



Processing Hereditary Cancer Panels in VarSeq

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CIOReview

20 most promising
Biotech Technology
Providers

pharma
TECH OUTLOOK

Top 10 Analytics
Solution Providers

Gartner.

Hype Cycle for
Life sciences



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Golden Helix – Who We Are



Golden Helix is a global bioinformatics company founded in 1998.



Variant Calling

- Filtering and Annotation
- Clinical Reports
- VSClinical
- CNV Analysis
- Pipeline: Run Workflows

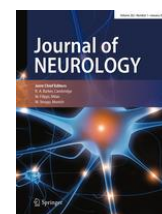
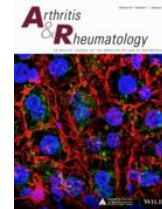
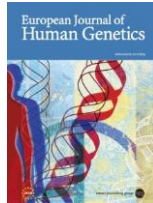
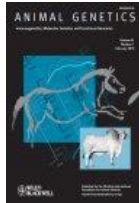
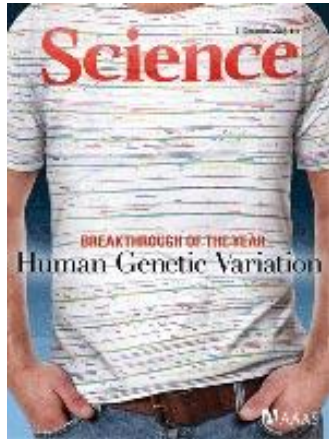


- Variant Warehouse
- Centralized Annotations
- Hosted Reports
- Sharing and Integration

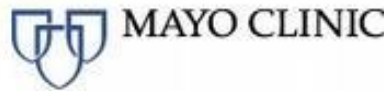


- GWAS
- Genomic Prediction
- Large-N-Population Studies
- RNA-Seq
- Large-N CNV-Analysis

Cited in over 1200 peer-reviewed publications



Over 350 customers globally



Golden Helix – Who We Are



When you choose a Golden Helix solution, you get more than just software

- REPUTATION
- TRUST
- EXPERIENCE



- INDUSTRY FOCUS
- THOUGHT LEADERSHIP
- COMMUNITY

- TRAINING
- SUPPORT
- RESPONSIVENESS





- INNOVATION and SPEED

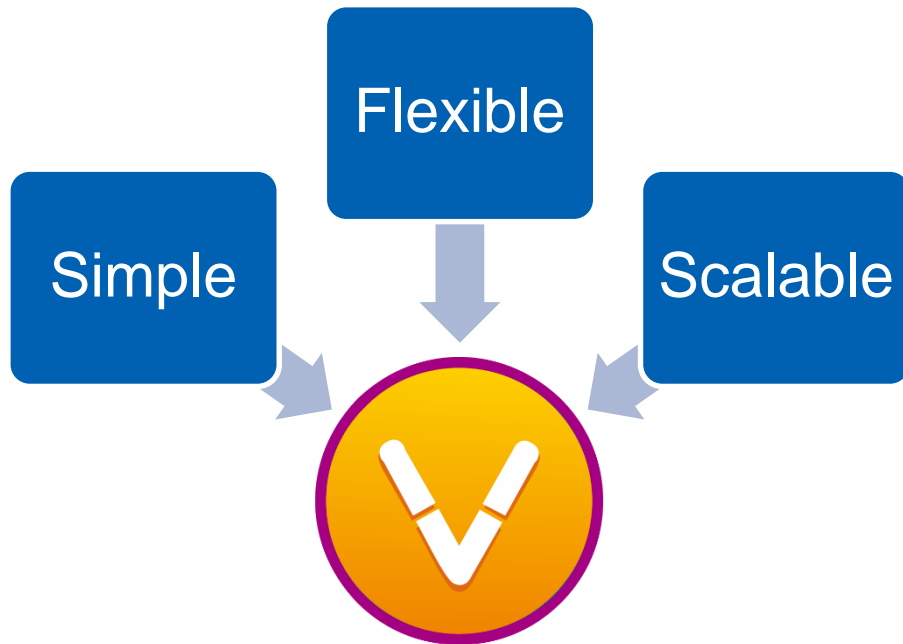
GENE PANEL

EXOME

GENOME

SEQUENCER

PRODUCTS	BIOINFORMATICS PIPELINE	FUNCTION
 DNaseq (Sentieon)  TNseq (Sentieon)  VS-CNV	FASTQ BAM VCF	<ul style="list-style-type: none"> ▶ Single nucleotide variation ▶ Copy number variation & loss of heterozygosity ▶ Chromosomal aberration
Annotations	Annotated VCF	<ul style="list-style-type: none"> ▶ Public & commercial annotations to enrich genomic data sets
 VarSeq  VSReports  VSPipeline	Clinical Report	<ul style="list-style-type: none"> ▶ Annotate & filter ▶ Visually inspect alignments ▶ Variant prioritization ▶ Clinical assessment
 VSclinical	Automated ACMG Guidelines	<ul style="list-style-type: none"> ▶ Clinical variant interpretation in concordance with ACMG Guidelines
 VSWarehouse	Data Warehousing Web-Enabled Interface + Powerful API: JSON, XML, TSV, CSV, SQL, FHIR	<ul style="list-style-type: none"> ▶ Clinical assessment catalog ▶ Advanced data querying ▶ Versioning ▶ Interoperability ▶ Compliance with HIPPA, CLIA & CAP data discovery



- **Variant annotation, filtering, and interpretation**
- **Powerful GUI with rich visualizations**
- **Repeatable workflows + pipeline**

varSEQ®



- **Building a project template**
 - **Focus on cancer panel**
 - **Target specific phenotypes/genes**
 - **Useful annotations**

- **Investigate interesting Variants**
 - **VSClinical/ACMG Guidelines – variant deep dive**
 - **Include variant in clinical report**

- **Save project as template**
 - **Demonstrate speed/efficiency of using template**
 - **Discuss other options for workflow efficiency**

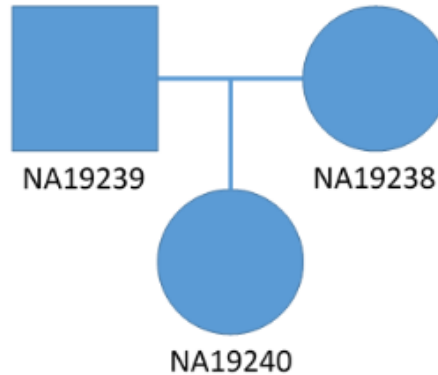
Example Trio Project



- Background – Public Data

- Yoruban Trio

- Mother NA12938
- Father - 39
- Proband (female) - 40



- Trio Analysis including

- De Novo Candidate
- Dominant Heterozygous
- Compound Heterozygous
- Recessive Homozygous
- X-Linked
- Known Rare Pathogenic

Category	Criteria	Count
de Novo Candidate	Read Depths (DP) (Current) > 10	712
	Genotype Qualities (GQ) (Current) >	709
	All MAF < 0.01 OR missing	196
	Effect (Combined) is (LoF, Missense)	80
	Mendel Error (Current) is de Novo All	3
Compound Heterozygous	Read Depths (DP) (Current) > 10	712
	Genotype Qualities (GQ) (Current)	709
	All MAF < 0.01 OR missing	196
	Effect (Combined) is (LoF, Missense)	80
	Compound Het? (Current) is true	2
Dominant Heterozygous	Read Depths (DP) (Current) > 10	712
	Genotype Qualities (GQ) (Current) >	709
	All MAF < 0.01 OR missing	196
	Effect (Combined) is (LoF, Missense)	80
	Zygosity (Current) is Heterozygous	40
Recessive Homozygous	Read Depths (DP) (Current)	712
	Genotype Qualities (GQ) (C	709
	All MAF < 0.01 OR missing	196
	Effect (Combined) is (LoF, I	80
	Recessive Inheritance Mod	1
Known Rare Pathogenic	All MAF < 0.01 OR mi	205
	Zygosity (Current) is	144
	Clinical Significance	1



■ Included Default Workflows

- Trio Analysis including

- De Novo Candidate
- Dominant Heterozygous
- Compound Heterozygous
- Recessive Homozygous
- X-Linked
- Known Rare Pathogenic

- Hereditary Gene Panel

- Somatic Mutation Workflows

- Cancer Gene Panels
- Tumor/Normal Pair Analysis

■ Example Projects

- Example TruSight Cardio Gene Panel
- Example YRI Exome Trio Analysis
- Example Tumor-Normal Pair Analysis

Data Curation of Annotation Sources



- **VarSeq is backed by an extensive list of curated public data sources**
 - 1kG Phase3 Variant Frequencies
 - ClinVar, NCBI
 - COSMIC
 - dbNSFP Functional Predictions
 - dbSNP
 - ExAC
 - RefSeq Genes, NCBI
 - ClinGen Dosage Sensitivity Mapping
- **Your workflows lock down specific versions**
- **Cloud Annotations:**
 - **OMIM** Genes, Phenotypes and Variants
 - **CADD**, tool for scoring deleteriousness of SNVs and Indels in the human genome.

Select Data Source

Select tracks to use as annotation sources against the imported variant set.

Locations Public Annotations

Filter: * Variants Homo sapiens (Human), GRCh37 g1k (Feb 2) Latest

Name	Size	Date
<input type="checkbox"/> ClinVar 2015-05-04, NCBI	4.6M	2015-05-12
<input type="checkbox"/> ClinVitaE 2014-02-09, Invitae	2.5M	2014-02-11
<input type="checkbox"/> COSMIC Mutations Left Aligned 71 v2, GHI	59M	2015-03-13
<input type="checkbox"/> dbNSFP Functional Predictions 2.9, GHI	435M	2015-04-14
<input type="checkbox"/> dbNSFP Functional Predictions and Scores 2.9, GHI	6.2G	2015-04-13
<input type="checkbox"/> dbSNV Splice Altering Predictions 2014-11-09, GHI	220M	2014-09-28
<input type="checkbox"/> dbSNP 137, UCSC	857M	2012-12-10
<input type="checkbox"/> dbSNP 142v2, NCBI	2.1G	2015-04-20
<input type="checkbox"/> dbSNP Common 137, UCSC	217M	2012-12-10
<input type="checkbox"/> dbSNP Common 141, NCBI	554M	2014-09-18
<input type="checkbox"/> dbSNP Flagged 137, UCSC	911K	2012-12-10
<input type="checkbox"/> dbSNP Flagged 141, NCBI	243K	2014-09-17
<input type="checkbox"/> dbSNP Multiple Loci 137, UCSC	53M	2012-12-10
<input type="checkbox"/> ExAC Variant Frequencies 0.3, BROAD	756M	2015-04-07
<input checked="" type="checkbox"/> ExAC VEP Annotations 0.3, BROAD	827M	2015-04-22
<input type="checkbox"/> NHLBI ESP6500SI-V2-SSA137 Exomes Variant Frequencies 0.0.30, GHI	86M	2015-04-22
<input type="checkbox"/> PolyPhen2 dbSNP131, UCSC	3.2M	2011-03-28
<input type="checkbox"/> SIFT Prediction for SNVs 2011-01-10, JCVI	254M	2011-01-10
<input type="checkbox"/> Supercentenarian 17 Variant Frequencies, GHI	112M	2015-03-05

Information showing (23/378), 0 selected (0 bytes) Clear

ExAC VEP Annotations 0.3, BROAD

Description

The Exome Aggregation Consortium (ExAC) aggregates and summarizes exome sequencing data from a variety of large-scale sequencing projects. The data set spans

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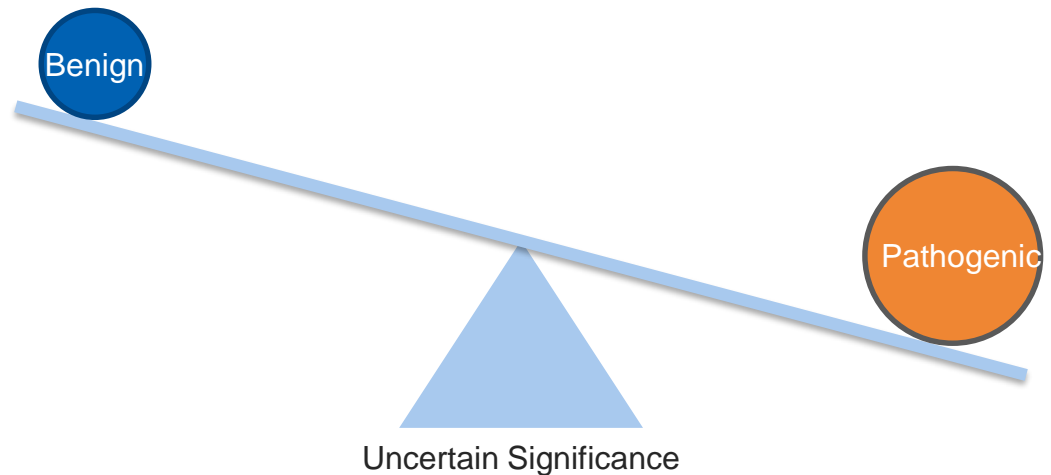


■ Evaluation of Evidence:

- Clinical presentation
- Gene function
- Bioinformatic evidence
- Population frequencies

■ ACMG Guidelines:

- 33 criteria for evaluating evidence
- 5 classifications from the scored criteria
- Caveats and discussion about how to evaluate criteria in different context





- **High level**
- **Consistent results**
 - Time irrelevant
 - No fatigue impact
- **Up to speed quickly**
- **Ramping up workforce**
- **We working on developments and you benefit**



▼ ACMG Classification

Scored Criteria by Strength:

Pathogenic	Very Strong		x0
	Strong		x0
	Moderate		x0
	Supporting		x0
Benign	Supporting	BP4, BP5	x2
	Strong	BS1	x1
	Stand Alone		x0

ACMG Classification:

Likely Benign

The classification of Likely Benign applies with scored criteria of 1 very strong pathogenic along with 2 or more moderate pathogenic and no benign.

Recommended Criteria:

- Perform functional assay to determine the effect of the variant in the gene.
- Establish the presence of the variant in the parents

Analysis Workflow with VSClinical



1. Follow your existing VarSeq annotation and filtering workflow
2. Add new ACMG Auto Classifier algorithm:
 - Looks up if variant annotated in previous sample
 - Scores 18 criteria based on available evidence from 7 sources
3. Select variants to evaluate using the ACMG Guidelines
4. Score and Finalize each variant, selecting which to report
5. Finalize the sample, review and report

The screenshot shows the 'Filter Chain' interface in VSClinical. It displays a list of filters applied to a set of variants, with the total number of variants remaining after each filter step. The filters are:

- Filter Chain**: 961 variants
- Filter (Current) is PASS**: 730 variants
- Read Depths (DP) (Current) > 100**: 678 variants
- Clinical Significance is (Pathogenic, Uncertain Significance)**: 10 variants
- All MAF < 0.3 OR missing**: 8 variants
- Effect (Combined) is (LoF, Missense)**: 6 variants

The 'Effect (Combined) is (LoF, Missense)' filter is expanded, showing the following breakdown:

Effect	Count
LoF	1
Missense	5
Other	2
Missing	0
Total	6



- **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 HELIX

Enabling Precision Medicine

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Patient Information

Name NA19240	Gender Male	Date of Birth July 10, 2018	Id 1234
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Mother Information

Name NA19238	Date of Birth July 10, 2018	Id 1235
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Father Information

Name NA19239	Date of Birth July 10, 2018	Id 1236
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Reference Information

Physician	Identification Number	Institution
Case Id		

Sample Information

Sample Site	Sample Type	Collection Method	Collection Date July 10, 2018	Receipt Date July 10, 2018	Report Date July 10, 2018
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Results - Positive

Mutations with an established link detected.

Primary Findings

Gene	Exon	Variant	Zygosity	Pathogenicity
SMAD4	12	NM_005359.5:c.1498A>G (NP_005350.1:p.Ile500Val)	Heterozygous	Pathogenic

Affected Genes



Interpretation Summary

VSPipeline - High throughput



- **Command-line interface that automates pipelines and workflows**
- **Build template in VarSeq then automate with VSpipeline**



UP-TO-DATE ANNOTATIONS



POWER AND FLEXIBILITY FOR HIGH THROUGHPUT ENVIRONMENTS



REPEATABLE CLINICAL WORKFLOWS



BUILT FOR CLINICAL SETTINGS





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20th Anniversary License Specials



20-month license for the price of a 12-month license

- (~~2~~ 1 left) SVS License 1 user - \$2,995
- (~~3~~ 1 left) VarSeq License 1 user - \$4,795
- (1) VarSeq License (w/ VSReports & VS-CNV) 1 user - \$12K
- (~~3~~ 1 left) VSClinical License (w/ VarSeq, VSReports, CADD & OMIM) 1 user - \$12K
- (2) VSClinical & VS-CNV License (Small Lab Starter) 2 user - \$24K
- (2) VarSeq, VS-Reports, VS-CNV, Tier 1 Sentieon (1 users) \$17.5K
- (~~3~~ 2 left) Sentieon Tier 2 License - \$10K
- (2) Small Warehouse License (VS-CNV, VSClinical, Sentieon Tier 1, VSReports, VSPipeline) 2 user - \$48K
- ~~(1) Warehouse License (VS-CNV, VSClinical, Sentieon Tier 1, VSReports, VSPipeline) Up to 10 users - \$120K~~
- ~~(1) SVS Server License with Imputation 2 user - \$7,995~~

These offers will expire on September 15, 2018



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