

**Patient Name:** 한중덕  
**Gender:** Male  
**Sample ID:** N26-34

**Primary Tumor Site:** Lung  
**Collection Date:** 2026.01.16.

## Sample Cancer Type: Lung Cancer

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## Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	None detected	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	<b>ERBB2 exon 20 insertion</b>	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

  

Genomic Alteration	Finding
Tumor Mutational Burden	<b>3.81 Mut/Mb measured</b>

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
<b>IA</b>	<b>ERBB2 exon 20 insertion</b> erb-b2 receptor tyrosine kinase 2 Allele Frequency: 21.28% Locus: chr17:37880997 Transcript: NM_004448.4	<b>trastuzumab deruxtecan</b> <sup>1,2 / II+</sup> <b>zongertinib</b> <sup>1 / II+</sup> <b>sevabertinib</b> <sup>1</sup> ado-trastuzumab emtansine <sup>II+</sup>	neratinib neratinib + hormone therapy neratinib + trastuzumab + hormone therapy	31
<b>IIC</b>	<b>BRCA2 p.(K437Ifs*22) c.1310_1313delAAGA</b> BRCA2, DNA repair associated Allele Frequency: 5.79% Locus: chr13:32906915 Transcript: NM_000059.4	None*	<b>abiraterone + niraparib</b> <sup>1,2 / II+</sup> <b>bevacizumab + olaparib</b> <sup>1,2 / II+</sup> <b>niraparib</b> <sup>1 / II+</sup> <b>olaparib</b> <sup>1,2 / II+</sup> <b>rucaparib</b> <sup>1 / II+</sup> <b>talazoparib + hormone therapy</b> <sup>1 / II+</sup> bevacizumab + niraparib <sup>II+</sup> talazoparib <sup>II+</sup> olaparib + hormone therapy	13

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

\* Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Line of therapy: I: First-line therapy, II+: Other line of therapy

Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

**Alerts informed by public data sources:** Contraindicated, Resistance, Breakthrough, Fast Track

*ERBB2 exon 20 insertion* **zongertinib**<sup>1</sup>

Public data sources included in alerts: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, ESMO

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*MAP2K7 deletion, Microsatellite stable, TP53 c.919+2T>G, UGT1A1 p.(G71R) c.211G>A, FAT1 p.(T2369Rfs\*2) c.7105delA, HLA-B deletion, NOTCH1 deletion, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ERBB2	p.(G776delinsVC)	c.2326_2327insTGT	COSM12553	chr17:37880997	21.28%	NM_004448.4	nonframeshift Insertion
BRCA2	p.(K437Ifs*22)	c.1310_1313delAAGA	.	chr13:32906915	5.79%	NM_000059.4	frameshift Deletion
TP53	p.(?)	c.919+2T>G	.	chr17:7577017	11.02%	NM_000546.6	unknown
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	42.26%	NM_000463.3	missense
FAT1	p.(T2369Rfs*2)	c.7105delA	.	chr4:187540634	27.90%	NM_005245.4	frameshift Deletion
OR2L8	p.(Y217R)	c.649_650delTAinsCG	.	chr1:248112808	2.70%	NM_001001963.1	missense
CDH10	p.(S173F)	c.518C>T	.	chr5:24537497	5.62%	NM_006727.5	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	53.30%	NM_002439.5	nonframeshift Insertion
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsT CA	.	chr6:31324208	80.00%	NM_005514.8	missense, missense
TMEM233	p.(V85A)	c.254T>C	.	chr12:120067608	38.15%	NM_001136534.3	missense

### Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MAP2K7	chr19:7968792	0.23	0.64
HLA-B	chr6:31322252	0	0.48
NOTCH1	chr9:139390441	0.45	0.69
CD276	chr15:73991923	0.48	0.7

## Biomarker Descriptions

### ERBB2 exon 20 insertion

*erb-b2 receptor tyrosine kinase 2*

**Background:** The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family<sup>1</sup>. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family<sup>95</sup>. All

## Biomarker Descriptions (continued)

ERBB/HER proteins encode transmembrane receptor tyrosine kinases<sup>96</sup>. However, ERBB2/HER2 is an orphan receptor with no known ligand<sup>96</sup>. ERBB2 preferentially binds other ligand-bound ERBB/HER family members to form heterodimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival<sup>97</sup>. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types<sup>97</sup>. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding<sup>98,99,100</sup>.

**Alterations and prevalence:** ERBB2 gene amplification occurs in 10-25% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers<sup>8,9,101,102,103,104,105,106</sup>. ERBB2 gene amplification in pediatric population is observed in 2% of peripheral nervous system cancers (2 in 91 patients) and less than 1% of leukemia (1 in 250 cases)<sup>9</sup>. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types<sup>9,107,108</sup>. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772\_A775dup.

**Potential relevance:** The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2<sup>109,110</sup>. Trastuzumab<sup>111</sup> was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab<sup>112</sup> (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine<sup>113</sup> (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer<sup>114</sup>. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib<sup>115</sup>, with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib<sup>116</sup>, an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib<sup>116</sup> in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbitinib<sup>117</sup> was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line<sup>46</sup>. In 2024, a bispecific HER2 antibody, zanidatamab<sup>118</sup>, was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab<sup>119</sup> in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab<sup>120</sup>, received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). The humanized anti-HER2 antibody drug conjugate disitamab vedotin<sup>121</sup> (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788<sup>122</sup> received fast track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies<sup>123,124,125,126,127</sup>. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies<sup>128,129</sup>. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy<sup>130</sup>. However, this was shown to be overcome by neratinib in combination with therapies targeting ER<sup>130</sup>. Additionally, in 2025, FDA approved the kinase inhibitors zongertinib<sup>131</sup> and sevabertinib<sup>132</sup> for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 tyrosine kinase domain activating mutations. In 2025, a 9 amino acid transmembrane peptide of the HER2/neu protein, GLSI-100 (GP-2)<sup>133</sup>, received fast track designation for the prevention of breast cancer recurrence following surgery.

### BRCA2 p.(K437Ifs\*22) c.1310\_1313delAAGA

*BRCA2, DNA repair associated*

**Background:** The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA<sup>60,61</sup>. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity<sup>60,61</sup>. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer<sup>62,63,64</sup>. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%<sup>62,65</sup>.

**Alterations and prevalence:** Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer<sup>66,67,68,69,70,71,72,73</sup>. Somatic alterations in BRCA2 are observed in 5-15% of

## Biomarker Descriptions (continued)

uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme<sup>8,9</sup>.

**Potential relevance:** Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)<sup>74</sup>. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells<sup>75,76</sup>. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib<sup>77</sup> (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib<sup>77</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib<sup>78</sup> is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib<sup>79</sup> (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib<sup>79</sup> in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes BRCA2. Niraparib<sup>80</sup> (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate<sup>81</sup> received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. In 2019, niraparib<sup>82</sup> received breakthrough designation for the treatment of patients with BRCA1/2 gene-mutated mCRPC who have received prior taxane chemotherapy and androgen receptor (AR)-targeted therapy. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported<sup>83</sup>. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality<sup>84</sup>. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>85</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

### MAP2K7 deletion

*mitogen-activated protein kinase kinase 7*

**Background:** The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7<sup>1</sup>. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10<sup>56,57,58</sup>. Activation of MAPK proteins occurs through a kinase signaling cascade<sup>56,57,59</sup>. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members<sup>56,57,59</sup>. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation<sup>56,57,59</sup>.

**Alterations and prevalence:** Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma<sup>8,9</sup>. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma<sup>8,9</sup>.

**Potential relevance:** Currently, no therapies are approved for MAP2K7 aberrations.

### Microsatellite stable

**Background:** Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome<sup>33</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>34,35</sup>. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2<sup>36</sup>. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250<sup>37</sup>. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)<sup>37</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>38,39,40,41,42</sup>. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes<sup>35</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>34,35,39,43</sup>.

## Biomarker Descriptions (continued)

**Alterations and prevalence:** The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma<sup>34,35,44,45</sup>. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers<sup>44,45</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>46</sup> (2014) and nivolumab<sup>47</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>46</sup> is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication<sup>46</sup>. Dostarlimab<sup>48</sup> (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer<sup>40,49</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>50</sup> (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location<sup>40,51,52</sup>. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients<sup>52</sup>. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors<sup>53,54</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>53,54</sup>.

### TP53 c.919+2T>G

*tumor protein p53*

**Background:** The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair<sup>1</sup>. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis<sup>10</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>11</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>12,13</sup>.

**Alterations and prevalence:** TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)<sup>8,9,14,15,16,17</sup>. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282<sup>8,9</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>18,19,20,21</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>8,9</sup>. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)<sup>8,9</sup>. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)<sup>8,9</sup>.

**Potential relevance:** The small molecule p53 reactivator, PC14586<sup>22</sup> (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation<sup>23,24</sup>. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma<sup>25</sup>. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)<sup>26,27,28,29,30</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>31</sup>. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system<sup>32</sup>.

### UGT1A1 p.(G71R) c.211G>A

*UDP glucuronosyltransferase family 1 member A1*

**Background:** The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily<sup>1,134</sup>. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites<sup>134,135</sup>. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance<sup>136</sup>. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active

## Biomarker Descriptions (continued)

drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation<sup>136,137,138,139</sup>. Furthermore, UGT1A1 polymorphisms, such as UGT1A1\*28, UGT1A1\*93, and UGT1A1\*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38<sup>140</sup>.

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma<sup>8,9</sup>.

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

### FAT1 p.(T2369Rfs\*2) c.7105delA

*FAT atypical cadherin 1*

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats<sup>1,55</sup>. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions<sup>55</sup>. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion<sup>55</sup>. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/ $\beta$ -catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition<sup>55</sup>. Alterations of FAT1 lead to downregulation or loss of function, supporting a tumor suppressor role for FAT1<sup>55</sup>.

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot<sup>8,9</sup>. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma<sup>8,9</sup>. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma<sup>8,9</sup>.

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

### HLA-B deletion

*major histocompatibility complex, class I, B*

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B<sup>1</sup>. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells<sup>2</sup>. MHC class I molecules are heterodimers composed of two polypeptide chains,  $\alpha$  and B2M<sup>3</sup>. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the  $\alpha$  polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self<sup>4,5,6</sup>. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B<sup>7</sup>.

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma<sup>8,9</sup>. Biallelic loss of HLA-B is observed in 5% of DLBCL<sup>8,9</sup>.

Potential relevance: Currently, no therapies are approved for HLA-B aberrations.

### NOTCH1 deletion

*notch 1*

Background: The NOTCH1 gene encodes the notch receptor 1 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH2, NOTCH3, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling<sup>86</sup>. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism<sup>87,88</sup>. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members<sup>89,90,91,92</sup>.

## Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in NOTCH1 are observed in 15-20% of head and neck cancer, 5-10% of glioma, melanoma, gastric, esophageal, lung, and uterine cancers<sup>8,9,15</sup>. Activating mutations in either the heterodimerization or PEST domains of NOTCH1 have been reported in greater than 50% of T-cell acute lymphoblastic leukemia<sup>93,94</sup>.

Potential relevance: Currently, no therapies are approved for NOTCH1 aberrations.

## Alerts Informed By Public Data Sources

### Current FDA Information

 Contraindicated
  Not recommended
  Resistance
  Breakthrough
  Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search [www.fda.gov](http://www.fda.gov).

### ERBB2 exon 20 insertion

#### zongertinib

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** ERBB2 TKD activating mutation

#### Supporting Statement:

The FDA has granted Breakthrough Therapy designation to the tyrosine kinase inhibitor, zongertinib (BI 1810631), for the first-line treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations.

#### Reference:

<https://www.prnewswire.com/news-releases/fda-grants-hernexeos-breakthrough-therapy-designation-for-first-line-use-in-her2-erbb2-mutant-advanced-nscl-302545360.html>

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNA1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO10, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLC01B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFB1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

### Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMP2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CEBP, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERF1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRD, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1,

## Genes Assayed (continued)

### Genes Assayed for the Detection of Copy Number Variations (continued)

SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSP02, RSP03, TERT

### Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBF3, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRF1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

## Relevant Therapy Summary

In this cancer type
  In other cancer type
  In this cancer type and other cancer types
  No evidence

### ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	●	●	●	●	● (II)
zongertinib	●	●	×	×	● (II)
sevabertinib	●	×	×	×	● (II)
ado-trastuzumab emtansine	×	●	×	×	×
neratinib	×	○	×	×	×
neratinib + fulvestrant	×	○	×	×	×
neratinib + trastuzumab + fulvestrant	×	○	×	×	×
sevabertinib, pembrolizumab, chemotherapy	×	×	×	×	● (III)
trastuzumab deruxtecan, pembrolizumab, chemotherapy	×	×	×	×	● (III)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ① In this cancer type and other cancer types    ✕ No evidence

### ERBB2 exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
zongertinib, pembrolizumab, chemotherapy	✕	✕	✕	✕	● (III)
pertuzumab + trastuzumab	✕	✕	✕	✕	● (II/III)
anti-PD-L1 antibody, pyrotinib	✕	✕	✕	✕	● (II)
pyrotinib	✕	✕	✕	✕	● (II)
pyrotinib, chemotherapy	✕	✕	✕	✕	● (II)
pyrotinib, thalidomide	✕	✕	✕	✕	● (II)
sintilimab	✕	✕	✕	✕	● (II)
toripalimab, chemotherapy	✕	✕	✕	✕	● (II)
tucatinib, ado-trastuzumab emtansine	✕	✕	✕	✕	● (II)
ABT-101	✕	✕	✕	✕	● (I/II)
AZD-9574, trastuzumab deruxtecan	✕	✕	✕	✕	● (I/II)
BH-30643	✕	✕	✕	✕	● (I/II)
DF-1001, sacituzumab govitecan	✕	✕	✕	✕	● (I/II)
HS-10376	✕	✕	✕	✕	● (I/II)
JIN-A-04	✕	✕	✕	✕	● (I/II)
ORIC-114	✕	✕	✕	✕	● (I/II)
STX-721	✕	✕	✕	✕	● (I/II)
trastuzumab deruxtecan, neratinib	✕	✕	✕	✕	● (I/II)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✕	✕	✕	✕	● (I)
BL-M07D1	✕	✕	✕	✕	● (I)
BM-230	✕	✕	✕	✕	● (I)
ENT-H-1, trastuzumab	✕	✕	✕	✕	● (I)
GQ-1005	✕	✕	✕	✕	● (I)
NVL-330	✕	✕	✕	✕	● (I)

### BRCA2 p.(K437Ifs\*22) c.1310\_1313delAAGA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	○	○	○	● (II)
bevacizumab + olaparib	○	○	○	○	✕

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type    ○ In other cancer type    ① In this cancer type and other cancer types    ✕ No evidence

### BRCA2 p.(K437Ifs\*22) c.1310\_1313delAAGA (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abiraterone + niraparib	○	○	○	✕	✕
niraparib	○	○	✕	○	✕
rucaparib	○	○	✕	○	✕
talazoparib + enzalutamide	○	○	✕	✕	✕
bevacizumab + niraparib	✕	○	✕	✕	✕
olaparib + abiraterone acetate	✕	○	✕	✕	✕
talazoparib	✕	✕	✕	○	● (II)
niraparib, dostarlimab	✕	✕	✕	✕	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✕	✕	✕	✕	● (II)
pamiparib, tislelizumab	✕	✕	✕	✕	● (II)
ZEN-3694, talazoparib	✕	✕	✕	✕	● (II)
AMXI-5001	✕	✕	✕	✕	● (I/II)
sacituzumab govitecan, berzosertib	✕	✕	✕	✕	● (I/II)
HS-10502	✕	✕	✕	✕	● (I)
niraparib, chemotherapy	✕	✕	✕	✕	● (I)
novobiocin	✕	✕	✕	✕	● (I)
olaparib, chemotherapy	✕	✕	✕	✕	● (I)
SNV-1521, trastuzumab deruxtecan	✕	✕	✕	✕	● (I)

\* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	<b>0.0%</b>
Not Detected	<b>Not Applicable</b>

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

Thermo Fisher Scientific's Ion Torrent OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from [www.fda.gov](http://www.fda.gov) and is current as of 2025-11-25. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-11-03. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-11-25. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://www.clinicaltrials.gov) by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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