

Introducing VSClinical AMP Guidelines: A Comprehensive Workflow for NGS Testing of Cancer

Gabe Rudy, VP Product & Engineering



20 Most Promising Biotech Technology Providers



Hype Cycle for Life sciences



Top 10 Analytics Solution Providers



Questions

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Questions	Questions	Audio	·	
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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 is a global bioinformatics company founded in 1998



Filtering and Annotation

ACMG Guidelines

Clinical Reports

CNV Analysis

Pipeline: Run Workflows

WARE-HOUSE



Variant Warehouse

Centralized Annotations

Hosted Reports

Sharing and Integration

CNV Analysis

GWAS | Genomic Prediction

Large-N Population Studies

RNA-Seq

Large-N CNV-Analysis

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Hallmarks of Cancer

Engines of Cancers

- Understanding cancer in a patient requires understanding its underlying biology
- Multiple hallmarks are required for tumorigenesis

A Disease of the Genome

- A given cancer gene plays a role in promoting or suppressing one or more of these hallmarks
- Genomic mutations enable hallmarks by:
 - Gain of function of a Oncogene
 - Loss of function of a Tumor Suppressor Gene (TSG)

Hallmarks for PTEN:

	Ρ	S
proliferative signalling		
ວັ້ງ suppression of growth		
escaping immunic response to cancer		
cell replicative immortality		
tumour promoting		
$\operatorname{Add}_{\operatorname{S}}$ invasion and metastasis		
angiogenesis		
genome instability and mutations		
୍କ୍ରି escaping programmed ଙିକି cell death		
change of cellular energetics		

Hanahan D., Weinberg R.A. Hallmarks of Cancer: The next generation. Cell . 2011; 144:646–674 Tate J et al. COSMIC: the Catalogue Of Somatic Mutations In Cancer, Nucleic Acids Research, Volume 47, Issue D1, 08 January 2019



Biomarkers

Testable Biological Markers

- Biomarkers are biological states or measurements that provide indications for treatment, prognostic or diagnostic outcomes
- Range from presence or absence of proteins, antigens and specific genomic attributes of the tumor.

Common Cancer Biomarkers Examples

- HER2+: High levels of HER2 receptor protein
- MSI-H: Microsatellite instability-high
- BRAF^{V600E}: Presence of activating mutation V600E
- ERBB2^{Amp}: Amplification of ERBB2
- BCR-ABL1: Activation of ABL1 through fusion with BCR
- 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*



Reporting Biomarkers

Reportable Biomarkers

- Molecular testing with NGS can detect many types of biomarkers.
- Activating Mutations for Oncogenes:
 - Missense mutations, CNV gains, gene fusions
- Inactivating of Tumor Suppressor Genes:
 - Truncating mutations, damaging missense mutations, CNV loss

Clinically Actionable Biomarkers

- Molecular genetics reports should provide actionable results with indications of the quality of the clinical evidence in the context of the patients tumor
- AMP Guidelines discuss best practices for clinical reporting and provides "Tier Levels" for rating the clinical evidence for drug response as well as prognostic and diagnostic implications.



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



Evidence Levels and Tiers

Tier I: Variants of Strong Clinical Significance

Therapeutic, prognostic & diagnostic

Level A Evidence

FDA-approved therapy Included in professional guidelines

Level B Evidence

Well-powered studies with consensus from experts in the field

Tier II: Variants of Potential Clinical Significance

Therapeutic, prognostic & diagnostic

Level C Evidence

FDA-approved therapies for different tumor types or investigational therapies

Multiple small published studies with some consensus

Level D Evidence Preclinical trials or a few case reports without consensus

Tier III: Variants of Unknown Clinical Significance

Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases

No convincing published evidence of cancer association

Tier IV: Benign or Likely Benign Variants

Observed at significant allele frequency in the general or specific subpopulation databases

> No existing published evidence of cancer association



VSClincial AMP Workflow

- Evaluate Which Variants to Report
- Classify Evidence Following AMP Guidelines
- Your Interpretations Saved & Re-Used
- Built In Auto-Scoring of Somatic & Germline (ACMG Guideline) Variants
- Integrated Reporting
- Results: Comprehensive, Consistent, Efficient

	Clinical Report	Results
	Outline	Biomarkers
		Secondary Germline
		Variants of Unknown Significance
ent		Coverage Report
		References



Integrated Data Sources

- COSMIC
 - Mutations
 - Fusions
 - Gene Census
 - Hallmarks of Cancer
- Clinical Evidence Sources:
 - DrugBank
 - CIViC
 - PMKB
- Golden Helix CancerKB Interpretation Knowledgebase (Beta)
 - Jump start your interpretations
 - · Can contribute back anonymized interpretations
 - Provides well cited interpretations for most common biomarkers
- Others:
 - Genetic Home Reference
 - Clinical Genomic Database
 - CPDB Pathways
 - InterPro Protein Domains

- ICGC Somatic Variants
- MSK-Impact Somatic Variants
- TCGA Somatic Variants
- Cancer Hotspot Regions

Score	Catalo	gs In-Silio	co Litera	ature	Assessments	
Variant Co	ordinates	and Catalog	Entries:			C
	GRCh37:	7:140453136	A/T			
NC_00	0007.13:	g.140453136/	A>T			
	GRCh38:	7:140753336	A/T			
NC_00	0007.14:	g.140753336/	A>T			
NM_0	04333.4:	c.1799T>A				
NP_0	04324.2:	p.V600E (p.Val	600Glu)			
	dbSNP:	<u>rs113488022</u>	(added in v13	2)		
С	linVar ID:	<u>13961</u> (Pathog	genic, 1 star, 2	3 conditio	ons on 2019-05-01)	
ç	gnomAD:	1 of 251,260 (version 2.1.1)			
	COSMIC:	<u>COSM476</u> (28	296 samples	in v88)		
	CIViC ID:	<u>12</u> (79 evidend	e records on 2	2019-06-	01)	
COSMIC		CGC	MSK Im	pact	TCGA	

295

V600E

566

V600E

814

V600E

2829

V600E





Project Demonstration



Upcoming Webcasts

- July: Scoring of Somatic Variants for Oncogenicity with VSClinical
 - Present scoring similar to ACMG for classifying somatic variants rigorously
 - Dr. Nathan Fortier, Director of Research
- August: Using VSClinical AMP Guidelines to Perform Cancer Testing
 - Reporting Secondary Germline findings using ACMG guidelines
 - Customizing clinical report to match the requirements of your lab
 - Darby Kammeraad and Dr. Eli Sward, Field Application Scientists
- September: Cancer Interpretation Reuse and Golden Helix CancerKB
 - Saving and re-using interpretations with your own lab knowledgebase
 - Starting with 80% of your report written with Golden Helix CancerKB
 - Gabe Rudy, VP Product & Engineering



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New eBooks



Andreas Scherer, Ph.D.

CLINICAL VARIANT ANALYSIS FOR CANCER

Applying AMP Guidelines to Analyze Somatic Variants

GOLDEN HELIX



Andreas Scherer, Ph.D.

GENETIC TESTING FOR CANCER

Third Edition

GOLDEN HELK

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