Genoxus Labs

WHITE PAPER

From Genetic Variation to Disease Hypotheses

A Systematic Approach to Genomic Interpretation

Genoxus Variant Analysis™

version 1.0

Genoxus Labs

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Table of Contents

Executive Summary 3

Market & Industry Challenges 4

Product Overview 5

Technical Approach and Methodology 6

- Main Workflow 6
- Key Technologies 6
- Data Input, Processing, and Output 7
- Quality Control, Validation, and Reliability 8
- Technical Innovations and Differentiators 8

Key Benefits and Competitive Differentiation 10

- Key Benefits 10
- Comparison with Existing Approaches 10
- Case Study 1: Developmental Delay, Seizures, and a Characteristic MRI Finding 11
- Case Study 2: Developmental Delay and Nystagmus in a Toddler 12
- Case Study 3: Multi-Condition History with a Family History of Cancer 13

Service Delivery & Client Engagement 15

- Service Process 15
- Service Applications 15
- Data Security and Privacy 16
- Scientific Support and Collaboration 16

Conclusion and Call to Action 17

References 18

Executive Summary

Genoxus Variant Analysis (GVA) version 1.0 is a genomic analysis solution designed to help sequencing companies, geneticists, research laboratories, and healthcare organizations extract actionable research insights from whole-exome sequencing (WES) data. Going beyond predefined disease-related gene panels, GVA1.0 systematically analyzes genetic variants across the sequencing data to identify variants potentially associated with medical conditions, collects pathogenic and likely pathogenic variants, and highlights Variants of Uncertain Significance (VUS). GVA1.0 delivers a structured report organizing prioritized findings into three categories: primary findings, linking variants to reported medical conditions; pathogenic findings, capturing variants classified as pathogenic or likely pathogenic; and VUS findings, highlighting variants requiring further investigation. In addition to the report, GVA1.0 delivers an Excel file with a comprehensive and structured list of identified variants across all three categories for downstream analysis and review. By combining broad variant assessment with clear and organized deliverables, GVA1.0 complements existing sequencing and interpretation workflows, supports research investigations, and helps organizations derive greater value from genomic data.

KEY TAKEAWAYS

- **Broader than a gene panel:** GVA1.0 assesses variants across the entire submitted whole-exome sequencing (WES) dataset and links them to documented disease and trait associations.
- **Three clearly separated outputs:** Primary Findings, Pathogenic Findings, and VUS Findings, delivered with a supplementary Excel file for downstream analysis.
- **One integrated workflow:** variant annotation (VEP with AI plugins), curated evidence from Genoxus Annotation™, and association scoring and prioritization.
- **Decision support, not diagnosis:** findings are intended for expert review alongside the clinical presentation, family history, and other relevant evidence.
- **Practical engagement:** reports typically become available within 5 business days of VCF submission, with data handled through a secure portal and encrypted storage.

Market & Industry Challenges

The global genomics data analysis market is growing as next-generation sequencing (NGS) becomes increasingly important in biomedical research, precision medicine, and the investigation of rare and complex diseases. According to Grand View Research (https://www.grandviewresearch.com/) [10], the market was valued at approximately $6.5 billion in 2025 and is projected to reach $18.1 billion by 2033, representing a compound annual growth rate (CAGR) of 13.4%. Variant calling and annotation accounted for more than 29.8% of market revenue in 2025, highlighting the demand for tools that help translate sequencing data into meaningful insights.

$6.5B	$18.1B	13.4%	29.8%
Global genomics data analysis market, 2025	Projected market size by 2033	Projected compound annual growth rate	Share of 2025 revenue from variant calling and annotation

Source: Grand View Research [10]

Despite these advances, translating large volumes of genomic data into clear, interpretable findings remains challenging. Sequencing and research laboratories, genetic counselors, and healthcare providers must integrate variant-level evidence with an individual's medical history, prioritize potentially relevant variants, and distinguish established pathogenic findings from variants of uncertain significance (VUS). Even with sophisticated analytical pipelines, results may remain inconclusive, and reviewing, interpreting, and communicating findings can require substantial time and specialized expertise.

The market offers a range of genomic analysis solutions, including variant annotation tools, bioinformatics platforms, automated reporting systems, and clinical interpretation workflows. However, these solutions differ in scope, accessibility, and intended use. Some focus on predefined gene panels or specific clinical applications, while others emphasize annotation, secondary analysis, or specialist bioinformatics workflows. Automated and AI-assisted approaches can support interpretation but do not eliminate the need for professional review or resolve every complex case.

Consequently, a gap remains between generating genomic data and producing a structured overview of findings relevant to an individual's reported medical conditions, established pathogenic classifications, and variants that may warrant further investigation. Addressing this gap requires analytical approaches that organize evidence, support variant prioritization, and communicate findings in an accessible and systematic format.

Product Overview

GVA1.0 is a genomic variant interpretation solution designed to help users extract meaningful insights from genetic testing data. It analyzes genetic variants ranging from single-nucleotide variants (SNVs) and small insertions and deletions (indels) to structural variants (SVs), maps variants to known disease and human-trait associations, and organizes the results into a structured report. GVA1.0 is primarily intended for genetic counselors, research scientists, and other professionals or users with the expertise to interpret genetic test results. It can support research investigations and provide organized evidence for professional review in diagnostic workflows.

GVA1.0 combines four core capabilities to support systematic genetic variant assessment: **(1) AI-empowered variant annotation** enriches variants with relevant biological and functional information to facilitate interpretation; **(2) variant–disease/trait association** identifies relationships between genetic variants and known diseases or human traits by querying expert-curated databases; **(3) association scoring** evaluates the strength or relevance of these relationships; and **(4) variant prioritization** ranks findings based on predicted variant impact and the strength of disease or trait associations, helping users focus on variants that warrant closer investigation. Together, these capabilities provide a structured approach to interpreting genetic variation and identifying potentially relevant findings for clinical review and research.

GVA1.0 is designed to support the interpretation and prioritization of genetic variants in research-oriented and professional review settings. Its applications include investigating potential genetic contributors to reported medical conditions, reviewing variants with established pathogenic or likely pathogenic classifications, highlighting variants of uncertain significance for further study, and organizing findings for downstream analysis. The structured report is intended to help users review and communicate relevant results, while the accompanying variant-level data can support additional research and interpretation. GVA1.0 is a decision-support resource, not a substitute for expert judgment, genetic counseling, or comprehensive clinical evaluation. Its findings should be reviewed in the context of the available evidence and the individual's clinical information; the product should not be used as a standalone basis for medical diagnosis or treatment decisions.

Technical Approach and Methodology

Main Workflow

GVA1.0 is designed to support the analysis and interpretation of whole-exome sequencing (WES) results. As illustrated in Figure 1, the workflow begins with a VCF file, which is annotated using the Ensembl Variant Effect Predictor (VEP)[1] with AI plugins. The annotated VCF is then parsed, and variants are filtered based on intrinsic features and quality information from the sequencing data. The retained variants are mapped to known disease and/or human-trait associations using Genoxus Annotation™, after which findings are prioritized according to the relevance and liability of the corresponding assertions in Genoxus Annotation™. The AI plugins supplement conventional annotation with additional information about the potential biological and functional effects of genetic variants. The final outputs include a structured report organizing potentially relevant findings, pathogenic and likely pathogenic variants, and variants of uncertain significance (VUS), together with a supplementary Excel file for further review and analysis.

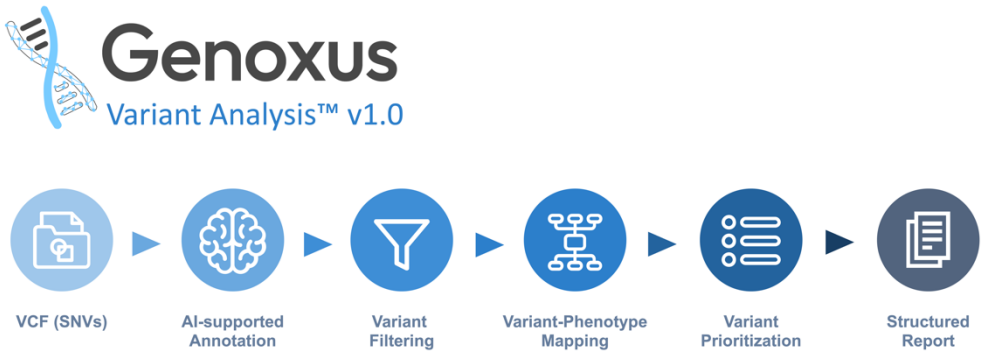


Figure 1. Main flow of GVA1.0.

Key Technologies

Customized VCF Parsing and Quality Control

GVA1.0 uses a customized VCF parsing component to extract variant records and relevant fields from customer-provided WES data. Initial checks assess whether the input can be processed and whether the required variant information is available. Variant-level quality checks are applied as appropriate to the fields and quality metrics present in the VCF. These steps help identify records that may be unsuitable for downstream analysis and establish a consistent input for annotation and prioritization.

AI-supported Variant Annotation

GVA1.0 uses VEP to annotate genetic variants with information such as their genomic context, affected transcripts, and predicted consequences. AI-enabled models supplement this annotation with additional biological and functional context relevant to interpreting potential variant effects. This combined annotation provides supporting information for downstream assessment; computational predictions are treated as evidence for investigation rather than as definitive proof of pathogenicity.

Variant–Phenotype Mapping with Genoxus Annotation™

GVA1.0 uses Genoxus Annotation™, a previously developed variant-to-disease and variant-to-human-trait mapping engine, to connect annotated variants with documented associations. The resource integrates information from curated and established genetics databases, including ClinVar[2], the GWAS Catalog[3], OMIM, ClinGen[4], and gnomAD[5]. These resources contribute different types of evidence, including clinical variant classifications, disease and trait associations, gene–disease evidence, and population allele-frequency information. The resulting mappings provide a knowledge-based foundation for evaluating which variants may be relevant to the conditions under investigation.

Variant Prioritization and Association Scoring

After variant filtering and phenotype mapping, GVA1.0 evaluates the relevance of candidate findings and generates prioritization scores to help users focus their review. This stage considers the strength and validity of available variant–disease or variant–trait evidence, together with relevant information about variant impact. The scores support comparative prioritization within the analysis; they should not be interpreted as calibrated probabilities of disease, independent confirmation of causality, or substitutes for clinical classification. The prioritized results are then organized into the report categories used by GVA1.0.

Data Input, Processing, and Output

GVA1.0 accepts customer-provided VCF files derived from WES. Files are uploaded through a secured portal and processed by the GVA1.0 workflow. Input files, intermediate artifacts generated during processing, and final reports are stored in Genoxus's encrypted Amazon Web Services (AWS) S3 storage environment. The workflow produces two primary deliverables:

- **Structured analysis report:** organizes prioritized findings into Primary Findings, Pathogenic Findings, and VUS Findings to support review of potentially relevant variants.
- **Supplementary Excel file:** provides a structured listing of identified variants across the report categories for detailed inspection, downstream analysis, and record keeping.

The input VCF, intermediate processing artifacts, and final outputs support traceability across the analysis workflow. The exact contents retained and the applicable access, retention, and deletion controls should be documented in the product's operational and data-handling policies.

Quality Control, Validation, and Reliability

GVA1.0 incorporates quality-control considerations at multiple stages to help maintain the consistency and interpretability of its outputs.

Input and variant-level checks. The input file is checked for processability and the presence of required fields. Available variant-level quality information is reviewed to identify records that may require caution or exclusion from downstream analysis. Because VCF contents and quality annotations can vary across sequencing pipelines, the checks depend in part on the information supplied in the input file.

Annotation and database consistency. Variants are annotated through VEP and mapped using Genoxus Annotation™. Reliable interpretation depends on consistent reference-genome and variant representations, appropriate transcript and annotation versions, and up-to-date association resources. Database-derived classifications and associations should be distinguished from computational predictions and from conclusions made during downstream professional review.

Prioritization review. Association scores and ranking are intended to organize candidate findings, not to establish a diagnosis by themselves. The strength of a reported association depends on the underlying evidence, the type of association, and the quality and completeness of the available data. Findings should be interpreted in the context of the individual's reported conditions, clinical presentation, family history, and other relevant evidence.

Ongoing verification and improvement. As part of product development and maintenance, GVA1.0 can be evaluated using representative VCF files, known variants, expected annotation and mapping results, and regression tests to check whether software or database updates introduce unexpected changes. Where suitable benchmark datasets and reference interpretations are available, concordance and prioritization performance can be assessed and documented. Any performance claims should specify the datasets, evaluation criteria, and limitations involved.

GVA1.0 is a research-oriented variant analysis tool intended to support professional review. Unless and until formal validation evidence is available for a particular use, its outputs should not be regarded as independently validated clinical diagnoses or used as the sole basis for medical management decisions.

Technical Innovations and Differentiators

Broad variant assessment beyond predefined gene panels. Rather than limiting its analysis to a user-selected list of disease-associated genes, GVA1.0 is designed to assess variants across the submitted WES dataset. This broader approach can help users investigate potential genetic contributors that may not have been anticipated at the outset, while recognizing that findings remain limited by the coverage and quality of the input data and the scope of the analysis.

Integration of annotation, curated associations, and prioritization. GVA1.0 connects variant annotation with disease and human-trait mapping through Genoxus Annotation™ and then applies an association-

scoring and prioritization stage. Bringing these capabilities into a single workflow helps organize information that might otherwise require separate tools and manual review.

AI-assisted interpretation support. AI-enabled models supplement conventional variant annotation with additional biological and functional context. Used alongside established databases and variant-level information, this additional context can help users investigate potential effects. AI-derived outputs are treated as supporting evidence and require appropriate interpretation, rather than being presented as definitive statements of clinical significance.

Structured findings for different review needs. The separation of Primary Findings, Pathogenic Findings, and VUS Findings helps distinguish variants potentially related to reported medical conditions from variants classified as pathogenic or likely pathogenic and those with uncertain significance. The accompanying Excel file supports detailed review, filtering, and downstream analysis.

Designed to complement professional workflows. By combining broad variant assessment, evidence mapping, and organized reporting, GVA1.0 can provide an additional layer of analysis for research investigations and professional review of genetic test results, including cases that remain unresolved after initial assessment. It is designed to complement, not replace, expert interpretation and established clinical evaluation.

Key Benefits and Competitive Differentiation

GVA1.0 helps researchers and genetics professionals investigate potential genetic contributors to reported medical conditions by combining broad WES variant assessment, evidence integration, and structured reporting.

Key Benefits

- **Broad variant discovery:** Assesses variants across the submitted WES dataset rather than restricting analysis to a predefined list of disease-associated genes, helping identify candidates beyond the scope of targeted panels.
- **Integrated evidence analysis:** Combines variant annotation, population-frequency data, and curated disease/trait associations in a connected workflow, reducing the effort required to gather information from multiple sources.
- **Evidence-informed prioritization:** Uses association scoring and variant prioritization to help users focus on findings that may be relevant to the conditions under investigation.
- **Structured findings:** Separates variants potentially associated with reported medical conditions (Primary Findings), variants classified as pathogenic or likely pathogenic (Pathogenic Findings), and variants of uncertain significance (VUS Findings), supporting systematic review and follow-up investigation.

Comparison with Existing Approaches

Existing genomic analysis solutions vary in scope and workflow. Compared with common approaches, GVA1.0 offers three key distinctions:

- **Beyond predefined gene panels:** Targeted panels focus on selected genes, whereas GVA1.0 assesses variants across the submitted WES dataset to support broader investigation.
- **Beyond standalone annotation:** Annotation tools provide variant-level information, while GVA1.0 combines annotation with curated genetic evidence and prioritization to help identify candidates for further review.
- **Beyond fragmented workflows:** When annotation, evidence gathering, and prioritization rely on separate tools, users may need to consolidate results manually. GVA1.0 brings these steps together and provides a structured report with an accompanying Excel file for detailed review and downstream analysis.

GVA1.0 is designed to complement existing research and professional interpretation workflows. Its findings require expert review and should be interpreted alongside clinical presentation, family history,

and other relevant evidence. GVA1.0 does not independently establish a diagnosis or replace professional clinical judgment.

Case Study 1: Developmental Delay, Seizures, and a Characteristic MRI Finding

> **CASE SNAPSHOT**
> The testee was an 8-year-old girl with significant global developmental delay, including delays in walking and speech, as well as a history of seizures and nystagmus (involuntary eye movements). Brain MRI revealed the characteristic "molar tooth sign," a structural finding associated with Joubert syndrome. These neurological and developmental complications provided the clinical context for the whole-exome sequencing (WES) analysis.

GVA1.0 analyzed the submitted genetic variant data and identified several variants associated in the report with neurological, neurodevelopmental, or seizure-related conditions. These findings were organized to help highlight potential connections between the testee's clinical features and reported gene–disease associations.

GVA1.0 Findings

1. ***ARL13B* — Joubert syndrome 8:** The homozygous variant NM_001174150.2(ARL13B):c.599G>A (p.Arg200His) was reported as likely pathogenic and associated with Joubert syndrome 8. This association is particularly relevant to the testee's MRI finding of the molar tooth sign and her developmental and neurological complications.
2. ***DIAPH1* — Progressive microcephaly, seizures, cortical blindness, and developmental delay syndrome:** The heterozygous variant NM_005219.5(DIAPH1):c.3149-2A>G was reported as likely pathogenic and associated with a disorder that can involve seizures and developmental delay. These reported features overlap with some of the testee's clinical complications and may warrant further evaluation.
3. ***PNPO* — Pyridoxal phosphate-responsive seizures:** The heterozygous variant NM_018129.4(PNPO):c.*643C>T was listed with uncertain clinical significance and associated with pyridoxal phosphate-responsive seizures. Given the testee's history of seizures, this association may be relevant for further investigation; however, the variant's clinical significance remains unresolved.
4. ***CEP41* — Joubert syndrome 15:** The heterozygous variant NM_018718.3(CEP41):c.*1385T>G was listed as a variant of uncertain significance and associated with Joubert syndrome 15. The reported gene–disease association is relevant to the broader Joubert syndrome context, but the available information does not establish that this specific variant contributes to the testee's condition.

The association between ***ARL13B* and Joubert syndrome** is supported by published research. Cantagrel et al. (2008) identified disease-associated *ARL13B* variants in families affected by Joubert syndrome and reported that affected individuals displayed the characteristic molar tooth sign on brain imaging[6]. Functional studies further supported a role for *ARL13B* in ciliary function. These findings provide independent scientific support for prioritizing the testee's homozygous *ARL13B* variant, c.599G>A (p.Arg200His), in light of the testee's clinical presentation. However, the study does not specifically validate this exact variant; its clinical significance should therefore be assessed using variant-specific evidence and professional review.

Case Study 2: Developmental Delay and Nystagmus in a Toddler

> **CASE SNAPSHOT**
> The testee was a 2-year-old boy with global developmental delay, hypotonia (low muscle tone), microcephaly (a smaller-than-expected head size), nystagmus (involuntary eye movements), difficulty holding his head upright, and cerebral palsy. Previous evaluations included chromosomal microarray analysis, exome sequencing, and neurological assessments. GVA was used to organize reported genetic findings, connect variants with relevant disease and trait associations, and highlight findings that may warrant further investigation.

GVA1.0 Findings

1. ***TYR* — Pathogenic:** The heterozygous variant NM_000372.5(TYR):c.1255G>A (p.Gly419Arg) was classified as pathogenic in the report and associated with albinism and congenital nystagmus. The reported association with nystagmus is relevant to the testee's clinical presentation. However, the variant's contribution to the testee's symptoms, including whether an associated pigment or visual phenotype is present, requires clinical assessment.
2. ***PEX5* — Likely Pathogenic/Pathogenic:** The report identified *PEX5* splice-region variants, NM_001351132.2:c.147+4A>G and c.147+2T>G, alongside a reported chromosome 12 region finding. These findings were associated with peroxisome biogenesis disorders, including Zellweger spectrum disorders. Given the reported classification and potentially serious disease associations, this result warrants careful review of the underlying genomic calls, copy-number interpretation, and inheritance information before any clinical conclusion is drawn.
3. ***MCPH1* — Variant of Uncertain Significance (VUS):** The heterozygous variant NM_024596.5(MCPH1):c.783T>A (p.Asp261Glu) was classified as a VUS and associated with autosomal recessive primary microcephaly. The association is relevant to the testee's reported microcephaly, but a single heterozygous VUS does not establish MCPH1-related disease. Additional evidence, including assessment for a second disease-associated allele, would be needed.

The reported *TYR* variant, NM_000372.5:c.1255G>A (p.Gly419Arg), is classified as pathogenic in the Genoxus report. The *TYR* gene encodes tyrosinase, an enzyme essential for melanin production, and pathogenic variants in both copies of *TYR* are an established cause of oculocutaneous albinism type 1[7]. Albinism can affect visual development and is frequently accompanied by nystagmus.

A 2024 mouse study by Johnson et al. provides additional biological context. The researchers observed spontaneous nystagmus in all tested B6 albino mice carrying a *TYR* mutation, supporting a potential mechanistic relationship between *TYR*–associated albinism and abnormal eye movements[8]. However, animal-model findings cannot independently establish that a specific human *TYR* variant causes nystagmus. The study therefore provides supportive biological evidence, rather than direct validation of the testee's variant–phenotype relationship.

An important limitation is that the report lists p.Gly419Arg as heterozygous, whereas TYR-related oculocutaneous albinism is typically inherited in an autosomal recessive manner. The available information does not establish whether a second disease-associated *TYR* variant is present or whether the testee has clinical features of albinism. Accordingly, the variant's relevance to the reported nystagmus should be interpreted cautiously, with review of the original sequencing data, assessment for a second *TYR* variant where appropriate, and correlation with ophthalmologic and pigmentation findings.

Case Study 3: Multi-Condition History with a Family History of Cancer

> **CASE SNAPSHOT**
> The testee has a reported history of irritable bowel syndrome (IBS), Crohn's disease, Hashimoto's thyroiditis, hypercholesterolemia, and endometriosis, along with a family history of ovarian and uterine cancer. To identify potentially relevant genetic findings, GVA1.0 assessed variants associated with broader or standardized disease terms, including inflammatory bowel disease, hypothyroidism, hypercholesterolemia, endometriosis, ovarian cancer, and uterine cancer, as well as variants classified as pathogenic. These search terms were used to broaden the analysis and do not necessarily correspond directly to the client's reported diagnoses. For example, IBS and Crohn's disease are distinct conditions, while Crohn's disease is a form of inflammatory bowel disease and Hashimoto's thyroiditis can cause hypothyroidism.

GVA1.0 Findings

1. ***APOE*:** The client was reported to be homozygous for the *APOE* ε4 allele, with the p.Cys130Arg substitution present on both copies. The *APOE* ε4 isoform is associated with altered lipid metabolism, including higher LDL cholesterol in some individuals, and an increased risk of late-onset Alzheimer's disease[9]. This finding indicates a genetic risk association; it does not establish a diagnosis or predict with certainty that the client will develop Alzheimer's disease.

2. ***BRCA1/BRCA2*:** Multiple heterozygous variants in *BRCA1* and *BRCA2* were identified. Given the reported family history of ovarian and uterine cancer, these findings may warrant further evaluation. Their relevance to hereditary cancer risk depends on the classification and evidence for each individual variant; the presence of variants alone does not establish an inherited cancer predisposition.
3. ***MTRR*:** A homozygous stop-gain variant, NM_002454.3:c.524C>A (p.Ser175Ter), was identified in *MTRR*. This variant introduces a premature termination codon and is predicted to produce a truncated protein, potentially disrupting *MTRR* function. Biallelic pathogenic variants in *MTRR* are associated with rare disorders of cobalamin metabolism, and *MTRR* has also been investigated in relation to folate-sensitive neural tube defects. The clinical significance of this finding requires interpretation alongside the client's clinical and family history and the available variant-specific evidence.
4. **Other findings:** Variants associated in the analysis with IBS-related traits and hypothyroidism were also identified but were classified as benign or likely benign. They were therefore not included among the reportable findings, although they remain available in the accompanying Excel file for reference.

The findings should be interpreted according to the strength of the evidence supporting each variant and its associated condition. The *APOE* ε4 finding is best understood as a risk-associated genotype rather than a deterministic prediction of disease. For *BRCA1* and *BRCA2*, variant-level classification and clinical review are necessary before drawing conclusions about hereditary cancer risk. The *MTRR* stop-gain variant has a predicted protein-truncating effect, but the extent to which it impairs protein function and contributes to a specific clinical condition cannot be established from the predicted consequence alone. Review of the original sequencing data, confirmation of relevant genotypes, and correlation with clinical and family history would help clarify these findings.

Service Delivery & Client Engagement

GVA1.0 is a genomic variant interpretation service designed to help clients derive structured, evidence-informed insights from whole-exome sequencing (WES) data. Genoxus works with clients to define the scope of each analysis, interpret potentially relevant findings in the context of reported medical conditions, and deliver a structured report with supplementary Excel files. The service can complement existing sequencing, research, and clinical interpretation workflows without requiring clients to adopt a new software platform.

Service Process

A typical engagement follows five steps:

1. **Scoping:** Genoxus and the client confirm the analysis objectives, reported medical conditions, and relevant family history. These details guide the selection of disease and trait terms used to identify potentially relevant findings.
2. **Data Submission:** The client submits a WES-derived VCF file through the designated secure portal. The reference genome build and available genotype and sequencing-quality fields help determine the scope of analysis and quality assessment. The case studies in this white paper use GRCh38/hg38 coordinates.
3. **Variant Analysis:** Genoxus processes the submitted data through its annotation, filtering, disease-association mapping, and prioritization workflow.
4. **Report Delivery:** The client receives a structured report organized into Primary, Pathogenic, and VUS Findings, together with supplementary Excel files containing detailed variant information.
5. **Review and Follow-up:** Genoxus can address questions about the analysis and its deliverables. Clients and their qualified professionals can assess the findings in context and determine whether further review, confirmatory testing, or genetic counseling is appropriate.

WES reports typically become available within 5 business days after VCF file submission.

Service Applications

GVA1.0 can support several types of analysis engagements. These include further investigation of cases that remain unresolved after an initial assessment, research-oriented analysis of individual samples or cohorts, and interpretation services offered in collaboration with sequencing providers. The scope and deliverables are agreed upon for each engagement.

Reports provide a structured overview of findings potentially relevant to the conditions specified by the client, pathogenic or likely pathogenic classifications represented in the available evidence, and variants of uncertain significance. Supplementary Excel files provide additional detail for further filtering and

review. Findings should be interpreted in light of the available clinical information and supporting evidence; they do not replace professional clinical judgment or appropriate confirmatory testing.

Data Security and Privacy

Genomic data are highly sensitive and potentially identifying, making data protection an important part of service delivery. Client-provided VCF files are submitted through a secure portal. Input files, intermediate processing artifacts, and final reports are stored in Genoxus's encrypted Amazon Web Services (AWS) S3 environment to support data management and traceability throughout the analysis workflow. Access, retention, and deletion are governed by Genoxus's applicable operational and data-handling policies. Data in-transit or at-rest is encrypted.

Direct personal identifiers are not required for variant analysis itself. Clients are encouraged to use coded sample identifiers and provide only the clinical information necessary to define the analysis scope.

Scientific Support and Collaboration

Scientific consultation. Genoxus can discuss the analysis scope, explain report organization and supporting evidence, and address questions about individual findings with the client's professional team.

Case-specific analysis. Because Primary Findings are defined in relation to the reported conditions, the analysis can use broader or standardized disease and trait terms when necessary to capture relevant associations. Additional review or an addendum may be considered when new information or further assessment warrants it.

Research and industry partnerships. Genoxus welcomes collaboration with sequencing providers seeking to offer an interpretation service alongside their sequencing deliverables, research laboratories investigating individual cases or cohorts, and healthcare organizations interested in evaluating the service within their existing workflows.

For service inquiries and collaboration opportunities, contact Genoxus Labs at support@genoxuslabs.com or visit genoxuslabs.com.

Conclusion and Call to Action

The growing use of whole-exome sequencing has shifted the central challenge in genomics from generating data to interpreting it. Many individuals remain without an explanation after initial analysis, and professionals must review, prioritize, and communicate large numbers of variants with evidence of varying strength. Genoxus Variant Analysis (GVA) addresses this challenge by assessing variants across the submitted WES dataset, mapping them to documented disease and trait associations, scoring and prioritizing the resulting findings, and organizing them into Primary, Pathogenic, and VUS Findings with a structured Excel file for downstream analysis.

The case studies in this paper show how this design operates across presentations ranging from pediatric neurodevelopmental and neurological presentations to an adult with a multi-condition history and a family history of cancer: findings are separated by relevance and evidence strength, uncertainty is stated explicitly, and elements that call for confirmation are flagged. GVA1.0 is a research-oriented decision-support resource that complements, and does not replace, expert interpretation, genetic counseling, and clinical evaluation.

Next steps. Organizations interested in GVA1.0 can begin in any of the following ways.

1. **Request a sample report and Excel file** to evaluate the structure, level of detail, and language of the deliverables.
2. **Submit a pilot VCF**, ideally from a previously analyzed case that remains unresolved, to compare GVA1.0 findings with existing results.
3. **Schedule a scientific consultation** to define the scope of an analysis, discuss integration with existing workflows, and explore partnership options.

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NOTICE

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