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Consulting physician		Patient		Sample	
Provider	General Hospital	Name	Michelle Doe	Accession Number	D19-03598_S3
Physician	Dr. E Smith	Age	54	Collection site	Bone Marrow
Pathologist	Dr. R Jones	Gender	Female	Type	Biopsy
Report Date	Sep 1, 2020	Diagnosis	Acute myeloid leukemia	Collection date	Sep 1, 2020

Panel Analysis: Hematological Cancer

Comprehensive genomic next generation sequencing test that targets variants in key genes known to be involved in myeloid malignancies such as AML, MDS, MPN, CML, CMML, and JMML.

Overall comment

Patient specific comment

NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis [PMID:16076867, PMID:18450602, PMID: 16455956, PMID:27288520, PMID:27055875].

Analysis results: Positive

2 Variants of strong clinical significance, Tier 1	Approved treatments	Other findings
FLT3: p.Y597_E598insDYVDFREY, Pathogenic	Midostaurin	Trials: 1 Expanded Access 2 Phase 3 2 Phase 2 1 Phase 1/Phase 2
NPM1: p.W288fs*?, Pathogenic	-	Trials: 1 Phase 2
2 Variants of potential clinical significance, Tier 2	**Approved treatments**	**Other findings**
RAD21 †: p.L183fs*7, Likely Pathogenic	-	-
WT1: p.A387fs*4, Pathogenic	-	-
	3 Variants of uncertain significance, Tier 3	

† Allele Fraction (AF) >40%. AF suggests that it may be germline and pathogenic or likely pathogenic. Recommend obtaining confirmatory germline testing.

Interactions

Clinically relevant co-occurring variants are reported in the "interactions" section starting on page 2.

Guidelines

Potentially relevant guidelines are reported in the "guidelines" section starting on page 2.

Approval

Electronically signed on: Sep 1, 2020 by Dr. Jones, Lab Director

Report content

GUIDELINES

The 2017 ELN recommendations for AML note that screening for mutations in NPM1, CEBPA, RUNX1, FLT3 (for ITD and TKD alterations as well as mutant-to-wild-type ratio), TP53, and ASXL1 may be useful for diagnosis, risk assessment, prognostication, and treatment [31]. The 2017 ELN recommendations place AML patients with wild-type NPM1 plus a high allelic ratio of FLT3-ITD (greater than or equal to 0.5) in the adverse risk category, while patients with mutated NPM1 plus a high allelic ratio of FLT3-ITD, as well as patients with wild-type NPM1 plus a low allelic ratio of FLT3-ITD (less than 0.5), are placed in the intermediate risk category.; AML patients with mutated NPM1 and a low allelic ratio of FLT3 are placed in the favorable risk category [31]. These guidelines additionally state that midostaurin plus standard chemotherapy may be considered for both induction and consolidation therapy in AML patients aged 18-60 years with an activating FLT3 mutation [31].

INTERACTIONS

NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis [112, 110, 124, 83, 130].

TREATMENT OPTIONS

Therapies with potential clinical benefit (1)

MIDOSTAURIN

Midostaurin, a kinase inhibitor, is FDA- and EMA-approved for treating adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL); midostaurin is FDA-approved for treating adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive, as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation (midostaurin is not indicated as a single-agent induction therapy for the treatment of patients with AML); midostaurin is EMA-approved for treating adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy.

Sensitive

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA

AVAILABLE CLINICAL TRIALS

Expanded Access clinical trials (1)

CRENOLANIB

Compassionate Use of Crenolanib for Cancers With Platelet Derived Growth Factor Receptor Alpha (PDGFRa) Mutations, PDGFRa Amplifications or Fms-like Tyrosine Kinase 3 (FLT3) Mutations
NCT03620318

Qualifying variant			Contact
Gene	Classification	Variant	Vinay Jain, MD; info@arogpharma.com; 214-593-0500;
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	

Phase 3 clinical trials (2)

GILTERITINIB, MIDOSTAURIN

A Phase 3, Multicenter, Open-label, Randomized, Study of Gilteritinib Versus Midostaurin in Combination With Induction and Consolidation Therapy Followed by One-year Maintenance in Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) or Myelodysplastic Syndromes With Excess Blasts-2 (MDS-EB2) With FLT3 Mutations Eligible for Intensive Chemotherapy (HOVON 156 AML / AMLSG 28-18)
NCT04027309

Qualifying variant			Contact
Gene	Classification	Variant	M. Raaijmakers, Prof. Dr.; hdc@erasmusmc.nl; +31 (0)10 7041560;
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c.1770_1793dupCTACGTTGATTTCAGAGAATATGA	

IDARUBICIN, CRENOLANIB, CYTARABINE, FLUDARABINE PHOSPHATE, MITOXANTRONE

Phase III Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy of the Addition of Crenolanib to Salvage Chemotherapy Versus Salvage Chemotherapy Alone in Subjects ≤ 75 Years of Age With Relapsed/Refractory FLT3 Mutated Acute Myeloid Leukemia
NCT03250338

Qualifying variant			Contact
Gene	Classification	Variant	United States: CA, FL, IL, KS, MI, NC, NY General Contact; info@arogpharma.com; 214-593-0500;

Phase 3 clinical trials (2)

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c. 1770_1793dupCTACGTTGATTTC AGAGAATATGA

Phase 2 clinical trials (3)

PONATINIB

Phase 2 Study of Ponatinib (Iclusig) for Prevention of Relapse After Allogeneic Stem Cell Transplantation (Allo-SCT) in FLT3-ITD AML Patients: the PONALLO Trial."
NCT03690115

Qualifying variant

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c. 1770_1793dupCTACGTTGATTTC AGAGAATATGA

Contact
Laure MORISSET; lmorisset@ch-versailles.fr;
+33139239785;

DECITABINE, MIDOSTAURIN

A Randomized Phase II Multicenter Study to Assess the Tolerability and Efficacy of the Addition of Midostaurin to 10-day Decitabine Treatment in Unfit Adult Acute Myeloid Leukemia and High Risk Myelodysplasia Patients
NCT04097470

Qualifying variant

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c. 1770_1793dupCTACGTTGATTTC AGAGAATATGA

Contact
Gerwin Huls, Prof.; g.huls@umcg.nl;
+31503612354;

PEMBROLIZUMAB, 5-AZACYTIDINE

MRD-guided Treatment With Pembrolizumab and Azacitidine in NPM1mut AML Patients With an Imminent Hematological Relapse
NCT03769532

Qualifying variant

Gene	Classification	Variant
NPM1	Tier 1A Pathogenic	p.W288fs*? c.860_863dupTCTG

Contact
Uwe Platzbecker, MD; Uwe.Platzbecker@medizin.uni-leipzig.de;
+49 351 458 x2722;

Phase 1/Phase 2 clinical trials (1)

NMS-03592088

A Phase I/II Study of NMS-03592088, a FLT3, KIT and CSF1R Inhibitor, in Patients With Relapsed or Refractory AML or CMML
NCT03922100

Qualifying variant

Gene	Classification	Variant
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c. 1770_1793dupCTACGTTGATTTC AGAGAATATGA

Contact
Frank Gan; frank.gan@nervianoms.com;
+39.334.6513171;

VARIANT DETAILS

Variants of strong clinical significance (2)

FLT3 Y597_E598insDYVDFREY

Gene: FLT3
Exon: 14
Nucleotide:
NM_004119.2:
g.28608262_2860826
3insTCATATTCTCTGA
AATCAACGTAG
c.1770_1793dupCTAC
GTTGATTTCAGAGAATA

Biomarker summary: FLT3-Y597_E598insDYVDFREY is predicted to be an activating mutation.

Clinical relevance: Activating FLT3 alterations have been reported to promote proliferation, inhibit apoptosis, and result in oncogenic transformation [48, 72, 140, 71, 84]. Activating alterations in FLT3 may predict sensitivity to small molecule multi-tyrosine kinase inhibitors, several of which have been approved by numerous agencies for certain indications [109, 105, 151, 78]. Midostaurin has been approved by the EMA for FLT3-positive acute myelocytic leukemia patients [118]. Additional second-generation inhibitors with greater specificity for Flt3 are also in clinical development [135, 25, 43].

Variants of strong clinical significance (2)

TGA
Amino Acid: p.Y597_E598insDYVDFREY
Allelic Fraction: 31.0% (of 13551 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Sensitive
6 Trials

Disease summary: Constitutive activation of Flt3 by internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutations has been reported to result in the activation of several signaling pathways, including those of Akt and Stat5, and has been reported to promote proliferation, survival, and transformation of myeloid cells [20, 60, 10, 96, 61, 76]. FLT3 mutations have been associated with elevated white blood cell and bone marrow blast counts in studies of acute myelocytic leukemia (AML), and have been reported most commonly in patients with normal cytogenetics [117, 42, 65, 6]. FLT3-ITD mutations in normal karyotype AML have been associated with poor prognosis in numerous scientific studies [98, 117, 134, 42, 65, 69]. However, recent studies have suggested that AML patients with a low allelic ratio of FLT3-ITD (generally defined as a mutant-to-wild-type ratio of lower than 0.5 as determined by quantitative DNA fragment length analysis) and concurrent NPM1 mutations have a favorable prognosis; patients with wild-type NPM1 and a low allelic ratio of FLT3-ITD or mutant NPM1 and a high allelic ratio of FLT3-ITD (greater than or equal to 0.5) have an intermediate prognosis; and patients with wild-type NPM1 and a high allelic ratio of FLT3-ITD have a poor prognosis [31, 49, 101, 132, 115].

Molecular function: The FLT3 alteration reported here results in the insertion of a single amino acid followed by the tandem duplication of seven amino acids within exon 14, corresponding to the juxtamembrane domain of the Flt3 protein (Integrative Genomics Viewer, v.2.3). FLT3-ITD alterations similar to the one reported here have been found to result in ligand-independent dimerization, constitutive Flt3 kinase activity, activation of downstream signaling pathways, and oncogenic transformation [82, 20, 61, 62, 60]. Therefore, although this alteration has not been functionally characterized, is predicted to be activating.

Incidence: FLT3 mutations have been reported in 23% (16351/70387) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). FLT3 mutations have been reported in 6.7-30% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). FLT3 mutations have been reported as the most common alteration in AML, with FLT3 internal tandem duplication (FLT3-ITD) and tyrosine kinase domain (FLT3-TKD) mutations cited in 12-35% and 4-10% of cases, respectively, and found to occur more frequently in AML with a normal karyotype [17, 35, 146, 80, 94, 108, 58, 85, 125, 6, 7, 61, 29].

NPM1 W288fs*?

Gene: NPM1
Exon: 11
Nucleotide: NM_002520.6: g.170837543_170837544insTCTG c.860_863dupTCTG
Amino Acid: p.W288fs*?
Allelic Fraction: 40.0% (of 3453 reads)
Classification: Tier 1A
Assessment: Pathogenic

Treatment options
1 Trial

Biomarker summary: NPM1-W288fs exhibits altered function compared to wild-type.

Clinical relevance: NPM1 encodes nucleophosmin (Npm1), a multifunctional protein that regulates the ARF /p53 pathway and enhances Myc oncogenic activities [45, 75, 59, 77]. NPM1 mutations, particularly C-terminal truncations, have been reported frequently in myeloid malignancies, and although mutation has not been commonly found in solid tumors, overexpression of the Npm1 protein has been reported [41, 124, 40, 59, 95, 57]. There are currently no therapeutic approaches targeting alterations in NPM1 or changes in Npm1 protein expression.

Disease summary: NPM1 mutation in AML has been shown to result in the aberrant cytoplasmic localization of Npm1, in contrast to its normal nucleolar localization, and has been reported to play a role in the development of AML through the mislocalization and inhibition of Npm1 binding partners, including the tumor suppressor ARF [37, 38, 150, 24, 40]. NPM1 mutations in AML have been associated with M4 and M5 morphology, increased leukocyte and bone marrow blast counts, female sex, and decreased expression of CD34; NPM1 mutations have been reported more frequently in cytogenetically normal AML (CN-AML) and often occur in combination with FLT3, IDH1/2, NRAS, and DNMT3A mutations [32, 112, 124, 131, 93, 91, 107]. AML with mutant NPM1 is recognized as a subtype of AML with recurrent genetic abnormalities in the WHO classification of myeloid neoplasms and acute leukemia [3]. NPM1 mutations in the absence of FLT3-ITD have been associated with favorable outcomes in AML, especially in cytogenetically normal AML (CN-AML), while NPM1 mutations in the presence of FLT3-ITD have been associated with an intermediate prognosis [112, 110, 124, 83, 130]. Additionally, monitoring of mutant NPM1 transcript levels has been reported to be useful in the detection of minimal residual disease (MRD) and prediction of disease relapse [111, 68, 113, 53, 56].

Molecular function: NPM1 W288fs is expected to effectively truncate the Npm1 protein at amino acid 288 of 294 (UniProt). This truncation results in the loss of two tryptophan residues, W288 and W290, that are critical for nucleolar localization of Npm1 [88, 39]. In addition, the resulting protein would also lack a lysine residue at position 292, one of six lysines that undergo acetylation, which enhances the interaction of Npm1 with acetylated histones and is required for the enhancement of chromatin transcription [121]. Several C-terminal NPM1 W288 truncating and frameshift alterations have been reported to result in mislocalization of Npm1, as well as a gain in oncogenic function through deregulation of downstream pathways [24, 39, 40, 19, 103, 38]. The most common NPM1 W288fs alteration, type A, is the result of the insertion/duplication of a TCGT tetranucleotide, but many similar alterations resulting in W288fs have been reported [2, 5]. Therefore, although this alteration results in loss of the nucleolar localization domain, it is predicted to be associated with promotion of tumorigenesis.

Incidence: NPM1 mutations have been reported in 31% (6308/20330) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). NPM1 mutations have been reported in 0.7-27% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). NPM1 mutations, predominately resulting in C-terminal truncations, have been reported in 14-35% of AML samples and in 46-53% of cytogenetically normal AML (CN-AML) samples analyzed in scientific studies [100, 145, 8, 16, 124, 110, 32, 112, 131, 93]. In addition, one study analyzing the TAGET dataset has reported NPM1 mutations in 7.6% (66/869) of pediatric AML cases [138].

Variants of potential clinical significance (2)

RAD21 L183fs*7

Gene: RAD21
Exon: 6
Nucleotide: NM_006265.2: g.117869645_117869646delTA c.548_549delTA
Amino Acid: p.L183fs*7
Allelic Fraction: 44.0% (of 6364 reads)
Classification: Tier 2C
Assessment: Likely Pathogenic

Biomarker summary: RAD21-L183fs*7 is an inactivating mutation.

Clinical relevance: RAD21 encodes the Rad21 protein, a key component of the cohesin complex which maintains fidelity in chromosome segregation [64, 139, 12, 13]. At present, there are no therapies that directly address loss of Rad21 activity; however, inactivation of Rad21 and other cohesin complex components has been associated with enhanced sensitivity to PARP inhibitors in preclinical models [81, 9]. Although Rad21 has been implicated as a tumor suppressor in some contexts, it has also been described as activated or essential for cell proliferation and survival in various cancer cell line lineages [79, 4, 28, 147, 141]. Therefore, the potential relevance of any targeted therapies must be carefully considered in each situation.

Disease summary: RAD21 mutations have been reported in 3.3% (165/4946) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). RAD21 mutations have been reported in 0.7-3.0% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). Literature studies have reported RAD21 mutations in 2-17% of AML samples [127, 126, 30]. The role of RAD21 in AML has not been a significant subject of study reported in the scientific literature (PubMed, May 2019).

Molecular function: The RAD21 frameshift alteration reported here is expected to effectively truncate the 631-amino acid Rad21 protein prior to or within the C-terminal Smc1-binding domain (UniProt, Interpro) [137, 27]. The interaction between Rad21 and Smc1 is required for the formation of the cohesin complex [128, 15]. In addition, one study has reported RAD21 truncation alterations (including I621fs) in myeloid malignancies and that the alterations correlated with low RAD21 expression [127]. Therefore, this alteration is predicted to be inactivating.

Incidence: RAD21 mutations have been reported in 3.3% (165/4946) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). RAD21 mutations have been reported in 0.7-3.0% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). Literature studies have reported RAD21 mutations in 2-17% of AML samples [127, 126, 30].

WT1 A387fs*4

Gene: WT1
Exon: 7
Nucleotide: NM_024426.6: g.32417907_32417908insCCGA c.1156_1159dupTCGG
Amino Acid: p.A387fs*4
Allelic Fraction: 20.0% (of 13717 reads)
Classification: Tier 2C
Assessment: Pathogenic

Biomarker summary: WT1-A387fs*4 is an inactivating mutation.

Clinical relevance: WT1 encodes the Wilms tumor 1 protein (Wt1). Wt1 has been reported to have both tumor suppressive and tumorigenic properties [54, 119]. There are no approved targeted therapies for WT1 mutations or expression. Wt1 vaccines are in clinical trials for Wt1-expressing hematologic and solid tumor cancers, including renal cell carcinoma, biliary tract cancers, and non-small cell lung cancer [119, 89, 123, 122]. In the case of an inactivating alteration, as reported here, Wt1 vaccines are not expected to be relevant.

Disease summary: In studies of AML, both overexpression of WT1 mRNA and inactivating mutations of WT1 have been reported [102]. WT1 mRNA transcript levels have been reported to be elevated in the blood and bone marrow of leukemia patients and have been reported to serve in minimal residual disease monitoring [46, 104, 70, 97, 67]. WT1 mRNA expression has been positively associated with relapse and poor overall survival in several studies of AML [148, 46, 44, 114, 99, 144, 52, 87, 142]. WT1 mutations, predominately resulting in protein truncation, have been associated with younger patient age, cytogenetically normal (CN) AML, and the presence of FLT3 internal tandem duplication (ITD) mutations [18, 106, 52, 51, 14]. WT1 mutations have also been associated with reduced relapse-free, event-free, and overall survival in studies of AML, particularly in CN-AML patients [55, 106, 133, 52, 92, 51, 66, 33].

Molecular function: The WT1 frameshift alteration reported here is expected to effectively truncate the Wt1 protein before or within the zinc finger region, resulting in disruption of this region (UniProt). The zinc finger domains of Wt1 have been reported to be necessary for DNA binding and proper nuclear localization of the protein [21, 47, 36, 11]. Therefore, this alteration is expected to be inactivating.

Incidence: WT1 mutations have been reported in 7.8% (525/6762) of Acute myelocytic leukemia (AML) samples analyzed in COSMIC (May 2020). WT1 mutations have been reported in 3.3-6.5% of Acute myelocytic leukemia (AML) samples (cBioPortal for Cancer Genomics, May 2020). WT1 mutations, predominately resulting in protein truncation, have been reported in 4-7% of AML cases overall, with higher frequency of 7-13% observed in cytogenetically normal AML (CN-AML) and in pediatric AML cases [50, 18, 148, 34, 1, 66, 133, 52, 149, 129].

Variants of uncertain significance (3)

Gene	Variant	Allelic fraction	Classification
BCORL1	c.1123G>C p.A375P	13.0% (of 2140 reads)	Tier 3, Uncertain Significance
BCORL1	c.3073G>A p.V1025M	44.0% (of 5452 reads)	Tier 3, Uncertain Significance
STAG2	c.1580G>T p.C527F	20.0% (of 825 reads)	Tier 3, Uncertain Significance

REPORT INFORMATION

Genes tested (54)

ABL1, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CBLB, CBLC, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, HRAS, IDH1, IDH2, IKZF1, JAK2, JAK3, KDM6A, KIT, KRAS, MPL, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PHF6, PTEN, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2, ETV6, KMT2A

Methods and limitations

EXAMPLE Statement including sample type (FFPE, etc), method of extraction, amplification reactions, panel targeted regions, sequencing technology, etc. Additionally, a description of the data analysis software(s), genome of reference and the sensitivity of the methods should be described.

QIAGEN Clinical Insight (QCI™) is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (6.0.20200609), Ingenuity Knowledge Base (X-release), CADD (v1.4), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2019-10-01), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2020-08-19 13:28:30.0), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (X-release), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (May 11 16:21 iva-1.0.1458.jar), PhyloP hg18 (2009-11), PhyloP hg19 (2009-11), DbSNP (151), TargetScan (7.2), GENCODE (Release 31), CentoMD (5.3), OMIM (May 26, 2017), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2019-11-06), DGV (2016-05-15), COSMIC (v89), HGMD (2020.2), OncoTree (oncotree_2019_03_01), SIFT4G (2016-02-23)

Clinical significance of variants based on AMP / ASCO / CAP guidelines*

Strong clinical significance	Tier 1A	Biomarker predicts response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines for this diagnosis Biomarker included in professional guidelines is prognostic or diagnostic for this diagnosis
	Tier 1B	Biomarker predicts response or resistance to a therapy for this diagnosis based on well-powered studies Biomarker is prognostic or diagnostic for this diagnosis based on well-powered studies
Potential clinical significance	Tier 2C	Biomarker is associated with response or resistance to an FDA or EMA approved therapy, according to drug label or professional guidelines but only for different diagnosis Biomarker is an inclusion criterion for an active clinical trial Biomarker is prognostic or diagnostic based on multiple small studies
	Tier 2D	Biomarker shows plausible response or resistance based on case or preclinical studies Biomarker may assist in disease diagnosis or prognosis based on small studies
Uncertain clinical significance	Tier 3	Biomarker has uncertain clinical significance and not known to be likely benign or benign

*Adapted from PMID:27993330 jmd.amjpathol.org/article/S1525-1578(16)30223-9/pdf

SELECTED REFERENCES

1. Ahmad F, D'Souza W, Mandava S, Das BR (2011) Molecular analysis of WT1 and KIT mutations in patients from an Indian population with de novo acute myeloid leukemia: determination of incidence, distribution patterns, and report of a novel KIT mutation. Leuk Lymphoma. 2011 May;52(5):865-76 (PMID: 21504297)
2. Alpermann T, Schnittger S, Eder C, Dicker F, Meggendorfer M, Kern W, Schmid C, Aul C, Staib P, Wendtner CM, Schmitz N, Haferlach C, Haferlach T (2015) Molecular subtypes of NPM1 mutations have different clinical profiles, specific patterns of accompanying molecular mutations and varying outcomes in intermediate risk acute myeloid leukemia. Haematologica. 2016 Feb;101(2):e55-8. Epub 2015 Oct 15 (PMID: 26471486)
3. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. Epub 2016 Apr 11 (PMID: 27069254)
4. Atienza JM, Roth RB, Rosette C, Smylie KJ, Kammerer S, Rehbock J, Ekblom J, Denissenko MF (2005) Suppression of RAD21 gene expression decreases cell growth and enhances cytotoxicity of etoposide and bleomycin in human breast cancer cells. Mol Cancer Ther. 2005 Mar;4(3):361-8 (PMID: 15767545)
5. Bacher U, Dicker F, Haferlach C, Alpermann T, Rose D, Kern W, Haferlach T, Schnittger S (2014) Quantification of rare NPM1 mutation subtypes by digital PCR. Br J Haematol. 2014 Dec;167(5):710-4. Epub 2014 Jul 18 (PMID: 25039748)
6. Bacher U, Haferlach C, Kern W, Haferlach T, Schnittger S (2007) Prognostic relevance of FLT3-TKD mutations in AML: the combination matters--an analysis of 3082 patients. Blood. 2008 Mar 01;111(5):2527-37. Epub 2007 Oct 26 (PMID: 17965322)
7. Bacher U, Kern W, Schnittger S, Hiddemann W, Haferlach T, Schoch C (2005) Population-based age-specific incidences of cytogenetic subgroups of acute myeloid leukemia. Haematologica 2005 Nov;90(11):1502-10 (PMID: 16266897)

8. Baek DW, Lee JM, Kim JH, Cho HJ, Ham JY, Suh JS, Sohn SK, Moon JH (2019) Favorable long-term survival using consolidation chemotherapy without allogeneic hematopoietic cell transplantation for acute myeloid leukemia with wild-type *NPM1* without *FLT3*-ITD. Blood Res 2019 Sep;54(3): 189-197 (PMID: 31730679)

9. Bailey ML, O'Neil NJ, van Pel DM, Solomon DA, Waldman T, Hieter P (2014) Glioblastoma cells containing mutations in the cohesin component STAG2 are sensitive to PARP inhibition. Mol Cancer Ther 2014 Mar;13(3):724-32 (PMID: 24356817)

10. Baldwin BR, Li L, Tse KF, Small S, Collector M, Whartenby KA, Sharkis SJ, Racke F, Huso D, Small D (2007) Transgenic mice expressing Tel-FLT3, a constitutively activated form of FLT3, develop myeloproliferative disease. Leukemia. 2007 Apr;21(4):764-71. Epub 2007 Feb 1 (PMID: 17268528)

11. Bardeesy N, Pelletier J (1998) Overlapping RNA and DNA binding domains of the wt1 tumor suppressor gene product. Nucleic Acids Res. 1998 Apr 01;26(7):1784-92 (PMID: 9512553)

12. Bauerschmidt C, Arrichiello C, Burdak-Rothkamm S, Woodcock M, Hill MA, Stevens DL, Rothkamm K (2009) Cohesin promotes the repair of ionizing radiation-induced DNA double-strand breaks in replicated chromatin. Nucleic Acids Res. 2010 Jan;38(2):477-87. Epub 2009 Nov 11 (PMID: 19906707)

13. Beauchene NA, Díaz-Martínez LA, Furniss K, Hsu WS, Tsai HJ, Chamberlain C, Esponda P, Giménez-Abián JF, Clarke DJ (2010) Rad21 is required for centrosome integrity in human cells independently of its role in chromosome cohesion. Cell Cycle. 2010 May;9(9):1774-80. Epub 2010 May 15 (PMID: 20404533)

14. Becker H, Marcucci G, Maharry K, Radmacher MD, Mrózek K, Margeson D, Whitman SP, Paschka P, Holland KB, Schwind S, Wu YZ, Powell BL, Carter TH, Kolitz JE, Wetzler M, Carroll AJ, Baer MR, Moore JO, Caligiuri MA, Larson RA, Bloomfield CD (2010) Mutations of the Wilms tumor 1 gene (WT1) in older patients with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. Blood. 2010 Aug 05;116(5):788-92. Epub 2010 May 4 (PMID: 20442368)

15. Bernard P, Drogat J, Maure JF, Dheur S, Vaur S, Genier S, Javerzat JP (2006) A screen for cohesion mutants uncovers Ssl3, the fission yeast counterpart of the cohesin loading factor Scc4. Curr Biol 2006 May 9;16(9):875-81 (PMID: 16682348)

16. Bezerra MF, Lima AS, Piqué-Borràs MR, Silveira DR, Coelho-Silva JL, Pereira-Martins DA, Weinhäuser I, Franca-Neto PL, Quek L, Corby A, Oliveira MM, Lima MM, de Assis RA, de Melo Campos P, Duarte BK, Bendit I, Rocha V, Rego EM, Traina F, Saad ST, Beltrão EI, Bezerra MA, Lucena-Araujo AR (2020) Co-occurrence of DNMT3A, NPM1, FLT3 mutations identifies a subset of acute myeloid leukemia with adverse prognosis. Blood 2020 Mar 12;135(11):870-875 (PMID: 31977039)

17. Bhattacharyya J, Nath S, Saikia KK, Saxena R, Sazawal S, Barman MP, Kumar D (2017) Prevalence and Clinical Significance of FLT3 and NPM1 Mutations in Acute Myeloid Leukaemia Patients of Assam, India. Indian J Hematol Blood Transfus. 2018 Jan;34(1):32-42. Epub 2017 Apr 28 (PMID: 29398797)

18. Bolouri H, Farrar JE, Triche T, Ries RE, Lim EL, Alonzo TA, Ma Y, Moore R, Mungall AJ, Marra MA, Zhang J, Ma X, Liu Y, Liu Y, Auvil JMG, Davidsen TM, Gesuwan P, Hermida LC, Salhia B, Capone S, Ramsingh G, Zwaan CM, Noort S, Piccolo SR, Kolb EA, Gamis AS, Smith MA, Gerhard DS, Meshinchi S (2017) The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. Nat Med. 2018 Jan;24(1):103-112. Epub 2017 Dec 11 (PMID: 29227476)

19. Bonetti P, Davoli T, Sironi C, Amati B, Pelicci PG, Colombo E (2008) Nucleophosmin and its AML-associated mutant regulate c-Myc turnover through Fbw7 gamma. J Cell Biol. 2008 Jul 14;182(1):19-26 (PMID: 18625840)

20. Brandts CH, Sargin B, Rode M, Biermann C, Lindtner B, Schwäble J, Buerger H, Müller-Tidow C, Choudhary C, McMahon M, Berdel WE, Serve H (2005) Constitutive activation of Akt by Flt3 internal tandem duplications is necessary for increased survival, proliferation, and myeloid transformation. Cancer Res. 2005 Nov 01;65(21):9643-50 (PMID: 16266983)

21. Bruening W, Moffett P, Chia S, Heinrich G, Pelletier J (1996) Identification of nuclear localization signals within the zinc fingers of the WT1 tumor suppressor gene product. FEBS Lett. 1996 Sep 09;393(1):41-7 (PMID: 8804420)

22. Canudas S, Smith S (2009) Differential regulation of telomere and centromere cohesion by the Scc3 homologues SA1 and SA2, respectively, in human cells. J Cell Biol. 2009 Oct 19;187(2):165-73. Epub 2009 Oct 12 (PMID: 19822671)

23. Carramolino L, Lee BC, Zaballos A, Peled A, Barthelemy I, Shav-Tal Y, Prieto I, Carmi P, Gothelf Y, González de Buitrago G, Aracil M, Márquez G, Barbero JL, Zipori D (1997) SA-1, a nuclear protein encoded by one member of a novel gene family: molecular cloning and detection in hemopoietic organs. Gene. 1997 Aug 22;195(2):151-9 (PMID: 9305759)

24. Colombo E, Martinelli P, Zamponi R, Shing DC, Bonetti P, Luzi L, Volorio S, Bernard L, Pruneri G, Alcalay M, Pelicci PG (2006) Delocalization and destabilization of the Arf tumor suppressor by the leukemia-associated NPM mutant. Cancer Res 2006 Mar 15;66(6):3044-50 (PMID: 16540653)

25. Cortes JE, Kantarjian H, Foran JM, Ghirdaladze D, Zodelava M, Borthakur G, Gammon G, Trone D, Armstrong RC, James J, Levis M (2013) Phase I study of quizartinib administered daily to patients with relapsed or refractory acute myeloid leukemia irrespective of FMS-like tyrosine kinase 3-internal tandem duplication status. J Clin Oncol 2013 Oct 10;31(29):3681-7 (PMID: 24002496)

26. Damm F, Chesnais V, Nagata Y, Yoshida K, Scourzic L, Okuno Y, Itzykson R, Sanada M, Shiraishi Y, Gelsi-Boyer V, Renneville A, Miyano S, Mori H, Shih LY, Park S, Dreyfus F, Guerci-Bresler A, Solary E, Rose C, Cheze S, Prébet T, Vey N, Legentil M, Duffourd Y, de Botton S, Preudhomme C, Birnbaum D, Bernard OA, Ogawa S, Fontenay M, Kosmider O (2013) BCOR and BCORL1 mutations in myelodysplastic syndromes and related disorders. Blood. 2013 Oct 31;122(18):3169-77. Epub 2013 Sep 18 (PMID: 24047651)

27. Deardorff MA, Wilde JJ, Albrecht M, Dickinson E, Tennstedt S, Braunholz D, Mönnich M, Yan Y, Xu W, Gil-Rodríguez MC, Clark D, Hakonarson H, Halbach S, Michelis LD, Rampuria A, Rossier E, Spranger S, Van Maldergem L, Lynch SA, Gillessen-Kaesbach G, Lüdecke HJ, Ramsay RG, McKay MJ, Krantz ID, Xu H, Horsfield JA, Kaiser FJ (2012) RAD21 mutations cause a human cohesinopathy. Am J Hum Genet. 2012 Jun 08;90(6):1014-27. Epub 2012 May 24 (PMID: 22633399)

28. Deb S, Xu H, Tuynman J, George J, Yan Y, Li J, Ward RL, Mortensen N, Hawkins NJ, McKay MJ, Ramsay RG, Fox SB (2014) RAD21 cohesin overexpression is a prognostic and predictive marker exacerbating poor prognosis in KRAS mutant colorectal carcinomas. Br J Cancer. 2014 Mar 18; 110(6):1606-13. Epub 2014 Feb 18 (PMID: 24548858)

29. Deol A, Sengsayadeth S, Ahn KW, Wang HL, Aljurf M, Antin JH, Battiwalla M, Bornhauser M, Cahn JY, Camitta B, Chen YB, Cutler CS, Gale RP, Ganguly S, Hamadani M, Inamoto Y, Jagasia M, Kamble R, Koreth J, Lazarus HM, Liesveld J, Litzow MR, Marks DI, Nishihori T, Olsson RF, Reshef R, Rowe JM, Saad AA, Sabloff M, Schouten HC, Shea TC, Soiffer RJ, Uy GL, Waller EK, Wiernik PH, Wirk B, Woolfrey AE, Bunjes D, Devine S, de Lima M, Sandmaier BM, Weisdorf D, Khoury HJ, Saber W (2016) Does FLT3 mutation impact survival after hematopoietic stem cell transplantation for acute myeloid leukemia? A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis. Cancer 2016 Oct;122(19):3005-3014 (PMID: 27315441)

30. Dolnik A, Engelmann JC, Scharfenberger-Schmeer M, Mauch J, Kelkenberg-Schade S, Haldemann B, Fries T, Krönke J, Kühn MW, Paschka P, Kayser S, Wolf S, Gaidzik VI, Schlenk RF, Rücker FG, Döhner H, Lottaz C, Döhner K, Bullinger L (2012) Commonly altered genomic regions in acute myeloid leukemia are enriched for somatic mutations involved in chromatin remodeling and splicing. Blood. 2012 Nov 01;120(18):e83-92. Epub 2012 Sep 13 (PMID: 22976956)

31. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD (2016) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-447. Epub 2016 Nov 28 (PMID: 27895058)

32. Döhner K, Schlenk RF, Habdank M, Scholl C, Rücker FG, Corbacioglu A, Bullinger L, Fröhling S, Döhner H (2005) Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. Blood. 2005 Dec 01;106(12):3740-6. Epub 2005 Jul 28 (PMID: 16051734)

33. Eisfeld AK, Kohlschmidt J, Mims A, Nicolet D, Walker CJ, Blachly JS, Carroll AJ, Papaioannou D, Kolitz JE, Powell BE, Stone RM, de la Chapelle A, Byrd JC, Mrózek K, Bloomfield CD (2020) Additional gene mutations may refine the 2017 European LeukemiaNet classification in adult patients with de novo acute myeloid leukemia aged<60 years. Leukemia 2020 May 27; (PMID: 32461631)

34. Eisfeld AK, Kohlschmidt J, Mrózek K, Blachly JS, Walker CJ, Nicolet D, Orwick S, Maharry SE, Carroll AJ, Stone RM, de la Chapelle A, Wang ES, Kolitz JE, Powell BL, Byrd JC, Bloomfield CD (2018) Mutation patterns identify adult patients with de novo acute myeloid leukemia aged 60 years or older who respond favorably to standard chemotherapy: an analysis of Alliance studies. Leukemia 2018 Jun;32(6):1338-1348 (PMID: 29563537)

35. El Gammal MM, Ebid GT, Madney YM, Abo-Elazm OM, Kelany AK, Torra OS, Radich JP (2019) Clinical Effect of Combined Mutations in DNMT3A, FLT3-ITD, and NPM1 Among Egyptian Acute Myeloid Leukemia Patients. Clin Lymphoma Myeloma Leuk. 2019 Jun;19(6):e281-e290. Epub 2019 Feb 14 (PMID: 30926392)

36. Englert C, Vidal M, Maheswaran S, Ge Y, Ezzell RM, Isselbacher KJ, Haber DA (1995) Truncated WT1 mutants alter the subnuclear localization of the wild-type protein. Proc Natl Acad Sci U S A. 1995 Dec 19;92(26):11960-4 (PMID: 8618823)

37. Falini B, Bolli N, Shan J, Martelli MP, Liso A, Pucciarini A, Bigerna B, Pasqualucci L, Mannucci R, Rosati R, Gorello P, Diverio D, Roti G, Tiacci E, Cazzaniga G, Biondi A, Schnittger S, Haferlach T, Hiddemann W, Martelli MF, Gu W, Mecucci C, Nicoletti I (2006) Both carboxy-terminus NES motif and mutated tryptophan(s) are crucial for aberrant nuclear export of nucleophosmin leukemic mutants in NPMc+ AML. Blood. 2006 Jun 01;107(11):4514-23. Epub 2006 Feb 2 (PMID: 16455950)

38. Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, La Starza R, Diverio D, Colombo E, Santucci A, Bigerna B, Pacini R, Pucciarini A, Liso A, Vignetti M, Fazi P, Meani N, Pettirossi V, Saglio G, Mandelli F, Lo-Coco F, Pelicci PG, Martelli MF, GIMEMA Acute Leukemia Working Party (2005) Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med. 2005 Jan 20;352(3):254-66 (PMID: 15659725)

39. Falini B, Nicoletti I, Bolli N, Martelli MP, Liso A, Gorello P, Mandelli F, Mecucci C, Martelli MF (2007) Translocations and mutations involving the nucleophosmin (NPM1) gene in lymphomas and leukemias. Haematologica 2007 Apr;92(4):519-32 (PMID: 17488663)

40. Falini B, Nicoletti I, Martelli MF, Mecucci C (2006) Acute myeloid leukemia carrying cytoplasmic/mutated nucleophosmin (NPMc+ AML): biologic and clinical features. Blood. 2007 Feb 01;109(3):874-85. Epub 2006 Sep 28 (PMID: 17008539)

41. Federici L, Falini B (2013) Nucleophosmin mutations in acute myeloid leukemia: a tale of protein unfolding and mislocalization. Protein Sci. 2013 May;22(5):545-56. Epub 2013 Mar 18 (PMID: 23436734)

42. Fröhling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, Döhner H, Döhner K, AML Study Group Ulm. Acute myeloid leukemia (2002) Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood. 2002 Dec 15;100(13):4372-80. Epub 2002 Aug 8 (PMID: 12393388)

43. Galanis A, Ma H, Rajkhowa T, Ramachandran A, Small D, Cortes J, Levis M (2013) Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. Blood. 2014 Jan 02;123(1):94-100. Epub 2013 Nov 13 (PMID: 24227820)

44. Gianfaldoni G, Mannelli F, Ponziani V, Longo G, Bencini S, Bosi A, Vannucchi AM (2010) Early reduction of WT1 transcripts during induction chemotherapy predicts for longer disease free and overall survival in acute myeloid leukemia. Haematologica 2010 May;95(5):833-6 (PMID: 20107153)

45. Grisendi S, Mecucci C, Falini B, Pandolfi PP (2006) Nucleophosmin and cancer. Nat Rev Cancer 2006 Jul;6(7):493-505 (PMID: 16794633)

46. Hao Y, Cheng Y, Wu Q, Zhang A, Jiang X, Xu X (2018) Combined usage of Wilms' tumor gene quantitative analysis and multiparameter flow cytometry for minimal residual disease monitoring of acute myeloid leukemia patients after allogeneic hematopoietic stem cells transplantation. Exp Ther Med 2018 Feb;15(2):1403-1409 (PMID: 29434724)

47. Hashimoto H, Olanrewaju YO, Zheng Y, Wilson GG, Zhang X, Cheng X (2014) Wilms tumor protein recognizes 5-carboxylcytosine within a specific DNA sequence. Genes Dev. 2014 Oct 15;28(20):2304-13. Epub 2014 Sep 25 (PMID: 25258363)

48. Hayakawa F, Towatari M, Kiyoi H, Tanimoto M, Kitamura T, Saito H, Naoe T (2000) Tandem-duplicated Flt3 constitutively activates STAT5 and MAP kinase and introduces autonomous cell growth in IL-3-dependent cell lines. Oncogene. 2000 Feb 03;19(5):624-31 (PMID: 10698507)

49. Ho AD, Schetelig J, Bochtler T, Schaich M, Schäfer-Eckart K, Hänel M, Rösler W, Einsele H, Kaufmann M, Serve H, Berdel WE, Stelljes M, Mayer J, Reichle A, Baldus CD, Schmitz N, Kramer M, Röllig C, Bornhäuser M, Thiede C, Ehninger G (2016) Allogeneic Stem Cell Transplantation Improves Survival in Patients with Acute Myeloid Leukemia Characterized by a High Allelic Ratio of Mutant FLT3-ITD. Biol Blood Marrow Transplant 2016 Mar;22(3):462-9 (PMID: 26551637)

50. Ho PA, Zeng R, Alonzo TA, Gerbing RB, Miller KL, Pollard JA, Stirewalt DL, Heerema NA, Raimondi SC, Hirsch B, Franklin JL, Lange B, Meshinchi S (2010) Prevalence and prognostic implications of WT1 mutations in pediatric acute myeloid leukemia (AML): a report from the Children's Oncology Group. Blood. 2010 Aug 05;116(5):702-10. Epub 2010 Apr 22 (PMID: 20413658)

51. Hollink IH, van den Heuvel-Eibrink MM, Zimmermann M, Balgobind BV, Arentsen-Peters ST, Alders M, Willasch A, Kaspers GJ, Trka J, Baruchel A, de Graaf SS, Creutzig U, Pieters R, Reinhardt D, Zwaan CM (2009) Clinical relevance of Wilms tumor 1 gene mutations in childhood acute myeloid leukemia. Blood. 2009 Jun 04;113(23):5951-60. Epub 2009 Jan 26 (PMID: 19171881)

52. Hou HA, Huang TC, Lin LI, Liu CY, Chen CY, Chou WC, Tang JL, Tseng MH, Huang CF, Chiang YC, Lee FY, Liu MC, Yao M, Huang SY, Ko BS, Hsu SC, Wu SJ, Tsay W, Chen YC, Tien HF (2010) WT1 mutation in 470 adult patients with acute myeloid leukemia: stability during disease evolution and implication of its incorporation into a survival scoring system. Blood. 2010 Jun 24;115(25):5222-31. Epub 2010 Apr 5 (PMID: 20368469)

53. Hubmann M, Köhnke T, Hoster E, Schneider S, Dufour A, Zellmeier E, Fiegl M, Braess J, Bohlander SK, Subklewe M, Sauerland MC, Berdel WE, Büchner T, Wörmann B, Hiddemann W, Spiekermann K (2014) Molecular response assessment by quantitative real-time polymerase chain reaction after induction therapy in NPM1-mutated patients identifies those at high risk of relapse. Haematologica. 2014 Aug;99(8):1317-25. Epub 2014 May 9 (PMID: 24816240)

54. Huff V (2011) Wilms' tumours: about tumour suppressor genes, an oncogene and a chameleon gene. Nat Rev Cancer. 2011 Feb;11(2):111-21. Epub 2011 Jan 20 (PMID: 21248786)

55. Ino K, Fuji S, Tajima K, Tanaka T, Okinaka K, Inamoto Y, Kurosawa S, Kim SW, Katayama N, Fukuda T (2017) Clinical Utility of Wilms' Tumor 1 Monitoring in Patients with Myeloid Malignancy and Prior Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2017 Oct;23(10):1780-1787 (PMID: 28673850)

56. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, Patel Y, Bhudia N, Farah H, Mason J, Wall K, Akiki S, Griffiths M, Solomon E, McCaughan F, Linch DC, Gale RE, Vyas P, Freeman SD, Russell N, Burnett AK, Grimwade D, UK National Cancer Research Institute AML Working Group (2016) Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med. 2016 Feb 04;374(5):422-33. Epub 2016 Jan 20 (PMID: 26789727)

57. Jeong EG, Lee SH, Yoo NJ, Lee SH (2007) Absence of nucleophosmin 1 (NPM1) gene mutations in common solid cancers. APMIS. 2007 Apr;115(4):341-6 (PMID: 17504301)

58. Juliusson G, Jädersten M, Deneberg S, Lehmann S, Möllgård L, Wennström L, Antunovic P, Cammenga J, Lorenz F, Ölander E, Lazarevic VL, Höglund M (2020) The prognostic impact of FLT3-ITD and NPM1 mutation in adult AML is age-dependent in the population-based setting. Blood Adv 2020 Mar 24;4(6):1094-1101 (PMID: 32203582)

59. Karhemo PR, Rivinoja A, Lundin J, Hyvönen M, Chernenko A, Lammi J, Sihto H, Lundin M, Heikkilä P, Joensuu H, Bono P, Laakkonen P (2011) An extensive tumor array analysis supports tumor suppressive role for nucleophosmin in breast cancer. Am J Pathol. 2011 Aug;179(2):1004-14. Epub 2011 Jun 2 (PMID: 21689627)

60. Kelly LM, Liu Q, Kutok JL, Williams IR, Boulton CL, Gilliland DG (2002) FLT3 internal tandem duplication mutations associated with human acute myeloid leukemias induce myeloproliferative disease in a murine bone marrow transplant model. Blood 2002 Jan 1;99(1):310-8 (PMID: 11756186)

61. Kiyoi H, Naoe T (2002) FLT3 in human hematologic malignancies. Leuk Lymphoma 2002 Aug;43(8):1541-7 (PMID: 12400596)

62. Kiyoi H, Ohno R, Ueda R, Saito H, Naoe T (2002) Mechanism of constitutive activation of FLT3 with internal tandem duplication in the juxtamembrane domain. Oncogene. 2002 Apr 11;21(16):2555-63 (PMID: 11971190)

63. Kleyman M, Kabeche L, Compton DA (2014) STAG2 promotes error correction in mitosis by regulating kinetochore-microtubule attachments. J Cell Sci. 2014 Oct 01;127(Pt 19):4225-33. Epub 2014 Jul 29 (PMID: 25074805)

64. Kon A, Shih LY, Minamino M, Sanada M, Shiraishi Y, Nagata Y, Yoshida K, Okuno Y, Bando M, Nakato R, Ishikawa S, Sato-Otsubo A, Nagae G, Nishimoto A, Haferlach C, Nowak D, Sato Y, Alpermann T, Nagasaki M, Shimamura T, Tanaka H, Chiba K, Yamamoto R, Yamaguchi T, Otsu M, Obara N, Sakata-Yanagimoto M, Nakamaki T, Ishiyama K, Nolte F, Hofmann WK, Miyawaki S, Chiba S, Mori H, Nakauchi H, Koeffler HP, Aburatani H, Haferlach T, Shirahige K, Miyano S, Ogawa S (2013) Recurrent mutations in multiple components of the cohesin complex in myeloid neoplasms. Nat Genet. 2013 Oct;45(10):1232-7. Epub 2013 Aug 18 (PMID: 23955599)

65. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, Walker H, Wheatley K, Bowen DT, Burnett AK, Goldstone AH, Linch DC (2001) The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001 Sep 15;98(6):1752-9 (PMID: 11535508)

66. Krauth MT, Alpermann T, Bacher U, Eder C, Dicker F, Ulke M, Kuznia S, Nadarajah N, Kern W, Haferlach C, Haferlach T, Schnittger S (2014) WT1 mutations are secondary events in AML, show varying frequencies and impact on prognosis between genetic subgroups. Leukemia. 2015 Mar;29(3):660-7. Epub 2014 Aug 11 (PMID: 25110071)

67. Kreuzer KA, Saborowski A, Lupberger J, Appelt C, Na IK, le Coutre P, Schmidt CA (2001) Fluorescent 5'-exonuclease assay for the absolute quantification of Wilms' tumour gene (WT1) mRNA: implications for monitoring human leukaemias. Br J Haematol 2001 Aug;114(2):313-8 (PMID: 11529849)

68. Krönke J, Schlenk RF, Jensen KO, Tschürtz F, Corbacioglu A, Gaidzik VI, Paschka P, Onken S, Eiwen K, Habdank M, Späth D, Lübbert M, Wattad M, Kindler T, Salih HR, Held G, Nachbaur D, von Lilienfeld-Toal M, Germing U, Haase D, Mergenthaler HG, Krauter J, Ganser A, Göhring G, Schlegelberger B, Döhner H, Döhner K (2011) Monitoring of minimal residual disease in NPM1-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. J Clin Oncol. 2011 Jul 01;29(19):2709-16. Epub 2011 May 9 (PMID: 21555683)

69. Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Kanamori H, Usuki K, Uoshima N, Yanada M, Takeuchi J, Mizuno I, Kanda J, Okamura H, Yano S, Tashiro H, Shindo T, Chiba S, Tomiyama J, Inokuchi K, Fukuda T (2020) The prognostic impact of FLT3-ITD, NPM1 and CEBPa in cytogenetically intermediate-risk AML after first relapse. Int J Hematol 2020 Aug;112(2):200-209 (PMID: 32495317)

70. Lasa A, Carricondo M, Estivill C, Bussaglia E, Gich I, Brunet S, Aventin A, Sierra J, Nomdedéu JF (2009) WT1 monitoring in core binding factor AML: comparison with specific chimeric products. Leuk Res 2009 Dec;33(12):1643-9 (PMID: 19427034)

71. Lee BH, Tothova Z, Levine RL, Anderson K, Buza-Vidas N, Cullen DE, McDowell EP, Adelsperger J, Fröhling S, Huntly BJ, Beran M, Jacobsen SE, Gilliland DG (2007) FLT3 mutations confer enhanced proliferation and survival properties to multipotent progenitors in a murine model of chronic myelomonocytic leukemia. Cancer Cell. 2007 Oct;12(4):367-80 (PMID: 17936561)

72. Lee BH, Williams IR, Anastasiadou E, Boulton CL, Joseph SW, Amaral SM, Curley DP, Duclos N, Huntly BJ, Fabbro D, Griffin JD, Gilliland DG (2005) FLT3 internal tandem duplication mutations induce myeloproliferative or lymphoid disease in a transgenic mouse model. Oncogene. 2005 Nov 24;24(53):7882-92 (PMID: 16116483)

73. Leroy C, Jacquemont ML, Doray B, Lamblin D, Cormier-Daire V, Philippe A, Nusbaum S, Patrat C, Steffann J, Colleaux L, Vekemans M, Romana S, Turleau C, Malan V (2015) Xq25 duplication: the crucial role of the STAG2 gene in this novel human cohesinopathy. Clin Genet. 2016 Jan;89(1):68-73. Epub 2015 Mar 5 (PMID: 25677961)

74. Li M, Collins R, Jiao Y, Ouillette P, Bixby D, Erba H, Vogelstein B, Kinzler KW, Papadopoulos N, Malek SN (2011) Somatic mutations in the transcriptional corepressor gene BCORL1 in adult acute myelogenous leukemia. Blood. 2011 Nov 24;118(22):5914-7. Epub 2011 Oct 11 (PMID: 21989985)

75. Li Z, Hann SR (2009) The Myc-nucleophosmin-ARF network: a complex web unveiled. Cell Cycle 2009 Sep 1;8(17):2703-7 (PMID: 19652540)

76. Lim Y, Gondek L, Li L, Wang Q, Ma H, Chang E, Huso DL, Foerster S, Marchionni L, McGovern K, Watkins DN, Peacock CD, Levis M, Smith BD, Merchant AA, Small D, Matsui W (2015) Integration of Hedgehog and mutant FLT3 signaling in myeloid leukemia. Sci Transl Med 2015 Jun 10;7(291):291ra96 (PMID: 26062848)

77. Liu Y, Zhang F, Zhang XF, Qi LS, Yang L, Guo H, Zhang N (2012) Expression of nucleophosmin/NPM1 correlates with migration and invasiveness of colon cancer cells. J Biomed Sci 2012 May 25;19:53 (PMID: 22631075)

78. Lu JW, Wang AN, Liao HA, Chen CY, Hou HA, Hu CY, Tien HF, Ou DL, Lin LI (2016) Cabozantinib is selectively cytotoxic in acute myeloid leukemia cells with FLT3-internal tandem duplication (FLT3-ITD). Cancer Lett 2016 Jul 1;376(2):218-25 (PMID: 27060207)

79. Mahmood SF, Gruel N, Chapeaublanc E, Lescure A, Jones T, Reyal F, Vincent-Salomon A, Raynal V, Pierron G, Perez F, Camonis J, Del Nery E, Delattre O, Radvanyi F, Bernard-Pierrot I (2013) A siRNA screen identifies RAD21, EIF3H, CHRAC1 and TANC2 as driver genes within the 8q23, 8q24.3 and 17q23 amplicons in breast cancer with effects on cell growth, survival and transformation. Carcinogenesis. 2014 Mar;35(3):670-82. Epub 2013 Oct 22 (PMID: 24148822)

80. Mat Yusoff Y, Abu Seman Z, Othman N, Kamaluddin NR, Esa E, Zulkiply NA, Abdullah J, Zakaria Z (2019) Identification of FLT3 and NPM1 Mutations in Patients with Acute Myeloid Leukaemia. Asian Pac J Cancer Prev. 2019 Jun 01;20(6):1749-1755. Epub 2019 Jun 1 (PMID: 31244296)

81. McLellan JL, O'Neil NJ, Barrett I, Ferree E, van Pel DM, Ushey K, Sipahimalani P, Bryan J, Rose AM, Hieter P (2012) Synthetic lethality of cohesins with PARPs and replication fork mediators. PLoS Genet. 2012;8(3):e1002574. Epub 2012 Mar 8 (PMID: 22412391)

82. Meshinchi S, Appelbaum FR (2009) Structural and functional alterations of FLT3 in acute myeloid leukemia. Clin Cancer Res. 2009 Jul 01;15(13):4263-9. Epub 2009 Jun 23 (PMID: 19549778)

83. Metzeler KH, Herold T, Rothenberg-Thurley M, Amler S, Sauerland MC, Görlich D, Schneider S, Konstandin NP, Dufour A, Bräundl K, Ksienzyk B, Zellmeier E, Hartmann L, Greif PA, Fiegl M, Subklewe M, Bohlander SK, Krug U, Faldum A, Berdel WE, Wörmann B, Büchner T, Hiddemann W, Braess J, Spiekermann K, AMLCG Study Group (2016) Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood. 2016 Aug 04;128(5):686-98. Epub 2016 Jun 10 (PMID: 27288520)

84. Mizuki M, Fenski R, Halfter H, Matsumura I, Schmidt R, Müller C, Grüning W, Kratz-Albers K, Serve S, Steur C, Büchner T, Kienast J, Kanakura Y, Berdel WE, Serve H (2000) Flt3 mutations from patients with acute myeloid leukemia induce transformation of 32D cells mediated by the Ras and STAT5 pathways. Blood. 2000 Dec 01;96(12):3907-14 (PMID: 11090077)

85. Nasilowska-Adamska B, Czyz A, Markiewicz M, Rzepecki P, Piatkowska-Jakubas B, Paluszewska M, Dzierzak-Mietla M, Solarska I, Borg K, Prochorec-Sobieszek M, Szydlo R, Lewandowski K, Skotnicki A, Jedrzejczak WW, Kyrcz-Krzemien S, Komarnicki M, Warzocha K (2016) Mild chronic graft-versus-host disease may alleviate poor prognosis associated with FLT3 internal tandem duplication for adult acute myeloid leukemia following allogeneic stem cell transplantation with myeloablative conditioning in first complete remission: a retrospective study. Eur J Haematol 2016 Mar;96(3):236-44 (PMID: 25912052)

86. Nasmyth K (2002) Segregating sister genomes: the molecular biology of chromosome separation. Science. 2002 Jul 26;297(5581):559-65 (PMID: 12142526)

87. Niavarani A, Herold T, Reyal Y, Sauerland MC, Buchner T, Hiddemann W, Bohlander SK, Valk PJ, Bonnet D (2016) A 4-gene expression score associated with high levels of Wilms Tumor-1 (WT1) expression is an adverse prognostic factor in acute myeloid leukaemia. Br J Haematol 2016 Feb;172(3):401-11 (PMID: 26597595)

88. Nishimura Y, Ohkubo T, Furuichi Y, Umekawa H (2002) Tryptophans 286 and 288 in the C-terminal region of protein B23.1 are important for its nucleolar localization. Biosci Biotechnol Biochem. 2002 Oct;66(10):2239-42 (PMID: 12450141)

89. Okusaka T, Ueno M, Sato T, Heike Y (2012) Possibility of immunotherapy for biliary tract cancer: how do we prove efficacy? Introduction to a current ongoing phase I and randomized phase II study to evaluate the efficacy and safety of adding Wilms tumor 1 peptide vaccine to gemcitabine and cisplatin for the treatment of advanced biliary tract cancer (WT-BT trial). J Hepatobiliary Pancreat Sci 2012 Jul;19(4):314-8 (PMID: 22273718)

90. Pagan JK, Arnold J, Hanchard KJ, Kumar R, Bruno T, Jones MJ, Richard DJ, Forrest A, Spurdle A, Verdin E, Crossley M, Fanciulli M, Chenevix-Trench G, Young DB, Khanna KK (2007) A novel corepressor, BCoR-L1, represses transcription through an interaction with CtBP. J Biol Chem. 2007 May 18;282(20):15248-57. Epub 2007 Mar 22 (PMID: 17379597)

91. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, Potter NE, Heuser M, Thol F, Bolli N, Gundem G, Van Loo P, Martincorena I, Ganly P, Mudie L, McLaren S, O'Meara S, Raine K, Jones DR, Teague JW, Butler AP, Greaves MF, Ganser A, Döhner K, Schlenk RF, Döhner H, Campbell PJ (2016) Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med. 2016 Jun 09;374(23):2209-2221 (PMID: 27276561)

92. Paschka P, Marcucci G, Ruppert AS, Whitman SP, Mrózek K, Maharry K, Langer C, Baldus CD, Zhao W, Powell BL, Baer MR, Carroll AJ, Caligiuri MA, Kolitz JE, Larson RA, Bloomfield CD (2008) Wilms' tumor 1 gene mutations independently predict poor outcome in adults with cytogenetically normal acute myeloid leukemia: a cancer and leukemia group B study. J Clin Oncol. 2008 Oct 01;26(28):4595-602. Epub 2008 Jun 16 (PMID: 18559874)

93. Patel JP, Gönen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, Van Vlierberghe P, Dolgalev I, Thomas S, Aminova O, Huberman K, Cheng J, Viale A, Socci ND, Heguy A, Cherry A, Vance G, Higgins RR, Ketterling RP, Gallagher RE, Litzow M, van den Brink MR, Lazarus HM, Rowe JM, Luger S, Ferrando A, Paietta E, Tallman MS, Melnick A, Abdel-Wahab O, Levine RL (2012) Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012 Mar 22;366(12):1079-89. Epub 2012 Mar 14 (PMID: 22417203)

94. Patkar N, Kakirde C, Bhanshe P, Joshi S, Chaudhary S, Badrinath Y, Ghoghale S, Deshpande N, Kadechkar S, Chatterjee G, Kannan S, Shetty D, Gokarn A, Punatkar S, Bonda A, Nayak L, Jain H, Bagal B, Menon H, Sengar M, Khizer SH, Khattry N, Tembhare P, Gujral S, Subramanian P (2019) Utility of Immunophenotypic Measurable Residual Disease in Adult Acute Myeloid Leukemia-Real-World Context. Front Oncol 2019;9:450 (PMID: 31263671)

95. Pianta A, Puppin C, Passon N, Franzoni A, Romanello M, Tell G, Di Loreto C, Bulotta S, Russo D, Damante G (2011) Nucleophosmin delocalization in thyroid tumour cells. Endocr Pathol. 2011 Mar;22(1):18-23 (PMID: 21258971)

96. Poitras JL, Heiser D, Li L, Nguyen B, Nagai K, Duffield AS, Gamper C, Small D (2016) Dnmt3a deletion cooperates with the Flt3/ITD mutation to drive leukemogenesis in a murine model. Oncotarget. 2016 Oct 25;7(43):69124-69135 (PMID: 27636998)

97. Polak J, Hajkova H, Haskovec C, Cechova H, Marinov I, Mikulenkova D, Markova J, Markova M, Vitek A, Valkova V (2013) Quantitative monitoring of WT1 expression in peripheral blood before and after allogeneic stem cell transplantation for acute myeloid leukemia - a useful tool for early detection of minimal residual disease. Neoplasma 2013;60(1):74-82 (PMID: 23067220)

98. Port M, Böttcher M, Thol F, Ganser A, Schlenk R, Wasem J, Neumann A, Pouryamout L (2014) Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: a systematic review and meta-analysis. Ann Hematol. 2014 Aug;93(8):1279-86. Epub 2014 May 7 (PMID: 24801015)

99. Pozzi S, Geroldi S, Tedone E, Luchetti S, Grasso R, Colombo N, Di Grazia C, Lamparelli T, Gualandi F, Ibatici A, Bregante S, Van Lint MT, Raiola AM, Dominietto A, Varaldo R, Signori A, Bacigalupo A (2013) Leukaemia relapse after allogeneic transplants for acute myeloid leukaemia: predictive role of WT1 expression. Br J Haematol 2013 Feb;160(4):503-9 (PMID: 23294252)

100. Prassek VV, Rothenberg-Thurley M, Sauerland MC, Herold T, Janke H, Ksienzyk B, Konstandin NP, Goerlich D, Krug U, Faldum A, Berdel WE, Wörmann B, Braess J, Schneider S, Subklewe M, Bohlander SK, Hiddemann W, Spiekermann K, Metzeler KH (2018) Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. Haematologica 2018 Nov;103 (11):1853-1861 (PMID: 29903761)

101. Pratcorona M, Brunet S, Nomdedéu J, Ribera JM, Tormo M, Duarte R, Escoda L, Guàrdia R, Queipo de Llano MP, Salamero O, Bargay J, Pedro C, Martí JM, Torrebadell M, Díaz-Beyá M, Camós M, Colomer D, Hoyos M, Sierra J, Esteve J (2013) Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. Blood 2013 Apr 4; 121(14):2734-8 (PMID: 23377436)

102. Rampal R, Figueroa ME (2016) Wilms tumor 1 mutations in the pathogenesis of acute myeloid leukemia. Haematologica 2016 Jun;101(6):672-9 (PMID: 27252512)

103. Rau R, Brown P (2009) Nucleophosmin (NPM1) mutations in adult and childhood acute myeloid leukaemia: towards definition of a new leukaemia entity. Hematol Oncol. 2009 Dec;27(4):171-81 (PMID: 19569254)

104. Rautenberg C, Pechtel S, Hildebrandt B, Betz B, Dienst A, Nachtkamp K, Kondakci M, Geyh S, Wieczorek D, Haas R, Germing U, Kobbe G, Schroeder T (2018) Wilms' Tumor 1 Gene Expression Using a Standardized European LeukemiaNet-Certified Assay Compared to Other Methods for Detection of Minimal Residual Disease in Myelodysplastic Syndrome and Acute Myelogenous Leukemia after Allogeneic Blood Stem Cell Transplantation. Biol Blood Marrow Transplant 2018 Nov;24(11):2337-2343 (PMID: 29753838)

105. Ravandi F, Cortes JE, Jones D, Faderl S, Garcia-Manero G, Konopleva MY, O'Brien S, Estrov Z, Borthakur G, Thomas D, Pierce SR, Brandt M, Byrd A, Bekele BN, Pratz K, Luthra R, Levis M, Andreeff M, Kantarjian HM (2010) Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia. J Clin Oncol 2010 Apr 10;28(11):1856-62 (PMID: 20212254)

106. Renneville A, Boissel N, Zurawski V, Llopis L, Biggio V, Nibourel O, Philippe N, Thomas X, Dombret H, Preudhomme C (2009) Wilms tumor 1 gene mutations are associated with a higher risk of recurrence in young adults with acute myeloid leukemia: a study from the Acute Leukemia French Association. Cancer. 2009 Aug 15;115(16):3719-27 (PMID: 19536888)

107. Rose D, Haferlach T, Schnittger S, Perglerová K, Kern W, Haferlach C (2017) Subtype-specific patterns of molecular mutations in acute myeloid leukemia. Leukemia 2017 Jan;31(1):11-17 (PMID: 27285584)

108. Sakaguchi M, Yamaguchi H, Kuboyama M, Najima Y, Usuki K, Ueki T, Oh I, Mori S, Kawata E, Uoshima N, Kobayashi Y, Kako S, Tajika K, Shono K, Kayamori K, Hagihara M, Kanda J, Uchiyama H, Kuroda J, Uchida N, Kubota Y, Kimura S, Kurosawa S, Date K, Nakajima N, Marumo A, Omori I, Fujiwara Y, Terada K, Yui S, Wakita S, Arai K, Kitano T, Kakihana K, Kanda Y, Ohashi K, Fukuda T, Inokuchi K (2019) Significance of FLT3-tyrosine kinase domain mutation as a prognostic factor for acute myeloid leukemia. Int J Hematol 2019 Nov;110(5):566-574 (PMID: 31432396)

109. Schittenhelm MM, Yee KW, Tyner JW, McGreevey L, Haley AD, Town A, Griffith DJ, Bainbridge T, Braziel RM, O'Farrell AM, Cherrington JM, Heinrich MC (2006) FLT3 K663Q is a novel AML-associated oncogenic kinase: Determination of biochemical properties and sensitivity to Sunitinib (SU11248). Leukemia. 2006 Nov;20(11):2008-14. Epub 2006 Sep 14 (PMID: 16990784)

110. Schlenk RF, Döhner K, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, Habdank M, Späth D, Morgan M, Benner A, Schlegelberger B, Heil G, Ganser A, Döhner H, German-Austrian Acute Myeloid Leukemia Study Group (2008) Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med. 2008 May 01;358(18):1909-18 (PMID: 18450602)

111. Schnittger S, Kern W, Tschulik C, Weiss T, Dicker F, Falini B, Haferlach C, Haferlach T (2009) Minimal residual disease levels assessed by NPM1 mutation-specific RQ-PCR provide important prognostic information in AML. Blood. 2009 Sep 10;114(11):2220-31. Epub 2009 Jul 8 (PMID: 19587375)

112. Schnittger S, Schoch C, Kern W, Mecucci C, Tschulik C, Martelli MF, Haferlach T, Hiddemann W, Falini B (2005) Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype. Blood. 2005 Dec 01;106(12):3733-9. Epub 2005 Aug 2 (PMID: 16076867)

113. Shayegi N, Kramer M, Bornhäuser M, Schaich M, Schetelig J, Platzbecker U, Röllig C, Heiderich C, Landt O, Ehninger G, Thiede C (2013) The level of residual disease based on mutant NPM1 is an independent prognostic factor for relapse and survival in AML. Blood 2013 Jul 4;122(1):83-92 (PMID: 23656730)

114. Shimada A, Taki T, Koga D, Tabuchi K, Tawa A, Hanada R, Tsuchida M, Horibe K, Tsukimoto I, Adachi S, Kojima S, Hayashi Y (2012) High WT1 mRNA expression after induction chemotherapy and FLT3-ITD have prognostic impact in pediatric acute myeloid leukemia: a study of the Japanese Childhood AML Cooperative Study Group. Int J Hematol 2012 Oct;96(4):469-76 (PMID: 22915059)

115. Shouval R, Labopin M, Bomze D, Baerlocher GM, Capria S, Blaise D, Hänel M, Forcade E, Huynh A, Saccardi R, Milone G, Zuckerman T, Reményi P, Versluis J, Esteve J, Gorin NC, Mohty M, Nagler A (2020) Risk stratification using FLT3 and NPM1 in acute myeloid leukemia patients autografted in first complete remission. Bone Marrow Transplant 2020 May 10; (PMID: 32388535)

116. Solomon DA, Kim T, Diaz-Martinez LA, Fair J, Elkahloun AG, Harris BT, Toretsky JA, Rosenberg SA, Shukla N, Ladanyi M, Samuels Y, James CD, Yu H, Kim JS, Waldman T (2011) Mutational inactivation of STAG2 causes aneuploidy in human cancer. Science. 2011 Aug 19;333(6045):1039-43 (PMID: 21852505)

117. Song Y, Magenau J, Li Y, Braun T, Chang L, Bixby D, Hanauer DA, Chughtai KA, Gatza E, Couriel D, Goldstein S, Pawarode A, Reddy P, Riwes M, Connelly J, Harris A, Kitko C, Levine J, Yanik G, Parkin B, Choi SW (2016) FLT3 mutational status is an independent risk factor for adverse outcomes after allogeneic transplantation in AML. Bone Marrow Transplant 2016 Apr;51(4):511-520 (PMID: 26191952)

118. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H (2017) Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med 2017 Aug 3;377(5):454-464 (PMID: 28644114)

119. Sugiyama H (2010) WT1 (Wilms' tumor gene 1): biology and cancer immunotherapy. Jpn J Clin Oncol. 2010 May;40(5):377-87. Epub 2010 Apr 15 (PMID: 20395243)

120. Sumara I, Vorlaufer E, Gieffers C, Peters BH, Peters JM (2000) Characterization of vertebrate cohesin complexes and their regulation in prophase. J Cell Biol. 2000 Nov 13;151(4):749-62 (PMID: 11076961)

121. Swaminathan V, Kishore AH, Febitha KK, Kundu TK (2005) Human histone chaperone nucleophosmin enhances acetylation-dependent chromatin transcription. Mol Cell Biol. 2005 Sep;25(17):7534-45 (PMID: 16107701)

122. Takahashi H, Okamoto M, Shimodaira S, Tsujitani S, Nagaya M, Ishidao T, Kishimoto J, Yonemitsu Y (2013) Impact of dendritic cell vaccines pulsed with Wilms' tumour-1 peptide antigen on the survival of patients with advanced non-small cell lung cancers. Eur J Cancer 2013 Mar;49(4):852-9 (PMID: 23245331)

123. Takakura K, Koido S, Kan S, Yoshida K, Mori M, Hirano Y, Ito Z, Kobayashi H, Takami S, Matsumoto Y, Kajihara M, Misawa T, Okamoto M, Sugiyama H, Homma S, Ohkusa T, Tajiri H (2015) Prognostic markers for patient outcome following vaccination with multiple MHC Class I/II-restricted WT1 peptide-pulsed dendritic cells plus chemotherapy for pancreatic cancer. Anticancer Res 2015 Jan;35(1):555-62 (PMID: 25550602)

124. Thiede C, Koch S, Creutzig E, Steudel C, Illmer T, Schaich M, Ehninger G (2006) Prevalence and prognostic impact of NPM1 mutations in 1485 adult patients with acute myeloid leukemia (AML). Blood. 2006 May 15;107(10):4011-20. Epub 2006 Feb 2 (PMID: 16455956)

125. Thiede C, Steudel C, Mohr B, Schaich M, Schäkel U, Platzbecker U, Wermke M, Bornhäuser M, Ritter M, Neubauer A, Ehninger G, Illmer T (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood. 2002 Jun 15;99(12):4326-35 (PMID: 12036858)

126. Thol F, Bollin R, Gehlhaar M, Walter C, Dugas M, Suchanek KJ, Kirchner A, Huang L, Chaturvedi A, Wichmann M, Wiehlmann L, Shahswar R, Damm F, Göhring G, Schlegelberger B, Schlenk R, Döhner K, Döhner H, Krauter J, Ganser A, Heuser M (2013) Mutations in the cohesin complex in acute myeloid leukemia: clinical and prognostic implications. Blood. 2014 Feb 06;123(6):914-20. Epub 2013 Dec 13 (PMID: 24335498)

127. Thota S, Viny AD, Makishima H, Spitzer B, Radivoyevitch T, Przychodzen B, Sekeres MA, Levine RL, Maciejewski JP (2014) Genetic alterations of the cohesin complex genes in myeloid malignancies. Blood. 2014 Sep 11;124(11):1790-8. Epub 2014 Jul 8 (PMID: 25006131)

128. Tomonaga T, Nagao K, Kawasaki Y, Furuya K, Murakami A, Morishita J, Yuasa T, Sutani T, Kearsey SE, Uhlmann F, Nasmyth K, Yanagida M (2000) Characterization of fission yeast cohesin: essential anaphase proteolysis of Rad21 phosphorylated in the S phase. Genes Dev 2000 Nov 1;14 (21):2757-70 (PMID: 11069892)

129. Toogeh G, Ramzi M, Faranoush M, Amirizadeh N, Haghpanah S, Moghadam M, Cohan N (2015) Prevalence and Prognostic Impact of Wilms' Tumor 1 (WT1) Gene, Including SNP rs16754 in Cytogenetically Normal Acute Myeloblastic Leukemia (CN-AML): An Iranian Experience. Clin Lymphoma Myeloma Leuk. 2016 Mar;16(3):e21-6. Epub 2015 Nov 22 (PMID: 26725263)

130. Tsai CH, Hou HA, Tang JL, Liu CY, Lin CC, Chou WC, Tseng MH, Chiang YC, Kuo YY, Liu MC, Liu CW, Lin LI, Tsay W, Yao M, Li CC, Huang SY, Ko BS, Hsu SC, Chen CY, Lin CT, Wu SJ, Tien HF (2016) Genetic alterations and their clinical implications in older patients with acute myeloid leukemia. Leukemia 2016 Jul;30(7):1485-92 (PMID: 27055875)

131. Verhaak RG, Goudswaard CS, van Putten W, Bijl MA, Sanders MA, Hugens W, Uitterlinden AG, Erpelinck CA, Delwel R, Löwenberg B, Valk PJ (2005) Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. Blood. 2005 Dec 01;106(12):3747-54. Epub 2005 Aug 18 (PMID: 16109776)

132. Versluis J, In 't Hout FE, Devillier R, van Putten WL, Manz MG, Vekemans MC, Legdeur MC, Passweg JR, Maertens J, Kuball J, Biemond BJ, Valk PJ, van der Reijden BA, Meloni G, Schouten HC, Vellenga E, Pabst T, Willemze R, Löwenberg B, Ossenkoppele G, Baron F, Huls G, Cornelissen JJ (2017) Comparative value of post-remission treatment in cytogenetically normal AML subclassified by NPM1 and FLT3-ITD allelic ratio. Leukemia 2017 Jan;31(1):26-33 (PMID: 27416910)

133. Virappane P, Gale R, Hills R, Kakkas I, Summers K, Stevens J, Allen C, Green C, Quentmeier H, Drexler H, Burnett A, Linch D, Bonnet D, Lister TA, Fitzgibbon J (2008) Mutation of the Wilms' tumor 1 gene is a poor prognostic factor associated with chemotherapy resistance in normal karyotype acute myeloid leukemia: the United Kingdom Medical Research Council Adult Leukaemia Working Party. J Clin Oncol. 2008 Nov 20;26(33):5429-35. Epub 2008 Jun 30 (PMID: 18591546)

134. Wagner K, Damm F, Thol F, Göhring G, Görlich K, Heuser M, Schäfer I, Schlegelberger B, Heil G, Ganser A, Krauter J (2011) FLT3-internal tandem duplication and age are the major prognostic factors in patients with relapsed acute myeloid leukemia with normal karyotype. Haematologica. 2011 May;96(5):681-6. Epub 2011 Jan 17 (PMID: 21242187)

135. Wander SA, Levis MJ, Fathi AT (2014) The evolving role of FLT3 inhibitors in acute myeloid leukemia: quizartinib and beyond. Ther Adv Hematol. 2014 Jun;5(3):65-77 (PMID: 24883179)

136. Wang L, Yamaguchi S, Burstein MD, Terashima K, Chang K, Ng HK, Nakamura H, He Z, Doddapaneni H, Lewis L, Wang M, Suzuki T, Nishikawa R, Natsume A, Terasaka S, Dauser R, Whitehead W, Adekunle A, Sun J, Qiao Y, Marth G, Muzny DM, Gibbs RA, Leal SM, Wheeler DA, Lau CC (2014) Novel somatic and germline mutations in intracranial germ cell tumours. Nature. 2014 Jul 10;511(7508):241-5. Epub 2014 Jun 4 (PMID: 24896186)

137. Xu H, Tomaszewski JM, McKay MJ (2011) Can corruption of chromosome cohesion create a conduit to cancer? Nat Rev Cancer 2011 Mar;11(3):199-210 (PMID: 21326324)

138. Xu LH, Fang JP, Liu YC, Jones AI, Chai L (2020) Nucleophosmin mutations confer an independent favorable prognostic impact in 869 pediatric patients with acute myeloid leukemia. Blood Cancer J 2020 Jan 9;10(1):1 (PMID: 31915364)

139. Yamamoto G, Irie T, Aida T, Nagoshi Y, Tsuchiya R, Tachikawa T (2006) Correlation of invasion and metastasis of cancer cells, and expression of the RAD21 gene in oral squamous cell carcinoma. Virchows Arch. 2006 Apr;448(4):435-41. Epub 2006 Jan 14 (PMID: 16416296)

140. Yamamoto Y, Kiyoi H, Nakano Y, Suzuki R, Kodera Y, Miyawaki S, Asou N, Kuriyama K, Yagasaki F, Shimazaki C, Akiyama H, Saito K, Nishimura M, Motoji T, Shinagawa K, Takeshita A, Saito H, Ueda R, Ohno R, Naoe T (2001) Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. Blood. 2001 Apr 15;97(8):2434-9 (PMID: 11290608)

141. Yi BQ, Zhao B, Wang ZJ (2011) Comparison of clinicopathological features and hRad21 expression between telomerase-dependent and telomerase-independent colorectal cancer. Hepatogastroenterology 2011 May-Jun;58(107-108):785-9 (PMID: 21830390)

142. Yi-Ning Y, Xiao-rui W, Chu-xian Z, Chun W, You-wen Q (2015) Prognostic significance of diagnosed WT1 level in acute myeloid leukemia: a meta-analysis. Ann Hematol 2015 Jun;94(6):929-38 (PMID: 25572170)

143. Yingjun X, Wen T, Yujian L, Lingling X, Huimin H, Qun F, Junhong C (2014) Microduplication of chromosome Xq25 encompassing STAG2 gene in a boy with intellectual disability. Eur J Med Genet. 2015 Feb;58(2):116-21. Epub 2014 Oct 24 (PMID: 25450604)

144. Yoon JH, Kim HJ, Shin SH, Yahng SA, Lee SE, Cho BS, Eom KS, Kim YJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS, Park CW, Lim JH (2013) Serial measurement of WT1 expression and decrement ratio until hematopoietic cell transplantation as a marker of residual disease in patients with cytogenetically normal acute myelogenous leukemia. Biol Blood Marrow Transplant 2013 Jun;19(6):958-66 (PMID: 23542687)

145. Zhang Y, Wang F, Chen X, Liu W, Fang J, Wang M, Teng W, Cao P, Liu H (2018) Mutation profiling of 16 candidate genes in de novo acute myeloid leukemia patients. Front Med. 2019 Apr;13(2):229-237. Epub 2018 May 26 (PMID: 29806051)

146. Zhang YY, Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, Chen YH, Han W, Wang FR, Wang JZ, Sun YQ, Liu KY, Huang XJ (2019) FLT3 internal tandem duplication does not impact prognosis after haploidentical allogeneic hematopoietic stem cell transplantation in AML patients. Bone Marrow Transplant 2019 Sep;54(9):1462-1470 (PMID: 30710101)

147. Zhao B, Wang ZJ, Yi BQ, Ma HC, Xu HM (2010) hRad21 overexpresses and localizes to the ALT-associated promyelocytic leukemia body in ALT cells. Cancer Biol Ther 2010 Jun 15;9(12):978-83 (PMID: 20364118)

148. Zhu YM, Wang PP, Huang JY, Chen YS, Chen B, Dai YJ, Yan H, Hu Y, Cheng WY, Ma TT, Chen SJ, Shen Y (2017) Gene mutational pattern and expression level in 560 acute myeloid leukemia patients and their clinical relevance. J Transl Med 2017 Aug 22;15(1):178 (PMID: 28830460)

149. Zidan MA, Kamal Shaaban HM, Elghannam DM (2014) Prognostic impact of Wilms tumor gene mutations in Egyptian patients with acute myeloid leukemia with normal karyotype. Hematology 2014 Jul;19(5):267-74 (PMID: 24074521)

150. den Besten W, Kuo ML, Williams RT, Sherr CJ (2005) Myeloid leukemia-associated nucleophosmin mutants perturb p53-dependent and independent activities of the Arf tumor suppressor protein. Cell Cycle 2005 Nov;4(11):1593-8 (PMID: 16205118)

151. von Bubnoff N, Engh RA, Aberg E, Sänger J, Peschel C, Duyster J (2009) FMS-like tyrosine kinase 3-internal tandem duplication tyrosine kinase inhibitors display a nonoverlapping profile of resistance mutations in vitro. Cancer Res. 2009 Apr 01;69(7):3032-41. Epub 2009 Mar 24 (PMID: 19318574)

152. European Medicines Agency. Midostaurin. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004095/WC500237581.pdf

153. U.S. Food and Drug Administration. Midostaurin. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207997s004lbl.pdf

154. (2020) Acute Myeloid Leukemia NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Acute Myeloid Leukemia V.2.2020 https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf