GOLDEN HELIX
Enabling Precision Medicine

AMP-Based Variant Classification with VSClinical

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CIOReview
20 Most Promising Biotech Technology Providers

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Top 10 Analytics Solution Providers

Questions & Answers

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- 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+AMP 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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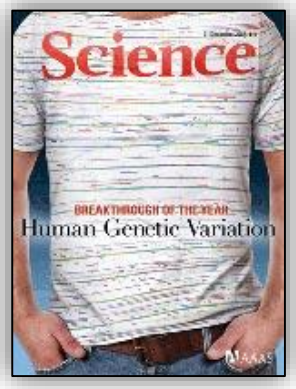

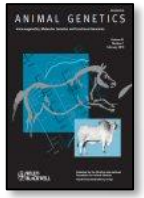

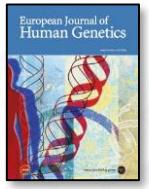

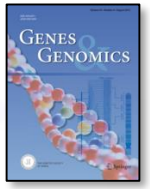

Over 400 Customers Globally

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

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 & AMP Guidelines	‣ Clinical variant interpretation in concordance with ACMG & AMP 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

VarSeq Suite

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VarSEQ®

Simple

Flexible

Scalable

Variant annotation
filtering, and interpretation

Powerful GUI with
rich visualizations

Repeatable
workflows

VarSeq – Getting Started

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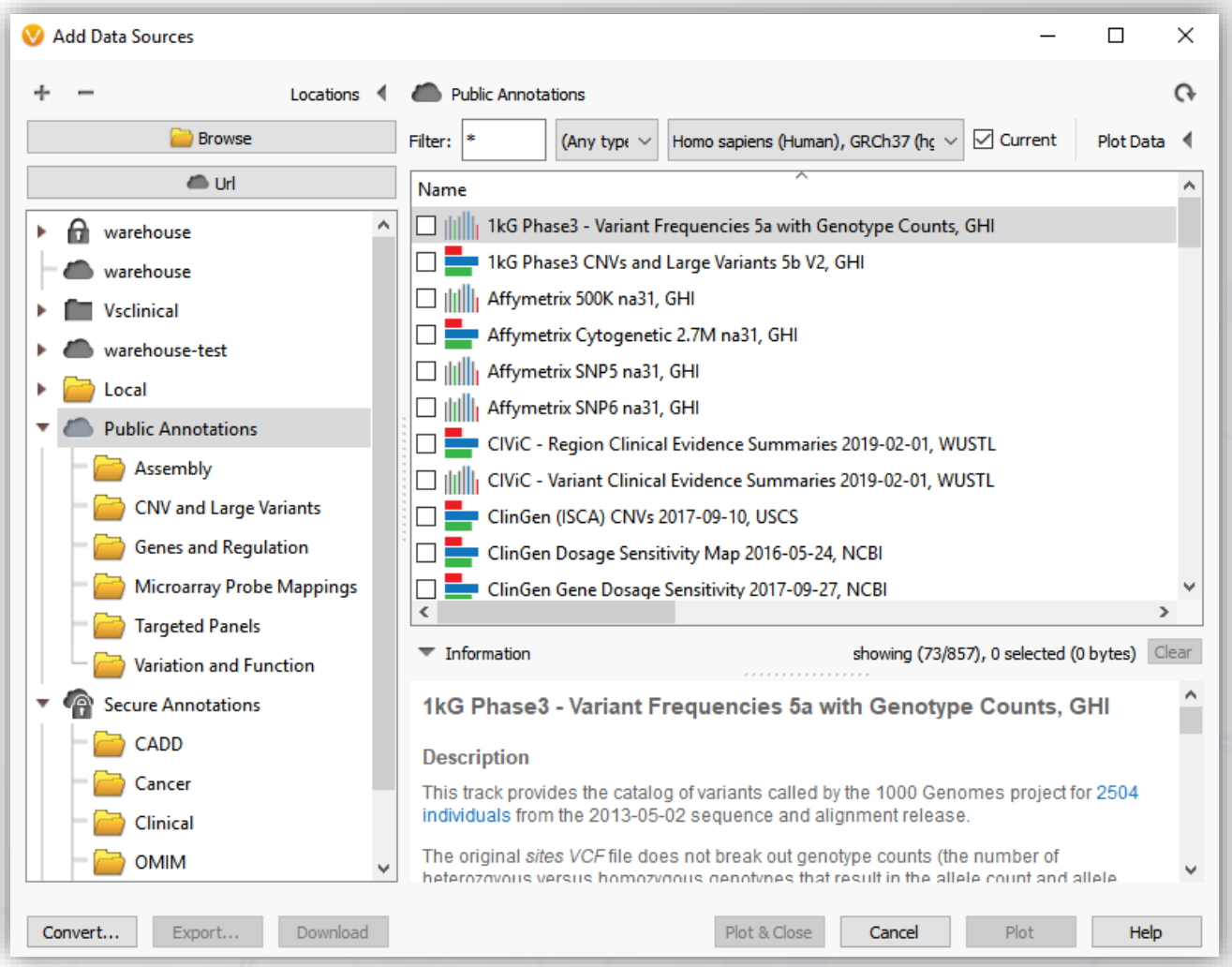
- **Included Default Workflows**
  - **Trio Analysis**
    - De novo candidates
    - Dominant Heterozygous
    - Compound Heterozygous
    - Recessive Homozygous
    - X-Linked
    - Known Rare Pathogenic
  - **Hereditary Gene Panel**
  - **Somatic Mutation Workflows**
    - Cancer Gene Panels
    - Tumor/Normal Pair Analysis

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

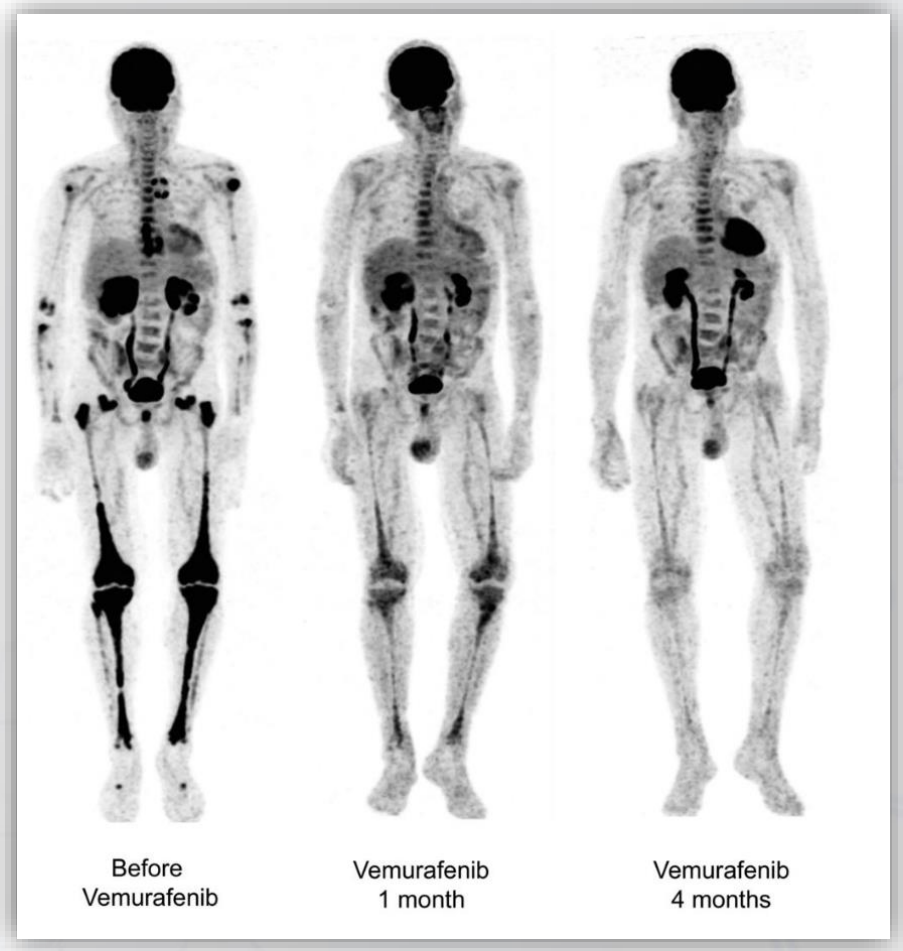
VarSeq – Annotations

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



VSClinical - AMP Guidelines: Analyzing Biomarkers

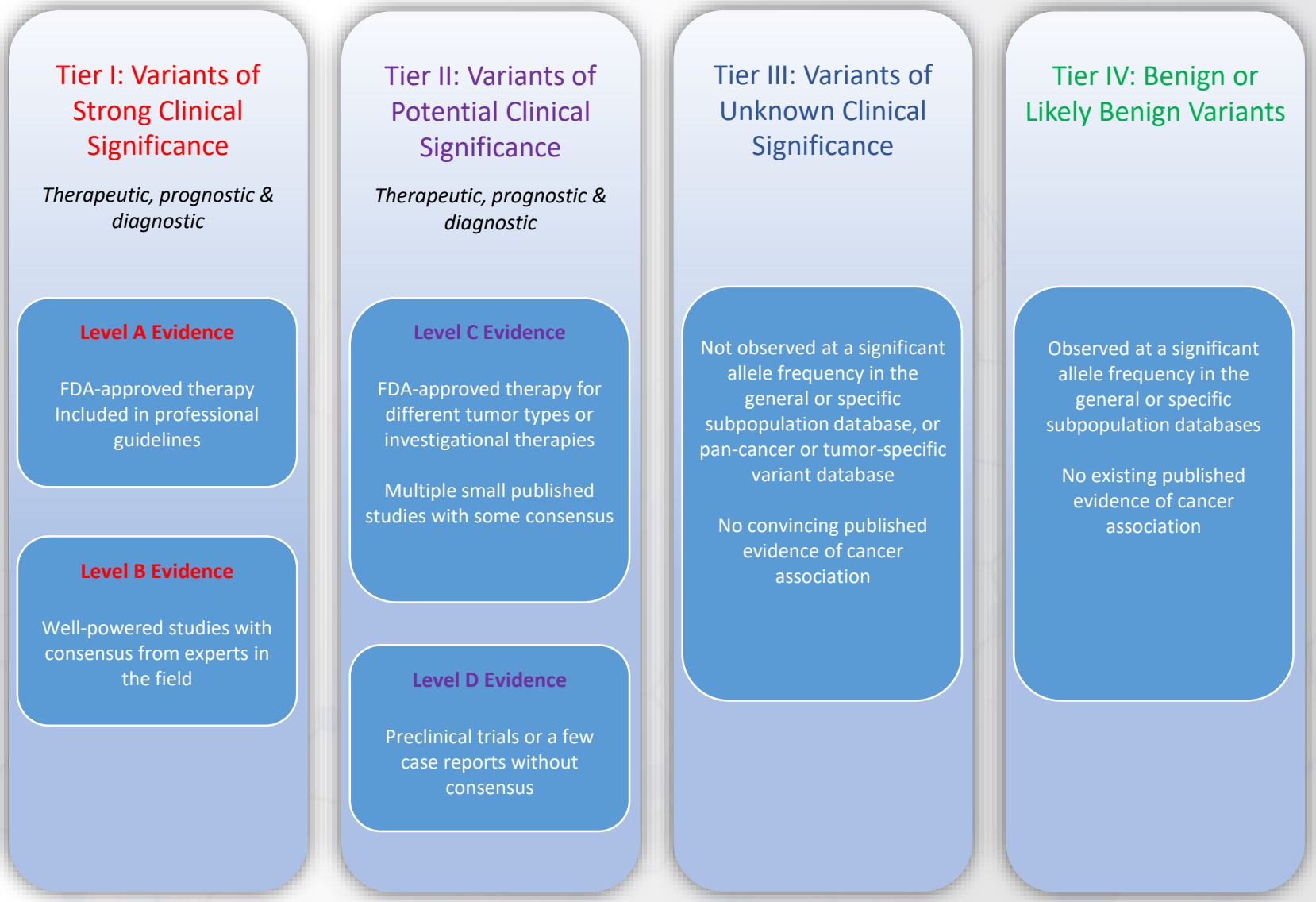
- **Biomarker Definition**
  - Biological states with indications for treatments, prognostic, or diagnostic outcomes
  - Presence or absence of proteins, antigens, and specific genomic attributes of the tumor
- **Common Cancer Biomarkers**
  - HER2+: High levels of HER2 receptor protein
  - MSI-H: Microsatellite instability-high
  - $BRAF^{V600E}$: Activating mutation V600E
  - $ERBB2^{Amp}$: Amplification of ERBB2
  - BCR-ABL1: Activation of ABL1 with BCR fusion
  - $TP53^{WT}$: No significant alterations of critical TSG



Haroche J. et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the *BRAF* V600E mutation. *Blood 2013 121*

VSClinical - AMP Guidelines: Reporting Biomarkers

- **Clinically Actionable Biomarkers**
  - AMP guidelines best practice with clinical significance “Tiers” for drug response + prognostic/diagnostic implications
  - Reports should include actionable results and include quality of clinical evidence in context to patient’s tumor



(2017) Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer:

VSClinical – AMP Guidelines: 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**
   - Somatic

   - Oncogenicity scoring, Drug sensitivity, Drug Resistance, Prognostic and Diagnostic
   - Secondary Germline

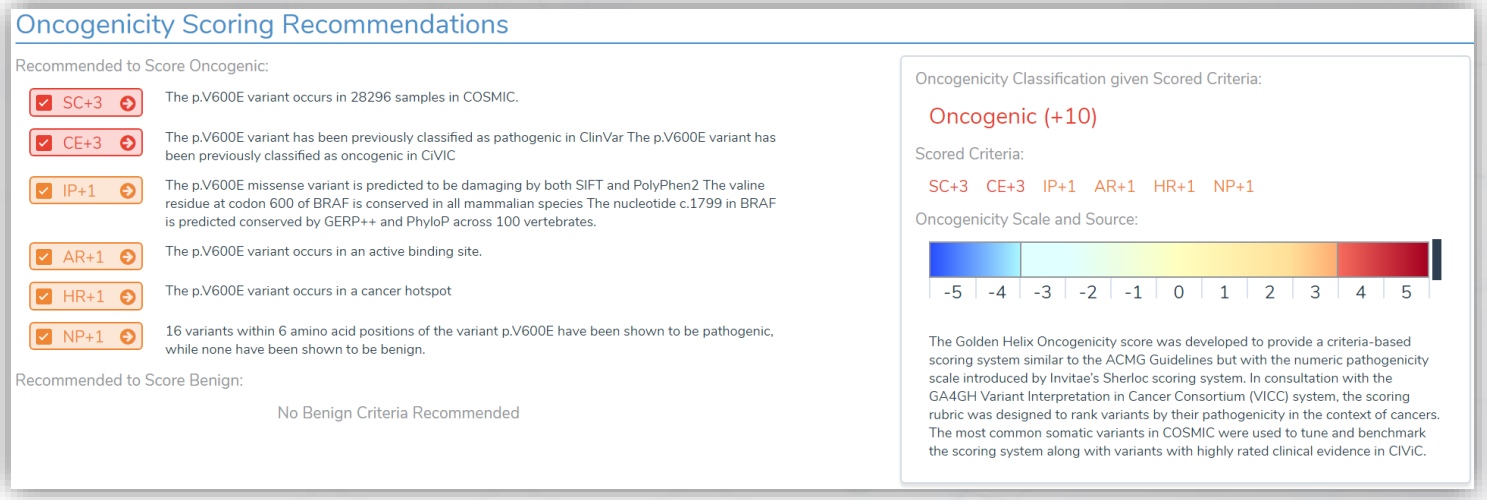
   - ACMG based classification criteria
4. **Include interpretations in final clinical report**

VSClinical – AMP and ACMG Guidelines: One Suite

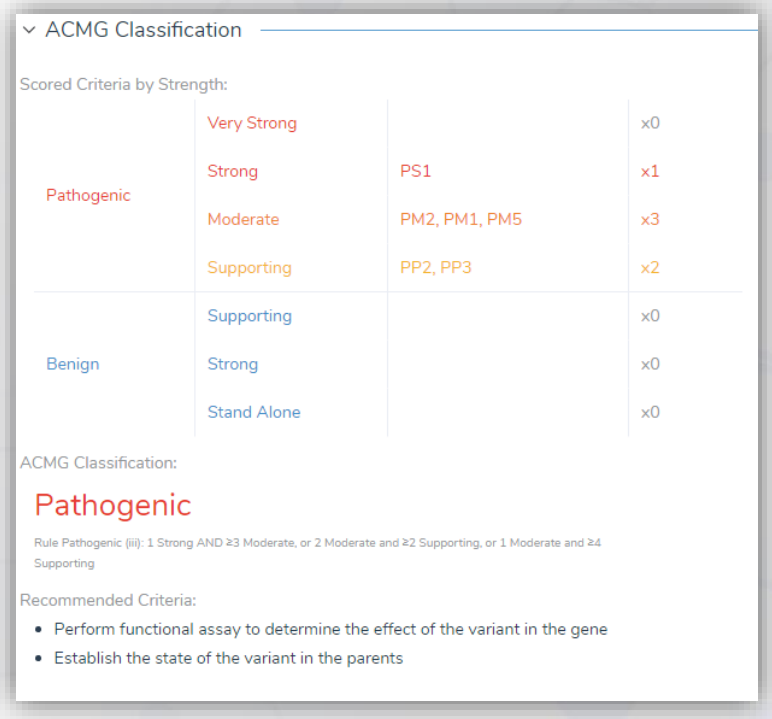
VSClinical®

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

Somatic



Germline



AMP Guidelines – Annotations

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Population Database to exclude common variants

Database	Web Address
1000 Genomes	http://www.internationalgenome.org/data/
dbSNP	https://www.ncbi.nlm.nih.gov/snp/
dbVAR	https://www.ncbi.nlm.nih.gov/dbvar/
ExAC	http://exac.broadinstitute.org/about
gnomad	https://gnomad.broadinstitute.org/

Cancer Specific Databases

Database	Web Address
COSMIC	https://cancer.sanger.ac.uk/cosmic/
My Cancer Genome	https://www.mycancergenome.org/
Clinical Trials	https://clinicaltrials.gov/
CiVIC	https://civicdb.org
Cancer Hotspots	http://www.cancerhotspots.org
PMKB	https://pmkb.weill.cornell.edu/
ICGC Data Portal	https://dcc.icgc.org/
MSK-IMPACT	https://www.mskcc.org/msk-impact
TCGA	https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga

Sequence Repositories

Database	Web Address
NCBI genome	https://www.ncbi.nlm.nih.gov/genome/
RefSeqGene	https://www.ncbi.nlm.nih.gov/refseq/rsg/
Ensemble	https://grch37.ensembl.org/index.html

Clinical, Drug, and Prediction annotations

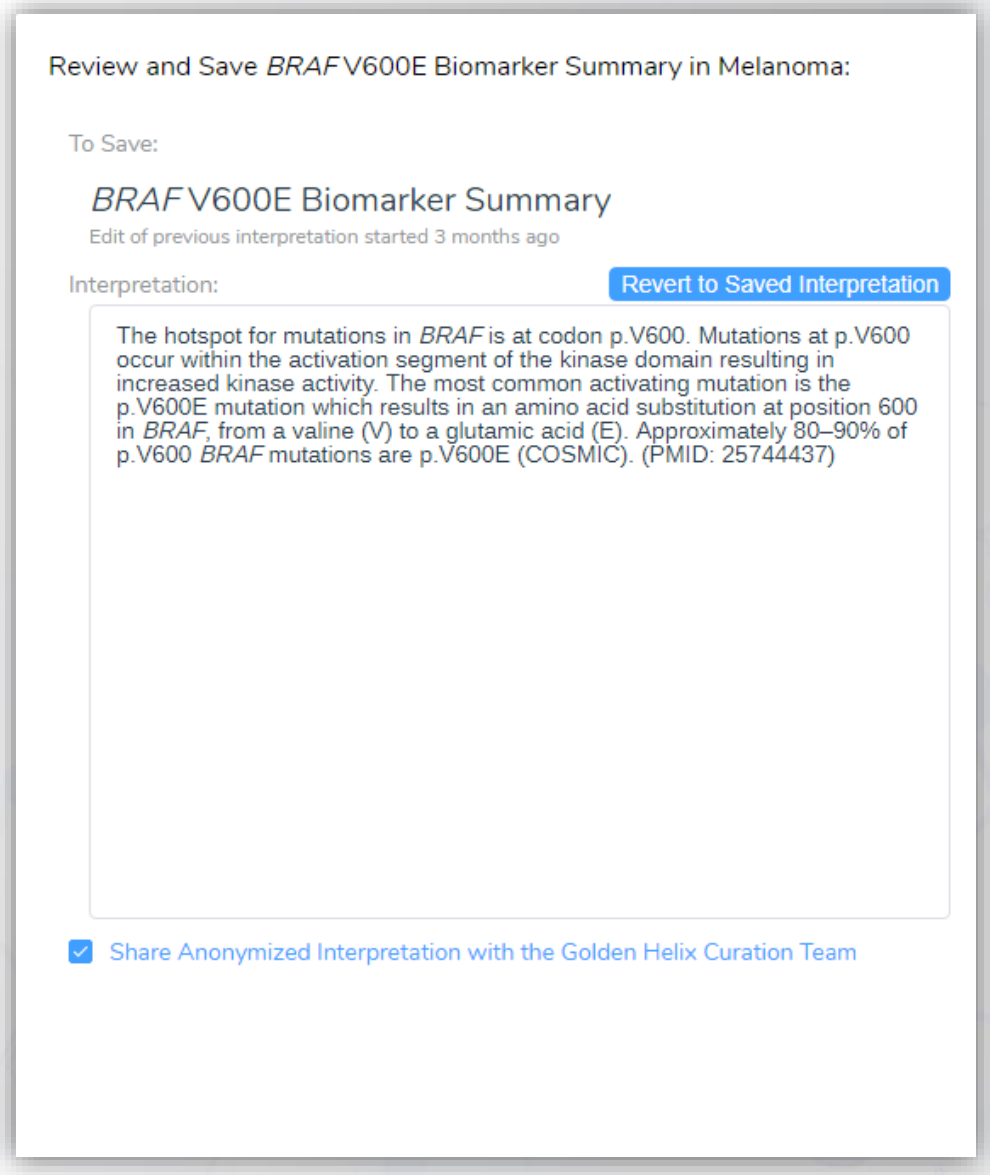
Database	Web Address
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/
Leiden	http://www.lovd.nl/
dbSNFP Predictor	https://sites.google.com/site/jpopgen/dbNSFP
Ensemble Predictor	https://uswest.ensembl.org/info/genome/index.html
DrugBank	https://www.drugbank.ca/
Clinical Genomic Database	https://research.nhgri.nih.gov/CGD/
Genetics Home Reference	https://ghr.nlm.nih.gov/

Splice Site and Functional Prediction Algorithms

Database	Web Address
Human Splicing Finder	http://www.umd.be/HSF/
MaxEntScan	https://www.hollywood.mit.edu/burgelab/maxent/Xmentscan_scoreseq.html
NetGene2	http://www.cbs.dtu.dk/services/NetGene2/
NNSplice	http://www.fruitfly.org/seq_tools/splice.html
GeneSplicer	https://ccb.jhu.edu/software/genesplicer/
PolyPhen2	http://genetics.bwh.harvard.edu/pph2/
SIFT	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC168916
CADD	https://cadd.gs.washington.edu/
GERP++	http://mendel.stanford.edu/SidowLab/downloads/gerp

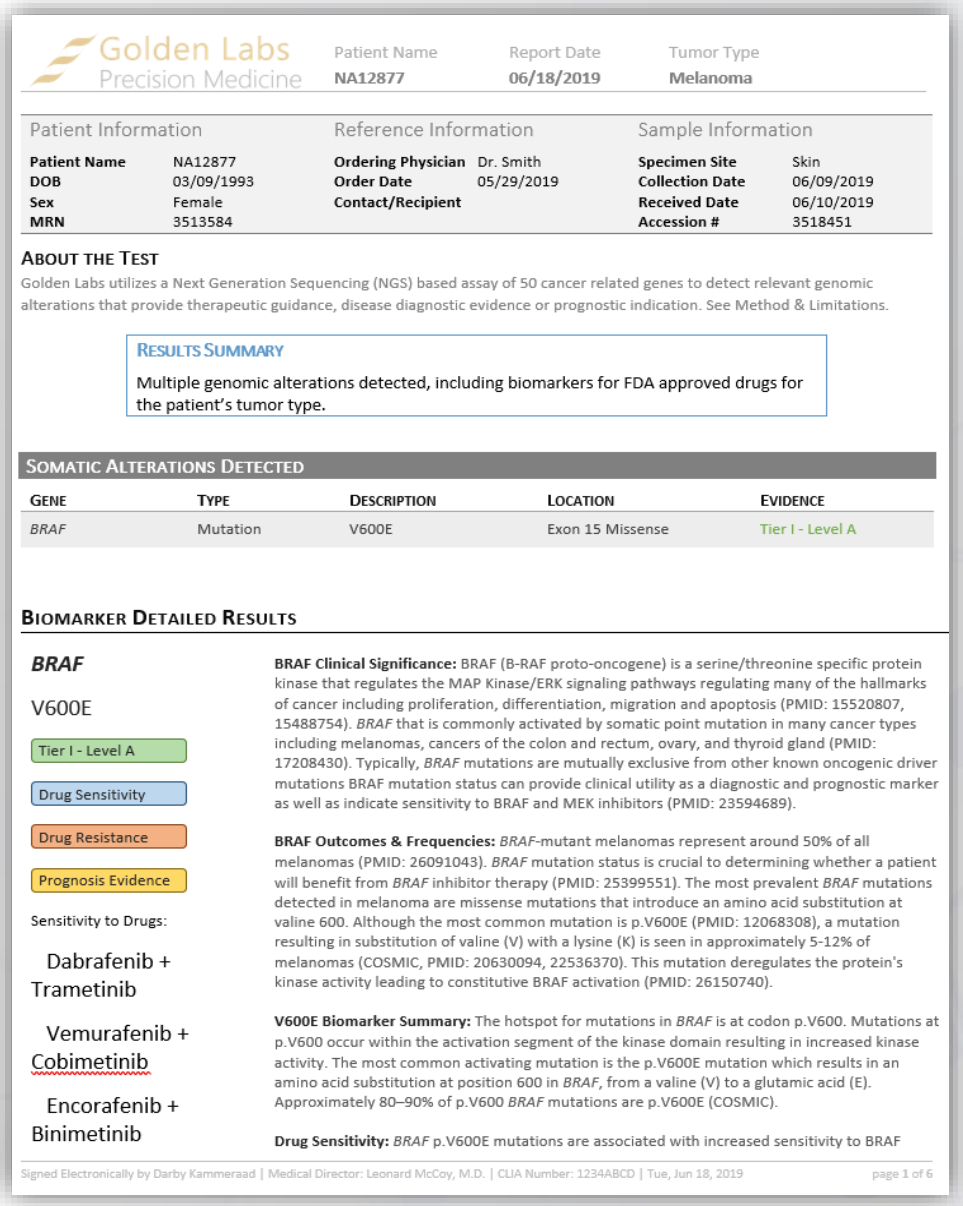
Golden Helix - CancerKB

- **Cancer Interpretation Catalog**
  - Included with AMP Guidelines
- **Primary Values**
  - Curated by professionals in the clinical context
  - Jump starts interpretation
  - Accelerates time to reporting



VSClinical – Clinical Report

- **VSClinical conducts the clinical variant analysis based on ACMG and AMP guidelines**
  - Automated population of the clinical report-based workflow outcome
  - Standardizing of variant level interpretation based on customizable assessment catalogs
  - For somatic variants, GHI provides predefined clinical assessments via our CancerKB catalog
- **Rendering of clinical reports within seconds**
- **Supported output formats**
  - Word
  - PDF



Golden Labs Precision Medicine

Patient Name	Report Date	Tumor Type
NA12877	06/18/2019	Melanoma

Patient Information		Reference Information		Sample Information	
Patient Name	NA12877	**Ordering Physician**	Dr. Smith	**Specimen Site**	Skin
DOB	03/09/1993	**Order Date**	05/29/2019	**Collection Date**	06/09/2019
Sex	Female	**Contact/Recipient**		**Received Date**	06/10/2019
MRN	3513584			**Accession #**	3518451

ABOUT THE TEST

Golden Labs utilizes a Next Generation Sequencing (NGS) based assay of 50 cancer related genes to detect relevant genomic alterations that provide therapeutic guidance, disease diagnostic evidence or prognostic indication. See Method & Limitations.

RESULTS SUMMARY

Multiple genomic alterations detected, including biomarkers for FDA approved drugs for the patient's tumor type.

SOMATIC ALTERATIONS DETECTED

GENE	TYPE	DESCRIPTION	LOCATION	EVIDENCE
BRAF	Mutation	V600E	Exon 15 Missense	Tier I - Level A

BIOMARKER DETAILED RESULTS

BRAF

V600E

Tier I - Level A

Drug Sensitivity

Drug Resistance

Prognosis Evidence

Sensitivity to Drugs:

Dabrafenib + Trametinib

Vemurafenib + Cobimetinib

Encorafenib + Binimetinib

BRAF Clinical Significance: BRAF (B-RAF proto-oncogene) is a serine/threonine specific protein kinase that regulates the MAP Kinase/ERK signaling pathways regulating many of the hallmarks of cancer including proliferation, differentiation, migration and apoptosis (PMID: 15520807, 15488754). *BRAF* that is commonly activated by somatic point mutation in many cancer types including melanomas, cancers of the colon and rectum, ovary, and thyroid gland (PMID: 17208430). Typically, *BRAF* mutations are mutually exclusive from other known oncogenic driver mutations BRAF mutation status can provide clinical utility as a diagnostic and prognostic marker as well as indicate sensitivity to BRAF and MEK inhibitors (PMID: 23594689).

BRAF Outcomes & Frequencies: *BRAF*-mutant melanomas represent around 50% of all melanomas (PMID: 26091043). *BRAF* mutation status is crucial to determining whether a patient will benefit from *BRAF* inhibitor therapy (PMID: 25399551). The most prevalent *BRAF* mutations detected in melanoma are missense mutations that introduce an amino acid substitution at valine 600. Although the most common mutation is p.V600E (PMID: 12068308), a mutation resulting in substitution of valine (V) with a lysine (K) is seen in approximately 5-12% of melanomas (COSMIC, PMID: 20630094, 22536370). This mutation deregulates the protein's kinase activity leading to constitutive BRAF activation (PMID: 26150740).

V600E Biomarker Summary: The hotspot for mutations in *BRAF* is at codon p.V600. Mutations at p.V600 occur within the activation segment of the kinase domain resulting in increased kinase activity. The most common activating mutation is the p.V600E mutation which results in an amino acid substitution at position 600 in *BRAF*, from a valine (V) to a glutamic acid (E). Approximately 80–90% of p.V600 *BRAF* mutations are p.V600E (COSMIC).

Drug Sensitivity: *BRAF* p.V600E mutations are associated with increased sensitivity to BRAF

Signed Electronically by Darby Kammeraad | Medical Director: Leonard McCoy, M.D. | CLIA Number: 1234ABCD | Tue, Jun 18, 2019 page 1 of 6

VSClinical – AMP Guidelines: Project Demonstration

- **Trusight Myeloid Gene Panel (568 Targets)**
  - Pre-run coverage and sample statistics
  - Exploring multiple variants
    - SNV: somatic missense $BRAF^{V600E}$
    - CNV: $ERBB2^{Amp}$
    - Fusion: BCR-ABL1
- **Explore VSClinical – AMP Guideline tabs**
  - Patient info
  - Mutation selection
  - Variant oncogenicity score
  - Biomarker interpretation + treatment options
  - Clinical report

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Project Demonstration

Questions & Answers

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Summer AMP Sale

VSClinical Cancer Pack	VSClinical Cancer PowerPack	Small Warehouse Pack	Large Warehouse Pack
$23,995/15 months	**$29,995/15 months**	**$47k/15 months**	**$120k/15 months**
2 users	2 users	2 users	Up to 10 users
VSClinical	VSClinical	VSClinical	VSClinical
AMP Add-On	AMP Add-On	AMP Add-On	AMP Add-On
	VS-CNV	VS-CNV	VS-CNV
	Sentieon Tier 1	Sentieon Tier 1	Sentieon Tier 1
		VSReports	VSReports
		VSPipeline	VSPipeline
		VSWarehouse	VSWarehouse
Packs Remaining: 3	Packs Remaining: 3	Packs Remaining: 3	Packs Remaining: 1

Buy two years, get the third year for free!

Questions & Answers