Proposal for a Clinical Decision Support Tool for Variant Interpretation at WMRGL

## Executive Summary

The Genomics department is currently facing a transition period due to the upcoming decommissioning of the Alissa Interpreter software, which has served as a clinical decision support system (DSS) for variant interpretation. This tool has been a core part of the workflow for clinical scientists, especially in the interpretation workflow for both the panHO and TSO500 pipelines, enabling clinical scientists to visualise variant calls, apply structured filters, annotate with up-to-date reference databases (RefSeq, GnomAD, COSMIC, ClinVar), and export structured Excel reports.

Filtering settings are defined using a decision tree model which reduces the number of variants requiring manual interpretation. Filtering logic incorporates a range of parameters, including variant allele frequency (VAF), read depth, region-based inclusion, population frequency thresholds and variant quality indicators. This filtering capability is vital to maintain high-quality, focused clinical interpretation.

Without a suitable replacement, variant interpretation and reporting will be severely disrupted, potentially compromising both the quality and timeliness of clinical services, it would also increase the risk of human error and could compromise the consistency and regulatory compliance of clinical reports.

This document outlines three potential options moving forward: continuing without a replacement ("do nothing"), exploring the adoption of Congenica as an alternative, or building a bespoke DSS solution in-house. Each option is assessed in terms of feasibility, clinical suitability, financial impact and risk.

We recommend moving forward with investigating an in-house solution, designed and tailored specifically for cancer variant interpretation workflows, with direct input from clinical scientists and system developing stakeholders. This approach, while resource-intensive initially, offers long-term sustainability and alignment with the evolving needs of our genomics service.

## Options Appraisal

**Option 1: Do Nothing**

Continuing without a DSS is not viable. The existing clinical services rely on structured variant output, dynamic filtering, and curated annotations to interpret somatic mutations efficiently; thus, manual processes would not meet current volume or turnaround expectations.

Key missing features in a "do nothing" scenario include:

* Annotation with RefSeq, GnomAD, Revel score, and other data sources
* Filtered Excel reports for variant interpretation
* Tabular CNV output integration
* VAF- and BED-based filtering for pipelines like TSO500

**Risks:** Loss of data integrity, increased turnaround time, regulatory and accreditation issues and significant operational disruption.

**Option 2: Congenica**

Congenica is a commercial genomic interpretation tool primarily geared towards rare disease diagnostics. While the platform offers some filtering and annotation capabilities, its design is not optimised for cancer-focused pipelines like panHO and TSO500. Functional gaps may include poor support for somatic-specific metrics, CNV handling, or flexible filtering based on tumour-specific thresholds (e.g. variant allele frequency, population frequency, read depth).

Moreover, the TSO500 pipeline requires structured outputs including CNV, SNP, and quality metrics in separate tabs of a filtered Excel report, this functionality is not available with Congenica.

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| Benefits | Risks |
| Vendor-supported product with user support and documentation | Platform misaligned with departmental cancer workflows |
| Quicker to implement than a build-from-scratch tool/ already in use in department | Limited customisation and vendor dependent updates |
| Designed for clinical use | Potential for sunk cost if later deemed unsuitable. |
| Likely compliant with IVDR; externally maintained for regulatory alignment. | Data privacy concerns with third-party vendor. |

**Option 3: Build an In-House Solution**

A custom-built DSS would allow the department to replicate and improve upon Alissa’s core functionalities, specifically tailored to our pipelines. The in-house tool could also support the inclusion of blank fields for interpretation notes and a buildable database to track recurrent variants across patient cohorts. This approach ensures long-term adaptability and integration with departmental workflows.

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| Benefits | Risks |
| Fully tailored to current clinical workflows | Significant upfront development time and staff resources |
| Easily adaptable to future features, will support regulatory compliance | Potential delays in delivery |
| No ambiguity in ownership and responsibility, less concerns about data security and compliance | Requires extensive validation |
| Long-term cost savings, no vendor lock-in which builds internal capability. |  |

**Conclusion**

After thorough evaluation of the available options, building an in-house clinical decision support system represents the most sustainable and strategic path forward. While this approach requires initial investment in time and resources, it provides the highest degree of flexibility, control, and alignment with both clinical and technical needs specific to our cancer-focused workflows.

An internally developed solution can be tailored to meet the evolving requirements of the panHO and TSO500 pipelines, ensure integration with existing systems, and allow for future enhancements such as TMB support, disease-specific databases, and variant tracking. Furthermore, it positions the organisation to maintain compliance with regulatory standards while safeguarding ethical standards around data use and patient care.

The in-house option also fosters cross-disciplinary collaboration between clinical scientists and developers, enabling a shared understanding of the tools that underpin clinical services. This collaborative model supports continuous improvement and innovation.