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GOTO **EDA DAY 2023**

A Year of Diagnosing Pediatric Cancer with Event Driven Architecture



Grant Lammi

Steve and Cindy Rasmussen Institute for Genomic Medicine
Nationwide Children's Hospital



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Disclaimers

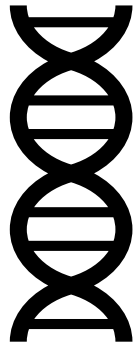
- No conflicts of interest
- No endorsements

Agenda

- World's worst explanation of genomics
- Overview of the MCI project
- Current solution
- What we've learned, where we are going

Genomics 101

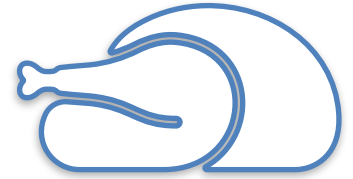
(For developers)



DNA



RNA



Protein

Source Code

Object /
Byte Code

Binary



Source
Code

ACGGTAGTGCA**G**TGTAC



NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

Let's eat grandma!

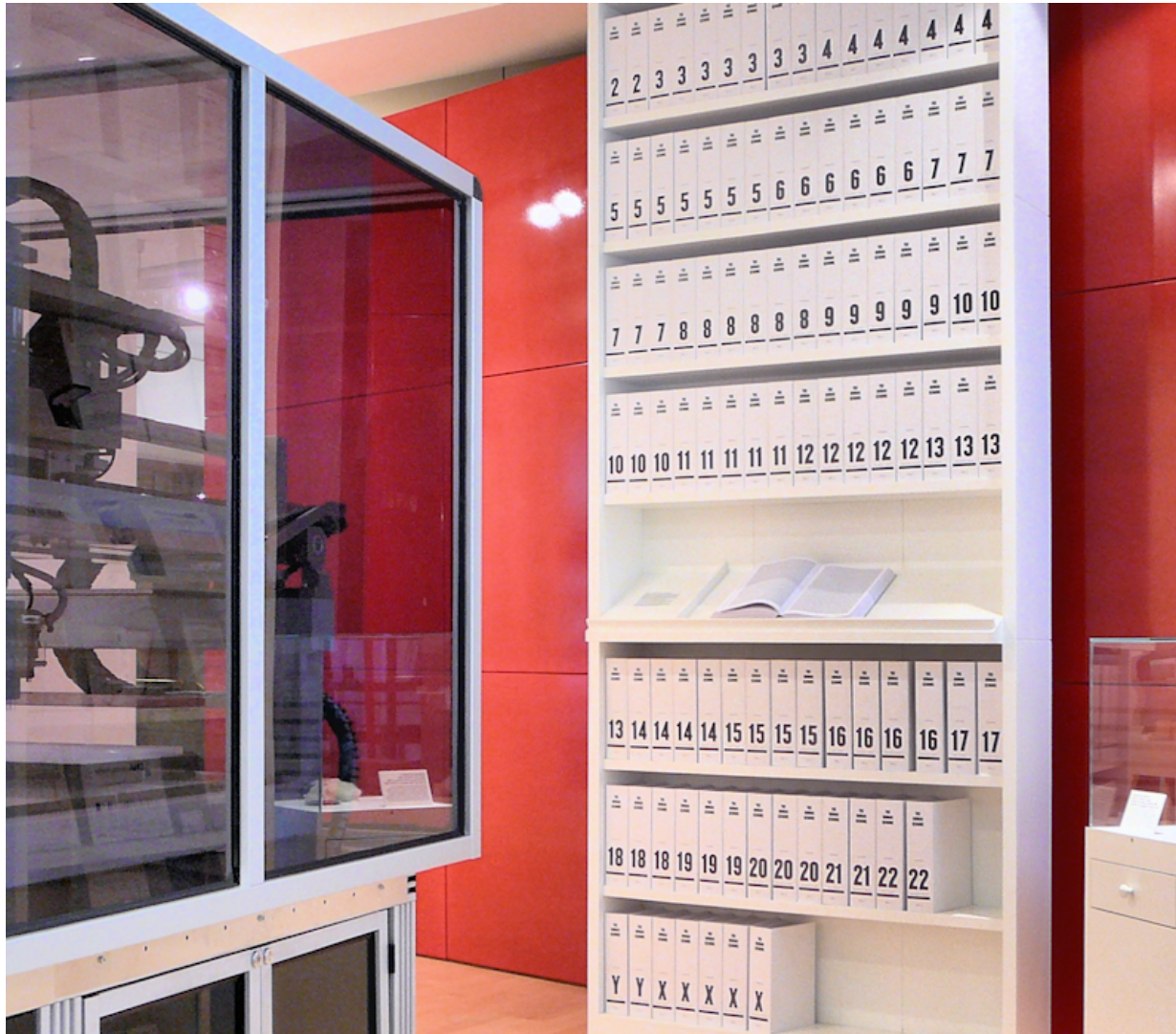


Let's eat, grandma!

**Punctuation
Saves Lives.**



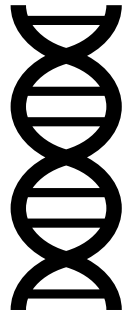
NATIONWIDE CHILDREN'S®
When your child needs a hospital, everything matters.



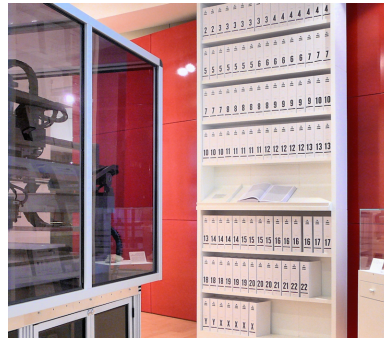
NATIONWIDE CHILDREN'S®
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```
decrypt unaligned.fastq >  
aligned.bam
```

diff



Source
Code

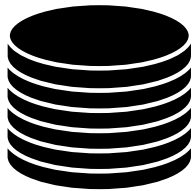


> results.vcf



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```
git blame results.vcf > annotated_results.diff
```



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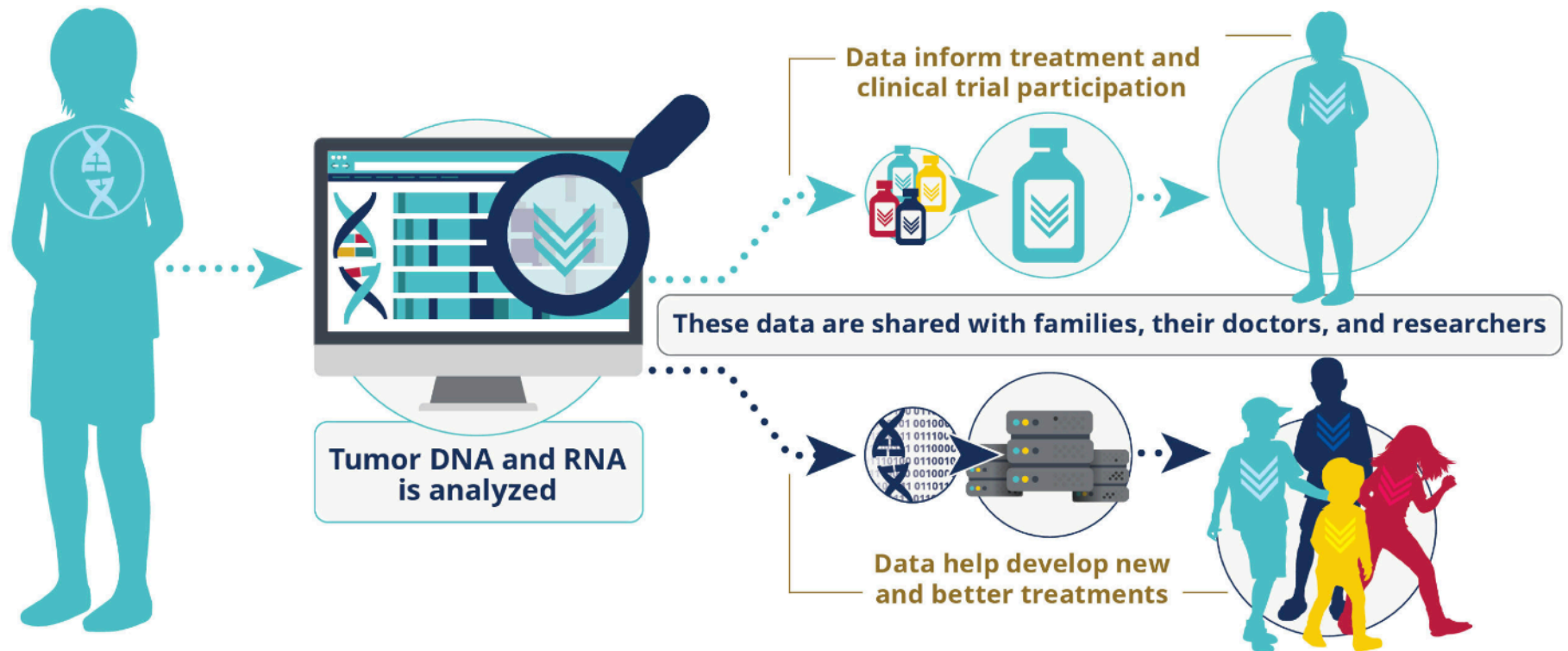
analyze → report.pdf

```
scp report.pdf doctor@hospital:~/
```

git push

Molecular Characterization Initiative

WHAT IS THE CCDI Molecular Characterization Initiative?



Three Clinically Validated Assays

- WES Tumor/Normal
- Methylation
- Archer Fusion

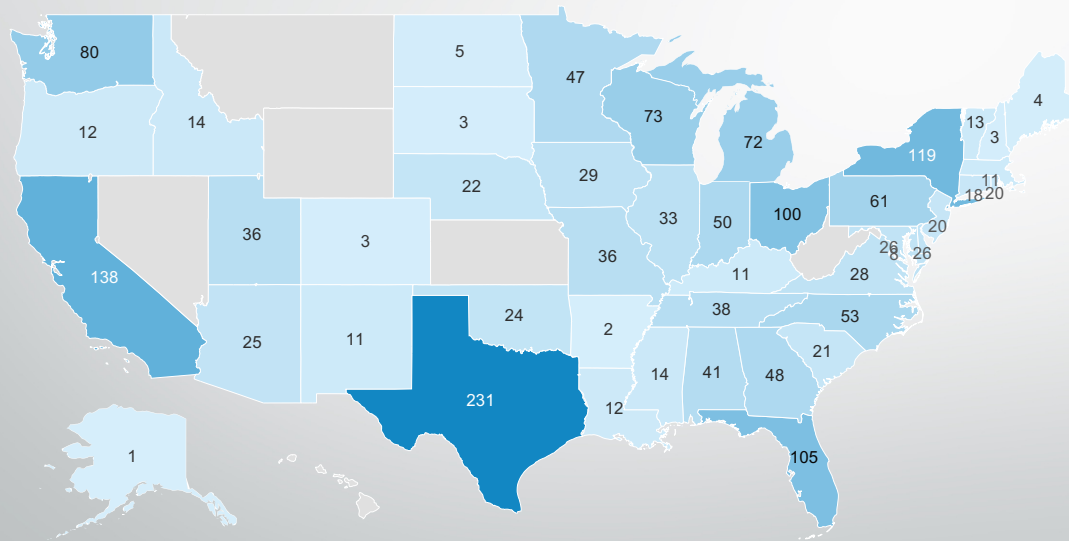
Enrollment

Sample Submitted

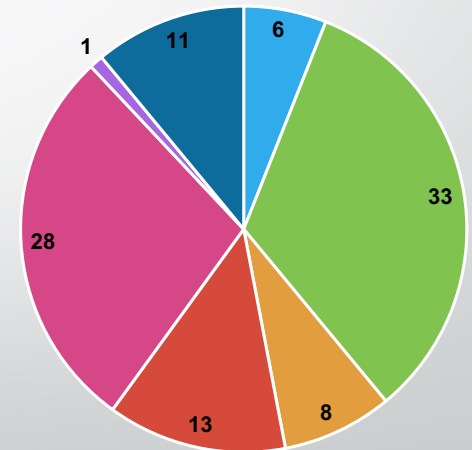
- Doctor enrolls patient
- Sample extracted
- Shipped to NCH

Patient/Sample Origin

- Patients from 45 states, Washington DC, and Puerto Rico
- 196 international patients (Canada, Australia, New Zealand)



Patients from Ohio= 100



- Akron Children's Hospital
- Cincinnati Children's Hospital Medical Center
- Cleveland Clinic
- Dayton Children's Hospital
- Nationwide Children's Hospital
- ProMedica
- University Hospitals

Processing

Sample sent to IGM

- Stored at Biopathology Center (BPC)
- Accessions samples
- Creates IGM IDs
- Pulls in order info electronically

IGM Lab

- Techs put samples on sequencers in the lab
- Then enter sample information into IGMSeq

IGM Lab

- Genetic counselors write up the case in IGMSeq
- Associate different samples into the same case
 - Tumor sample
 - Normal sample

Cloud

Three Step Bioinformatics Pipeline - Two Step Results

- igmprimary (Primary)
- Churchill (Secondary)
- Varhouse (Tertiary)
- Publishing clinical report
- Sharing de-identified molecular data

igmprimary (primary)



Receives:
Old style S3
Event Notifications

Event notifications (2)

Send a notification when specific events occur in your bucket. [Learn more](#) 

[Edit](#)[Delete](#)[Create event notification](#)

☐	Name	Event types	Filters	Destination type	Destination
☐	igmprimary-prod-research-kickoff	Put	sequencer_run_metadata/, RunInfo.xml	Lambda function	igmprimary-prod-research-proxy 
☐	igmprimary-prod-clinical-kickoff	Put	sequencer_run_metadata/, unParameters.xml	Lambda function	igmprimary-prod-clinical-proxy 

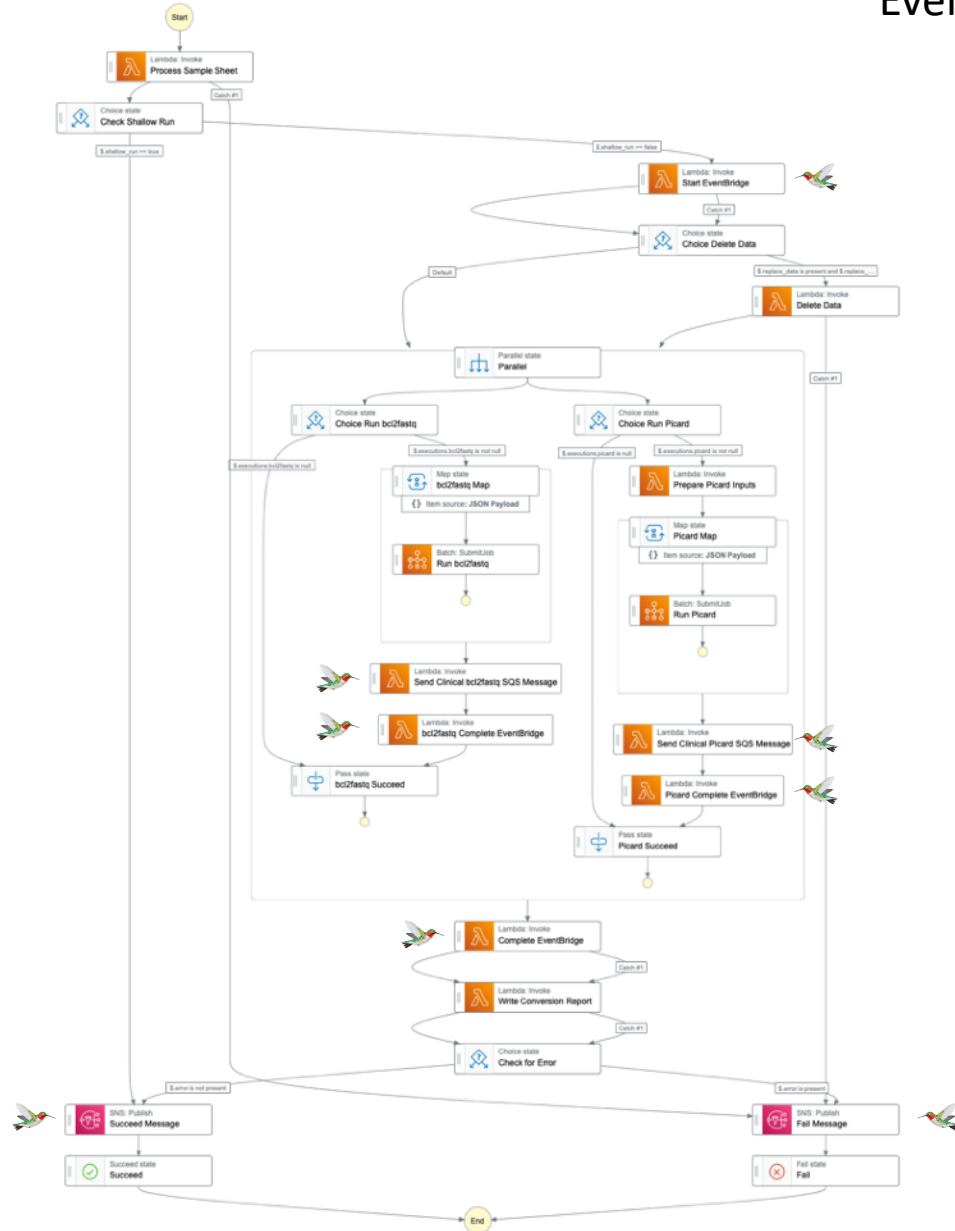


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igmpprimary



Sends:
SQS, SNS,
EventBridge



IGMSeq*

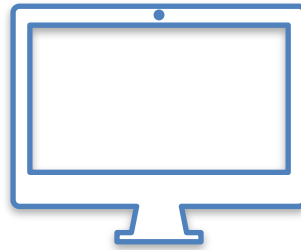


Receives:

SQS

Sends:

API call

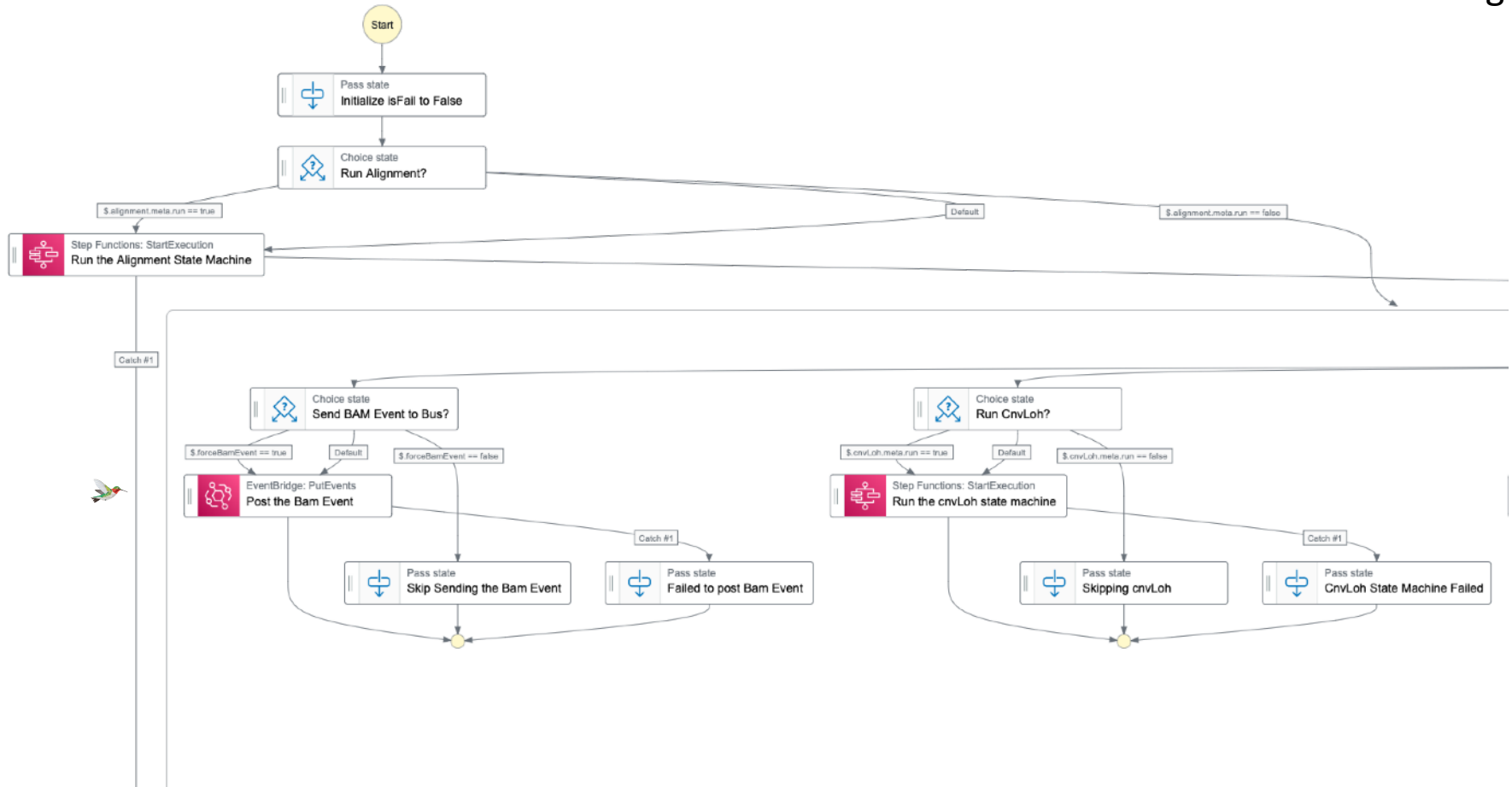


Churchill

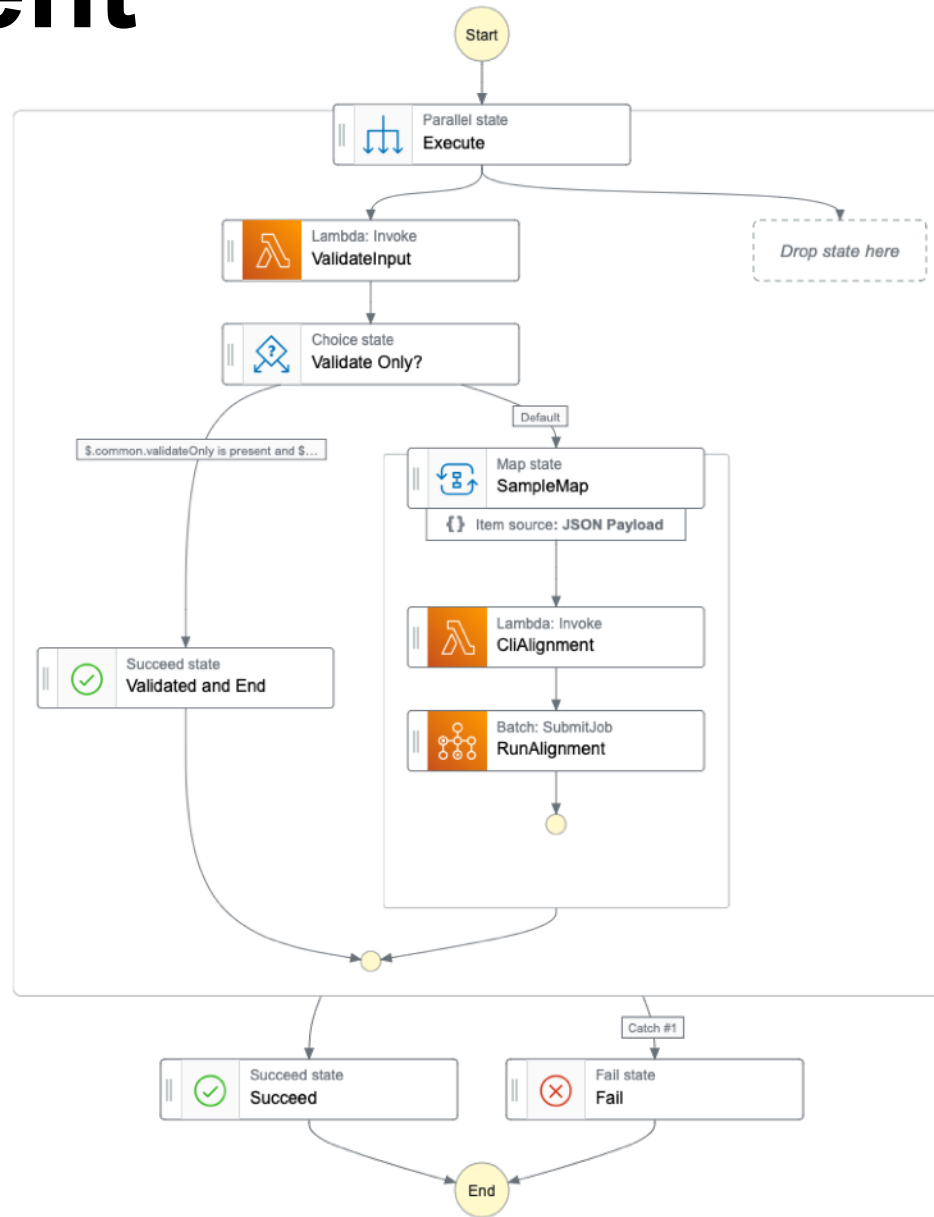


Receives:
API Call

Sends:
EventBridge



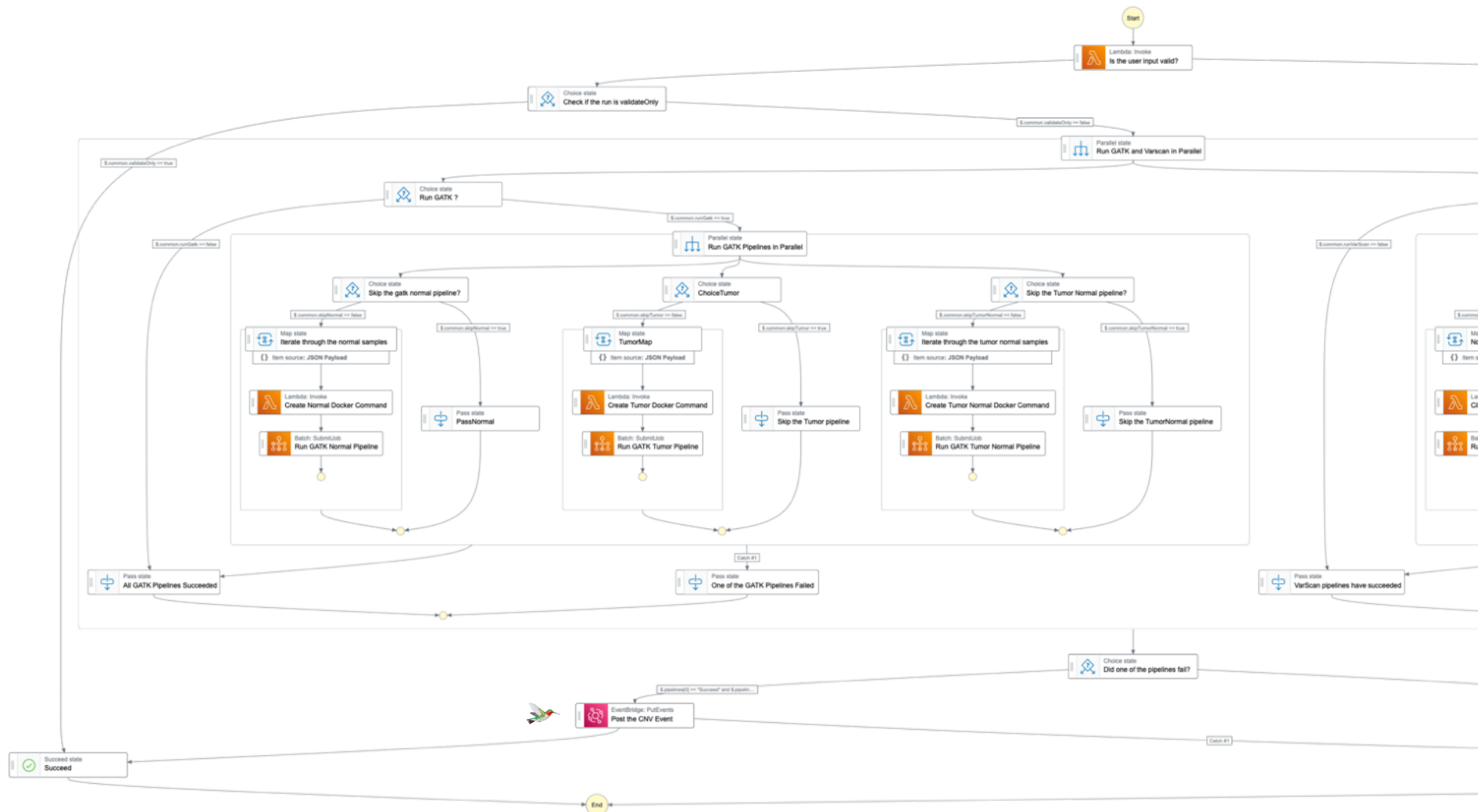
Alignment



CNV LOH



Sends:
EventBridge

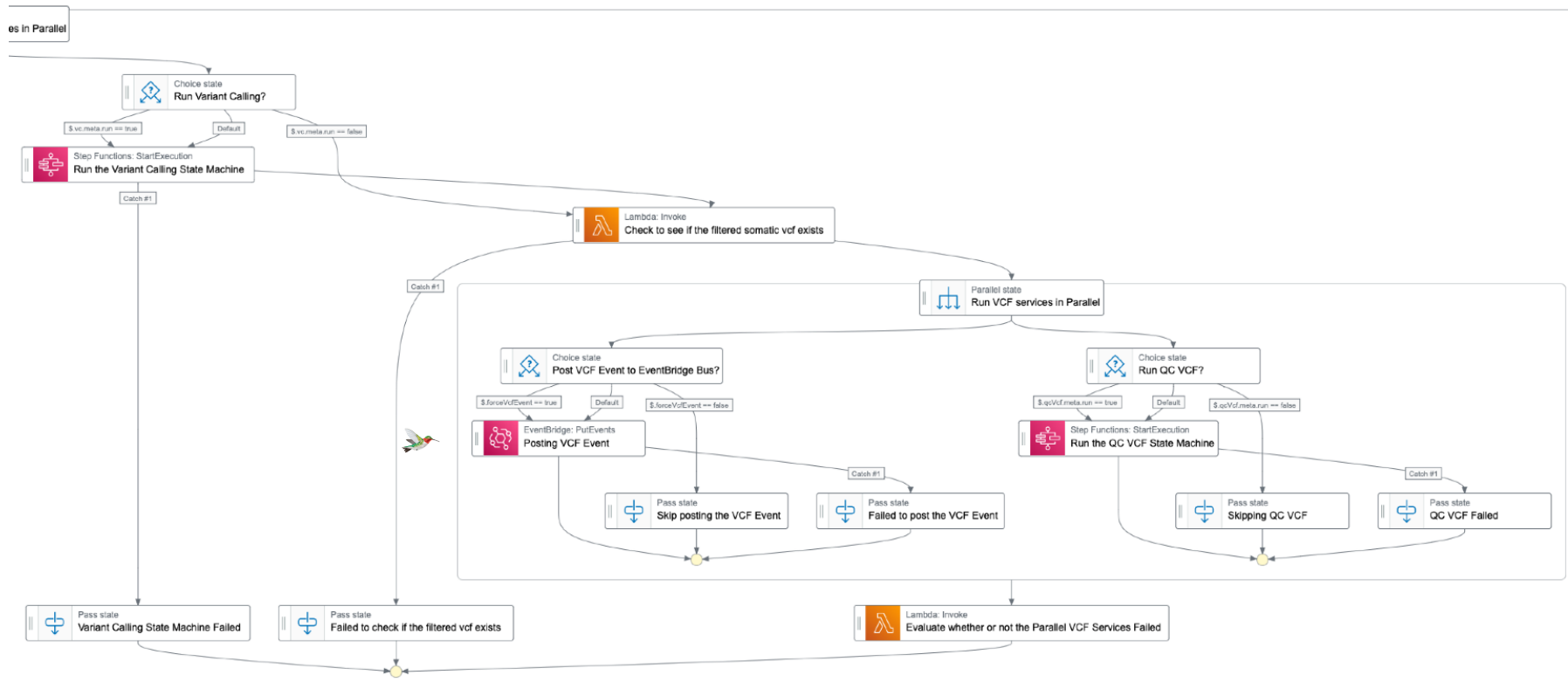


Churchill

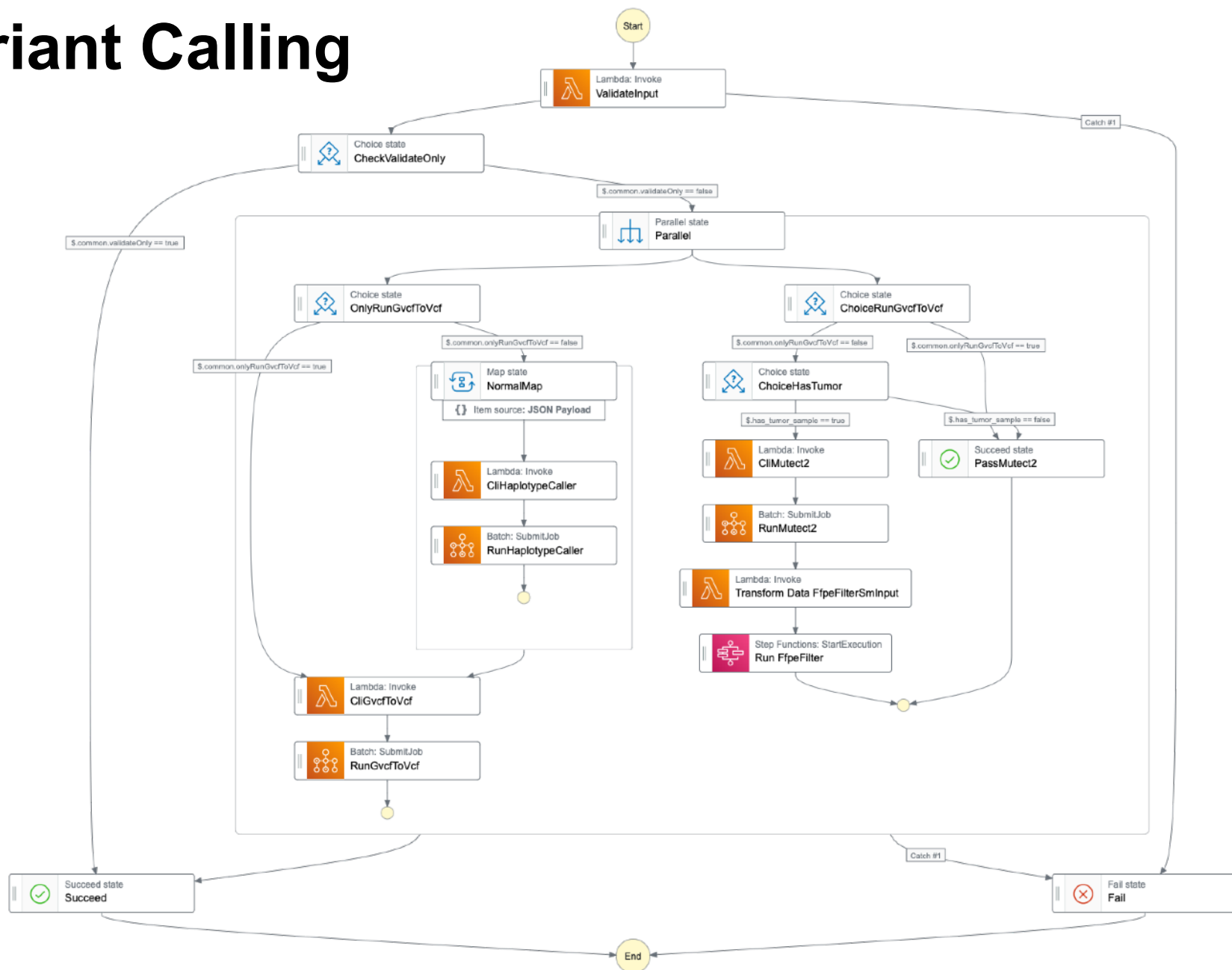


Receives:
API Call

Sends:
EventBridge



Variant Calling

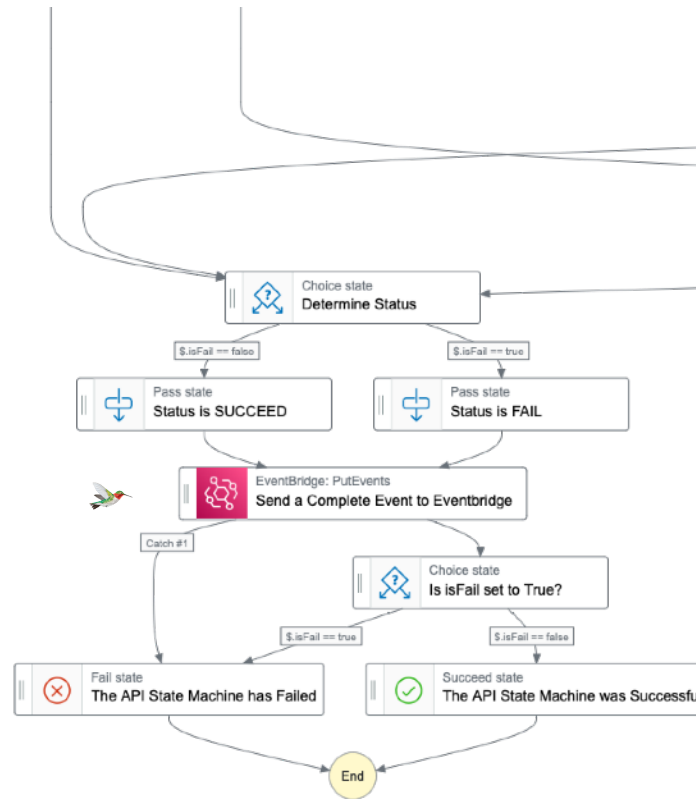


Churchill - Complete



Receives:
API Call

Sends:
EventBridge

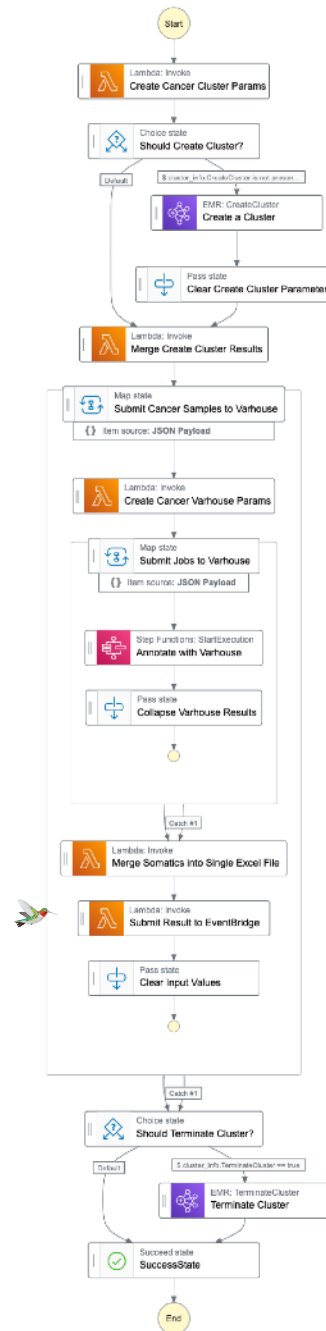


Varhouse (Tertiary)

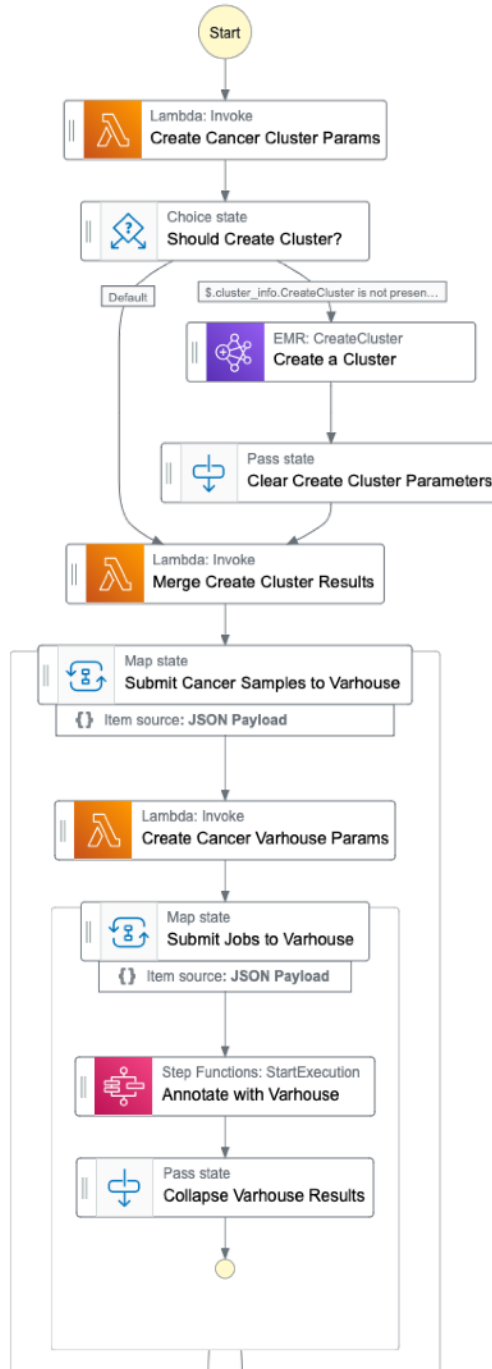


Receives:
EventBridge

Sends:
EventBridge



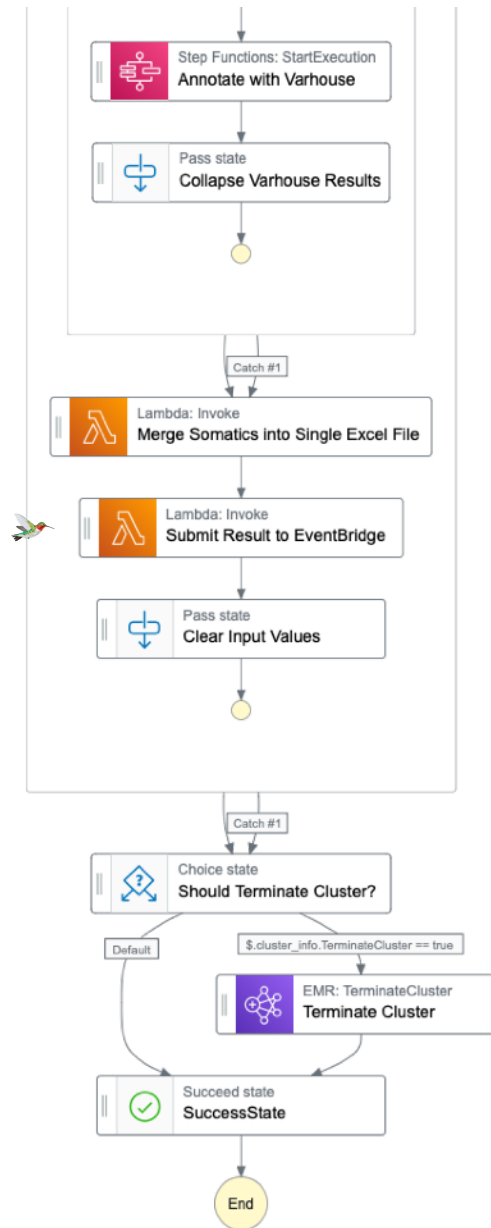
Varhouse (Tertiary)



Varhouse (Tertiary)



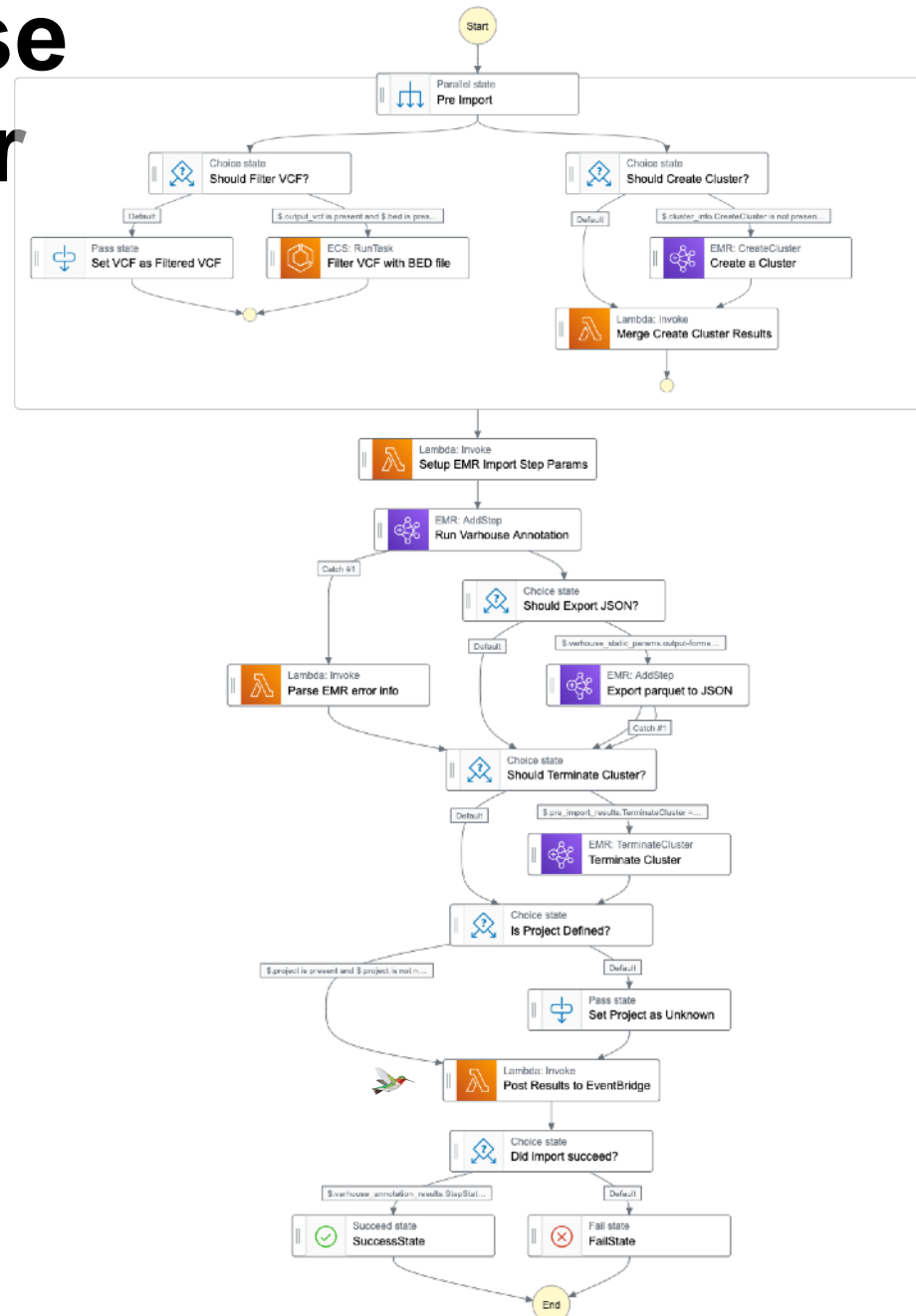
Sends:
EventBridge



Varhouse Importer



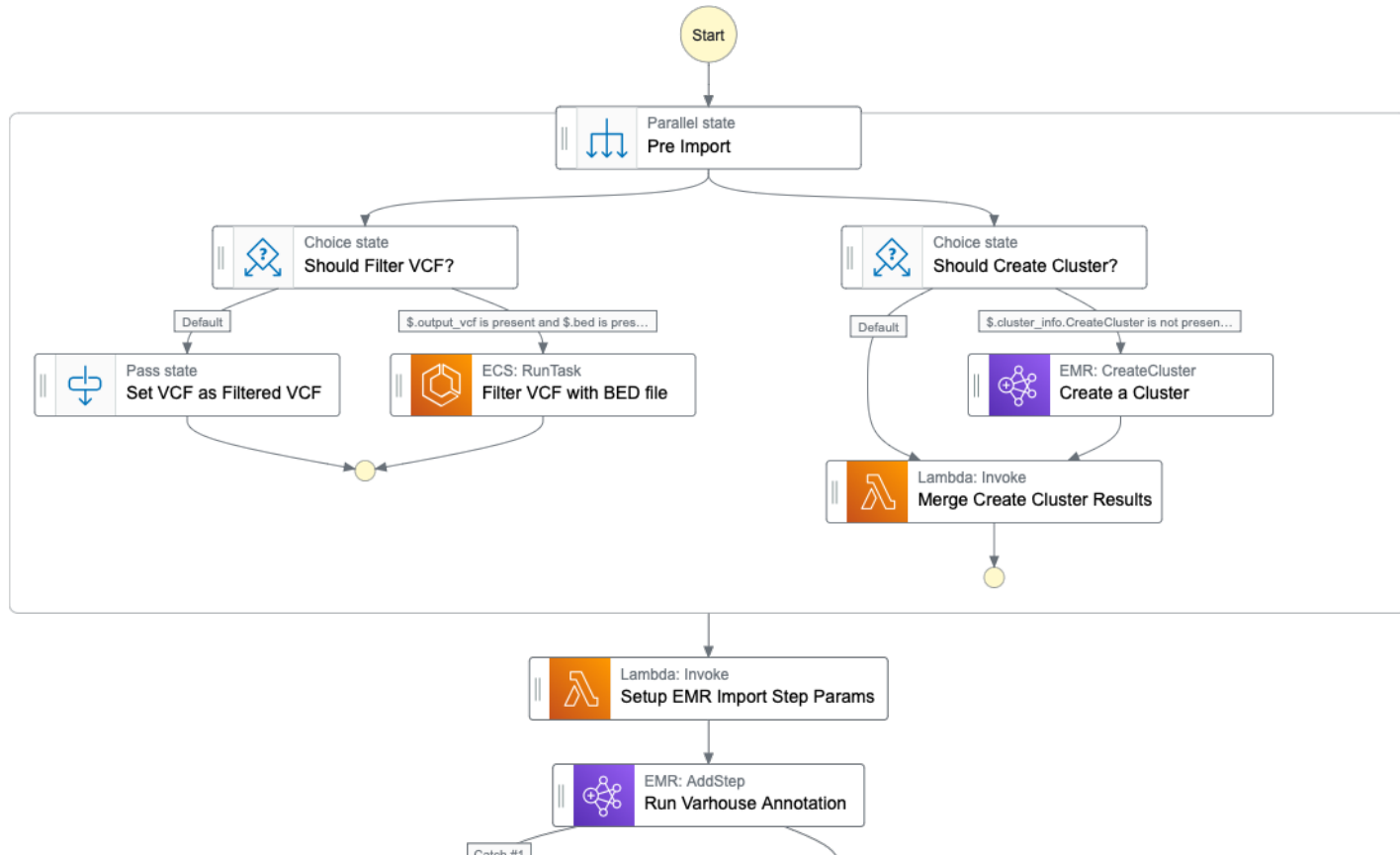
Sends:
EventBridge



Varhouse Importer



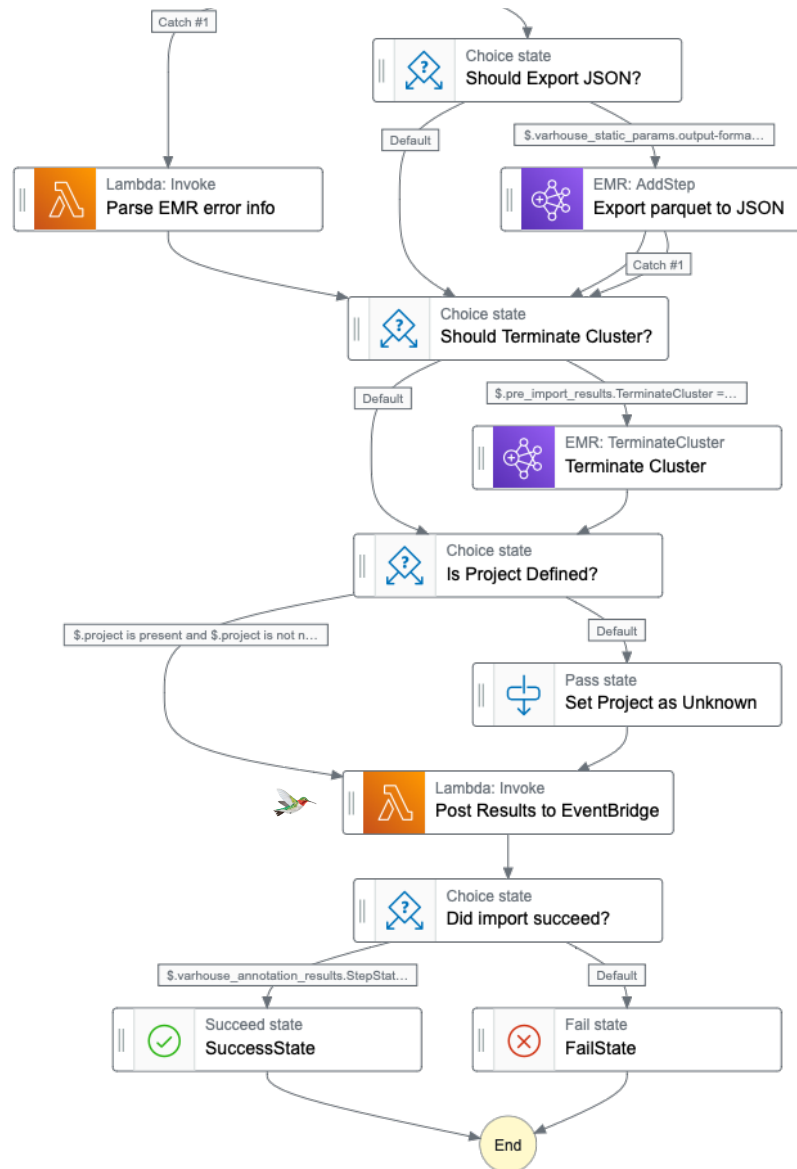
Sends:
EventBridge



Varhouse Importer



Sends:
EventBridge

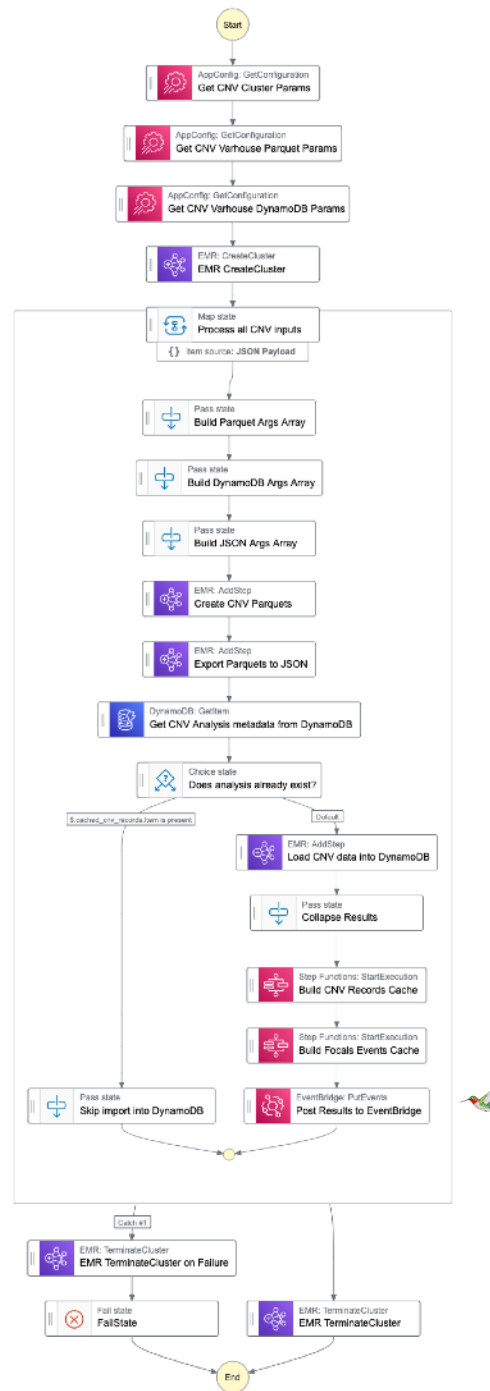


Varhouse CNV



Receives:
EventBridge

Sends:
EventBridge

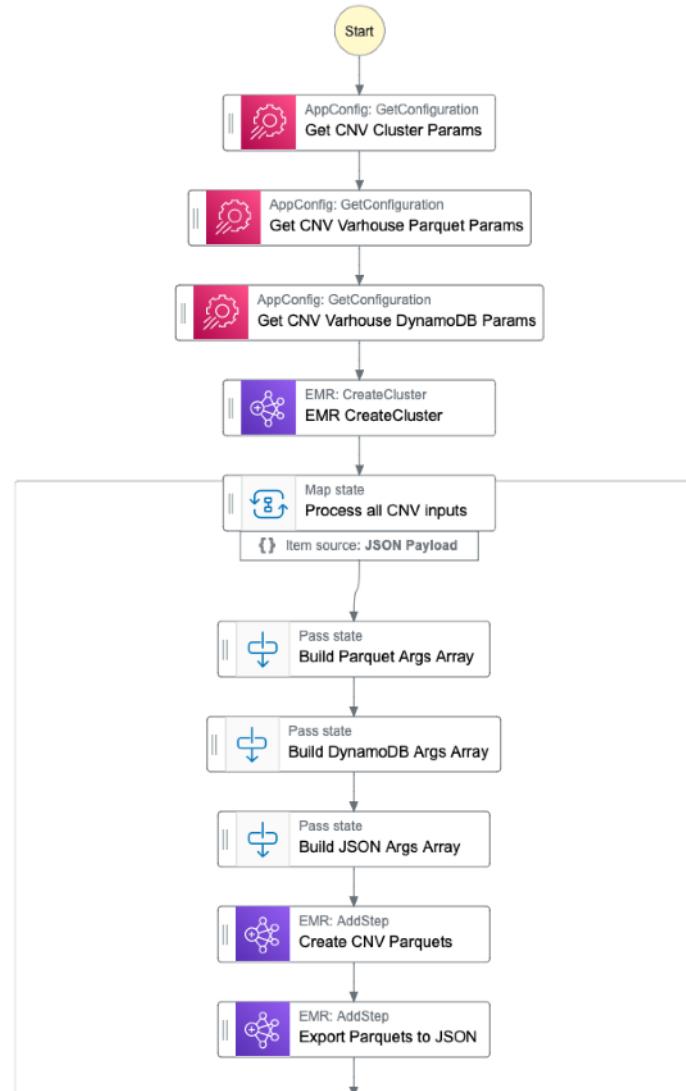


Varhouse CNV



Receives:
EventBridge

Sends:
EventBridge

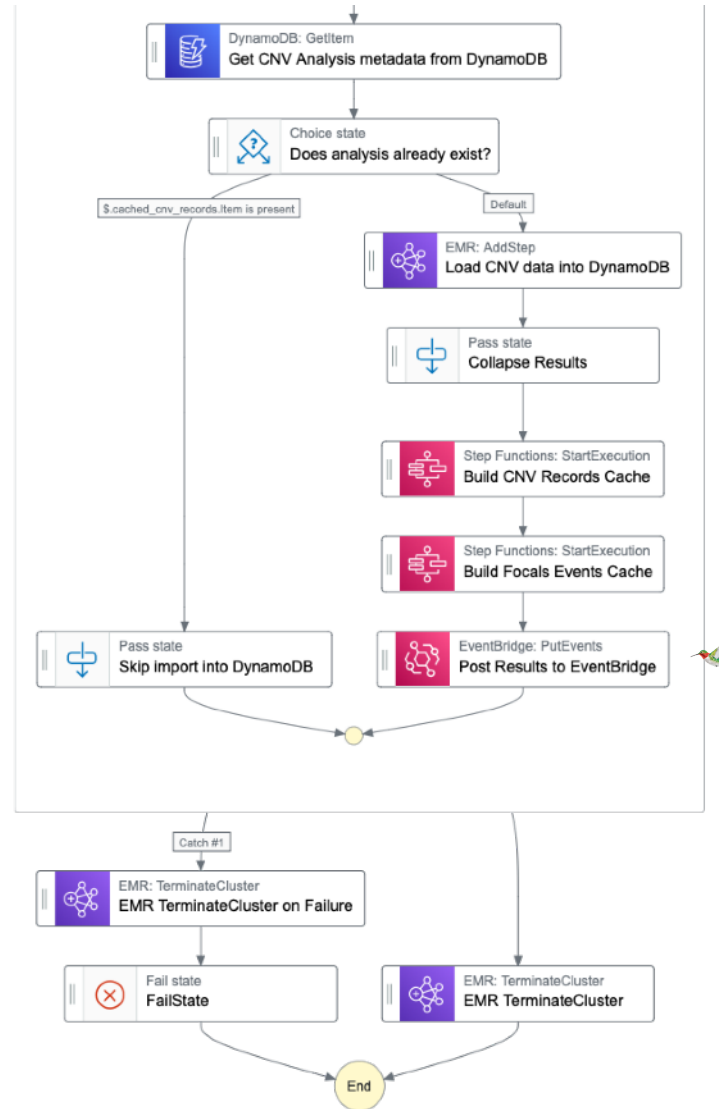


Varhouse CNV



Receives:
EventBridge

Sends:
EventBridge





Plots Tracks Segments Focals Genes Analyze

Gene List

Cancer Genes

Settings

Save Settings

Reset



CNV Log2 Cutoff: 0.25

0.25

LOH BAF Cutoff: 0.42

0.42

Cellularity: 1

1

Log2 Offset: 0

0

Focal SD Cutoff: 2

2

Points

Bins

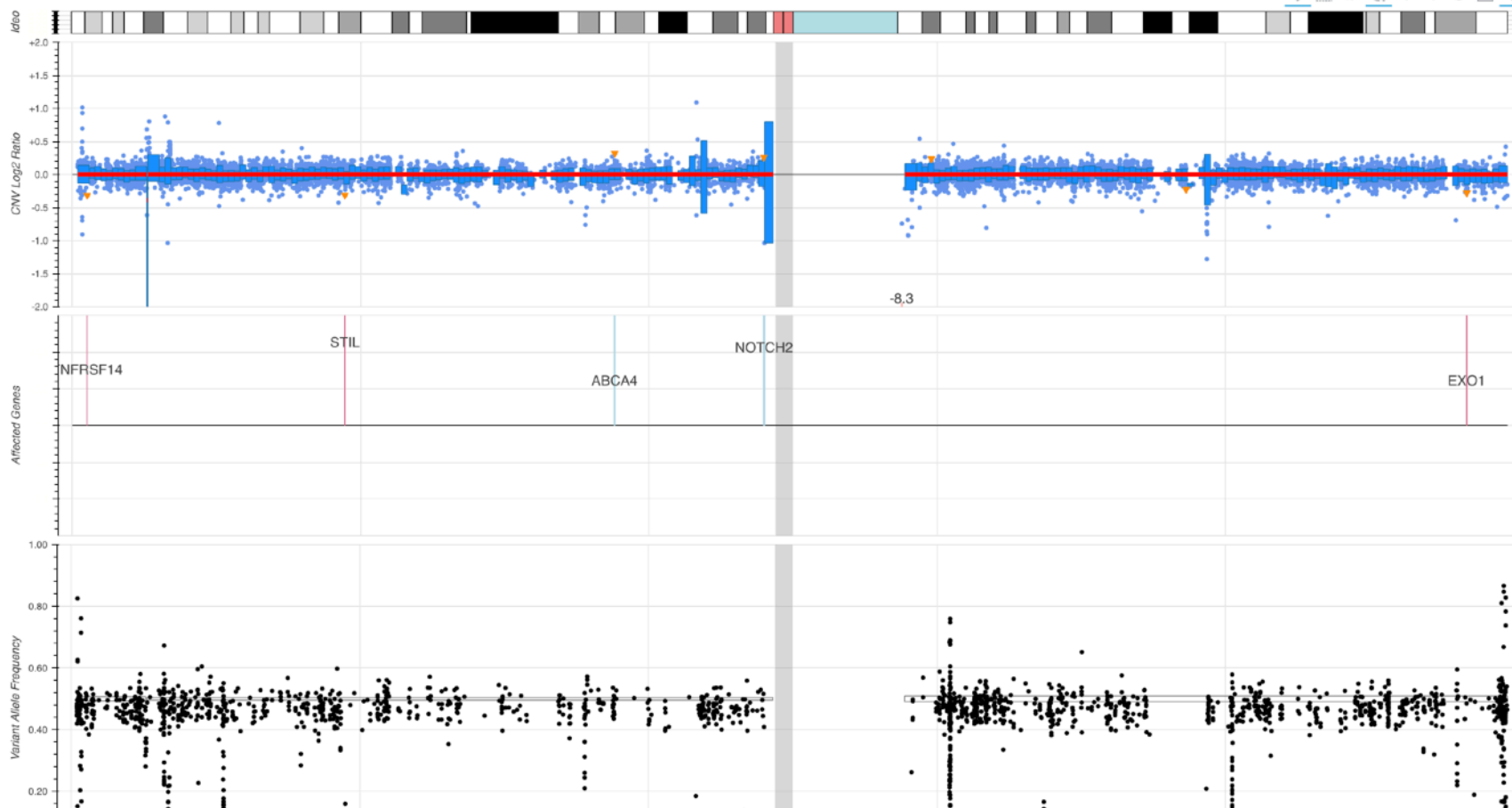
Both

Hide Labels

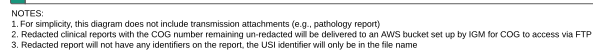
Show Labels

Phenotype Genes

All Genes



**All these events seem intentional...
Why?**



→ PII Reports (PDF) delivered to IGM portal

→ PII Redacted Reports w/COG Reg. Number (PDF) delivered to AWS for COG access²

Programmatically call LabVantage with the Sample Number and have it return the USI

USI

Rename all files using USI, replacing Clinical Lab IDs

BAM to CRAM replaces Clinical Lab IDs with USI

Find & Replace Clinical Lab IDs with USI in file metadata

Clinical Report and Specimen Data

USI

De-identified PII Redacted report³ (.pdf)

Biospecimen Data (.json)

T/N Exome Sequencing

USI

Germline Read Alignment (.cram & .crai)

Somatic Read Alignment (.cram & .crai)

Germline VCF (.gz & .tbi)

Somatic VCF (.gz & .tbi)

Archer Fusion Analysis

USI

Targeted RNA Read Alignment (.cram & .crai)

Archer Fusion Results (.txt)

Methylation Analysis

USI

Illumina EPIC Array Intensity File (.idat)

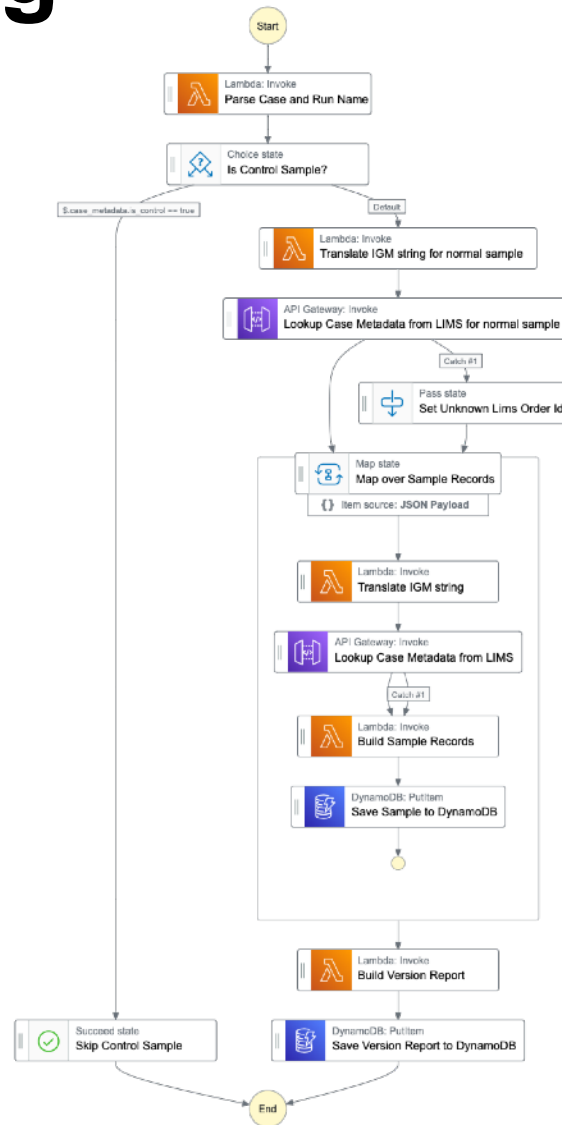
DKFZ Classification (.html)

Cancer Data Service

IGM Tracking Alignment



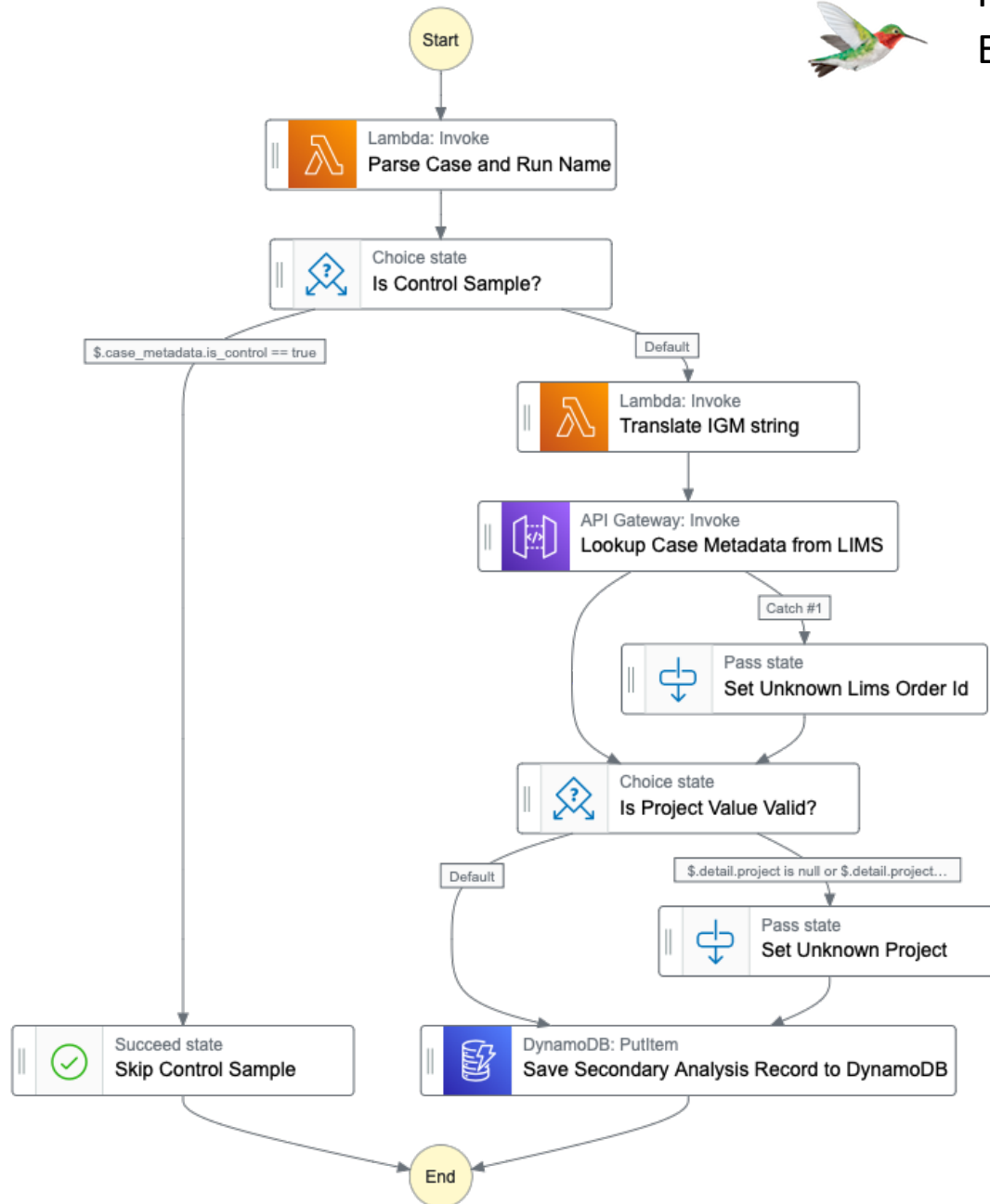
Receives:
EventBridge



IGM Tracking Variant Calling



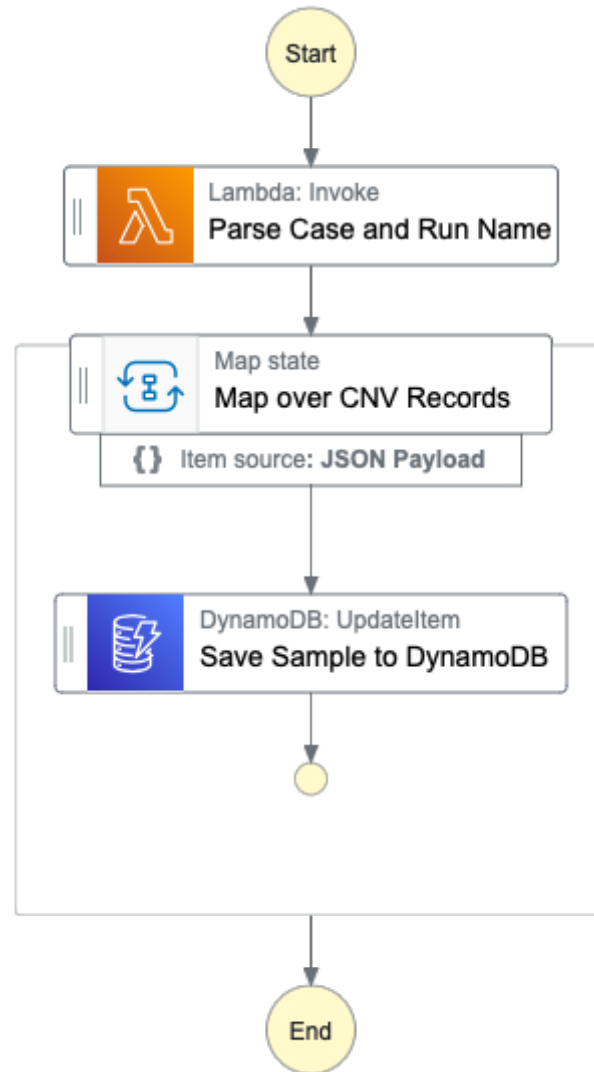
Receives:
EventBridge



IGM Tracking CNV LOH



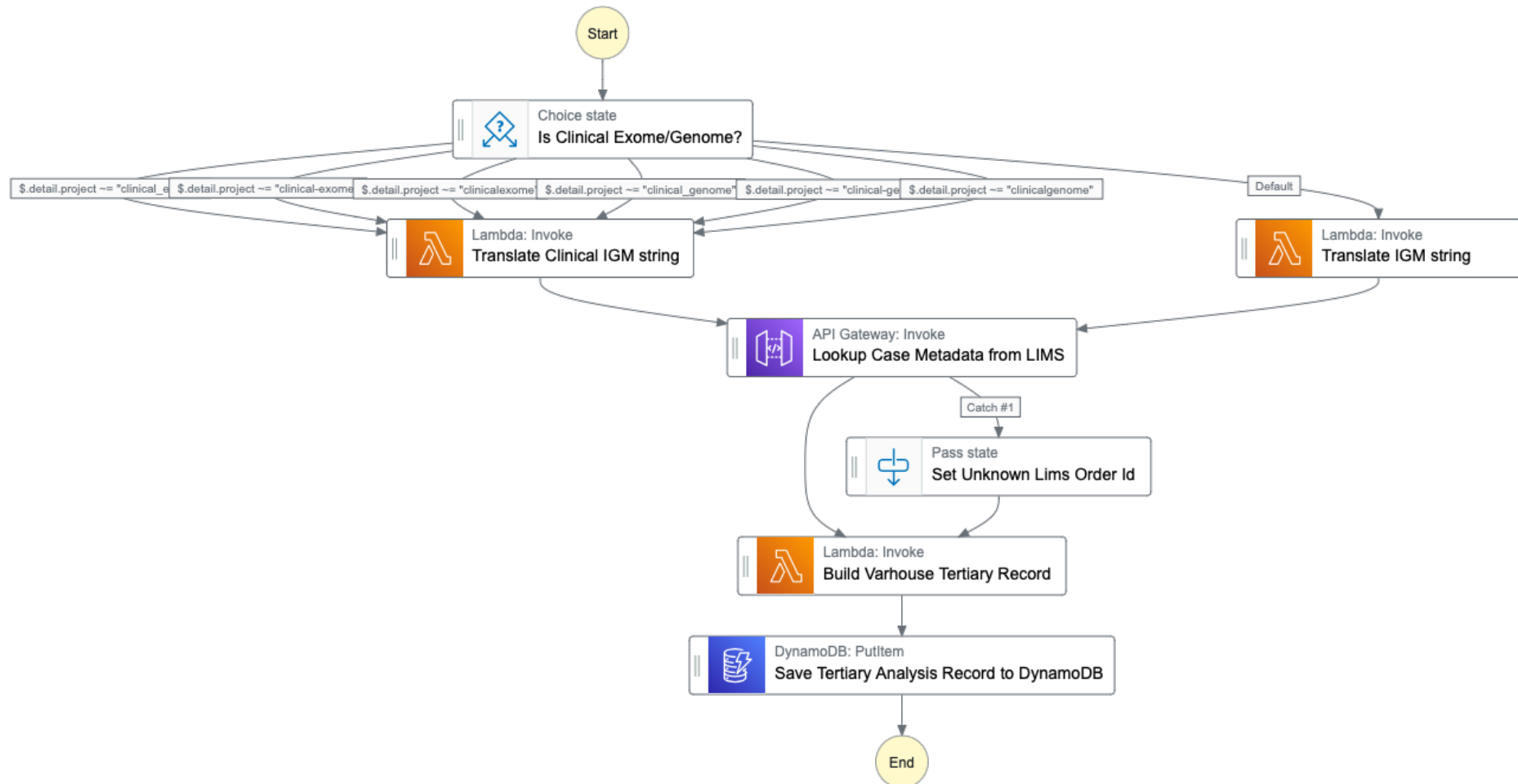
Receives:
EventBridge



IGM Tracking Varhouse



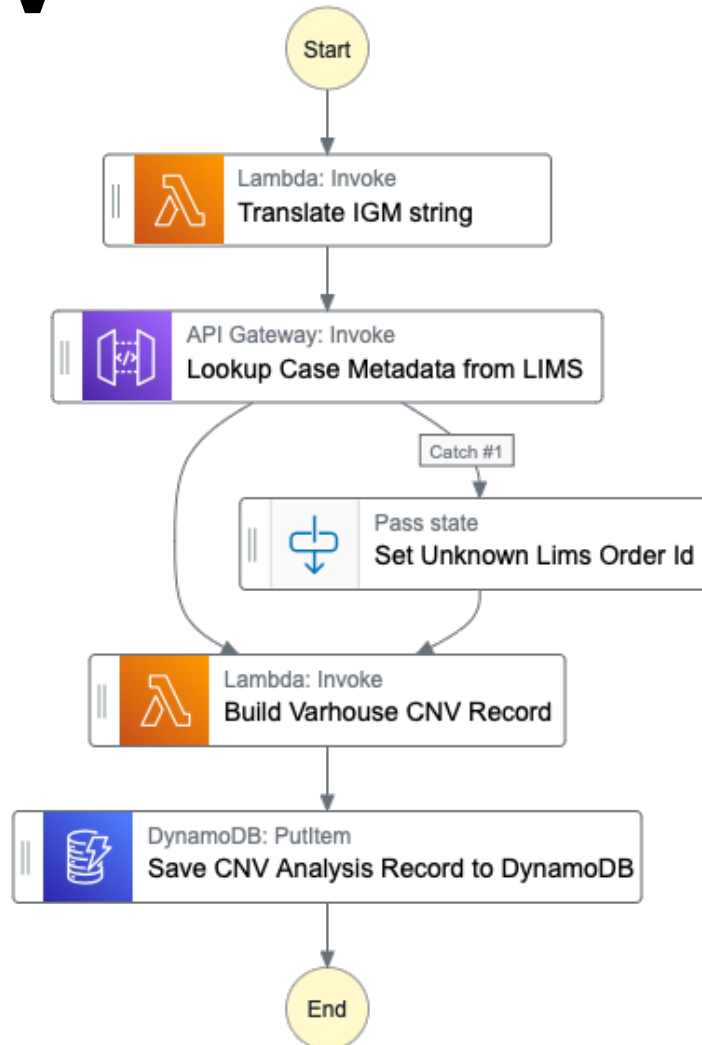
Receives:
EventBridge



IGM Tracking Varhouse CNV



Receives:
EventBridge



Interpretation

Variant Scientists

- Variant scientists review assays
- Select variants to interpret
- Do research on variants
- Write draft of clinical report
 - Tumor sample
 - Normal sample

Clinical Directors

- Review variant list and classification from variant scientists
- Review and sign off on report

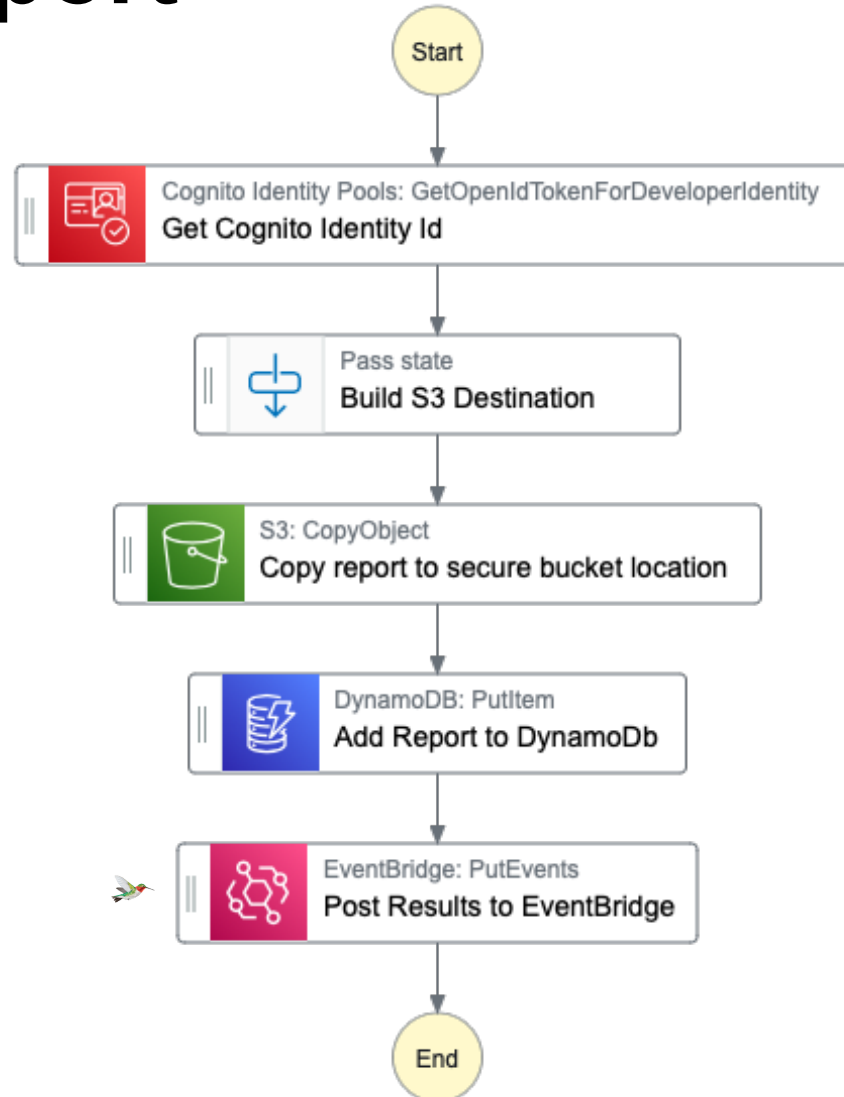
Delivery

IGM Portal Cleartext report



Receives:
API Call

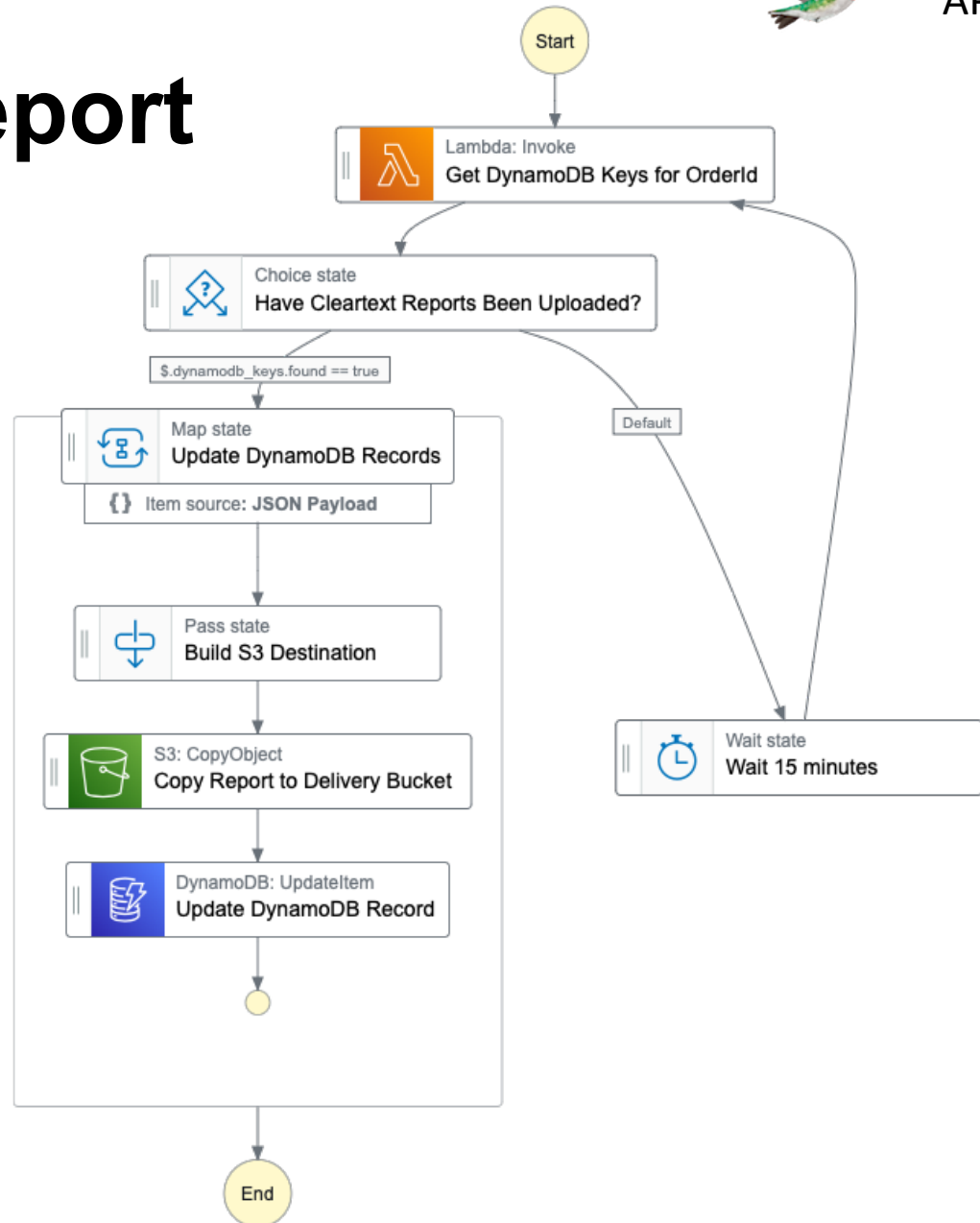
Sends:
EventBridge



IGM Portal Redacted report



Receives:
API Call

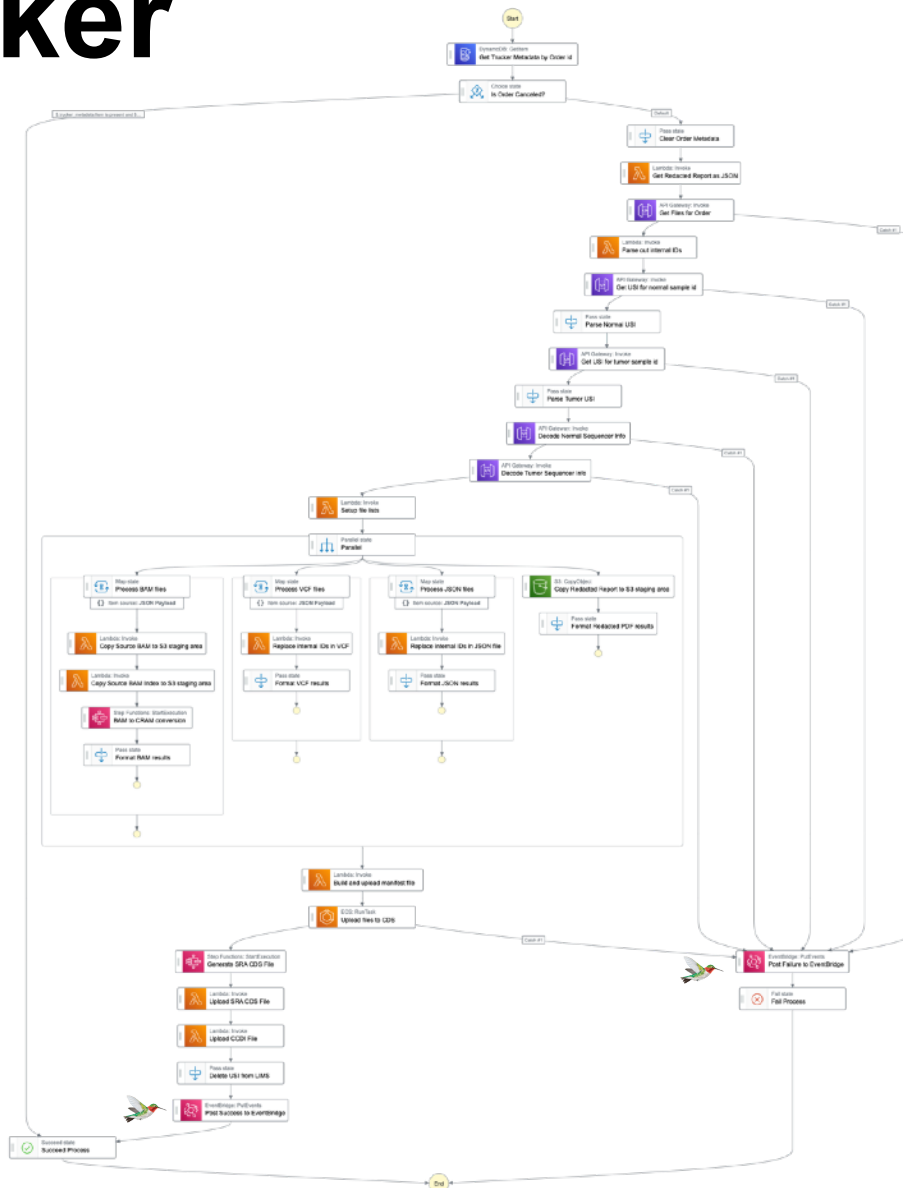


IGM Trucker



Receives:
EventBridge

Sends:
EventBridge

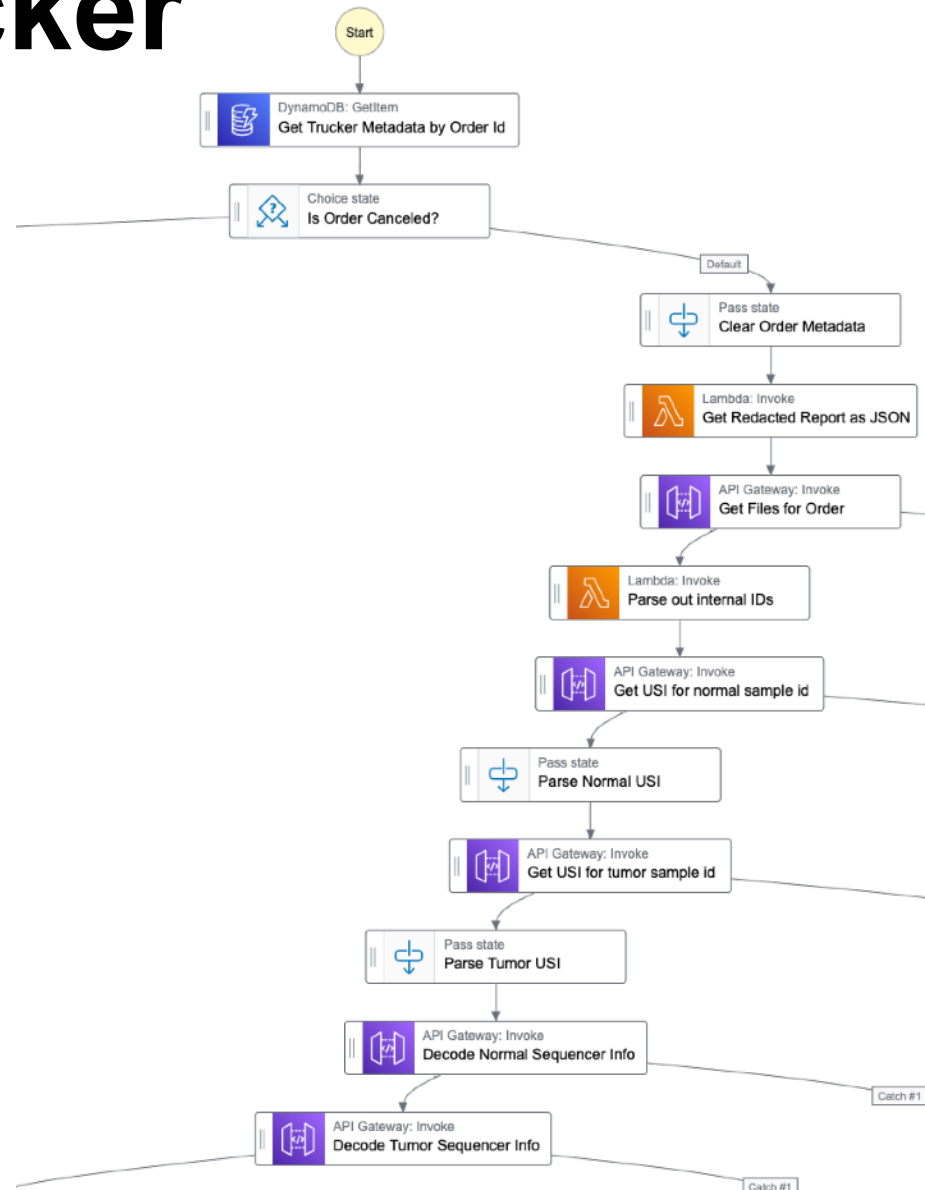


IGM Trucker



Receives:
EventBridge

Sends:
EventBridge

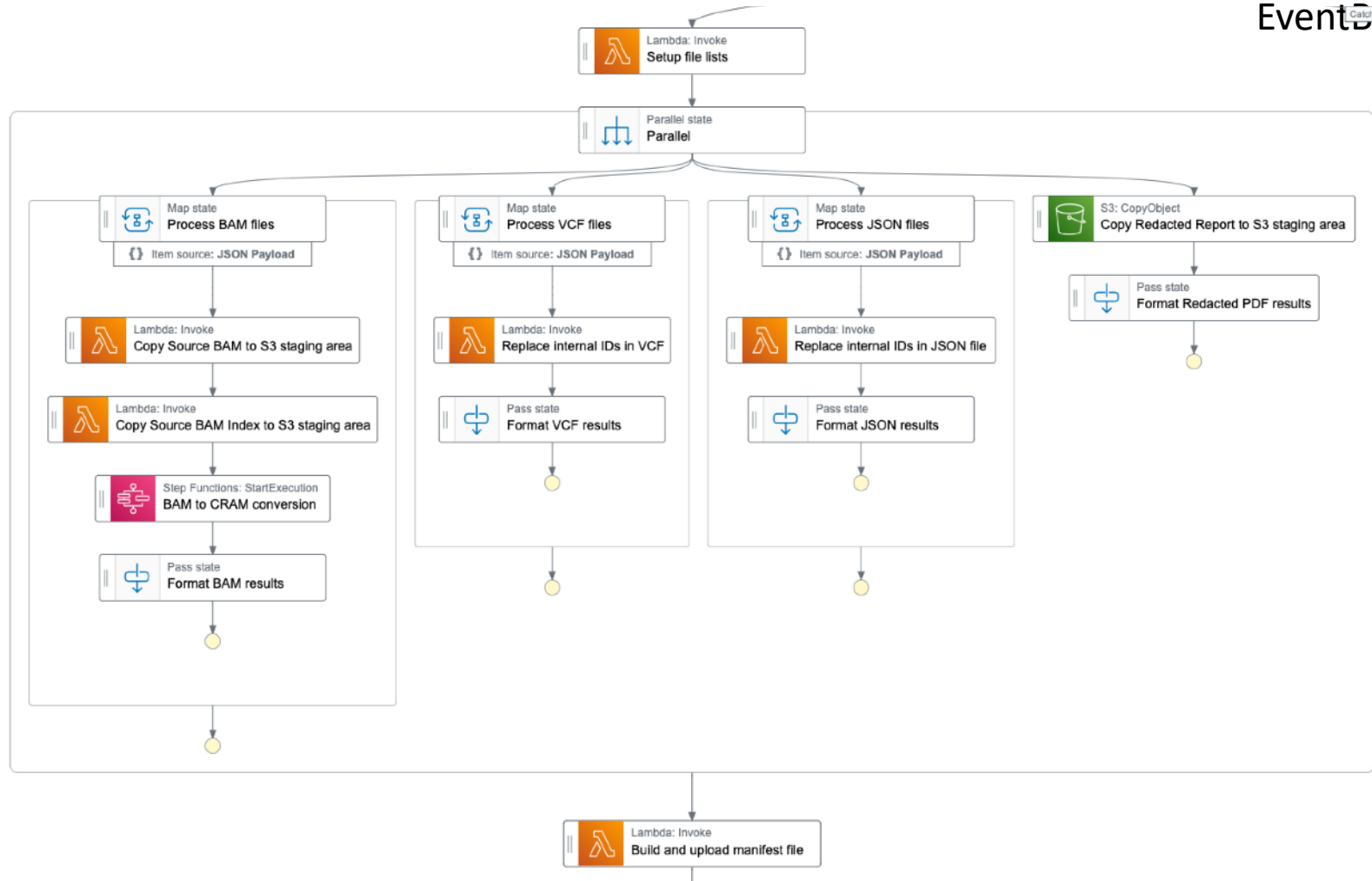


IGM Trucker



Receives:
EventBridge

Sends:
EventBridge

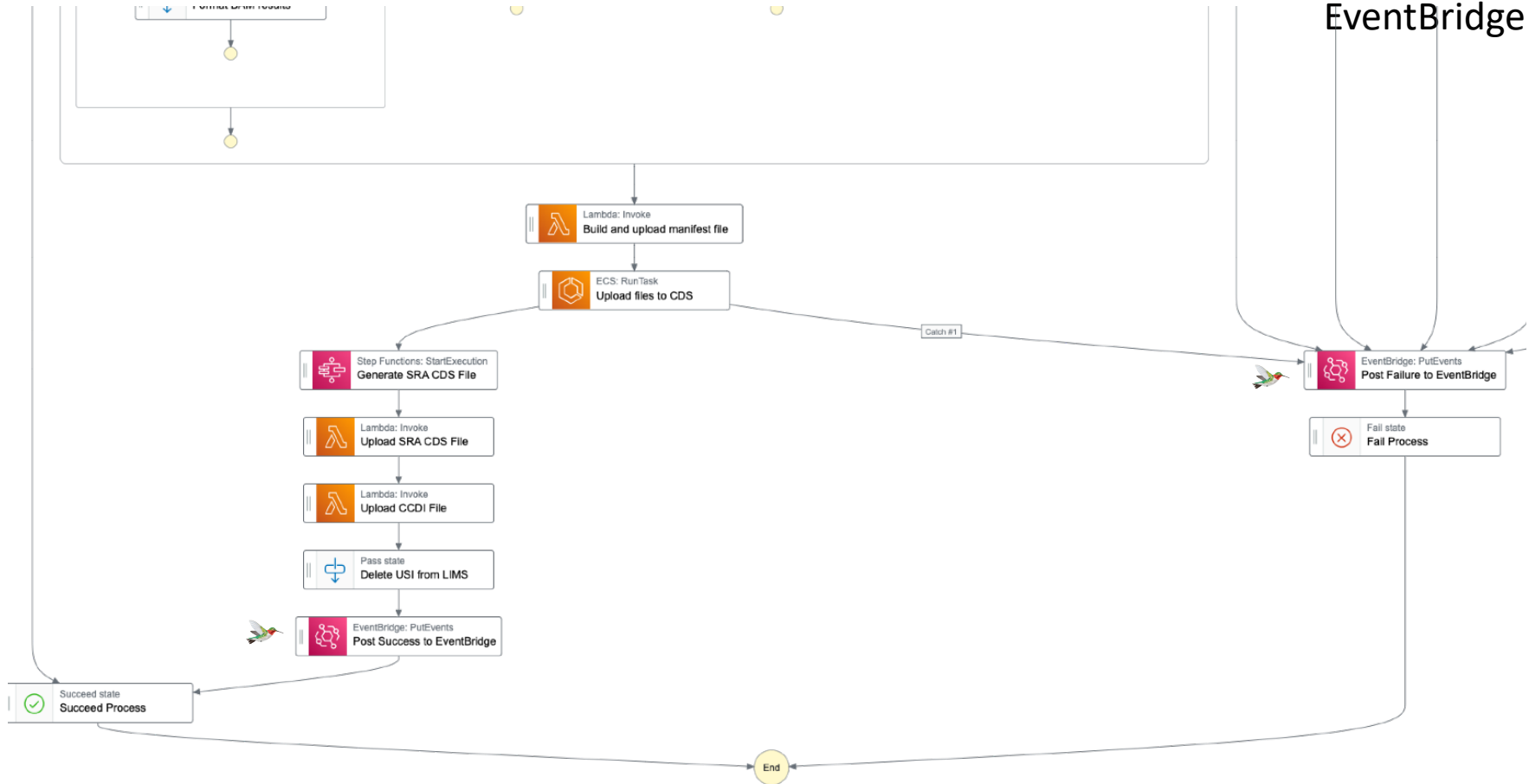


IGM Trucker



Receives:
EventBridge

Sends:
EventBridge



Lessons

Pros

- Security built in
- Scalable
- Extensible
 - Notifications
 - New algorithms and tests without touching anything else!

Report Date

10/1/23

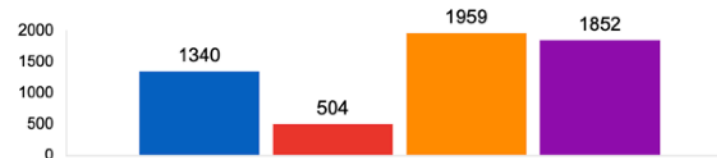
IGM Cumulative Data

IGM - Patients and Orders Totals



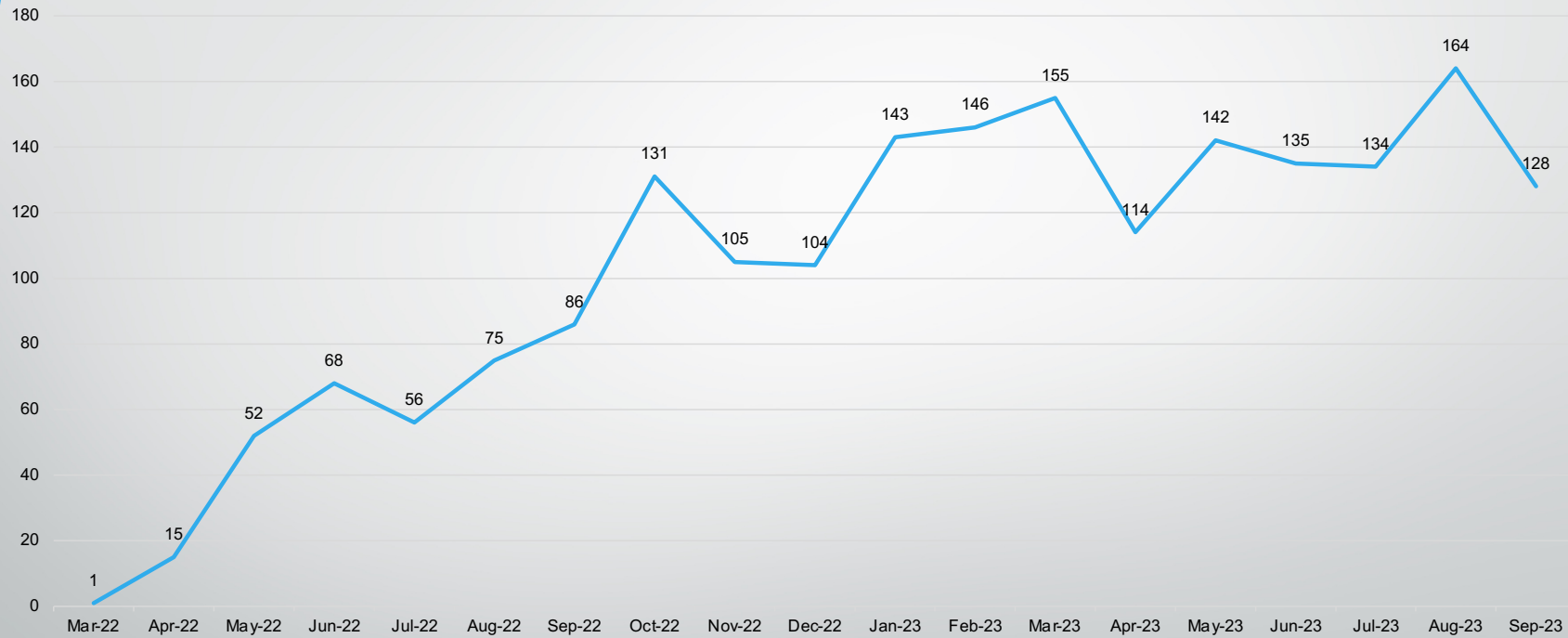
● Total Patients ● Total Orders Received

IGM - Total Orders by Test



● Total CNS Methylation ● Total Research Methylation ● Total Fusion ● Total SDGC Exome

Cases Received



Total= 1954 Cases

Challenges

- Humans need help
- Interpreting results takes time
- Writing reports takes time
- Results are static in time

Varhouse v1

- An elephant in the room
- The output is Excel
- Works, but is clunky



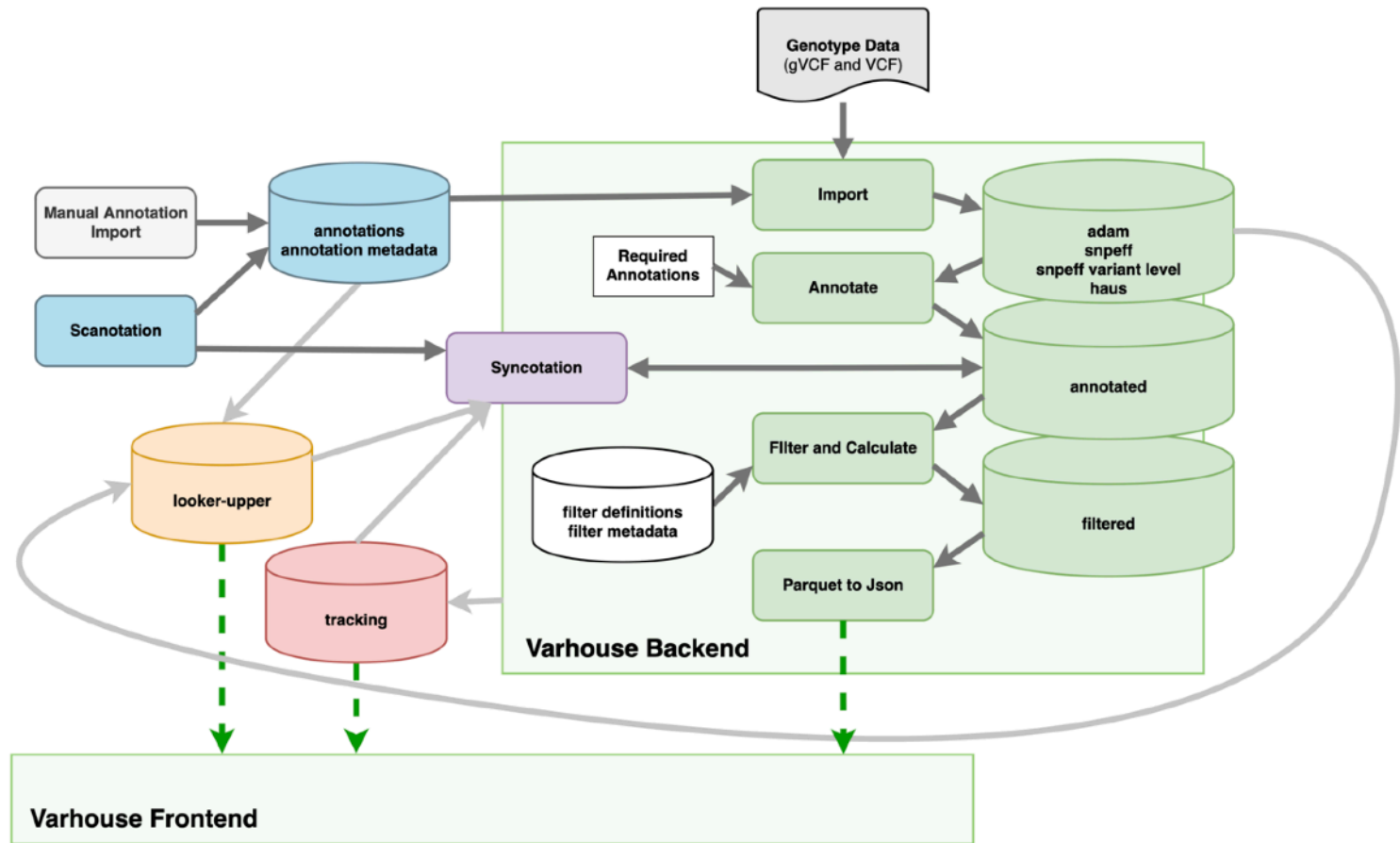
Other problems

- Have to rerun entire pipeline to reanalyze with latest annotations
- Excel limits us to a two dimensional view
- Evidence is kept as screenshots inside an Excel form
- Have we assessed this variant before?



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Have to rerun entire pipeline to reanalyze with latest annotations

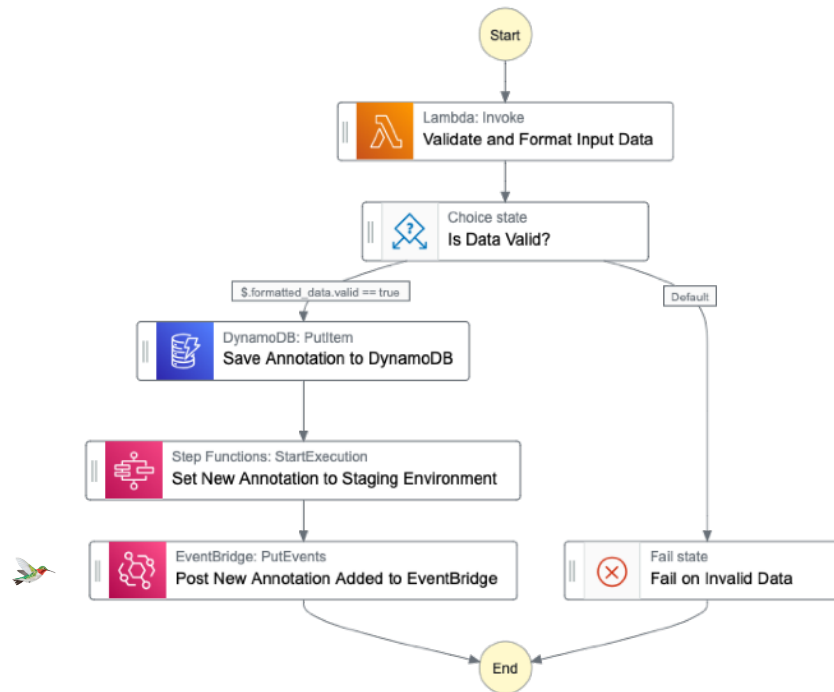


IGM Annotations - Add



Receives:
EventBridge

Sends:
EventBridge

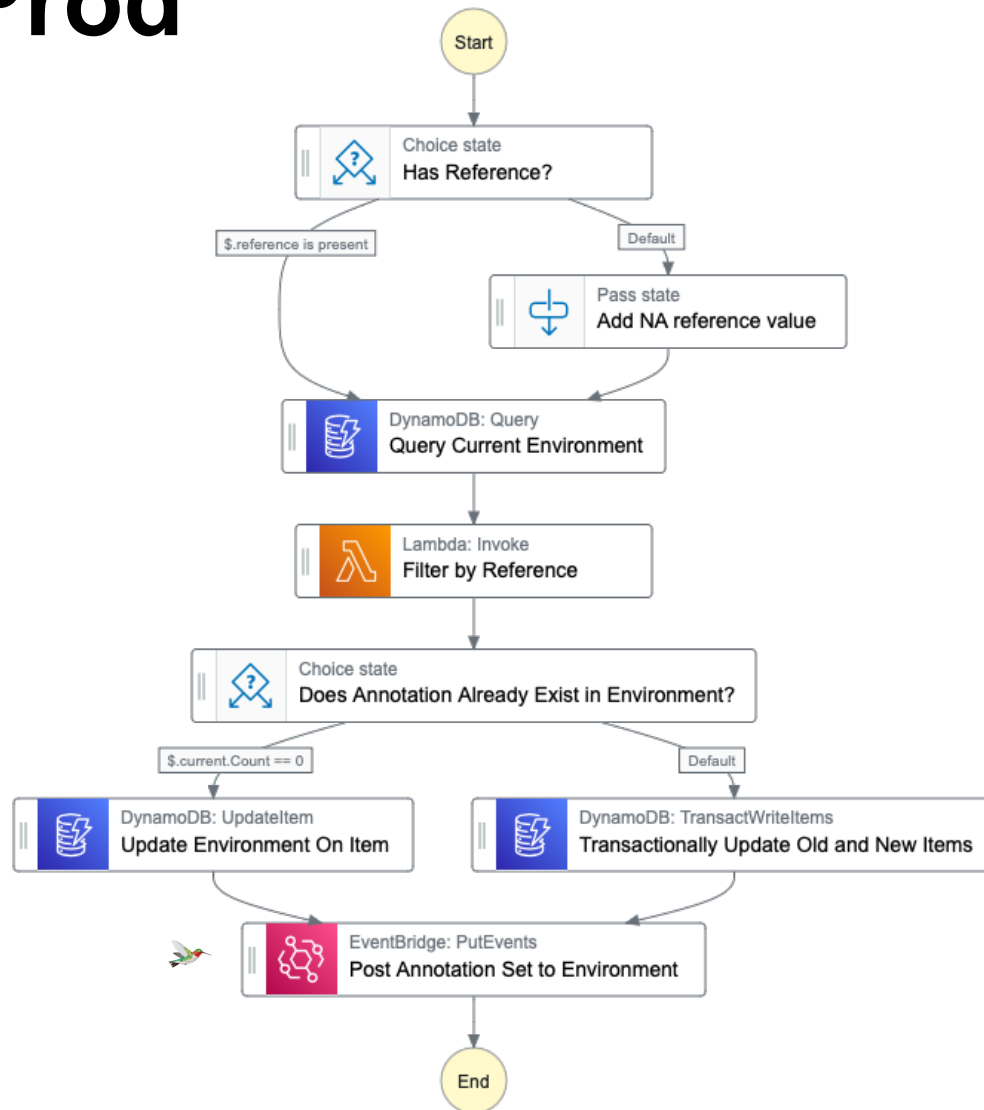


IGM Annotations Deploy to Prod

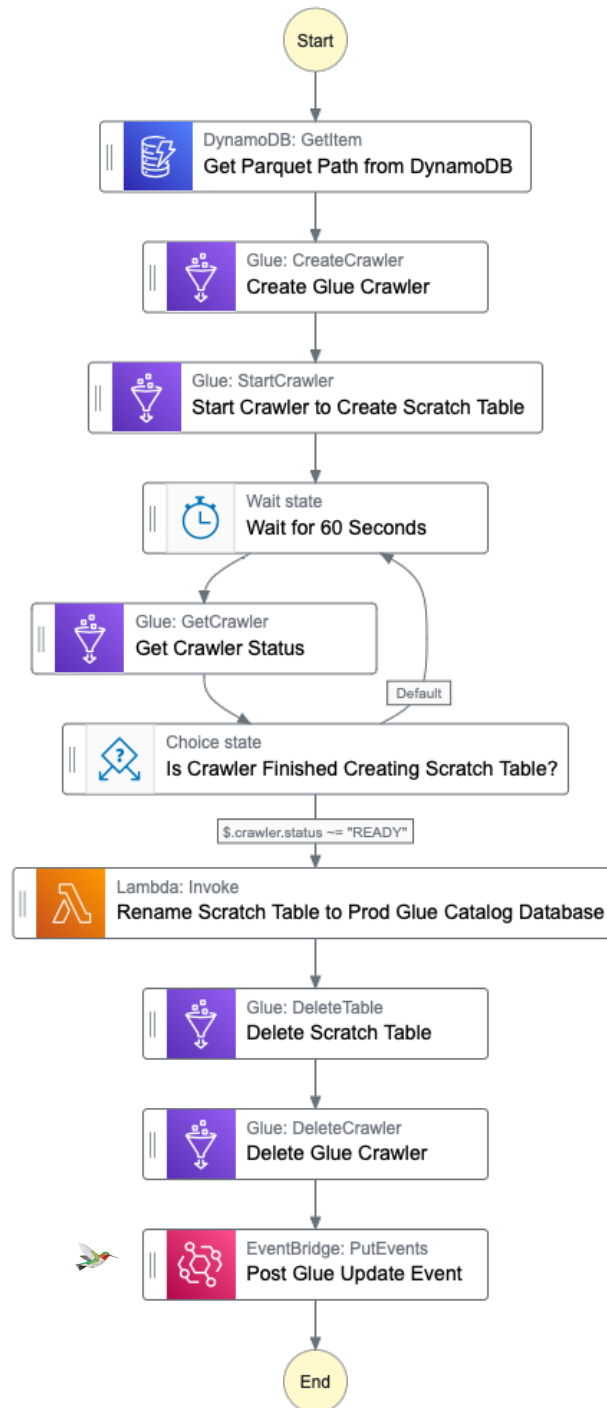


Receives:
EventBridge

Sends:
EventBridge



IGM Annotations - Expose in Athena



Receives:
EventBridge

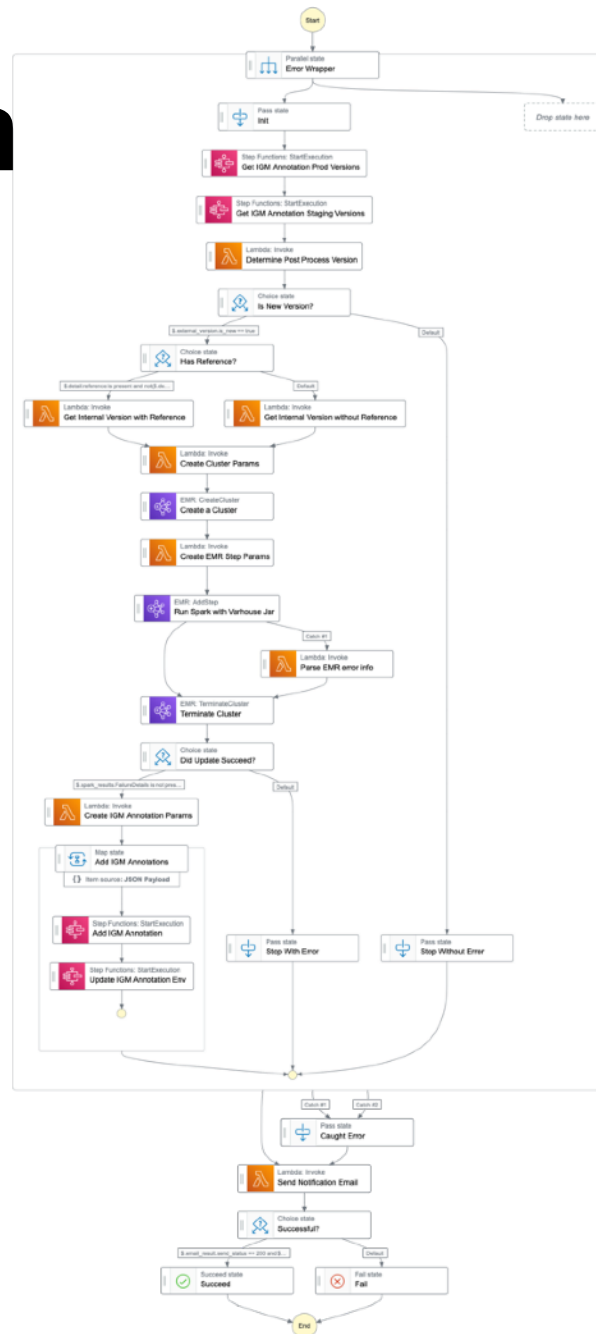
Sends:
EventBridge

Scanotation



Receives:
EventBridge

Sends:
EventBridge

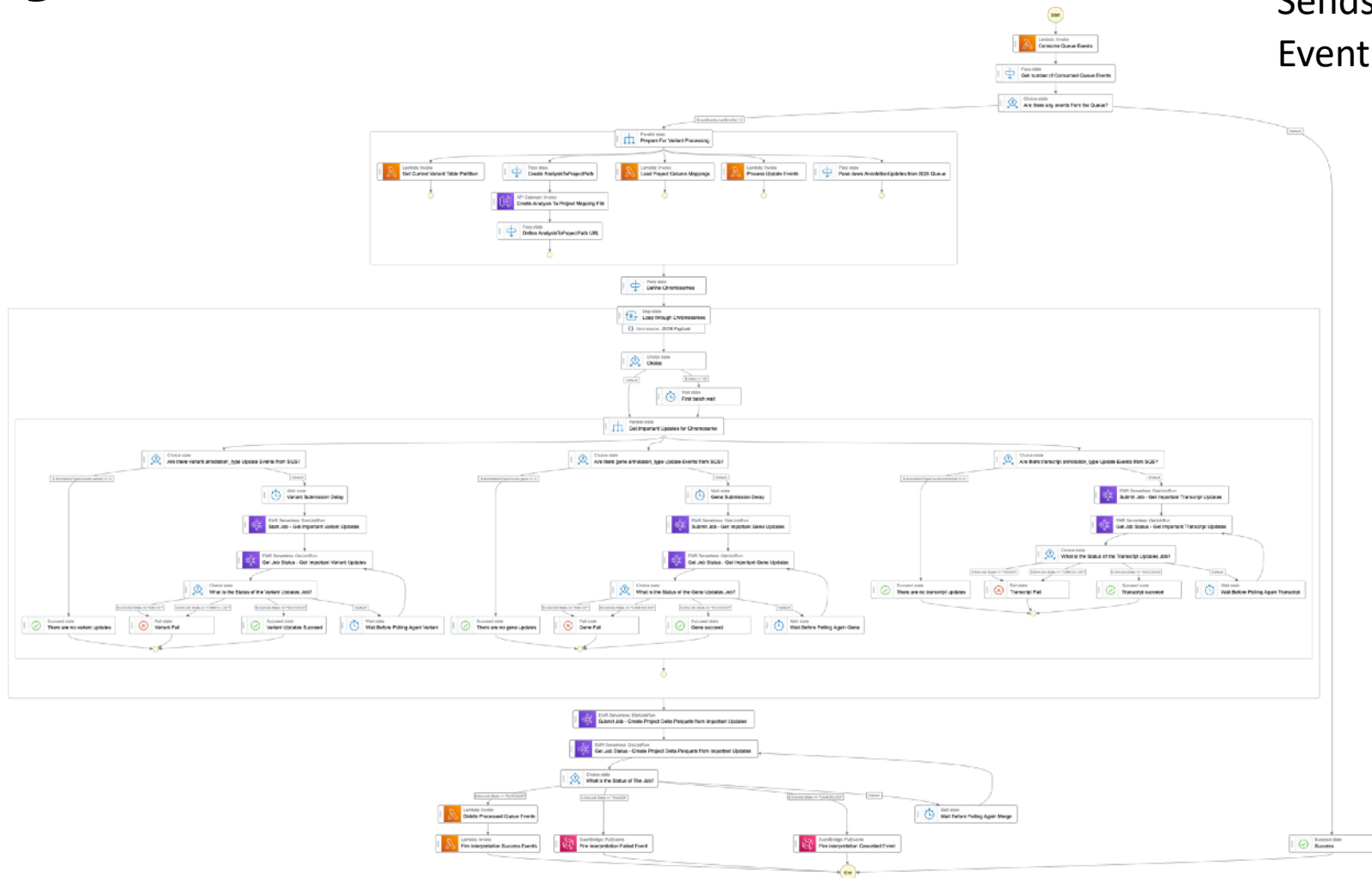


Syncotation



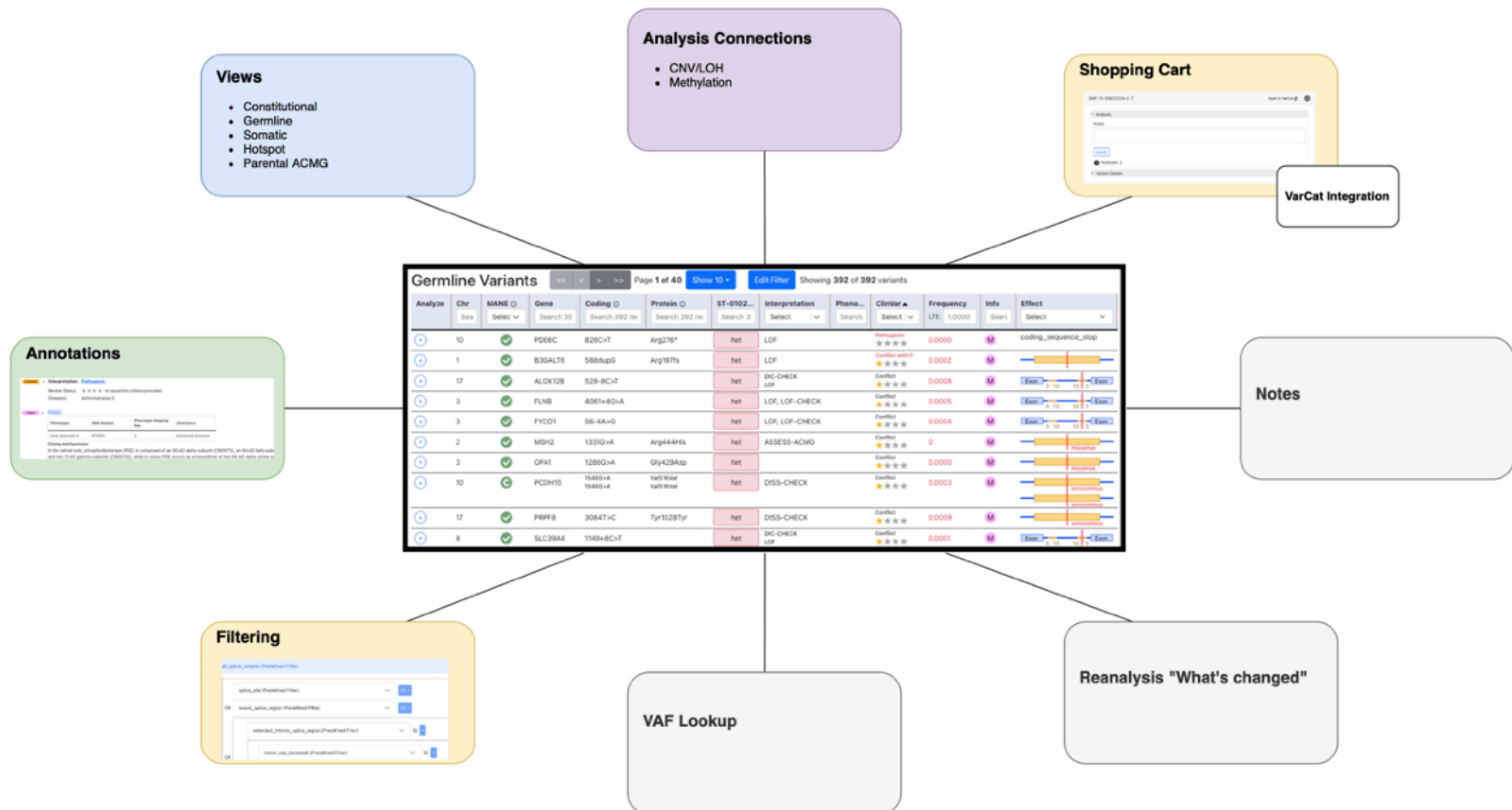
Receives:
EventBridge

Sends:
EventBridge



Evidence is kept as screenshots inside an Excel form

Excel limits us to a two dimensional view



alpha.clinical.varhouse.org

Varhouse Clinical (a) Home

Grant Lammi

GermlineSomaticCNVMethylationAnalyze

Somatic

556 of 556 variants

<<<>>>Page 1 of 56Show 10

Analyze	Chr	MANE	Gene	Coding	Protein	N	T	T-N	Interpretation	ClinVar	Frequency	Info	Effect
	Sea	Selec	Search St	Search 556 re	Search 556 re	Search	Search	Search	Select	Select	LTE: 1.0000	Seac	Select
+	2	✓	MSH6	3261dupC	Pha1088fs	0.0% (151)	3.5% (141)	+3.5%	ASSESS-ACMG LOF	Pathogenic ★★★★	0.0000	M O	frameshift
+	7	✓	BRAF	1799T>A 1919T>A	Val600Glu Val640Glu	0.6% (179)	23.5% (187)	+22.9%		Pathogenic ★★★★	0	M O	missense
+	21	✓	COL18A1	2823_2832delCG	Gly942fs	0.5% (204)	2.2% (227)	+1.7%	LOF	Pathogenic ★★★★	0.0001	M	frameshift
+	9	✓	ABL1	1826_1828delAGA	Lys609del	0.7% (271)	2.1% (291)	+1.4%		Pathogenic ★★★★	0.0004	M O	inframe deletion
+	7	✓	KMT2C	1013C>T	Ser338Leu	0.0% (94)	1.2% (81)	+1.2%	IGM>=50	Pathogenic ★★★★	0.0001	M O	missense
+	7	✓	KMT2C	1013-2A>G		0.0% (92)	1.3% (80)	+1.3%	IGM>=50 LOF (1/0.66)-CHECK	VUS ★★★★	0.0001	M O	Exon 12 missense
+	7	✓	KMT2C	1038G>A	Val346Val	3.2% (124)	1.6% (123)	-1.6%	DISC-CHECK IGM>=50	Likely benign ★★★★	0.0003	M O	synonymous
+	10	✓	MKI67	4991_4992delCA	Thr1664fs	1.4% (291)	3.0% (302)	+1.6%	LOF NOD	Pathogenic ★★★★	0.0002	M	frameshift
+	10	✓	MKI67	7899_7900delCA	His2633fs	3.7% (294)	2.5% (280)	-1.2%	LOF NOD		0	M	frameshift
+	1	✓	ARV1	518delA	Lys173fs	1.4% (285)	2.3% (300)	+0.9%	LOF	Likely pathogenic ★★★★	0.0001	M	frameshift

Variant: 2-47803500-A-AC

Previously assessed

InformationFrequencyTranscriptsScoresCasesGenotypePhenotypeGermlineCNV/LOH

LISTS

	ACMG Actionable	IGM Carrier	IGM Cancer Predisposition
MSH6	✓	--	✓

CLINVAR

Interpretation: Pathogenic

Review Status: ★★★★★ reviewed by expert panel

Diseases: Hereditary nonpolyposis colorectal neoplasms; Lynch syndrome 5; Endometrial carcinoma; MSH6-related disorders; Gastric cancer; Lynch syndrome; Breast and/or ovarian cancer; Hereditary cancer-predisposing syndrome; Mismatch repair cancer syndrome 3; Lynch-like syndrome

OMIM

No Data

ORPHA

MSH6

Syndrome	Prevalence	Age of Onset	Inheritance
Lynch syndrome	Unknown	Adult	Autosomal dominant
Constitutional mismatch repair deficiency syndrome	--	Childhood	Autosomal recessive
Muir-Torre syndrome	Unknown	Adult	Autosomal dominant

MANE

MSH6

MANE Status	Chr	Strand	GRCh38 Range	Refseq Id	Refseq Prot	Ensembl Id	Ensembl Prot	MANE Name	HGNC Id
Select	NC_000002.12	+	47783145-47806953	NM_000179.3	NP_000170.1	ENST00000234420.11	ENSP00000234420.5	mutS homolog 6	7329

alpha.clinical.varhouse.org

Varhouse Clinical (a) Home

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GermlineSomaticCNVMethylationAnalyze

Somatic

556 of 556 variants

<<<>>>Page 1 of 56Show 10

Analyze	Chr	MANE	Gene	Coding	Protein	N	T	T-N	Interpretation	ClinVar	Frequency	Info	Effect
	Sea	Selec	Search 5f	Search 556 re	Search 556 re	Search	Search	Search	Select	Select	LTE: 1.0000	Searc	Select
+	2		MSH6	3261dupC	Phe1088fs	0.0% (151)	3.5% (141)	+3.5%	ASSESS-ACMG LOF	Pathogenic ★★★★	0.0000	M O	frameshift
+	7		BRAF	1799T>A 1919T>A	Val600Glu Val640Glu	0.6% (175)	23.5% (187)	+22.9%		Pathogenic ★★★★	0	M O	missense
+	21		COL18A1	2823_2832delCG	Gly942fs	0.5% (204)	2.2% (227)	+1.7%	LOF	Pathogenic ★★★★	0.0001	M	frameshift
+	9		ABL1	1826_1828delAGA	Lys609del	0.7% (271)	2.1% (291)	+1.4%		Pathogenic ★★★★	0.0004	M O	inframe deletion
+	7		KMT2C	1013C>T	Ser338Leu	0.0% (94)	1.2% (81)	+1.2%	IGM>=50	Pathogenic ★★★★	0.0001	M O	missense
+	7		KMT2C	1013-2A>G		0.0% (92)	1.3% (80)	+1.3%	IGM>=50 LOF LOF(1/0.66)-CHECK	VUS ★★★★	0.0001	M O	Exon 12 missense
+	7		KMT2C	1038G>A	Val346Val	3.2% (124)	1.6% (123)	-1.6%	DISS-CHECK IGM>=50	Likely benign ★★★★	0.0003	M O	synonymous
+	10		MKI67	4991_4992delCA	Thr1664fs	1.4% (291)	3.0% (302)	+1.6%	LOF NOD	Pathogenic ★★★★	0.0002	M	frameshift
+	10		MKI67	7899_7900delCA	His2633fs	3.7% (294)	2.5% (280)	-1.2%	LOF NOD		0	M	frameshift
+	1		ARV1	518delA	Lys173fs	1.4% (285)	2.3% (300)	+0.9%	LOF	Likely pathogenic ★★★★	0.0001	M	frameshift

Variant: 2-47803500-A-AC

Previously assessed

InformationFrequencyTranscriptsScoresCasesGenotypePhenotypeGermlineCNV/LOH

GNOMAD

Genome

Popmax FAF (95%): 0.0000
Allele Frequency: 0.0001
Allele Count: 9
Allele Number: 150,380
Number of homozygotes: 0

Exome

Popmax FAF (95%): 0.0000
Allele Frequency: 0.0001
Allele Count: 16
Allele Number: 249,750
Number of homozygotes: 0

	Genome				Exome			
Population	Allele Count	Allele Number	Homozygotes	Allele Frequency	Allele Count	Allele Number	Homozygotes	Allele Frequency
African/African-American	2	40,806	0	0.0000	2	16,126	0	0.0001
Amish	0	904	0	0	-	-	-	-
Ashkenazi Jewish	0	3,456	0	0	0	10,032	0	0
East Asian	0	5,136	0	0	0	18,302	0	0
European (Finnish)	1	10,370	0	0.0001	2	21,590	0	0.0001
European (non-Finnish)	6	67,594	0	0.0001	8	112,624	0	0.0001
Latino/Admixed American	0	14,988	0	0	1	34,460	0	0.0000
Middle Eastern	0	314	0	0	-	-	-	-
Other	0	2,070	0	0	2	6,104	0	0.0003
South Asian	0	4,742	0	0	1	30,512	0	0.0000
XX (FEMALE)	4	77,052	0	0.0001	-	-	-	-

Default

<

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Germline

Somatic

CNV

Methylation

Analyze

Somatic

556 of 556 variants

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Analyze	Chr	MANE	Gene	Coding	Protein	N	T	T-N	Interpretation	ClinVar	Frequency	Info	Effect
	Sea	Selec	Search 56	Search 556 re	Search 556 re	Search	Search	Search	Select	Select	LTE: 1.0000	Search	Select
	2		MSH6	3261dupC	Phe1088fs	0.0% (151)	3.5% (141)	+3.5%	ASSESS-ACMG LOF	Pathogenic ★★★★	0.0000	M	frameshift
	7		BRAF	1799T>A 1919T>A	Val600Glu Val640Glu	0.6% (179)	23.5% (187)	+22.9%		Pathogenic ★★★★	0	M	missense
	21		COL18A1	2823_2832delCG	Gly942fs	0.5% (204)	2.2% (227)	+1.7%	LOF	Pathogenic ★★★★	0.0001	M	frameshift
	9		ABL1	1826_1828delAGA	Lys609del	0.7% (271)	2.1% (291)	+1.4%		Pathogenic ★★★★	0.0004	M	inframe deletion
	7		KMT2C	1013C>T	Ser338Leu	0.0% (94)	1.2% (61)	+1.2%	IGM>=50	Pathogenic ★★★★	0.0001	M	missense
	7		KMT2C	1013-2A>G		0.0% (92)	1.3% (80)	+1.3%	IGM>=50 LOF LOF(1/0.86)-CHECK	VUS ★★★★	0.0001	M	Exon 12 21
	7		KMT2C	1038G>A	Val346Val	3.2% (124)	1.6% (123)	-1.6%	DTSS-CHECK IGM>=50	Likely benign ★★★★	0.0003	M	synonymous
	10		MKI67	4991_4992delCA	Thr1664fs	1.4% (291)	3.0% (302)	+1.6%	LOF NOD	Pathogenic ★★★★	0.0002	M	frameshift
	10		MKI67	7899_7900delCA	His2633fs	3.7% (294)	2.5% (280)	-1.2%	LOF NOD		0	M	frameshift
	1		ARV1	518delA	Lys173fs	1.4% (285)	2.3% (300)	+0.9%	LOF	Likely pathogenic ★★★★	0.0001	M	frameshift

Variant: 2-47803500-A-AC

Previously assessed

Information

Frequency

Transcripts

Scores

Cases

Genotype

Phenotype

Germline

CNV/LOH

MSH6

Copy-Neutral, Chr 2:41258-241873624

Event Details

Copies: 2.0

Chr: 2

Size: 241.8 Mb

Log2: 0.00

Start: 41258

Start Cytoband: p25.3

LOH: No

End: 241873624

End Cytoband: q37.3

FBXO11

Comments (0)

GL

Grant Lammi

Type your comment here.

Cancel

Post

Clear

OMIM LYNCH SYNDROME 1; LYNCH1 (1 gene) [Change Disease](#)

INS: 2-47803500-A-AC [Open in VarCat](#)

Analysis

Notes

Previously assessed

We have seen this before in a similar case that suggested Lynch syndrome. The CNV status is copy neutral so nothing to see here.

Submit

Variant Details

Variant: 2-47803500-A-AC

Previously assessed

ClinVar: ★★ ★ Pathogenic
Frequency: 0.0000
Info: ORPHA

Information
Frequency
Transcripts
Scores
Cases
Genotype
Phenotype
CNV/LOH

Copy-Neutral, Chr 2:41258-241873624

Event Details		
Copies: 2.0	Log2: 0.00	LOH: No
Chr: 2	Start: 41258	End: 241873624
Size: 241.8 Mb	Start Cytoband: p25.3	End Cytoband: q37.3

FBX011

Have we assessed this variant before?

Varhouse Clinical (a) Home Grant Lammi

[Germline](#) [Somatic](#) [CNV](#) [Methylation](#) [Analyze](#)

Somatic

 519 of 519 variants << < > >> Page 1 of 52 Show 10

Analyze	Chr	MANE	Gene	Coding	Protein	N	T	T-N	Interpretation	Pheno...	ClinVar	Frequency	Info	Effect
Sea	Selec	Search 51	Search 519 rec	Search 519 rec	Search 519 rec	Search	Search	Search	Select	Search	Select	LTE: 1.0000	Search	Select
+	15	✓	BLM	1544delA	Asn515fs	1.0% (207)	2.2% (273)	+1.2%	ASSESS-Carrier LOF		Pathogenic ★★★★★	0.0001	M O	frameshift
+	7	✓	PMS2	1239delA	Asp414fs	0.4% (263)	1.4% (289)	+1.0%	ASSESS-ACMG LOF		Pathogenic ★★★★★		M O	frameshift
+	6	✓	JARID2	1272delG	Arg425fs	0.0% (201)	2.1% (188)	+2.1%	LOF		Pathogenic ★★★★★		M	frameshift
+	8	✓	CHD7	7212_7214delGAG	Arg2405del	1.3% (312)	1.2% (253)	-0.1%			Conflict ★★★★★	0.0002	M O	inframe deletion
+	2	✓	KIF1A	2745_2753delGGA	Glu915_Glu917del	2.2% (92)	10.0% (130)	+7.8%			Conflict ★★★★★	0.0007	M O	inframe deletion
+	12	✓	KMT2D	11756_11758delAG	Gln3919del	0.8% (240)	3.4% (324)	+2.6%			Conflict ★★★★★	0.0002	M O	inframe deletion
+	5	✓	NKX2-5	639_641delGCC	Pro214del	0.9% (273)	2.3% (213)	+1.4%			Conflict ★★★★★	0.0004	M O	inframe deletion
+	9	✓	NOTCH1	7244_7246delCAC	Pro2415del	1.2% (253)	2.6% (227)	+1.4%			Conflict ★★★★★	0.0000	M O	inframe deletion
+	21	✓	RUNX1	1270T>C	Ser424Pro	7.6% (86)	13.2% (163)	+5.6%			Conflict ★★★★★	0.0002	M O	missense
+	21	✓	RUNX1	1268G>C	Arg423Pro	3.5% (57)	6.8% (59)	+3.3%			VUS ★★★★★	0	M O	missense

Variant: 15-90760908-GA-G

Not previously assessed
[Information](#) [Frequency](#) [Transcripts](#) [Scores](#) [Cases](#) [Genotype](#) [Phenotype](#) [Germline](#) [CNV/LOH](#)

Genome Popmax FAF (95%): 0 Allele Frequency: 0.0000 Allele Count: 1 Allele Number: 150,032 Number of homozygotes: 0

Exome Popmax FAF (95%): 0.0001 Allele Frequency: 0.0000 Allele Count: 11 Allele Number: 241,074 Number of homozygotes: 0

Population	Genome				Exome			
	Allele Count	Allele Number	Homozygotes	Allele Frequency	Allele Count	Allele Number	Homozygotes	Allele Frequency
African/African-American	1	40,808	0	0.0000	3	15,514	0	0.0002
Amish	0	904	0	0	-	-	-	-
Ashkenazi Jewish	0	3,448	0	0	0	9,728	0	0
East Asian	0	5,180	0	0	0	17,666	0	0
European (Finnish)	0	10,076	0	0	1	19,786	0	0.0001
European (non-Finnish)	0	67,424	0	0	7	109,306	0	0.0001
Latino/Admixed American	0	15,088	0	0	0	33,368	0	0
Middle Eastern	0	314	0	0	-	-	-	-

Have we assessed this variant before?

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[Germline](#) [Somatic](#) [CNV](#) [Methylation](#) [Analyze](#)

Gnomad Popmax Point 1 pct and Priority

 2879 of 2879 variants << < > >> Page 1 of 288 Show 10

Analyze	Chr	MANE	Gene	Coding	Protein	N	T	T-N	Interpretation	Pheno...	ClinVar	Frequency	Info	Effect
	Sea	Select	Search 28	Search 2879	Search 2879	Search	Search	Search	Select	Search	Select	LTE: 1.0000	Search	Select
+	3	✓	PIK3CA	3140A>G	His1047Arg	0.0% (342)	39.9% (153)	+39.9%			Pathogenic ★★★★	0	M O	missense
+	2	✓	AGXT	33dupC	Lys12fs	1.0% (409)	3.9% (152)	+2.9%	LOF		Pathogenic ★★★★	0.0002	M O	frameshift
+	8	✓	ESCO2	760delA	Thr254fs	2.1% (582)	2.6% (196)	+0.5%	LOF		Pathogenic ★★★★	0.0000	M O	frameshift
+	8	✓	ESCO2	760dupA	Thr254fs	0.5% (573)	2.6% (196)	+2.1%	LOF		Pathogenic ★★★★	0.0006	M O	frameshift
+	12	✓	HNF1A	863_864insC	Pro289fs	3.6% (276)	6.2% (55)	+2.6%	ASSESS-ACMG LOF		Pathogenic ★★★★	0.0005	M O	frameshift
+	12	✓	HNF1A	864delG	Pro291fs	1.4% (280)	6.1% (56)	+4.7%	ASSESS-ACMG LOF		Likely pathogenic ★★★★	0.0001	M O	frameshift
+	12	✓	HNF1A	1590G>T	Leu530Leu	0.0% (357)	7.0% (129)	+7.0%	ASSESS-ACMG DISC-CHECK				M O	synonymous
+	17	✓	PAFAH1B1	337C>T	Arg113*	0.0% (368)	3.1% (194)	+3.1%	LOF		Pathogenic ★★★★		M O	coding_sequence_stop
+	7	✓	PEX1	1108dupA	Ile370fs	1.4% (497)	3.7% (181)	+2.3%	LOF		Pathogenic ★★★★	0	M O	frameshift
+	4	✓	PROM1	1697dupA	Asn506fs	0.0% (319)	2.2% (137)	+2.2%	LOF		Pathogenic ★★★★	0.0000	M O	frameshift

Variant: 3-179234297-A-G

Previously assessed

[Information](#) [Frequency](#) [Transcripts](#) [Scores](#) [Cases](#) [Genotype](#) [Phenotype](#) [Germline](#) [CNV/LOH](#)

Pathogenicity Scores

META

0/2

Score Name	Prediction	Score	Rankscore
METALR	Tolerated	-0.56	0.61
METASVM	Tolerated	-0.56	0.66
REVEL	--	0.46	0.75

INDV PRED

5/7

Score Name	Prediction	Score	Rankscore
SIFT	Damaging	0.02	0.50
LRT	Damaging	0.00	0.84
MUTATIONTASTER	Disease causing	1.00	0.81
MUTATIONASSESSOR	Neutral	0.60	0.16

EDA Bonus...

Same
pattern...

Event pattern

Targets

Monitoring

Tags

Event pattern

Info

Edit

1 {

2 "detail-type": ["Churchill VCF Event"],

3 "source": ["org.nationwidechildrens.igm.churchill3"],

4 "detail": {

5 "project": ["clinical-cancer", "validation-cancer"]

6 }

7 }

Copy

Prod v1

Event pattern

Targets

Monitoring

Tags

Targets

Edit

Details	Target Name	Type	Arn	Input	Role
▼	igm-varhouse-clinical-cancer-Prod-ChurchillTrigger	Lambda function	arn:aws:lambda:us-east-2:257995316808:function:igm-varhouse-clinical-cancer-Prod-ChurchillTrigger	Matched event	-
Input to target:		Matched event			
Additional parameters:		--			
Dead-letter queue (DLQ):		-			

New v2

Event pattern

Targets

Monitoring

Tags

Targets

Edit

Details	Target Name	Type	Arn	Input	Role
▼	igm-varhouse2-clinical-cancer-Prod-ChurchillTrigger	Lambda function	arn:aws:lambda:us-east-2:257995316808:function:igm-varhouse2-clinical-cancer-Prod-ChurchillTrigger	Matched event	-
Input to target:		Matched event			
Additional parameters:		--			
Dead-letter queue (DLQ):		-			

EDA is really great...

- Works now for us in prod, under load
- Design that allows of expandability
 - Updates to the annotations
 - Shopping cart saves to the database
- As many environments as you want

...especially for **clinical** stuff

Thanks!

<https://www.nationwidechildrens.org/specialties/institute-for-genomic-medicine>

@glammi



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