GOLDEN HELIX
Enabling Precision Medicine

ACMG Guidelines with VSClinical

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Field Application Scientist

CIOReview
20 Most Promising Biotech Technology Providers

Gartner
Hype Cycle for Life sciences

pharma TECH OUTLOOK
Top 10 Analytics Solution Providers

NIH Grant Funding Acknowledgments

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    - Award Number R43GM128485-01
    - Award Number R43GM128485-02
    - Award Number 2R44 GM125432-01
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    - Montana SMIR/STTR Matching Funds Program Grant Agreement Number 19-51-RCSBIR-005
- PI is Dr. Andreas Scherer, CEO Golden Helix.
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Who Are We?

GOLDEN HELIX
Enabling Precision Medicine

Golden Helix is a global bioinformatics company founded in 1998

varSEQ®
Filtering and Annotation
ACMG Guidelines
Clinical Reports
CNV Analysis
Pipeline: Run Workflows

VARIANT WARE-HOUSE
Variant Warehouse
Centralized Annotations
Hosted Reports
Sharing and Integration

SNP & VARIATION SUITE
CNV Analysis
GWAS | Genomic Prediction
Large-N Population Studies
RNA-Seq
Large-N CNV-Analysis

Cited in 1,000s of Peer-Reviewed Publications

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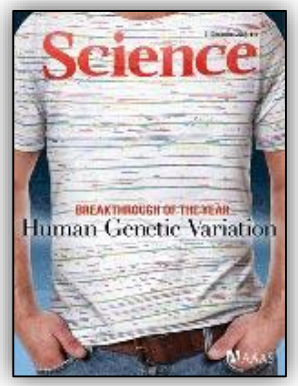

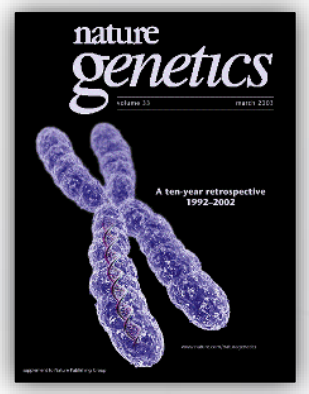

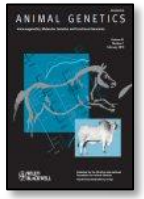

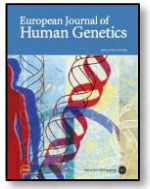

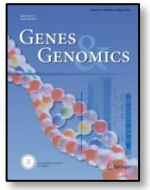

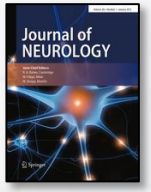

Over 400 Customers Globally

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When you choose Golden Helix, you receive more than just the software

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SOFTWARE IS VETTED

- 20,000+ users at 400+ organizations
- Quality & feedback

DEEPLY ENGRAINED IN SCIENTIFIC COMMUNITY

- Give back to the community
- Contribute content and support

SIMPLE, SUBSCRIPTION-BASED BUSINESS MODEL

- Yearly fee
- Unlimited training & support

INNOVATIVE SOFTWARE SOLUTIONS

- Cited in 1,000s of publications

Gene Panel | Exome | Genome

Sequencer

Products	Bioinformatics Pipeline	Function
DNAseq (Sentieon) TNseq (Sentieon) VS-CNV	FASTQ BAM VCF	▸ Single nucleotide variation ▸ Copy number variation & loss of heterozygosity ▸ Chromosomal aberration
Annotations	Annotated VCF	▸ Public & commercial annotations to enrich genomic data sets
VarSeq VSReports VSPipeline	Clinical Report	▸ Annotate & filter ▸ Visually inspect alignments ▸ Variant prioritization ▸ Clinical assessment
VSClinical	Automated ACMG Guidelines	▸ Clinical variant interpretation in concordance with ACMG Guidelines
VSWarehouse	Data Warehousing Web-Enabled Interface + Powerful API: JSON, XML, TSV, CSV, SQL, FHIR	▸ Clinical assessment catalog ▸ Advanced data querying ▸ Versioning ▸ Interoperability ▸ Compliance with HIPPA, CLIA & CAP data discovery

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VarSeq Suite

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VarSEQ®

Simple

Flexible

Scalable

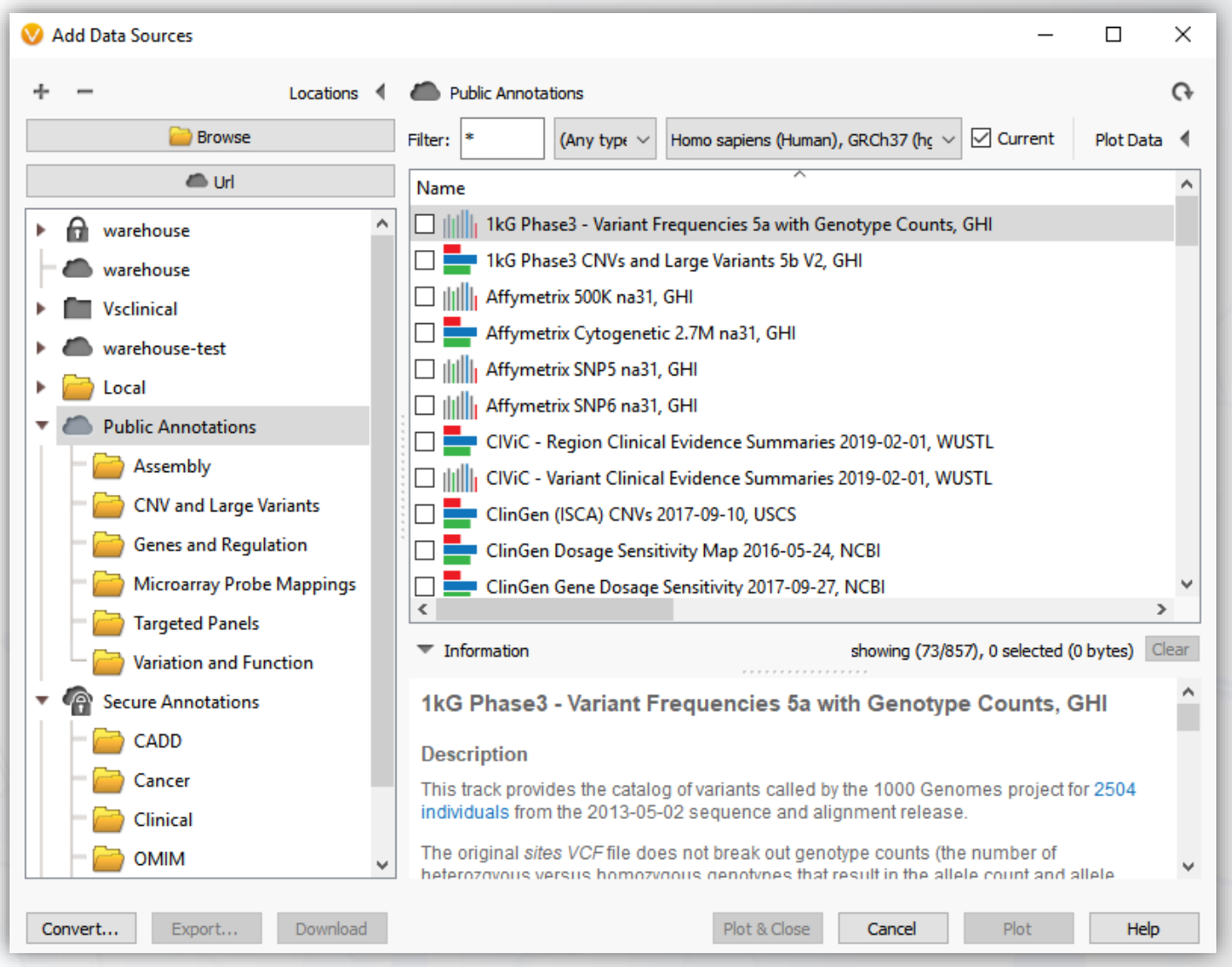
Variant annotation
filtering, and interpretation

Powerful GUI with
rich visualizations

Repeatable
workflows

VarSeq - Annotations

- Curated Public Databases
  - 1kG Phase3 Variant Frequencies
  - RefSeq Genes, NCBI
  - ClinGen Dosage Sensitivity Mapping
  - dbNSFP Functional Predictions
  - dbSNP
  - ExAC
  - ClinVar
  - CIViC
- Lock down version
- Notifications for track updates
- Premium Annotations:
  - CADD
  - COSMIC
  - Conservation Scores
  - SIFT/PolyPhen2
  - Splice Site Algorithms
  - OMIM phenotypes and Genes



VSClinical - Value

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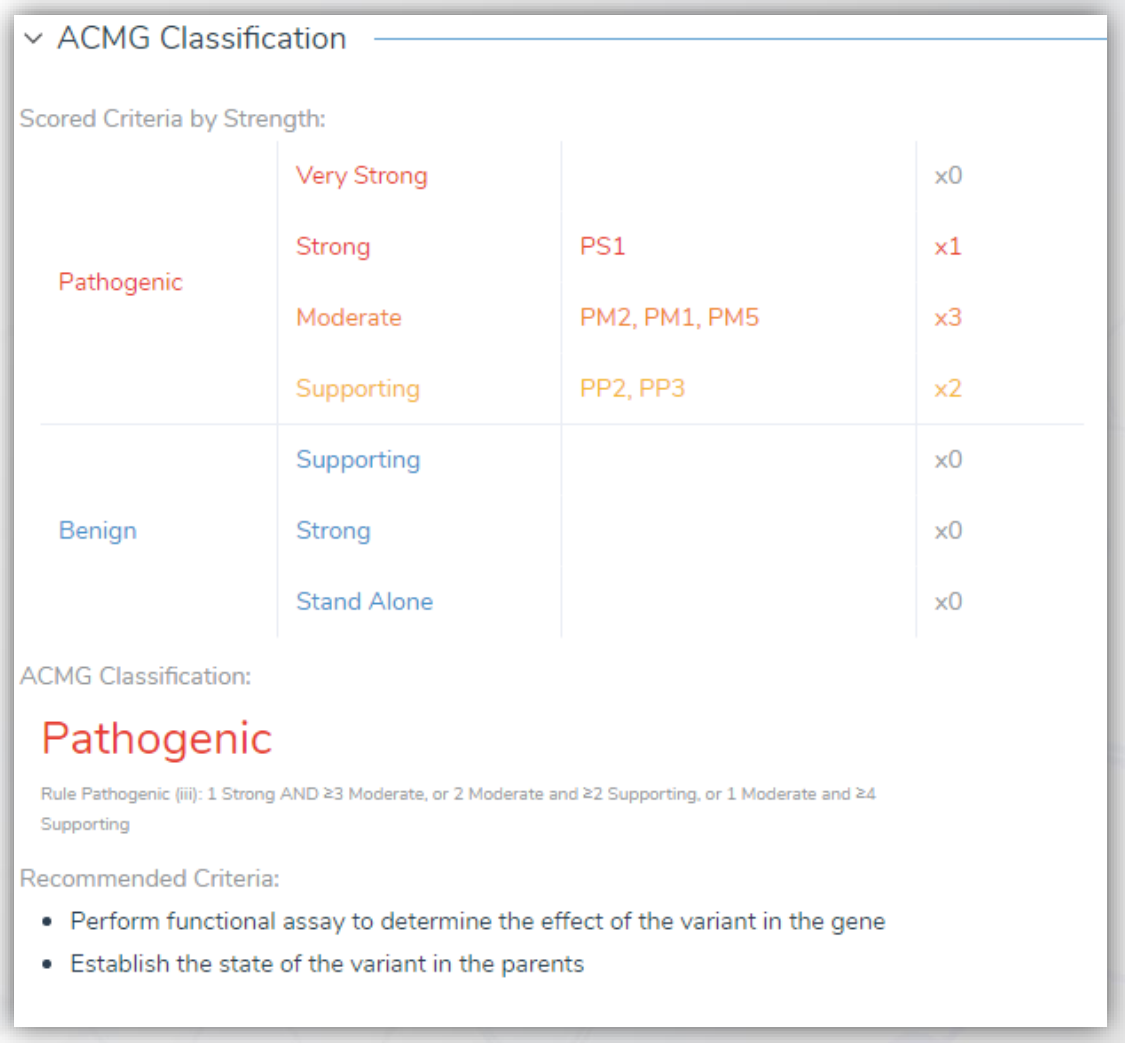
VSClinical®

- Consistent results
- Shorten learning curve
- Staying abreast of new developments



VSClinical - ACMG Rules for Classification

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Pathogenic

(i) 1 Very strong (PVS1) *AND*
- (a) ≥1 Strong (PS1–PS4) *OR*
- (b) ≥2 Moderate (PM1–PM6) *OR*
- (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR*
- (d) ≥2 Supporting (PP1–PP5)

(ii) ≥2 Strong (PS1–PS4) *OR*

(iii) 1 Strong (PS1–PS4) *AND*
- (a)≥3 Moderate (PM1–PM6) *OR*
- (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR*
- (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)

Likely Pathogenic

(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR*

(ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR*

(iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR*

(iv) ≥3 Moderate (PM1–PM6) *OR*

(v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR*

(vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)

Uncertain Significance

(i) Other criteria shown above are not met OR

(ii) the criteria for benign and pathogenic are contradictory

Likely Benign

(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR*

(ii) ≥2 Supporting (BP1–BP7)

Benign

(i) 1 Stand-alone (BA1) *OR*

(ii) ≥2 Strong (BS1–BS4)

Rules Presented in VSClinical

ACMG Classification:

Pathogenic

Rule Pathogenic (iii): 1 Strong AND ≥3 Moderate, or 2 Moderate and ≥2 Supporting, or 1 Moderate and ≥4 Supporting

Richards *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. 2015, Genet Med 17: 405-424.

VSClinical – Four-Phased Workflow

1. Filter and select variants for evaluation
   - Follows existing VarSeq filter workflow
2. Assess all evidence for variant
   - Presented in VSClinical interpretation hub
3. Develop final classification
   - Directly follows ACMG Guidelines
     - 33 criteria for evaluating evidence
     - 5 possible classifications built from criteria
     - Include caveats and discussion for evaluating criteria in different contexts
   - Develop and catalog variant interpretation
4. Include interpretation in final clinical report

VSClinical – Clinical Report

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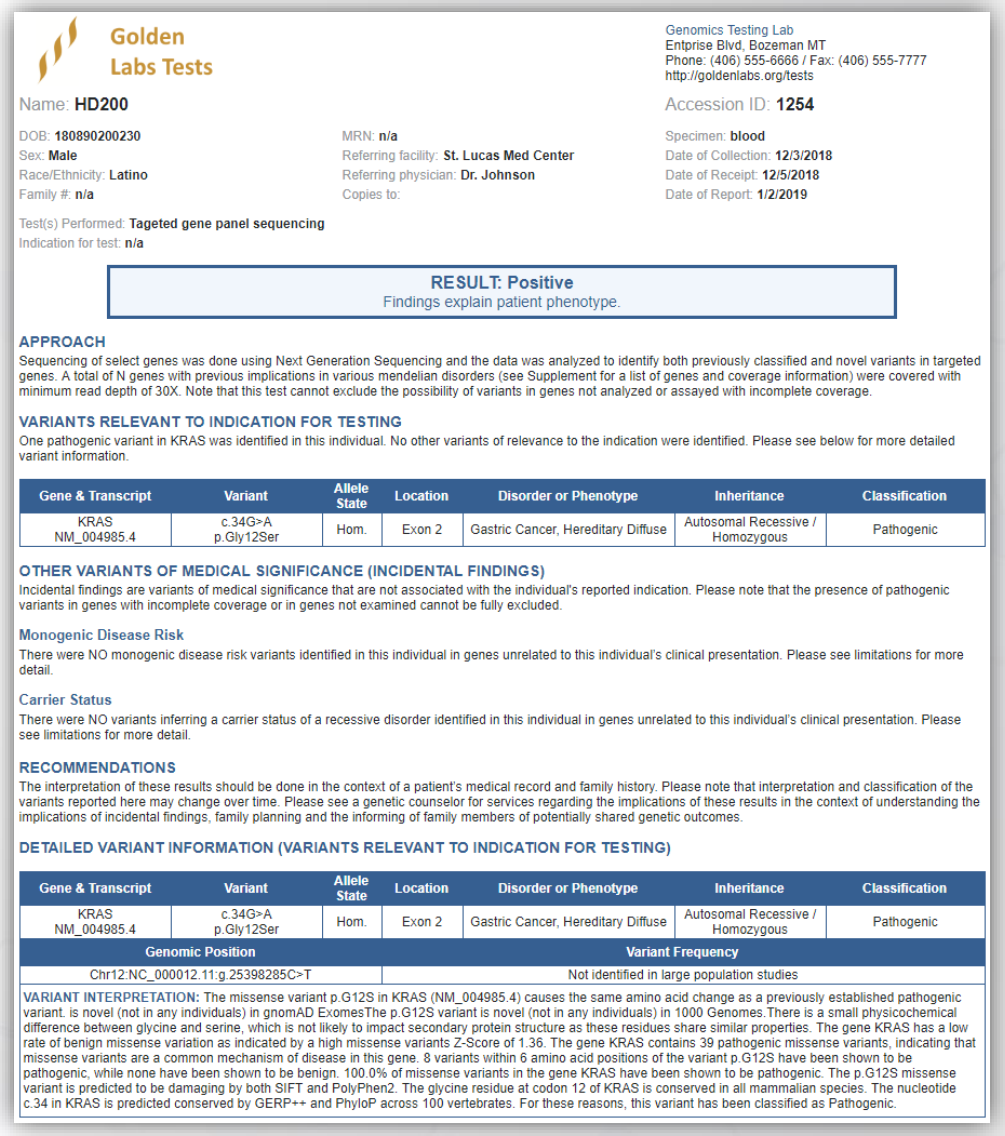
- Prepared “Templates”
  - ACMG Standard Germline Report
  - Configurable Global Settings
    - Logo
    - Lab information
    - Test description/disclaimers
- Customizable Sample Inputs
  - Patient Information
  - Test Results
- Selected Variants Added
  - Per-Variant Information
- Customizable
  - Default values are scriptable
  - Rendering is entirely programmatic



Golden Labs Tests

Genomics Testing Lab
Entprise Blvd, Bozeman MT
Phone: (406) 555-6666 / Fax: (406) 555-7777
http://goldenlabs.org/tests

Name: **HD200**

Accession ID: **1254**

DOB: **180890200230**
Sex: **Male**
Race/Ethnicity: **Latino**
Family #: **n/a**

MRN: **n/a**
Referring facility: **St. Lucas Med Center**
Referring physician: **Dr. Johnson**
Copies to:

Specimen: **blood**
Date of Collection: **12/3/2018**
Date of Receipt: **12/5/2018**
Date of Report: **1/2/2019**

Test(s) Performed: **Tageted gene panel sequencing**
Indication for test: **n/a**

RESULT: Positive
Findings explain patient phenotype.

APPROACH

Sequencing of select genes was done using Next Generation Sequencing and the data was analyzed to identify both previously classified and novel variants in targeted genes. A total of N genes with previous implications in various mendelian disorders (see Supplement for a list of genes and coverage information) were covered with minimum read depth of 30X. Note that this test cannot exclude the possibility of variants in genes not analyzed or assayed with incomplete coverage.

VARIANTS RELEVANT TO INDICATION FOR TESTING

One pathogenic variant in KRAS was identified in this individual. No other variants of relevance to the indication were identified. Please see below for more detailed variant information.

Gene & Transcript	Variant	Allele State	Location	Disorder or Phenotype	Inheritance	Classification
KRAS NM_004985.4	c.34G>A p.Gly12Ser	Hom.	Exon 2	Gastric Cancer, Hereditary Diffuse	Autosomal Recessive / Homozygous	Pathogenic

OTHER VARIANTS OF MEDICAL SIGNIFICANCE (INCIDENTAL FINDINGS)

Incidental findings are variants of medical significance that are not associated with the individual's reported indication. Please note that the presence of pathogenic variants in genes with incomplete coverage or in genes not examined cannot be fully excluded.

Monogenic Disease Risk

There were NO monogenic disease risk variants identified in this individual in genes unrelated to this individual's clinical presentation. Please see limitations for more detail.

Carrier Status

There were NO variants inferring a carrier status of a recessive disorder identified in this individual in genes unrelated to this individual's clinical presentation. Please see limitations for more detail.

RECOMMENDATIONS

The interpretation of these results should be done in the context of a patient's medical record and family history. Please note that interpretation and classification of the variants reported here may change over time. Please see a genetic counselor for services regarding the implications of these results in the context of understanding the implications of incidental findings, family planning and the informing of family members of potentially shared genetic outcomes.

DETAILED VARIANT INFORMATION (VARIANTS RELEVANT TO INDICATION FOR TESTING)

Gene & Transcript	Variant	Allele State	Location	Disorder or Phenotype	Inheritance	Classification
KRAS NM_004985.4	c.34G>A p.Gly12Ser	Hom.	Exon 2	Gastric Cancer, Hereditary Diffuse	Autosomal Recessive / Homozygous	Pathogenic
Genomic Position			**Variant Frequency**			
Chr12:NC_000012.11:g.25398285C>T			Not identified in large population studies			

VARIANT INTERPRETATION: The missense variant p.G12S in KRAS (NM_004985.4) causes the same amino acid change as a previously established pathogenic variant. is novel (not in any individuals) in gnomAD ExomesThe p.G12S variant is novel (not in any individuals) in 1000 Genomes.There is a small physicochemical difference between glycine and serine, which is not likely to impact secondary protein structure as these residues share similar properties. The gene KRAS has a low rate of benign missense variation as indicated by a high missense variants Z-Score of 1.36. The gene KRAS contains 39 pathogenic missense variants, indicating that missense variants are a common mechanism of disease in this gene. 8 variants within 6 amino acid positions of the variant p.G12S have been shown to be pathogenic, while none have been shown to be benign. 100.0% of missense variants in the gene KRAS have been shown to be pathogenic. The p.G12S missense variant is predicted to be damaging by both SIFT and PolyPhen2. The glycine residue at codon 12 of KRAS is conserved in all mammalian species. The nucleotide c.34 in KRAS is predicted conserved by GERP++ and PhyloP across 100 vertebrates. For these reasons, this variant has been classified as Pathogenic.

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Project Demonstration

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