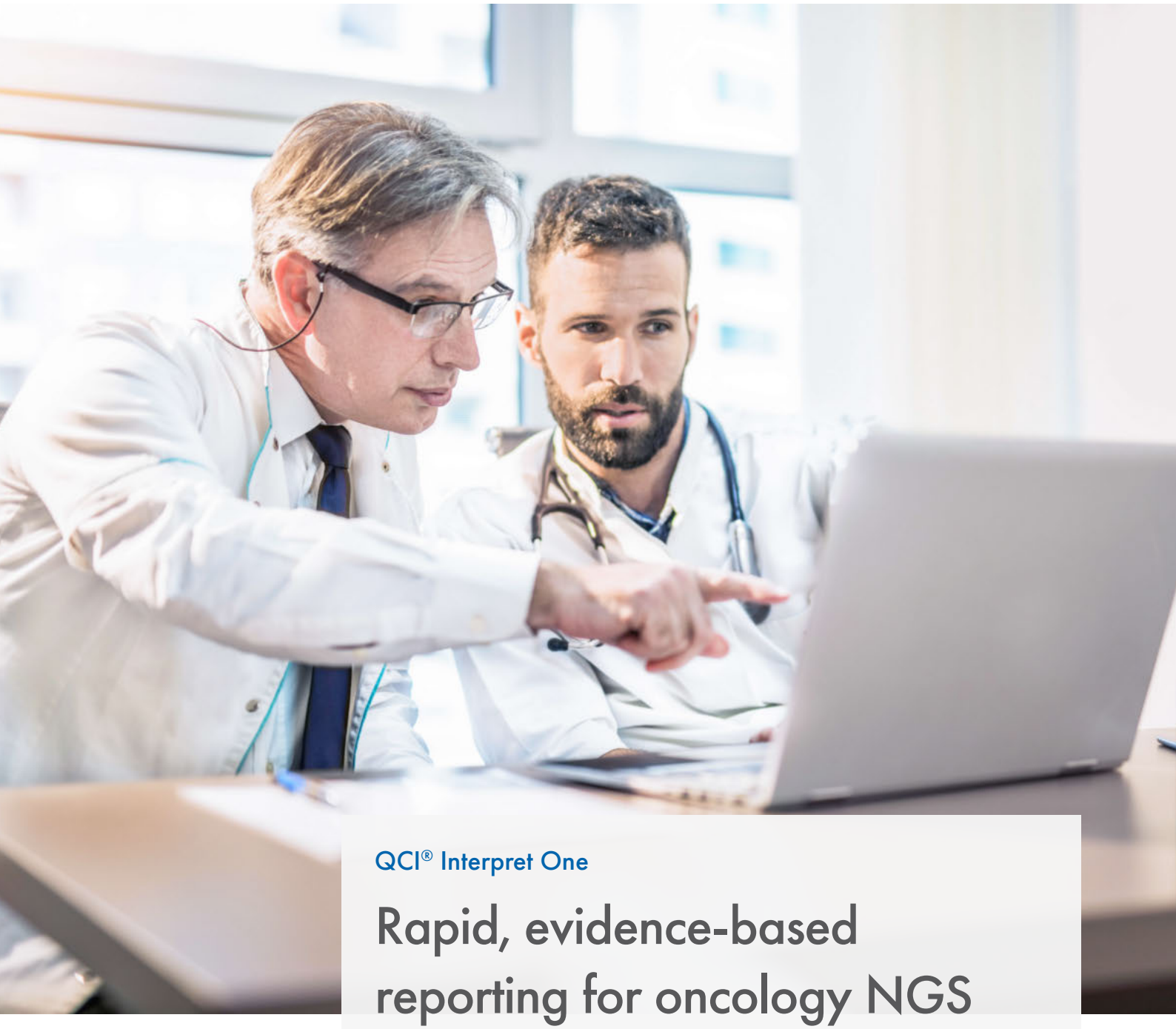
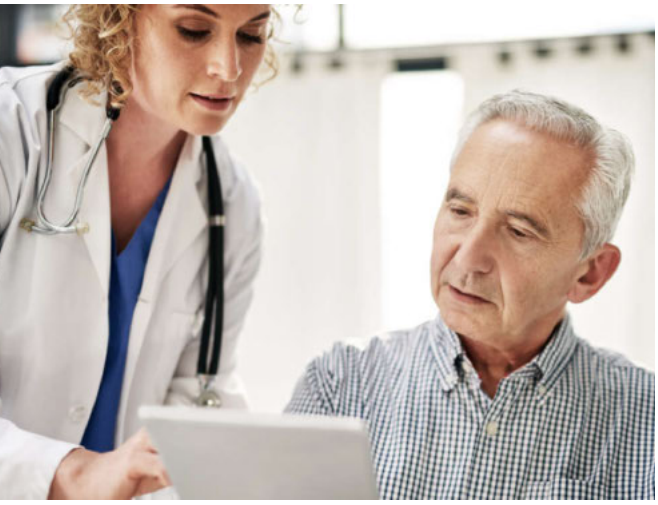
QIAGEN



QCI® Interpret One

Rapid, evidence-based reporting for oncology NGS tests at scale

Sample to Insight



Deliver oncologist-ready variant interpretation reports

Competing to offer an in-house comprehensive genomic profiling service for tumor samples is challenging, especially as panels increase in size and complexity. Today's clinical labs are under mounting pressure to interpret next-generation sequencing (NGS) tests faster and with greater precision than ever before. That's why we created QCI Interpret One.

With QCI Interpret One, lab directors can prepare, prioritize and report on clinically relevant variants associated with solid tumors and hematological malignancies without the time-consuming step of researching and writing variant- and disease-specific evidence summaries. Users get access to an "expert second opinion" for variant classification, and they can deliver professional reports directly to physicians and oncologists to better inform clinical decision making.

By combining flexible and automatable QIAGEN Clinical Insights software, powered by superior structured content in the QIAGEN Clinical Knowledge Base, with the trusted services of N-of-One, a QIAGEN company and world-leading provider of somatic variant interpretation, QCI Interpret One helps clinical labs advance their complex genomic profiling services to enable personalized cancer care.

Confidently interpret variants

In addition to expertly curated sources, such as professional guidelines, FDA and EMA therapies, clinical trials, and published literature, QCI Interpret One provides access to decision-ready oncologist-reviewed variant interpretive comments for confident decision-making.

Accelerate test turn-around-time

Speed up variant interpretation with dynamically computed disease-specific variant classification, immediate access to interpretive comments, and automatable workflows to help you scale for higher test volumes.

Deliver oncologist-ready reports

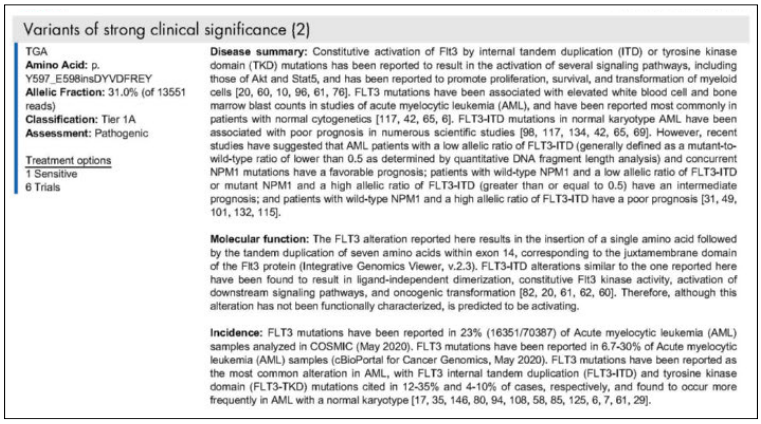
Generate customizable and standardized clinical reports with variant- and disease-specific information, including molecular function, and diagnostic, prognostic, and therapeutic relevance, available treatments, and open and recruiting clinical trials.

Confident classifications for every variant, for every disease, for every patient

The content core of QCI Interpret One, the QIAGEN Clinical Knowledge Base transforms unstructured data into actionable insight. By aggregating, manually curating, and modeling scientific literature and professional guidelines with semantic consistency, the QIAGEN Clinical Knowledge Base captures biological, phenotypic, therapeutic, and outcomes information that enables QCI Interpret One to compute variant- and disease-specific classifications for every alteration in every disease for every patient case.

Over 200,000 tumors interpreted

New to QIAGEN Clinical Insights is the inclusion of oncologist-reviewed interpretative comments from N-of-One. With over a decade of experience in clinical genomics interpretation for oncology, N-of-One's team has interpreted more than 200,000 tumor samples for pathologists and lab directors. Variant scientists and oncologists translate molecular data specific to each patient into state-of-the-art clinical insights within minutes, giving you immediate access to variant-and disease-specific expert summaries. Aggregated knowledge from N-of-One experts and the QIAGEN Clinical Knowledge Base allows you to confidently classify variants and better determine their clinical significance.


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].

Sample of an oncology interpretation summary customizable with additional ready-to-use in-depth information on the diagnostic, prognostic, therapeutic significance and supporting study outcomes of relevant Phase 1-3 clinical studies and preclinical studies.

Superior structured content

The QIAGEN Clinical Knowledge Base delivers superior structured content directly to your variant interpretation pipeline allowing you to instantly prioritize variants and dynamically review the clinical relevance based on the phenotype. For every variant in over 31,000 cancer types, you receive a computed ACMG and AMP classification, computed molecular function, the alteration's incidence in disease, structured interpretative comments, information on hereditary clinical cases, treatment information, including alteration-specific drug sensitivity and resistance, and a list of open and recruiting clinical trials. All the information you need is in one location, saving you time and money.

Through QCI Interpret One, you access:

- Oncologist-reviewed variant- and disease-specific interpretation summaries
- > 170,000 variant-specific expert molecular impact summaries
- FDA- and EMA-approved therapeutics
- Worldwide open and recruiting clinical trials
- Professional guidelines (ACMG, AMP/ASCO/CAP, NCCN WHO, ESMO, and ELN)
- Curated bibliography of >300,000 variant-specific articles with hyperlinked citations for quick confirmation
- >25 databases, including COSMIC, ClinVar, and population frequency database, such gnomAD and QIAGEN's Allele Frequency Community (AFC)
- Weekly updated therapeutic, prognostic, and diagnostic evidence, including drug labels, recruiting clinical trials, practice guidelines, and clinical/functional studies

Accelerate test turnaround time

QCI Interpret One enables clinical labs to speed up variant interpretation through automatable workflows and integrated curation and interpretation services.

Decision-ready interpretations at your fingertips

QCI Interpret One instantly delivers concise oncologist-reviewed evidence for each biomarker in the context of the cancer sub-type, listing information on the mutation's molecular characteristics, roles in disease, and therapeutic, prognostic, and diagnostic implications. Saving you significant time by eliminating the need for manual curation and providing you with over 170,000 decision-ready interpretive comments for your reports, QCI Interpret One helps you accelerate test turnaround time and increase caseload volume.

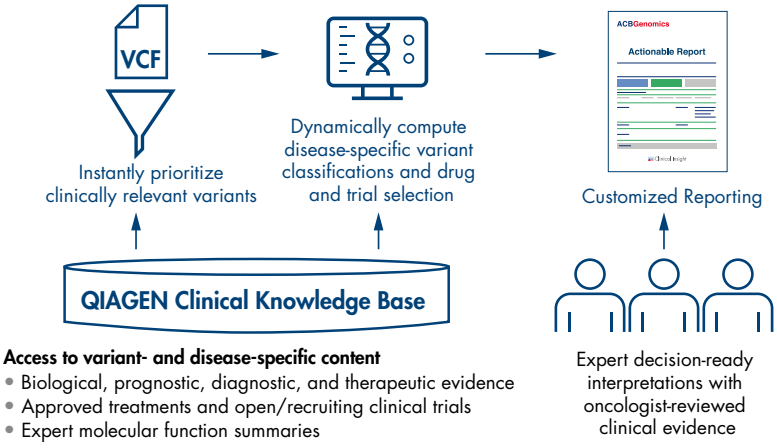
Configurable and automatable workflows

With QCI Interpret One, you can reduce hands-on time with configurable and automatable NGS interpretation workflows. Plus, you can access preconfigured, ready-to-use workflows for QIAGEN and commercial panels. The software also lets you customize your lab's specific reporting policies to automate variant reporting and drug and trial selection, and you can leverage a feature-rich API to integration with your LIMS to scale-up your case processing.

On-demand clinical curation and interpretation services

Leave the heavy-lifting to QIAGEN. On top of accessing over 170,000 decision-ready interpretive comments, you can submit your variants to QIAGEN to receive customized, oncologist-reviewed interpretations and summary comments for every clinically relevant variant detected. An ideal solution for labs working with rare or novel variants, QCI Interpret One's on-demand clinical curation and interpretation services does the research, curation, and interpretation for you, replacing labor intensive processes with automated simplicity. Any somatic NGS panel can be submitted, and depending on size and complexity, results can be returned within hours.

VCF to report in three simple steps with QCI Interpret One



Need a secondary NGS analysis solution? QIAGEN Clinical Analysis and Interpretation Services provide managed secondary NGS analysis services.

Learn more at **https://digitalinsights.qiagen.com/services-overview/clinical-analysis-and-interpretation-services/**

Deliver customized oncologist-ready reports

The content, transparency, and delivery of clinical oncology NGS test reports are critical for timely and effective patient care. QCI Interpret One supports customizable and standardized reporting to ensure adherence with industry guidelines, while also making reports easy to understand and act upon by oncologists and clinicians.

QCI Interpret One is designed to augment in-house expertise. By providing you with all of the content necessary to generate a comprehensive, patient-specific report, yet giving you full control over final classifications, comments, and recommendations, the software and service enhance decision-making in the clinical workflow. With over 170,000 oncologist-reviewed variant- and disease-specific interpretive comments, AMP/ASCO/CAP and ACMG/AMP-based classifications, and customizable report components to support your unique panel, reporting policies, and customer need, QCI Interpret One enables professional, up-to-date clinical oncology reporting.

"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."

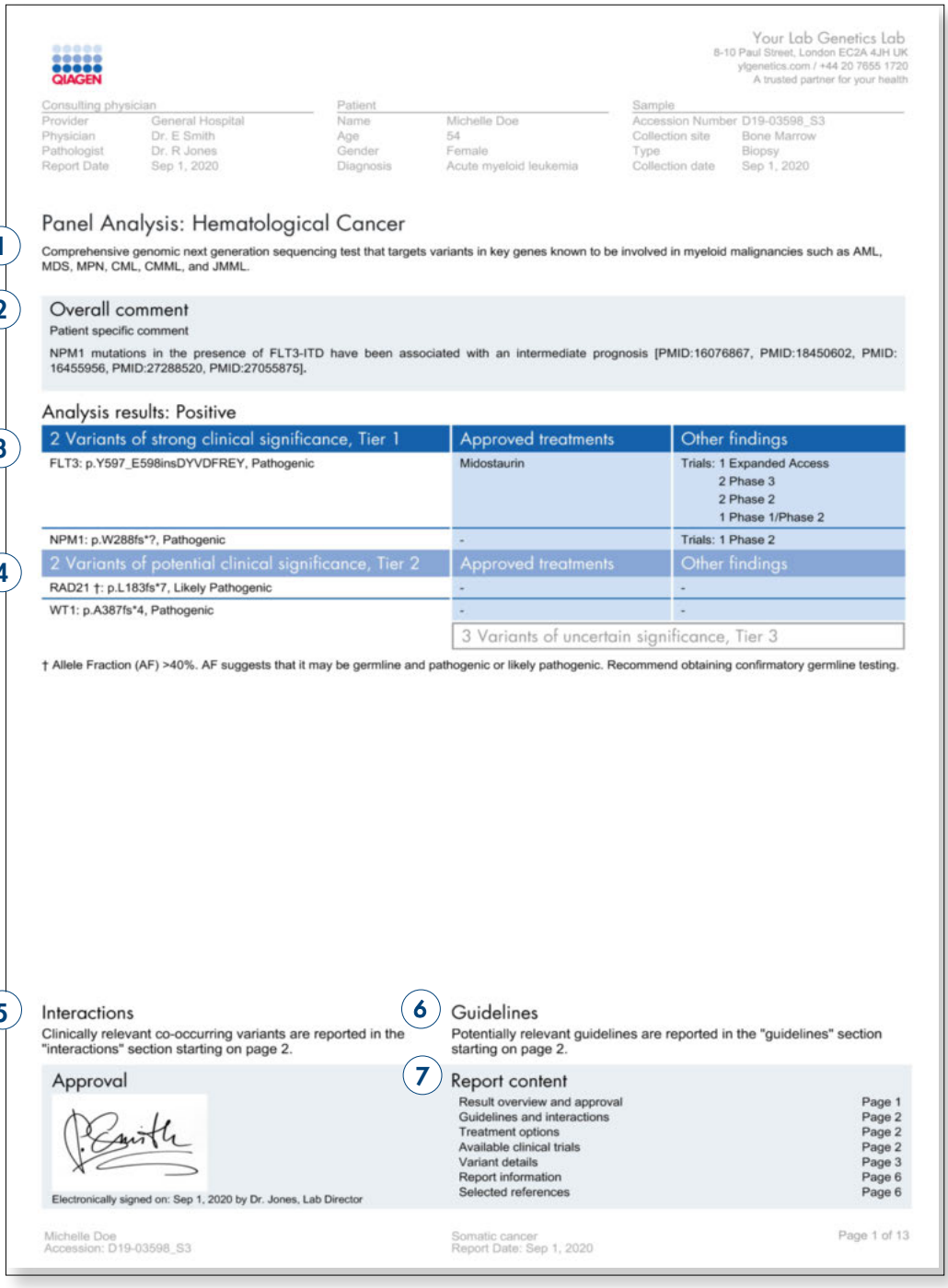
Ravindra Kolhe, MD, PhD
Chief, Section of Molecular and Genetic Pathology, Augusta University

QCI Interpret One reports include:

- Oncologist-reviewed variant- and disease-specific interpretation summaries offering concise, intermediate, or comprehensive information on:
  - Molecular function
  - Therapeutic, prognostic, and diagnostic
  - Variant interactions, such as effect of co-occurring variants on therapies, drug resistance and sensitivities
- Clinical practice guideline recommendations (EMA/ESMO/ELN/WHO)
- Relevant local recruiting clinical trials
- EMA-approved drug therapies
- Primary literature references

Deliver oncologist-ready reports in minutes with clinic

1. Provide a panel description.
2. Include summary comments of test results.
3. Identify clinically significant variants with respect to potential treatments.
4. Include variants with potential clinical significance and associated therapies.
5. Notify your oncologist of potential interactions.
6. Guide oncologists to the summary of relevant guidelines for patient management.
7. Provide a Table of Contents to orient oncologist 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

Panel Analysis: Hematological Cancer

1

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.

2

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

3

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

4

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.

5

Interactions

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

6

Guidelines

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

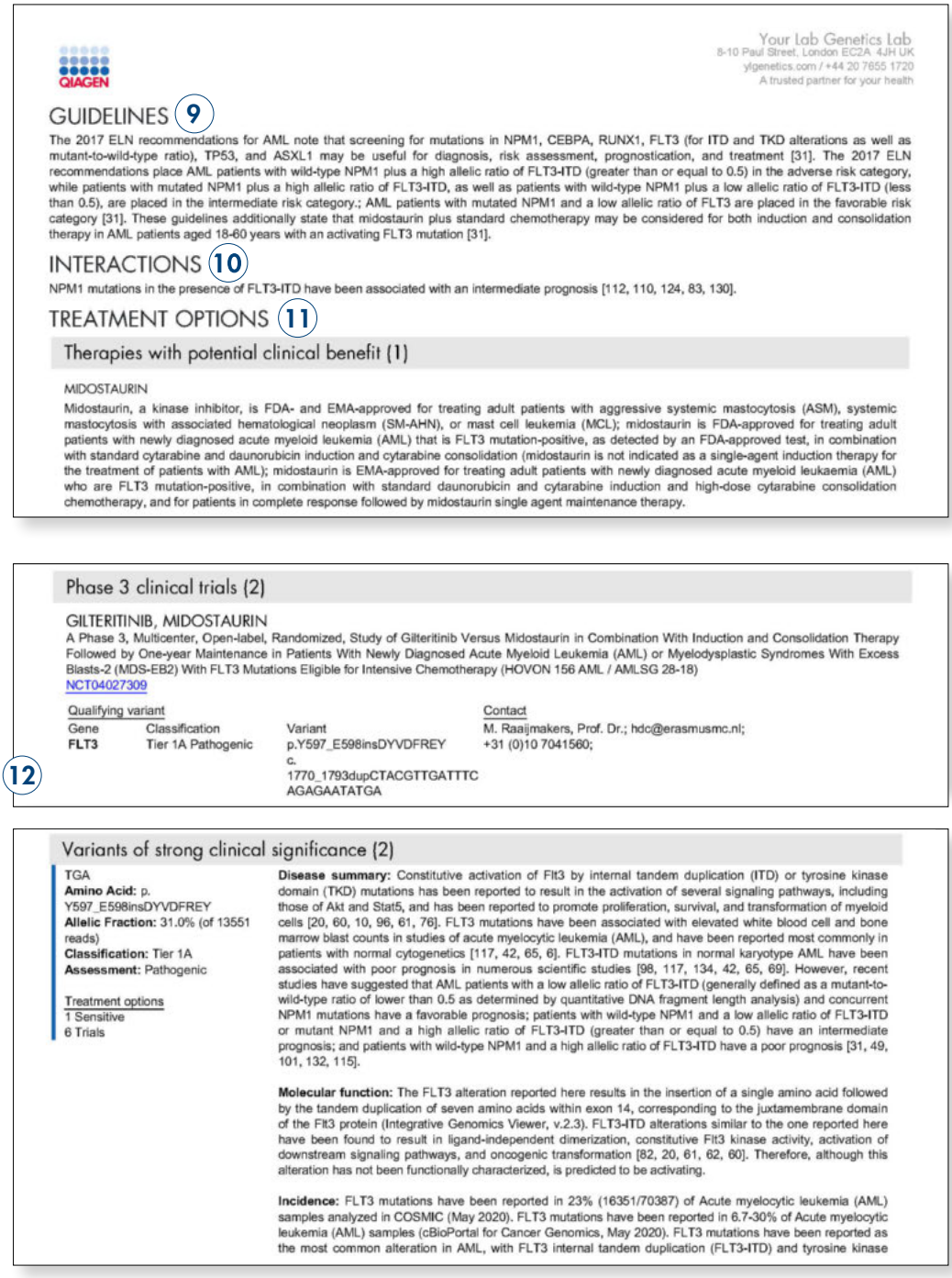
Approval

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

7

Report content

ally actionable evidence and recommendations



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GUIDELINES 9

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 10

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

TREATMENT OPTIONS 11

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.

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;
FLT3	Tier 1A Pathogenic	p.Y597_E598insDYVDFREY c. 1770_1793dupCTACGTTGATTTC AGAGAATATGA	+31 (0)10 7041560;

12

Variants of strong clinical significance (2)

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Allelic Fraction: 31.0% (of 13551 reads)
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9 Clearly convey the professional guideline evidence for each variant in the context of disease.

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

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

12 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.

Choose the clinical oncology NGS test interpretation solution that best fits your needs

QIAGEN Clinical Insights (QCI)

A clinical genomics interpretation portfolio offering expert-curated knowledge, software and services, QCI supports clinical NGS testing for any indication, on your platform, with unlimited scalability.

		QCI Interpret Clinical decision support software	QCI Interpret One Clinical decision support software with on-demand interpretation service	QCI Precision Insights Professional interpretation service
Integration Need	LIMS integration	●	●	●
	API upload of VCF, metadata, annotated files	●	●	●
Interpretation Need	Germline interpretation	●		
	Somatic interpretation		●	●
	Multi-omics interpretation			●
Resources/Expertise	Report-ready evidence summaries	Gene level	Variant and disease level	Variant and disease level
	Oncologist-reviewed clinical evidence		●	●
	Up -to-date and structured content	●	●	●
Variant Filtering/ Bioinformatics	VCF/variant filtering	●	●	
	Report-ready evidence summaries		●	●
Reporting	Flexible report pdf generation	●	●	
	Flexibility to build your own report using XML with external report generators	●	●	●

Learn more about QCI Interpret One and the QCI portfolio at
www.digitalinsights.qiagen.com/qci-interpret-one

QCI Interpret One is an evidence-based decision support software and service intended as an aid in the interpretation of variants observed in genomic next-generation sequencing data. The software and service evaluates genomic variants in the context of published biomedical literature, professional association guidelines, publicly available databases, annotations, drug labels, and clinical trials. Based on this evaluation, the software proposes a classification and bibliographic references to aid in the interpretation of observed variants. The software and service is NOT intended as a primary diagnostic tool by physicians or to be used as a substitute for professional healthcare advice. Each laboratory is responsible for ensuring compliance with applicable international, national, and local clinical laboratory regulations and other specific accreditations requirements.