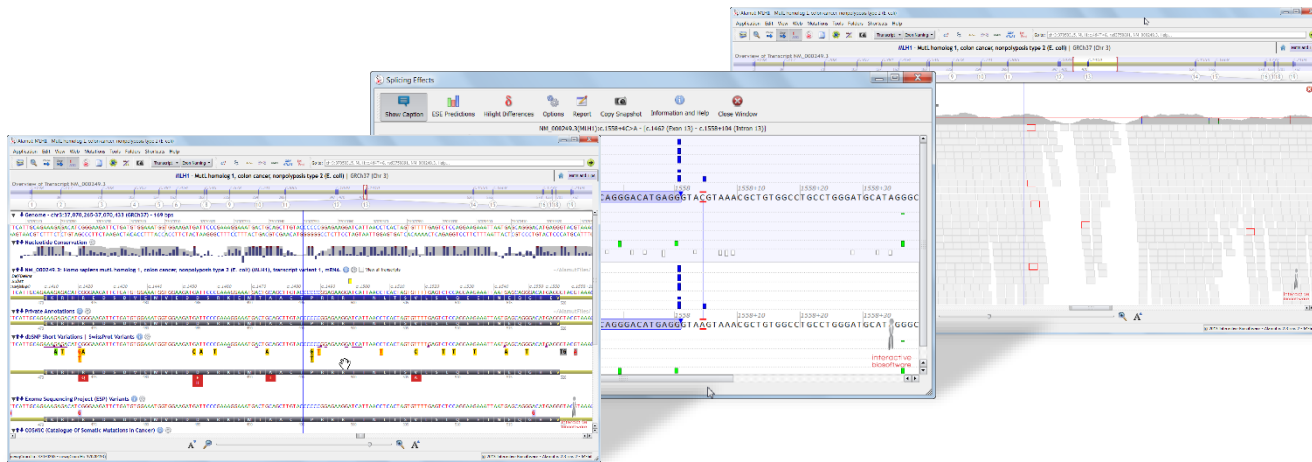




interactive  
biosoftware





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# Société



- Créée en 2007
- Basée à Rouen
- Editeur de logiciels pour la biologie moléculaire
- Principaux produits:





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# Produits

---

- Alamut Visual

- Système d'aide à l'interprétation de variations en génétique humaine
- Analyse visuelle – Bas débit



- Alamut Batch

- Annotation de variants pour le NGS
- Analyse automatisée – Haut débit



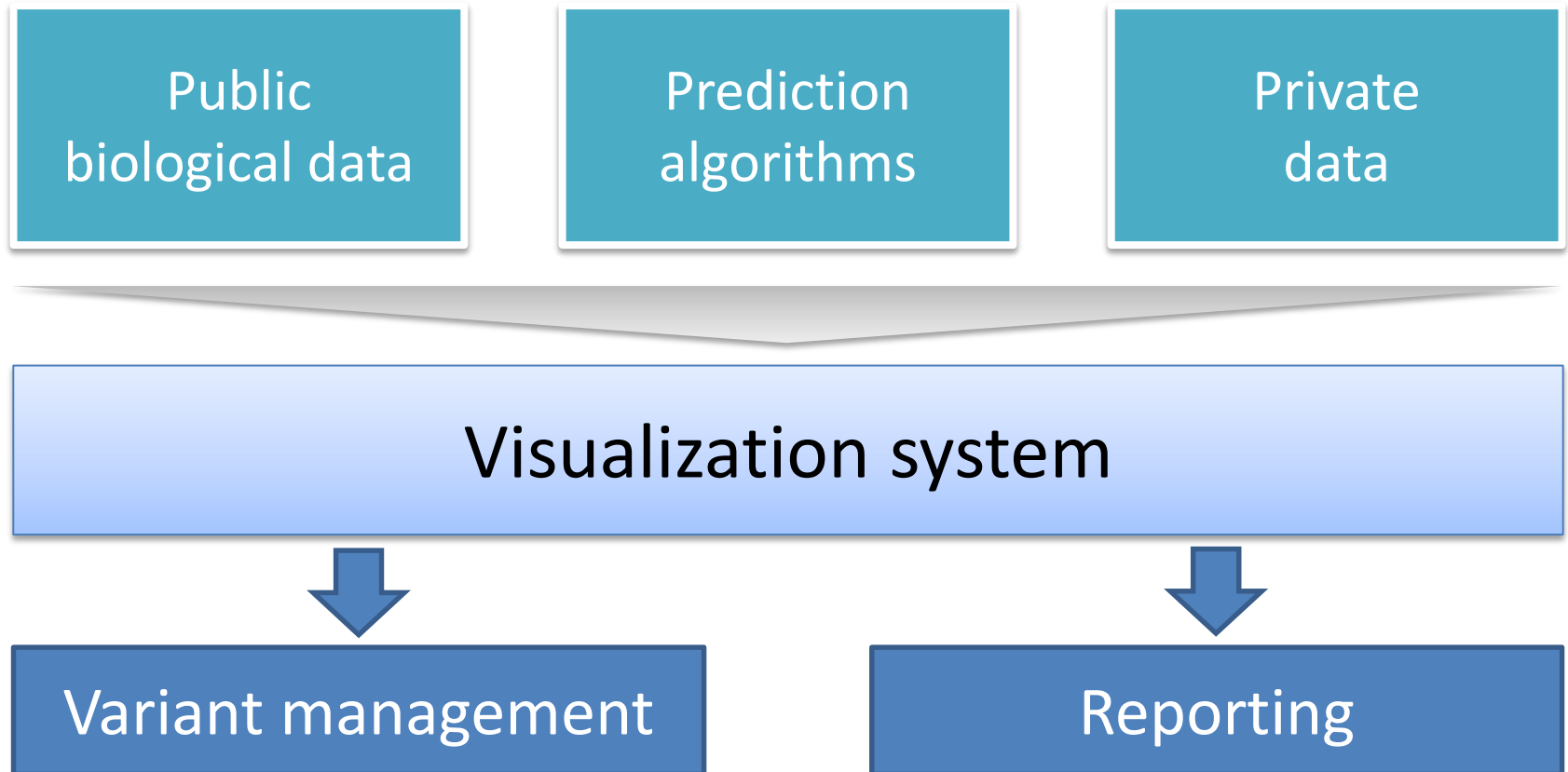
- Alamut Focus



# Alamut Visual

---

- Améliorer la productivité de l'interprétation de variants
  - Convivialité
  - Données pertinentes et à jour
  - Algorithmes de prédiction reconnus
- Support des bonnes pratiques
- Evoluer avec les avancées techniques et scientifiques





# alamut visual

# Visualization system

## Data

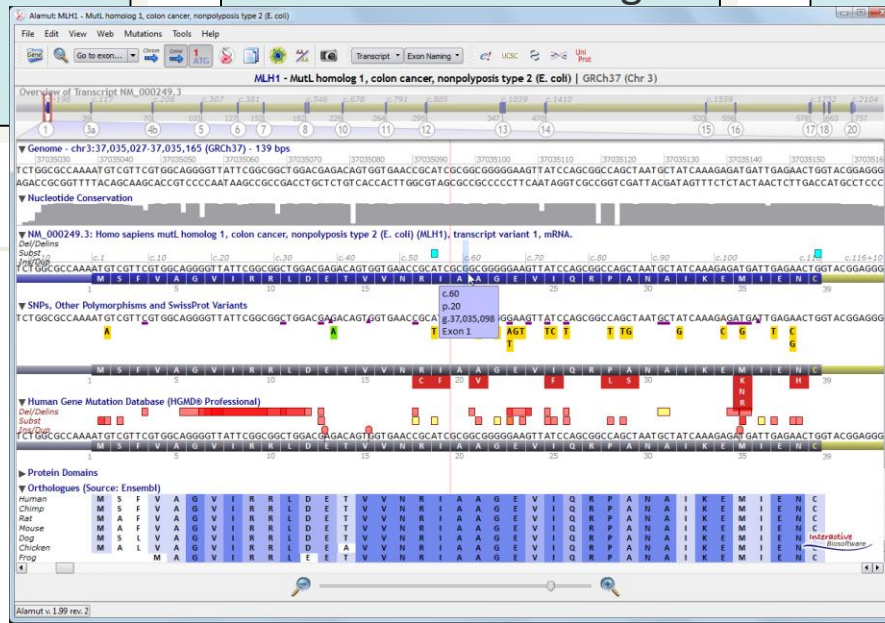
- Genome
- Genes
- Transcripts
- Polymorphisms
- Mutations
- Proteins

## Algorithms

- Coding Effects
- Nomenclature
- Missense Scoring
- Splicing Effects
- Literature Mining

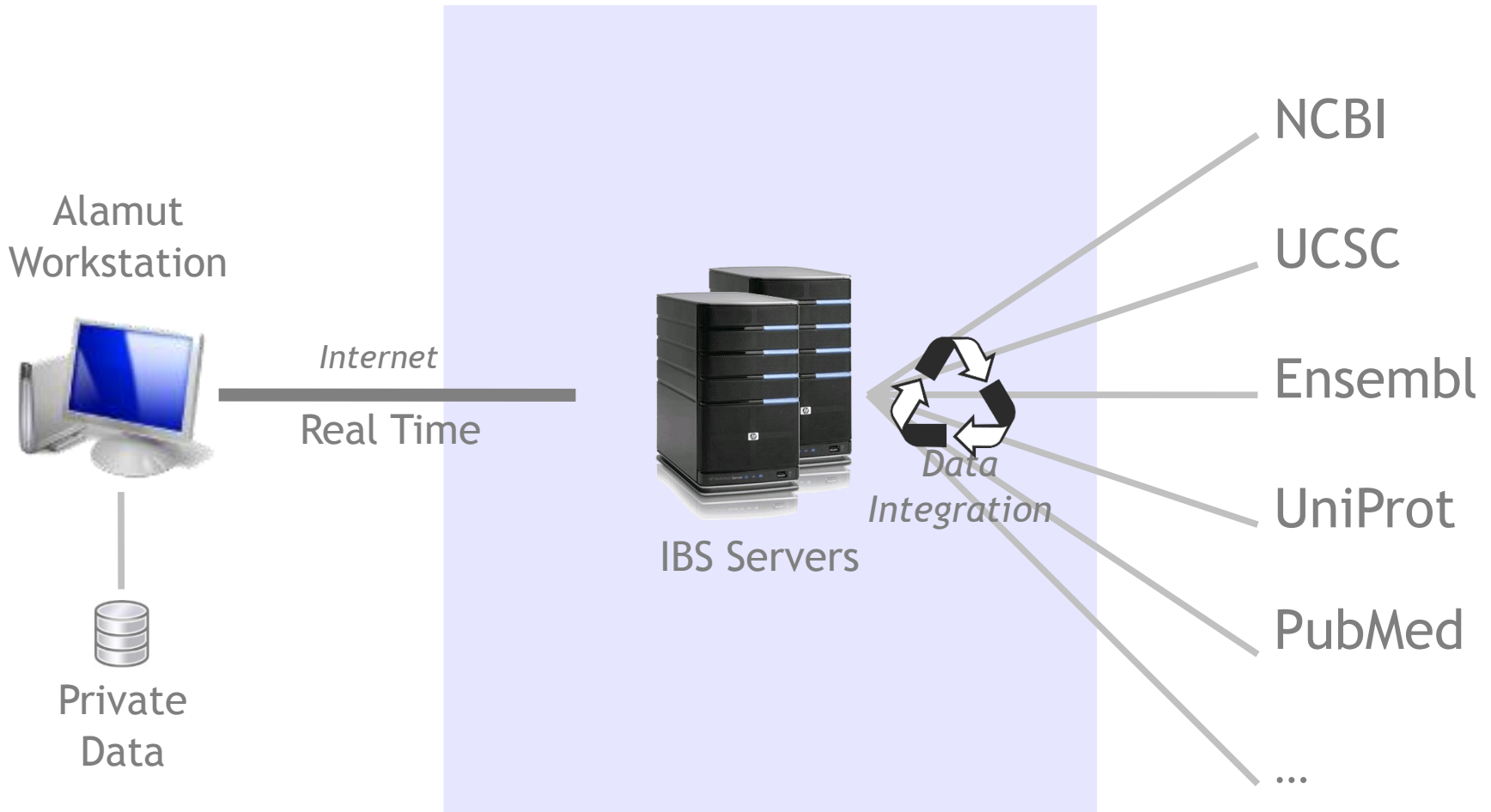
## GUI

- Gene Browser
- Consistent Display
- Intuitive Navigation and Interactions
- Dynamic Zooming
- BAM Viewer





# Architecture



Alamut: MLH1 - MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)

Application Edit View Web Mutations Tools Folders Shortcuts Help

Gene Chrom ooc Gene ooc 1 ATG UCSC OMIM GEN ATLAS Uni Prot Go to: chr3:37050315, MLH1:c.464T>G, rs63750891, NM\_000249.3, Help...

MLH1 - MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli) | GRCh37 (Chr 3)

Overview of Transcript NM\_000249.3

▼ Genome - chr3:37,053,473-37,053,619 (GRCh37) - 147 bps

▼ Nucleotide Conservation

▼ NM\_000249.3: Homo sapiens mutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli) (MLH1), transcript variant 1, mRNA.

▼ dbSNP Short Variations | SwissProt Variants

▼ Exome Sequencing Project (ESP) Variants

▼ Human Gene Mutation Database (HGMD® Professional)

▼ Protein Domains

▼ Orthologues (Source: Interactive Biosoftware)

Ref. Genome

Conservation

Ref. transcripts

dbSNP variations

ESP variations

HGMD mutations

Protein domains

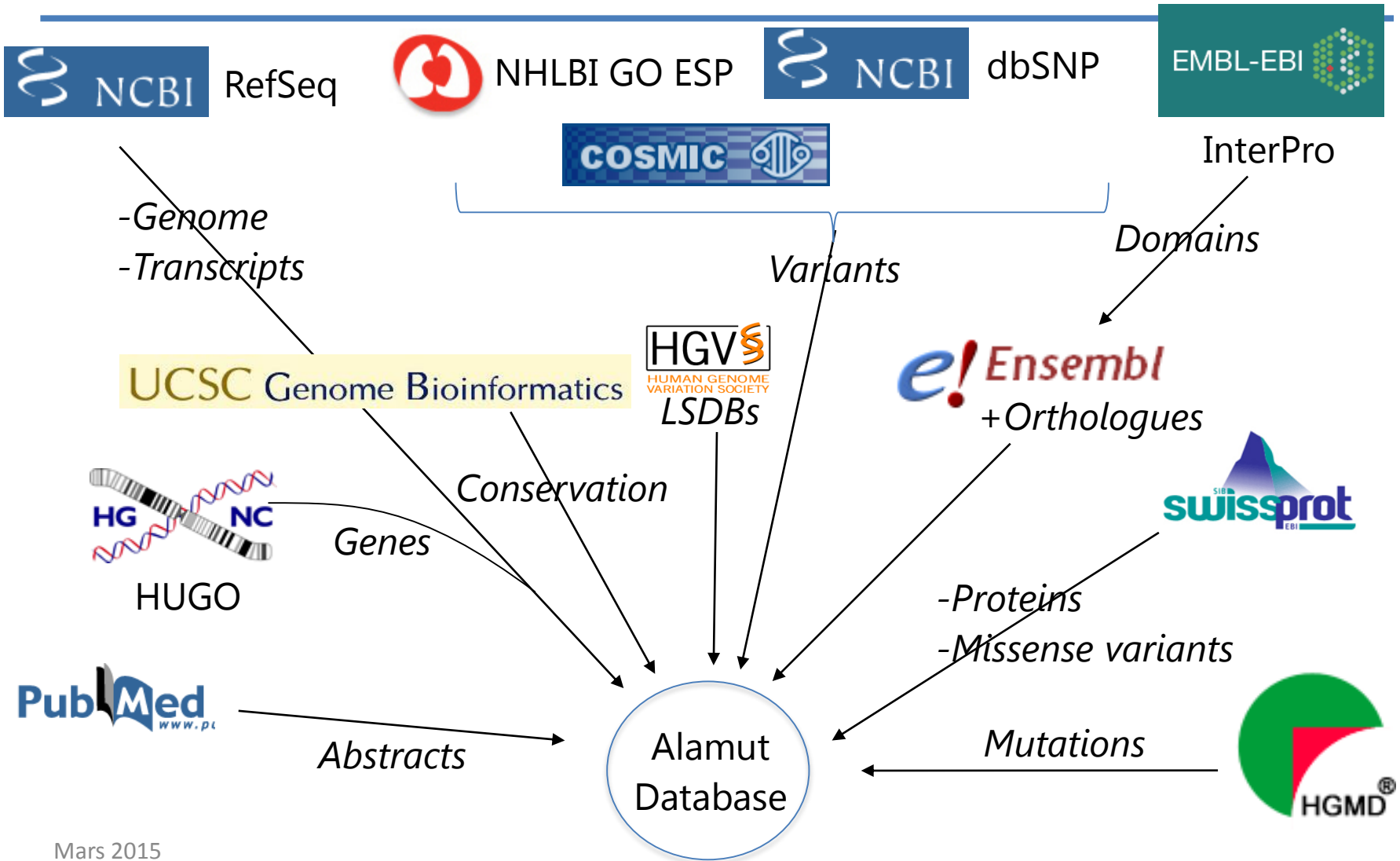
Orthologues





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# Data Sources





# Missense Predictions

The screenshot shows a software window titled "Variant NM\_000249.3(MLH1):c.739T>G [Unsaved]". The interface is divided into several sections:

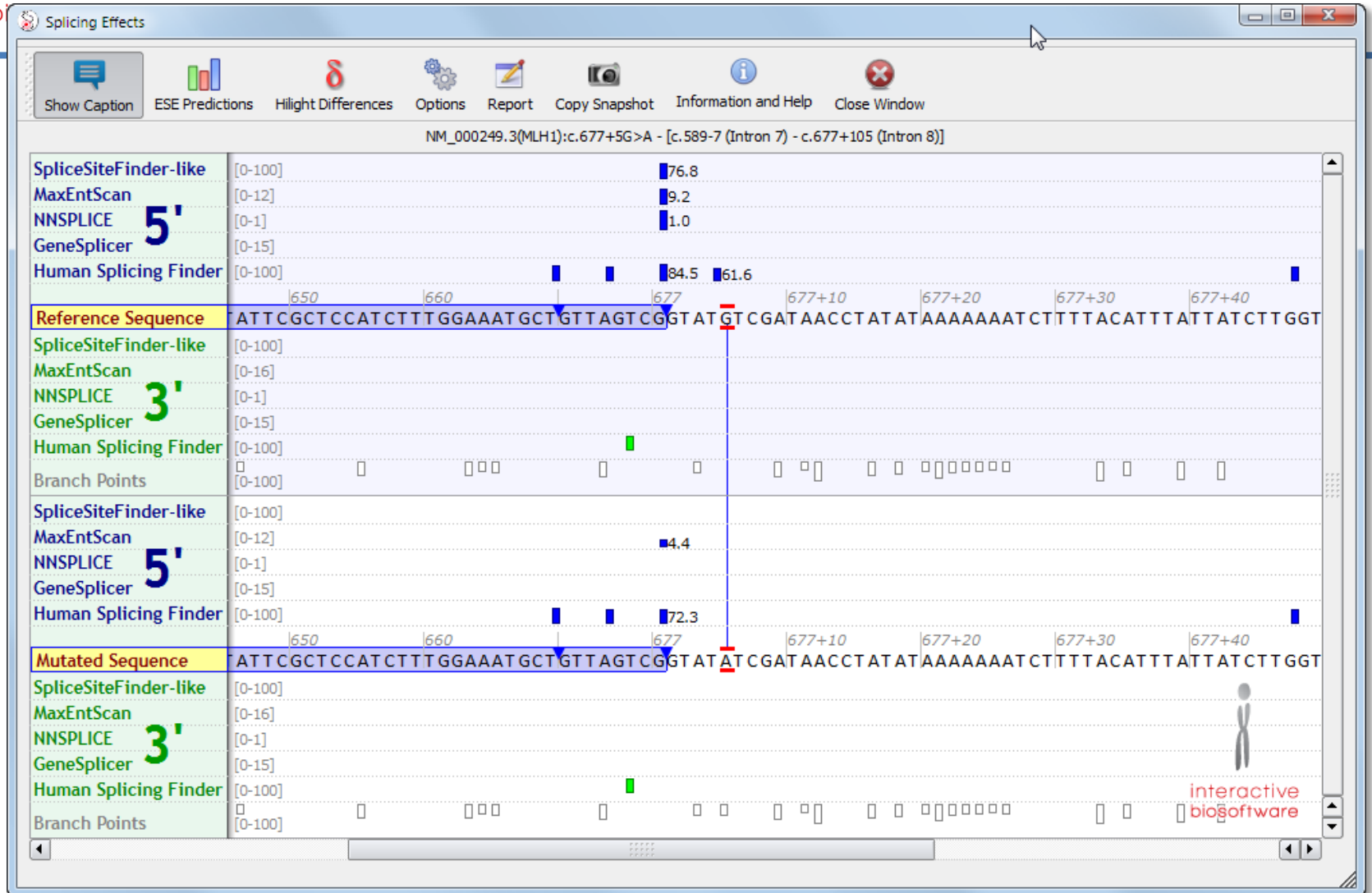
- Variant Features:** gDNA: Chr3(GRCh38):g.37014493T>G; cDNA: NM\_000249.3(MLH1):c.739T>G; Location: Exon 9; Type: Substitution; Coding Effect: Missense; AA/AA: p.Ser247Ala.
- Classification:** 5 Classes; Class: Class 3-Unknown pathogenicit.
- Comment:** Pathogenicity class is NOT automatically computed.
- Known Variations:** dbSNP: rs63750948; Clin. signif.: **vided,pathogenic**.
- Missense Predictions:** A table with two columns: "Invoke Manually" and "Automatically computed". The "Automatically computed" column contains: Class C0 (GV: 57.75 - GD: 49.44), Deleterious (score: 0.02), Disease causing (p-value: 1), and two empty rows.
- Splicing Predictions:** Check predictions in the Splicing Window: [Splicing Window]
- Report and Export:** Summary, Export to: Tab.
- Buttons:** Save, Cancel.



# Splicing Predictions

interactive

b





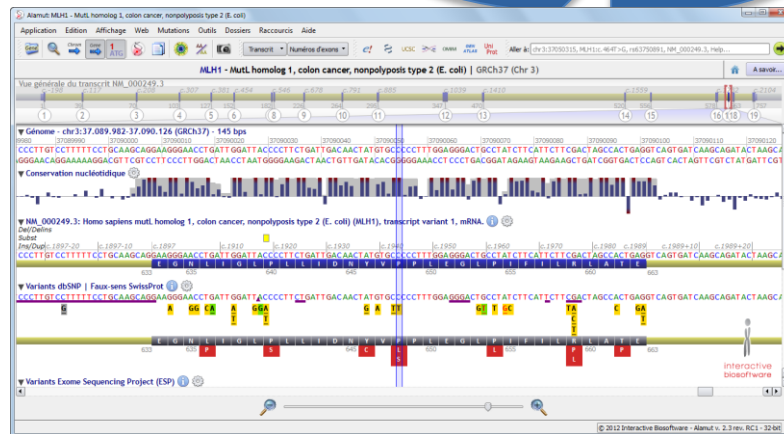
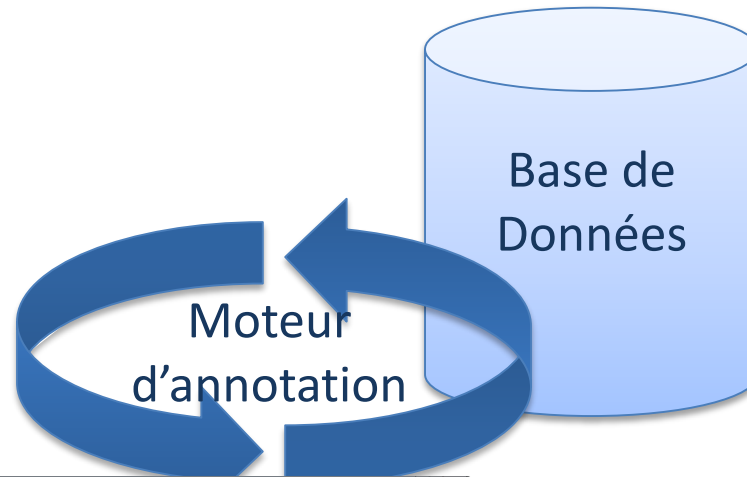
interactive  
biosoftware

# NGS BAM Viewer

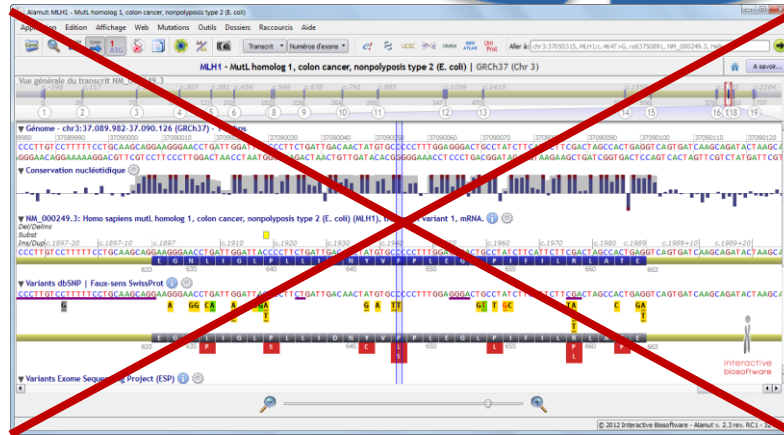
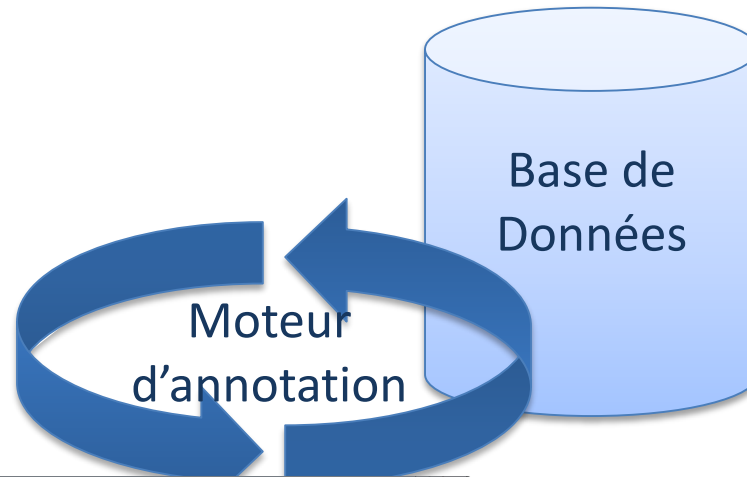
The screenshot displays the Alamut NGS BAM Viewer interface. The window title is "Alamut: MLH1 - MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli)". The menu bar includes "Application", "Edit", "View", "Web", "Mutations", "Tools", "Folders", "Shortcuts", and "Help". The toolbar contains various icons for gene, chromosome, transcript, ATG, and other genomic features. The main display area shows the "Overview of Transcript NM\_000249.3" for "MLH1 - MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli) | GRCh37 (Chr 3)". The transcript structure is shown with exons numbered 1 to 19 and introns represented by lines. The "BAM Alignment (T3.bam)" track shows a dense set of reads aligned to the transcript, with a "Targets (exons)" track above it indicating the maximum coverage of 116x. The "dbSNP Short Variations" and "SwissProt Variants" tracks are visible at the bottom. The interface includes a search bar with "Go to: chr4:69057688" and a "Hints and Tips" button. The Alamut logo and version information "Alamut v. 2.4 rev. 1 - 64-bit © 2014 Interactive Biosoftware" are located in the bottom right corner.



# Visual → Batch

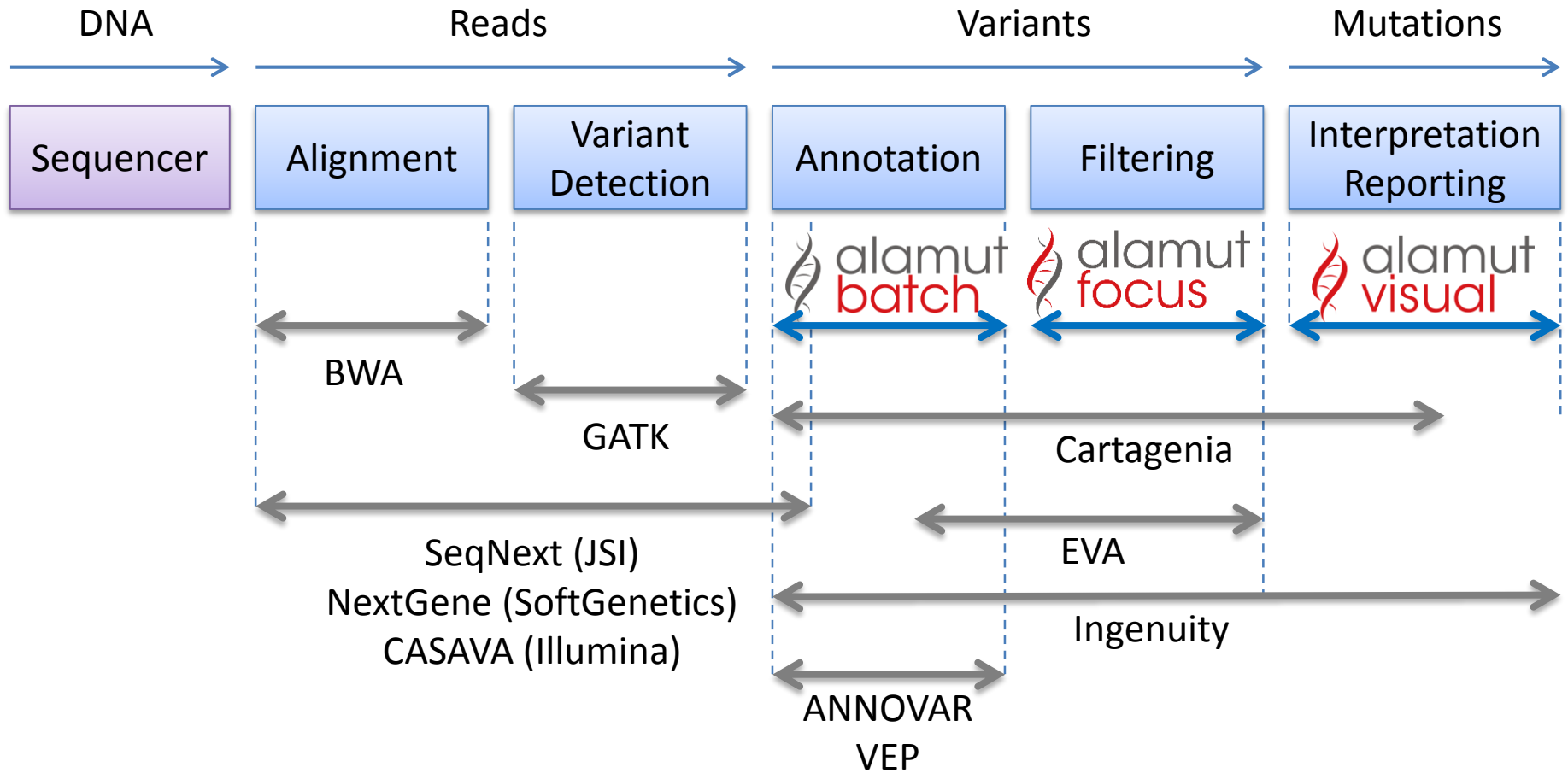


# Visual → Batch





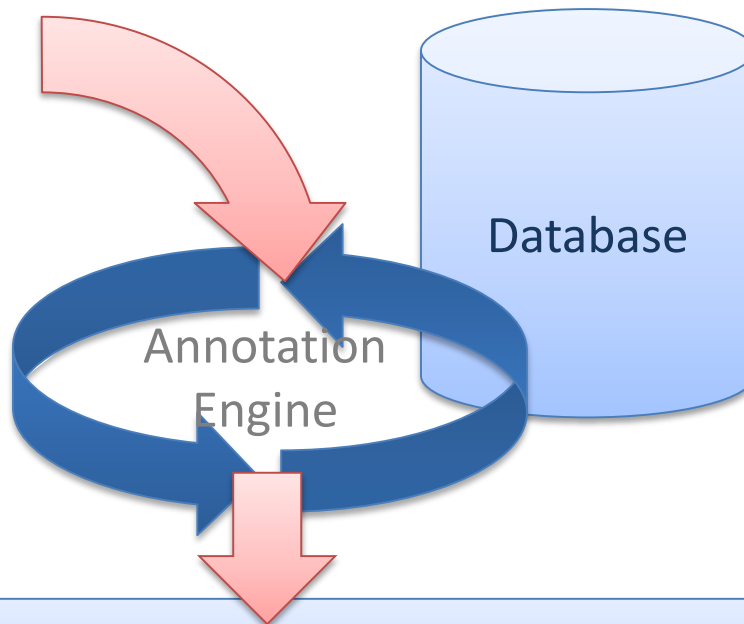
# Positionnement





## Raw variants (VCF)

```
Chr3:g.37090029C>A
Chr5:g.68876554del
Chr7:g.3962135A>T
Chr13:g.723693insGT
.....
```



## Annotated variants

MLH1	NM_000249.3	c.1918C>A	p.Pro640Thr	rs63749792	0.003	...
MLH1	NM_001167617.1	c.1624C>A	p.Pro542Thr	rs63749792	0.003	...
MLH1	NM_001167618.1	c.1195C>A	p.Pro399Thr	rs63749792	0.003	...
.....						



# Annotations fournies

---

- Gène(s), transcrit(s), protéine(s)
- Conservation
- Variant: type, localisation, effet
- Fréq alléliques: dbSNP, 1000g, ESP, ExAC, ClinVar, HGMD, COSMIC
- Protéine/AA: domaines, conservation, scores physico-chimiques
- Faux-sens: Align GVDG, SIFT, MAPP
- Epissage: site naturel le + proche, voisinage du variant

~160 champs

# Exemple de sortie

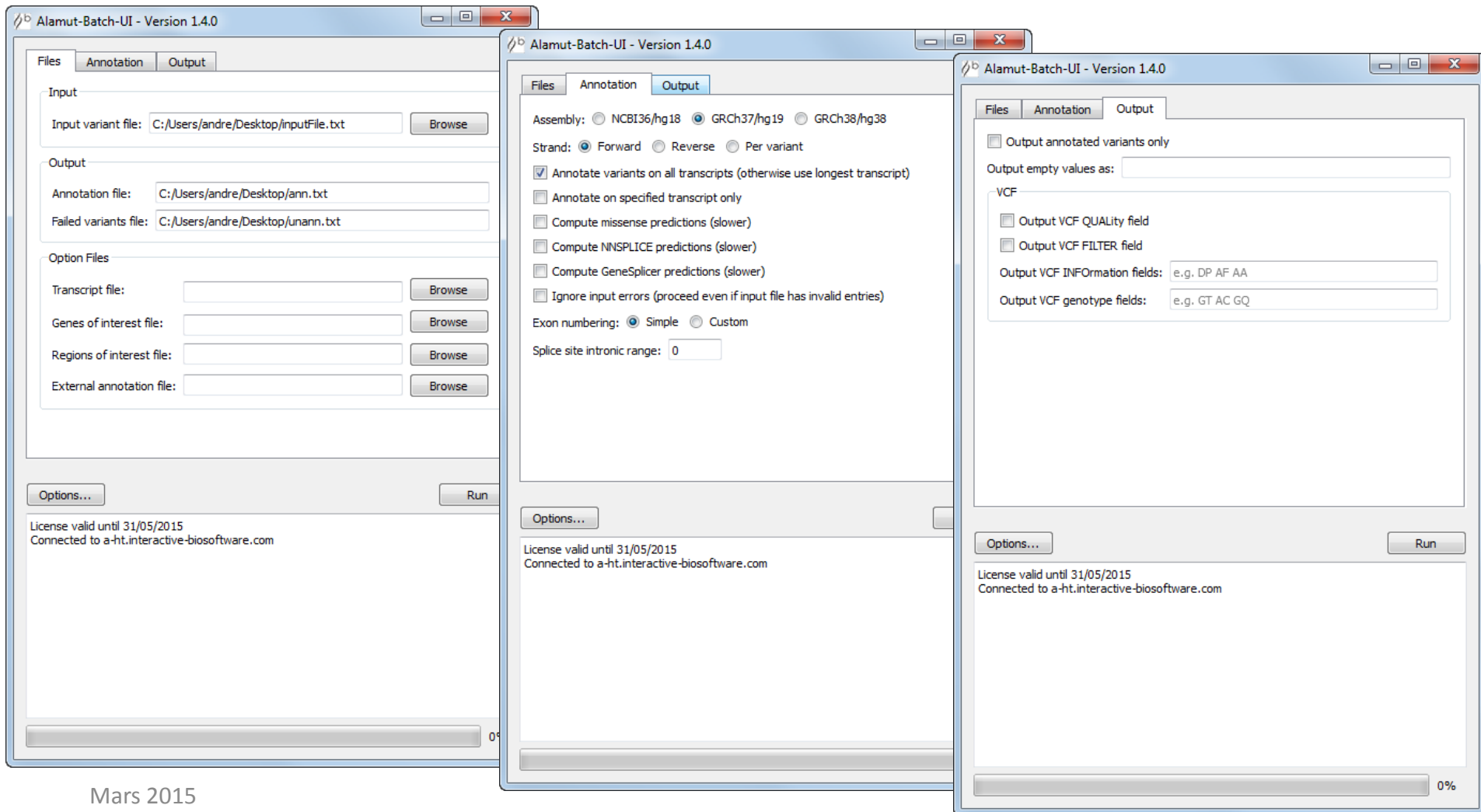
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	
1	id	gene	genelid	chrom	transcr	protein	varType	coding	varLoca	assemb	gDNAst	gDNAe	gNome	cDNAst	cDNAe	cNome	pNome	alt_pN	exon	intron	omi
2	id13148	ABCD1	61	X	NM_0000	NP_00002	substitutii	missense	exon	NCBI36	1.53E+08	1.53E+08	g.1526558	1463	1463	c.1463T>G	p.Val488G	p.Val488G	5		3
3	id13155	ABCD1	61	X	NM_0000	NP_00002	substitution		intron	NCBI36	1.53E+08	1.53E+08	g.1526621	1992-32	1992-32	c.1992-32	(p.?)	p.?	10	9	3
4	id13165	ABCD1	61	X	NM_0000	NP_00002	substitution		3'UTR	NCBI36	1.53E+08	1.53E+08	g.1526629	*530	*530	c.*530G>A	p.?	p.?	10		3
5	id13167	ABCD1	61	X	NM_0000	NP_00002	substitution		3'UTR	NCBI36	1.53E+08	1.53E+08	g.1526632	*870	*870	c.*870G>T	p.?	p.?	10		3
6	id13169	ABCD1	61	X	NM_0000	NP_00002	substitution		3'UTR	NCBI36	1.53E+08	1.53E+08	g.1526632	*901	*901	c.*901G>A	p.?	p.?	10		3
7	id13170	ABCD1	61	X	NM_0000	NP_00002	substitution		3'UTR	NCBI36	1.53E+08	1.53E+08	g.1526632	*903	*903	c.*903G>A	p.?	p.?	10		3
8	id13171	ABCD1	61	X	NM_0000	NP_00002	substitution		3'UTR	NCBI36	1.53E+08	1.53E+08	g.1526633	*948	*948	c.*948C>T	p.?	p.?	10		3
9	id5239	ACE2	13557	X	NM_0218	NP_06857	substitution		intron	NCBI36	15517571	15517571	g.1551757	584-71	584-71	c.584-71A	p.?	p.?	5	4	3
10	id5543	ACOT9	17152	X	NM_0010	NP_00103	substitution		intron	NCBI36	23633182	23633182	g.2363318	1020-64	1020-64	c.1020-64	p.?	p.?	14	13	
11	id5544	ACOT9	17152	X	NM_0010	NP_00103	substitution		intron	NCBI36	23633305	23633305	g.2363330	1020-187	1020-187	c.1020-18	p.?	p.?	14	13	
12	id12343	AFF2	3776	X	NM_0020	NP_00201	substitution		intron	NCBI36	1.48E+08	1.48E+08	g.1476992	1086+114	1086+114	c.1086+11	p.?	p.?	4	4	3
13	id12356	AFF2	3776	X	NM_0020	NP_00201	substitution		intron	NCBI36	1.48E+08	1.48E+08	g.1478700	3623+57	3623+57	c.3623+57	p.?	p.?	19	19	3
14	id10704	AGTR2	338	X	NM_0006	NP_00067	substitution		3'UTR	NCBI36	1.15E+08	1.15E+08	g.1152197	*1103	*1103	c.*1103G>	p.?	p.?	3		3
15	id11338	AIFM1	8768	X	NM_0042	NP_00419	substitution		intron	NCBI36	1.29E+08	1.29E+08	g.1290976	1305+40	1305+40	c.1305+40	p.?	p.?	12	12	3
16	id11342	AIFM1	8768	X	NM_0042	NP_00419	substitution		intron	NCBI36	1.29E+08	1.29E+08	g.1291073	606-104	606-104	c.606-104	p.?	p.?	6	5	3
17	id11344	AIFM1	8768	X	NM_0042	NP_00419	substitutii	synonymc	exon	NCBI36	1.29E+08	1.29E+08	g.1291112	273	273	c.273T>C	p.=	p.Asp91A	3		3
18	id10909	AKAP14	24061	X	NM_1788	NP_84892	substitution		intron	NCBI36	1.19E+08	1.19E+08	g.1189380	494+75	494+75	c.494+75C	p.?	p.?	6	6	3
19	id10527	AMMECR1	467	X	NM_0153	NP_05618	substitution		3'UTR	NCBI36	1.09E+08	1.09E+08	g.1093262	*2114	*2114	c.*2114A>	p.?	p.?	6		3
20	id10676	AMOT	17810	X	NM_1332	NP_57357	substitution		3'UTR	NCBI36	1.12E+08	1.12E+08	g.1119083	*146	*146	c.*146C>G	p.?	p.?	12		3
21	id11264	APLN	16665	X	NM_0174	NP_05910	substitution		3'UTR	NCBI36	1.29E+08	1.29E+08	g.1286091	*384	*384	c.*384G>A	p.?	p.?	3		3
22	id11265	APLN	16665	X	NM_0174	NP_05910	substitution		3'UTR	NCBI36	1.29E+08	1.29E+08	g.1286095	*36	*36	c.*36G>T	p.?	p.?	3		3
23	id8652	AR	644	X	NM_0000	NP_00003	substitution		intron	NCBI36	66858322	66858322	g.6685832	2319-78	2319-78	c.2319-78	p.?	p.?	6	5	3
24	id6248	ARAF	646	X	NM_0016	NP_00164	substitution		intron	NCBI36	47309559	47309559	g.4730955	459-36	459-36	c.459-36C	p.?	p.?	6	5	3
25	id6255	ARAF	646	X	NM_0016	NP_00164	substitution		intron	NCBI36	47315401	47315401	g.4731540	1686+46	1686+46	c.1686+46	p.?	p.?	15	15	3
26	id6256	ARAF	646	X	NM_0016	NP_00164	substitution		intron	NCBI36	47315615	47315615	g.4731561	1687-51	1687-51	c.1687-51	(p.?)	p.?	16	15	3

# Paramètres

---

- 1 ou n transcrits
- $\pm$  prédictions de faux-sens
- $\pm$  prédictions d'épissage
- Gènes d'intérêt
- Régions d'intérêt
- Intégration d'annotations externes
- Extraction d'annotations VCF (ex: génotypes)

# Interface



# Ligne de commande

---

```
alamut-batch
  [--help]
  [--listgenes <output file name> NCBI36|GRCh37|GRCh38]
  --in <variant file name>
  --ann <annotation file name>
  --unann <unannotated log file name>
  [--from <n>] (start annotating from the nth variant)
  [--to <n>] (annotate up to the nth variant)
  [--assembly NCBI36|GRCh37|GRCh38] (default: GRCh37)
  [--strand 1|-1|0] (default: 1; 0: per variant - not applicable to VCF
    input)
  [--alltrans] (annotate variants on all transcripts)
  [--spectrans] (annotate variants only on specified per-variant
    Transcripts - not applicable to VCF input)
  [--translist <transcript file name>] (annotate variants only on listed
    preferred transcripts)
  [--glist <gene list file name>] (list of genes of interest)
  [--roilist <ROI list BED file name>] (list of regions of interest)
  [--nomispred] (no missense predictions; faster)
  [--nonnsplice] (no NNSPLICE predictions; faster)
  [--nogenesplicer] (no GeneSplicer predictions; faster)
  [--ignoreInputErrors] (proceed even if input has incorrect entries)
  [--exonnums simple|custom] (default: simple)
  [--ssIntronicRange <n>] (set varLocation as 'splice site' if variant is
    intronic and within this range)
  [--extAnnFile <external annotation file name>] (include additional
    annotations from external file)
  [--outputannonly] (output only annotated variants in annotation output)
  [--outputVCFQuality]
  [--outputVCFFilter]
  [--outputVCFInfo ID ... ID]
  [--outputVCFGenotypeData ID ... ID]
  [--outputEmptyValuesAs <value>] (e.g. NULL)
  [--hgmdUser <HGMD Pro user name>]
  [--hgmdPasswd <HGMD Pro password>]
  [--proxyserver <proxy server name>]
  [--proxyport <proxy server port number>]
  [--proxyuser <proxy user login>]
  [--proxypasswd <proxy password>]
  [--processes <#processes>] (Standalone version only)
```

# Architecture : 2 versions

---

- Client/Serveur
  - Base de données distante
  - Annotation locale
  - Performance modeste
  
- Standalone
  - Base de données locale
  - Annotation locale
  - Performance élevée

# Exemples de débits

---

- Ordinateur standard – version client/serveur
  - Avec prédictions: ~4000 variants/h
  - Sans prédictions: ~10.000 variants/h
- Ordinateur puissant – version standalone
  - Avec prédictions: ~15.000 variants/h
  - Sans prédictions: ~100.000 variants/h
- Processus hautement **parallélisable**



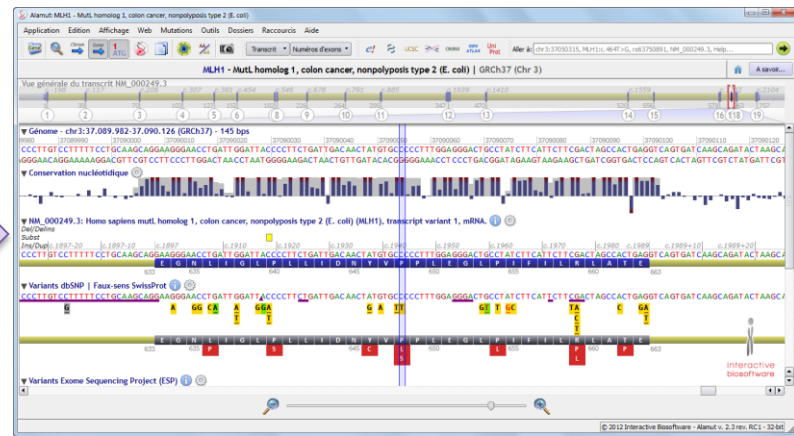
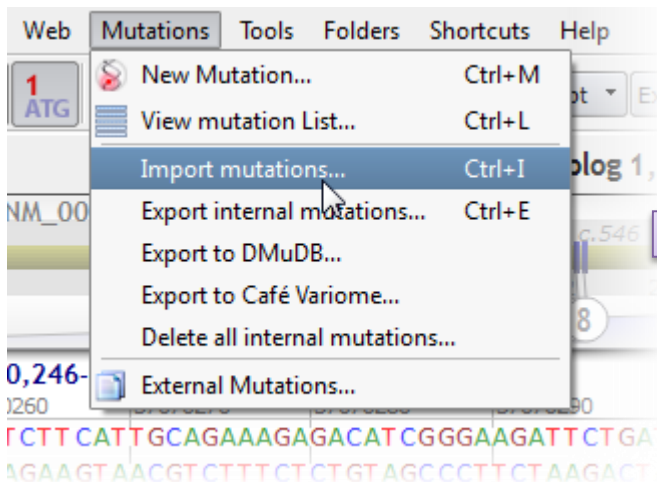


The screenshot displays the Alamut Focus software interface. At the top, the menu bar includes 'Application', 'Variants', 'Filter', 'Project', 'View', and 'Help'. A 'Go to:' field is present. Below the menu is the 'Data tab' with a 'General' sub-tab. The 'Description' section shows variant files and their qualifications (Father, Mother, Study case). The 'Inheritance Mode' section includes options for 'De Novo', 'Autosomal', 'Dominant', 'Recessive', 'Recessive (Compound Heterozygosity)', and 'X-Linked Recessive'. A 'Filter Panel' on the right shows a 'Filter summary' with categories like 'Globals', 'Filter', 'Population', 'Coding Effect', 'In Silico Prediction', and 'Sources'. The main area is the 'Gene/Transcript View', which contains a table of variants. A context menu is open over the variant at position 45190324, with options: 'Open in Alamut Visual', 'Hide column', 'Refresh', and 'Edit variant'. The 'Variants Table' at the bottom shows columns for chromosome, pos\_start, pos\_end, seq\_ref, seq\_alt, annotation\_type, gene, genid, transcript, strand, protein, Uniprot, varType, codingEffect, varLocation, assembly, gDNAstart, and gDNAend. The table is currently displaying 100 lines out of 219.

chromosome	pos_start	pos_end	seq_ref	seq_alt	annotation_type	gene	genid	transcript	strand	protein	Uniprot	varType	codingEffect	varLocation	assembly	gDNAstart	gDNAend
1	21099952	21099952	G	T	alamut_batch	HP1BP3	24973	NM_016287.3	-1	NP_057371.2	Q55515	substitution	missense	exon	GRCh37	21099952	21099952
1	25944761	25944761	G	T	alamut_batch	MAN1C1	19080	NM_020379.2	1	NP_065112.1	Q9NR34	substitution	missense	exon	GRCh37	25944761	25944761
1	26608843	26608843	G	T	alamut_batch	UBXN11	30600	NM_001077262.1	-1	NP_001070730.1		substitution	missense	exon	GRCh37	26608843	26608843
1	26608843	26608843	G	T	alamut_batch	UBXN11	30600	NM_183008.2	-1	NP_892120.2	Q5T124	substitution	missense	exon	GRCh37	26608843	26608843
1	26608843	26608843	G	T	alamut_batch	UBXN11	30600	NM_145345.2	-1	NP_663320.2		substitution	missense	exon	GRCh37	26608843	26608843
1	38218593	38218593	G	T	alamut_batch	EPHA10	19987	NM_001099439.1	-1	NP_001092909.1	Q5I2Y3	substitution	missense	exon	GRCh37	38218593	38218593
1	45190324	45190324	G	T	alamut_batch	Clorf228	34345	NM_001145636.1	1	NP_001139108.1	Q6PV15	substitution	missense	exon	GRCh37	45190324	45190324
1	75139187	75139187	G	T	alamut_batch	ERIC4	25346	NM_001002912.4	-1	NP_001002912.4	Q5RHP9	substitution	missense	exon	GRCh37	75139187	75139187
1	87025897	87025897	G	T	alamut_batch	CLCA4	2018	NM_012128.3	1	NP_036260.2	Q14CN2	substitution	missense	exon	GRCh37	87025897	87025897
1	110026628	110026628	G	T	alamut_batch	ATXN7L2	28713	NM_153340.4	1	NP_699171.3	Q5T6C5	substitution	missense	exon	GRCh37	110026628	110026628
1	111968024	111968024	G	T	alamut_batch	OVGP1	8524	NM_002557.3	-1	NP_002548.3	Q12889	substitution	missense	exon	GRCh37	111968024	111968024
1	120934573	120934573	G	A	alamut_batch	FCGR1B	3614	NM_001017986.3	-1	NP_001017986.1	Q92637	substitution	missense	exon	GRCh37	120934573	120934573
1	145281633	145281633	C	A	alamut_batch	NOTCH2NL	31862	NM_203458.3	1	NP_982283.2	Q7Z359	substitution	missense	exon	GRCh37	145281633	145281633
1	152186178	152186178	G	A	alamut_batch	HRNR	20846	NM_001009931.1	-1	NP_001009931.1	Q86Y23	substitution	missense	exon	GRCh37	152186178	152186178
1	161049668	161049668	C	T	alamut_batch	PVRL4	19688	NM_030916.2	-1	NP_112178.2	Q86NV8	substitution	missense	exon	GRCh37	161049668	161049668
1	161642774	161642774	T	G	alamut_batch	FCGR2B	3618	NM_004001.4	1	NP_003992.3	P31994	substitution	missense	exon	GRCh37	161642774	161642774
1	161642774	161642774	T	G	alamut_batch	FCGR2B	3618	NM_001002274.1	1	NP_001002274.1		substitution	missense	exon	GRCh37	161642774	161642774
1	161642774	161642774	T	G	alamut_batch	FCGR2B	3618	NM_001190828.1	1	NP_001177757.1		substitution	missense	exon	GRCh37	161642774	161642774
1	161642774	161642774	T	G	alamut_batch	FCGR2B	3618	NM_001002275.1	1	NP_001002275.1		substitution	missense	exon	GRCh37	161642774	161642774
1	161642774	161642774	T	G	alamut_batch	FCGR2B	3618	NM_001002273.2	1	NP_001002273.1		substitution	missense	exon	GRCh37	161642774	161642774
1	197141314	197141314	G	A	alamut_batch	ZBTB41	24819	NM_194314.2	-1	NP_919290.2	Q5SVQ8	substitution	missense	exon	GRCh37	197141314	197141314
1	215960153	215960153	T	G	alamut_batch	USH2A	12601	NM_206933.2	-1	NP_996816.2	O75445	substitution	missense	exon	GRCh37	215960153	215960153

# Batch → Visual

1

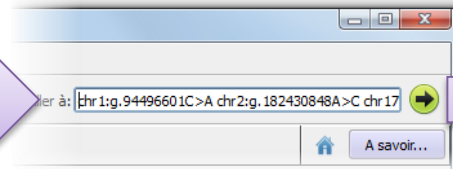


2

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	A	B	C	D	E	F	G
1		#id	gene	geneid	chrom	transcript	strand
2	chr1:g.94496601C>A	17	ABCA4	34	1	NM_000350.2	-
3	chr2:g.182430848A>C	49	CERKL	21699	2	NM_201548.4	-
4	chr17:g.6331702T>A	37	AIPL1	359	17	NM_014336.3	-
5	chr8:g.87660100T>C	58	CNGB3	2153	8	NM_019098.4	-
6	chr17:g.7917279T>A	80	GUCY2D	4689	17	NM_000180.3	+
7	chr9:g.2719046T>A	95	KCNV2	19698	9	NM_133497.3	+
8	chrX:g.38134398T>A	178	RPGR	10295	X	NM_000328.2	-
9	chr14:g.21769193C>A	198	RPGRIP1	13436	14	NM_020366.3	+
10	chr1:g.156146546C>T	221	SEMA4A	10729	1	NM_022367.3	+
11	chr12:g.56117809T>G	140	RDHS	9940	12	NM_002905.3	+

*coller*



Gene	Details
ABCA4	chr1(GRCh37):g.94496601C>A
CERKL	chr2(GRCh37):g.182430848A>C
AIPL1	chr17(GRCh37):g.6331702T>A
CNGB3	chr8(GRCh37):g.87660100T>C
GUCY2D	chr17(GRCh37):g.7917279T>A
KCNV2	chr9(GRCh37):g.2719046T>A
RPGR	chrX(GRCh37):g.38134398T>A
RPGRIP1	chr14(GRCh37):g.21769193C>A
SEMA4A	chr1(GRCh37):g.156146546C>T
RDHS	chr12(GRCh37):g.56117809T>G

# Caractères distinctifs

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- Orientation clinique (humaine)
  - RefSeq, RefSeqGene, LRG
  - Nomenclature HGVS
- Prédiction d'épissage
  - Jonction proximale
  - Voisinage
- Cohérence avec Alamut Visual
- Produit commercial

# Utilisation

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- 45 laboratoires
- VaRank: a simple and powerful tool for ranking genetic variants  
Geoffroy V, Pizot C, Redin C, Piton A, Vasli N, Stoetzel C, Blavier A, Laporte J, Muller J. (2015)  
PeerJ 3:e796 <https://dx.doi.org/10.7717/peerj.796>
- A systematic approach to assessing the clinical significance of genetic variants  
Duzkale H, Shen J, McLaughlin H, Alfares A, Kelly MA, Pugh TJ, Funke BH, Rehm HL, Lebo MS  
Clinical Genetics [2013, 84(5):453-463]