QCI Interpret One (EMEA): Hematological Cancer

Deliver oncologist-ready reports in minutes with clinically actionable evidence and recommendations

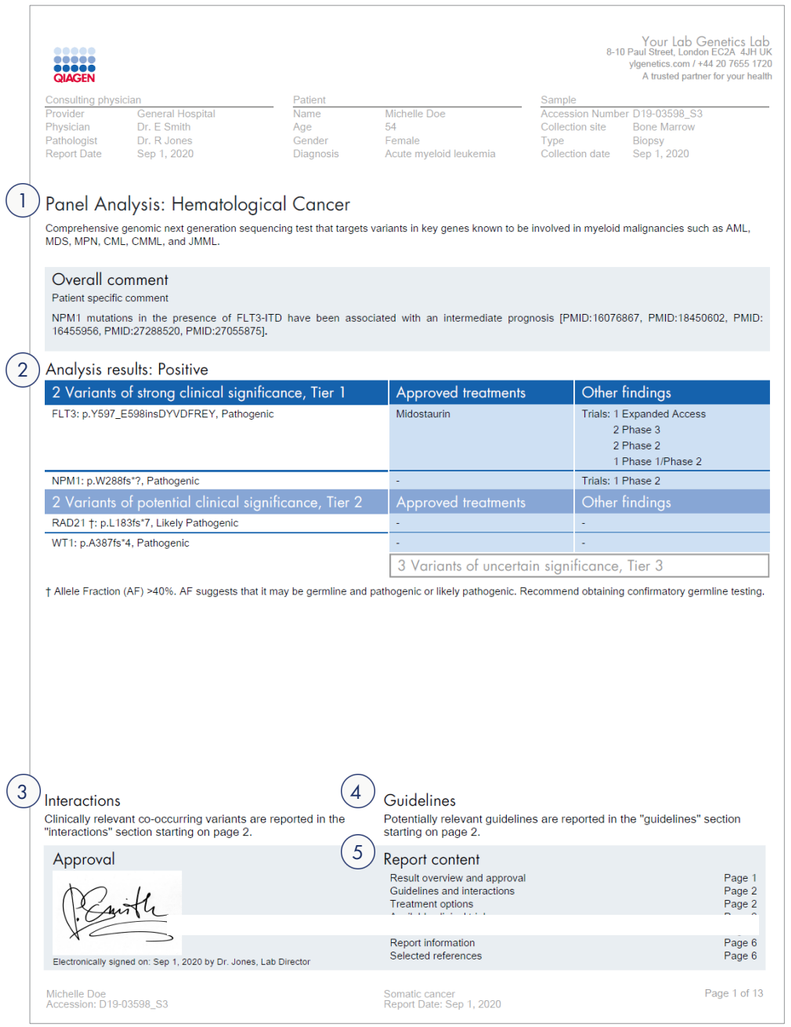
1 Provide a panel description and include summary comments of test results.

2 Identify clinically significant variants with respect to potential treatments, variants with potential clinical significance and associated therapies, and variants with biological significance.

3 Notify oncologists of potential interactions.

4 Guide oncologists to the summary of relevant guidelines for patient management.

5 Provide a Table of Contents to orient oncologists for fast review.



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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

1 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].

2 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.

3 Interactions

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

4 Guidelines

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

5 Report content

Approval

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

*This is a sample report that has been edited to illustrate key components.

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6 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].

7 INTERACTIONS

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

8 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

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

Treatment options
1 Sensitive
6 Trials

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].

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 s
by the tandem duplication of seven amino acids within exon 14, corresponding to th
of the Flt3 protein (Integrative Genomics Viewer, v.2.3). FLT3-ITD alterations similar
have been found to result in ligand-independent dimerization, constitutive Flt3 kin
downstream signaling pathways, and oncogenic transformation [82, 20, 61, 62, 60]
alteration has not been functionally characterized, is predicted to be activating.

6 Clearly convey the professional guideline evidence for each variant in the context of disease.

7 Inform on co-occurring variants with prognostic and diagnostic relevance and drug sensitivity and resistance.

8 List molecularly targeted therapies specific to your country for each clinically significant biomarker with the type and level of evidence supporting the selection.

9 Use oncologist-reviewed interpretive comments in three levels of detail with variant- and disease-specific information, including molecular function, and diagnostic, prognostic, and therapeutic relevance.

"QIAGEN's new QCI Interpret One is impressive. It combines the former N-of-One interpretation summaries with QIAGEN's QCI Interpret structured variant interpretation database. No one is better than QIAGEN for variant interpretation."

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