterations that may predict response to a targeted drug and the corresponding OncoKB level of evidence assigning their level of **clinical actionability**.  
If you notice any mistakes or missing alterations / citations, please contact@oncoKB.org.

Search ...

Level	Alteration	Cancer Type	Drugs	Citations
1	G719	Non-Small Cell Lung Cancer	Afatinib	3
1	Exon 19 deletion	Non-Small Cell Lung Cancer	Afatinib	16
1	S768I	Non-Small Cell Lung Cancer	Afatinib	4
1	T790M	Non-Small Cell Lung Cancer	Osimeertinib	4
1	L858R	Non-Small Cell Lung Cancer	Osimeertinib	16
1	L861Q	Non-Small Cell Lung Cancer	Afatinib	6
2	A763_Y764insFQEA	Non-Small Cell Lung Cancer	Erlotinib	6
2	Kinase Domain Duplication	Non-Small Cell Lung Cancer	Afatinib	3

**Osimeertinib has an evidence level of 1 for EGFR T790M**

**Hovering the cursor over the citations displays the references**

**AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer.**  
Janne PA et al. N Engl J Med. PMID: 2015 25923549

**CNS Efficacy of Osimeertinib in Patients With T790M-Positive Advanced Non-Small-Cell Lung Cancer.**

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## Q: What is the biological significance of the variants detected in Cases 1 and 2, and what are the candidate drugs?

### Case 1

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section
Tumor Mutational Burden - TMB-Low (5 Muts/Mb)	No therapies or clinical trials. see Biomarker Findings section
GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)
PALB2 - L9F	Niraparib Olaparib
10 Trials see p. 16	Rucaparib
PIK3CA - H1047R	Alpelisib Everolimus
10 Trials see p. 19	Temsirolimus

### Case 2

Simulated cases

RG summary report draft							
Test information							
Test name	NCC Oncopanel Test						
System name	OncoGuide TM NCC Oncopanel System						
Gene mutation							
Gene name	Variant allele frequency	CDS variant	Amino acid variant	COSMIC ID (No. of registrations)			
APC	72.1 (782/1,084)	exon10:c.1312+1G>A		4166472 (1)			
ATM	14.3 (51/350)	exon3:c.103C>T	R35*	922965 (2)			
Number of somatic cell mutations							
Region division		SNV		InDel		Total	
		Number of mutation	Mutation appearance	Number of mutation	Mutation appearance	Number of mutation appearances	Mutation appearance
Exon	nonsyn	0	0.0/Mb	0	0.0/Mb	0	0.0/Mb
	syn	0	0.0/Mb				
Non-exon		2	2.1/Mb	1	1.1/Mb	3	3.2/Mb
Entire region		2	1.6/Mb	1	0.8/Mb	3	2.3/Mb

\*2 Mutation appearance rate = number of mutations per 1 Mbp

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## Information written in the report for Cases 1 and 2

### Foundation One CDx Tumor Analysis Only

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	
Tumor Mutational Burden - TMB-Low (5 Muts/Mb)	No therapies or clinical trials. see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
<b>PALB2 - L9F</b>	Niraparib	Talazoparib
10 Trials see p. 16	Olaparib	
<b>PIK3CA - H1047R</b>	Rucaparib	
10 Trials see p. 19	none	Alpelisib
		Everolimus
		Temsirolimus

Items mentioned:

- Whether there is microsatellite instability
- Tumor mutational burden
- Gene name
- Amino acid variant
- Name of candidate drug

### NCC Oncopanel Tumor/Normal tissue Pair Analysis

RG summary report draft

Test information						
Test name		NCC Oncopanel Test				
System name		OncoGuide TM NCC Oncopanel System				
Gene mutation						
Gene name	Variant allele frequency	CDS variant	Amino acid variant	COSMIC ID (No. of registrations)		
APC	72.1 (782/1,084)	exon10.c.1312+1G>A		4166472 (1)		
ATM	14.3 (51/350)	exon3.c.103C>T	R35*	922965 (2)		
Number of somatic cell mutations						
Region division	SNV		InDel		Total	
	Number of mutation	Mutation appearance	Number of mutation	Mutation appearance	Number of mutation appearances	Mutation appearance
Exon	nonsyn	0	0.0/Mb	0	0	0.0/Mb
	syn	0	0.0/Mb			
Non-exon		2	2.1/Mb	1	1.1/Mb	3.2/Mb
Entire region		2	1.6/Mb	1	0.8/Mb	2.3/Mb

Items mentioned:

- Gene name
- Mutation/allele frequency
- CDS variant
- Amino acid variant
- COSMIC ID (number of registrations)
- Tumor mutational burden

\*2 Mutation appearance rate = number of mutations per 1 Mb

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## A. Case 1

### Tumor analysis only

#### Foundation One CDx

BIOMARKER FINDINGS	ACTIONABILITY	
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section	
Tumor Mutational Burden - TMB-Low (5 Muts/Mb)	No therapies or clinical trials. see Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
<b>PALB2 - L9F</b>	Niraparib	Talazoparib
10 Trials see p. 16	Olaparib	
<b>PIK3CA - H1047R</b>	Rucaparib	
10 Trials see p. 19	none	Alpelisib
		Everolimus
		Temsirolimus

Woman in her 50s, stomach cancer

Candidate drug with PIK3CA^mutation and evidence level (CIViC)

DIS	DRUGS	DESC	EL	ET	ED	CS	VO	ER
Breast Cancer	Alpelisib, Fulvestrant (Combination)		A					5★
Her2-receptor Positive Breast Cancer	Everolimus		B					4★
Colorectal Cancer	Anti-EGFR Monoclonal Antibody		B					4★
Cancer	Capiarsertib		B					4★

Access date: 2020/12/25

### Interpretation

- No microsatellite instability
- Tumor mutational burden 5/Mb: Not high
- Assignment of biological significance
  - PALB2 L9F**  
Missense mutation in a tumor suppressor gene  
No. of COSMIC registrations: 1  
gnomAD registrations: None  
→ Mutation of unknown significance
  - PIK3CA H1047R**  
Oncogene missense mutation  
No. of COSMIC registrations: 3656  
→ Activating mutation
- Candidate drug and evidence (see CIViC)
  - Only evidence for combination therapy with other drugs for PIK3CA activating mutation  
→ No recommended treatment

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## A. Case 2

### NCC Oncopanel

RG summary report draft							
Test information							
Test name		NCC Oncopanel Test					
System name		OncoGuide TM NCC Oncopanel System					
Gene mutation							
Gene name	Variant allele frequency	CDS variant	Amino acid variant	COSMIC ID (No. of registrations)			
APC	72.1 (782/1,084)	exon10:c.1312+1G>A		4166472 (1)			
ATM	14.3 (51/350)	exon3:c.103C>T	R35*	922965 (2)			
Number of somatic cell mutations							
Region division		SNV		InDel		Total	
		Number of mutation	Mutation appearance rate	Number of mutation	Mutation appearance rate	Number of mutation appearances	Mutation appearance rate
Exon	nonsyn	0	0.0/Mb	0	0.0/Mb	0	0.0/Mb
	syn	0	0.0/Mb				
Non-exon		2	2.1/Mb	1	1.1/Mb	3	3.2/Mb
Entire region		2	1.6/Mb	1	0.8/Mb	3	2.3/Mb

\*2 Mutation appearance rate = number of mutations per 1 Mb

### Interpretation

- Assignment of biological significance
    - *APC* c.1312+1G>A  
Splicing site base substitution mutation in a tumor suppressor gene  
→ Truncating loss-of-function mutation
    - *ATM* R35\*  
Tumor suppressor gene truncating mutation  
→ Loss-of-function mutation
    - Tumor mutational burden 2.3/Mb: Not high
  - Candidate drug and evidence level
    - There are no candidate drugs for *APC* loss-of-function mutations
    - Candidate drug for *ATM* loss-of-function mutation
- Olaparib:** Evidence level A/1 in prostate cancer (CIViC/OncoKB)  
→ **Evidence level 3B** in other cancers (**OncoKB**)

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## Reference Material

- NCC Oncopanel Report Explanation

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## Results Report: Sequencing Report①

Sequencing report	
Reference No.	Report draft creation date
Sample information	
Sample	Test registration No. (B)
Tumor tissue sequencing information	
Panel	NCC oncopanel v4
Reagent	SureSelect XT HS Reagent
Sequencer run date	10-Dec-18
Name of read data	
Total number of reads	3,19,22,686
Read mapping rate (%)	78.26
Duplication rate (%)	72.55
Discordance rate (%)	0.3
Mismatch rate (%)	0.29
Deletion rate (%)	0.00
Insertion rate (%)	0.00
Mean read depth	706.6
Median read depth	616.0
Mean insert size	1297.7
Median insert size	206.0
Normal tissue sequencing information	
Panel	NCC oncopanel v4
Reagent	SureSelect XT HS Reagent
Sequencer run date	10-Dec-18
Name of read data	
Total number of reads	95,84,714
Read mapping rate (%)	86.99
Duplication rate (%)	12.53
Discordance rate (%)	0.29
Mismatch rate (%)	0.28
Deletion rate (%)	0.01
Insertion rate (%)	0.00
Mean read depth	706.6
Median read depth	616.0
Mean insert size	1297.7
Median insert size	206.0
Data analysis	
Module	cisCall-7.1.6, cisGermline-1.0.1, cisAnnotate-1.1.3
Dataset	Dataset-1.00-180411
Genetic abnormality selection conditions (SNV, InDel)	Exon/Splicing, -Syn, -SNP(+COSMIC), VAF≥0.05
Genetic abnormality selection conditions (CNV)	CNR≥4.0
Genetic abnormality selection conditions (Fusion)	target

Sequencing information  
Tumor tissue  
Mean read depth, etc.

Sequencing information  
Normal tissue

Data analysis  
Analysis pipeline version information, detection conditions of each mutation

- Describes information regarding NGS analysis and candidate genetic abnormalities.
- Describes which detected genetic abnormalities might be **pathogenic**.
- Does not describe when the likelihood of polymorphism is extremely high (**frequencies of 1% or higher** registered in either SNP database).
- Includes **mutations of unknown significance**, rare SNPs (frequency of less than 1%).

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## Results Report: Sequencing Report②

### Gene Mutation entry example

Genetic mutation information	
1	Gene name (Ensemble Expression ID) KRAS (COSMIC-R, ENST00000311936)
	Mutation type nonsynonymous SNV
	Physical location (Chromosome: base) 12:25,398,284
	Gene copy number ratio (Corrected) 1.12
	Mutation allele frequency (%) 11.3 (42/371)
	CDS variant exon2:c.35G>T
	Amino acid variant G12V
	COSMIC ClinVar Registration ID 520 RCV00013413.4
	COSMIC ClinVar Registration No. 7,326 9
	COSMIC Status ClinVar Significance Confirmed_somatic_variant Pathogenic
	SNP database
	Detection method matched, known (somatic)
2	Gene name (Ensemble Expression ID) TP53 (COSMIC-R, ENST00000269395)
	Mutation type frameshift insertion
	Physical location (Chromosome: base) 17:7,579,315
	Gene copy number ratio (Corrected) 1.02
	Mutation allele frequency (%) 15.5 (159/1,023)
	CDS variant exon4:c.371_372insG
	Amino acid variant C124fs*25
	COSMIC ClinVar Registration ID 1268350 -
	COSMIC ClinVar Registration No. 3 -
	COSMIC Status ClinVar Significance Variant_of_unknown_origin -
	SNP database
	Detection method matched
⋮	
Germline genetic mutation information	
	TSC1 R692Q
	BRC1A1 E797fs*3

Registration status in **COSMIC** and **ClinVar** databases. Describes the ID, number of registrations, and additional information in each database.

COSMIC Status : Whether the somatic mutation has been confirmed  
Confirmed\_somatic\_variant – Confirmed  
Variant\_of\_unknown\_origin – Non confirmed

ClinVar Significance : Clinically significant variant  
Pathogenic, Likely pathogenic – pathogenic variant (likely)  
Uncertain\_significance – May be pathogenic, but evidence is lacking  
Likely\_benign, benign – Not a pathogenic variant (unlikely)

This shows the **components of the analysis program** that was used to detect the variant.

- Matched : Detected in comparison with patient's normal sample = somatic mutation
- Known (somatic) : Detected as a somatic mutation (previously reported important variant)
- Known (germline) : Detected as a germline variant (as above)
- gatk : Detected as a germline variant

Candidate **germline variants** are summarized separately in the bottom row. (including rare SNPs with a frequency of less than 1%).

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### Supplement: Mentioned items

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**Gene name (Ensemble Expression ID)**  
transcriptional products in the gene database. A -R is added (E.g. COSMIC-R) when these are the main transcriptional

**Mutation type**  
English notation of the

**CDS change**  
number base in the CDS sequence on the exon was changed on the sequence that codes (CDS) amino acids from

**Amino acid change**  
number amino acid sequence changes during translation to protein

**COSMIC|ClinVar Registration ID**  
If the mutation is registered in the COSMIC and ClinVar databases, then each ID is written

**COSMIC|ClinVar Registration No.**  
COSMIC and ClinVar databases, then the number of registrations is written

**Genetic mutation information**

Gene name (Ensemble Exp	AKT1 (COSMIC-R, ENST00000349310)
Mutation type	nonsynonymous SNV
Physical location (Chromos	14:105,246,551
Gene copy number ratio (C	0.76
Mutation allele frequency	58.9 (379/642)
CDS variant	exon4:c.49G>A
Amino acid variant	E17K
COSMIC ClinVar Registrat	33765 RCV00015017.4
COSMIC ClinVar Registrat	237 22
COSMIC Status ClinVar Sig	Confirmed_somatic_variant Pathogenic
SNP database	ExAC
Detection method	matched

**Physical location (Chromosome: base number)**  
Information on the genome position where the genetic abnormality occurs

**Gene copy number ratio (Corrected read)**  
normal number of gene copies being 1, to indicate gene amplification or deletion  
**Fusion read number/gene 1 read number | gene fusion** (only included when gene fusion is detected)

**Mutation allele frequency (%)**  
Frequency of mutation sequences of the total number of read sequences

**SNP database**  
with alleles registered with less than 1% frequency

**COSMIC Status|ClinVar Significance**  
databases. Indicates that it has been detected in other cases or the pathogenic significance is known

**Detection method**  
mutations are written as matched and known (somatic), and germline variants are written as gatk and known (germline)

Cancer Genomic Medicine Gene Panel Testing Guidelines p.145 Igaku-Shoin

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### Results Report: Sequencing Report ③

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#### Copy Number Variant

Gene name (Ensemble Expression ID)	EGFR	CDKN2A
Mutation type	amplification	homozygous deletion
Physical location (Chromosome: base number)	7:55,086,714-55,275,773	9:21,967,751-21,994,490
Gene copy number ratio (Corrected read number ratio)	20.70	0.25
Mutation allele frequency (%)	*	*
CDS variant	*	*
Amino acid variant	*	*
COSMIC ClinVar Registration ID	* -	* -
COSMIC ClinVar Registration No.	* -	* -
COSMIC Status ClinVar Significance	* -	* -
SNP database	*	*
Detection method	matched	matched

Gene copy number ratio is measured and detected. The whole region of each exon gene is assessed, and no partial deletion is detected.

Points to note:

- Does not reflect the tumor cell ratio.
- Deletions are always described as homozygous deletions.

Copy number variant detection condition

- Amplification  $\geq 4$
- Deletion  $< 0.5$

#### Gene Fusion

Gene name (Ensemble Expression ID)	SLC34A2 ROS1
Mutation type	fusion
Physical location (Chromosome: base number)	4:25,679,257-6,117,648,089
Fusion read number/gene 1 read number   gene 2 read number	148/1,433 834
Mutation allele frequency (%)	10.33
CDS variant	*
Amino acid variant	*
COSMIC ClinVar Registration ID	* -
COSMIC ClinVar Registration No.	* -
COSMIC Status ClinVar Significance	* -
SNP database	*
Detection method	target

This is confirming genome sequence fusion, so the gene order is sometimes displayed in reverse. It is necessary to confirm what is known.

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# Results Report: Summary Report

Summary report draft		Expert panel date			
Sample information					
Gene mutation information					
Gene name	Variant allele frequency	CDS variant			
MTAS	11.3 (42/371)	exon2 c.35C>T			
TP53	15.5 (158/1,023)	exon4 c.371_372delG			
BRCA1	40.2 (81/200)	exon10 c.2389_2390delG			
Gene amplification/deletion information					
Gene name	Number of gene copies (corrected read number ratio)				
Gene rearrangement (fusion) information					
Gene name	Physical position				
*1 Variants where the read number fell below the threshold					
Number of somatic cell mutations					
Region division	SNV	indel		Total	
	Number of mutation appearances	Mutation appearance rate × 2	Number of mutation appearances	Mutation appearance rate × 2	Number of mutation appearances
Exon	1	2.8Mb	1	2.8Mb	3
Intron	1	2.8Mb	0	0.0Mb	2
Non-exon	2	2.1Mb	0	0.0Mb	2
Entire region	4	3.1Mb	1	0.8Mb	5
*2 Mutation appearance rate = number of mutations per 1 Mb					
Analysis report					
MTAS (G12E)	Known active variant				
TP53 (C124G>S)	Truncating mutation, therefore considered as a loss-of-function mutation				
BRCA1 (E797G>*)	Truncating mutation, therefore considered as a loss-of-function mutation				
Report draft creation date: 11 December 2018					
Confirmation signature:					
Used database version					
EP08	20180202_v5.2				
refGene	20171218				
ensGene	20140408				
1000 human genomes	Phase_3 (20130502)				
ESP500	V2-94137				
Ensembl	v81 (20160316)				
NCBI	v2.01 (20170201)				
COSMIC	v71 (20180228)				
ClinVar	20170905				
Ensembl	V1.00 (20180411)				
Disclaimer					
The analysis report based on this test should be used at the discretion of the medical institution after determining its applicability, validity and timeliness.					

The following information is extracted based on the description of the genetic abnormality in the sequencing report

**Somatic Genetic Abnormality:**     **Germline Pathogenic Variant:**

- Known druggable mutation
  - COSMIC DB registered mutation
  - Truncating mutation, splicing site mutation (tumor suppressor genes)
  - Gene amplification (copy number ratio ≥4)
  - Gene fusion (gene deletions are not described)
- <Genes of interest>  
*APC, BRCA1, BRCA2, MLH1, MSH2, PTEN, RB1, RET, STK11, SMAD4, TP53, TSC1, VHL*
- "Pathogenic" in ClinVar
  - Truncating mutation (tumor suppressor genes)

Not differentiated in the summary report

**Number of Somatic Mutations**

**Analysis Report**

Describes the frequency for each detected genetic abnormality

- Categorically described items are known to exhibit functional changes due to the mutation
- Mutations detectable with known companion diagnostics have "known" added at the beginning of the sentence