GENEYX

Better Data for Better Health

Geneyx Analysis Technical Datasheet: A clinical genetics data management platform

GENEYX ANALYSIS TECHNICAL DATASHEET: A CLINICAL GENETICS DATA MANAGEMENT PLATFORM

Overview:

Geneyx Analysis is a comprehensive bioinformatic solution for analyzing and interpreting DNA/RNA sequencing data for both NGS and microarrays. This solution offers scalability for short-read and long-read workflows and provides novel biomedical insights for variant-gene and gene-disease associations. With these capabilities, *Geneyx Analysis* has been adopted globally for research, academia, and clinical diagnostic workflows.

Introduction:

Geneyx Analysis empowers hospitals and genetic laboratories with an innovative solution for clinical applications and services spanning germline and somatic workflows. Ingenuity and useability are at the forefront of the application with alignment to both secondary and tertiary workflows. This enables FASTQ and VCF data uploads, among other file formats, for both individual and batch processes. For optimization, Geneyx Analysis leverages comprehensive and up-to-date annotation sources for all variant types. This includes single nucleotide variants (SNVs), insertions and deletions (Indels), copy number variations (CNVs), repeat expansions, and structural variations (SVs). Following variant analysis and interpretation, the results can be easily rendered into a customizable clinical report and integrated into a LIMS or EHR system.

Features:

Variant Analysis

For variant analysis, the platform offers an intuitive and robust variant browsing interface. Variants are prioritized using customizable filter logic and can be easily sorted using phenotypic prioritization. Annotations are condensed to display the most useful resources but can also be expanded to view the entire genomic information. Hyperlinks are interactive and data can be easily visualized in genome browse for validation purposes. Once a variant has been interpreted, the case can be transferred to other users in your organization and the status can be changed to reflect the current stage in the pipeline.

Rapid & Comprehensive Annotations

Geneyx Analysis optimizes annotation updates for over 50 data sources. These updates occur bi-monthly and include standard ACMG-recommended databases together with all publicly available annotation sources. Licensed annotations can also be integrated on request and all annotation source information can be pulled into a customizable clinical report.

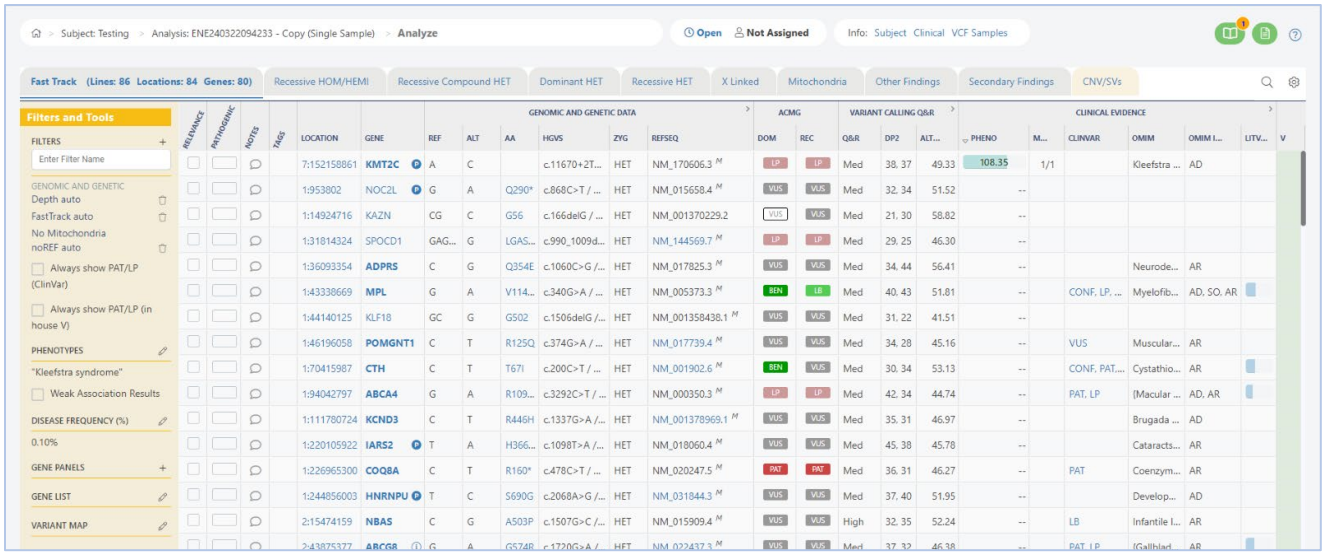
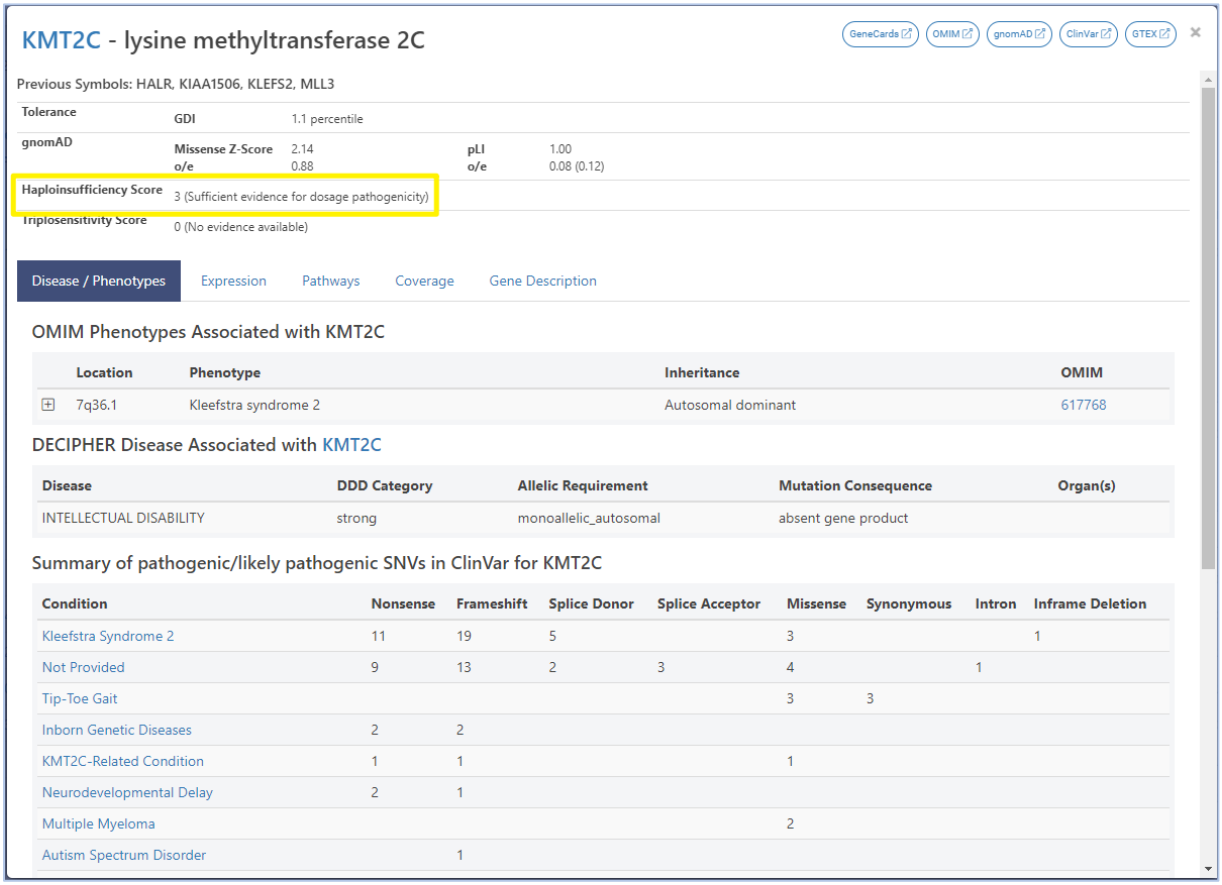


Figure 1 : Variant interpretation interface

Annotating a VCF file includes:

1. Variant frequency, clinical significance, and damage effect predictions
2. ClinGen Dosage Sensitivity is available: ClinGen Dosage Sensitivity collects evidence supporting or refuting the haploinsufficiency and triplosensitivity of genes and genomic regions.
3. OMIM for CNV/SV**:** OMIM phenotype information is now available for CNV/SV analysis. This new field will display OMIM information for all overlapping events observed in the database.
4. ClinVar Origin Annotation: The allele origin, being either germline or somatic, is now displayed when viewing the ClinVar hyperlink for SNVs of interest.
5. Recessive Het Tab: To accommodate for carrier screening workflows, or heterozygous variants with autosomal recessive mode of inheritance, a new Recessive Het tab has been developed that includes the ACMG classification using the autosomal recessive model.
6. Splitting multi-allelic variants and merging identical allelic variants on different transcripts as per ACMG interpretation guidelines.
7. Clinical interpretation of pathogenicity based on ACMG guidelines
8. Annotations based on the user account internal databases, including allele frequency and previous variant and gene annotations.



KMT2C - lysine methyltransferase 2C

GeneCards | OMIM | gnomAD | ClinVar | GTEX

Previous Symbols: HALR, KIAA1506, KLEFS2, MLL3

Tolerance	GDI	1.1 percentile		
gnomAD	Missense Z-Score	2.14	pLI	1.00
	o/e	0.88	o/e	0.08 (0.12)
Haploinsufficiency Score	3 (Sufficient evidence for dosage pathogenicity)			
Triplosensitivity Score	0 (No evidence available)			

Disease / Phenotypes | Expression | Pathways | Coverage | Gene Description

OMIM Phenotypes Associated with KMT2C

Location	Phenotype	Inheritance	OMIM
7q36.1	Kleefstra syndrome 2	Autosomal dominant	617768

DECIPHER Disease Associated with KMT2C

Disease	DDD Category	Allelic Requirement	Mutation Consequence	Organ(s)
INTELLECTUAL DISABILITY	strong	monoallelic_autosomal	absent gene product	

Summary of pathogenic/likely pathogenic SNVs in ClinVar for KMT2C

Condition	Nonsense	Frameshift	Splice Donor	Splice Acceptor	Missense	Synonymous	Intron	Inframe Deletion
Kleefstra Syndrome 2	11	19	5		3			1
Not Provided	9	13	2	3	4		1	
Tip-Toe Gait					3	3		
Inborn Genetic Diseases	2	2						
KMT2C-Related Condition	1	1			1			
Neurodevelopmental Delay	2	1						
Multiple Myeloma					2			
Autism Spectrum Disorder		1						

Figure 2 : HI/TP scores are available via ClinGen

CNVs and SVs can be investigated at the gene level and are annotated with clinical data and can be prioritized according to associated phenotype. Compound mutations can also be assessed to view SNVs within the CNV/SV with clinical significance.

Phenotype-Driven Variant Prioritization

- *Free Text Phenotypes* – Variants can be prioritized based on their association with any free-text biological term or HPO terms, and phenotype specificity is displayed to show gene heterogeneity of the phenotype entered. Multiple phenotypes can be entered using the advanced options and phenotypes can be modified once an analysis has been created.
- *Phenotypic Evidence Score* – Variant scores are created from investigating over 50+ biomedical data sources with the ability to deep-dive into relevant literature to find novel disease associations.
- The Geneyx's phenotyper will highlight association with regulatory regions, as well as enhancers.
- If a phenotype has been observed in a different sample and occurs in the same gene, the phenotypic score will increase based on integration of the users' Clinical Knowledgebase. This is performed on the backend and is proprietary to the users account.

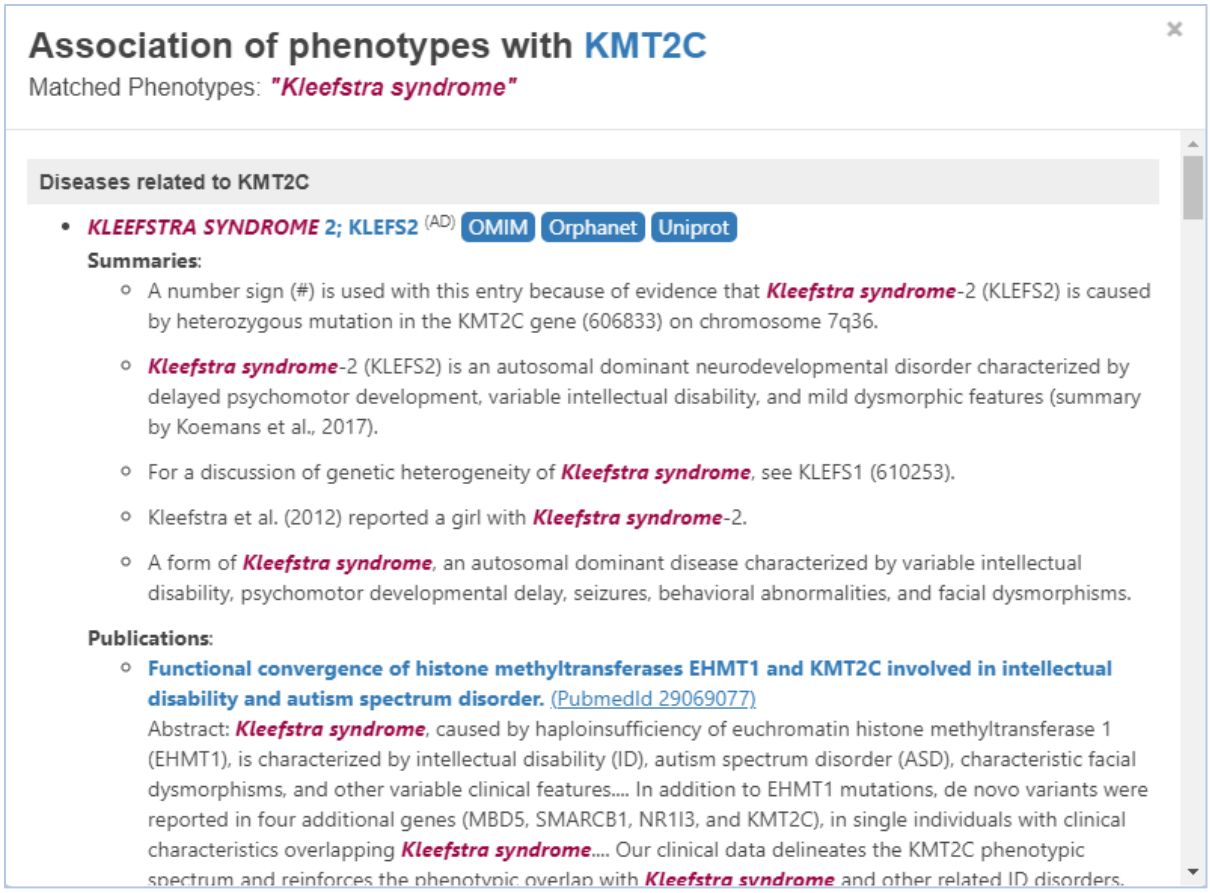


Figure 3: Phenotypic prioritization using key search terms

ACMG Guidelines

The American College of Medical Genetics and Genomics (ACMG) represents the interests of clinical geneticists, clinical laboratory geneticists, and genetic counselors by providing best practice guidelines,. Geneyx Analysis adheres to these guidelines by providing:

- *ACMG Automation* – Geneyx Analysis automates 18/28 ACMG criteria, reducing workflow complexity and ensuring best practices are followed. Users can define thresholds for application of a subset of criteria.
- *Sample & Case-context classification*- ACMG classifications automatically include case-level information such as inheritance models and relevant findings in associated samples.
- *Ability to modify* – If additional information or expertise is available, users can incorporate their data, modify criteria, make notes, and store changes for all downstream cases.
- Easy access to information relevant to manual curation of variant pathogenicity
- Support for reanalysis with updated evidence and annotations

Geneyx Analysis adherence to the ACMG Guidelines has been validated by labs in the United States, Europe, Israel, Hong Kong, and China. Further, it has been approved for use in CLIA-CAP genetic laboratories.

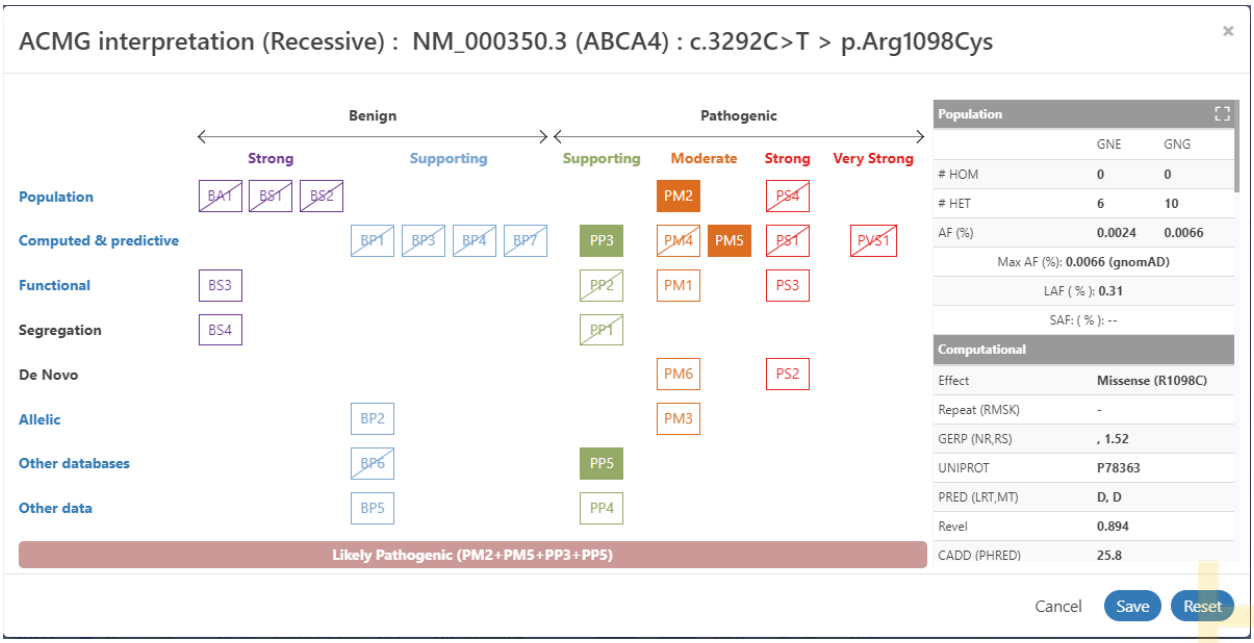


Figure 4: ACMG dialog with ability to modify criteria

Customer Local Database & Inter-Lab Sharing

Geneyx Analysis automatically calculates an 'in-house' allele frequency annotation for all variants in an account that is derived from all imported samples. This is useful to eliminate common variants or enable variant selection among different ethnic groups. The in-house database also includes annotations and interpretations previously entered by the analysts, which assists in applying accumulated in-house knowledge to new cases. Laboratories may also participate in Inter-Lab sharing, especially if an organization is present in several locations. This permits viewing variant allele frequency within all cases in accounts sharing the data.

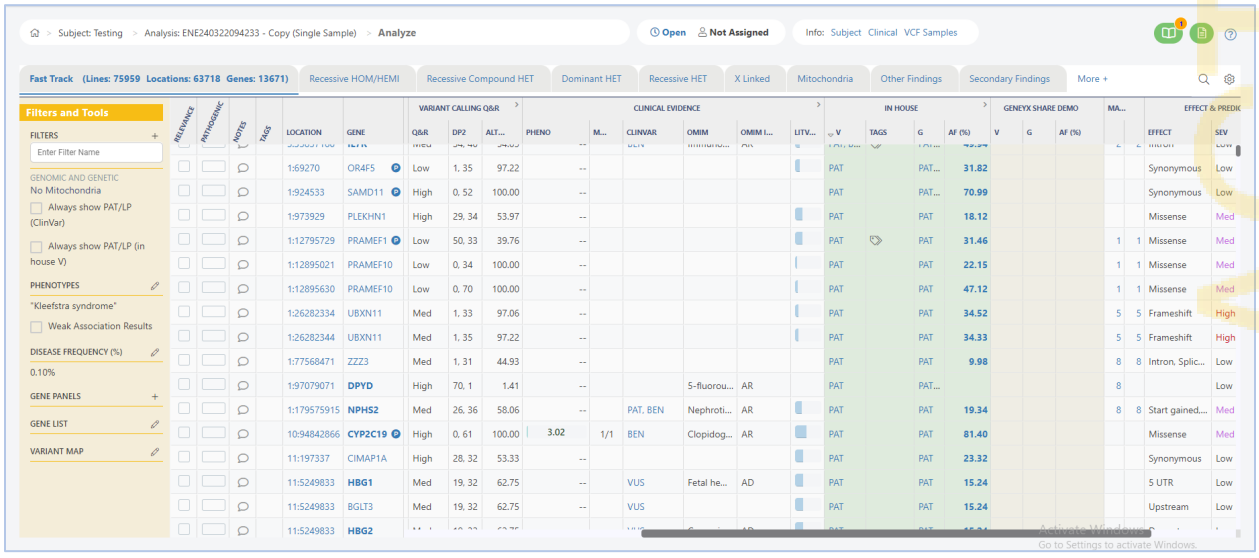


Figure 5: In-house database in green shows allele frequency and previous classifications from other samples

Whole Genome Sequencing Interpretation

Geneyx Analysis incorporates a comprehensive genome-wide map of regulatory elements including promoters and enhancers together with their gene associations from various sources. This enables the association of variants in non-coding regions to gene-phenotype relationships and subsequent prioritization.

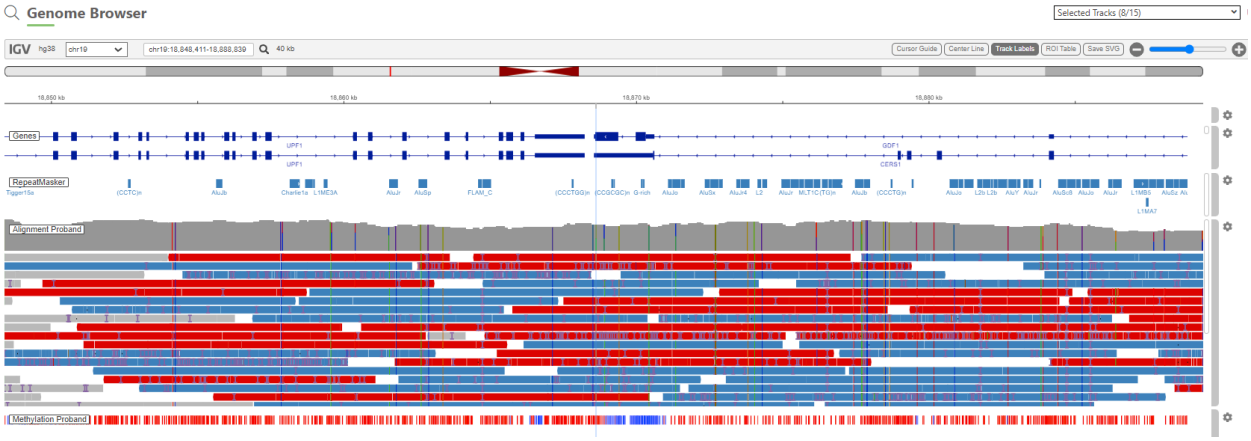


Figure : BAM file visualization using integrated IGV

Evidence Collection and Reporting

- *Automated evidence collection* – Geneyx Analysis supports automatic generation of comprehensive clinical reports leveraging available annotations & phenotypic evidence.
- *Customizable report templates* – Reports are fully customizable to include the organization logo and information that the user deems necessary for a distinctive design.
- Selected Variants' feature: Once the relevance and associated information is set, user can review the selections across all the genetic models using this feature.
- *Exporting flexibility* – Reports can be rendered in PDF and JSON format and integrated with LIMs/EHR systems where necessary.

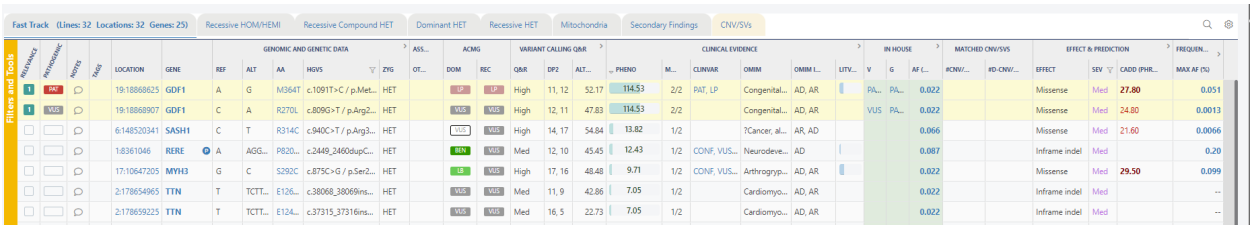


Figure 7 : Annotating variants to pull into report and in-house databases

Storage and Pipeline Management

- *Unlimited Cloud-based Genetic Data Storage* – Easily manage and stores genetic data in a secure private Geneyx Azure cloud, (HIPAA and GDPR-compliant).
- *Local or Hybrid Configurations* – On-premise configurations and Hybrid architecture are also available if an organization needs to remain behind local firewalls.

- *Account Management* – Restrictions can be set at a user or group level to ensure assigned, fixed workflows are utilized to streamline processing.
- Storage Allocation: Display the storage space allocated or consumed by the data files within the specified timeline. This information allows users to track their storage usage and manage their resources effectively.
- *Audit Trails* – All information from FASTQ to report is documented and can be reviewed at any time.

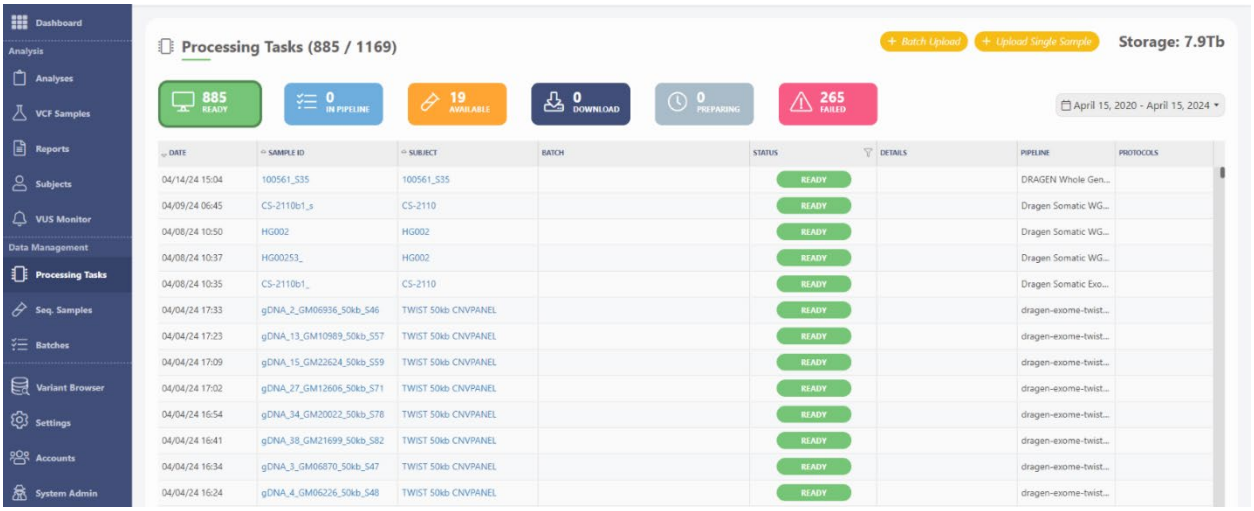


Figure 8 : Complete visibility of data workflows and management features

Customizable Workflows and Protocols

Geneyx Analysis provides customizable protocols which enable laboratories to standardize genetic test and analysis workflows. Protocols can include combinations of simple or complex filters on any set of annotation entities for any gene lists or genomic regions and can be locked as a protocol for defined users. Protocols can also be optimized to automatically render a report on the remaining variants and include any user interpretations for given variants.

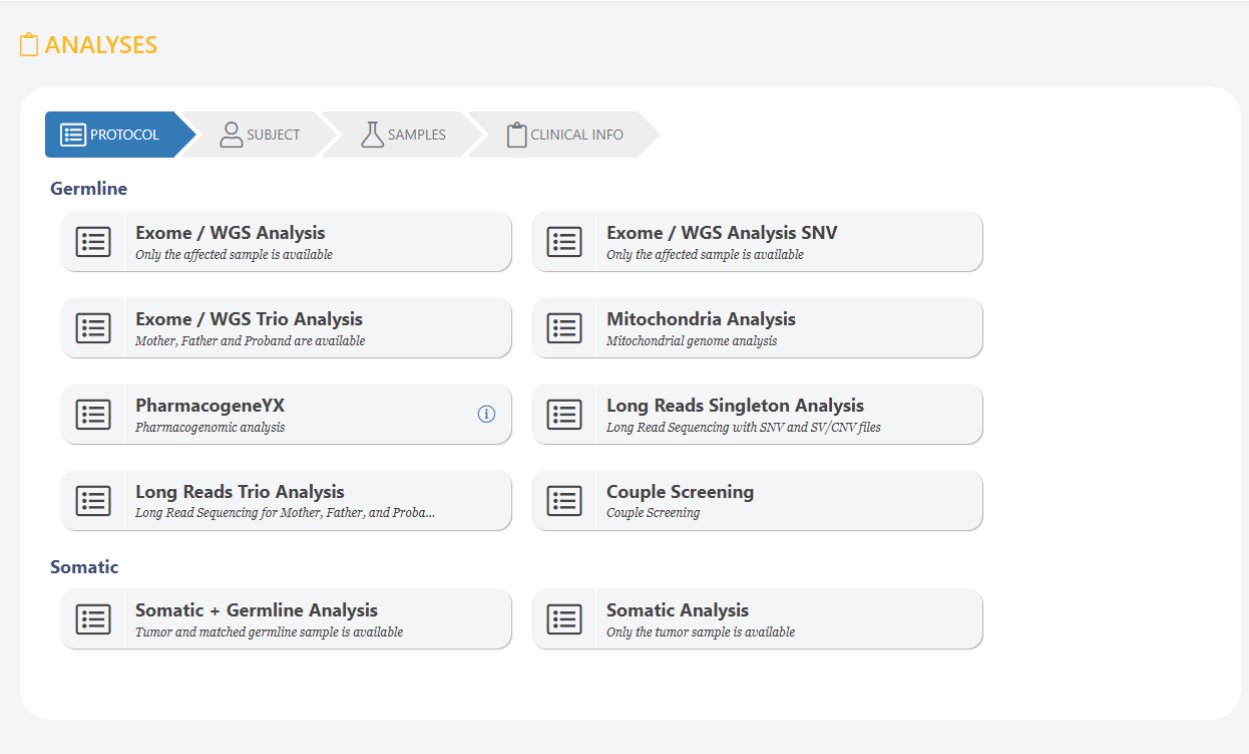


Figure 9: Default and customizable protocols are available

Automation and APIs

Geneyx Analysis API feature allows users to connect with existing LIMS/EHR systems and upload data using command line workflows.

1. Integration with primary and secondary analysis pipelines to allow automated import and annotation of VCF files. This works with single sample and batch workflows.
2. Integration with laboratory information management systems (LIMS) or electronic health record (EHR) systems enables the creation of automated analyses of patient clinical information and the streamlining of reports from Geneyx Analysis to the LIMS/EHR.
3. Auto-Reporting for SNVs/CNV/SVs to generate TSV files based on your customized filtering.

Other API features provided by Geneyx Analysis can be found here: https://github.com/geneyx/geneyx.analysis.api/.

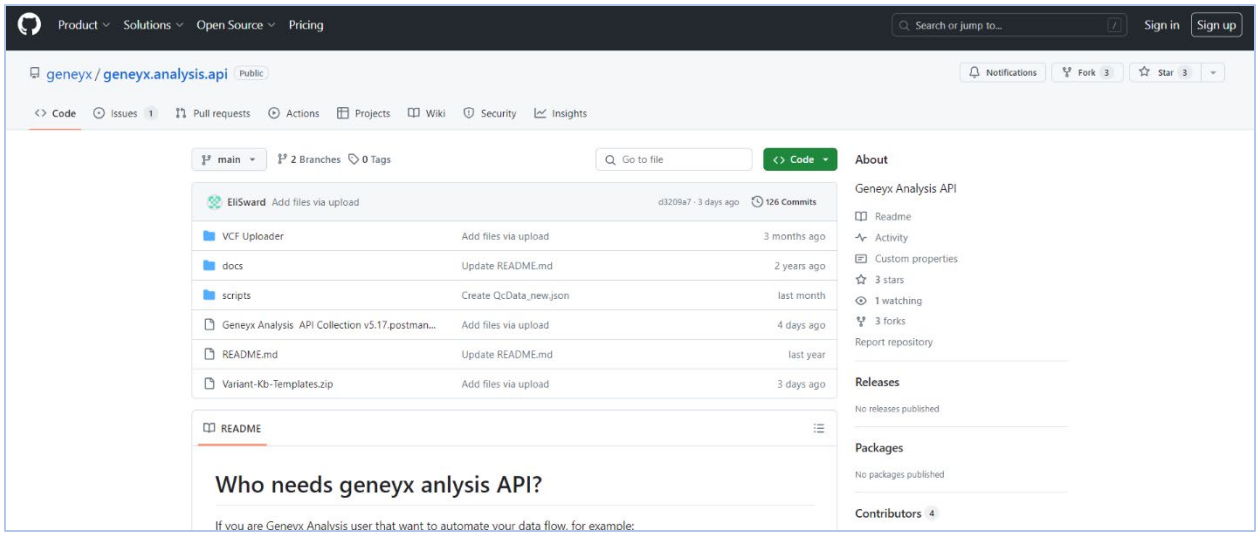


Figure 10: APIs available on our GitHub

Variant Knowledgebase

Geneyx's classified variants are organized within a knowledgebase, uniquely tied to each account. Users can now harness the capability to export and import this valuable data. An exemplary use case involves lifting over annotated variants to an alternate genome assembly, leveraging the transformed data as an allele frequency backlog for augmented evidence across different assemblies

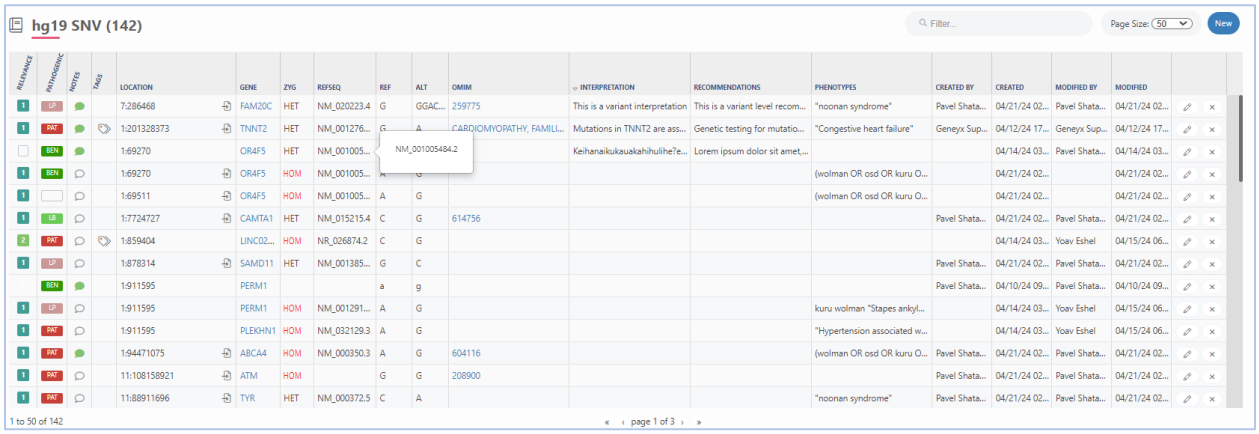


Figure 11: Variant Knowledgebase of interpreted variants

VUS Monitor

Keeping track of variant classification changes can be a daunting task. To simplify this process, we have implemented an auto-notification feature that alerts you whenever variants undergo classification changes according to ClinVar. This proactive notification provides comprehensive details, including a direct link to the analysis, enabling you to perform retrospective analyses with ease and precision.

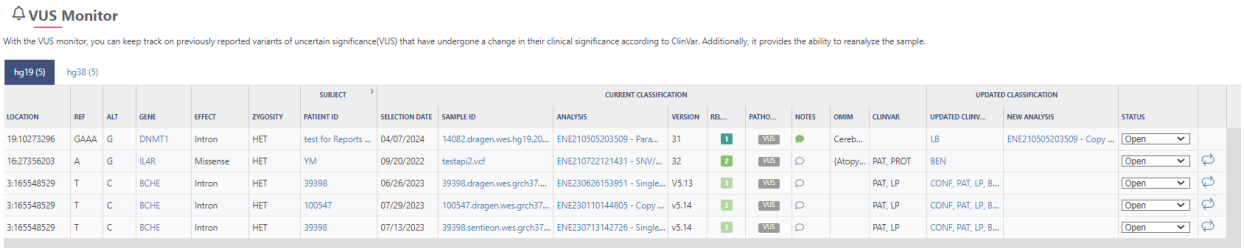
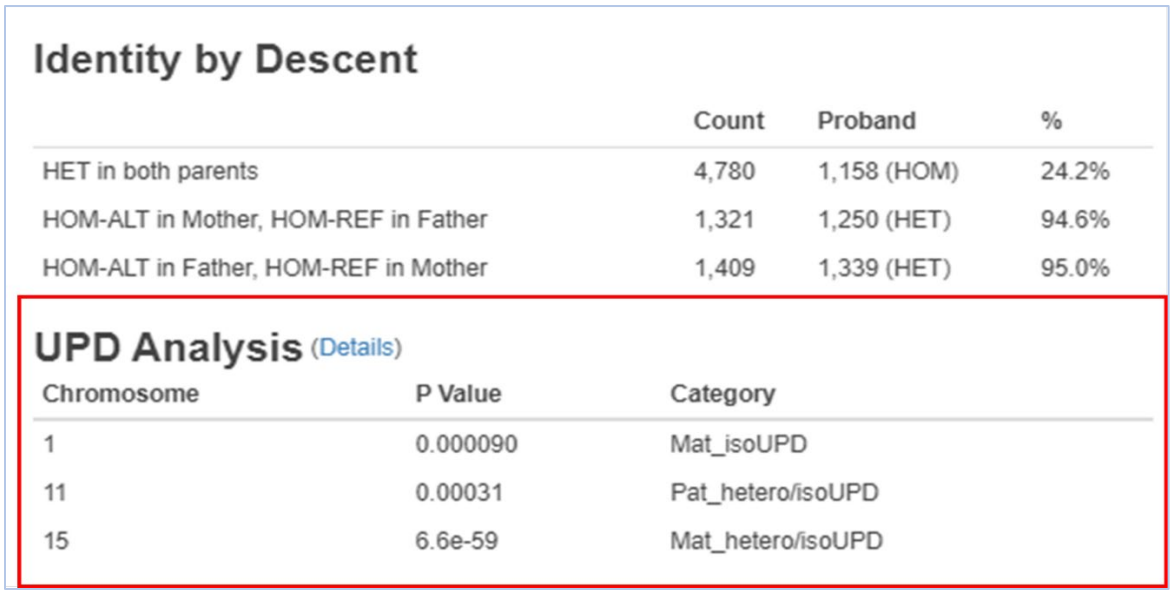


Figure 12: VUS Monitor to track variants of unknown significance through annotation updates

Uniparental Disomy

UPD is automatically calculated in *Geneyx Analysis* when running trio exomes and genomes by comparing each variant of the proband to the parents. Notifications are provided if significant results are identified.



Identity by Descent

	Count	Proband	%
HET in both parents	4,780	1,158 (HOM)	24.2%
HOM-ALT in Mother, HOM-REF in Father	1,321	1,250 (HET)	94.6%
HOM-ALT in Father, HOM-REF in Mother	1,409	1,339 (HET)	95.0%

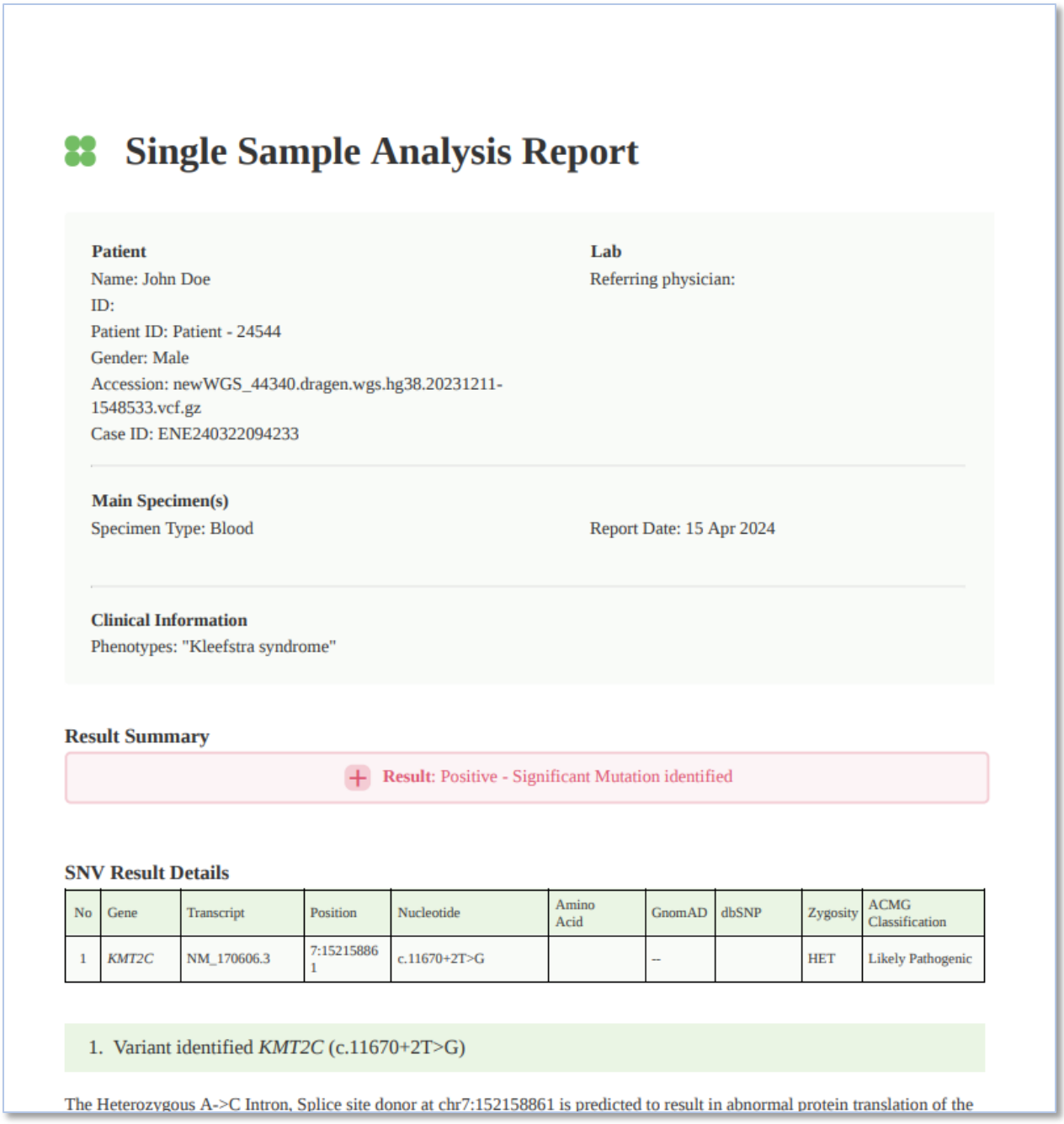
UPD Analysis (Details)

Chromosome	P Value	Category
1	0.000090	Mat_isoUPD
11	0.00031	Pat_hetero/isoUPD
15	6.6e-59	Mat_hetero/isoUPD

Figure 13: UPD Analysis is calculated for all trio workflows

Comprehensive and Customizable Reports

A comprehensive and flexible reporting system of modular tools and features that can be combined and customized to create personalized analysis pipelines. These tools cover a wide range of applications, including variant calling, annotation, filtration, pathway analysis, and interpretation. Users can select the relevant tools for each step of the analysis, configuring them to meet their specific requirements. The comprehensive clinical reports can be customized according to the organization's logo and formatting requirements to incorporate static and dynamic information. The reports are also offered in multiple languages, preventing the need to translate generic information.



Single Sample Analysis Report

Patient
Name: John Doe
ID:
Patient ID: Patient - 24544
Gender: Male
Accession: newWGS_44340.dragen.wgs.hg38.20231211-1548533.vcf.gz
Case ID: ENE240322094233

Lab
Referring physician:

Main Specimen(s)
Specimen Type: Blood

Report Date: 15 Apr 2024

Clinical Information
Phenotypes: "Kleefstra syndrome"

Result Summary

Result: Positive - Significant Mutation identified

SNV Result Details

No	Gene	Transcript	Position	Nucleotide	Amino Acid	GnomAD	dbSNP	Zygosity	ACMG Classification
1	*KMT2C*	NM_170606.3	7:152158861	c.11670+2T>G		–		HET	Likely Pathogenic

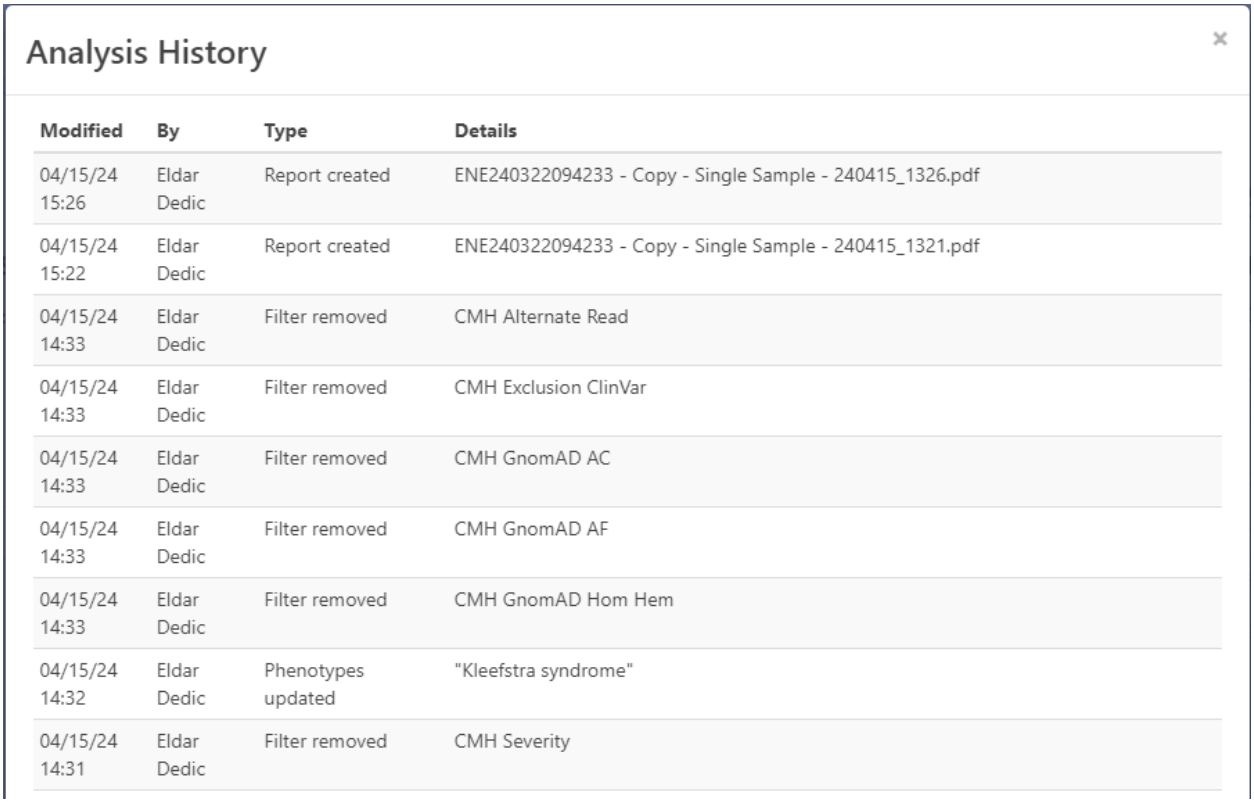
1. Variant identified *KMT2C* (c.11670+2T>G)

The Heterozygous A->C Intron, Splice site donor at chr7:152158861 is predicted to result in abnormal protein translation of the

Figure 14: Reporting outputs in Geneyx are fully customizable

Account Management and Audit Trails

Account management capabilities enable the group leader to set permissions for individual users to ensure complete control of all processes and steps performed by individual users to streamline workflow and manage data applications. All processes performed in the application are stored and can be reviewed, offering a comprehensive audit trail for laboratories.



Analysis History

Modified	By	Type	Details
04/15/24 15:26	Eldar Dedic	Report created	ENE240322094233 - Copy - Single Sample - 240415_1326.pdf
04/15/24 15:22	Eldar Dedic	Report created	ENE240322094233 - Copy - Single Sample - 240415_1321.pdf
04/15/24 14:33	Eldar Dedic	Filter removed	CMH Alternate Read
04/15/24 14:33	Eldar Dedic	Filter removed	CMH Exclusion ClinVar
04/15/24 14:33	Eldar Dedic	Filter removed	CMH GnomAD AC
04/15/24 14:33	Eldar Dedic	Filter removed	CMH GnomAD AF
04/15/24 14:33	Eldar Dedic	Filter removed	CMH GnomAD Hom Hem
04/15/24 14:32	Eldar Dedic	Phenotypes updated	"Kleefstra syndrome"
04/15/24 14:31	Eldar Dedic	Filter removed	CMH Severity

Figure 15: Audit trails output for all actions performed in an analysis

Long-Read sequencing

Geneyx Analysis provides a comprehensive tertiary analysis platform for the efficient processing of Oxford Nanopore Technologies and PacBio Long-Read sequencing data. We've introduced innovative features that facilitate rapid data ingestion and annotation of long-read data, streamlining the entire process of variant interpretation and reporting.

- Phasing analysis: Our specialized tools, including phasing and methylation analysis simplify the bioinformatics process, ensuring accurate variant annotation and classification.
- Comprehensive view of overlapping CNVs and SNVs for comphound heterozygous variant detection
- SMART Filtering to quickly reduce background noise associated with long read sequencing data
- Repeat Expansion analysis aimed to identify deleterious repeats and potential gene silencing events
- Ability to import all variant file outputs

Figure 16: Allele phasing integration where variant is observed in trans

Data Protection Compliance

- HIPAA (Health Insurance Portability and Accountability Act)
- GDPR (General Data Protection Regulation) compliant.
- ISO 13485(designed for medical equipment and software manufacturers to ensure an internationally recognized standard for quality management.)
- ISO 27001 (**standard for information security management systems (ISMS))**
- CE IVD Mark
- All private patient information is encrypted.

Overview Summary

Geneyx Analysis is a powerful secondary and tertiary analysis platform for annotation, analysis, and prioritization of coding and non-coding genomic variants using short and long-read sequencing analysis. This platform provides access to an extensive knowledge base of genomic annotations and offers intuitive and flexible configurations. The ease of use and transparency allows quick adaptation and implementation into clinical workflows and innovative features that simplify and accelerate variant interpretation. *Geneyx Analysis* is an end-to-end solution demonstrating a unique paradigm that can increase diagnostic yield and reduce turnaround time for all users.

Geneyx Analysis is available for trial at www.geneyx.com

Publications:

Beyond the Exome: Utility of Long-Read Whole Genome Sequencing in Exome-Negative Autosomal Recessive Diseases..