Better Data for Better Health

Technical introduction to

Geneyx Analysis

A clinical genetics data management platform

- **Genetic data storage & NGS pipeline management**
- **Comprehensive annotation with rapid analysis and interpretation**
- **Flexible workflows and reports**
- **Unique WGS interpretation**
- **Data protection and privacy & ACMG compliance**

Geneyx Analysis | Technical Data Sheet

Introduction

Geneyx Analysis empowers hospitals and genetic labs with a powerful analysis platform that supports a variety of clinical applications and services in diverse areas in medicine, including rare disorder analysis, disease risk assessment, and tumor biopsy. It offers VCF annotation, analysis, interpretation and comprehensive reporting and enables labs to rapidly adopt genetic testing, and define workflows (protocols) for standardization of tests. Geneyx Analysis leverages the Weitzman institute for scienc knowledgebase with its modules for rapid and accurate interpretation of genetic disorders for SNVs and short Indels, as well as CNVs (copy number variations) and SVs (structural variations), and provides comprehensive customizable reports.

Highlights

RAPID & ACCURATE VARIANT PRIORITIZATION

- **Free Text Phenotypes** - Prioritize variants based on their association with any free-text biological term, with automated keyword strength indications for optimization of ranking.
- **Clear phenotypical evidence** - Variant scores include detailed and comprehensive highlighting within original context based on more than 150 biomedical data sources.

AUTOMATED ACMG/CLINGEN CLASSIFICATION

- **Sample & Case-context classification -** ACMG classifications are not limited to variant-level annotations, but include case-level contextual information incl. inheritance models and associated samples.
- **Comprehensive assignment evidence -** Each classification is accompanied with relevant evidence from various annotations and case-level context.

EVIDENCE COLLECTION & REPORTING

- **Automated evidence collection** - Automatically generates full and comprehensive clinical reports leveraging structured data available in the Knowledgebase.
- **Customizable report templates** - Full customization enables you to offer your customers fully branded and uniquely designed clinical reports with out-of-the-box protocols for genetic diseases, health screening and tumor biopsies

STORAGE & NGS PIPELINE MANAGEMENT

- **Unlimited Cloud-based Genetic Data Storage** - Easily manage and store your genetic data in our HIPAA and GDPR-compliant secure cloud, together with all metadata and relevant clinical data.
- **Flexible NGS Pipeline Management** - Best practices-based pipelines for whole genome, whole exome and panels, with support for Copy Number Variations, Structural Variations and Repeats across the genome.

Detailed features:

Customizable Workflows and Protocols

Geneyx Analysis provides customizable protocols which enable labs to standardize genetic tests and analysis workflows.

Each Geneyx Analysis protocol defines a workflow that is mapped to a specific genetic test offered by the lab. It defines sets of genetic models to be analyzed, includes combinations of simple or more complex filters on any set of annotation entities, can be restricted to certain lists of genes or genomic regions, and specifies a template for a report, its structure, design and the included information.

Figure 1: Workflows, Protocols & Reports

Rapid and Comprehensive Annotations

Geneyx Analysis's annotation engine provides automated annotations for SNVs and short Indels, as well as CNVs and SVs, leveraging both standard ACMG-recommended databases, as well as the rich annotations available within the integrated GeneCards Suite Knowledge-base.

The SNV annotation process includes: (1) annotation from dozens of data sources, including frequency, clinical significance and damage effect prediction (2) splitting multi-allelic variants and merging identical allelic variants and merging identical variants on different transcripts as per ACMG interpretation guidelines, (3) clinical interpretation of pathogenicity based on ACMG guidelines, and (4) annotation based on user account's internal databases, including allele frequency and previous variant and gene annotations.

CNVs and SVs are matched to genes and regulatory regions and then annotated with clinical data and phenotype-specific scoring .

Integrated, Interactive Variant Browsing

Geneyx Analysis offers a user-friendly, streamlined variant browsing screen, which includes an interactive table, where each row represents a single genomic position with a variation, and each column is populated with the relevant details gathered during the annotation process.

Users can search or apply filters on any column; the resulting list or variants can be sorted according to any column, in order to examine the remaining list of variants by their relevance or by the probability of their being the causal variants.

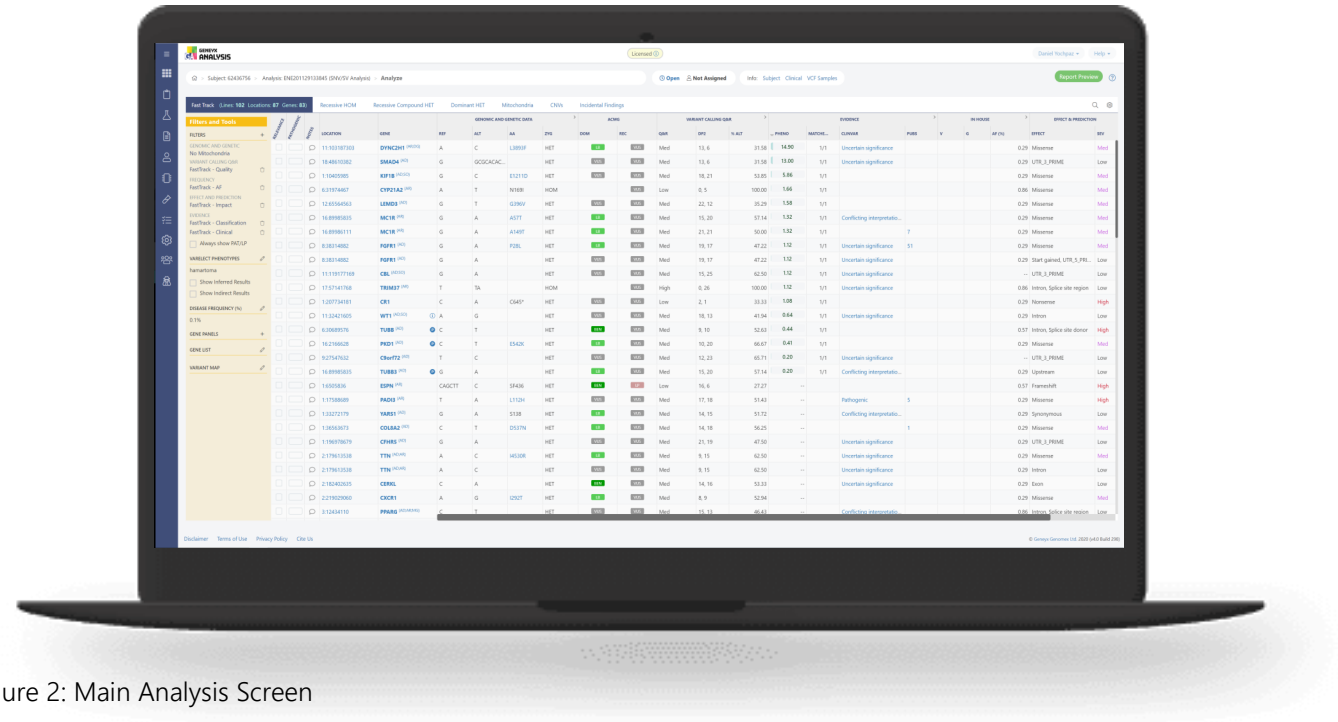


Figure 2: Main Analysis Screen

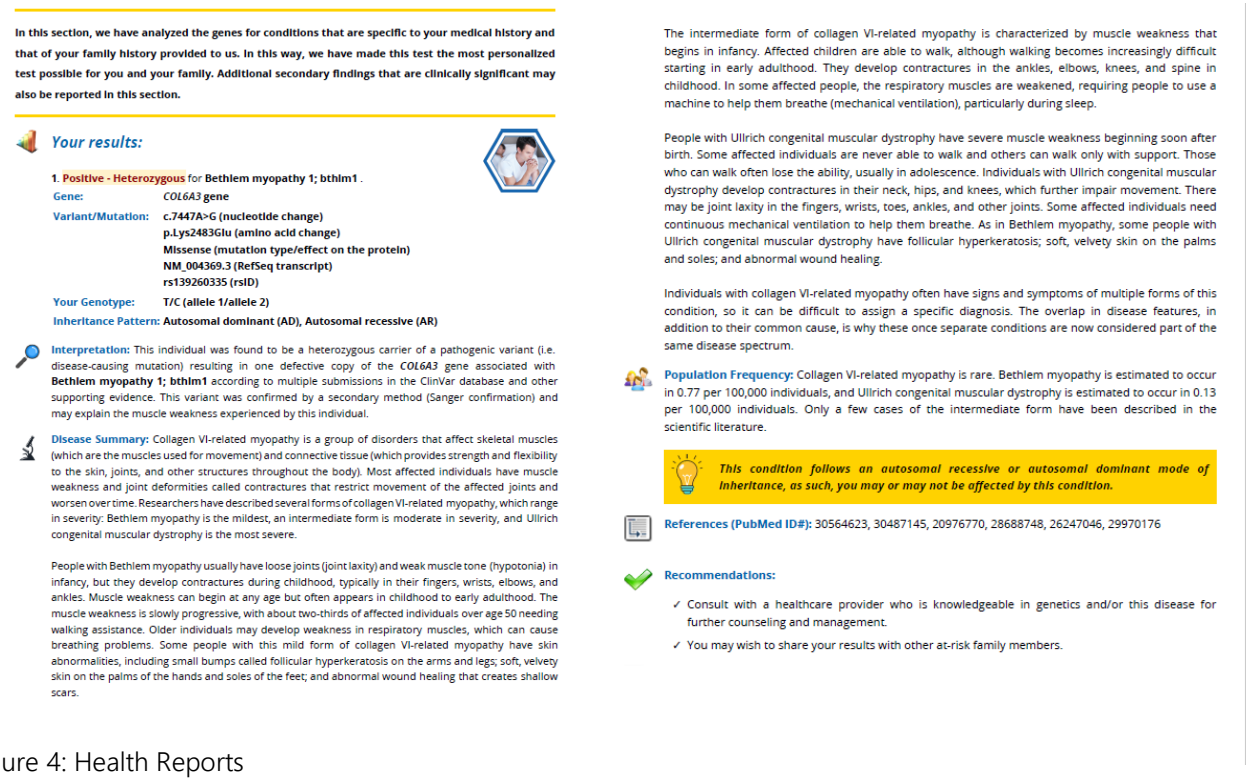
Customizable, Powerful Filters

Geneyx Analysis offers interactive, customizable filters that enable users to rapidly focus on variants of interest. These include standard filters based on allele frequency, quality & reliability, genomic and genetic filters, predicted effect and known disease association. Additional filters may be applied interactively by users on each variant using the interactive analysis screen, and custom filters on variants can be easily created for standardizing workflows, including custom virtual panels and variant maps.

Comprehensive and Customizable Reporting

Geneyx Analysis's comprehensive and flexible reporting system enables customers to define templates based on the various protocols and tests run in their labs.

The reporting engine leverages the capabilities of the vast amount of structured data available to automatically generate full and comprehensive clinical reports, and supports customizable branding and formatting for each report.



In this section, we have analyzed the genes for conditions that are specific to your medical history and that of your family history provided to us. In this way, we have made this test the most personalized test possible for you and your family. Additional secondary findings that are clinically significant may also be reported in this section.

Your results:

1. **Positive - Heterozygous** for **Bethlem myopathy 1; bthlm1** .

Gene: *COL6A3* **gene**

Variant/Mutation: **c.7447A>G (nucleotide change)**
p.Lys2483Glu (amino acid change)
Missense (mutation type/effect on the protein)
NM_004369.3 (RefSeq transcript)
rs139260335 (rsID)

Your Genotype: **T/C (allele 1/allele 2)**

Inheritance Pattern: **Autosomal dominant (AD), Autosomal recessive (AR)**

Interpretation: This individual was found to be a heterozygous carrier of a pathogenic variant (i.e. disease-causing mutation) resulting in one defective copy of the *COL6A3* gene associated with **Bethlem myopathy 1; bthlm1** according to multiple submissions in the ClinVar database and other supporting evidence. This variant was confirmed by a secondary method (Sanger confirmation) and may explain the muscle weakness experienced by this individual.

Disease Summary: Collagen VI-related myopathy is a group of disorders that affect skeletal muscles (which are the muscles used for movement) and connective tissue (which provides strength and flexibility to the skin, joints, and other structures throughout the body). Most affected individuals have muscle weakness and joint deformities called contractures that restrict movement of the affected joints and worsen over time. Researchers have described several forms of collagen VI-related myopathy, which range in severity: Bethlem myopathy is the mildest, an intermediate form is moderate in severity, and Ullrich congenital muscular dystrophy is the most severe.

People with Bethlem myopathy usually have loose joints (joint laxity) and weak muscle tone (hypotonia) in infancy, but they develop contractures during childhood, typically in their fingers, wrists, elbows, and ankles. Muscle weakness can begin at any age but often appears in childhood to early adulthood. The muscle weakness is slowly progressive, with about two-thirds of affected individuals over age 50 needing walking assistance. Older individuals may develop weakness in respiratory muscles, which can cause breathing problems. Some people with this mild form of collagen VI-related myopathy have skin abnormalities, including small bumps called follicular hyperkeratosis on the arms and legs; soft, velvety skin on the palms of the hands and soles of the feet; and abnormal wound healing that creates shallow scars.

The intermediate form of collagen VI-related myopathy is characterized by muscle weakness that begins in infancy. Affected children are able to walk, although walking becomes increasingly difficult starting in early adulthood. They develop contractures in the ankles, elbows, knees, and spine in childhood. In some affected people, the respiratory muscles are weakened, requiring people to use a machine to help them breathe (mechanical ventilation), particularly during sleep.

People with Ullrich congenital muscular dystrophy have severe muscle weakness beginning soon after birth. Some affected individuals are never able to walk and others can walk only with support. Those who can walk often lose the ability, usually in adolescence. Individuals with Ullrich congenital muscular dystrophy develop contractures in their neck, hips, and knees, which further impair movement. There may be joint laxity in the fingers, wrists, toes, ankles, and other joints. Some affected individuals need continuous mechanical ventilation to help them breathe. As in Bethlem myopathy, some people with Ullrich congenital muscular dystrophy have follicular hyperkeratosis; soft, velvety skin on the palms and soles; and abnormal wound healing.

Individuals with collagen VI-related myopathy often have signs and symptoms of multiple forms of this condition, so it can be difficult to assign a specific diagnosis. The overlap in disease features, in addition to their common cause, is why these once separate conditions are now considered part of the same disease spectrum.

Population Frequency: Collagen VI-related myopathy is rare. Bethlem myopathy is estimated to occur in 0.77 per 100,000 individuals, and Ullrich congenital muscular dystrophy is estimated to occur in 0.13 per 100,000 individuals. Only a few cases of the intermediate form have been described in the scientific literature.

This condition follows an autosomal recessive or autosomal dominant mode of inheritance, as such, you may or may not be affected by this condition.

References (PubMed ID#): 30564623, 30487145, 20976770, 28688748, 26247046, 29970176

Recommendations:

- ✓ Consult with a healthcare provider who is knowledgeable in genetics and/or this disease for further counseling and management.
- ✓ You may wish to share your results with other at-risk family members.

Figure 4: Health Reports

Versions, Data Updates and Traceability

Geneyx Analysis and the knowledgebase are frequently updated with the newest version of dozens of relevant data sources. Knowledgebase updates ensure that the analysis is performed using up-to-date biological information, and often include new annotation sources and new system features. Each report generated in Geneyx Analysis includes documentation of the specific version of the Whole Genome Sequencing Interpretation

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Whole Genome Sequencing Interpretation

Geneyx Analysis offers a pioneering approach for non-coding variants interpretation. Towards the goal of maximal exploitation of whole genome sequence analyses in the clinical genetics practice, Geneyx Analysis leverages database's comprehensive collection of ncRNA genes. Provides a unique non-redundant and comprehensive genome-wide map of ~400,000 scored enhancers and promoters, and their gene associations, and is the standard data source for regulatory elements on the UCSC Genome Browser. The combination enables translating the finding of an SV or SNV variant in a non-coding region into a variant-to-gene-to-phenotype annotation, enabling prioritization of phenotype associations of variant-containing elements via the elements' gene targets.

Customer Local Database & Inter-Lab Sharing

Geneyx Analysis handles thousands of samples in specific accounts or group of collaborating accounts and automatically calculates the 'in-house' allele frequency which can be crucial for variant selection especially in highly specific ethnic groups. The user interface also includes and highlights annotations and interpretations previously entered by the analysts, assisting in applying accumulated in-house knowledge to new cases. Labs may also participate in Inter-Lab sharing, which enables them to view allele frequency within all cases in accounts sharing data with their lab, including pointers to previously selected matching variants and genes in all analyzed cases in the sharing group and their annotations.

Automation and APIs

The Geneyx Analysis API allows integrators to optimally control the interaction with Geneyx Analysis within broader use-case contexts, including: (1) Integration with primary and secondary analysis pipelines, allowing automated upload and annotation of VCF files; and (2) Integration with laboratory information management systems (LIMS) or electronic health record (EHR) systems, by enabling the creation of automated analyses of patient clinical information, and the streamlining of reports from Geneyx Analysis to the LIMS/EHR. Geneyx Analysis also supports fully automated analyses, enabling sophisticated screening protocols to be implemented easily by private and hospital labs. These may include pharmacogenomics, cancer and carrier screening, and newborn screening, among others.

ACMG and ClinGen Compliance

The American College of Medical Genetics and Genomics (ACMG) is a professional membership organization that represents the interests of clinical geneticists, clinical laboratory geneticists, and genetic counselors in the USA. Geneyx Analysis complies with its set of standards and guidelines for interpretation of sequence variants by providing:

- Annotation of sequence variants based on required/recommended databases
- Use of *in silico* predictive programs for determination of the effect of sequence variants
- Automated classification of pathogenicity of variants based on defined ACMG criteria
- Display of all required information for assessment of sequence variants
- Straightforward workflow for classification of variants of interest, and inclusion of previous annotations for variants and genes of interest
- Easy access to information relevant to manual curation of variant pathogenicity
- Support for reanalysis with updated evidence and annotations.

Geneyx Analysis's 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 labs.

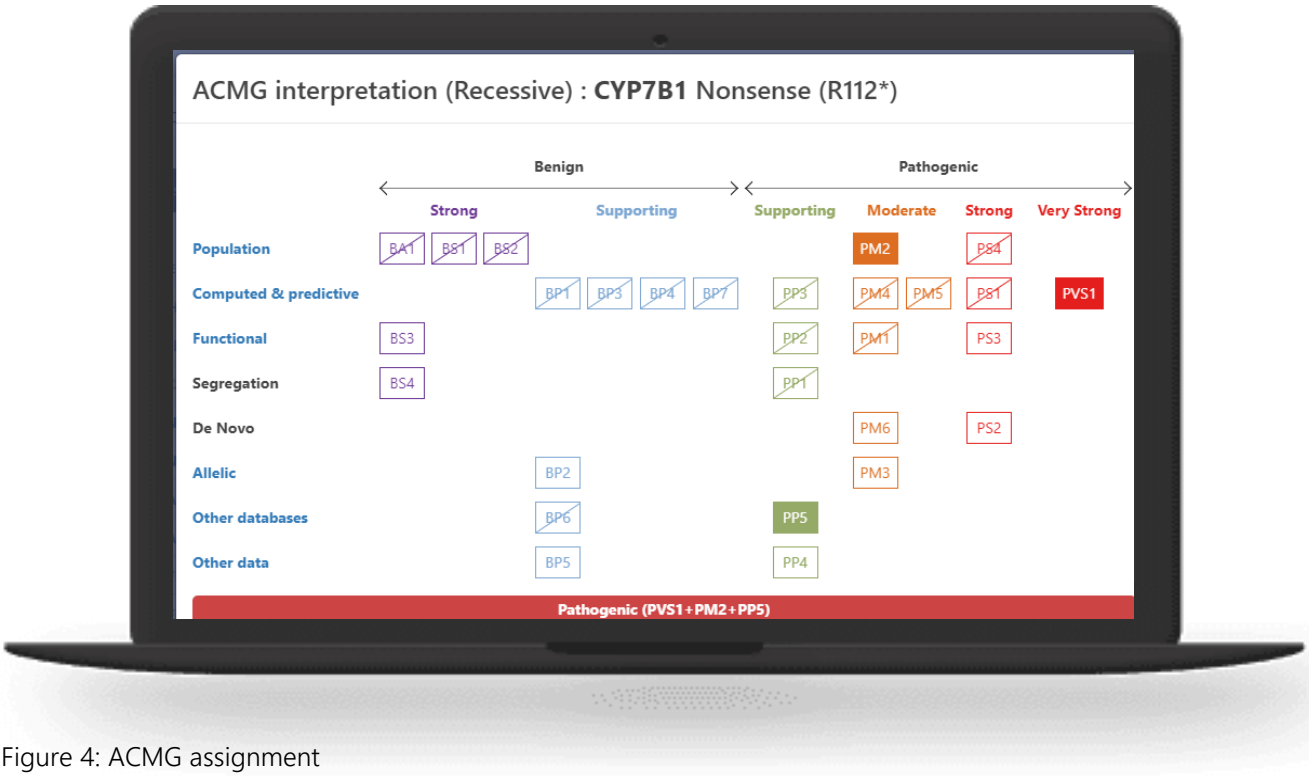

Figure 4: ACMG assignment

Data protection compliances

Geneyx Analysis is HIPAA (Health Insurance Portability and Accountability Act) and GDPR (General Data Protection Regulation) compliant. Private health information is encrypted

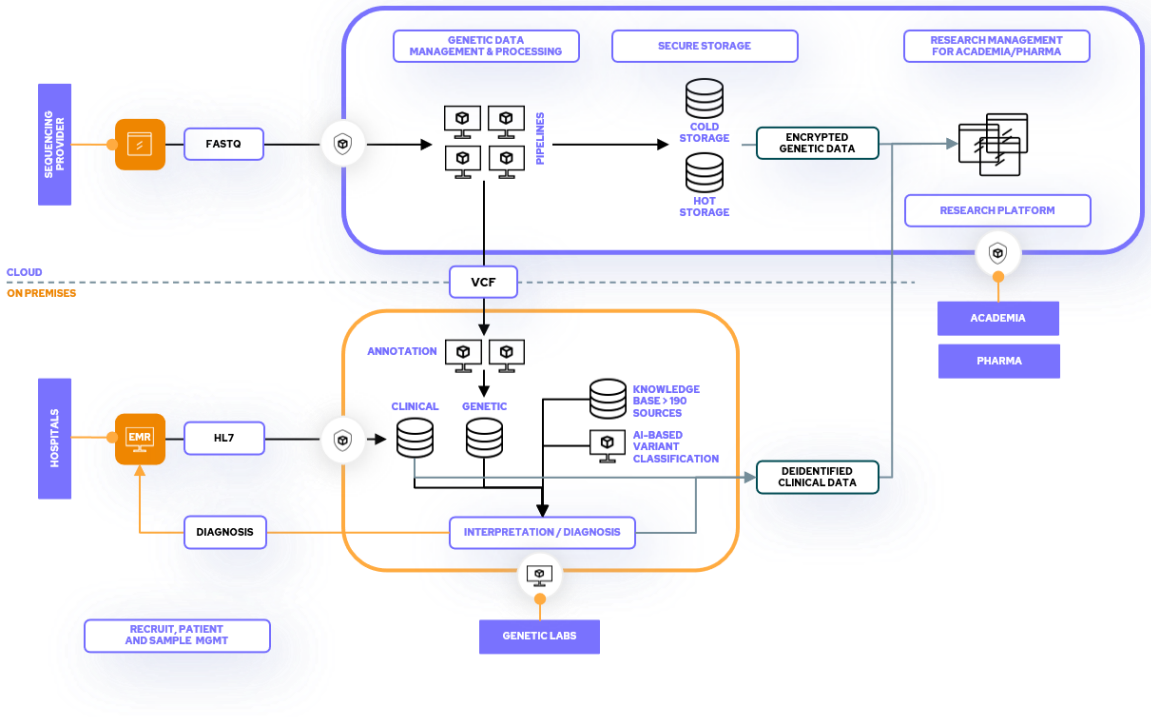

Figure 5: Geneyx Architecture Overview

Summary

Geneyx Analysis is a powerful secondary and tertiary analysis platform for annotation, analysis and prioritization of coding and non-coding genomic variants. It provides access to an extensive knowledgebase of genomic annotations, with intuitive and flexible configuration options, allowing quick adaptation, and addressing various workflow requirements, simplifying and accelerating variant interpretation.

Geneyx Analysis can be used in the various scenarios typically found in clinical organizations, and markedly reduces turn-around time by enabling methodical and faster analysis, powerful interpretation capabilities and comprehensive, customizable reporting capabilities.

Learn More:

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

References

Selected publications about the technology behind the Geneyx platform:

1. Dahary D, Yaron G, Yaron M, Ofer Z, et al. Genome analysis and knowledge-driven variant interpretation with TGex. BMC Med Genomics. 2019 Dec 30;12(1):200.
2. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. Curr Protoc Bioinformatics. 2016;54:1 30 1-1 3.
3. Stelzer G, Plaschkes I, Oz-Levi D, Alkelai A, Olender T, Zimmerman S, et al. VarElect: the phenotype-based variation prioritizer of the GeneCards Suite. BMC Genomics. 2016;17 Suppl 2:444.

Recent scientific publications describing novel clinical genetic findings using Geneyx:

1. A New Intronic Variant in ECEL1 in Two Patients with Distal Arthrogryposis Type 5D. Int. J. Mol. Sci. 2021
2. Homozygous HESX1 and COL1A1 Gene Variants in a Boy with Growth Hormone Deficiency and Early Onset Osteoporosis. Int. J. Mol. Sci. 2021
3. Biallelic variants in ZNF526 cause a severe neurodevelopmental disorder with microcephaly, bilateral cataract, epilepsy and simplified gyration. J. Med. Gen. 2021