Standardizing ACMG Variant Interpretation Guidelines

Gabe Rudy | VP of Product & Engineering

Golden Helix – Who We Are

Golden Helix is a global bioinformatics company founded in 1998.

GlaxoSmithKline

varSEQ®

- Variant Calling
- Filtering and Annotation
- **Variant Interpretation**
- Clinical Reports
- CNV Analysis
- Pipeline: Run Workflows

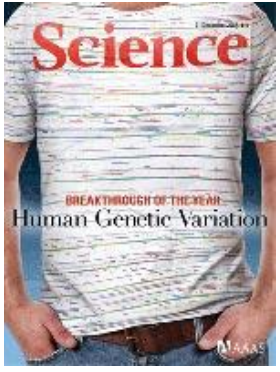
VARIANT WAREHOUSE

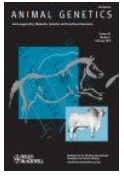
- Variant Warehouse
- Centralized Annotations
- Hosted Reports
- Sharing and Integration

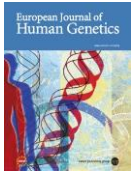
SNP & VARIATION SUITE

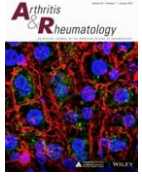
- **CNV Analysis**
- GWAS
- Genomic Prediction
- Large-N-Population Studies
- RNA-Seq
- Large-N CNV-Analysis

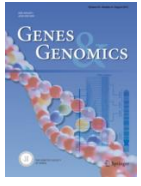
Cited in over 1,200 peer-reviewed publications

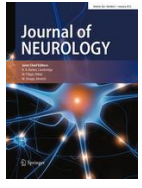












Over 350 customers globally

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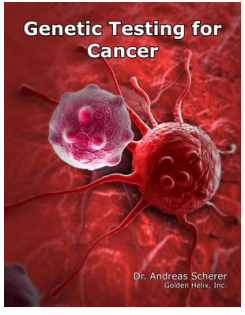
Golden Helix – Who We Are

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

- REPUTATION
- TRUST
- EXPERIENCE



- INDUSTRY FOCUS
- THOUGHT LEADERSHIP
- COMMUNITY

- TRAINING
- SUPPORT
- RESPONSIVENESS

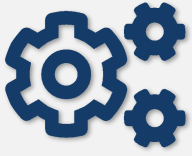
- INNOVATION and SPEED
- CUSTOMIZATIONS

Genetic Testing Process

Golden Helix Clinical Suite

Sample Prep

Sequencing



Align & Call

Sentieon & VS-CNV

Annotate & Filter

VarSeq

Variant Interpretation

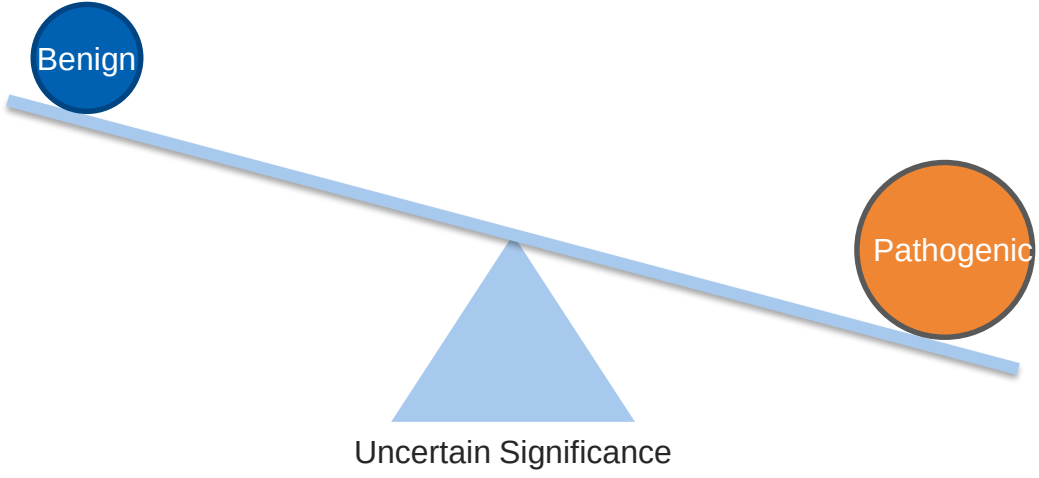
VSClinical

Report

VSReports

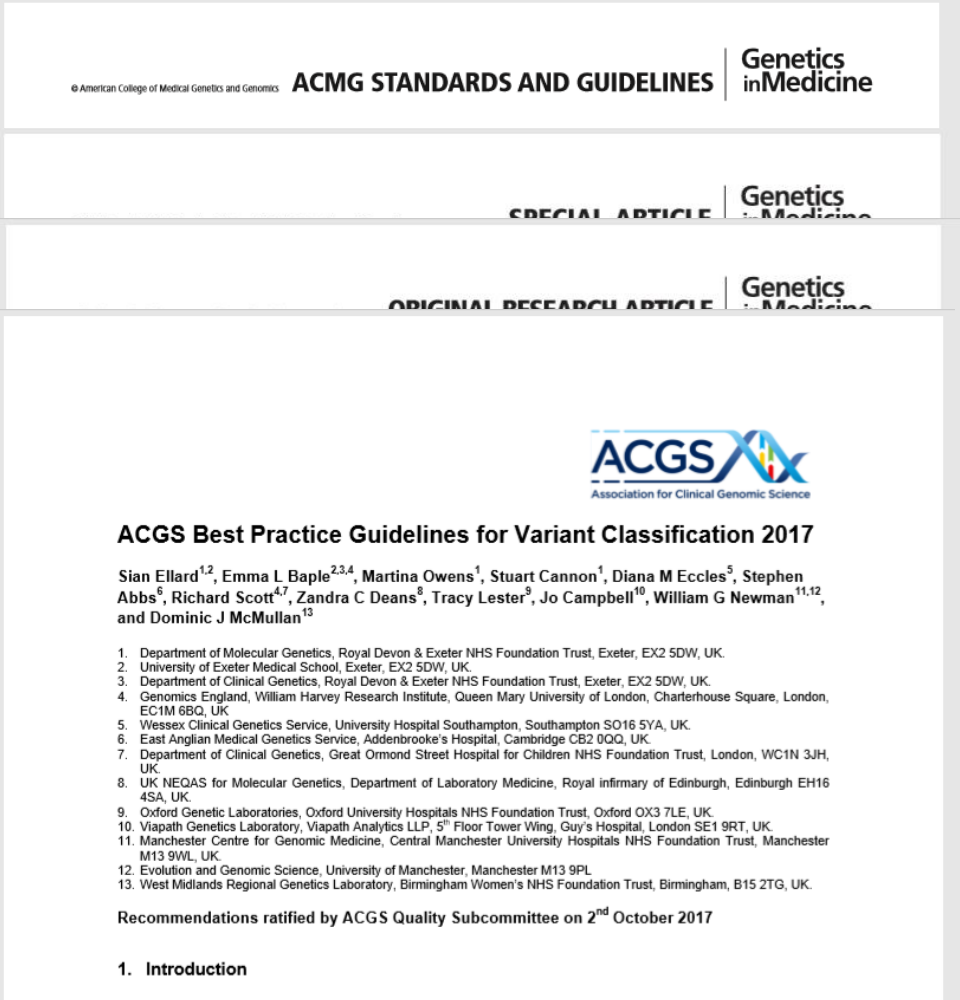
Variant Interpretation

- **Evaluation of Evidence:**
  - Clinical presentation
  - Gene function
  - Bioinformatic evidence
  - Population frequencies



ACMG Guidelines

- A standardized process for scoring variant for genes that cause Mendelian disorders.
- Widely adopted in US, and worldwide
- 33 criteria for evaluating a variants evidence
- Rules for combining criteria into a single Classification
- Not static, follow up papers and expanded recommendations published



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SPECIAL ARTICLE | Genetics in Medicine

ORIGINAL RESEARCH ARTICLE | Genetics in Medicine

ACGS Association for Clinical Genomic Science

ACGS Best Practice Guidelines for Variant Classification 2017

Sian Ellard[1,2], Emma L Baple[2,3,4], Martina Owens[1], Stuart Cannon[1], Diana M Eccles[5], Stephen Abbs[6], Richard Scott[4,7], Zandra C Deans[8], Tracy Lester[9], Jo Campbell[10], William G Newman[11,12], and Dominic J McMullan[13]

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Recommendations ratified by ACGS Quality Subcommittee on 2nd October 2017

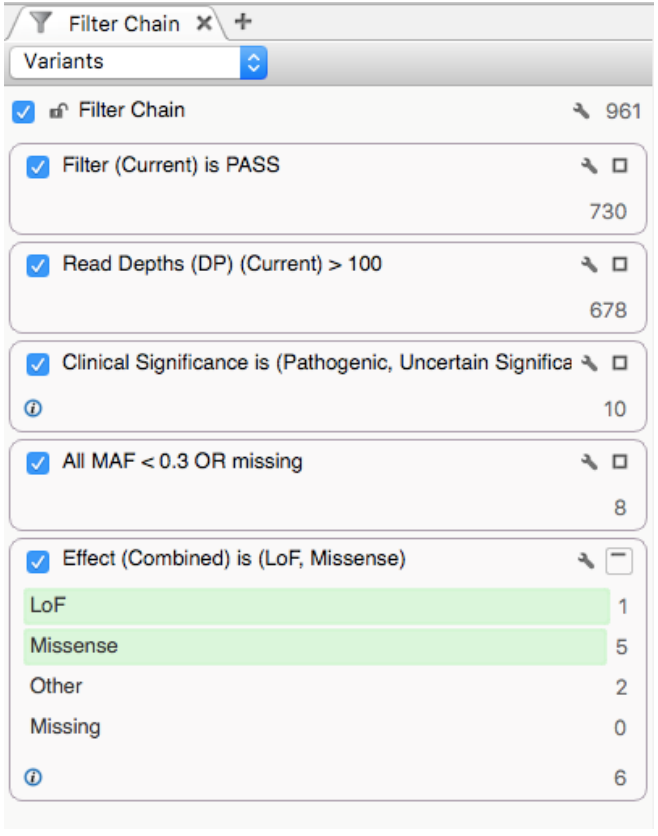
1. Introduction

VSClinical

- **Complete Support for ACMG Guideline Workflow:**
  - Implements a guided workflow for following the ACMG guideline scoring and classifying
  - Place criteria into conceptually related groups, paired with their opposites, and formatted as answerable question.
- **Aggregate and Automate:**
  - Questions have supporting evidence presented with rich and interactive visuals
  - Automatically computed recommendations for questions that have explicit bioinformatic evidence, with supporting reasons for each answer.
- **Expert and Beginner Friendly:**
  - Start with descriptive summaries and recommendations for a variant
  - Deep dive into Population Catalogs, Gene Impact, Published Studies and Clinical tabs
  - Integrated documentation, readings on scoring criteria and citations

Analysis Workflow with VSClinical

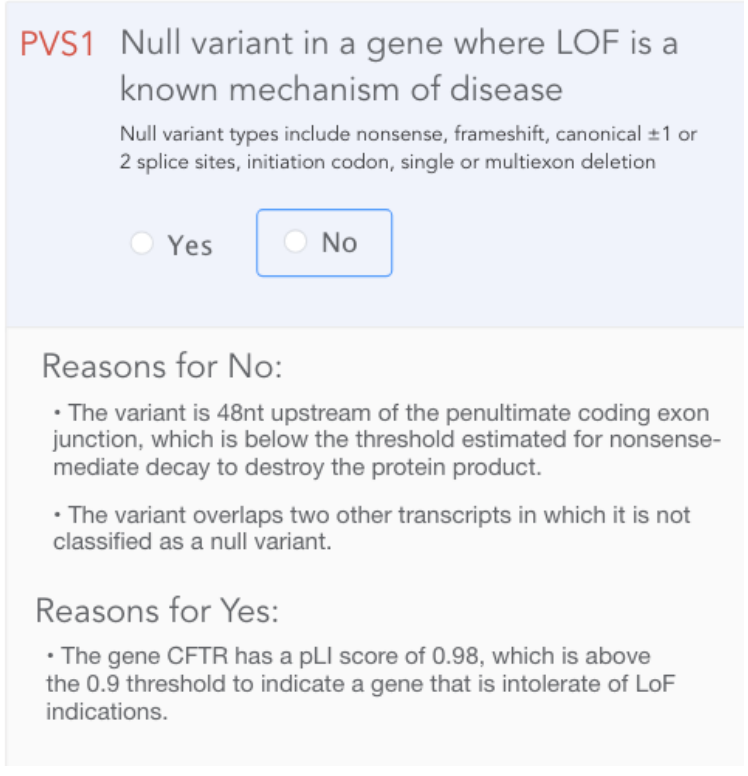
1. **Follow your existing VarSeq annotation and filtering workflow**
2. **Add new ACMG Auto Classifier algorithm:**
   - Looks up if variant annotated in previous sample
   - Scores 18 criteria based on available evidence from 7 sources
3. **Select variants to evaluate using the ACMG Guidelines**
4.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



[Demo in VarSeq]

How Does VSClinical Work?

- **7 Algorithms and 5 Annotation Sources**
- **On the fly computation, thinner projects**
- **Exclusive to VSClinical**
  - Splice Site Predictions
  - Multiple Sequence Alignment (MSA)
  - MSA derived GERP++ and phyloP
  - MSA derived SIFT and Polyphen2
  - ACMG Auto Classifier
- **New Annotation Sources**
  - ClinVar Assessments
  - Missense Badness



Golden Helix Pathogenicity Calculator

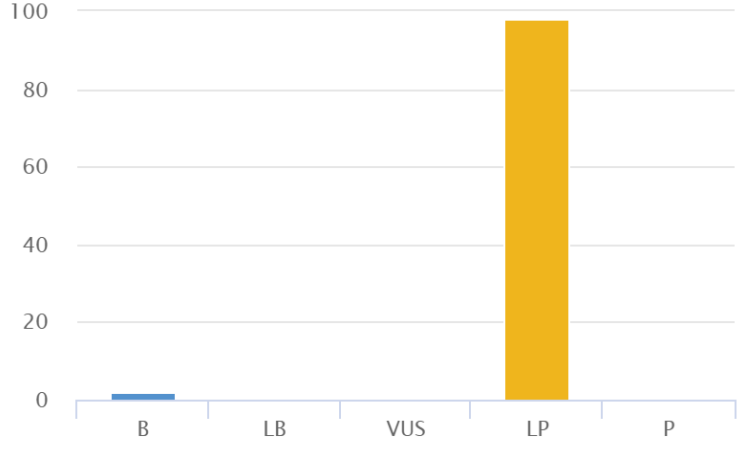
ACMG Classification

- **Probabilistic Model of Pathogenicity:**
  - Provide instantons feedback
  - Per classification probabilities
  - Combined pathogenicity probability
  - Necessary to classify a variant with conflicting criteria

Probability of Pathogenic given Scored Criteria:

Status: Probability of 0.93 is above 0.90 threshold for Likely Pathogenic

Probability for Each Classification:



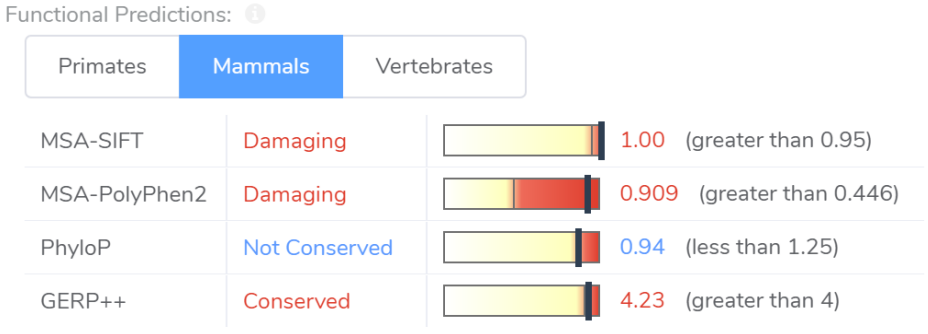
Transcript Aware Analysis

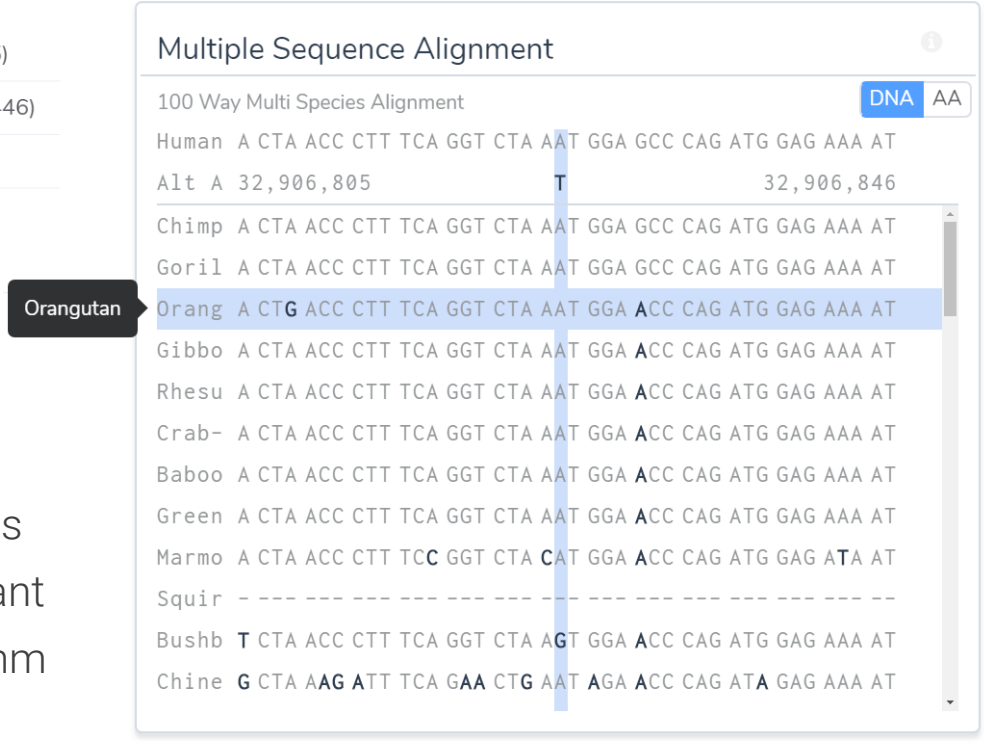
- **Updated selection of clinically relevant transcript based on ClinVar Assessments**
- **Warning if the the variant overlaps other transcripts that have a different effect**
- **Your transcript preferences saved and used in VarSeq + VSClinical**
- **Can switch to view/interpret on any other transcript**

Overlapping Transcripts for CDKN2A

Transcript	Used in Interpretations	Effect	HGVS	Length CDS/AA	Exon Position	Protein ID / LRG ID	Coding Status
NM_058197.4	Internal, ClinVar 2 Cases, 1 Assessment	Frameshift frameshift_variant	c.105dupG p.A36Gfs	351 bp 36 AA	1 of 3 30% of CDS	NP_478104.2	Complete
NM_001195132.1	Internal, ClinVar 2 Cases, 1 Assessment	Frameshift frameshift_variant	c.105dupG p.A36Gfs	504 bp 36 AA	1 of 4 21% of CDS	NP_001182061.1	Complete
NM_000077.4 Default for Gene , Has LRG	Internal, ClinVar 2 Cases, 1 Assessment	Frameshift frameshift_variant	c.105dupG p.A36Gfs	471 bp 36 AA	1 of 3 22% of CDS	LRG_11t1 NP_000068.1	Complete Default
NM_058195.3 Has LRG	Internal, ClinVar 2 Cases, 1 Assessment	Intron intron_variant	c.194-3515dupG false	399 bp false	2 of 3 false	LRG_11t2 NP_478102.2	Complete

Functional Predictions





- **Functional Predictions:**
  - 100-way multiple-sequence alignment
  - Run on Primates, Mammals, Vertebrates
  - Algorithms run on-demand for any variant
  - Can be run as a bulk annotation algorithm
  - *Upcoming webcast will cover more*

Splice Site Predictions

Splice Predictions:

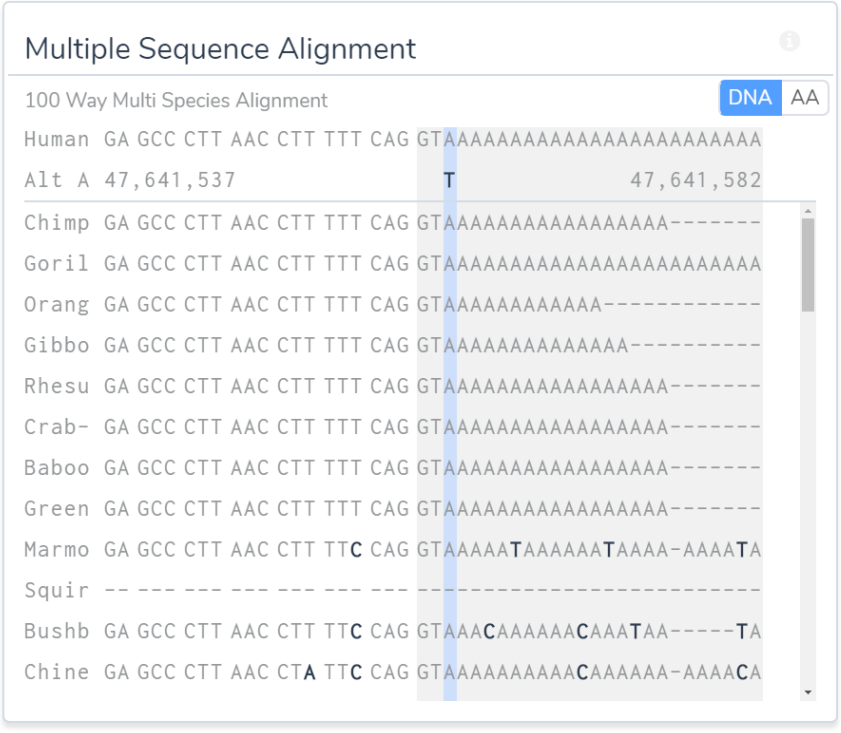
GeneSplicer	Disrupted	0.00	(less than 0.59)
MaxEntScan	Disrupted	0.13	(less than 0.42)
NNSplice	Disrupted	0.28	(less than 0.85)
PWM	Not Disrupted	0.71	(greater than 0.66)

Nearest Splice Site:

Donor of Exon 5 of 16

Distance to Splice Site:

2bp upstream (Intronic)

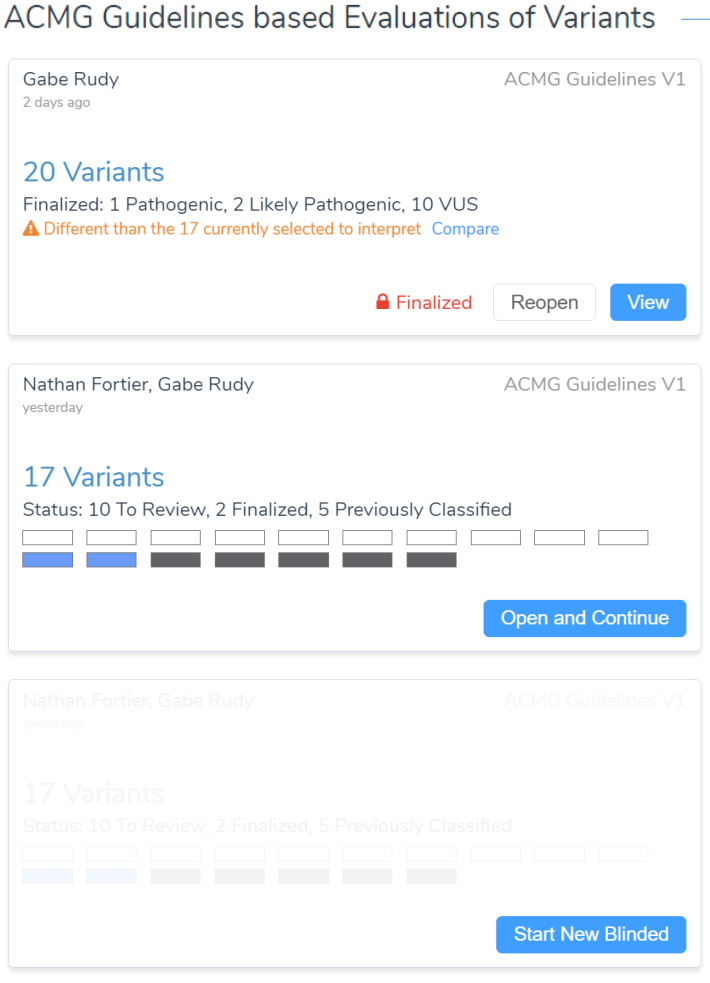


- **Required for ACMG Classification:**
  - Variants near splice site, synonymous
  - 4 algorithmic strategies
  - Detect deletion of canonical splice site
  - Run in VSClinical and as part of our gene annotation algorithm
  - *Upcoming webcast to cover more*

Splice Region Analysis

Standardize your Lab with VSClinical

- **Reduce Subjectivity / Errors**
  - Supports ”Blinded Analysis” of same sample by two lab personnel
- **Self-learning System**
  - Knowledge of assessments
  - Historical answers for same variant and similar variants in gene help inform decision
- **Scale up Interpretations**
  - Self guided exploration of details
  - Automate google searchers for variants in papers



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  - Dr. Jim Weber (PreventionGenetics, USA)
  - Dr. Qin Hae and Dr. Line Larsen (Amplexa, Denmark)
  - Dr. Val Hyland (Pathology Queensland, Australia).

Summary & Next Steps

- Contact us to evaluate!
  - New Product
  - Includes OMIM, CADD, VSReports
  - Splice site predictions
  - Functional predictions
- Part of upcoming VarSeq 2.0 release
- Shipping Q2, targeting end of May
- Contact us if you are interested in other workflows or customizations

VSClinical®