Methods	Type	Category	Core model	Damaging	Tolerable	Training data	Testing data	AUC clinvar benchmark	AUC TP53 benchmark	Version
FATHMM	Score	Functionnal	Hidden Markov models	≤ 1.5	> 1.5	SNVs from HGMD (November 2011) and UniProt (November 2011)	SNVs from VariBench database (November 2011), SwissVar (February 2011) and four cancer-associated genes (BRCA1, MSH2, MLH1, and TP53) (Hicks et al. 2011)	0.694	0.877	Current version: FATHMM v2.3
fitCons	Score	Functionnal	INSIGHT (Inference of Natural Selection from Interspersed Genomically coHerent elementS)	> 0.7	< 0.7	Genomes of 54 unrelated human individuals	three types of functional elements	0.611	0.521	Current version: V1.01 28-Aug-2014
LRT	Score	Functionnal	Likelihood ratio test of codon neutrality	< 0.001	> 0.001	Coding sequences of 32 vertebrate species	three human genomes (Levy et al. 2007; Wang et al. 2008; Wheeler et al. 2008)	0.789	0.731	Last updated: November 20, 2009
Mutation Assessor	Score	Functionnal	Combinatorial entropy formalism	> 1.9	≤ 1.9	SNVs from COSMIC database (release 49)	SNVs from UniProt (HUMSAVAR, release 2010_08), IARC TP53 database and COSMIC database (release 49)	0.850	0.880	Dec 31, 2015 Release3
MutationTaster	Score	Functionnal	Naive Bayes classifier	> 0.5	≤ 0.5	SNVs from dbSNP, OMIM, HGMD and the literature	SNVs from dbSNP, OMIM, HGMD and the literature	0.610	0.568	Apr 2014 Mutation Taster2 published. training SNVs from 1000 G and HGMD
PolyPhen2-HDIV	Score	Functionnal	Naive Bayes classifier	> 0.453	< 0.453	SNVs from UniRef100 (release 15.12 of 15-Dec-2009) and UniProtKB/Swiss-Prot (release 57.12 of 15-Dec-2009)	SNVs from UniProtKB/Swiss-Prot (release 57.12 of 15-Dec-2009)	0.839	0.865	Last updated: Mar 08, 2012; current version: PolyPhen-2 v2.2.2 (r394) Feb 23, 2012
PolyPhen2-HVAR	Score	Functionnal	Naive Bayes classifier	> 0.447	< 0.447	SNVs from UniRef100 (release 15.12 of 15-Dec-2009) and UniProtKB/Swiss-Prot (release 57.12 of 15-Dec-2009)	SNVs from UniProtKB/Swiss-Prot (release 57.12 of 15-Dec-2009)	0.865	0.883	Last updated: Mar 08, 2012; current version: PolyPhen-2 v2.2.2 (r394) Feb 23, 2012
PROVEAN	Score	Functionnal	Delta alignment score	≤ 2.5	> -2.5	SNVs from UniProt/HUMSAVAR (Release 2011_09)	SNVs from UniProt (Release 2011_09) and experimental datasets from mutagenesis experiments, previously carried out for the E.coli LacI protein (Markiewicz et al. 1994) and the human tumor suppressor TP53 protein	0.858	0.898	Last updated: Jan 30, 2015 current version: v1.1.5 May 7, 2014
SIFT	Score	Functionnal	Position-specific scoring matrix	≤ 0.05	> 0.05	1,750 deleterious and 2,254 tolerant nsSNVs of E. coli LacI gene	4004 substitutions from LacI (Markiewicz et al. 1994; Suckow et al. 1996), 336 substitutions from HIV-1 protease (Loeb et al. 1989), and 2015 substitutions from bacteriophage T4 lysozyme (Rennell et al. 1991)	0.860	0.879	Last updated: Aug 2011; current version: SIFT v. 1.03
VEST3	Score	Functionnal	Random Forest	> 0.5	< 0.5	SNVs from HGMD (2012v2) and the exome sequencing project (ESP6500 accessed 07/2012)	SNVs from HGMD (2012v2) and the exome sequencing project (ESP6500 accessed 07/2012)	0.929	0.912	most recent version: VEST-4. Positive class expanded and updated to HGMD (2017.1). Neutral class changed to ExAC Release 1 (2/2017)
GERP++	Score	Conservation	Maximum likelihood evolutionary rate estimation	> 2	< 2	Genomes of 34 mammals	Genomes of 33 other mammalian	0.739	0.732	not updated
phastCons	Score	Conservation	Two-state phylogenetic hidden Markov Model	> 0.999	≤ 0.999	Genomes of seven vertebrates, Genomes of 20 mammals	five vertebrate genomes, four insect genomes, two Caenorhabditis genomes, and seven Saccharomyces genomes.	0.767	0.751	Current version: PHAST 1.4 October, 2016, Genomes of 100 vertebrates
PhyloP	Score	Conservation	Distributions of the number of substitutions based on a phylogenetic hidden Markov model	> 2	< 2	Genomes of seven vertebrates, Genomes of 20 mammals	100,000 fourfold degenerate sites extracted from alignments of up to 19 species for the 44 ENCODE regions (Margulies et al. 2007)	0.848	0.802	Current version: PHAST 1.4 October, 2016, Genomes of 100 vertebrates
SiPhy	Score	Conservation	Inferring nucleotide substitution pattern	> 12	< 12	Genomes of 29 mammals	ENCODE regions (Birney et al., 2007)	0.776	0.731	Current version: 0.5 May 1, 2009
CADD	Metascore	Both	Linear kernel support vector machine	> 20	≤ 20	16,627,775 high-frequency human-derived alleles and 49,407,057 "simulated" variants	SNVs from MLL2 gene (Makythanasis et al), ESP, HBB gene and ClinVar database (release date June 16 2012), somatic mutations from p53, variants from two enhancers and one promoter	0.877	0.841	Current version: Webserver v1.3 CADD v1.1: Dec 2, 2014, a slighly extended and updated annotation set
DANN	Metascore	Both	Deep neural network	> 0.99	< 0.99	16,627,775 high-frequency human-derived alleles and 49,407,057 "simulated" variants	3,325,555 "observed" variants and "simulated" variants	0.807	0.752	not updated
Eigen	Metascore	Both	Hierarchical model	> 0	< 0	Variants from dbNSFP v2.7	variants from ClinVar database, MLL2, CFTR, BRCA1 and BRCA2 genes for Mendelian diseases, de novo mutations associated with ASD, EPI, ID and SCZ, GWAS and eQTL SNPs, noncoding cancer mutations from the COSMIC database	0.871	0.849	Current version: Eigen and Eigen-PC v1.1
FATHMM-MKL	Metascore	Both	Multiple kernel learning	> 0.5	≤ 0.5	SNVs from HGMD (release 2013.4) and 1000G	SNVs from HGMD (release 2013.4), 1000G and ClinVar	0.822	0.804	Current version: FATHMM v2.3
GenoCanyon	Metascore	Both	Statistical Model	> 0.999	≤ 0.999	ENCODE project	variants from ClinVar in June 2014	0.683	0.679	Not updated
M-CAP	Metascore	Both	Gradient boosting trees	> 0.025	≤ 0.025	SNVs from HGMD Pro version 2015.2 and ExAC version 0.3 (Jan 13, 2015 release)	rare SNVs from HGMD Pro version 2015.2, 1000G, patient exomes and Mendelian mutations associated with BRCA1, BRCA2, CFTR, MLL2	0.814	0.803	Not updated
MetaLR	Metascore	Both	logistic regression	> 0.5	≤ 0.5	SNVs from UniProt database	SNVs from 57 publications (after 1 January 2011) from the journal Nature Genetics, CHARGE sequencing project and VariBench dataset II	0.874	0.898	Not updated
MetaSVM	Metascore	Both	support vector machine	> 0	≤ 0	SNVs from Uniprot database	SNVs from 57 publications (after 1 January 2011) for the journal Nature Genetics, CHARGE sequencing project and VariBench dataset II	0.858	0.578	Not updated
REVEL	Metascore	Both	Random Forest	> 0.4	< 0.4	SNVs from HGMD version 2015.2, Missense exome sequencing variants from ESP, ARIC, KGP	SNVs from SwissVar disease (release 2015_10), ClinVar database and variants from ESP, ARIC, KGP	0.920	0.901	Not updated