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 recessive diseases (Foresight) and a panel of up to 36 genes for hereditary cancer risk assessment (Reliant). The identification of articles mentioning a specific disease-gene variant is crucial to the accurate and robust appraisal of variant pathogenicity, and it 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 (Figure 1). Pathogenicity is assessed using ACMG guidelines and is based on published case and functional studies, variant databases, population frequency, conservation, and in silico predictors.

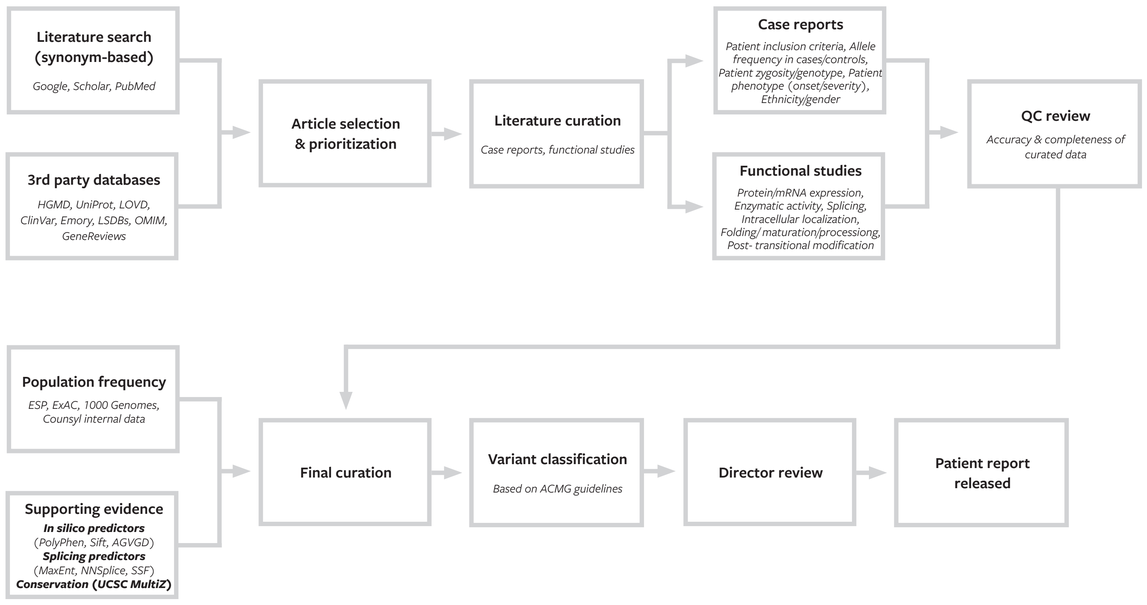

Figure 1: The manual curation workflow at Counsyl

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 training 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 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 a more comprehensive nature of article identification through their article-centric approach, which aims to capture all publications for a given variant (Figure 2A). By contrast, for reasons of efficiency, Counsyl curates a finite number of literature references to reach pathogenicity thresholds.

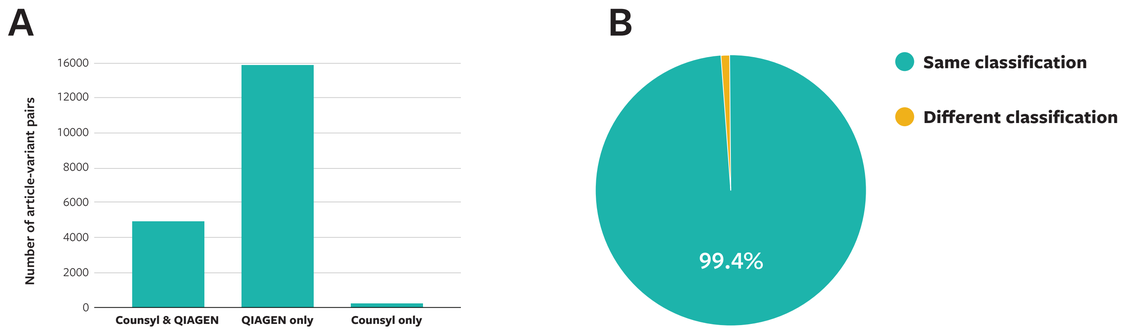

Figure 2: (A) Overlap of variant-specific references curated by Counsyl and within QCI Bibliographies. (B) Comparison of Counsyl classifications with those reached using QCI bibliographies.

Overall, there were a total of 682 variants classified as pathogenic in the three month evaluation set, and an additional 2926 variants have been classified as pathogenic since the adoption of QCI in Q4 2016. Of these, only 23 would be downgraded to VUS utilizing only QCI bibliographies (Figure 2B). Therefore, assuming the truth of Counsyl's curations, the false negative rate for using QCI's bibliographies is ~0.6%, and is expected to decrease further with additional QCI revisions. Furthermore, for a sample of 50 VUSs examined, none would change classification with additional unique references in QCI. This is primarily because QCI includes secondary reports and studies for other disease contexts that are not curated by Counsyl, but are instead separately listed in curations as reviewed (and not included in this analysis)

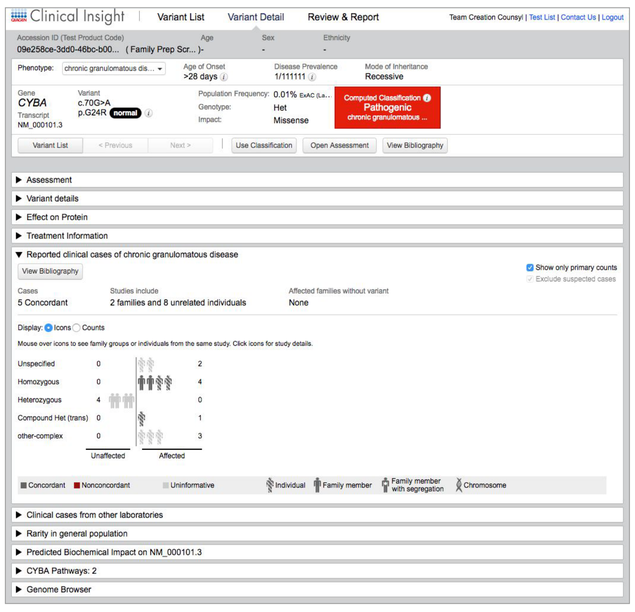

Figure 3 (left): An example variant-specific page in QCI.

As a result of these highly concordant findings, QCI bibliographies have been integrated into our manual curation workflow, and have eliminated the need for manual article search in the majority of cases. However, we continue to do manual searches for scenarios that resulted in downgrade to VUS, including variants on the borderline of VUS/ pathogenic, and genes with naming/mapping issues.

After several months, we performed a comparison of the time taken for reference searches before and after the adoption of QCI (Figure 4).

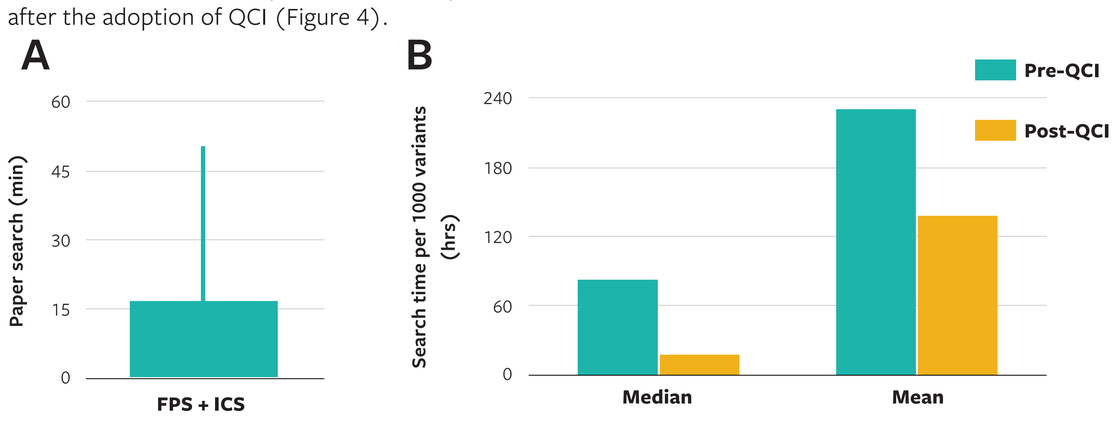

Figure 4: (A) Manual reference search time per variant with Counsyl's previous workflow. (B) Time savings from adoption of QCI bibliographies.

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 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 potentially impact turnaround time by increasing curation efficiency while maintaining classification accuracy in patient reports.