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QIAGEN® Clinical Insight Interpret Translational Release Notes

Dear valued customer,

At QIAGEN, we are continuously making improvements to provide the highest level of performance with our software. Consequently, we are pleased to inform you about the latest release of QCI® Interpret Translational.

Release Highlights

QCI leverages artificial intelligence (AI) to expand the bibliography: To provide broader coverage of the clinical exome, AI-derived literature references have been integrated into the Bibliography section. The new **Source** icons, "Context" disease details, and “Show Phenotype-Related References Only” filter provide full control over the use of these automatically extracted references.

Gene transcripts with MANE select status are now the default: QCII embraces this community effort to standardize clinical transcripts for reporting. “MANE Select” and “MANE Plus Clinical” labels appear in the variant viewer dropdown, in the "Effect on Protein" section of the Variant Details page.

Enhanced phenotype-driven ranking: Variant-specific qualities are now taken into account beyond the similarity of the gene–disease phenotypic spectrum to patient symptoms by providing an improved PDR score ranking of candidate variants for rapid clinical exome review.

More precise structural variant filtering: The Confidence filter now supports thresholds for copy number gains, losses, fusions, and rearrangements. A “gene-associated structural variants” filter enables retention of structural variants that are partly in non-coding gene regions.

Improved ACMG PVS1 criteria with the modified strength workflow and informative notices: ClinGen's PVS1-modified strength recommendations are now applied to improve the ACMG classification of loss of function variants. PVS1 notices indicate the specific decision tree branch applied.

Refined handling for multiple fusions with the same first breakpoint: On the Review & Report page, multiple fusions with the same first breakpoint location and gene pair were previously collapsed and shown as a single variant. Now the specific fusion breakpoint pair(s) are maintained on the Review & Report page for additional clarity.

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Advanced handling of EGFRvIII: EGFR exon 2–7 deletion and EGFR e1:e8 rearrangements are now handled the same for identifying treatments and clinical trials. Non-specific EGFR targeted treatments and trials are no longer automatically reported for EGFRvIII.

Increase privacy and protection: For security and data privacy, idle sessions now result in automatic logout after 30 minutes of inactivity. A notice appears minutes before a session will be ended which permits the session to be extended.

Release Information

Product(s):
QIAGEN Clinical Insight (QCI) Interpret Translational

Release Date: September 22, 2023

QCI Interpret Version: 9.2.0.20230922

Content Versions: Please see appendix

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Intended Use Statement

QCI Interpret Translational (QCIIT) is a variant analysis and interpretation tool for basic and translational research involving the analysis of human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret Translational evaluates genomic variants in the context of published/unpublished biomedical evidence, professional association guidelines, publicly available databases, annotations, drug label data, and clinical trials. QCIIT is for research use only and not for use in diagnostic procedures.

Introduction to QCI Interpret Translational (QCIIT)

QCI Interpret Translational is a web-based software application for the annotation, classification, and research of variants from next-generation sequencing (NGS) data in genomic laboratories. Published evidence curated by experts into QIAGEN Knowledge Base is used by QCIIT to provide a powerful tool for increasing the efficiency and accuracy of variant research and interpretation. QCIIT uses evidence-based approaches to automatically compute pathogenicity classifications (Pathogenic to Benign) and actionability classifications (Tier 1 to 4) for each alteration according to the 2015 professional guidelines from ACMG/AMP and AMP/ASCO/CAP, respectively. Pathogenicity and actionability classifications in QCIIT are accompanied by transparent references to the criteria and evidence supporting the classifications. This workflow starts with a variant call format (VCF) file, so it is compatible with the output from any NGS platform. The final analysis is sample-specific and includes candidate causal variants, their deep annotations, interpretations, and references specified throughout the assessment process. The assessment process also has customized automation capabilities allowing for streamlined variant research workflows.

The QCIIT platform helps research labs to:

- Quickly and accurately identify causal variants in the sample(s).
- Reduce time associated with variant research.
- Ensure variants are analyzed with the most comprehensive and up to date scientific evidence available.

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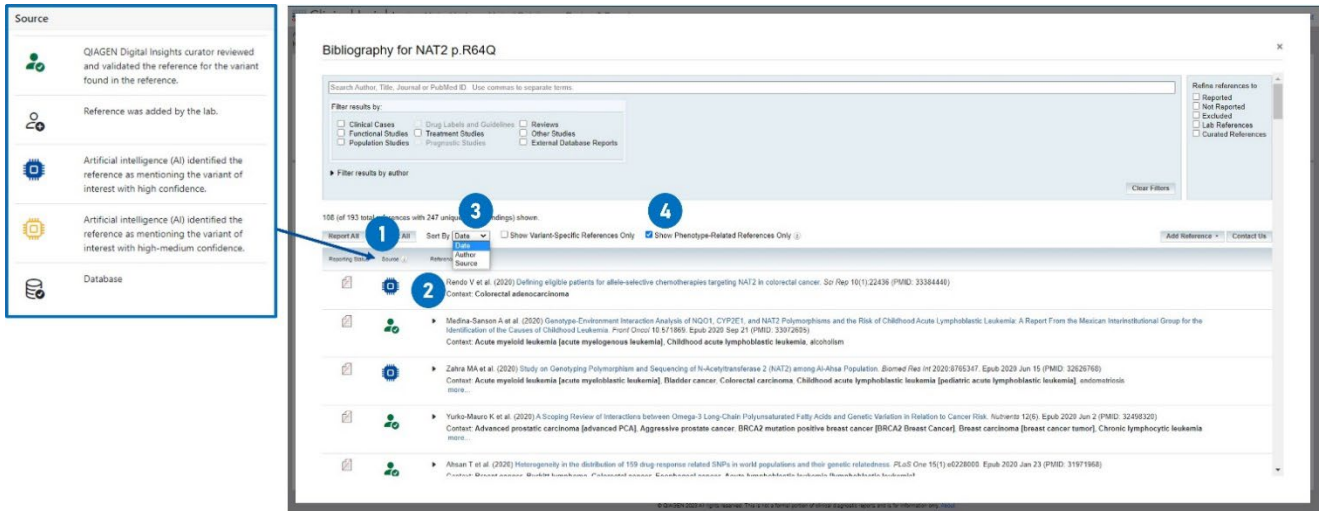
What's New in QCI Interpret

Expanded Bibliography with the Assistance of AI

AI-derived article references are now integrated into the Bibliography. This AI content broadens article coverage for variants in genes beyond the routinely tested certified genes that QIAGEN monitors and manually curates new publications on daily, to the clinical exome. Because this new AI content is not manually reviewed, it is categorized into medium and high accuracy based on estimated false positive rate. We added a new column with 'Source' icons (1) with the option to sort (2) and disease 'Context' details (when present) to all references (3). The new **Show Phenotype-Related References Only** filter option narrows down the results to focus exclusively on phenotype-related references (4).



Enhanced Phenotype-Driven Ranking of Variant List Page

Phenotype-Driven Ranking (PDR) filter score now considers attributes of the patient's variant in each gene, such as pathogenicity, mode of inheritance (MOI), and CADD score.

QCI Now Aligns to MANE Transcripts

The gene transcripts recommended for clinical reporting based on Matched Annotation from NCBI and EMBL-EBI (MANE) Select designations, are now the default transcripts. "MANE Select" and "MANE Plus Clinical" labels appear in the variant viewer transcript dropdown under the "Effect on Protein" section of the Variant Details page as well as the transcripts menu in the Variant Directory.

Known issue: A total of 30 genes have additional transcripts that are inferred to be MANE Select due to being orthologs. In rare cases, the inferred transcript is the default.

Notice for Users of NCBI36 (hg18)

The NCBI36 (hg18) reference genome and associated data will no longer be supported in the next release. Please plan to export any such results needed before the end of 2023. Currently, hg18 is only available in the United States.

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Improved Structural Variant Filtering

To provide more selective filtering control of structural variants that span both coding and non-coding regions, the “Exonic hard filter” option in the analysis creation workflow has been expanded to include such “gene-associated structural variants”.

Both the Confidence filter and Predicted Deleterious filters settings are updated and more expressive. The previous version of these filters follows the same logic as before. The filters can be edited and applied in existing analyses, or a new filter cascade can be created with the new versions and saved for use with existing test product profiles to use their new capabilities.

Confidence Filter Structural Variant Thresholds

The Confidence filter now has copy number (CN)/fold change (FC) thresholds for CN gains and CN losses, and breakpoint spanning read thresholds for fusions/rearrangements. Both are now separate from the read depth filter threshold applied to small variants.

Predicted Deleterious Filter Improvements

The **Predicted Deleterious** filter now enables structural variants that only overlap non-coding gene regions, which are not expected to impact transcription, to be exclude with the new 'gene associated structural variants' option.

The computed ACMG classification filtering criteria is based on the computed classifications for the respective hereditary and somatic workflows. Previously, QCII would filter out the EGFRvIII rearrangement in the somatic workflow because it was classified as a VUS in the hereditary context; now, EGFRvIII is retained in the somatic workflow since it is classified as pathogenic in the somatic context.

Previously, the **Predicted Deleterious** filter required CN values in the VCF to recognize structural variants for the “Copy Number Gain” and “Copy Number Loss” criteria. The filter has been improved to also recognize SVTYPE=DUP and INS as Amplification and SVTYPE=DEL as Deletion.

Previously, the Predicted Deleterious filter used only SVTYPE=Fusion to recognize structural variants for the “Gene Fusion” criteria. The filter has been improved to also recognize SVTYPE=INV and BND and has been renamed 'Gene Fusions/Rearrangements'.

Variant Details Page Improvements

Effect on Protein Section

The variant viewer in the "Effect on Protein" section of the Variant Details page now renders much faster.

The variant viewer now shows adjusted nonsense-mediated decay (NMD) positions (from the QIAGEN Knowledge Base) that differ from the standard location of "the last 50 bases of the penultimate exon".

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Improved Operability

Idle Session Logout

For data privacy and security compliance, after a long period of inactivity an automatic logout now occurs. This reduces the risk of a user leaving sensitive information visible in their browser while away from their computer. A warning notification is shown to continue the session with a click prior to the automatic logout at timeout.

ACMG/ClinGen-Related Improvements

QCII computed gene-disease validity provided for all gene-disease was updated to align with ClinGen's Clinical Validity SOP v9.

PVS1

The computed ACMG PVS1 classification now automatically applies the modified strength PVS1 workflow based on the ClinGen SVI PVS1 recommendations. PVS1 Notices indicate which decision branches were applied for clarity. The export XML will show the modified PVS1 strength, but it currently does not contain a notifications area to communicate the PVS1 Notices.

A new PVS1 Notice also indicates rare single nucleotide splice site substitutions that trigger PVS1 when the reference sequence, at the position of the variant of interest, does not match the consensus sequence GT or AG. Careful manual review of splice predictions is recommended. This new PVS1 Notice does not impact how PVS1 is triggered. QCI does not actively check if the reference sequence is the canonical/consensus GT-AG to determine if PVS1 workflow is applicable or not.

A new PVS1 Notice notes deletions in repeat regions in canonical splice variants that triggered PVS1. Careful review of these scenarios is recommended to confirm that PVS1 is applicable.

PA2

The QIAGEN PA2 criteria (founder mutations) now only matches specific genomic variants rather than less specific protein changes. No changes were made as to how PA2 is applied in terms of phenotype specificity.

BS1

The ACMG BS1 criteria now uses ClinGen's BS1 maximum expected pathogenic allele frequencies for 54 genes. These thresholds are lower than the default QCII computed BS1 thresholds which are derived from disease prevalence, which reduce variants of uncertain significance in favor of likely benign.

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Minor Improvements

- The “User Guide” link in the top-right navigation bar of QCIIT is updated to “Documentation” to link to a new webpage with the current user guide and release notes.
- The legacy customer support email **support-ingenuity@qiagen.com** has been removed from the app and is replaced with ts-bioinformatics@qiagen.com.
- When user clicks **Contact Us** from the Analysis List or Sample List page, the pop-up window now directs them to use the **Contact Us** button in the specific analysis or variant page if that is what they want to discuss.
- ActivationCode and PromotionCode XML elements were not used so are deprecated and no longer part of the current XML schema (1.19).

Known Issues

- With QCI’s recent support for the HG38 gene model, QIAGEN noticed an inconsistency in the number of genes that are available on the HG38 reference transcript. There is currently a gap on the new gene model that affects the following genes associated with either treatment or relevant gain/loss of function data: ATP10A, CD74, FFAR1, GSTT1, LAGE3, LOC102724788, MST1, NTF4, POU2F2, SNAPC4, and SULT1A1.
- With the implementation of MANE transcripts, 30 genes have additional transcripts that are inferred to be MANE Select due to them being orthologs. In rare cases, the inferred transcript could be selected as the default; however, this has minimal impact on the associated computed classifications.
- In the Common Variants filter, the "established Pathogenic common variant" does not appear as a blue hyperlink, although it is still clickable and functional.
- The PA2 criterion is supposed to only apply to the hereditary workflow; however, it is also being triggered in the somatic workflow.
- For the newly added PVS1 Notice of single nucleotide splice site substitutions that trigger PVS1, when the reference sequence does not match the consensus sequence GT or AG, QCI is specifically checking the reference nucleotide at the same position of the variant of interest (i.e., QCI checks for either G or T, or either A or G) and is not checking both reference nucleotides (i.e., G and T, or A and G).
- For the newly added ‘Context’ disease displayed as part of the Artificial Intelligence implementation, for a small set of articles some disease terms include extraneous curly brackets.
- The Bibliography for copy number variants is sorted by source rather than similarity score.
- For multi-sample analysis, when a sample does not pass filter criteria then the iconography in the Variant List table appears in solid black instead of light gray to indicate that the sample did not pass the filter criteria.
- The Publications column in the Variant List page (hereditary workflow only) is meant to reflect the number of unique PMIDs that the user can find in the Bibliography section for the variant of interest; however, a small number of cases will have a number that is slightly reduced because PMIDs that were sourced through AI or from treatment and trial-related references are currently not included in the total count.

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Bug Fixes

In order of appearance in the UI:

Issue number	Description
ICL-19297	In Step 3 of the analysis creation workflow (somatic workflow only), the URL to ISCN nomenclature was corrected.
ICL-20333	Some structural variants affecting a single gene were displaying the cytoband information as part of the variant display (e.g., “FGFR1-p11.22”). This has been corrected, so that the cytoband is no longer included in the variant display (e.g., “FGFR1 amplification” or “FGFR1 exon 2-18 amplification”).
ICL-19782	Bibliography section – references with special characters are now correctly displayed (e.g., Lavallée VP et al).
ICL-20355	Variant List page -- Previously, in Triage Mode if you began a new assessment for a variant, then clicked on another variant without saving the first one, a pop-up notice would ask if you wanted to save the changes. If you elected to save the changes, then changes to both the first and second variant would save. This has been corrected so that when you choose to save via the pop-up notice, only changes to the first variant are saved.
ICL-20124	Variant List page – Previously, in Triage Mode as the user progressed down the list of variants, a variant tile would turn white, and the page would need to be refreshed to correct itself. This has been fixed so that the variant tiles continue to display the color that corresponds to the computed classification or assessment.
ICL-18446	Variant List page (somatic workflow only) – In analyses with multiple samples for either cases or controls, QCI would show a “-“ under the “Case – Quantity” and “Control – Quantity” columns for all samples and then the user had to hover over each “-” to view any present values. Now, instead of a “-”, the values (i.e., copies, fold change, or reads) are displayed for cases with multiple samples.
ICL-20508	Variant List page (somatic workflow only) – Variants in genes with refuted evidence are now visible in the table when they were previously hidden.
ICL-20905	Variant Details – Under the Assessment section, users are now consistently given a notice when their assessment note exceeds the character limit. The **OK** button is also disabled to prevent submission of any lengthy note that could get truncated by the system.
ICL-21175	Variant Details – Under the Reported Functional Impact section, the Predicted Biochemical Impact results from MaxEntScan displayed “No Prediction” when there was no prediction as well as when the prediction was “Normal”. This has been corrected so that “Normal” is displayed when appropriate.
ICL-19297	In Step 3 of the analysis creation workflow (somatic workflow only), the URL to ISCN nomenclature was corrected.

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Content Sources and Versions

QIAGEN Clinical Insight Interpret 9.2.0.20230922

Source	Version
1000 Genome Frequency	phase3v5b
Allele Frequency Community	2019-09-25
BSIFT	2016-02-23
CADD	v1.6
CentoMD	5.3
Clinical Trials	K-release
Clinvar	2023-05-08
COSMIC	v97
dbSNP	NCBI36 (hg18) 151, GRCh37 (hg19) 155, GRCh38 155
dbVar	2021_04
DGV	2016-05-15
EVS	ESP6500SI-V2
ExAC	0.3.1
GENCODE	Release 41
gnomAD	GRCh37 (hg19) 2.1.1, GRCh38 (hg38) 3.1.2
HGMD	2023.1
Ingenuity Knowledge Base	K-release
Ingenuity Knowledge Base Snapshot Timestamp	2023-06-03 16:23:26.969
iva	Jun 15 11:47 iva-1.0.266.jar
JASPAR	2013-11
Matched Annotation from NCBI and EMBL-EBI (MANE)	0.95
MITOMAP: A Human Mitochondrial Genome Database. **www.mitomap.org**, 2019	2020-06-19
NCBI Gene	2022-02-22
OMIM	January 16, 2023
OncoTree	oncotree_2021_11_02
phyloP	NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05
PolyPhen-2	v2.2.2 (HumVar)
Refseq Gene Model	2022-08-30
SIFT4G	2016-02-23
TargetScan	7.2
TCGA	2013-09-05
Vista Enhancer	2012-07

If you have further questions, please contact your local QIAGEN representative or contact our Technical Support Center at **www.qiagen.com/support/technical-support**.

Best regards,
QIAGEN

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