genAP

Efficient clinical analysis of DNA sequencing data

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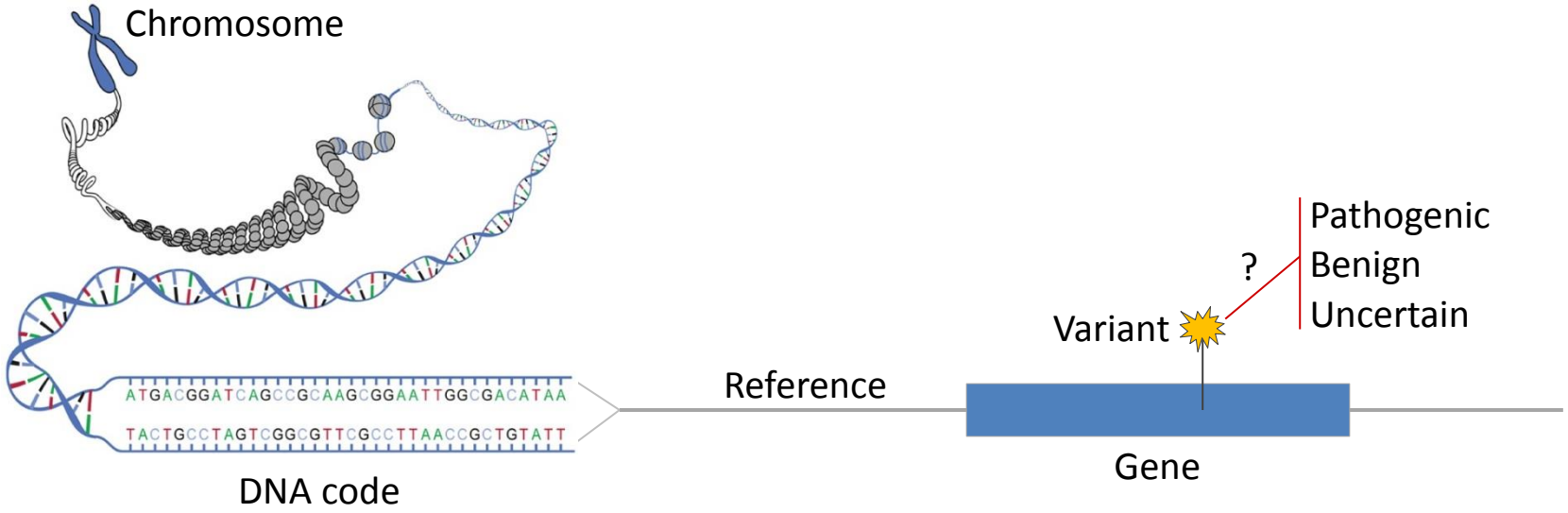
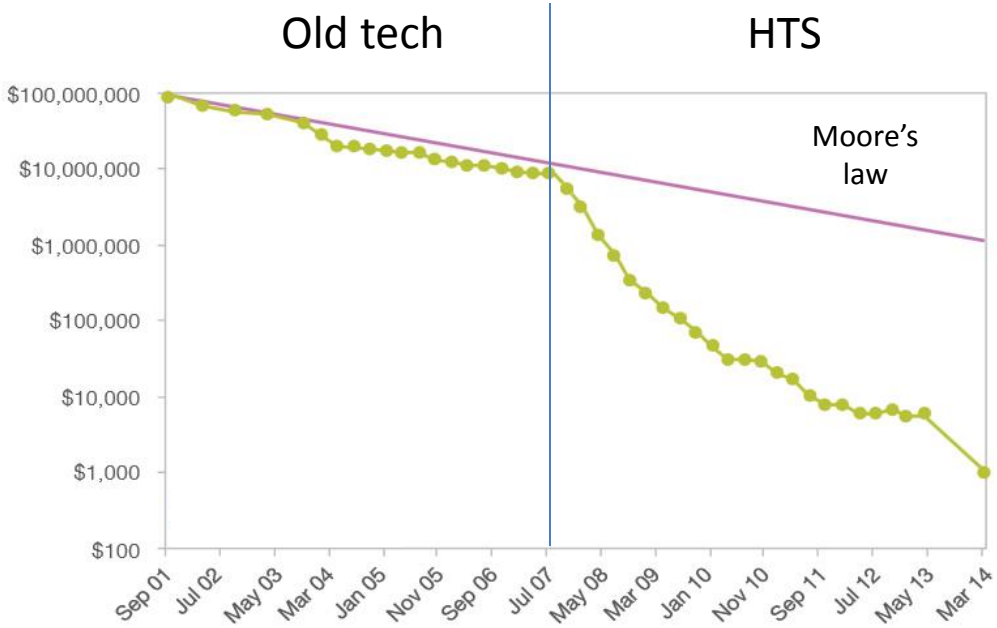
Genetic testing



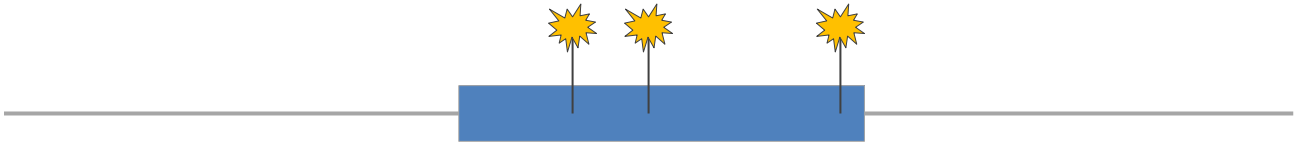
High-throughput DNA sequencing (HTS)



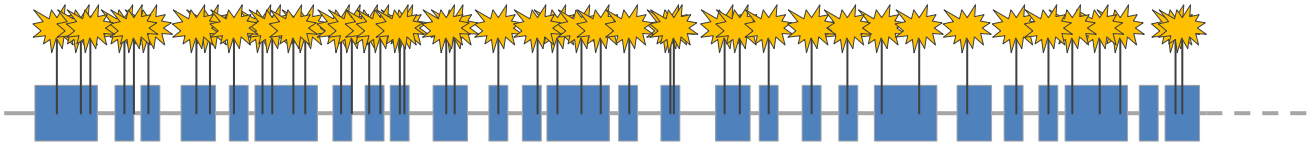
Cost of complete genome

Data increase

Old tech



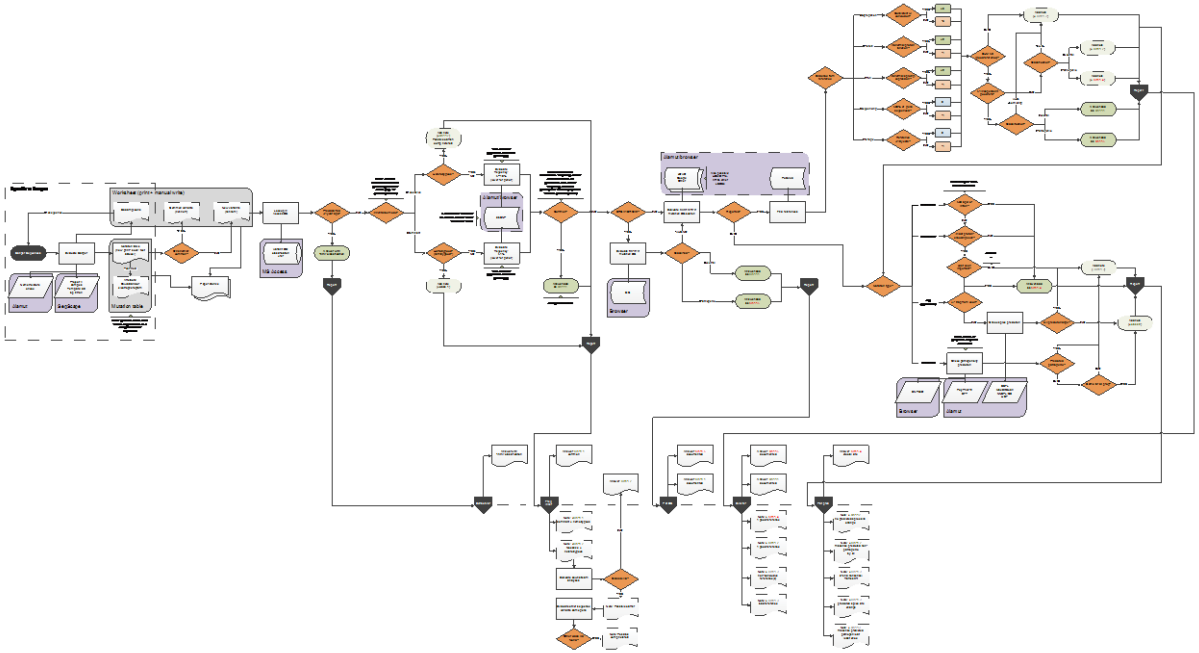
HTS



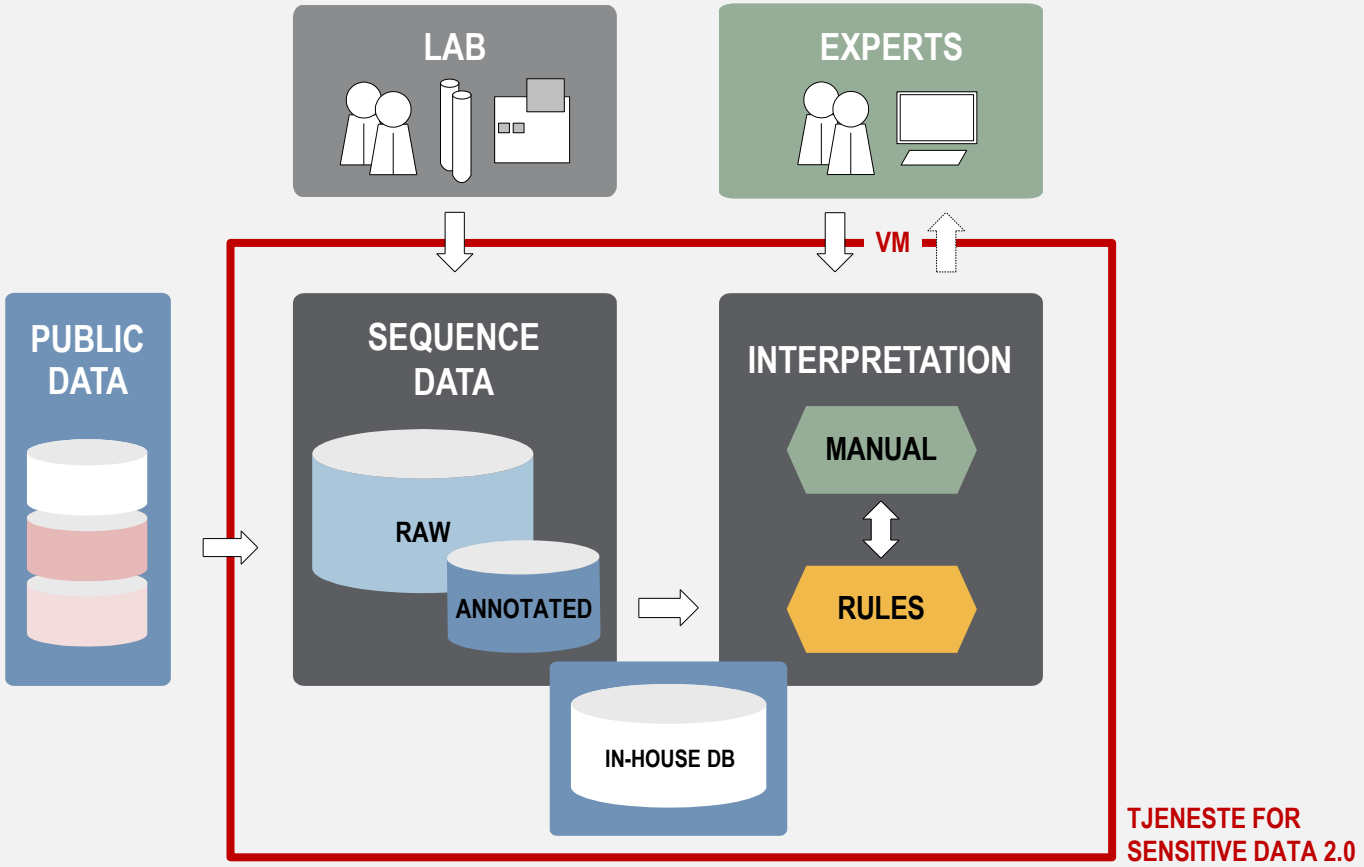
$1.000 genome - $1.000.000 interpretation

Challenges

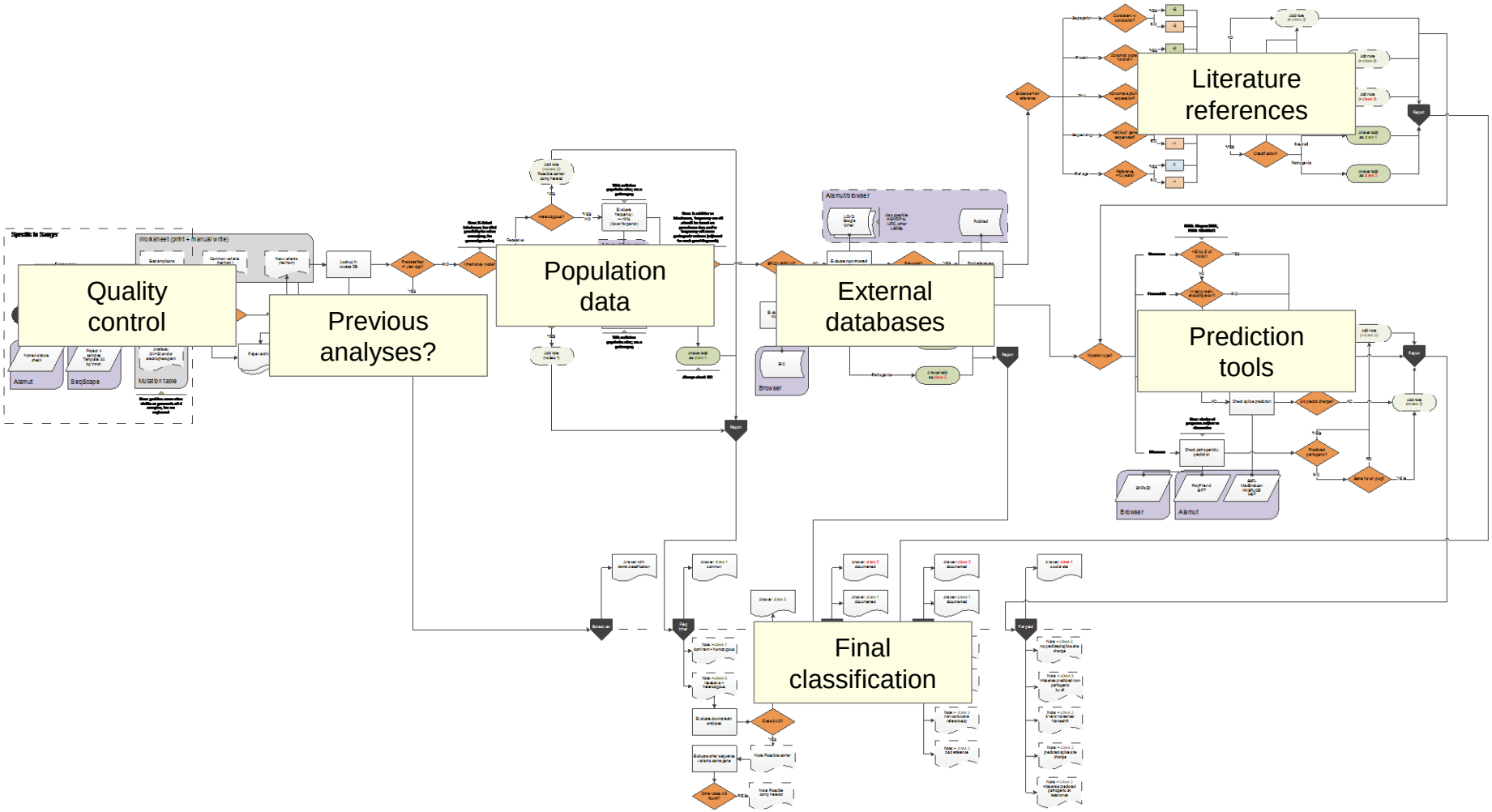
- Large amounts of sensitive data
- Complex interpretation process



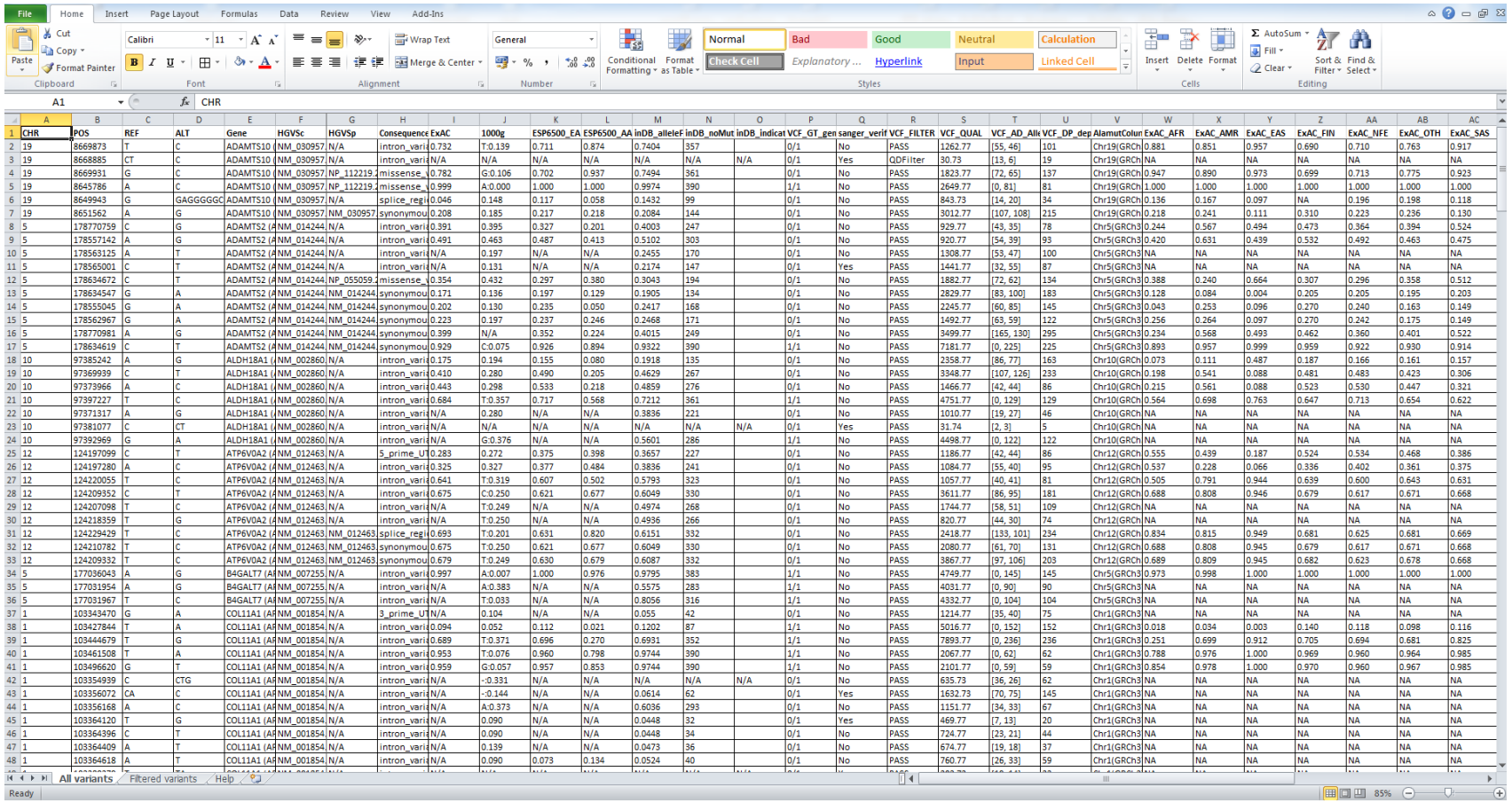
genAP Norwegian clinical genetic Analysis Platform



Interpretation

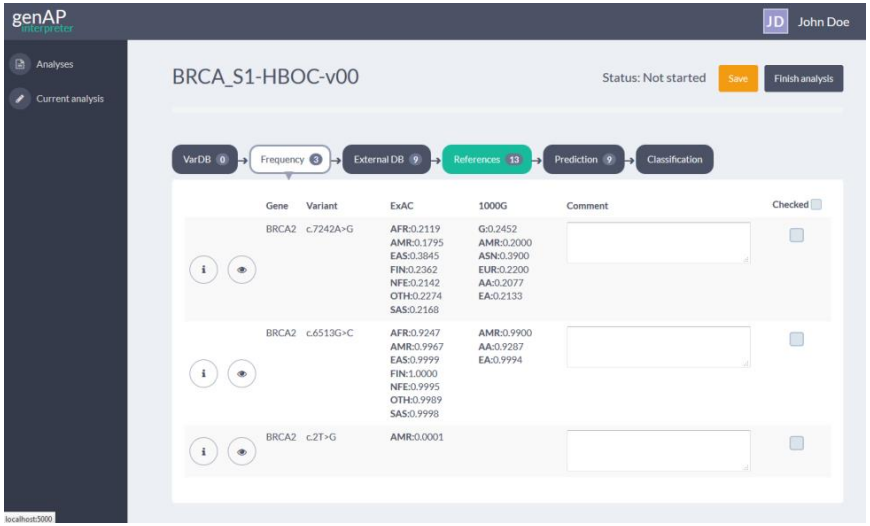


genAP interpreter



CHR	POS	REF	ALT	Gene	HGVSc	HGVSp	Consequence	ExAC	1000g	ESP6500_EA	ESP6500_AA	inDB_alleleF	inDB_noMut	inDB_indicat	VCF_GT_gen	sanger_verif	VCF_FILTER	VCF_QUAL	VCF_AD_Alle	VCF_DP_dep	AlamutColun	ExAC_AFR	ExAC_AMR	ExAC_EAS	ExAC_FIN	ExAC_NFE	ExAC_OTH	ExAC_SAS
19	8669873	T	C	ADAMTS10 (	NM_030957	N/A	intron_varia	0.732	T:0.139	0.711	0.874	0.7404	357		0/1	No	PASS	1262.77	[55, 46]	101	Chr19(GRCh	0.881	0.851	0.957	0.690	0.710	0.763	0.917
19	8668885	CT	C	ADAMTS10 (	NM_030957	N/A	intron_varia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/1	Yes	QDFilter	30.73	[13, 6]	19	Chr19(GRCh	NA	NA	NA	NA	NA	NA	NA
19	8669931	G	C	ADAMTS10 (	NM_030957	NP_112219.2	missense_v	0.782	G:0.106	0.702	0.937	0.7494	361		0/1	No	PASS	1823.77	[72, 65]	137	Chr19(GRCh	0.947	0.890	0.973	0.699	0.713	0.775	0.923
19	8645786	A	C	ADAMTS10 (	NM_030957	NP_112219.2	missense_v	0.999	A:0.000	1.000	1.000	0.9974	390		1/1	No	PASS	2649.77	[0, 81]	81	Chr19(GRCh	1.000	1.000	1.000	1.000	1.000	1.000	1.000
19	8649943	G	GAGGGGGC	ADAMTS10 (	NM_030957	N/A	splice_regi	0.046	0.148	0.117	0.058	0.1432	99		0/1	No	PASS	843.73	[14, 20]	34	Chr19(GRCh	0.136	0.167	0.097	NA	0.196	0.198	0.118
19	8651562	A	G	ADAMTS10 (	NM_030957	NM_030957	synonymou	0.208	0.185	0.217	0.218	0.2084	144		0/1	No	PASS	3012.77	[107, 108]	215	Chr19(GRCh	0.218	0.241	0.111	0.310	0.223	0.236	0.130
5	178770759	C	G	ADAMTS2 (A	NM_014244	N/A	intron_varia	0.391	0.395	0.327	0.201	0.4003	247		0/1	No	PASS	929.77	[43, 35]	78	Chr5(GRCh3	0.244	0.567	0.494	0.473	0.364	0.394	0.524
5	178557142	A	G	ADAMTS2 (A	NM_014244	N/A	intron_varia	0.491	0.463	0.487	0.413	0.5102	303		0/1	No	PASS	920.77	[54, 39]	93	Chr5(GRCh3	0.420	0.631	0.439	0.532	0.492	0.463	0.475
5	178563125	A	T	ADAMTS2 (A	NM_014244	N/A	intron_varia	N/A	0.197	N/A	N/A	0.2455	170		0/1	No	PASS	1308.77	[53, 47]	100	Chr5(GRCh3	NA	NA	NA	NA	NA	NA	NA
5	178565001	C	T	ADAMTS2 (A	NM_014244	N/A	intron_varia	N/A	0.131	N/A	N/A	0.2174	147		0/1	Yes	PASS	1441.77	[32, 55]	87	Chr5(GRCh3	NA	NA	NA	NA	NA	NA	NA
5	178634672	C	T	ADAMTS2 (A	NM_014244	NP_055059.2	missense_v	0.354	0.432	0.297	0.380	0.3043	194		0/1	No	PASS	1882.77	[72, 62]	134	Chr5(GRCh3	0.388	0.240	0.664	0.307	0.296	0.358	0.512
5	178634547	G	A	ADAMTS2 (A	NM_014244	NM_014244	synonymou	0.171	0.136	0.197	0.129	0.1905	134		0/1	No	PASS	2829.77	[83, 100]	183	Chr5(GRCh3	0.128	0.084	0.004	0.205	0.205	0.195	0.203
5	178555045	G	A	ADAMTS2 (A	NM_014244	NM_014244	synonymou	0.202	0.130	0.235	0.050	0.2417	168		0/1	No	PASS	2245.77	[60, 85]	145	Chr5(GRCh3	0.043	0.253	0.096	0.270	0.240	0.163	0.149
5	178562967	G	A	ADAMTS2 (A	NM_014244	NM_014244	synonymou	0.223	0.197	0.237	0.246	0.2468	171		0/1	No	PASS	1492.77	[63, 59]	122	Chr5(GRCh3	0.256	0.264	0.097	0.270	0.242	0.175	0.149
5	178770981	A	G	ADAMTS2 (A	NM_014244	NM_014244	synonymou	0.399	N/A	0.352	0.224	0.4015	249		0/1	No	PASS	3499.77	[165, 130]	295	Chr5(GRCh3	0.234	0.568	0.493	0.462	0.360	0.401	0.522
5	178634619	C	T	ADAMTS2 (A	NM_014244	NM_014244	synonymou	0.929	C:0.075	0.926	0.894	0.9322	390		1/1	No	PASS	7181.77	[0, 225]	225	Chr5(GRCh3	0.893	0.957	0.999	0.959	0.922	0.930	0.914
10	97385242	A	G	ALDH18A1 (	NM_002860	N/A	intron_varia	0.175	0.194	0.155	0.080	0.1918	135		0/1	No	PASS	2358.77	[86, 77]	163	Chr10(GRCh	0.073	0.111	0.487	0.187	0.166	0.161	0.157
10	97369939	C	T	ALDH18A1 (	NM_002860	N/A	intron_varia	0.410	0.280	0.490	0.205	0.4629	267		0/1	No	PASS	3348.77	[107, 126]	233	Chr10(GRCh	0.198	0.541	0.088	0.481	0.483	0.423	0.306
10	97373966	A	C	ALDH18A1 (	NM_002860	N/A	intron_varia	0.443	0.298	0.533	0.218	0.4859	276		0/1	No	PASS	1466.77	[42, 44]	86	Chr10(GRCh	0.215	0.561	0.088	0.523	0.530	0.447	0.321
10	97397227	T	C	ALDH18A1 (	NM_002860	N/A	intron_varia	0.684	T:0.357	0.717	0.568	0.7212	361		1/1	No	PASS	4751.77	[0, 129]	129	Chr10(GRCh	0.564	0.698	0.763	0.647	0.713	0.654	0.622
10	97371317	A	G	ALDH18A1 (	NM_002860	N/A	intron_varia	N/A	0.280	N/A	N/A	0.3836	221		0/1	No	PASS	1010.77	[19, 27]	46	Chr10(GRCh	NA	NA	NA	NA	NA	NA	NA
10	97381077	C	CT	ALDH18A1 (	NM_002860	N/A	intron_varia	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/1	Yes	PASS	31.74	[2, 3]	5	Chr10(GRCh	NA	NA	NA	NA	NA	NA	NA
10	97392969	G	A	ALDH18A1 (	NM_002860	N/A	intron_varia	N/A	G:0.376	N/A	N/A	0.5601	286		1/1	No	PASS	4498.77	[0, 122]	122	Chr10(GRCh	NA	NA	NA	NA	NA	NA	NA
12	124197099	C	T	ATP6V0A2 (A	NM_012463	N/A	5_prime_UT	0.283	0.272	0.375	0.398	0.3657	227		0/1	No	PASS	1186.77	[42, 44]	86	Chr12(GRCh	0.555	0.439	0.187	0.524	0.534	0.468	0.386
12	124197280	A	C	ATP6V0A2 (A	NM_012463	N/A	intron_varia	0.325	0.327	0.377	0.484	0.3836	241		0/1	No	PASS	1084.77	[55, 40]	95	Chr12(GRCh	0.537	0.228	0.066	0.336	0.402	0.361	0.375
12	124220055	T	C	ATP6V0A2 (A	NM_012463	N/A	intron_varia	0.641	T:0.319	0.607	0.502	0.5793	323		0/1	No	PASS	1057.77	[40, 41]	81	Chr12(GRCh	0.505	0.791	0.944	0.639	0.600	0.643	0.631
12	124209352	C	T	ATP6V0A2 (A	NM_012463	N/A	intron_varia	0.675	C:0.250	0.621	0.677	0.6049	330		0/1	No	PASS	3611.77	[86, 95]	181	Chr12(GRCh	0.688	0.808	0.946	0.679	0.617	0.671	0.668
12	124207098	T	C	ATP6V0A2 (A	NM_012463	N/A	intron_varia	N/A	T:0.249	N/A	N/A	0.4974	268		0/1	No	PASS	1744.77	[58, 51]	109	Chr12(GRCh	NA	NA	NA	NA	NA	NA	NA
12	124218359	T	G	ATP6V0A2 (A	NM_012463	N/A	intron_varia	N/A	T:0.250	N/A	N/A	0.4936	266		0/1	No	PASS	820.77	[44, 30]	74	Chr12(GRCh	NA	NA	NA	NA	NA	NA	NA
12	124229429	T	C	ATP6V0A2 (A	NM_012463	NM_012463	splice_regi	0.693	T:0.201	0.631	0.820	0.6151	332		0/1	No	PASS	2418.77	[133, 101]	234	Chr12(GRCh	0.834	0.815	0.949	0.681	0.625	0.681	0.669
12	124210782	T	C	ATP6V0A2 (A	NM_012463	NM_012463	synonymou	0.675	T:0.250	0.621	0.677	0.6049	330		0/1	No	PASS	2080.77	[61, 70]	131	Chr12(GRCh	0.688	0.808	0.945	0.679	0.617	0.671	0.668
12	124209332	T	C	ATP6V0A2 (A	NM_012463	NM_012463	synonymou	0.679	T:0.249	0.630	0.679	0.6087	332		0/1	No	PASS	3867.77	[97, 106]	203	Chr12(GRCh	0.689	0.809	0.945	0.682	0.623	0.678	0.668
5	177036043	A	G	B4GALT7 (A	NM_007255	N/A	intron_varia	0.997	A:0.007	1.000	0.976	0.9795	383		1/1	No	PASS	4749.77	[0, 145]	145	Chr5(GRCh3	0.973	0.998	1.000	1.000	1.000	1.000	1.000
5	177031954	A	G	B4GALT7 (A	NM_007255	N/A	intron_varia	N/A	A:0.383	N/A	N/A	0.5575	283		1/1	No	PASS	4031.77	[0, 90]	90	Chr5(GRCh3	NA	NA	NA	NA	NA	NA	NA
5	177031967	T	C	B4GALT7 (A	NM_007255	N/A	intron_varia	N/A	T:0.033	N/A	N/A	0.8056	316		1/1	No	PASS	4332.77	[0, 104]	104	Chr5(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103343470	G	A	COL11A1 (A	NM_001854	N/A	3_prime_UT	N/A	0.104	N/A	N/A	0.055	42		0/1	No	PASS	1214.77	[35, 40]	75	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103427844	T	A	COL11A1 (A	NM_001854	N/A	intron_varia	0.094	0.052	0.112	0.021	0.1202	87		1/1	No	PASS	5016.77	[0, 152]	152	Chr1(GRCh3	0.018	0.034	0.003	0.140	0.118	0.098	0.116
1	103444679	T	G	COL11A1 (A	NM_001854	N/A	intron_varia	0.689	T:0.371	0.696	0.270	0.6931	352		1/1	No	PASS	7893.77	[0, 236]	236	Chr1(GRCh3	0.251	0.699	0.912	0.705	0.694	0.681	0.825
1	103461508	T	A	COL11A1 (A	NM_001854	N/A	intron_varia	0.953	T:0.076	0.960	0.798	0.9744	390		1/1	No	PASS	2067.77	[0, 62]	62	Chr1(GRCh3	0.788	0.976	1.000	0.969	0.960	0.964	0.985
1	103496620	G	T	COL11A1 (A	NM_001854	N/A	intron_varia	0.959	G:0.057	0.957	0.853	0.9744	390		1/1	No	PASS	2101.77	[0, 59]	59	Chr1(GRCh3	0.854	0.978	1.000	0.970	0.960	0.967	0.985
1	103354939	C	CTG	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	-:0.331	N/A	N/A	N/A	N/A	N/A	0/1	No	PASS	635.73	[36, 26]	62	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103356072	CA	C	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	-:0.144	N/A	N/A	0.0614	62		0/1	Yes	PASS	1632.73	[70, 75]	145	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103356168	A	C	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	A:0.373	N/A	N/A	0.6036	293		0/1	No	PASS	1151.77	[34, 33]	67	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103364120	T	G	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	0.090	N/A	N/A	0.0448	32		0/1	Yes	PASS	469.77	[7, 13]	20	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103364396	C	T	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	0.090	N/A	N/A	0.0448	34		0/1	No	PASS	724.77	[23, 21]	44	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103364409	A	T	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	0.139	N/A	N/A	0.0473	36		0/1	No	PASS	674.77	[19, 18]	37	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA
1	103364618	A	T	COL11A1 (A	NM_001854	N/A	intron_varia	N/A	0.090	0.073	0.134	0.0524	40		0/1	No	PASS	760.77	[26, 33]	59	Chr1(GRCh3	NA	NA	NA	NA	NA	NA	NA

genAP interpreter

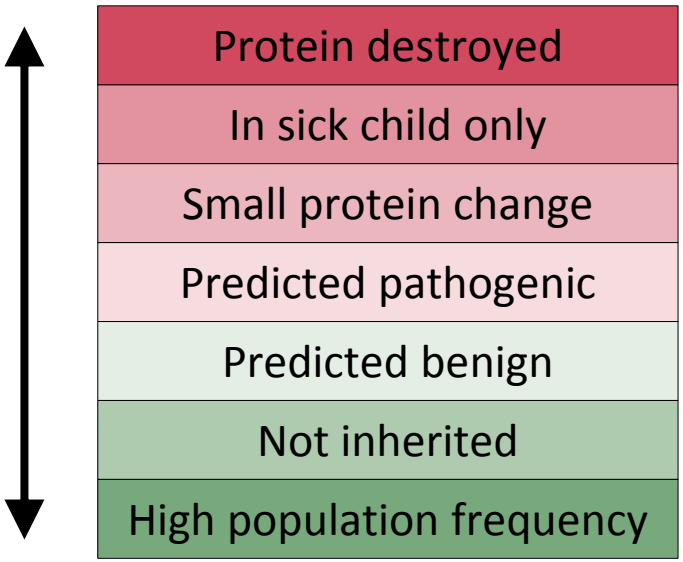


- Stepwise process
- Evaluate annotation
- Evaluate references
- Summary and clinical classification

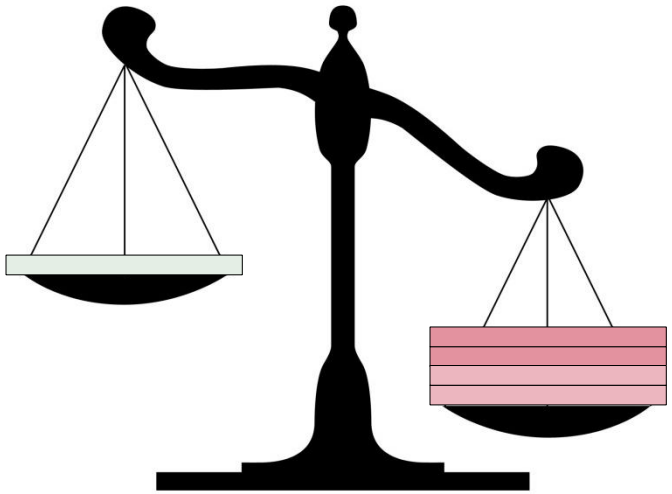
Rules-based interpretation

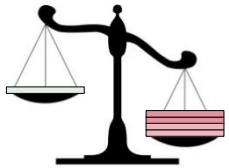
Pathogenic

Examples



Benign

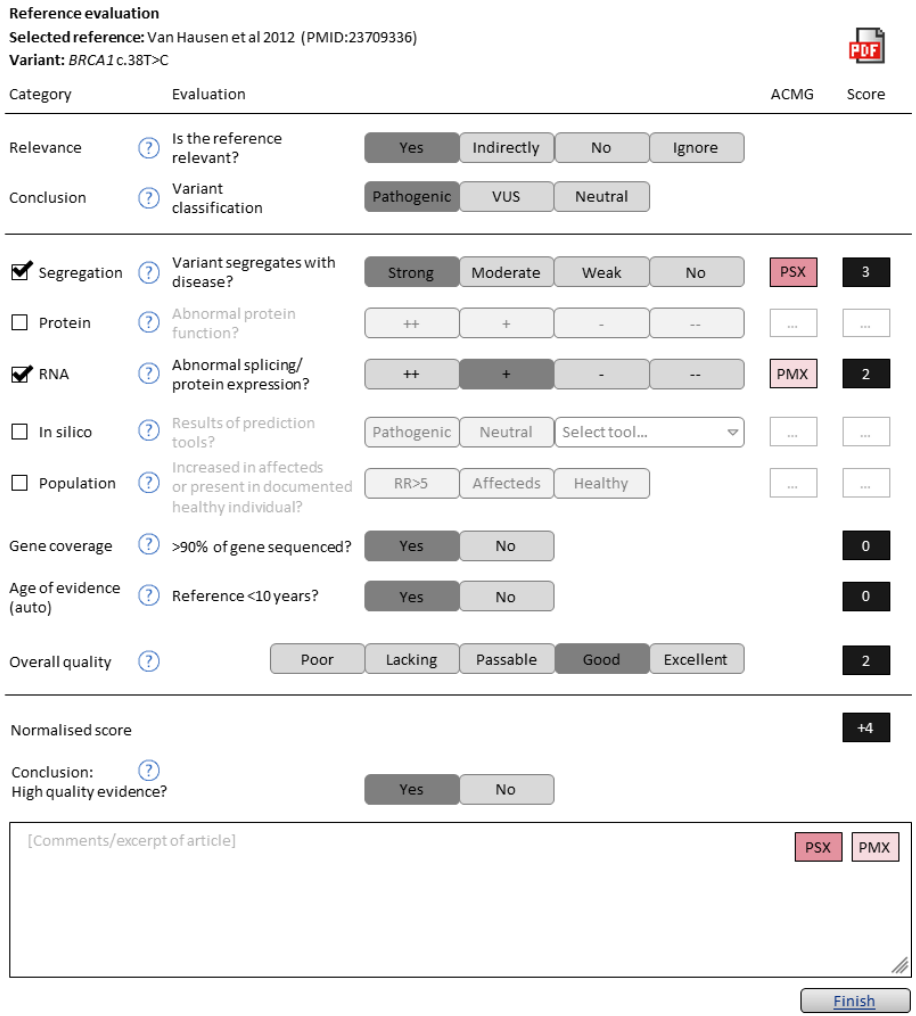




-rules from ACMG

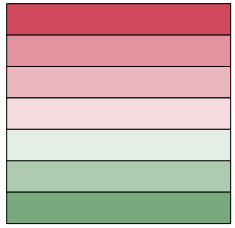
Classification	Rule	Colour
Pathogenic	(i) 1 Very strong (PVS1) AND (a) ≥1 Strong (PS1–PS4) OR (b) ≥2 Moderate (PM1–PM6) OR (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) OR (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) OR (iii) 1 Strong (PS1–PS4) AND (a) ≥3 Moderate (PM1–PM6) OR (b) 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR (c)1 Moderate (PM1–PM6) AND ≥4 supporting (PP1–PP5)	
Likely pathogenic	(i) 1 Very strong (PVS1) AND 1 moderate (PM1–PM6) OR (ii) 1 Strong (PS1–PS4) AND 1–2 moderate (PM1–PM6) OR (iii)1 Strong (PS1–PS4) AND ≥2 supporting (PP1–PP5) OR (iv) ≥3 Moderate (PM1–PM6) OR (v) 2 Moderate (PM1–PM6) AND ≥2 supporting (PP1–PP5) OR (vi)1 Moderate (PM1–PM6) AND ≥4 supporting (PP1–PP5)	
Benign	(i) 1 Stand-alone (BA1) OR (ii) ≥2 Strong (BS1–BS4)	
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) OR (ii) ≥2 Supporting (BP1–BP7)	
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory	

Literature reference evaluation

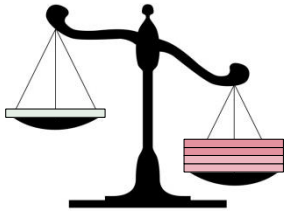


Rules-based answer

Collect and weigh data:
- annotation
- referance evaluation



Apply weighted rules



Suggested classification with summary

Response from test users:

“When is it available??”

Status

- In place
  - Automated sequence processing and annotation
  - Working prototype of interpreter on TSD 2.0 (wxPython)
- In development
  - Complete rewrite of the interpreter (WebUI+REST API)
  - New rules engine
  - Beta by December 2015
- Test access
  - Medicloud

Some of the people involved

- Project management:
  - Thomas Grünfeld (OUS)
- Steering group:
  - Dag Undlien (OUS)
  - Margunn Aanestad (IFI)
  - Hans Eide (USIT)
  - Sissel Jor (OUS)
- Legal issues:
  - Heidi Bentzen (JUR)
  - Marit Stubø (JUR)
- Clinical analyses:
  - Morten C. Eike (OUS)
  - Eidi Nafstad (OUS)
- System development:
  - Tony Håndstad (OUS)
  - Espen Skorve (IFI)
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