Two Clinical Workflows – From Unfiltered Variants to a Clinical Report

November 04, 2015

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GOLDEN HELIX
Accelerating the Quest for Significance™

Questions during the presentation

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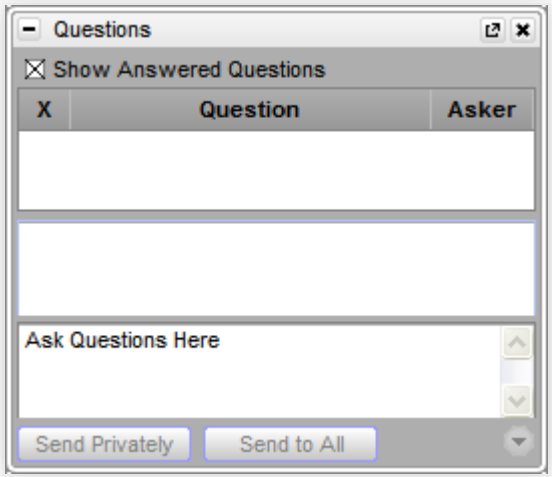


Golden Helix – Who We Are

Golden Helix is a global bioinformatics company founded in 1998.

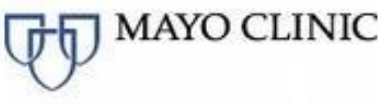
GlaxoSmithKline

We are cited in over 900 peer-reviewed publications

Our Customers

Over 200 organizations world wide, and thousands of users, trust our software.

Stanford University



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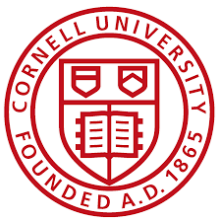
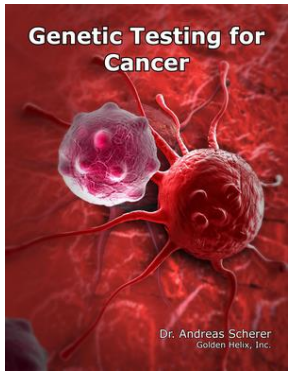


Golden Helix – Who We Are

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

- REPUTATION
- TRUST
- EXPERIENCE

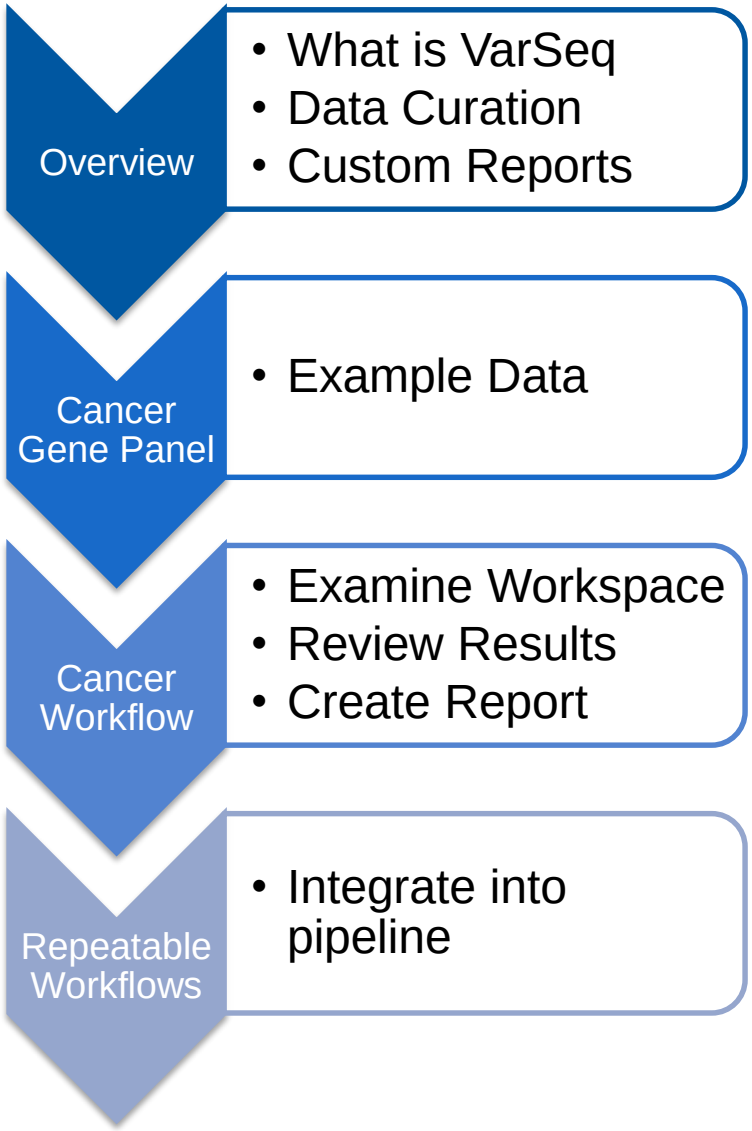


- INDUSTRY FOCUS
- THOUGHT LEADERSHIP
- COMMUNITY

- TRAINING
- SUPPORT
- RESPONSIVENESS

- TRANSPARENCY
- INNOVATION and SPEED
- CUSTOMIZATIONS

Outline



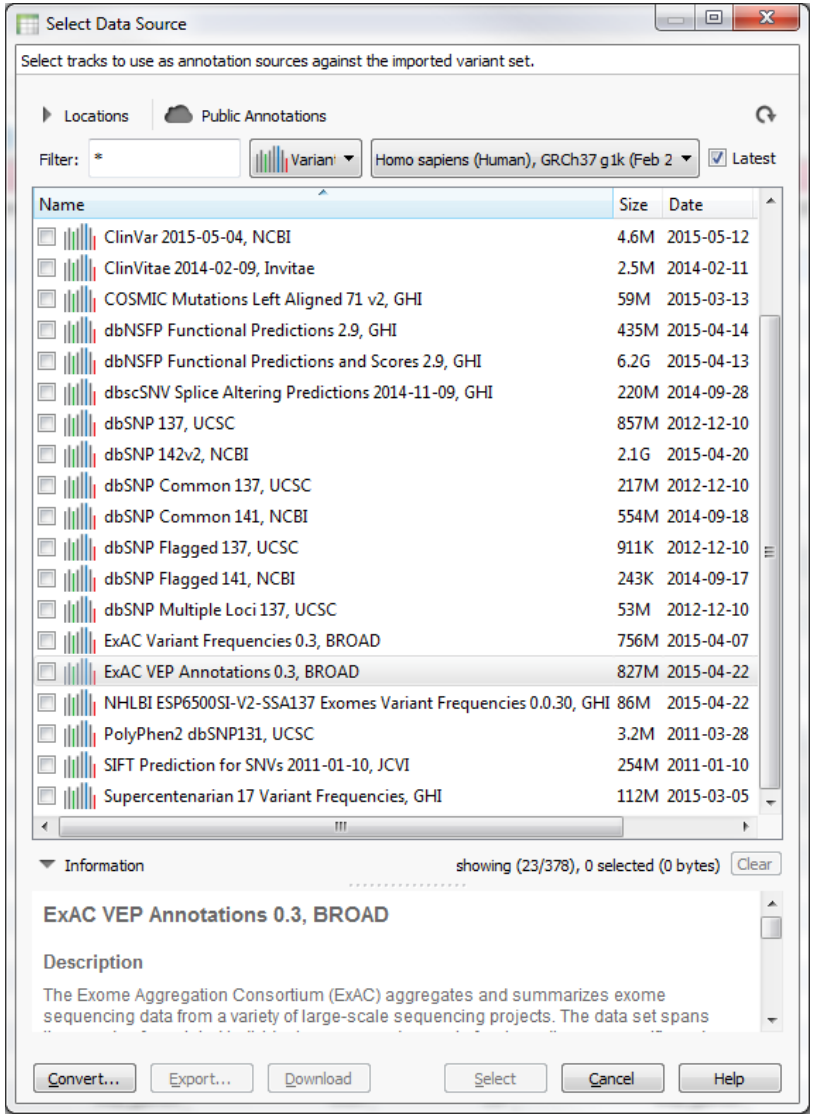
- VarSeq ships with the following support for cancer gene panels:
  - An example project
  - A project template
  - A report template
- Numerous targeted panels are available in the data repository for coverage statistics and filtering

What is VarSeq?

- Variant annotation, filtering and interpretation
- Repeatable workflows
- Rich visualizations with GenomeBrowse built-in
- Powerful GUI and command-line interfaces

Data Curation of Annotation Sources

- **VarSeq is backed by an extensive list of curated data sources**
  - 1kG Phase3 Variant Frequencies
  - ClinVar, NCBI
  - ClinVitae, Invitae
  - COSMIC
  - dbNSFP Functional Predictions
  - dbSNP
  - ExAC
  - RefSeq Genes, NCBI
  - Supercentenarian 17 Variant Frequencies
- **Your workflows lock down specific versions**
- **MedGenome OncoMD provides curated drug targeted mutations for Cancer, supporting clinical trials and functional evidence.**
- **OMIM Genes, Phenotypes and Variants**



Custom Reports

ACME Clinical Labs
203 Enterprise Blvd
Bozeman, 59718
Phone: 406-587-8137
Fax: 406-555-5555

Reference Information

Physician	Dr. Jane Smith
Institution	ACME General Hospital
Case Id	AGH-1234

Patient Information

Name	Jon Doe
Gender	Male
Date of Birth	7/4/65
Id	1234

Sample Information

Sample Site	Blood	**Avg. Read Depth**	5152x
Sample Type	Blood	**Collection Date**	10/16/15
Collection Method	Peripheral Draw	**Receipt Date**	10/18/15
Panel Coverage	86.23%	**Report Date**	11/3/15

Results

Positive Mutations with an established somatic link detected.

Affected Genes

ABL1 (0)	*ASXL1* (0)	*ATRX* (0)	*BCOR* (0)	*BCOR1* (0)	***BRAF*** **(1)**	*CALR* (0)	*CBL* (0)	*CBLB* (0)	*CBLC* (0)	*CDKN2A* (0)
CEBPA (0)	*CSF3R* (0)	***CUX1*** **(1)**	*DNMT3A* (0)	*ETV6/TEL* (0)	*EZH2* (0)	*FBXW7* (0)	*FLT3* (0)	*GATA1* (0)	*GATA2* (0)	*GNAS* (0)
HRAS (0)	*IDH1* (0)	*IDH2* (0)	*IKZF1* (0)	*JAK2* (0)	*JAK3* (0)	*KDM6A* (0)	*KIT* (0)	*KRAS* (0)	*MLL* (0)	*MPL* (0)
MYD88 (0)	*NOTCH1* (0)	*NPM1* (0)	*NRAS* (0)	*PDGFRA* (0)	*PHF6* (0)	*PTEN* (0)	*PTPN11* (0)	*RAD21* (0)	*RUNX1* (0)	*SETBP1* (0)
SF3B1 (0)	*SMC1A* (0)	*SMC3* (0)	*SRSF2* (0)	*STAG2* (0)	***TET2*** **(3)**	***TP53*** **(3)**	*U2AF1* (0)	*WT1* (0)	*ZRSR* (0)	

Genetic Variants

Gene	Zygosity	Variant	Exon	Pathogenicity
BRAF	Heterozygous	NM_004333.4:c.1799T>A(NP_004324.2:p.Val600Glu)	15	Pathogenic

Interpretation Summary

Although BRAF is most commonly associated with malignant melanoma, Lee et al. (2004) showed that BRAF is occasionally mutated in leukemias. As the patient presented with acute leukemia and a mutation associated with leukemia was found in the BRAF gene, we recommend treatment take advantage of known drugs targeting somatic mutations in this gene.

Recommendations

The drug Tafinlar + Mekinist has in other studies shown to be effective in somatic mutations in the BRAF gene.

Individual Variant Interpretations

ACME Labs
203 Enterprise Blvd
Bozeman, 59718
Phone: 406 587 8137
Fax: 406 555 5555

Provider Information

Physician	Dr. Jane Smith
Institution	ACME General Hospital
Case Id	AGH-1234

Patient Information

Name	Jon Doe
Gender	Male
Date of Birth	6/4/1965
Id	1234

Sample

Sample Site	Blood	**Avg. Read Depth**	5152x
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CEBPA (0)	*CSF3R* (0)	***CUX1*** **(1)**	*DNMT3A* (0)	*ETV6/TEL* (0)	*EZH2* (0)	*FBXW7* (0)	*FLT3* (0)	*GATA1* (0)	*GATA2* (0)	*GNAS* (0)
HRAS (0)	*IDH1* (0)	*IDH2* (0)	*IKZF1* (0)	*JAK2* (0)	*JAK3* (0)	*KDM6A* (0)	*KIT* (0)	*KRAS* (0)	*MLL* (0)	*MPL* (0)
MYD88 (0)	*NOTCH1* (0)	*NPM1* (0)	*NRAS* (0)	*PDGFRA* (0)	*PHF6* (0)	*PTEN* (0)	*PTPN11* (0)	*RAD21* (0)	*RUNX1* (0)	*SETBP1* (0)
SF3B1 (0)	*SMC1A* (0)	*SMC3* (0)	*SRSF2* (0)	*STAG2* (0)	***TET2*** **(3)**	***TP53*** **(3)**	*U2AF1* (0)	*WT1* (0)	*ZRSR2* (0)	

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Recommendations

The recommended drugs targeting the BRAF mutation are included in the table below as well as 10 of the clinical trials currently underway.

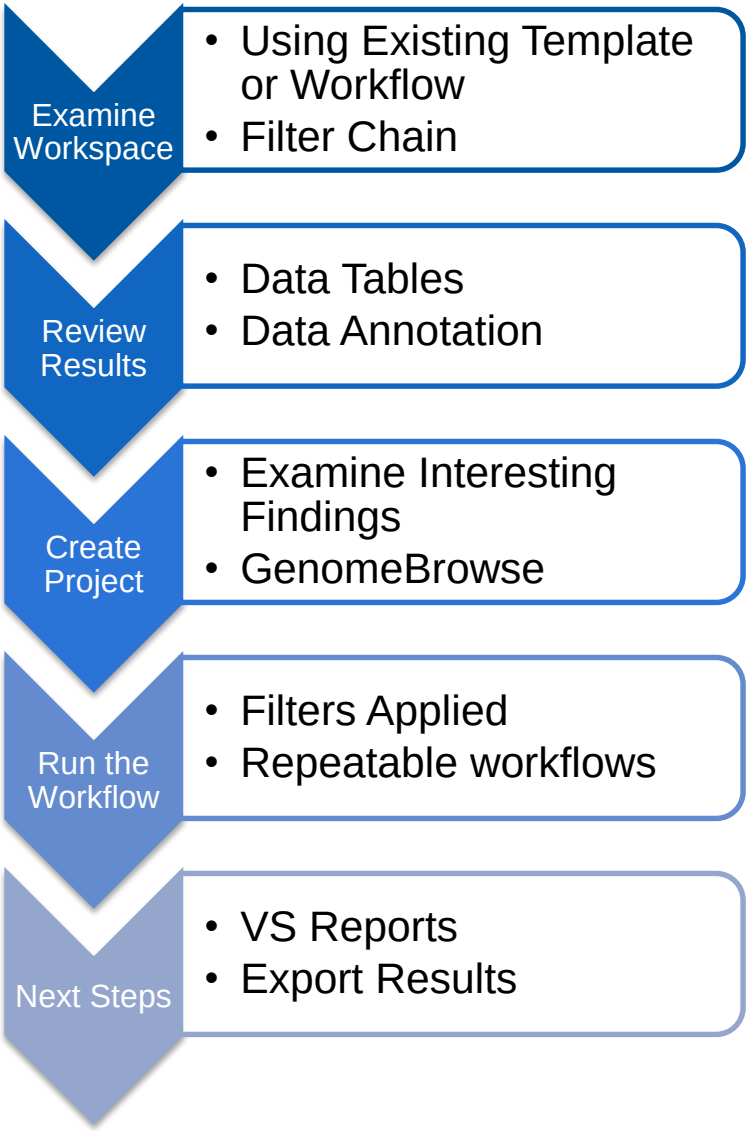
OncoMD Drug Summary

Sample Data for Cancer Gene Panels

- **Illumina TruSight Myeloid Sequencing Panel**
  - Three replicates at different percentages of Horizon Dx known somatic mutations with NA12877 (increase in dilution from 10%, 25% and 50%)
- **Comprehensive coverage of 54 genes designed to target exons of key tumor suppressor genes and frequently cited oncogenes mutated frequently in myeloid malignancies**
- **BAM and VCF files for each replicate are available**
- **Targeted regions are available in a BED file**
- **High Coverage, average read depth over the targeted regions**
  - For the three replicate the average read depth is over 4000 reads

VarSeq Demonstration

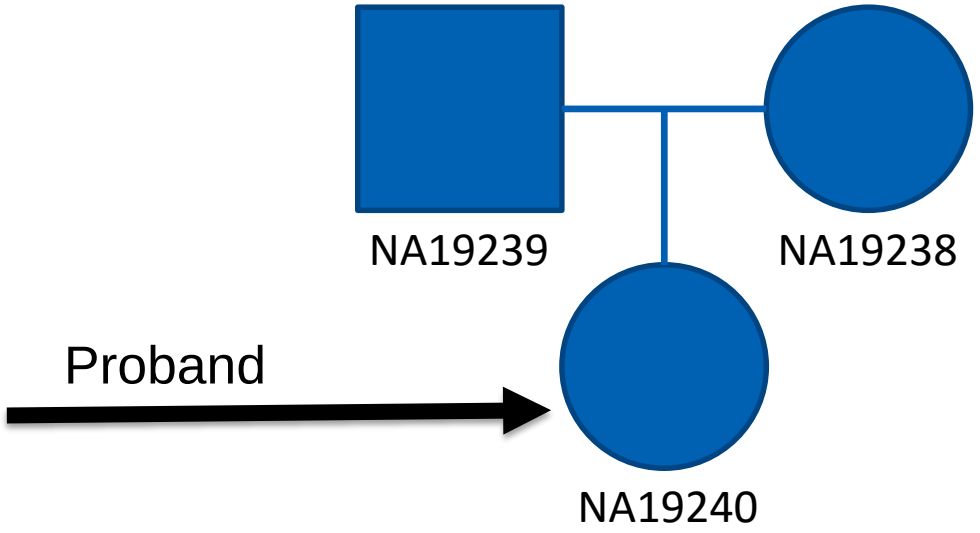
Outline



- VarSeq currently ships with default workflows for Trio Analysis:
  - De Novo Candidate
  - Dominant Heterozygous
  - Compound Heterozygous
  - Recessive Homozygous
  - X-Linked
  - Known Rare Pathogenic

Sample Data for Family Trio

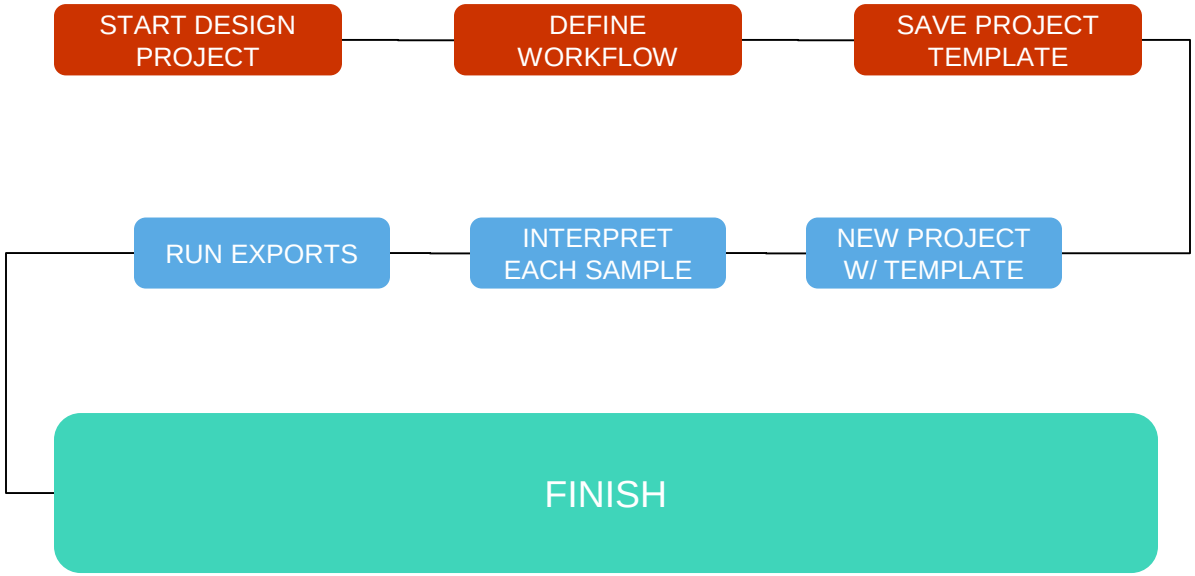
- **Proband NA19240 from International HapMap Project – Yoruba in Ibadan, Nigeria**
  - BAM files from 1000 Genomes Phase 3 Illumina Exome Alignment
  - We injected a variant in the proband's BAM file
  - Used SAM tools for variant calling.
- **BAM and VCF files for each sample are available**



VarSeq Demonstration

Batch Analysis Workflow

Define a Workflow that is Repeated for “Batches” of Samples

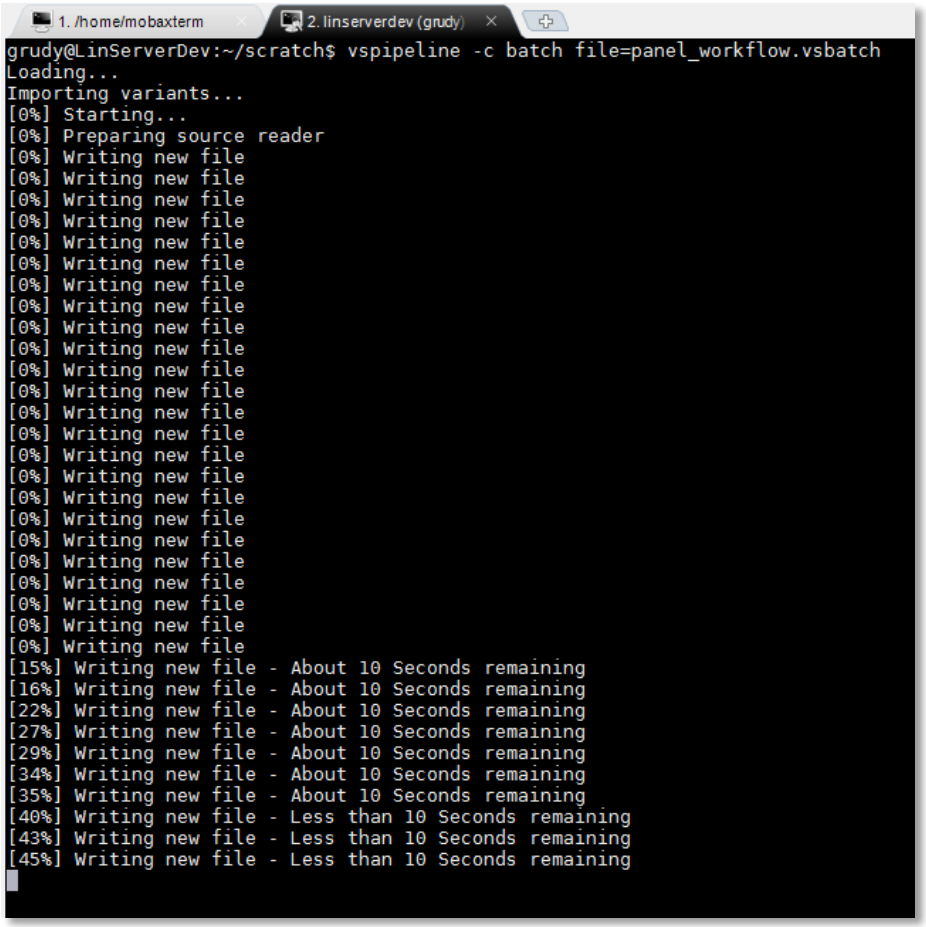


Design and Repeat

- Steps in RED are done once when designing a new workflow to be tuned to the upstream pipeline and test thresholds
- Steps in BLUE are done for each sample or set of samples that should repeat the workflow
- Steps in BLUE can be automated with **VSPIPELINE**

VSPipeline: High Throughput, Automated

- **Produce Automated "Deliverables"**
  - Filtered and annotated variant lists
  - Exported to Excel, VCF, Text
  - VarSeq Projects (openable by VarSeq, VarSeq Viewer)
- **Deploy a Project Template**
  - Support validation (like CAP/CLIA)
  - All steps logged
- **Integrated**
  - Run as part of pipeline that produces BAM/VCF files.



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