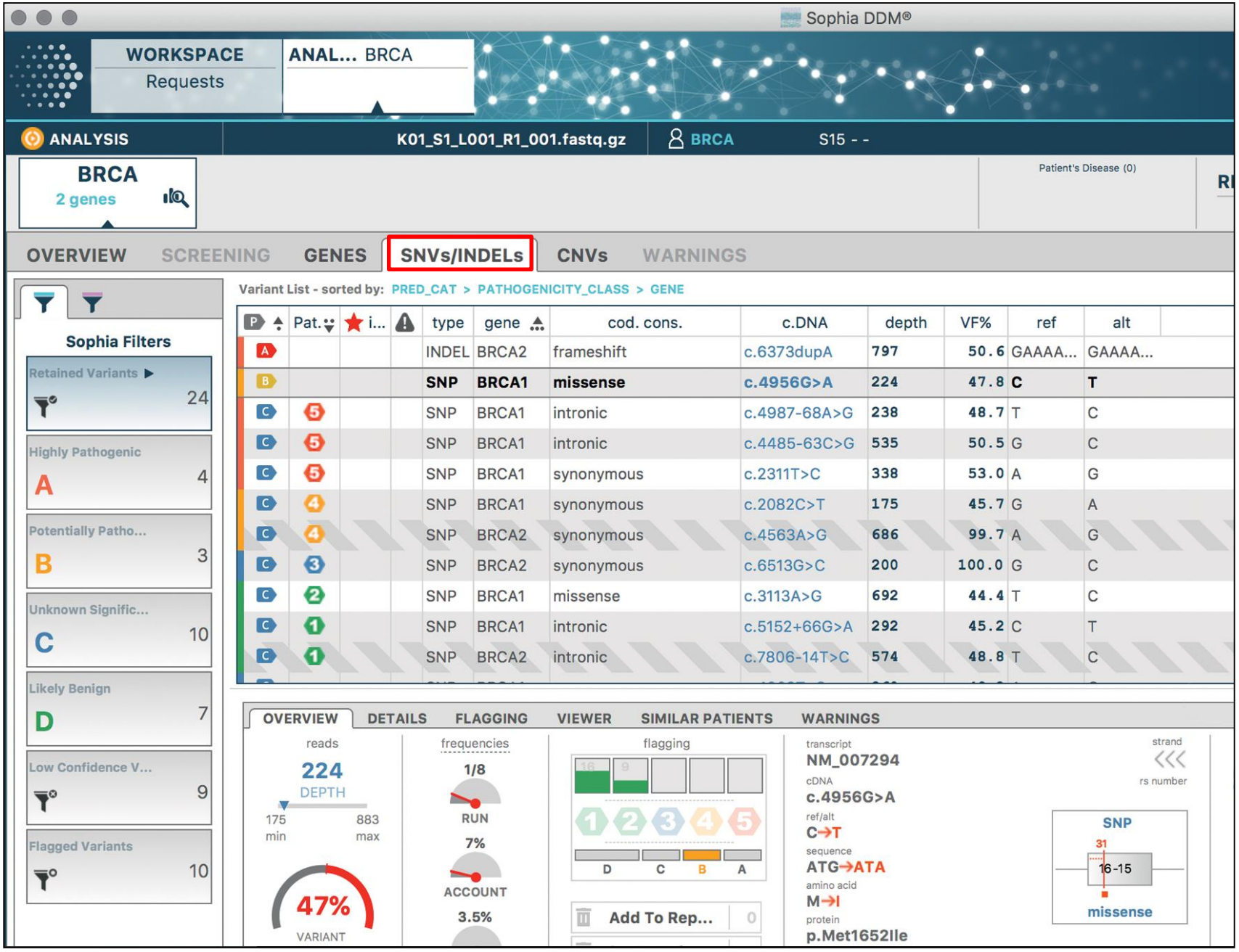
Note

Since we conducted the interviews in German language, these slides were translated for this publication.

1. SOPHiA GENETICS

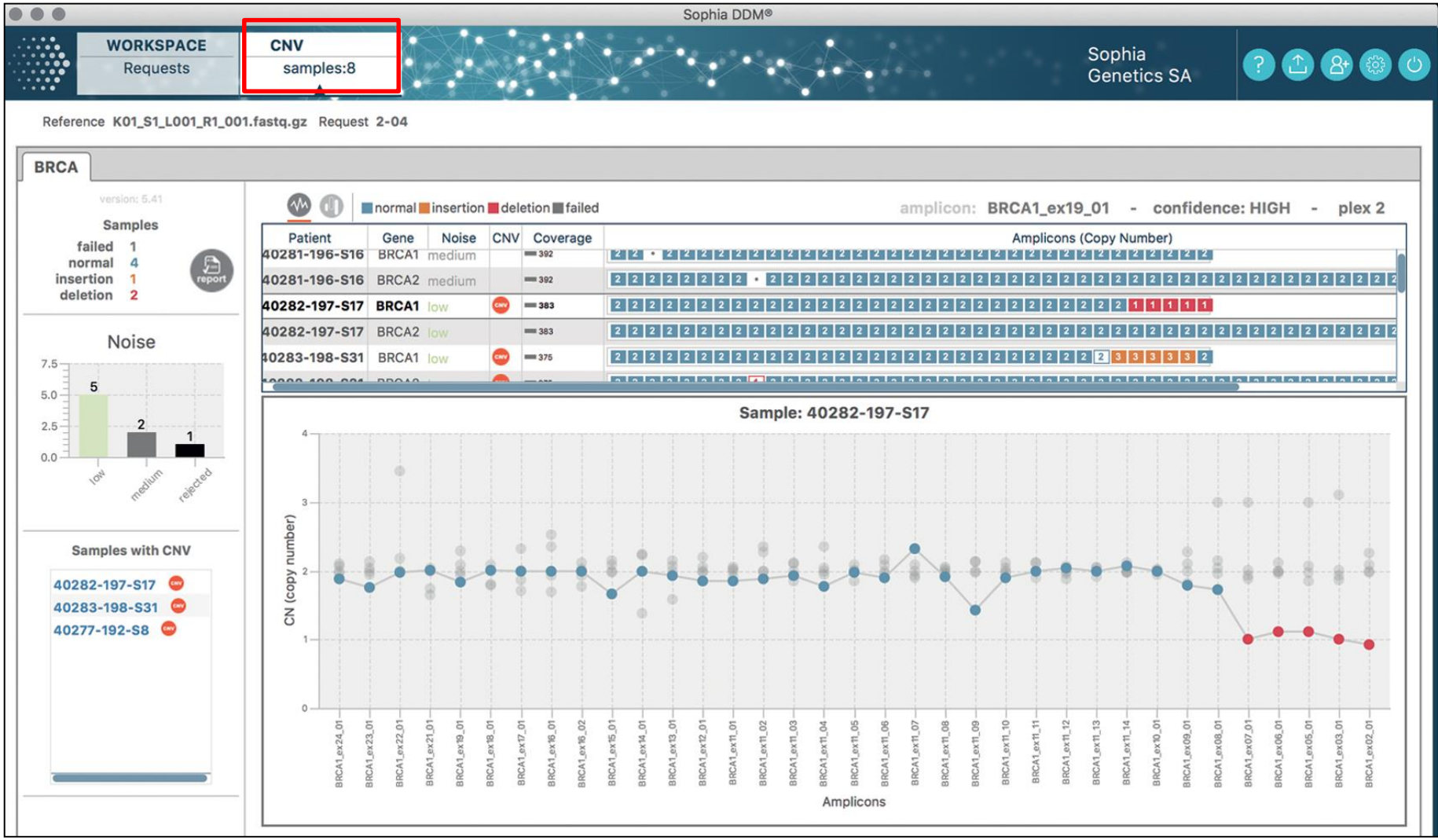
Online platform for analysis of high-throughput sequencing data and clinical interpretation of variants. It is also possible to share the evaluation of variants with other institutions.

SNV/INDELs



Requirements Analysis and Specification for a Molecular Tumor Board Platform Based on cBioPortal (Buechner P. et al.)
Supplementary File 4: Presentation of potential tools

CNVs



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Variants Report

SOPHiA GENETICS

Variant Report

Patient
First name:
Last name:
Patient ID: **SG10000002**
DOB: **2 Jan 1967**
Gender: **Female**
Father ethnicity: **-- Unknown --**
Mother ethnicity: **-- Unknown --**

Analysis by
SOPHiA™
The AI for Data-Driven Medicine

Analysis
Analysis ID: **40538**
MID: **S2**
Request run date:
Request run name: **HCS by Sophia**

RESULTS

SNVs/INDELs (selected in report)

Gene Transcript	Exon	c.DNA Protein alteration	Variant Fraction Coverage (ref / alt)	Coding consequence	Pathogenicity	ClinVar
BRCA1 NM_007294	10	c.4065.4068delTCAA p.Asn1355Lysfs*10	47.3 % (785 / 709)	frameshift	Prediction A I Highly Pathogenic	rs80357508
comment: The detected variant is highly pathogenic						

SNVs/INDELs (retained)

Gene Transcript	Exon	c.DNA Protein alteration	Variant Fraction Coverage (ref / alt)	Coding consequence	Pathogenicity	ClinVar
ATM NM_000051	3	c.146C>G p.Ser49Cys	51.7 % (1009 / 1081)	missense	Prediction B I Potentially Pathogenic	rs1800054
ATM NM_000051	40	c.5948A>G p.Asn1983Ser	100.0 % (0 / 1750)	missense	Prediction C I Unknown Significance	rs659243
BARD1 NM_000465	1	c.70C>T p.Pro24Ser	48.75 % (818 / 778)	missense	Prediction C I Unknown Significance	rs1048108
BARD1 NM_000465	6	c.1518T>C p.= (p.His506His)	100.0 % (0 / 1753)	synonymous	Prediction C I Unknown Significance	rs2070093

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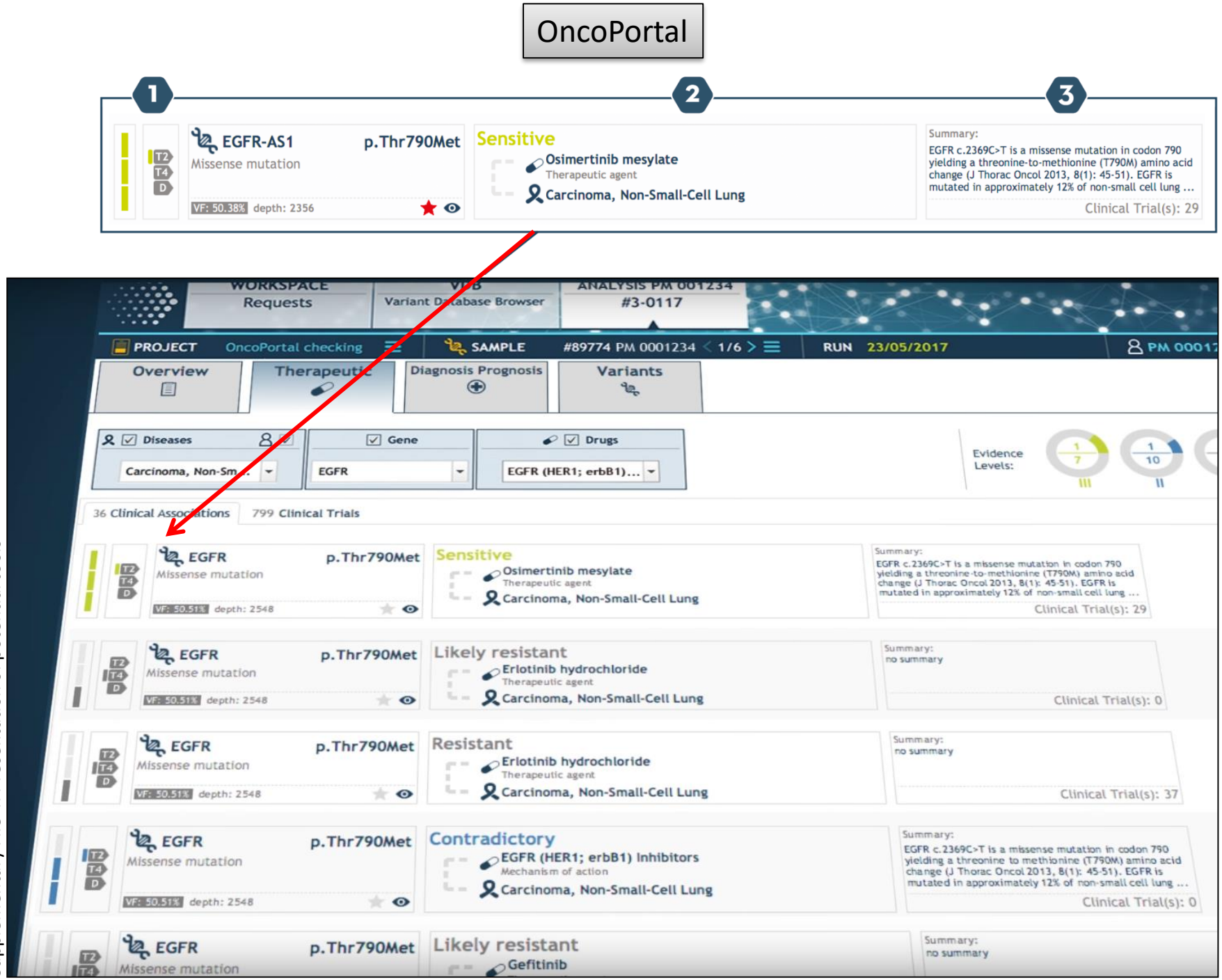
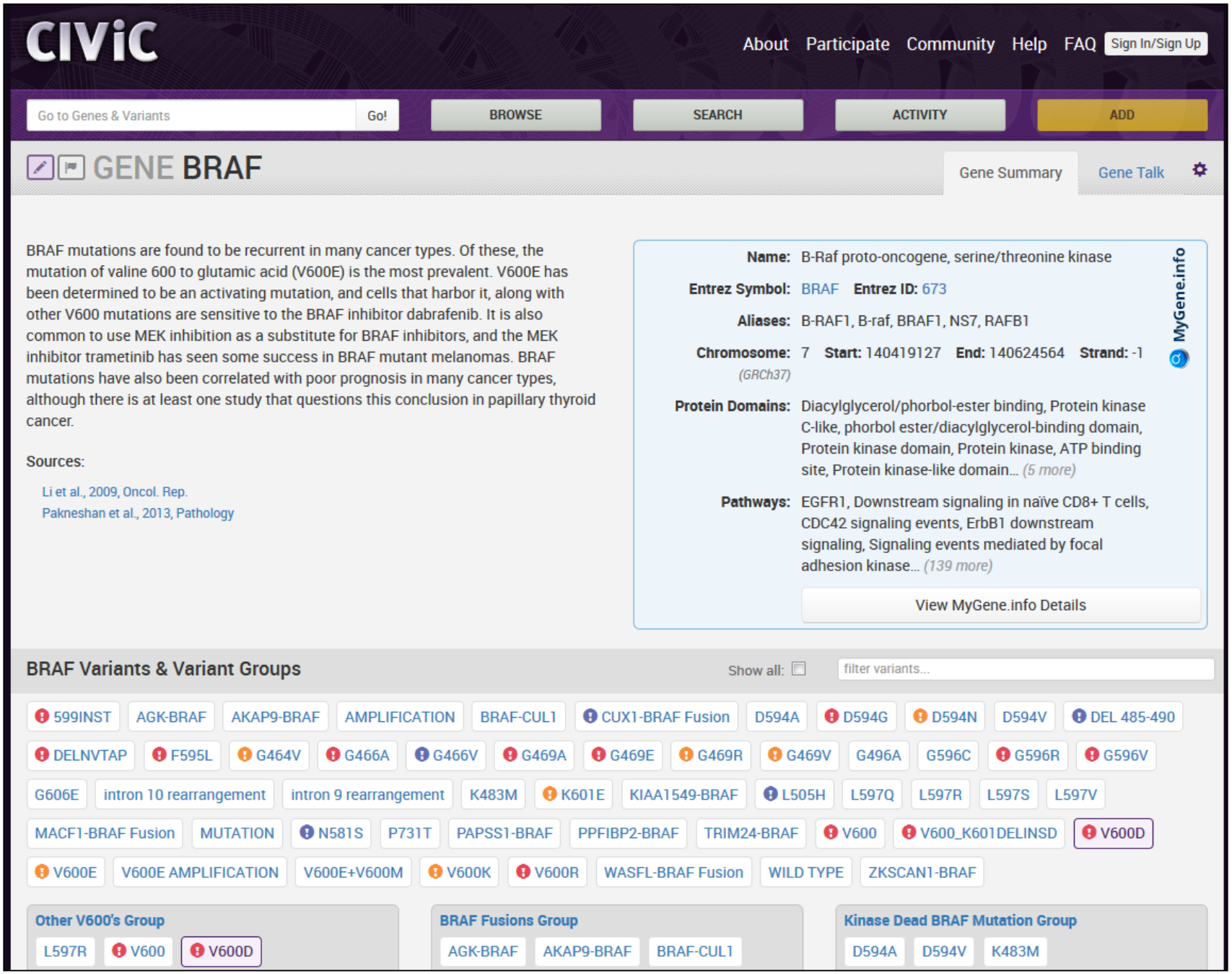


2. CIViC

Cites from CIViC homepage & nature paper:

- *"CIViC is an **open access, open source**, community-driven web resource for Clinical Interpretation of Variants in Cancer."*
- *"CIViC is an **expert-crowdsourced knowledgebase** for Clinical Interpretation of Variants in Cancer describing the therapeutic, prognostic, diagnostic and predisposing relevance of inherited and somatic variants of all types"*


CIViC
About
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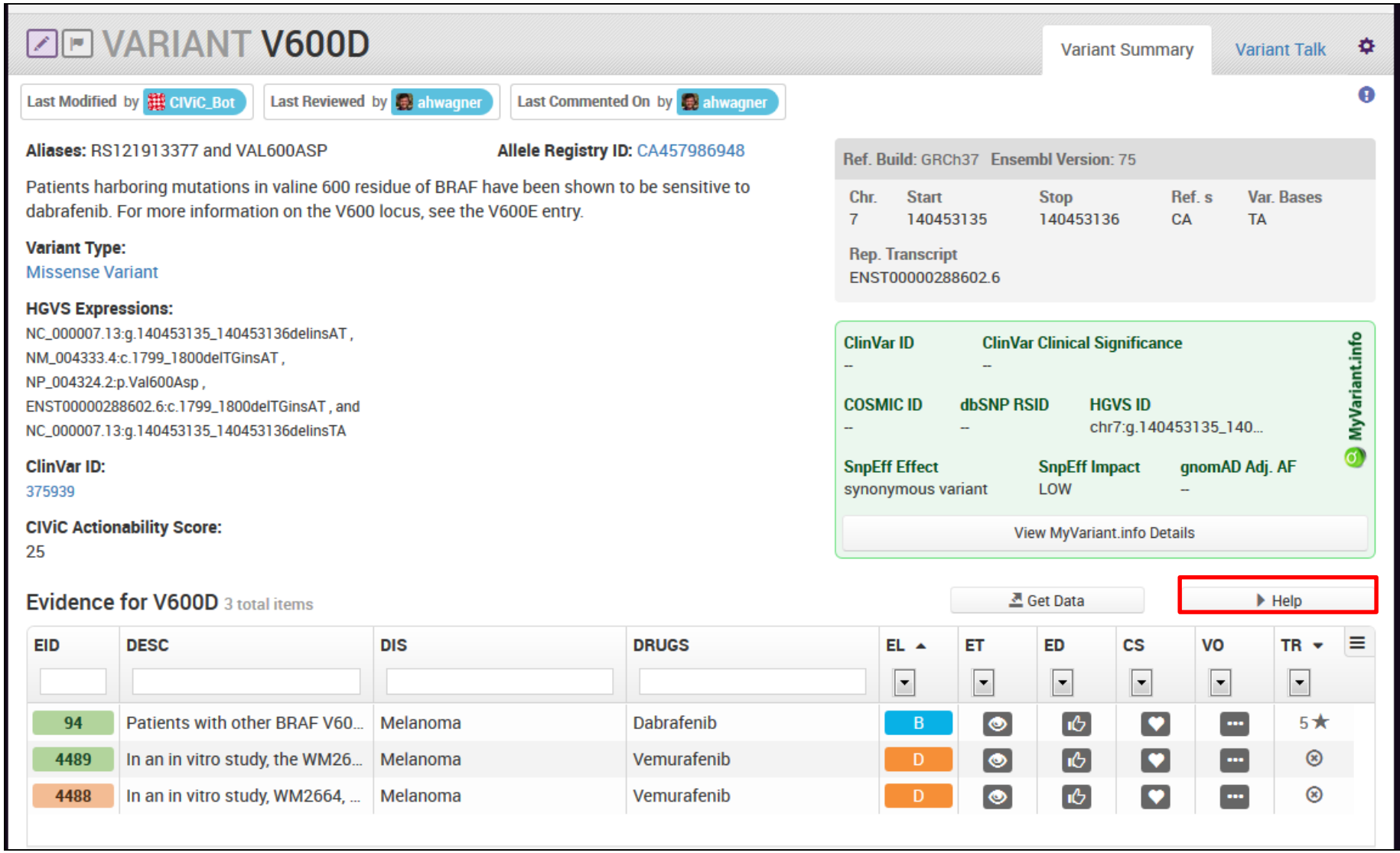
Help
FAQ
Sign In/Sign Up
Go to Genes & Variants
Go!
BROWSE
SEARCH
ACTIVITY
ADD
GENE BRAF
Gene Summary
Gene Talk
BRAF mutations are found to be recurrent in many cancer types. Of these, the mutation of valine 600 to glutamic acid (V600E) is the most prevalent. V600E has been determined to be an activating mutation, and cells that harbor it, along with other V600 mutations are sensitive to the BRAF inhibitor dabrafenib. It is also common to use MEK inhibition as a substitute for BRAF inhibitors, and the MEK inhibitor trametinib has seen some success in BRAF mutant melanomas. BRAF mutations have also been correlated with poor prognosis in many cancer types, although there is at least one study that questions this conclusion in papillary thyroid cancer.
Sources:
Li et al., 2009, Oncol. Rep.
Pakneshan et al., 2013, Pathology
Name: B-Raf proto-oncogene, serine/threonine kinase
Entrez Symbol: BRAF Entrez ID: 673
Aliases: B-RAF1, B-raf, BRAF1, NS7, RAFB1
Chromosome: 7 Start: 140419127 End: 140624564 Strand: -1
(GRCh37)
Protein Domains: Diacylglycerol/phorbol-ester binding, Protein kinase C-like, phorbol ester/diacylglycerol-binding domain, Protein kinase domain, Protein kinase, ATP binding site, Protein kinase-like domain... (5 more)
Pathways: EGFR1, Downstream signaling in naïve CD8+ T cells, CDC42 signaling events, ErbB1 downstream signaling, Signaling events mediated by focal adhesion kinase... (139 more)
MyGene.info
View MyGene.info Details
BRAF Variants & Variant Groups
Show all:
filter variants...
599INST
AGK-BRAF
AKAP9-BRAF
AMPLIFICATION
BRAF-CUL1
CUX1-BRAF Fusion
D594A
D594G
D594N
D594V
DEL 485-490
DELNVTAP
F595L
G464V
G466A
G466V
G469A
G469E
G469R
G469V
G496A
G596C
G596R
G596V
G606E
intron 10 rearrangement
intron 9 rearrangement
K483M
K601E
KIAA1549-BRAF
L505H
L597Q
L597R
L597S
L597V
MACF1-BRAF Fusion
MUTATION
N581S
P731T
PAPSS1-BRAF
PPFIBP2-BRAF
TRIM24-BRAF
V600
V600_K601DELINSD
V600D
V600E
V600E AMPLIFICATION
V600E+V600M
V600K
V600R
WASFL-BRAF Fusion
WILD TYPE
ZKSCAN1-BRAF
Other V600's Group
L597R
V600
V600D
BRAF Fusions Group
AGK-BRAF
AKAP9-BRAF
BRAF-CUL1
Kinase Dead BRAF Mutation Group
D594A
D594V
K483M



VARIANT V600D

Variant Summary | Variant Talk

Last Modified by CIViC_Bot | Last Reviewed by ahwagner | Last Commented On by ahwagner

Aliases: RS121913377 and VAL600ASP

Allele Registry ID: CA457986948

Patients harboring mutations in valine 600 residue of BRAF have been shown to be sensitive to dabrafenib. For more information on the V600 locus, see the V600E entry.

Variant Type:
Missense Variant

HGVS Expressions:
NC_000007.13:g.140453135_140453136delinsAT ,
NM_004333.4:c.1799_1800delTGinsAT ,
NP_004324.2:p.Val600Asp ,
ENST00000288602.6:c.1799_1800delTGinsAT , and
NC_000007.13:g.140453135_140453136delinsTA

ClinVar ID:
375939

CIViC Actionability Score:
25

Ref. Build: GRCh37 Ensembl Version: 75

Chr.	Start	Stop	Ref. s	Var. Bases
7	140453135	140453136	CA	TA

Rep. Transcript
ENST00000288602.6

ClinVar ID	ClinVar Clinical Significance
--	--

COSMIC ID	dbSNP RSID	HGVS ID
--	--	chr7:g.140453135_140...

SnpEff Effect	SnpEff Impact	gnomAD Adj. AF
synonymous variant	LOW	--

MyVariant.info

View MyVariant.info Details

Evidence for V600D 3 total items

Get Data | Help

EID	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
94	Patients with other BRAF V60...	Melanoma	Dabrafenib	B					5★
4489	In an in vitro study, the WM26...	Melanoma	Vemurafenib	D					
4488	In an in vitro study, WM2664, ...	Melanoma	Vemurafenib	D					

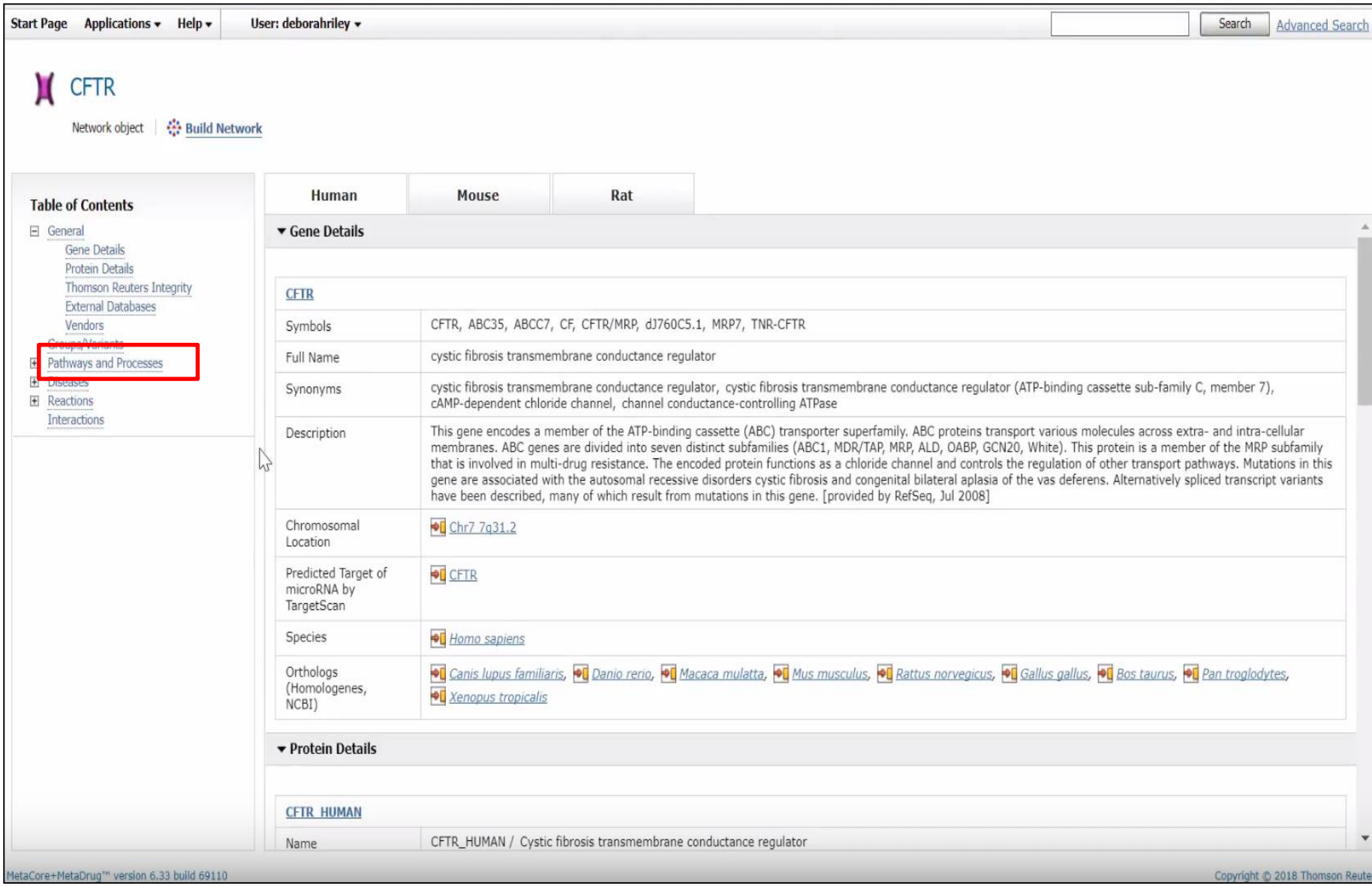
Column Abbreviation	Column Description
EID	Evidence ID Number
	Submitted
	Accepted
	Rejected
	Has pending revisions
DESC	Evidence Description
DIS	Disease
DRUG	Drug(s)
EL	Evidence Level
	A Validated
	B Clinical
	C Case Study
	D Preclinical
	E Inferential
ET	Evidence Type
	Predictive
	Diagnostic
	Prognostic
	Predisposing

Column Abbreviation	Column Description
ED	Evidence Direction
	Supports
	Does Not Support
CS	Clinical Significance
	Sensitivity/Response
	Resistance
	Better Outcome
	Poor Outcome
	Positive
	Negative
	Adverse Response
	Reduced Sensitivity
	Pathogenic
	Likely Pathogenic
	Benign
	Likely Benign
	Uncertain Significance
	N/A
VO	Variant Origin
	Germline Mutation
	Somatic Mutation
	Germline Polymorphism
	Unknown

3. Clarivate MetaCore® / Key Pathway Advisor®

commercial product
just for comparison with industrial products
no replacement for cBioPortal

Übersicht MetaCore



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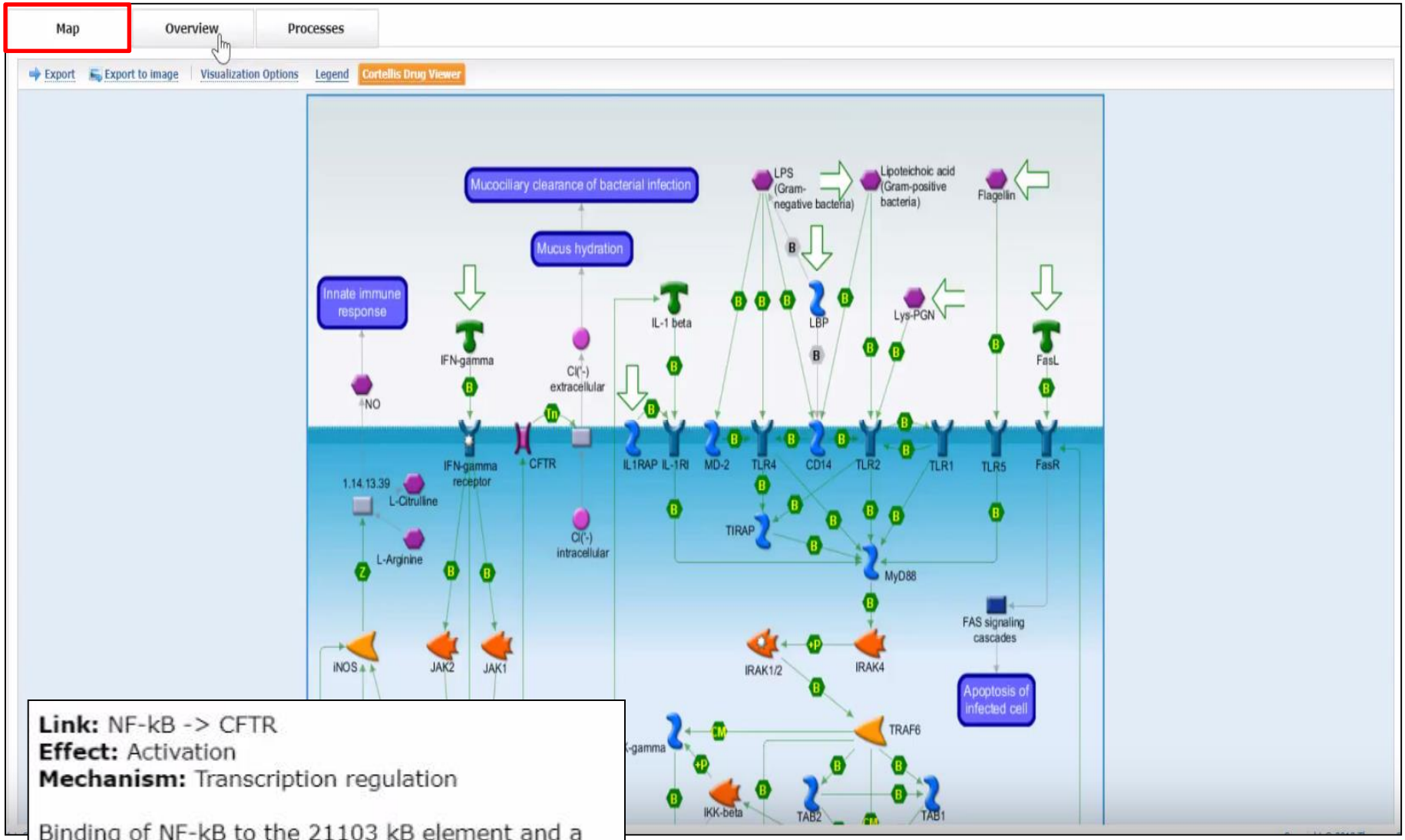
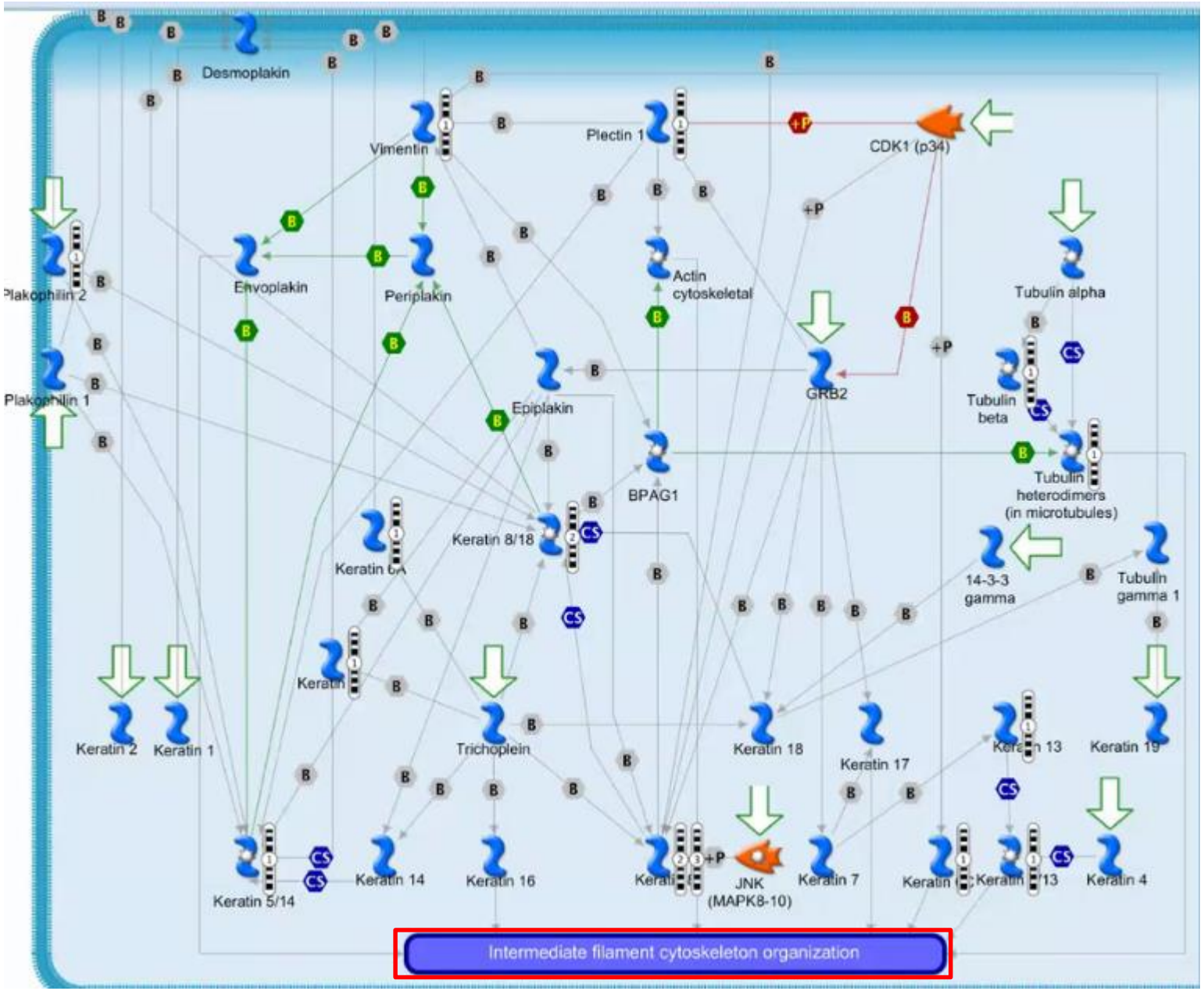
MetaCore: Map 1



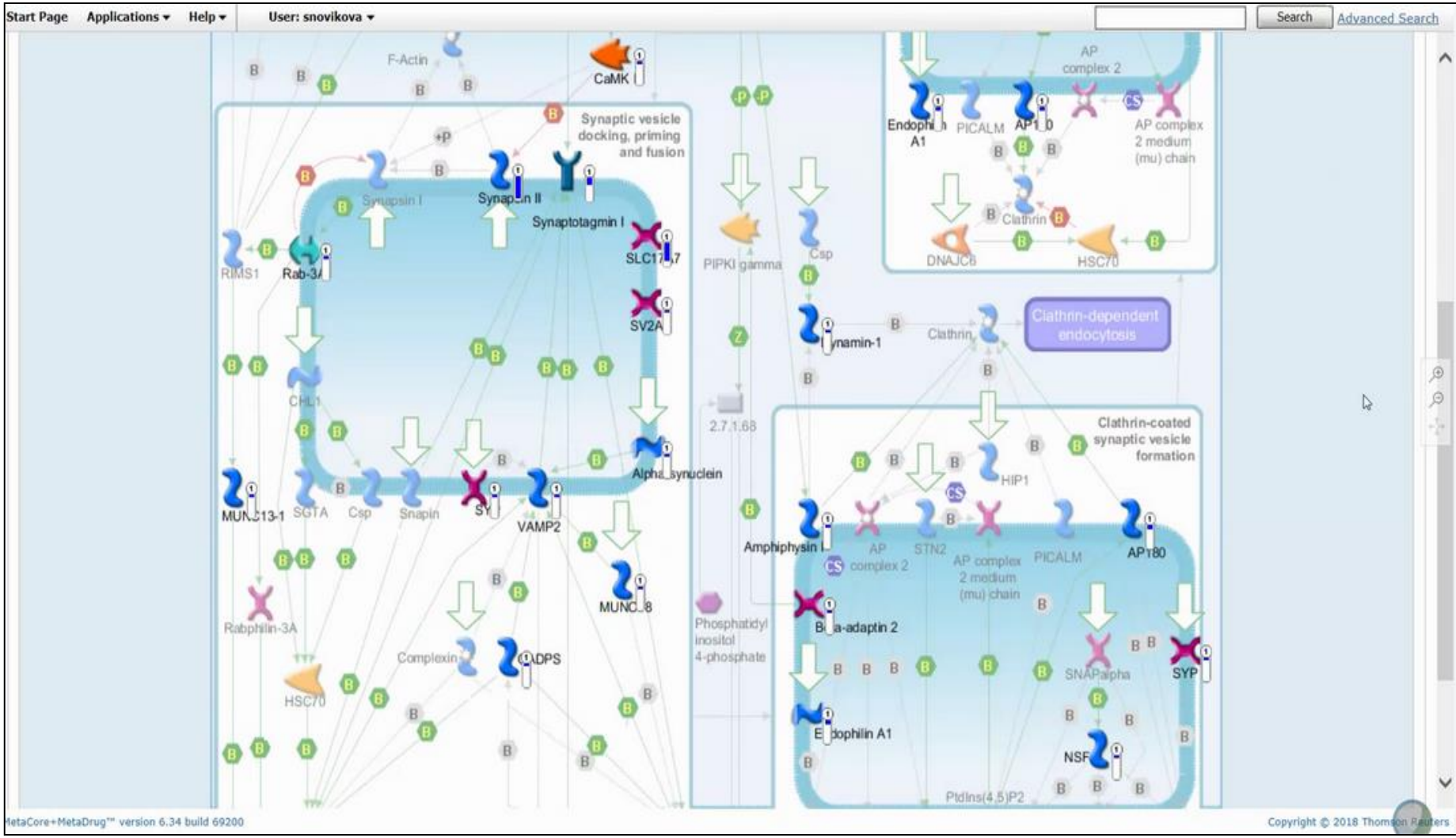
Link: NF-kB -> CFTR
Effect: Activation
Mechanism: Transcription regulation

Binding of NF-kB to the 21103 kB element and a subsequent increase in CFTR promoter activity leads to CFTR mRNA increase in response to IL-1 beta in Calu-3 cells.

MetaCore: Map 2



MetaCore: Map 3



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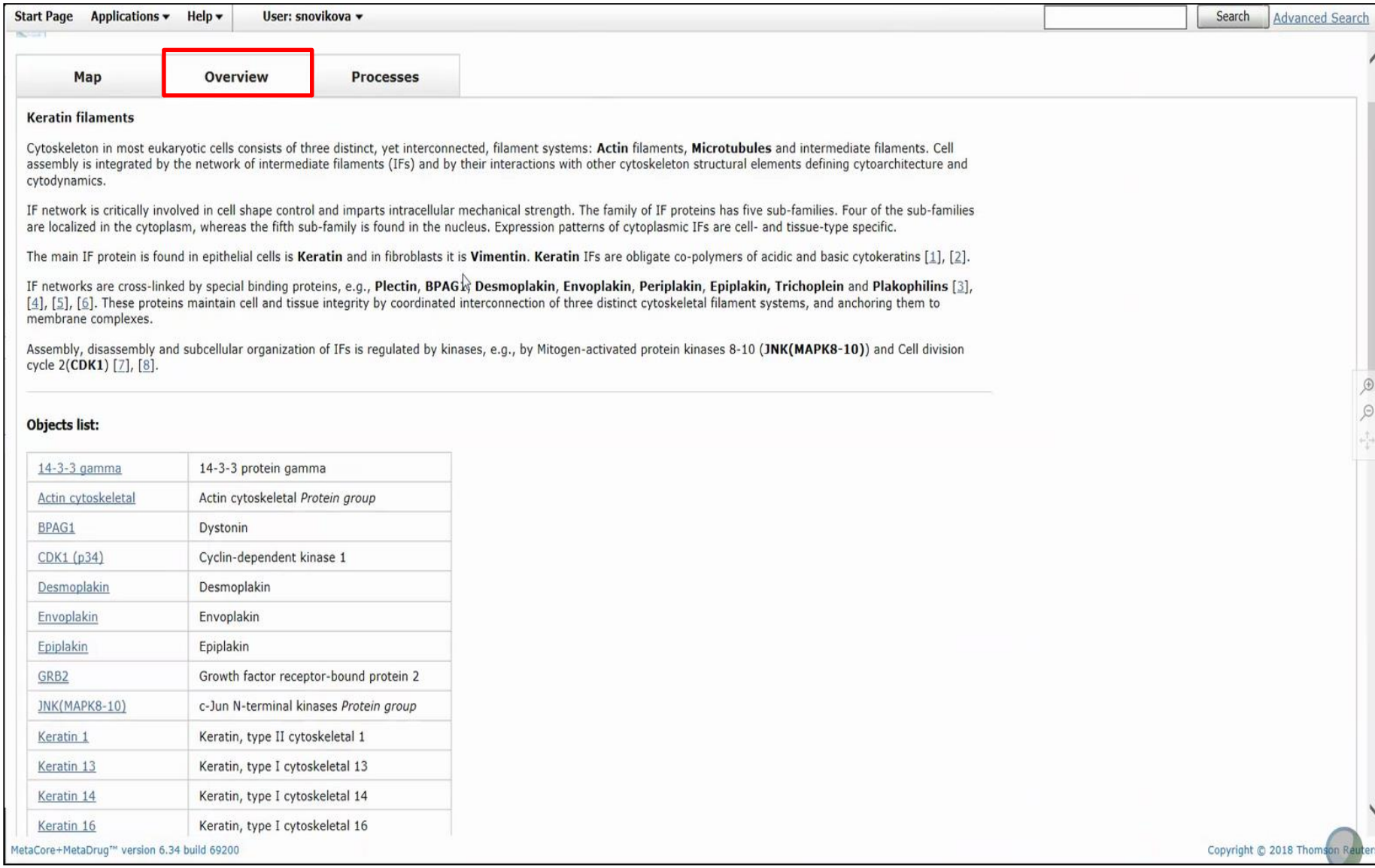
Übersicht MetaCore



MetaCore: Legende

METACORE QUICK REFERENCE GUIDE

USER DATA

NETWORKS

- Up-regulated (+) — Object has user data with positive value
- Down-regulated (-) — Object has user data with negative value
- Mixed-signal (+/-) — Object has user data with both positive and negative values
- Gene variants — Object has user data with gene variants
- Mixed data — Object has user data with both expression values and gene variants

MAPS

NETWORK OBJECTS

ENZYMES

- Generic enzyme

KINASE
- Generic kinase
- Protein kinase
- Lipid kinase

PHOSPHATASE
- Generic phosphatase
- Protein phosphatase
- Lipid phosphatase

PHOSPHOLIPASE
- Generic phospholipase

PROTEASE
- Generic protease
- Metalloprotease

GTPASE
- G-alpha
- RAS - superfamily

GENERIC CLASSES

- Receptor ligand
- Transcription factor
- Protein
- Compound
- Predicted metabolite or user's structure
- Inorganic ion
- Reaction
- DNA
- RNA
- Generic binding protein

CHANNELS/TRANSPORTERS

- Generic channel
- Ligand-gated ion channel
- Voltage-gated ion channel
- Transporter

RECEPTORS

- Generic
- GPCR
- Receptors with kinase activity

G PROTEIN ADAPTOR/REGULATORS

- G beta/gamma
- Regulators (GDI, GAP, GEF, etc.)

GROUPS OF OBJECTS

- A complex or a group — Proteins physically connected into a complex or related as a family
- Logical association — Proteins linked by logical relations or physical interactions
- Custom association — Group of collapsed objects chosen by user

INTERACTIONS BETWEEN OBJECTS

EFFECTS

- Positive / activation
- Negative / inhibition
- Unspecified

MECHANISMS

PHYSICAL INTERACTIONS

- Binding — Physical interaction between molecules
- Cleavage — Cleavage of a protein at a specific site yielding distinctive peptide fragments. Proteolytic cleavage can be carried out by both enzymes and compounds
- Covalent modifications — Covalent binding of a small chemical groups to protein amino acids or DNA/RNA nucleotides.
- Phosphorylation — Protein activity is altered via addition of a phosphate group
- Dephosphorylation — Protein activity is altered via removal of a phosphate group
- Transformation — Protein activity regulation by binding & hydrolysis of GTP
- Transport — Transport of a protein or a compound between organelles
- Catalysis — Catalysis of an enzymatic reaction
- Transcription regulation — Physical binding of a transcription factor to target gene's promoter
- Co-regulation of transcription — Influences on gene expression by direct binding with transcription machinery or by chromatin remodelling
- Regulation — Influence on the biochemical reaction by changing its composition
- MicroRNA binding — Regulation of gene expression by binding of microRNA to target mRNA

FUNCTIONAL INTERACTIONS

- Influence on expression — Indirect influence of chemical compound or protein on the amount of another protein
- Competition — When two molecules compete for the interaction with the third molecule
- Unspecified interactions — Influence on activity of protein or RNA without determined mechanism
- Processing — Protein is a product of posttranslational modification.
- Drug-Drug interactions. Pharmacological effect — Drugs change pharmacological effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters
- Drug-Drug interactions. Toxic effect — Drugs change toxic effects of other drugs, for instance by competing for drug metabolism enzymes or organic transporters

LOGICAL RELATIONS

- Group relation — Object belongs to a generic group of related objects
- Complex subunit — Protein is a subunit of a protein complex
- Similarity relation — Chemically similar compounds with chosen Tanimoto similarity score

LINKS ON NETWORKS

- Incoming interaction — When the mouse is over object, yellow link indicates direction to object
- Outgoing interaction — Cyan link indicates direction FROM the object

INTERACTIONS FROM CUSTOM LIST (MetaLink™)

- Interaction is in the network — Interaction is represented by a thin solid line and is highlighted in blue
- Interaction is in the base, but not in network — Interaction is highlighted in yellow
- Interaction is in the network — Interaction is highlighted in magenta

CANONICAL PATHWAYS

- Canonical pathway — The link is highlighted in a thick cyan or magenta line

LINKS ON MAPS

- Disrupts in disease
- Weakens in disease
- Emerges in disease
- Enhances in disease
- Species specific interactions

OBJECTS ON MAPS

LOCALIZATION

- Mitochondria
- EPR
- Golgi
- Nucleus
- Lysosome
- Peroxisome
- Cytoplasm
- Extracellular

OTHER MAP OBJECTS

Comments
- Note
- Normal process
- Pathological process

Blocks
- Normal process
- Pathological process

- Species specific object
- Path start

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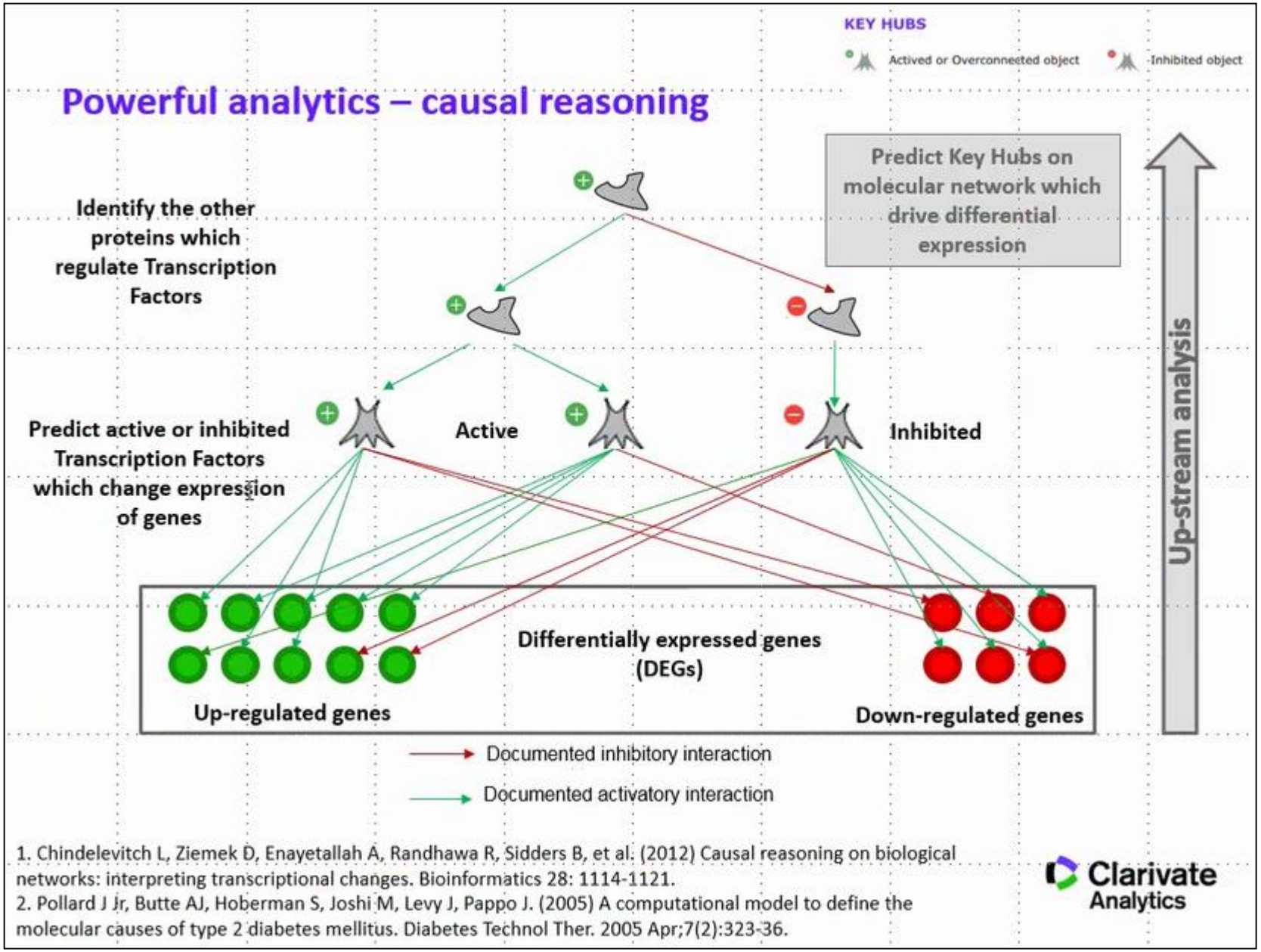
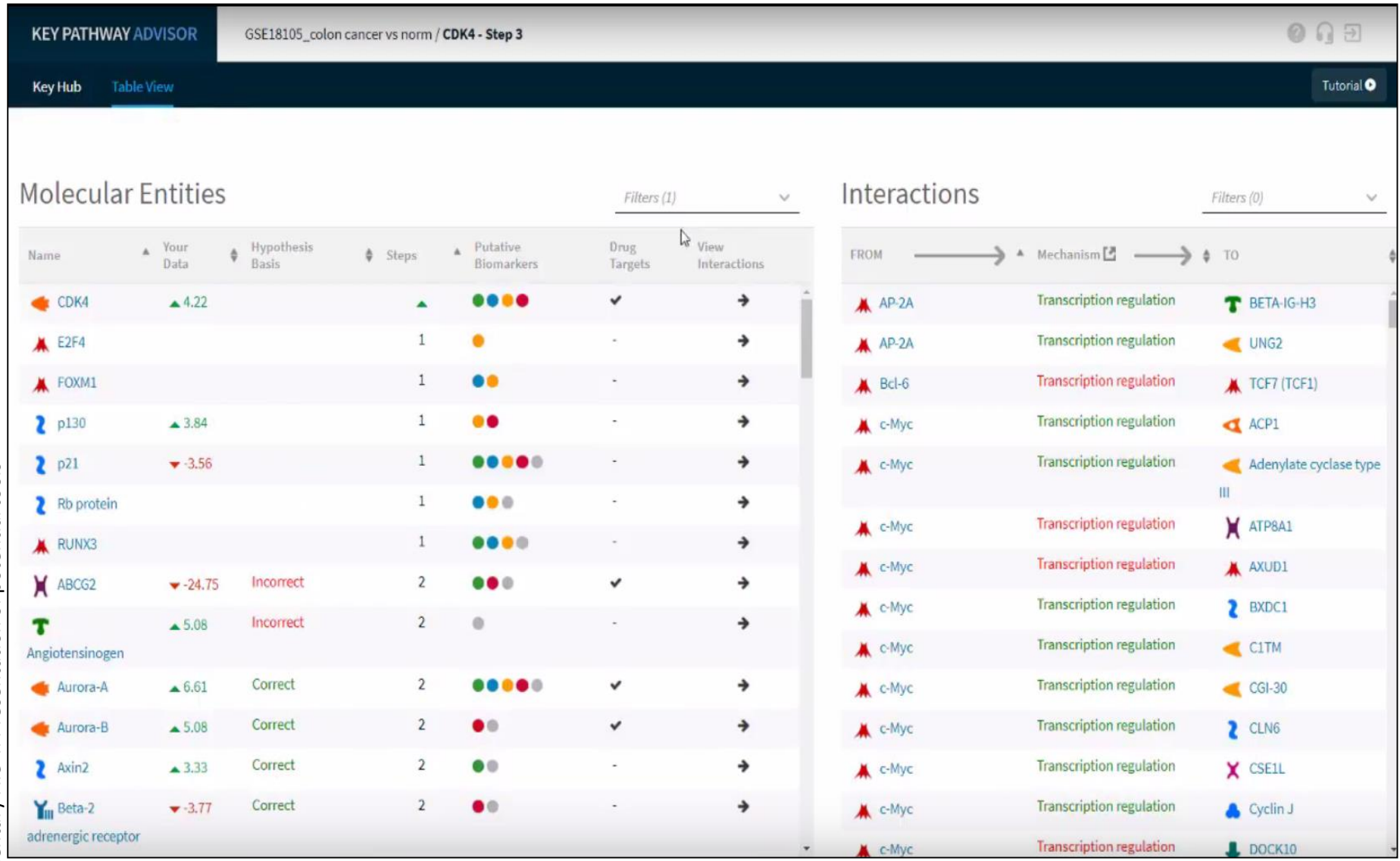
Kurzbeschreibung aus der Clarivate Sales Powerpoint-Präsentation



Key Pathway Advisor: Entities <-> Interactions



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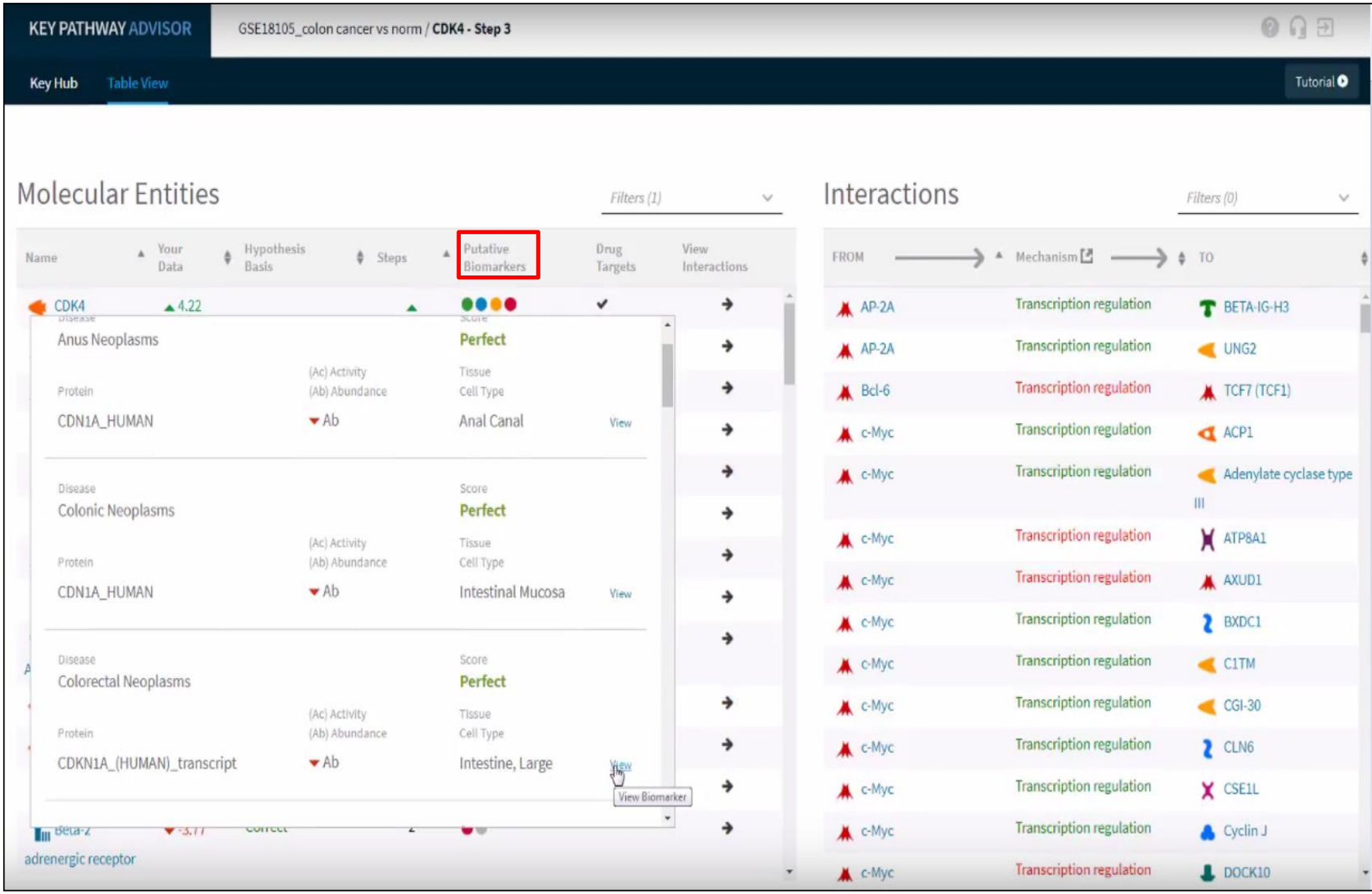
Key Pathway Advisor: Putative Biomarkers



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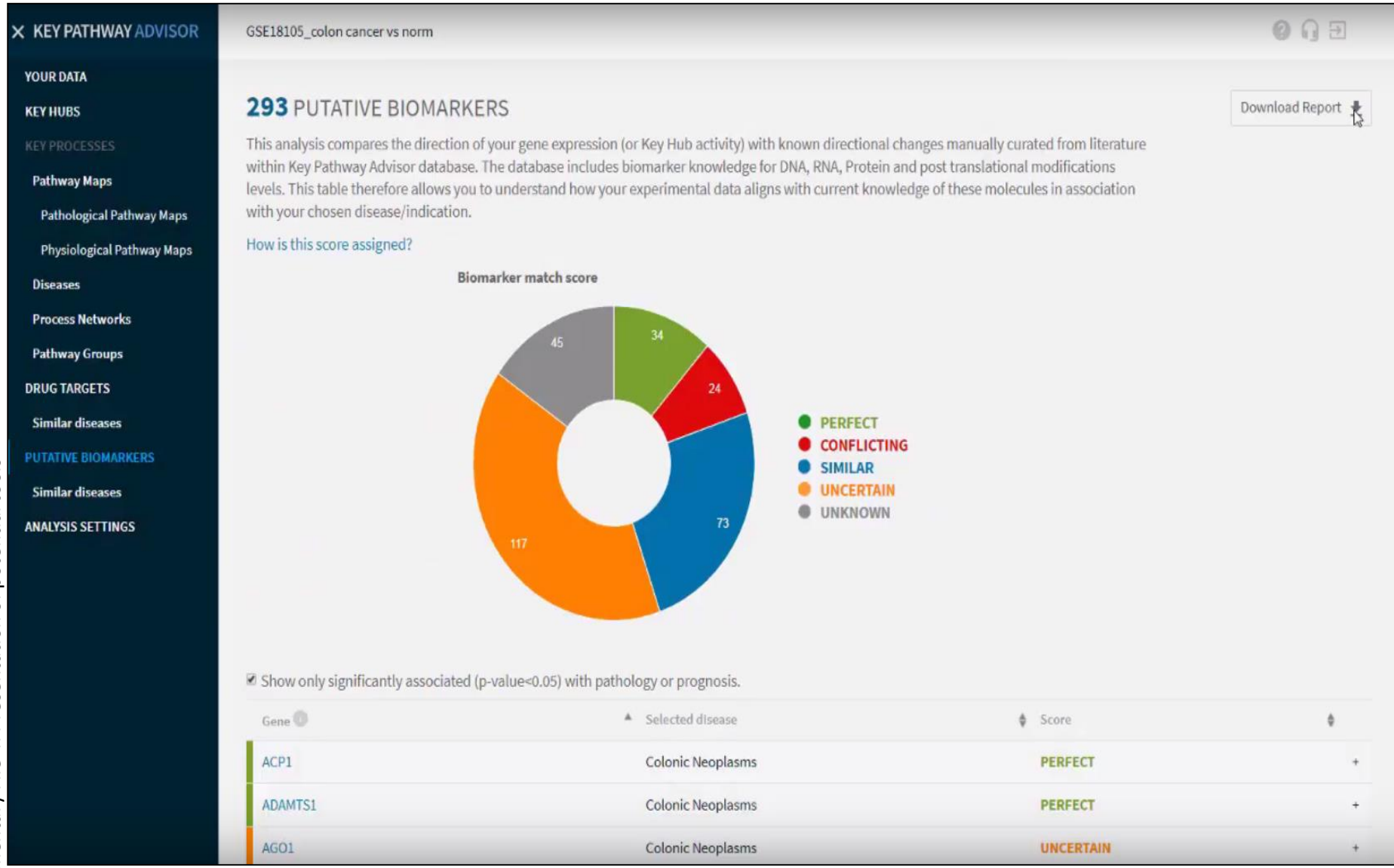
Key Pathway Advisor: Putative Biomarkers



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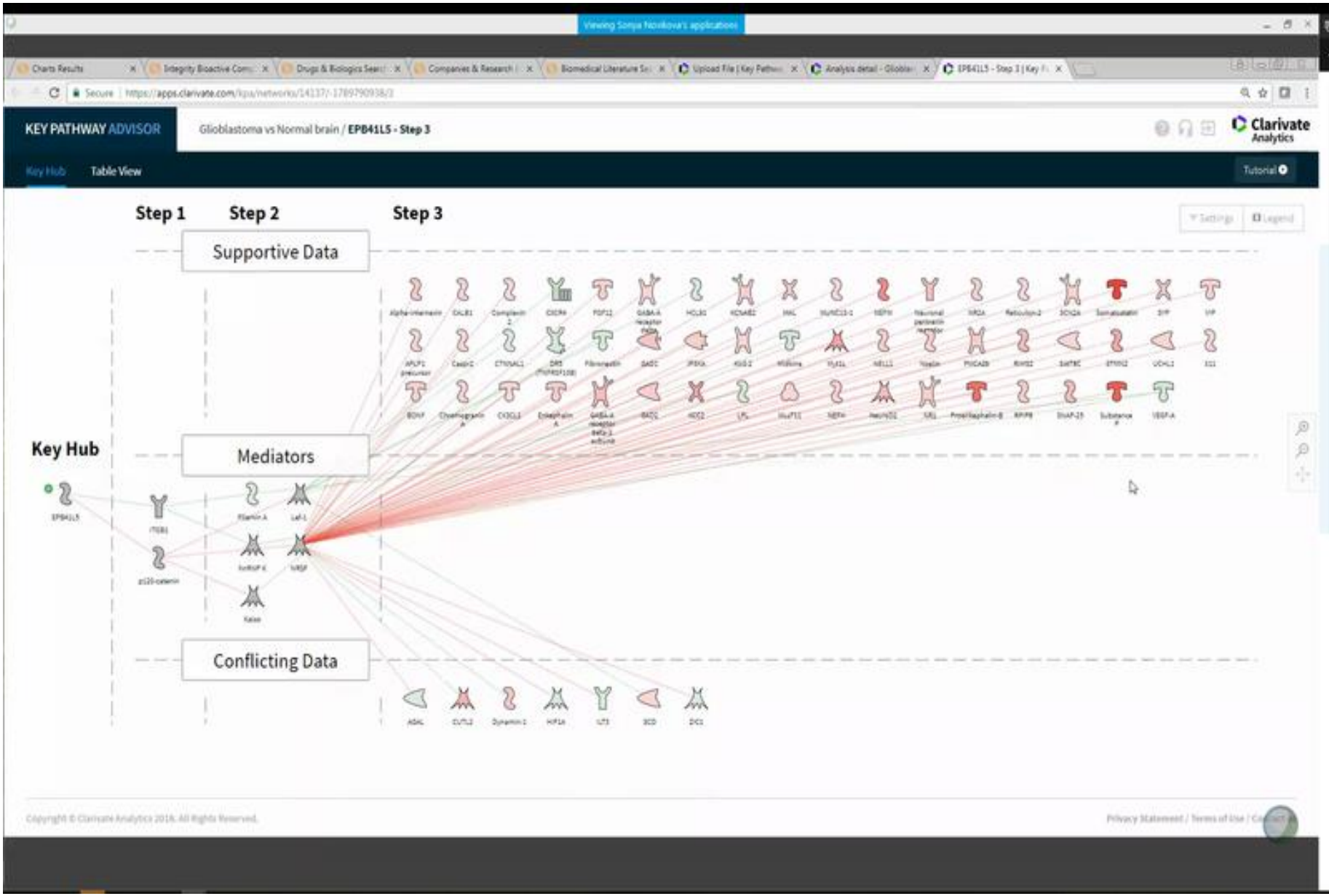
Key Pathway Advisor: Key Hub



4. COMPASS™ for My Geisinger