QCI™ Interpret

May 25, 2017 Release Notes
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Product Release Information

Product: QCI Interpret™

Release Date: May 25, 2017

Software and Content Versions: QIAGEN Clinical Insight-Interpret (4.4); Ingenuity Knowledge Base (Lorien), HGMD (2016.4), COSMIC (v79), dbSNP (Build 149), 1000 Genome Frequency (phase3v5b), EVS (ESP6500SI-V2), PhyloP (2009-11), SIFT4G (2016-02-23), BSIFT (2016-02-23), TCGA (09/05/2013), PolyPhen-2 (v2.2.2), Clinvar (2017-01-04), Allele Frequency Community (2017-01-31), ExAC (0.3.1), CADD (v.1.3).

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Intended Use Statement

QIAGEN® Clinical Insight Interpret is 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.

Introduction to QCI Interpret

QIAGEN® Clinical Insight (QCI™ Interpret) is a web-based software application for the annotation, classification, and reporting of actionable variants from next-generation sequencing (NGS) data in clinical genomics laboratories. Expertly curated, published content in QIAGEN's long-standing knowledge base is leveraged in QCI Interpret to provide a powerful tool for increasing the efficiency and accuracy of variant interpretation and reporting. QCI Interpret uses a rules-based approach to compute classifications of variants using an adaptation of the professional guidelines from the American College of Medical Genetics (ACMG), with clear visibility into the criteria comprising each computed classification. This workflow starts with a variant call format (VCF) file, so it is compatible with the output from any NGS platform, including both Illumina™ and Ion Torrent™ data analysis pipelines. The final report includes the variants, interpretations, and references specified throughout the assessment process, which has customizable automation capabilities allowing for even more streamlined clinical decision support workflows.

Release Highlights

- Navigate and prioritize variants in the new tabular view of the variant list, which allows for sorting on classifications, frequencies, mutation types, functional impacts, and more.
- Streamline and guarantee accuracy by using customized test product profiles that eliminate the need to manually type parameters including test product indications, report template names, reporting policy names, genes, and preferred transcripts for each sample submission.
- Take full advantage of QCI Interpret's automated variant classifications by viewing supporting data (population frequencies, statistical information, etc.) directly in the classification criteria text.

New Features

Variant List: New Alternate Tabular View with Enhanced Sorting

In this release, we have added a new, alternative way to view variants in the Variant List page: a tabular list view with new sorting capabilities for quick and meaningful survey of the variants.

- Choose between the tile view and the tabular view by selecting the desired “View” choice at the top of the variant list.
New Radio Buttons for Desired View

In the tabular view, a smaller version of the variant tile is present in the Gene column. Thus, the existing characteristics and functionalities that have been used in the tile view have been maintained in the tabular view. These include:

- color schemes corresponding to classification and reportability.
- actionability badges (e.g. 1, 2, R, and Ct in the somatic workflow).
- variant selection.
- filtering on Assessment status, Classification, Actionability, and Origin.

The information provided in the tabular view is specific to the somatic and hereditary workflows. Here is an overview of the column headers for the tabular view and their definitions:

- **Gene**: gene symbol reflecting standard nomenclature as recommended by the HUGO Gene Nomenclature Committee (HGNC); includes fusions in the somatic workflow
- **Alteration**: c-dot and p-dot names for the preferred transcript
- **Chr:Position**: genomic coordinates
- **Function**: experimentally-supported or inferred functional effect (e.g.'s gain, loss, normal)
- **Impact**: predicted protein impact due to variant (e.g.'s missense, nonsense, frameshift, etc.)
- **Phenotype** (*Hereditary workflow only): phenotype pertinent to the default computed classification and which corresponds to the user-submitted test product indication(s)
- **Genotype** (*Hereditary workflow only): zygosity (e.g. het)
- **Max Population Frequency** (*Hereditary workflow only): the maximum ExAC, ESP, or 1000 Genomes frequency with ethnic group provided where applicable
- **Allele Fraction** (*Somatic Workflow only): the fraction of total reads containing the variant in the sample (shown as a percent followed by number of reads)
- **Somatic Frequency for Diagnosis** (*Somatic Workflow only): composite, reported frequency of the selected variant in the patient’s cancer, sourced from COSMIC.
### Tabular View: Somatic

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Chr/Position</th>
<th>Function</th>
<th>Impact</th>
<th>Allele Fraction</th>
<th>Somatic Frequency for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>c.2239_2247delTTAAGAGAA</td>
<td>Chr7:55242406</td>
<td>gain</td>
<td>in-frame</td>
<td>8.48% (of 6697 reads)</td>
<td>0.070%</td>
</tr>
<tr>
<td>EGFR</td>
<td>c.22480C&gt;G</td>
<td>Chr7:55242478</td>
<td>gain</td>
<td>missense</td>
<td>14% (of 3989 reads)</td>
<td>0.010%</td>
</tr>
<tr>
<td>KRAS</td>
<td>c.430G&gt;A</td>
<td>Chr12:22937052</td>
<td>gain</td>
<td>missense</td>
<td>9.59% (of 365 reads)</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>c.263T&gt;C</td>
<td>Chr2:29450267</td>
<td>normal</td>
<td>synonymous</td>
<td>98% (of 2938 reads)</td>
<td>-</td>
</tr>
<tr>
<td>BRAF</td>
<td>c.1926G&gt;A</td>
<td>Chr7:140449150</td>
<td>normal</td>
<td>synonymous</td>
<td>16% (of 4420 reads)</td>
<td>-</td>
</tr>
<tr>
<td>EGFR</td>
<td>c.1562G&gt;A</td>
<td>Chr7:55229255</td>
<td>gain</td>
<td>missense</td>
<td>41% (of 6061 reads)</td>
<td>-</td>
</tr>
<tr>
<td>EGFR</td>
<td>c.236T&gt;A</td>
<td>Chr7:55240603</td>
<td>normal</td>
<td>synonymous</td>
<td>22% (of 1716 reads)</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: All columns are sortable in both the somatic and hereditary workflows, except for the Alteration and Chr:Position columns. For these columns,

### Tabular View: Hereditary

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Phenotype</th>
<th>Chr/Position</th>
<th>Function</th>
<th>Impact</th>
<th>Genotype</th>
<th>Max Population Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>c.594-2A&gt;C</td>
<td>hereditary breast and ovarian cancer</td>
<td>Chr17:41247941</td>
<td>-</td>
<td>Het</td>
<td>0.01% ESP (European-American)</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>c.5276_5286delCTTA</td>
<td>hereditary breast and ovarian cancer</td>
<td>Chr13:32913703</td>
<td>frameshift</td>
<td>Het</td>
<td>0.001% ExAC (European)</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>c.2796G&gt;T</td>
<td>Hereditary Nonpolyposis Colorectal Cancer</td>
<td>Chr2:47710068</td>
<td>step gain</td>
<td>Het</td>
<td>0.11% ExAC (East Asian)</td>
<td></td>
</tr>
</tbody>
</table>

- To sort on the various column headers, click on one or many choices in the “Sort By” menu at the top of the variant list. Note, all columns are sortable in both the somatic and hereditary workflows, except for the Alteration and Chr:Position columns. For these columns,
performing a sort by Gene Name naturally sorts the alterations by increasing c-dot number.

Sort Menu Example from a Hereditary Test

Sort Menu Example from a Somatic Test

User-Defined Test Product Profile(s)

In this release, test product profiles can be defined up front (with the help of a QIAGEN support representative) and specified by name in the metadata (API and QCI Uploader) upon sample submission, thus eliminating the need to specify redundant test product parameters with every single upload. The parameters that can currently make up a defined test product profile include:

- Test Product Name
- Workflow Type (somatic or hereditary)
- Test Code
- Report Template
- Report Policy (reporting method, treatments policy, trials policy)
- Test Product Indications
- Genes Tested
- Preferred Transcripts

For additional details, please see the QCIBridge and API Release Notes in this document.
Improved Features

Data Visibility for Computed Classification Criteria

In this release, we have brought enhanced visibility into the data that support specific computed classification criteria. The improvements cover three areas:

1. Population database frequency Information for BA1, BS1, BS2, and PM2 criteria: Population database frequency information has always been available in the Population Frequency field and the Rarity in the General Population section. Now view the population database frequency information (ExAC, ESP, 1000 Genomes) that support the auto-triggering of the BA1, BS1, BS2, and PM2 criteria directly in the criteria text.

BA1 Example

BS1 Example
### BS2 Example

<table>
<thead>
<tr>
<th>Gene</th>
<th>Transcript</th>
<th>Phenotype</th>
<th>Age of Onset</th>
<th>Disease Prevalence</th>
<th>Mode of Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTC21B</td>
<td>NM_024753.4</td>
<td>short-rib thoracic dysplasia</td>
<td>Congenital - 28 days</td>
<td>1/500000</td>
<td>Recessive</td>
</tr>
</tbody>
</table>

- **Population Frequency**: 1.49% ExAC (South Asian)
- **Genotype**: Het
- **Impact**: Missense
- **Computed Classification**: Benign
- **Short-rib thoracic dysplasia**

### PM2 Examples

#### PM2-Dominant: Frequency in ExAC, ESP, and 1000 Genomes is 0%

<table>
<thead>
<tr>
<th>Gene</th>
<th>Transcript</th>
<th>Phenotype</th>
<th>Age of Onset</th>
<th>Disease Prevalence</th>
<th>Mode of Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>NM_007294.3</td>
<td>hereditary breast and ovarian cancer</td>
<td>Variable</td>
<td>1/4000</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

- **Population Frequency**: 0% Mtn ExAC
- **Genotype**: Het
- **Impact**: Missense
- **Computed Classification**: Likely Pathogenic
- **Hereditary breast and ovarian cancer**

### Assessment

#### BS2 Example

- **Criteria**
  - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 20.7] (Supporting)
  - Allele frequency is greater than expected for disorder [Max Recesive Expected Frequency: 0.141%; ExAC Frequency: 1.490%] (Strong)
  - Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age (# homozygous control individuals: 7 (ExAC)) (Strong)
  - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

- **Criteria ID**: PP3, BS1, BS2, BP8
- **Strength**: Supporting, Strong

#### PM2 Example

- **Criteria**
  - Located in a mutational hot spot (Moderate)
  - Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or ExAC [In these sources of population frequency data, this variant’s frequency is 0% or <= 0.001%] (Moderate)
  - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 27.6, MaxEntScan] (Supporting)
  - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

- **Criteria ID**: PM1, PM2, PP3, PP5
- **Strength**: Moderate, Supporting
PM2-Recessive: Frequency in ExAC, ESP, and 1000 Genomes is low (falls below the max recessive expected frequency)

2. CADD scores for the PP3 criterion: CADD scores >20 automatically trigger the PP3 criterion. Now view the specific CADD score directly in the PP3 text.

PP3 Example

PM2-Recessive: Frequency in ExAC, ESP, and 1000 Genomes is low (falls below the max recessive expected frequency)
3. Confidence Interval for the PS4 criterion: Previously, the Odds Ratio and FET 2-tailed p-value were provided in the PS4 criterion text for cases where the PS4 criterion was auto-triggered by QCI Interpret, in addition to the links to supporting publications (in the Evidence column). In this release, we have added into the text for this criterion the 95% confidence interval supporting the odds ratio.

PS4 Example

Close-Up View of Informative PS4 Text

The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 17.70; 95% confidence interval = (7.46, 42.04); FET 2-tail p-value < 0.0001; ] (Strong)

Preferred Transcript Workflow

With the implementation of the test product profile feature came the notion of a “preferred” transcript that a user can specify for genes in the test product profile, and this transcript is the transcript which is used for reporting. This has implications on how transcripts are displayed in the new release.

- When a user specifies a preferred transcript as part of their test product profile definition, this transcript is now displayed in the header below the gene name. If no preferred transcript is specified, QCI Interpret picks the transcript with the most findings in the QIAGEN KB, which is typically the clinically-relevant (and longest) transcript.

Example of Preferred Transcript Display
• The preferred transcript serves as “truth” throughout the analysis and reporting. To this end, the isoform viewer in the Variant Detail page has changed to better facilitate this. Now in the isoform viewer, when the user selects a transcript in the menu that differs from the preferred transcript, the header of the Variant List and Variant Detail pages no longer changes to show variant nomenclature corresponding to the selected non-preferred transcript. However, the variant name corresponding to the non-preferred transcript is shown in the isoform viewer. Stated another way, the preferred transcript’s variant name stays static in the header and only in the isoform viewer can the user look at alternate variant names associated with other transcripts.

Example of Display When the Variant Name is Different in a Non-Preferred Transcript

• The isoform viewer was also improved to be explicit about transcripts that are not affected by the variant. Upon selecting such a transcript, it is now clear this is the case due to a note that states the transcript is not affected by the variant.

Example of Display When the Transcript is Not Affected by the Variant
Functional Impact Display

The functional impact (gain, loss, normal) has been removed from the isoform viewer in the Variant Detail page and added to the header of the Variant List and Variant Detail pages next to the variant name. This field is also present and able to be sorted upon in the alternate tabular view of the variant list. For a selected variant, click on the info icon next to the functional impact to see the explanation for the assignment.

Functional Impact in the Header and Tabular List View

![Image of the Functional Impact in the Header and Tabular List View]

Maximum Frequency in Population Frequency Field

In this release, the Population Frequency field now shows the maximum continental frequency from ExAC. That is, the highest frequency from any one ethnic group is displayed along with the ethnic group name in parentheses. Previously, the composite (total) frequency was displayed in the Population Frequency field. We made this display change to more closely align with the computed classification criteria which use population frequency data (ACMG criteria: BA1, BS1, and PM2). For these criteria, the maximum continental frequencies are used in accordance with ACMG recommendations there were given at the March 2017 ACMG conference. Note, this maximum continental frequency is also displayed in the hereditary workflow in the alternate tabular variant list in the Max Population Frequency field (described in the New Features section of these release notes).
Population Frequency Display

Expandable Notes Windows

In all places where free text notes can be added, the windows now expand to provide a larger space for writing comments. Just select the bottom right corner of the window to increase the size. Here are all the places that free text comments can be added, saved, viewed by the lab’s organization, and now expanded in size:

**Variant List and Variant Detail Pages**
- Bibliography (Add Note)
- Assessment (Add Rationale, Add Criterion, and View/Add Notes)

**Review and Report Page**
- Change State
- Add Overall Comment
- Reportable Variant Comments
- Reportable Treatment Comments

**Example of an Expanded Notes Window in the Assessment Section**
Flag for Drugs in Clinical Trials that are Approved for the Patient’s Cancer

In the Treatment Information section where clinical trials are listed, the clinical trials that use one or more approved drugs are flagged with an info icon. The flag is present as an alert that the trial may be using a standard of care control. This is helpful when vetting and prioritizing many clinical trials pertinent to a particular alteration to help set apart the trials that use new, experimental drugs from those using approved drugs for the patient’s cancer.

New Info Flag for Clinical Trials Using Approved Drugs

Post-Signout Review Results Option

In this release, QCI Interpret now has support for reviewing the data for a signed-out report without having to re-open the test. That is, for any signed-out reports, the user can click “View Results”, which takes them to a "read-only" view of the Review & Report page, allowing for review of the results that went into the report. Items (e.g. treatments, clinical trials, references) cannot be added/removed or reportability changed in this view; however, links to references remain live. While working in the read-only Review & Report page, there is an option to go back to the signed-out PDF by clicking “View PDF.”
New “View Results” Button Available Only for Tests in the Signed-Out State

Read-Only Review & Report Page for a Signed-Out Test

Key Bug Fixes

- We fixed an issue where a criterion was added to the assessment but this did not show up when using the “Add Assessment” feature in the report comment.
- We fixed an issue where the BP1 computed classification criterion triggered erroneously for a synonymous variant.
- We fixed an issue where changed functional impacts (e.g. from gain to loss) due to exclusion of functional study articles were not being carried through to the report.
- We fixed an issue where clinical trials location setting to a specific country was not working consistently.
- We fixed an issue where the treatment specificity filters were being reset upon setting clinical trials locations.
• The mode of inheritance displayed for TTN: hypertrophic cardiomyopathy was updated to “dominant.”
• The "rereport all" and "Hereditary reporting v1" reporting policies were updated to auto-report intronic variants.
• The BS1 computed classification criterion logic (allele frequency is greater than expected for the disorder) was updated to compare expected vs. observed allele frequencies rounded to 3 decimal places (e.g. 0.005%), where previously values up to 9 decimal places were being compared. This update allows for more fine-tuned, conservative auto-computation of this strongly-weighted, benign-supporting criterion when the expected vs. observed frequencies are extremely close in value to one another.
QCIBridge and API Release Notes

Key Features

Define Test Product Profiles

Labs can now define a number of metadata fields to routinely apply to VCF uploads by establishing a Test Product Profile. Test Product Profiles can be defined and associated with any QCI Group, which lab administrators can setup and manage by using the QCI group management tool. The steps for configuring and using a Test Product Profile is outlined below.

1) Lab administrator creates a QCI Group and manages user membership within that group, in the 'User Groups" tab.

Each group will have a user-specified name as well as a group ID, which is used later to associate with Test Product Profiles. For each customer account, QIAGEN Licensing can designate one or more users as administrators.

Managing QCI Groups

https://apps.ingenuity.com/iat

2) QIAGEN Product/Support team collaborates with customer to tailor policies and configurations for a particular test offering, resulting in a Test Product Profile.

During the first phase of this roll-out, defining and managing Test Product Profiles in the API is limited to the QIAGEN Product/Support team, as part of the QCI product on-boarding process. Over time, we anticipate this aspect will become self-service and managed by the customer. Once a Test Product
Profile has been defined for a QCI group, it can be used by all members of the group, in both API and QCI Uploader submissions.

Registering a Test Product Profile*

**API method:**

```
POST /v1/qciGroups/{qciGroupId}/testProductProfiles
```

**Description**

Create a Test Product Profile for a QCI Group.

**Inputs**

testProductProfile **string** Name for the profile
workflowType **string** The type of workflow that this Test Product Profile serves ("hereditary" or "somatic")
testProductCode **string** The <TestProduct><Code> to apply to each test upload
reportTemplate **string** (optional) The <TestProduct><ReportTemplate> to apply to each test upload
reportingMethod **string** (optional) The <TestProduct><ReportingMethod> to apply to each test upload
preferredTranscripts **array of strings** (optional) The <TestProduct><PreferredTranscripts> to apply to each test upload.
genestested **array of strings** (optional) The <TestProduct><Genestested> to apply to each test upload
indcations **string** (optional) The <TestProduct><Indications> to apply to each test upload. Only applicable for workflowType = hereditary
treatmentsPolicy **string** (optional) The <TestProduct><TreatmentsPolicy> to apply to each test upload. Only applicable for workflowType = somatic
trialsPolicy **string** (optional) The <TestProduct><TrialsPolicy> to apply to each test upload. Only applicable for workflowType = somatic

**Outputs**

**Errors**

- 400 Invalid Input (qciGroupId or one of the fields in TestProductProfile is of invalid format)
- 404 Resource Not Found (The specified qciGroupId does not exist)
- 401 Unauthorized (The user is not authorized to define a Test Product Profile for this group)
- 409 Conflict (There already exists a test product profile with the same name for this group)

*Limited to QIAGEN Product/Support Team

3) User references a pre-defined Test Product Profile during new QCI test upload

Use Test Product Profile in QCI Uploader
Reference Test Product Profile in API submissions

Updated XSD: qciXSD_v1_7.zip
Set Variant Assessments Through API

We are providing labs with the ability to make variant assessments directly through the API, modeled after the functionality that is currently provided in the UI --> Variant Detail --> Assessment section. This is particularly useful for labs handling a large number of variant assessment updates in bulk, or wanting to set the baseline reporting for historical variants that have been previously seen and assessed. The latter enables labs to quickly set up the precedents in QCI that is necessary for leveraging automated variant re-reporting framework, either through QCI default or custom policies. This new API endpoint allows for updating some or all of the variants that reside in a previously uploaded test in QCI-I, where nomenclature for describing and matching variants is based on what was supplied in the original VCF for that test. Once the assessment update has been successfully processed, users will receive a link to the test in QCI where they can visually inspect the changes.

API method:

PUT /v1/test/{accessionID}/variantAssessment

Description
Update assessments for one or more variants in an existing QCI test

Inputs

- variantAssessments array of mappings Set an assessment for one or more variants in the test
  - chromosome string Chromosome number for the variant to update, (e.g. "chr14")
  - position integer Reference position for the variant to update
  - reference string Reference base(s) for the variant to update
  - alternate string Alternate base(s) observed in the sample for the variant to update
  - assessment string Computed ACMG classification for the variant ("Pathogenic", “Likely Pathogenic”, “Uncertain Significance”, "Likely Benign", or "Benign")
  - phenotype string Phenotype or disease context that is used for the computed ACMG classification. This value must be the same as Diagnosis (Somatic), or match one of terms provided in Phenotypes of Interest or Test Product Indications (Hereditary).
  - reportability string Whether or not the variant should be included in the report (“Not Reportable”, “Reportable”, or “Secondary Finding”)
  - author string (optional) Email of user that is making the assessment update. If not provided, then the user issuing the API request will be used for context.
  - comments string (optional) Additional comments related to the assessment that can be seen by others in your organization

Outputs

- accession string Accession ID of the test that was modified
- variantAssessments array of mappings
  - chromosome string Chromosome number for the variant to update, (e.g. "chr14")
  - position integer Reference position for the variant to update
  - reference string Reference base(s) for the variant to update
  - alternate string Alternate base(s) observed in the sample for the variant to update
- **status string** Whether or not the requested variant assessment update was successfully made ("updated" or "not found")
- **applicationUrl string** URL to open the updated test in QCI-Interpret

**Errors**

400 Invalid Input (Assessment, phenotype, or reportability is not one of the allowed values)
400 Invalid State (the specified test state is not one of the allowed values - "Pending", "In Review", "Needs Approval")
400 Accession ID Not Unique (Accession ID resolves to more than 1 test)
404 Resource Not Found (The specified accession ID does not exist)
404 All Variants Not Found (None of the variants specified could be found in the corresponding test)
403 Permission Denied (author does not have access to this test ID)