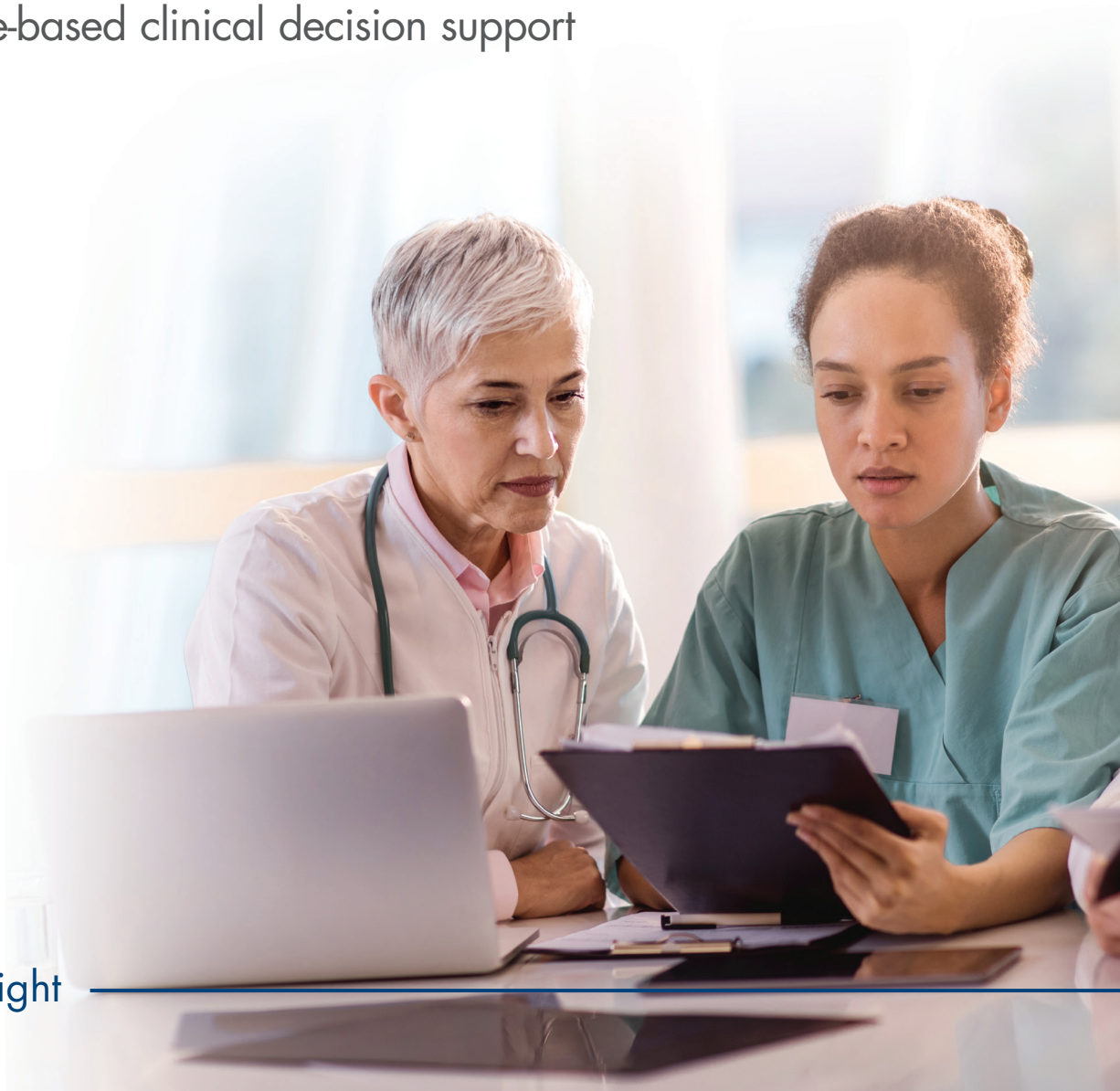
QIAGEN

Brochure

Bioinformatics for Clinical Oncology Testing

Complete automation for NGS interpretation and reporting with evidence-based clinical decision support



Sample to Insight

Powering clinical insights from genomic cancer testing with QCI™ Interpret

Stay current with the QIAGEN Knowledge Base, the most trusted source of clinical and biological findings for clinical reporting

Highlights

- Increase the throughput of your clinical genetics and variant analysis capability for interpretation and reporting
- Stay current with the industry's leading knowledgebase of accurate, up-to-date, curated content based on scientific, clinical, therapeutic, prognostic, and clinical trials evidence
- Improve clinical decision-making by automatically applying relevant professional guidelines and variant classification rules to deliver actionable, evidence-based clinical insights from patient test results
- Get maximum flexibility for integration and customization of your lab's policies, workflows, and reporting rules
- Develop a private, lab-specific variant knowledgebase by securely capturing, learning, and re-using results from prior analyses

Introduction

Next-generation sequencing (NGS) is transforming the way genetic testing is being performed and integrated into patient care. The massive scalability of NGS enables scientists to diagnose and characterize diseases by a multitude of genetic variants rather than by a single genetic test. The massive adoption of NGS capabilities in genetics and clinical research has created an enormous and continuously expanding body of scientific findings reported in the scientific literature. These findings, which must be assessed for relevance to any given patient test, together with rapidly changing information on drug labels, clinical trials, professional guidelines, and public databases, create challenges for any clinical testing laboratory to accurately survey and compile all sources of evidence that are necessary to interpret and report patient test results.

QIAGEN Clinical Insight (QCI) Interpret is an advanced enterprise software platform specifically designed for production-scale, clinical-grade genomic testing laboratories. QCI Interpret is a secure, scalable, cloud-based clinical decision support solution that offers best-in-class interpretation and reporting of NGS cancer test results for clinical testing entities and their requesting physicians and oncologists. QCI Interpret is powered by QIAGEN's continuously curated and proprietary Knowledge Base, including more than 13 million biological, scientific, and clinical findings.

QCI Interpret identifies and classifies cancer variants according to professional guidelines, with matches to clinical trials, drug labels, and precedent clinical cases. QCI Interpret also leverages the QIAGEN Knowledge Base to annotate variants with the most relevant supporting literature, clinical cases, and biological contexts with interpretive comments.

QCI Interpret enables any clinical genomic testing laboratory to improve the accuracy of its evidence-based reports, shorten the time to introduce new cancer tests to market, accelerate test volume through differentiated informatics, and cost-effectively scale business to address the growing volume of cancer patients who can benefit from personalized medical diagnosis and treatment.

"Getting from raw sequencing data to accurate and timely curation of clinically actionable variants and reporting in a user-friendly format for our ordering physicians continues to be a significant challenge for complex molecular testing. Working in collaboration with QIAGEN on the development and validation of its new Clinical Insight platform in support of somatic cancer testing has resulted in scalable and reproducible results in addressing our lab's unmet bioinformatics needs and challenges. We look forward to continued validation work and realizing the full potential of the QIAGEN Clinical Insight platform."

Dr. Gregory J. Tsongalis
Director of the Molecular Pathology and Translational Research Program
at the Dartmouth-Hitchcock Medical Center

Enhanced test interpretation and reporting throughput

QCI Interpret reduces inefficiencies in clinical testing labs that must implement extensive and rigorous manual processes for identifying, reading, and synthesizing a multitude of disparate information sources to effectively interpret NGS test results. This challenge is compounded by the dynamic nature of these data sources. According to current estimates, up to 50% of a clinical geneticist's or variant scientist's time is consumed with sourcing and synthesizing all this information. Many labs struggle to stay up-to-date given the increased volume and costs of accessing all relevant clinical data.

QCI Interpret addresses this by leveraging the QIAGEN Knowledge Base (QKB), a unique information resource for genomic and disease biology based on the Ingenuity Knowledge Base acquired by QIAGEN in 2013. Now developed, curated, and maintained by QIAGEN, the QKB is a single, commercial grade, publicly available repository of aggregated, unified, and synthesized genomic information for human disease. It includes all major publicly available sources of relevant genomic information as well as a significant number of biological, clinical, and disease genetics findings that have been curated directly by QIAGEN and are unique to the QKB. All information sources in the QKB, including the unique QIAGEN content, is consistently structured and quality-controlled according to defined vocabularies, ontologies, and schemas for cancer indications. By uniformly aggregating and consistently structuring this content, sophisticated bioinformatics algorithms and guideline-driven decision rules can automatically compute evidence-based variant classifications according to

any clinical reporting policy, including ACMG and NCCN guidelines. These rules efficiently select the few prioritized actionable and high-risk disease-causing variants (including co-occurring alterations) for reporting. For clinical exomes or genomes, this reduces the time required to accurately interpret a patient's test result from hours or days to less than 15 minutes per test. These efficiencies can translate to substantial increases in test reporting throughput by reducing turnaround time without compromising quality or reporting standards.

Operational Efficiencies Achieved with QCI Interpret

Through a collaborative project with a leading genomic testing company, we performed an analysis of time allocation of internal clinical geneticists and variant scientists across the various functional areas. We determined that the activities for these stakeholders are allocated across:

1. Literature curation
2. Variant interpretation
3. Secondary review
4. QA and compliance
5. Meta-analysis
6. Test menu expansion

We compared their allocation of time across these activities when performed internally with manual and internal approaches and after implementation of QCI. Prior to implementation of QCI, the stakeholders allocated approximately 80% of their time to literature curation and variant interpretation (50% and 30%, respectively) (Figure 1).

This massive consumption of time detracted from essential activities that are necessary for the long-term commercial viability of the testing laboratory and for reviewing test results with critical or equivocal findings. The commercial viability of a testing laboratory is largely dependent on the ability of its stakeholders to identify new variants and

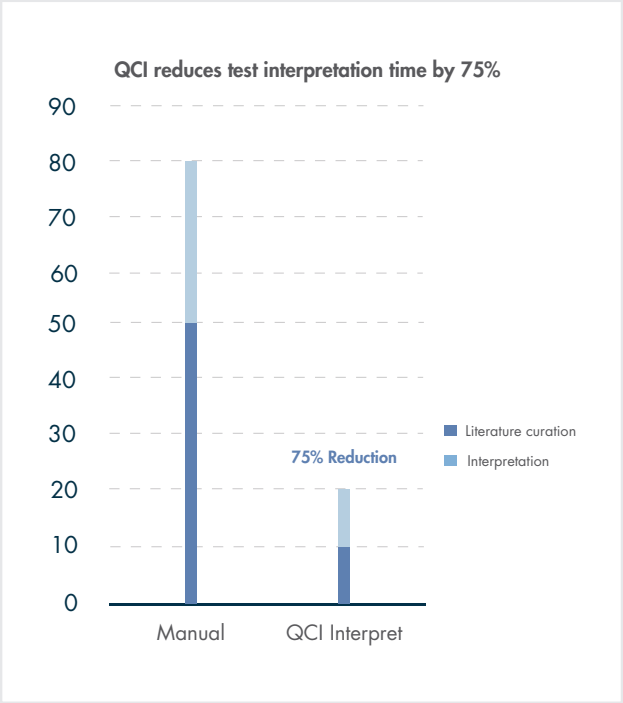


Figure 1. Time-savings for literature curation and interpretation using QCI Interpret.

content for expansion of test content and menu. This is achieved by allocation of resources to meta-analysis of prior test results and investigation of new indications for business expansion.

A significant source of inefficiency and time consumption is driven by the increasing number of variants of unknown significance (VUS's) identified in a patient test result. Many times, clinical laboratories do not have access to a knowledge base of sufficient depth to rapidly interpret VUS's, causing an excessive burden on the variant sciences team of the laboratory.

Stakeholders allocated 10% of their time for secondary review of test results with equivocal or critical findings. Equivocal test results are often due to sample insuf-

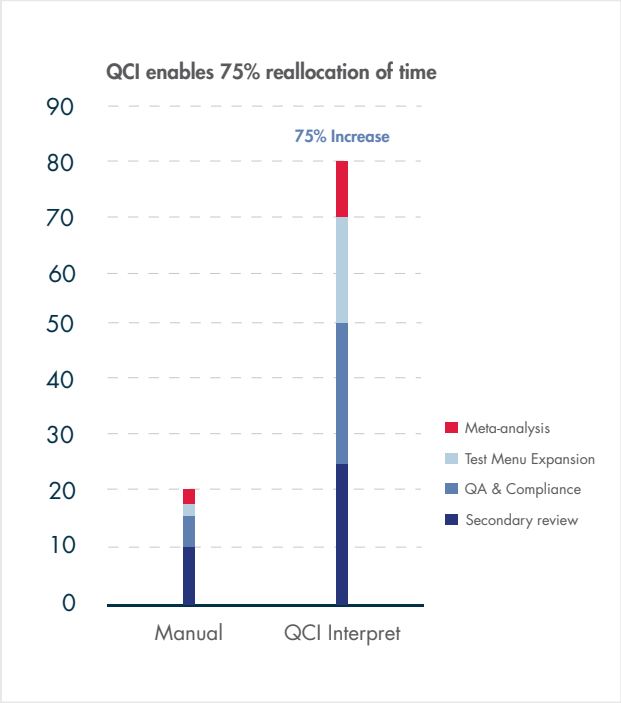


Figure 2. Reallocation of time using QCI Interpret.

ficiency, analytical errors, or the detection of rare findings. Conversely, critical findings that have major clinical implications for patients also require secondary review for unequivocal ascertainment of accuracy. Many times, these samples require additional validation testing with separate test modalities or re-analysis. Overall, these stakeholders were able to expand their allocation of time by 75% toward these activities, including quality compliance and proficiency testing (Figure 2).

The implementation of QCI allowed lab members to achieve tremendous efficiencies by reducing the time allocation for literature curation and variant interpretation. This enabled clinical geneticists and variant scientists to reallocate precious resources toward activities that will help them expand their business. Additionally, increasing efficiency made it possible for the laboratory to drastically scale its test interpretation and reporting throughput without incremental operating expenses.

Stay current with the industry's leading and continously curated knowledge base

Tracking the many growing sources of information about genomic research is beyond the capability of any individual laboratory. Attempting to do so requires a lab to establish broad and expensive capabilities for licensing, acquiring, mining, and continually curating information sources.

As a lab's test menu grows to address multiple disease indications, so must these processes expand to cover a greater breadth of clinical genetics and disease biology knowledge. QIAGEN has developed the only publicly available, industrial-scale, clinical-grade technology platform that can cost-effectively enable this capability for NGS testing laboratories (Figure 3). By leveraging an army of hundreds of expert PhD clinical curators, the QIAGEN platform can deliver this capability to NGS labs at a fraction of the cost and time required to develop them in-house.

QIAGEN's integration process for third-party databases and information sources involves correcting errors and gaps, as well as restructuring data formats to enable computation of rules across aggregated data sets. For example, clinical trial records imported from sources like ClinicalTrials.gov are manually curated to identify, structure, and model key details of the trial such as genetic inclusion and exclusion criteria, which facilitates intelligent patient-to-trial matching not possible from the original textual descriptions of the clinical trials. QIAGEN's curation processes select and consolidate the most relevant information from numerous sources under rigorous QC and QA procedures across its entire expert curation process. Overall, the QIAGEN Knowledge Base has significantly more clinical-grade, oncology-relevant knowledge than any other commercial or open access provider.

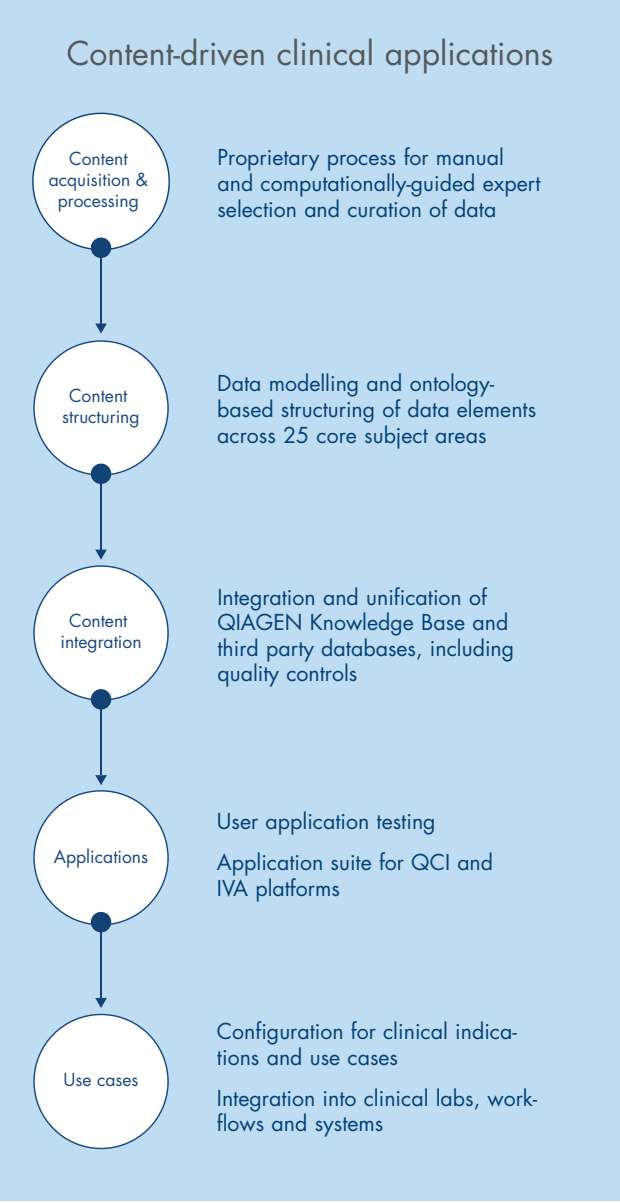


Figure 3. QIAGEN's infrastructure for acquiring content to support clinical uses cases.

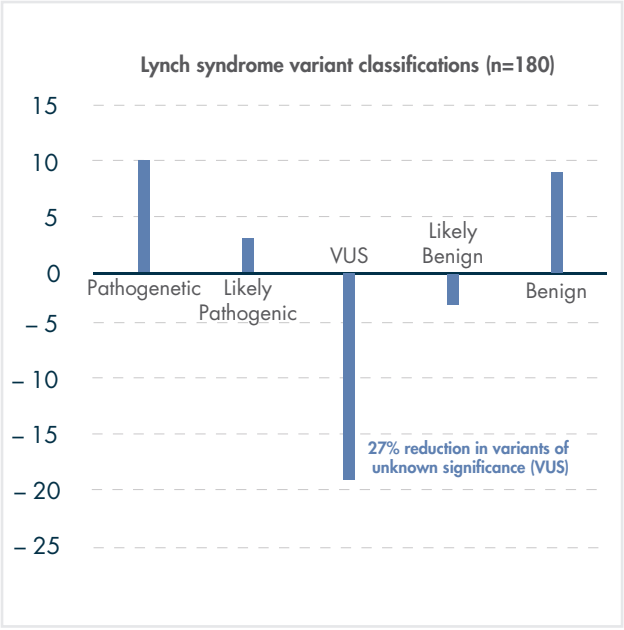


Figure 4. Variant classifications for Lynch Syndrome using QCI Interpret with and without QIAGEN curated primary literature. Data is represented as the difference between variant classifications with QIAGEN content minus variant classifications without QIAGEN content (i.e. public data sources only).

Demonstrated value of the QIAGEN Knowledge Base

Other clinical decision support products annotate variants using sources such as HGMD and ClinVar, but they lack curated content from the primary literature. This burdens users with the time-consuming task of searching articles and curating their own papers to fully classify variants. This is especially problematic for workflows that incorporate ACMG guidelines for variant interpretation, since these guidelines require information that public sources can't provide — examples include co-segregation data, de novo status, co-occurrence with other pathogenic variants, functional study data, and case-control study data.

To demonstrate the challenge of interpreting variants without using peer-reviewed literature, we classified 180 randomly selected variants associated with Lynch syndrome (n=180) (Figure 4) using QCI Interpret with and without content from the curated primary literature. The number of variants classified as having unknown significance (VUS) based on ACMG guidelines was 27% lower in the datasets interpreted with primary literature than in the datasets relying only on public sources.

That significantly increased the number of variants with clinically meaningful classifications (pathogenic, benign, likely pathogenic, and likely benign).

Actionable insights for improved clinical decisions

Treatment and care decisions for cancer patients require extensive clinically relevant information to support decision-making for individual patients, and matching that against the breadth of genetic and genomic variation observed in cancer. QCI Interpret can seamlessly accommodate the range of genetic alterations typically encountered in cancer to support the analysis of resistance mutations, fusions, CNVs, cancer genes, splice predictions, gene-specific functional predictions, and disease-causing SNPs. A unique capability of QCI Interpret is the ability to recognize and interpret genetic factors that span multiple variants. Unlike alternative approaches that interpret a patient's genetic profile on a variant-by-variant basis, QCI Interpret assesses the genetic profile in its entirety, matching combination variants that can influence the selection of appropriate treatment or clinical trial.

The extensive body of cancer-specific genomic information and prioritized clinical oncology evidence provided by QCI Interpret through the QKB allows physicians and oncologists to develop patient-specific recommendations supported by documented evidence and guidelines-based clinical reasoning. Additionally, this same evidence can be used to inform reimbursement justification, increase patient accrual in clinical trials, and document compliance with clinical treatment pathways. This approach provides testing laboratories and physicians with complete transparency across all evidence selected to support the variant classification, including manually curated clinical case counts, functional studies, clinical trials, and drug labels with digital links directly to source materials. QIAGEN performs extensive external validation of its rules and final reports with key external testing laboratories to ensure concordance with standard clinical reporting policies and evidence obtained by leading cancer centers.

Flexibility and continuous learning

Many NGS testing laboratories develop and accrue proprietary knowledge for their particular population or clinical use case. This knowledge is often used to develop new rules or amend existing rules for variant classification that requires integration into their clinical reporting policy. Additionally, laboratories may identify novel variants that require integration into a reporting policy. QCI Interpret allows laboratories to integrate and modify rules for variant classification, based on their accrued knowledge. QCI Interpret has a continuous learning capability to allow variant finding in earlier tests to inform the interpretation process for future tests. QCI Interpret also offers configurable flexibility for customization of report layout, signout procedures, and compliance with reporting policies and credentialing of users.

Customization

QIAGEN's professional and development services are available to support many customization options including:

- Integration with LIMS/LIS/CRM/accessioning and pipeline
- Report configuration, private labeling, and customization
- Variant databasing
- Compliance for clinical reporting policy and sign-out procedures
- Content and clinical use case development
- Expert curation services for test menu expansion

Compliance & Security

Technology

- Encryption in-flight and at-rest
- Firewall segregated architecture

Datacenter Physical Security

- 24x7x365 guards/CCTV
- Biometric access

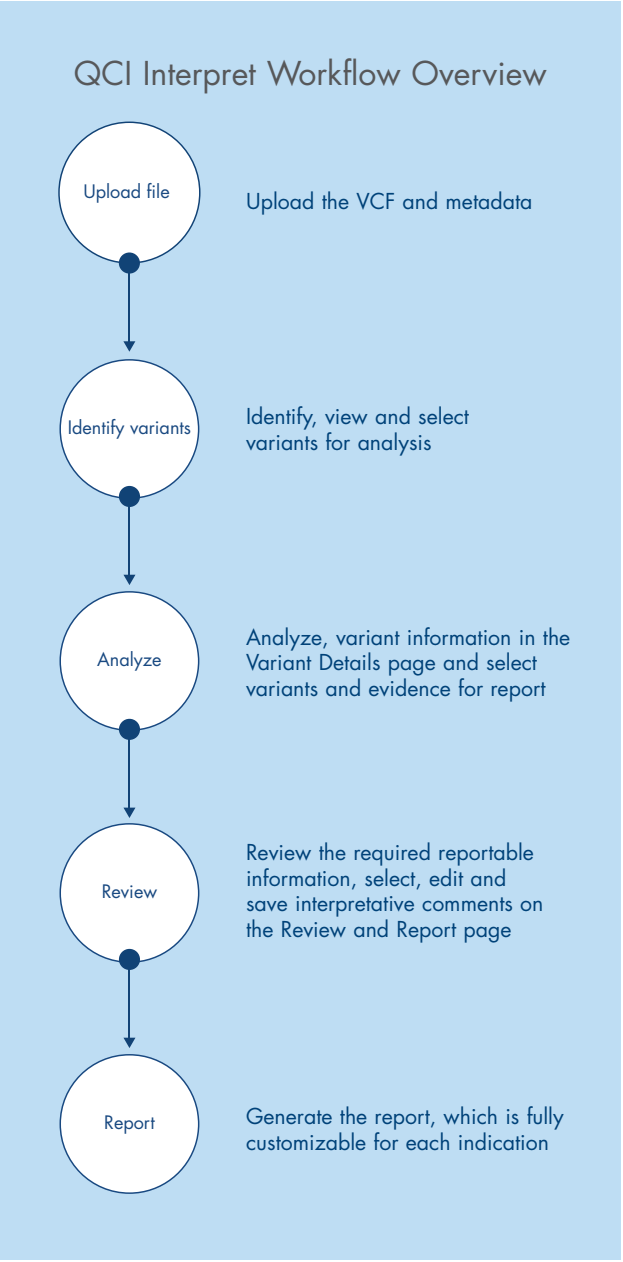
Business Processes

- Password / user management
- SFDC, business intelligence and warehousing

Accreditations

Summary

QCI Interpret's integration of highly curated knowledge and rules enables automation for much of the interpretation and reporting process for any NGS cancer testing laboratory. Together with the flexible features and customization options, QCI Interpret supports virtually any clinical testing laboratory in developing and implementing a robust production pipeline for its cancer patient population. The extensibility of QCI Interpret is useful for testing applications related to diagnosis, treatment, monitoring, and risk assessment for somatic and hereditary cancers.

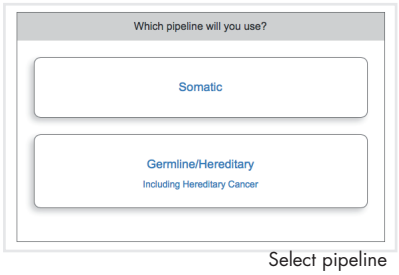


"Clinical labs rolling out NGS-based tests are confronted with two key challenges: the complexity of turning molecular profiling information into precise medical recommendations, and the time and effort it takes to generate actionable reports. QIAGEN Clinical Insight provides a rich and detailed, yet very clear and concise, report that suggests management and treatment options based on the patient's gene variations that profile their disease and outline causal links. It is this kind of interpretation that gives clinical value to the data, and what enables the actual insights into a patient's specific disease and treatment options."

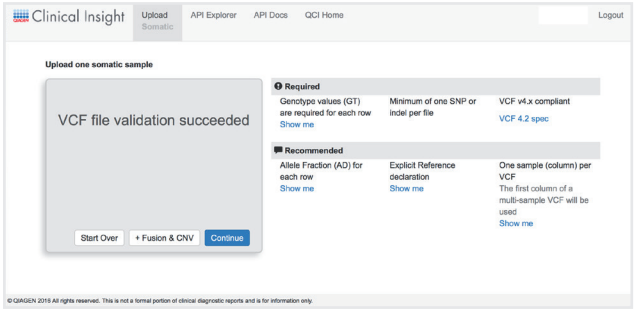
Madhuri Hegde, PhD, FACMG
Professor of Human Genetics at the Emory University School of Medicine
and Executive Director of the Emory Genetics

QCI Interpret workflow overview

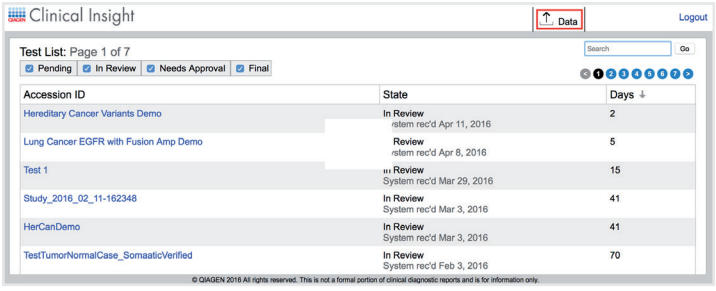
Step 1: Pipeline Selection and Sample Upload
Select the test indication pipeline to run and upload the VCF and metadata to tune treatment and clinical trials matching to the appropriate tissue type. Review the list of tests ready for analysis.



Select pipeline

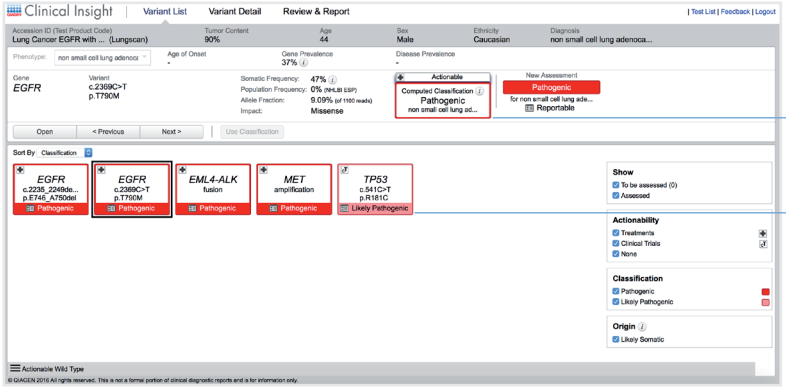


Upload VCF



Review Test List

Step 2: Variant Identification
Identify and review the list of variants and the computed classifications for pathogenicity and actionability of variants in the test sample. Select a variant of interest to continue into the analysis step.

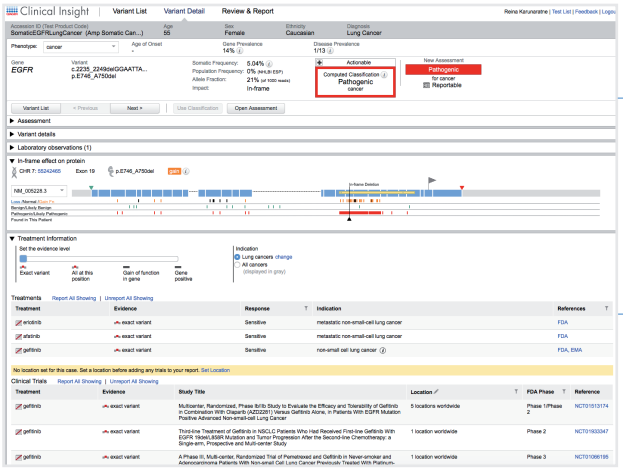


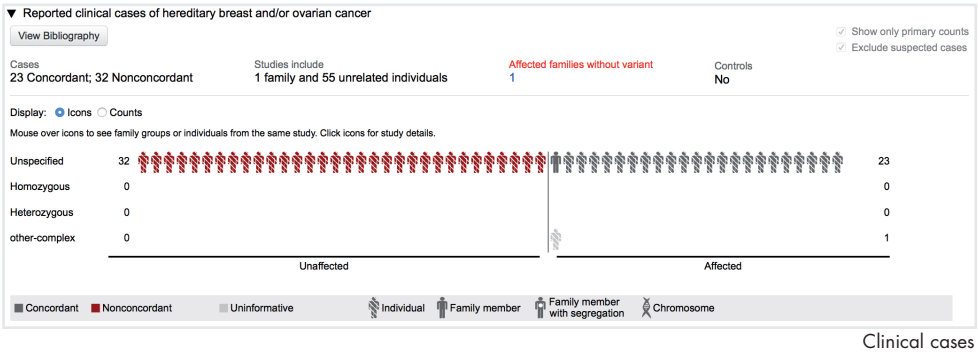
Computed classification

Variant List

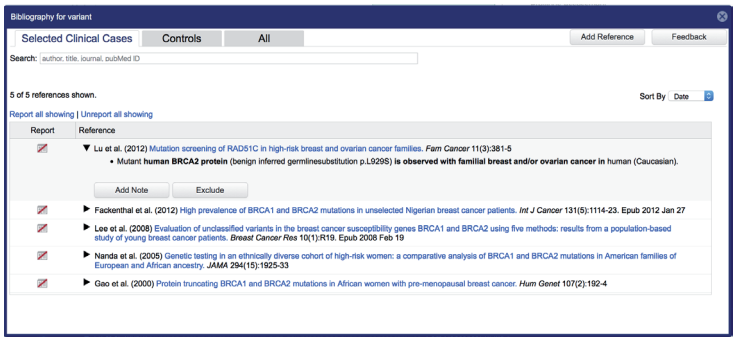
Step 3: Variant Analysis

Analyze the variant details and select variants of interest for reporting. Inspect the variant classification criteria in greater detail, investigate the clinical cases, examine literature evidence in the bibliography, and assess treatment and trial information. Make selections for inclusion in the final report.





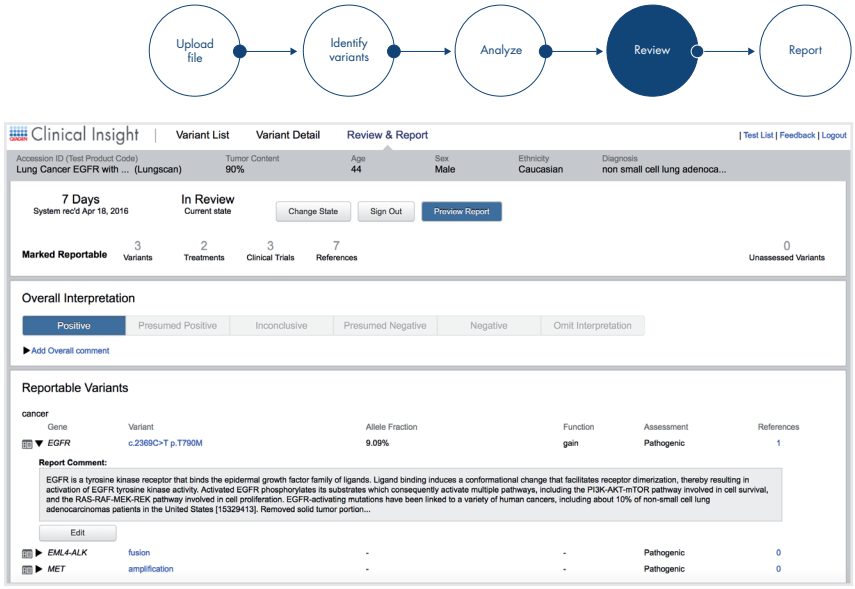
Clinical cases



Bibliography

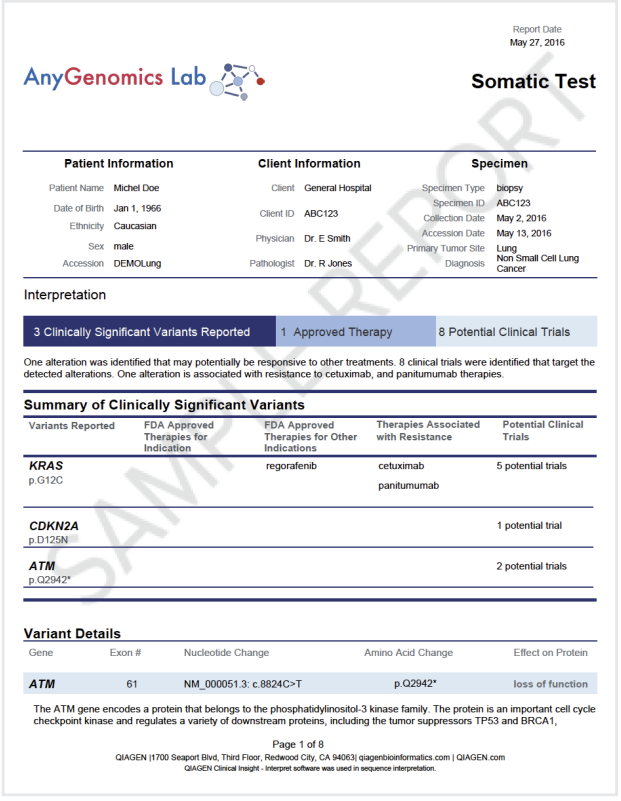
Step 4: Review

Review and edit the required reportable information and edit and save interpretive comments on the review and report page.



Step 5: Report

Generate a fully customizable final report for sharing with requesting physician or oncologist.


Report Date
May 27, 2016

AnyGenomics Lab

Somatic Test

SAMPLE REPORT

Patient Information

Patient Name: Michel Doe
Date of Birth: Jan 1, 1966
Ethnicity: Caucasian
Sex: male
Accession: DEMOLung

Client Information

Client: General Hospital
Client ID: ABC123
Physician: Dr. E Smith
Pathologist: Dr. R Jones

Specimen

Specimen Type: biopsy
Specimen ID: ABC123
Collection Date: May 2, 2016
Accession Date: May 13, 2016
Primary Tumor Site: Lung
Diagnosis: Non Small Cell Lung Cancer

Interpretation

3 Clinically Significant Variants Reported | 1 Approved Therapy | 8 Potential Clinical Trials

One alteration was identified that may potentially be responsive to other treatments. 8 clinical trials were identified that target the detected alterations. One alteration is associated with resistance to cetuximab, and panitumumab therapies.

Summary of Clinically Significant Variants

Variants Reported	FDA Approved Therapies for Indication	FDA Approved Therapies for Other Indications	Therapies Associated with Resistance	Potential Clinical Trials
KRAS p.G12C		regorafenib	cetuximab, panitumumab	5 potential trials
CDKN2A p.D125N				1 potential trial
ATM p.Q2942*				2 potential trials

Variant Details

Gene	Exon #	Nucleotide Change	Amino Acid Change	Effect on Protein
ATM	61	NM_000051.3: c.8824C>T	p.Q2942*	loss of function

The ATM gene encodes a protein that belongs to the phosphatidylinositol-3 kinase family. The protein is an important cell cycle checkpoint kinase and regulates a variety of downstream proteins, including the tumor suppressors TP53 and BRCA1,

QIAGEN |1700 Seaport Blvd, Third Floor, Redwood City, CA 94063| qiagenbioinformatics.com | QIAGEN.com
QIAGEN Clinical Insight - Interpret software was used in sequence interpretation.

Test Indication Information:

- QCI Interpret for Somatic Cancer
- QCI Interpret for Hereditary Cancer
- QCI Interpret for Hematological Cancers

To learn more from a sales or support solution specialist, contact us using the information below:

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Regulatory Statement

QCI Interpret is an evidence-based decision support software intended as an aid in the interpretation of variants observed in genomic next-generation sequencing data. The software 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 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.