Evaluation of QIAGEN Clinical Insight as a content resource for variant curation in a CLIA laboratory

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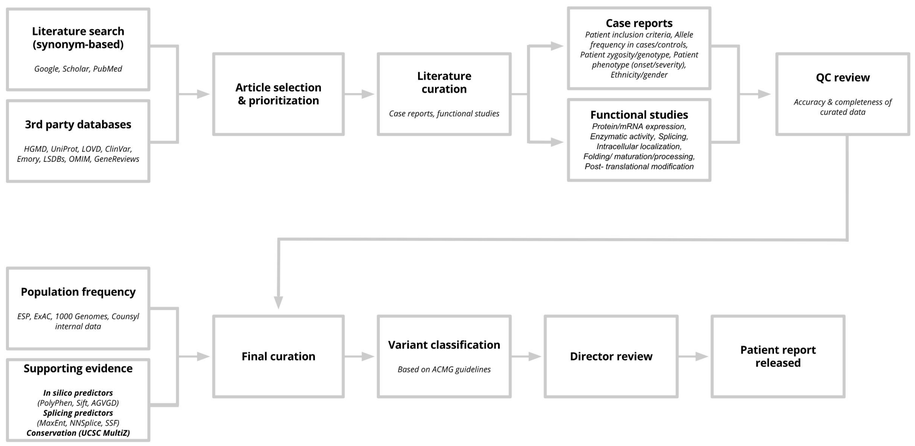
Introduction

Counsyl is a health technology company that offers an expanded carrier screen for >175 of the most relevant recessive diseases and a panel of up to 36 genes for hereditary cancer risk assessment. The identification of articles mentioning a specific disease-gene variant is crucial to the accurate and robust appraisal of variant pathogenicity, and forms a central component of manual curation at Counsyl. Counsyl performs “real-time” curation of variants identified across our NGS-based screening products. Within our curation workflow, automated proprietary software initially classifies detected variants with high population frequency or which have not been previously reported. The remaining variants undergo curation by PhD scientists and genetic counselors before approval by board-certified laboratory directors (below). Pathogenicity is assessed using ACMG guidelines and is based on published case and functional studies, variant databases, population frequency, conservation, and in silico predictors.



For the identification of pertinent published evidence, Counsyl relies on variant databases, an in-house article library, and online searches to find variant-specific references. As part of a constant drive to improve patient reporting and turnaround time by advancing curation accuracy and efficiency, we examined available third party resources that could potentially augment our curation pipeline.

QIAGEN Clinical Insight (QCI™) is a clinical decision support platform that provides manually curated clinical case evidence with computed ACMG classifications and a comprehensive bibliography of articles. Articles describing variants in the relevant genes are identified through natural language processing of abstracts and PubMed annotations. The full text of the articles is reviewed by scientists that have undergone a rigorous training program and curate clinical case details by entering them into a web-based curation tool. QIAGEN uses third party User Acceptance Testing to validate high-level coverage and accuracy in compliance with quality targets.

In this study we evaluated and validated QCI as a solution for reducing manual searches, with quantitative and qualitative assessment of variant-specific coverage.

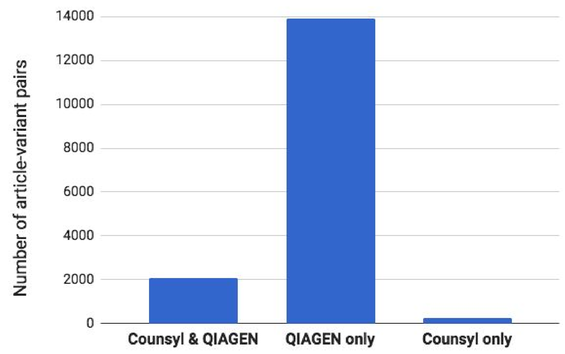
Methods

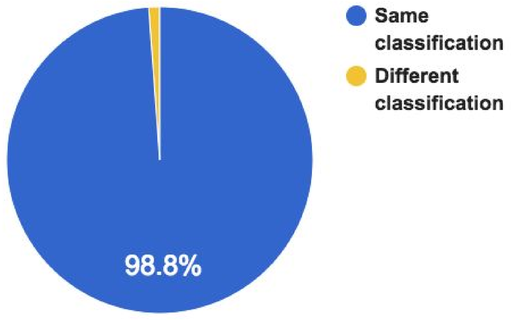
The analyses used ~2000 variants manually reviewed over a 3 month production period for 53 of the genes from our expanded carrier screen and inherited cancer panels. A quantitative assessment compared references selected for Counsyl curation with corresponding QCI bibliographies for these variants. The extent of reference overlap and the proportion of unique articles was determined.

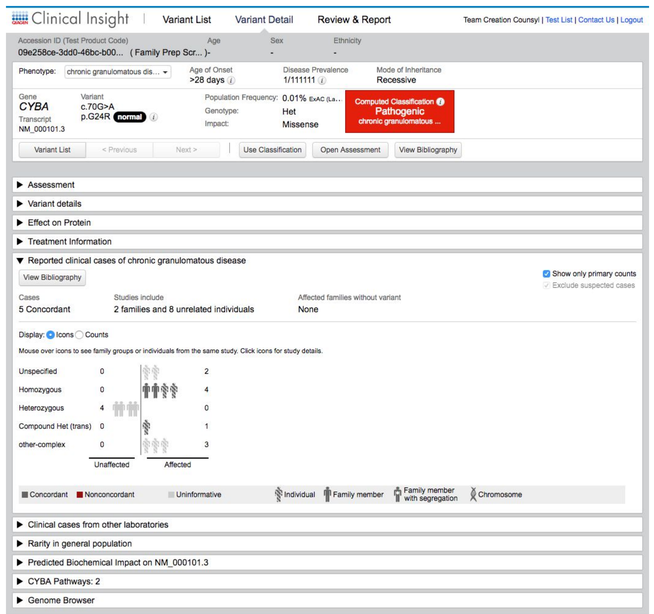
To ascertain the potential impact on classification and reporting, a qualitative assessment of QCI bibliographic content was performed. We assessed whether use of QCI references would result in the same variant classifications as with articles identified by Counsyl.

Results

We found 89.3% (2075/2324) of article-variant pairs identified by Counsyl to be present in QCI’s variant-specific reference lists. QCI held 13,938 additional article-variant pairs for the evaluated variants, reflecting the comprehensive nature of their article-centric approach, which aims to capture all publications for a given variant (below, left). By contrast, for reasons of efficiency, Counsyl curates a sufficient number of literature references to reach pathogenicity thresholds.



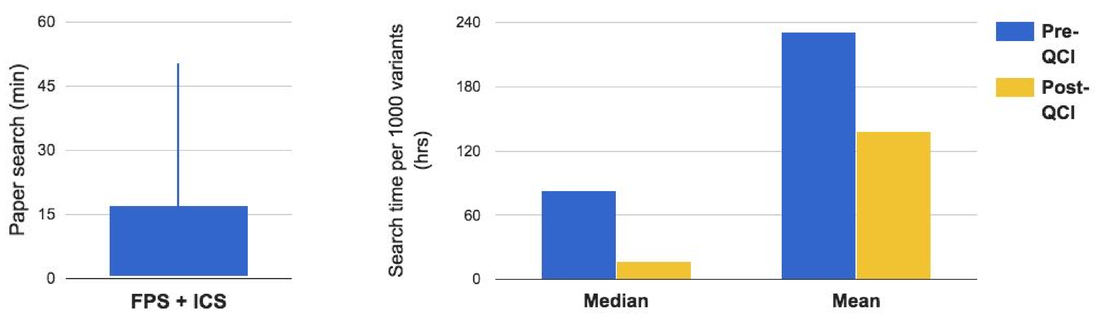




Overall, there were a total of 682 variants classified as pathogenic in the three month production set. Of these, only eight would be downgraded to VUS utilizing only QCI bibliographies (above, right). Therefore, the false negative rate for using QCI’s bibliographies was ~1.2%, and is expected to decrease to <1%. Furthermore, for a sample of 50 VUS variants examined, none would change classification with additional unique references in QCI, primarily because QCI includes secondary reports and studies for other disease contexts that may be listed as 'reviewed but not curated' in Counsyl curations.

As a result of these positive findings, QCI bibliographies have been integrated into our manual curation workflow, and have eliminated the need for manual search in the majority of cases. (Left: variant-specific page in QCI).

After several months, we performed a comparison of the time taken for reference searches before and after the adoption of QCI (below).



Conclusions

The goal of this evaluation was to assess whether utilization of QIAGEN’s variant-specific bibliographies could match the level of accuracy and quality of Counsyl’s more time-intensive manual article selection approach. We conclude that there are clear benefits for adopting QCI for reference identification: an exceptionally high variant-specific article coverage, and significant time savings in a search process that can take up to ~45 minutes. The results also serve to validate the efficacy of Counsyl’s previous article search and selection method, with the vast majority of variant classifications being unaltered by use of QIAGEN’s bibliographies. Counsyl now employs QCI bibliographies for every curated variant. Consequently, manual search methods are still employed at Counsyl, but can now be reserved for variants nearer VUS/pathogenic evidence thresholds.

QCI has already proven a valuable resource for increasing the efficiency of Counsyl’s in-house curation. Work is underway to additionally incorporate QIAGEN’s continually-updated bibliographies into the automated components of our variant classification workflows: the initial software-based auto-curation step for newly-identified variants, and the identification of those requiring re-curation in response to new publications becoming available. Accordingly, we expect QCI to further contribute to Counsyl’s continuing efforts to improve turnaround time by increasing curation efficiency while maintaining classification accuracy in patient reports.