Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 王玉
Gender: Female
ID No.: F228804068
History No.: 30487402
Age: 84

Ordering Doctor: DOC1654E 林庭安
Ordering REQ.: H45DB31
Signing in Date: 2023/01/18

Path No.: M112-00010
MP No.: MY23005
Assay: Oncomine Myeloid Assay
Sample Type: Blood
Date of blood drawing: 2023/01/13

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Myelodysplastic Syndrome

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Relevant Myelodysplastic Syndrome Variants

Gene	Finding	Gene	Finding
ASXL1	***ASXL1 p.(R404*) c.1210C>T***	NPM1	None detected
BCOR	None detected	NRAS	None detected
CBL	None detected	NUP214	None detected
CREBBP	None detected	RUNX1	None detected
ETV6	None detected	SF3B1	***SF3B1 p.(K700E) c.2098A>G***
EZH2	None detected	SRSF2	None detected
FLT3	None detected	STAG2	None detected
GATA2	None detected	TP53	None detected
IDH2	None detected	U2AF1	None detected
KIT	None detected	WT1	None detected
KMT2A	None detected	ZRSR2	None detected

Relevant Myelodysplastic Syndrome Variants (continued)

Gene	Finding	Gene	Finding
MECOM	None detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*SF3B1 p.(K700E) c.2098A>G* splicing factor 3b subunit 1 Allele Frequency: 26.01% **Prognostic significance:** NCCN: Favorable **Diagnostic significance:** Myelodysplastic Syndrome	luspatercept	hypomethylating agent + lenalidomide lenalidomide luspatercept	0
IA	*ASXL1 p.(R404*) c.1210C>T* ASXL transcriptional regulator 1 Allele Frequency: 5.60% **Prognostic significance:** NCCN: Poor	None	allogeneic stem cells azacitidine cytarabine cytarabine + daunorubicin cytarabine + daunorubicin + etoposide cytarabine + etoposide + idarubicin cytarabine + fludarabine + idarubicin + filgrastim cytarabine + idarubicin cytarabine + mitoxantrone decitabine gemtuzumab ozogamicin + chemotherapy venetoclax + chemotherapy	0

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Prevalent cancer biomarkers without relevant evidence based on included data sources
SETBP1 p.(G870S) c.2608G>A

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
SF3B1	p.(K700E)	c.2098A>G	COSM84677	chr2:198266834	26.01%	NM_012433.4	missense	1999
SETBP1	p.(G870S)	c.2608G>A	COSM1234973	chr18:42531913	27.25%	NM_015559.3	missense	2000
ASXL1	p.(R404*)	c.1210C>T	.	chr20:31021211	5.60%	NM_015338.6	nonsense	2000
DNMT3A	p.(M801V)	c.2401A>G	.	chr2:25462006	26.45%	NM_022552.4	missense	2000
EZH2	p.(D90Ifs*9)	c.268delG	.	chr7:148529820	51.04%	NM_004456.5	frameshift Deletion	1979

Biomarker Descriptions

ASXL1 (ASXL transcriptional regulator 1)

Background: The ASXL1 gene encodes the ASXL transcriptional regulator 1 protein, a ligand-dependent co-activator and epigenetic scaffolding protein involved in transcriptional regulation[1,2]. ASXL1 belongs to the ASXL gene family, which also includes ASXL2 and ASXL3[2]. ASXL proteins contain a conserved c-terminal plant homeodomain (PHD) which facilitates interaction with DNA and histones[2,3]. ASXL1 influences chromatin remodeling and transcription through interaction with BAP1 and polycomb repressive complex (PRC) proteins, as well as other transcriptional activators and repressors[2,4]. In cancer, ASXL1 is the target of somatic mutations which often result in a truncated ASXL1 protein and loss of its PHD[5,6,7]. Such mutations can lead to impaired protein function and consequent upregulation of HOXA gene expression, supporting a tumor suppressor role for ASXL1[8].

Alterations and prevalence: Missense, nonsense, and frameshift mutations in ASXL1 are reported in 3-6% of de novo acute myeloid leukemia (AML), up to 36% of secondary AML, approximately 15% of myelodysplastic syndromes (MDS), up to 23% of myeloproliferative neoplasms (MPN), up to 30% of systemic mastocytosis (SM), and approximately 45% of chronic myelomonocytic leukemia (CMML)[4,9,10,11,12,13,14,15,16]. The ASXL1 G646Wfs*12 mutation accounts for over 50% of ASXL1 mutated cases in myeloid malignancies[6,11,17]. This mutation results from a single nucleotide expansion that occurs within an eight base pair guanine repeat that extends from c.1927 to c.1934. It is proposed that the high prevalence of the G646Wfs*12 variant is due to replication slippage which can occur in areas of repetitive sequence[18]. As a consequence, detection of G646Wfs*12 may result as an artifact of PCR and/or sequencing[19]. However, multiple studies observe an increase in the frequency of G646Wfs*12 in myeloid cancer relative to normal suggesting that G646Wfs*12 is a bona fide somatic mutation[9,18,20].

Potential relevance: The majority of frameshift and nonsense mutations in ASXL1 that result in protein truncation and removal of the PHD domain are considered pathogenic[21]. Mutations in ASXL1 confer poor/adverse risk in AML and are associated with poor outcomes and adverse risk[16]. Additionally, ASXL1 nonsense or frameshift mutations are independently associated with poor prognosis in MDS and CMML[22]. Moreover, ASXL1 mutations are independently associated with inferior overall survival (OS) in patients with MPN or SM[23,24].

SETBP1 (SET binding protein 1)

Background: The SETBP1 gene encodes the SET binding protein 1, a multi-functional protein which contributes to several cellular processes including transcriptional regulation, proliferation, differentiation, and transformation[25]. SETBP1 contains a SET binding domain, which enables SETBP1 to form complexes with SET domain containing proteins, including the nuclear SET oncoprotein, a potent inhibitor of protein phosphatase 2A (PP2A)[25,26,27]. SETBP1 binding stabilizes SET, leading to elevated SET expression and increased inhibition of PP2A[25,28,29]. SETBP1 mediated inhibition of PP2A facilitates leukemic transformation in hematological malignancies including acute myeloid leukemia (AML)[29]. SETBP1 also contains three AT-hook domains, three nuclear localization motifs, and a SKI-homologous region which can influence transcriptional regulation[25]. SETBP1 is the target of somatic mutations in both hematological malignancies as well as solid tumors[12,30]. SETBP1 mutations often result in a gain of function and can lead to HOX gene upregulation, suggesting an oncogenic role for SETBP1 in cancer[30,31]. Additionally, germline gain of function mutations in SETBP1 are found to be causal of Schinzel-Giedion syndrome (SGS), a rare developmental disorder characterized by multiple malformations, severe neurological alterations and increased risk of cancer[32].

Alterations and prevalence: SETBP1 mutations are observed in up to 32% of atypical chronic myeloid leukemia (aCML), 24% of juvenile myelomonocytic leukemia (JMML), 18% of chronic myelomonocytic leukemia (CMML), 10% of myelodysplastic/myeloproliferative neoplasms (MDS/MPN), 1-3% of primary AML and up to 17% of secondary AML (sAML)[12,30,33,34,35]. Additionally, mutations in SETBP1 are reported in solid tumors including up to 12% of melanoma, 11% of lung adenocarcinoma, 9% of stomach and uterine cancer, as well as, 6% of esophageal and colorectal carcinoma[12]. SETB1 mutations are predominantly missense, the most recurrent involving amino acid substitutions at D868, G870, and I871[30,34,35]. SETBP1 fusions have also been described in hematological malignancies. The t(11;18)(p15;q12)/NUP98-SETBP1 and t(12;18)(p13;q12)/ETV6-SETBP1 fusions have been reported in individual cases of T-cell acute lymphoblastic leukemia (T-ALL) and AML, respectively[36,37].

Potential relevance: The presence of SETBP1 mutations is one of the diagnostic criteria for CMML as defined by the World Health Organization(WHO)[38]. Overexpression of SETBP1 is associated with accelerated leukemic transformation and poor prognosis in AML[29,33]. Additionally, mutations in SETBP1 are associated with poor prognosis in MDS/MPN, CMML, JMML, and aCML[33,35,39,40].

SF3B1 (splicing factor 3b subunit 1)

Background: The SF3B1 gene encodes the splicing factor 3b subunit 1 protein, a core component of the U2 small nuclear ribonucleoprotein (snRNP) complex of the spliceosome responsible for RNA splicing. SF3B1 is involved in recognition of the branch point sequence during selection of the 3' splice site. Recurrent somatic mutations in SF3B1 and other components of the splicing machinery including SRSF2, U2AF1, and ZRSR2, are common in myelodysplasia. These components experience mutations in a mutually exclusive manner suggesting a common impact on RNA splicing and the pathogenesis of myelodysplasia[41]. SF3B1 mutations

Biomarker Descriptions (continued)

are believed to contribute to aberrant post-translational inactivation of the regulatory complex PPP2R5A of protein phosphatase 2A (PP2A), leading to the activation and stabilization of MYC activation and impairing apoptosis[42].

Alterations and prevalence: SF3B1 mutations occur in the majority (70-80%) of myelodysplastic syndromes (MDS) with ring sideroblasts (RS) and at lower frequency in other myeloid neoplasms including MDS without RS (7%), chronic myelomonocytic leukemia (5-6%), therapy-related acute myeloid leukemia (AML) or AML with MDS features (5%), and de novo AML (3%)[41,43,44]. Recurrent somatic SF3B1 mutations are also common in certain solid cancers including uveal melanoma (20-30%) and breast cancer (2%) and at lower frequencies in diverse cancer types[12,45,46,47,48,49,50,51]. Cancer-associated recurrent missense mutations in SF3B1 occur within the HEAT repeat domains 5-9 at codon positions R625, K666, K700, G742, and D781[52]. The functional significance of recurrent SF3B1 mutations is to alter branch point selection thus inducing cryptic 3' splice site selection[52,53,54]

Potential relevance: Currently, no therapies are approved for SF3B1 aberrations. SF3B1 mutations are associated with aggressive disease and shorter survival in patients diagnosed with chronic lymphocytic leukemia (CLL)[55]. Investigational inhibitors of the spliceosome are in early clinical development[56,57].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

SF3B1 p.(K700E) c.2098A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
luspatercept	✖	○	✖	●	✖
hypomethylating agent + lenalidomide	✖	○	✖	✖	✖
lenalidomide	✖	○	✖	✖	✖

ASXL1 p.(R404*) c.1210C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Allogeneic hematopoietic stem cell transplantation	✖	○	✖	✖	✖
azacitidine	✖	○	✖	✖	✖
cytarabine	✖	○	✖	✖	✖
cytarabine + daunorubicin	✖	○	✖	✖	✖
cytarabine + daunorubicin + etoposide	✖	○	✖	✖	✖
cytarabine + etoposide + idarubicin	✖	○	✖	✖	✖
cytarabine + fludarabine + idarubicin + filgrastim	✖	○	✖	✖	✖
cytarabine + idarubicin	✖	○	✖	✖	✖
cytarabine + mitoxantrone	✖	○	✖	✖	✖
decitabine	✖	○	✖	✖	✖
gemtuzumab ozogamicin + cytarabine + daunorubicin	✖	○	✖	✖	✖
venetoclax + azacitidine	✖	○	✖	✖	✖

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

ASXL1 p.(R404*) c.1210C>T (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
venetoclax + cytarabine	✖	○	✖	✖	✖
venetoclax + decitabine	✖	○	✖	✖	✖

Relevant Therapy Details

Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2022-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

SF3B1 p.(K700E) c.2098A>G

○ hypomethylating agent + lenalidomide

Cancer type: Myelodysplastic/Myeloproliferative Neoplasm

Variant class: SF3B1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

○ lenalidomide

Cancer type: Myelodysplastic/Myeloproliferative Neoplasm

Variant class: SF3B1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

SF3B1 p.(K700E) c.2098A>G (continued)

luspatercept

Cancer type: Myelodysplastic/Myeloproliferative Neoplasm

Variant class: SF3B1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Line of therapy not specified); Consider

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

ASXL1 p.(R404*) c.1210C>T

cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia

Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia

Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia

Variant class: ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

ASXL1 p.(R404*) c.1210C>T (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Allogeneic hematopoietic stem cell transplantation

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Consolidation therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

ASXL1 p.(R404*) c.1210C>T (continued)

cytarabine + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + mitoxantrone

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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gemtuzumab ozogamicin + cytarabine + daunorubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

ASXL1 p.(R404*) c.1210C>T (continued)

venetoclax + cytarabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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venetoclax + decitabine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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azacitidine

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy)

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + daunorubicin + etoposide

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

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cytarabine + etoposide + idarubicin

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

ASXL1 p.(R404*) c.1210C>T (continued)

cytarabine + fludarabine + idarubicin + filgrastim

Cancer type: Acute Myeloid Leukemia **Variant class:** ASXL1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- (Induction therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Acute Myeloid Leukemia [Version 2.2022]

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2022-11-01. For the most up-to-date information, search www.esmo.org.

SF3B1 p.(K700E) c.2098A>G

● luspatercept

Cancer type: Myelodysplastic Syndrome **Variant class:** SF3B1 mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):
- Refractory (Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Myelodysplastic Syndromes [Annals of Oncology (2020), https://doi.org/10.1016/j.annonc.2020.11.002]

Prognostic Details

Current NCCN Information

NCCN information is current as of 2022-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

SF3B1 p.(K700E) c.2098A>G

Prognostic significance: NCCN: Favorable

Cancer type: Myelodysplastic Syndrome **Variant class:** SF3B1 K700E mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® independently associate the biomarker with favorable prognosis

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

ASXL1 p.(R404*) c.1210C>T

Prognostic significance: NCCN: Poor

Cancer type: Myelodysplastic Syndrome **Variant class:** ASXL1 truncating mutation

NCCN Recommendation category: 2A

Summary:
- NCCN Guidelines® independently associate the biomarker with poor prognosis in MDS and CMML

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

Diagnostic Details

Current NCCN Information

NCCN information is current as of 2022-11-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

SF3B1 p.(K700E) c.2098A>G

Diagnostic significance: Myelodysplastic Syndrome

Variant class: SF3B1 mutation

NCCN Recommendation category: 2A

Diagnostic notes:

- 2022 WHO Classification of Myelodysplastic Neoplasms (MDS); MDS-SF3B1 (low blasts) with mutated SF3B1 variant allele frequency (VAF) ≥10%. ≥15% ring sideroblasts (RS) may substitute for SF3B1 mutation (MDS with low blasts and ring sideroblasts). Normal karyotype or any cytogenetic abnormality other than del(5q), monosomy 7, inv(3) or abnormal 3q26, complex (≥3) or somatically mutated TP53, RUNX1, or EZH2 genes

Reference: NCCN Guidelines® - NCCN-Myelodysplastic Syndromes [Version 1.2023]

Signatures

Testing Personnel: Shu-Ying Wang 2023.01.19 13:37:00 +08'00'

Laboratory Supervisor: 2023.01.19 13:37:09 +08'00'

Pathologist: Yi-Chu Yeh 2023.01.19 13:37:20 +08'00'

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