Supplemental Online Content

AlDubayan SH, Conway JR, Camp SY, et al. Detection of pathogenic variants with germline genetic testing using deep learning vs standard methods in patients with prostate cancer and melanoma. *JAMA*. doi: 10.1001/jama.2020.20457

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eTable 1 is in Supplement 2

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Patient cohorts and genomic data collection

Germline whole-exome sequencing (WES) data of a convenience cohort of 1072 patients with prostate cancer were used for the initial performance evaluation of Genome Analysis ToolKit (GATK) and DeepVariant (DV) (Figure 1 and eFigure 1). These patients were sequenced as part of large cancer genomics sequencing projects including the Cancer Genome Atlas (TCGA) and the Stand Up 2 Cancer-Prostate Cancer Foundation (SU2C-PCF) studies [1–3]. Details of the clinical and molecular data of these patients have been previously described [3]. Raw sequencing data of these patients are accessible through dbGAP (https://www.ncbi.nlm.nih.gov/gap/). Tumor WES data of 268 PC patients were available for somatic validation of the detected germline putative loss-of-function (pLOF) variants in the OMIM genes as well as the 12 multi-gene panels.

To evaluate if variant detection performance findings of GATK and DV, on the prostate cancer cohort, extends to other histopathological and clinical phenotypes, we used germline WES data of an independent convenience cohort of 1295 patients with primary or metastatic melanoma from 10 previously published studies including the Cancer Genome Atlas [4], Hodis et al., 2012 [5], Hayward et al., 2017 [6], Krauthammer et al., 2015 [7], Van Allen et al., 2014 [8], Snyder et al., 2014 [9], Wagle et al., 2014 [10], Van Allen et al., 2015 [11], Johnson et al. 2017 [12], and Miao et al., 2018b [13] (Figure 1 and eFigure 1). Germline data of these patients were generated by sequencing circulating lymphocytes or adjacent normal tissue which had a normal histopathological examination. In addition to the germline genomic data of these patients, paired tumor WES data from 286 patients with prostate cancer and all patients with melanoma were used for secondary analyses to validate the presence of germline pLOF variants that were detected in the germline samples. All cohorts had institutional review board (IRB) approval for access from the original studies. All germline WES data were generated by the original studies using paired-end, short-read Illumina platforms (Illumina, Inc, San Diego, USA).

Data harmonization and quality control

Raw genomic data of all samples were obtained from the respective data repository, as previously described [3]. All “FASTQ” and binary alignment map (BAM) files aligned to GRCh37 were realigned to hg19 using “Picard tool kits (https://github.com/broadinstitute/picard). GATK (version 3.7) DepthOfCoverage [14] was used to determine the mean target coverage of germline and tumor samples, and deTiN [15] was used to estimate the degree of tumor-in-normal contamination. A genetic relatedness method was run on the germline samples of the prostate cancer and melanoma cohorts to exclude potential duplicates. The final sample sets (PC: 1072 patients, melanoma: 1295 patients) of this study only included unique unrelated samples. For the discovery analysis, we applied stringent quality control (QC) steps. Germline WES with a sample-wide mean depth of coverage under 20X or those with significant tumor-in-normal (TiN) contamination were excluded from all analyses. All germline WES of 1072 PC patients used for the discovery analysis passed all QC metrics (eFigure 2 A-C). To mimic challenging genomic analysis scenarios, we validated our findings using a heterogenous germline WES dataset of 1295 patients with melanoma who were sequenced at multiple time

points using different sequencing platforms with variable quality and depth of sequencing (eFigure 2 D-F).

Detection of germline variants

To evaluate the performance of GATK, the standard germline variant detection method, against the deep learning-based method, DeepVariant (DV), we ran both algorithms on the germline WES data of the prostate cancer and melanoma cohorts (Figure 1 and eFigure 1). For each sample, the same BAM file was used to run GATK and DV without any further preprocessing.

1- GATK:

Genome Analysis Toolkit (GATK) HaplotypeCaller (HC) pipeline (version 3.7) was used to call germline variants according to the GATK "Best Practices" [16]. More specifically, we ran GATK HC on each sample individually to call single nucleotide variants (SNVs) and short indels via the de-novo assembly of haplotypes of the examined regions. This per sample analysis generates an intermediate file called genomic variant calling format (gVCF) file that has a record for every position of the examined genomic intervals. We then aggregated the generated single sample gVCFs and performed joint genotyping using GATK "GenotypeGVCFs" as recommended by the current germline variant calling Best Practices [14,16]. At each position of the input gVCFs, GATK "GenotypeGVCFs" module evaluates the genotype likelihood across all the samples and produce one quality score for each unique genomic alteration across the cohort (n=1072 for the prostate cancer cohort and n=1295 for the melanoma cohort), which is then used by the GATK "Variant Quality Score Recalibration (VQSR)" module to assign a "Quality Tranche to each variant and perform variant filtering. To filter low-quality calls, VQSR uses highly validated variant callsets (such as dbSNP and the 1000 Genomes) to build a model that can be then applied to calculate the probability of each variant being real. As recommended by the GATK Best Practices, the SNVs VQSR model was trained using HapMap3.3 and 1KG Omni 2.5 SNP sites, and a 99.6% sensitivity threshold was applied to filter variants. In addition, Mills et. al. 1KG gold standard and Axiom Exome Plus sites were used for VQSR indel recalibration using a 99% sensitivity threshold [17]. Specific commands and parameters used for the GATK pipeline are summarized in the Supplementary Note.

2- DeepVariant:

Germline variants of the prostate cancer and melanoma cohorts were also independently called using DeepVariant version 0.6.0 (eFigure 1). DeepVariant is a deep convolutional neural network, based on the inception framework, trained to identify inherited variants from read pileup pseudo-images. We ran DeepVariant using recommended settings for the analysis of exomes (https://github.com/google/deepvariant). First, candidate variants were identified within the targeted sequencing region using "make_examples." Next, candidate variants were classified through the "call_variants" module, using the saved Exome checkpoint for version 0.6.0, and "postprocess_variants" was run to format the VCF file. All computation was performed on the Google Cloud Platform, and Nvidia K80 GPUs were used to perform inference. Specific commands used for the DV and its parameters are summarized in the Supplementary Note.

Selection of Mendelian gene sets

In this study, we analyzed disease-causing variants in three gene sets, the germline cancer predisposition genes, the American College of Medical Genetics (ACMG) genes, and the Online Mendelian Inheritance in Men (OMIM) genes. The germline cancer predisposition genes were selected based on the level of evidence supporting their Mendelian disease susceptibility. This is composed of the well-curated COSMIC germline cancer census gene set (v86; http://cancer.sanger.ac.uk/census) and the germline cancer gene set listed in Huang et al. 2018 [18] and Rahman 2014 [19]. Cancer genes with preliminary evidence of cancer association or those with no established inheritance pattern were removed. In total, 118 cancer predisposition genes were examined in the prostate cancer and melanoma cohorts (eTable 1). In addition to cancer genes, we also examined 59 Mendelian high-penetrance genes associated with severe life-threatening diseases that have been deemed clinically actionable by the American College of Medical Genetics (ACMG) (eTable 1). Given the well-established clinical utility, pathogenic variants in the ACMG genes are highly recommended to be disclosed to patients, even if discovered incidentally, regardless of the patient's phenotype [20]. Finally, we also expanded our head-to-head comparison of the examined methods by performing an exome-wide analysis of the clinically relevant genes by evaluating putative loss-of-function (pLOF) variants in 5197 Mendelian disease-causing genes in the OMIM database (collectively called the OMIM genes) (eTable 1) (https://www.omim.org/). In addition to these three gene sets, we also evaluated the number of validated pathogenic variants detected by each method in 12 multi-gene panels clinically used to evaluate cardiovascular disorders, ciliopathies, dermatological disorders, hearing loss, hematological disorders, mitochondrial disorders, neurological disorders, neuromuscular disorders, pulmonary disorders, renal disorders, retinal disorders, and expanded prenatal screening (eTable 2).

Functional annotation

Germline variant annotation of all variants was performed using Variant Effect Predictor (VEP) (version 92.0) from Ensembl [21]. Only variants impacting the canonical transcript of the examined genes were included.

Ancestry inference

To infer the genetic ancestry of the prostate cancer and melanoma samples, we first performed principal-component analysis (using hail v0.2- https://hail.is/docs/0.2/index.html) and uniform manifold approximation and projection (using umap v0.4.3- https://pypi.org/project/umap-learn/) on these samples and 1000G reference samples. Next, we trained a Random Forest classifier (using sklean v0.20.0- https://scikit-learn.org/stable/whats_new/v0.20.html#version-0-20-0) on the first 10 principal components and UMAP values from 2504 participants in the 1000 Genome cohort that have self-reported ancestry information. We then used the trained random forest classifier to assign one of the five 1000 Genome defined super populations - European, African American, Admixed American, East Asian, and South Asian - to each of our prostate cancer and melanoma samples. A more detailed description of subpopulations included in 1000 Genome continental ancestries can be found here, https://www.internationalgenome.org/category/population/.

Germline variant pathogenicity evaluation

Pathogenicity of the detected germline variants in the cancer predisposition and ACMG gene sets across all cohorts was evaluated using the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) clinically-oriented guidelines [22]. Germline variants detected by GATK and DV in the prostate cancer and melanoma cohorts were independently evaluated for pathogenicity, by two clinical geneticists, against the published literature and publicly-available databases such as ClinVar and gene-specific databases. Population minor allele frequencies were extracted from publicly-available databases such as the Exome Aggregation Consortium (ExAC) and the Genome Aggregation Database (gnomAD) [23]. Based on the available evidence, germline variants were classified into five categories: benign, likely benign, variants of unknown significance, likely pathogenic, and pathogenic [22]. Only germline variants that had sufficient evidence of pathogenicity to be classified as pathogenic or likely pathogenic variants were included in this study (hereafter collectively referred to as pathogenic variants). Variants of unknown significance (VUSs) were excluded from all analyses. For the expanded analysis using 5197 OMIM genes, we analyzed the performance of each germline variant detection tool by examining putative LOF (pLOF) variants in this expanded gene set. Putative LOF variants were defined as 1) rare variants with minor allele frequency (MAF) <1% in all reference populations in gnomAD that are expected to produce a truncated gene product (i.e., stop codon, frameshift, and canonical splice site variants) and 2) rare missense variants (MAF<1%) that are annotated as pathogenic or likely pathogenic in the Clinical Variation database (ClinVar) (https://www.ncbi.nlm.nih.gov/clinvar/).

Validation of detected germline variants

1- Manual review of the variants using a genome browser:

Pathogenic germline variants in the germline cancer predisposition and ACMG gene sets, that were detected by the standard variant detection method and deep learning, were validated by examining the Binary Alignment Map (BAM) file using the integrative Genomics Viewer (IGV; v2.3.81) (Figure 1) [24]. IGV snapshots of pathogenic variants were generated using the IGV Snapshot Generator (https://github.com/stevekm/IGV-snapshot-automator). IGV snapshots of each called pathogenic variants (in the cancer predisposition and ACMG gene sets) were independently manually evaluated, in a blind fashion, by three computational biologists with expertise in next-generation sequencing analysis. Variants were marked as “True Positive” or “False Positive,” depending on the depth of sequencing, the number of alternative allele reads, the variant allelic fraction (VAF), and the presence of artifacts at or around the examined variant site. Variants that were called “True Positive” by at least two examiners were considered real variants. Otherwise, the variant was labeled as an artifactual call.

2- Tumor-profiling:

Although the manual review of the IGV snapshot of detected variants is considered the standard protocol for variant review [24], this method is not easily scalable to validate detected pLOF variants in 5197 clinically-relevant protein-coding genes. To examine the validity of variants across the clinically relevant OMIM genes, germline pLOF variants exclusively called by a single method (i.e. *only* GATK or DV) were validated using the matched tumor samples (Figure 1). We

followed the following process to validate candidate germline variants using tumor sequencing data:

1. Collected tumor base-pair counts using Samtools [25].
2. Determined if the tumor sequencing depth is sufficient to identify three or more alternate reads given the observed reads in the normal tissue sample.
    a. For sites without a somatic copy number alteration event, this power was computed using the beta-binomial distribution; a site was considered powered if $p(X > 3 \mid N,a,b) > 0.95$. Where a and b are the normal alternate and reference counts, respectively, and N is the sequencing depth in the tumor.
    b. For sites with somatic copy number alterations, power was computed using the binomial distribution were sites were considered powered if $p(X>=3 \mid N,p) > 0.95$ where N is the sequencing depth of the tumor and p is the minor allele fraction of the overlapping copy number segment.
3. If the tumor is sequenced sufficiently deeply, the site is considered validated if 3 or more alternate reads supporting the variant were found in the tumor; otherwise, the site is called a “False Positive”.

For the prostate cancer cohort (n=1072), only 286 tumor WES data were available for tumor-based validation, while all matched tumor samples of the melanoma cohort (n=1295) were available for this analysis.

Performance metrics

We evaluated the ability of the standard variant detection method, GATK, and deep learning, DV, to detect clinically relevant variants in the cancer predisposition genes, the ACMG genes, and the OMIM genes. For each gene set, we looked at the absolute number of manually validated pathogenic germline or computationally validated pLOF variants called by each method . We also evaluated the sensitivity (also known as the true positive rate or recall) of each method by looking at the proportion of validated variants detected by that method to the total number of real pathogenic variants detected by the combined approaches in that gene set (eTable 3). Similarly, the specificity (also known as the true negative rate) of GATK and DV were calculated as the proportion of validated negative calls (i.e. correctly identifying the reference allele as such) by each method relative to the total number of true reference (non-variant) alleles in that gene set. The reference variant set that was used to compare GATK and DV performance in this study was created through manual review of IGV snapshots (see Validation of detected germline variants). In addition, we looked at precision, defined as the proportion of correctly called variants to the total number of called variants, and accuracy, which is defined as the ratio of the total number of correct assignments (i.e., true positive and true negative) to the total number of all evaluated variants [26]. In addition, for each method, we evaluated the positive predictive value (PPV), defined as the probability of a called variant being a validated “real” variant, and negative predictive value (NPV), defined as the probability of a called reference allele being a truly reference allele (i.e., not an alternative variant). Finally, we looked at the absolute number of validated variants that were detected by the standard approach and deep learning in 12 commonly used multi-gene panels (eTable 2).

Characteristics of variants exclusively detected by DV or GATK

To evaluate the properties of variants exclusively detected by deep learning and the standard method, the sequencing depth of true positive and false positive variants exclusively called by DV and GATK was compared using the non parametric Mann–Whitney tests. In addition, we calculated the likelihood of each variant category (frameshift, stop codon, and splice variants) to be correctly identified by deep learning and standard methods by generating odds ratios (ORs), 95% CI and P values using two-sided Fisher's exact test.

Post hoc analysis for adopting a more stringent criterion (3 of 3 examiners) for "true-positive" variants

To evaluate the effect of defining "True-Positive" variants as variants that were judged to be valid variants by all three examiners on the primary outcomes of this study (see Validation of detected germline variants), the absolute number and fraction of manually validated pathogenic variants in the cancer-predisposition genes were calculated. The sensitivity of each method was calculated by assessing the fraction of true-positive variants to the total number of detected variants (true-positives and false-positives). The sensitivity values of both methods were compared using two-sided Chi-square tests.

Calculation of the Receiver Operating Characteristics (ROC) curve

For both models, DV and GATK, a set of potential thresholds of the quality scores (QUAL for GATK, and GQ for DV) are calculated for the called variants. For each threshold (th) in the thresholds set, a new model prediction is calculated (a variant is called if QUAL>th). The new predictions are compared to the ground truth (present in the BAM file or not) and the True positive (TP), True Negatives (TN), False Positive (FP), and False Negative (FN) rates are calculated. The true positive rate is calculated as the number of true positives divided by the sum of the number of true positives and the number of false negatives:

```
True Positive Rate (TPR) = True Positives (TP) / (True Positives (TP)
+ False Negatives (FN))
```

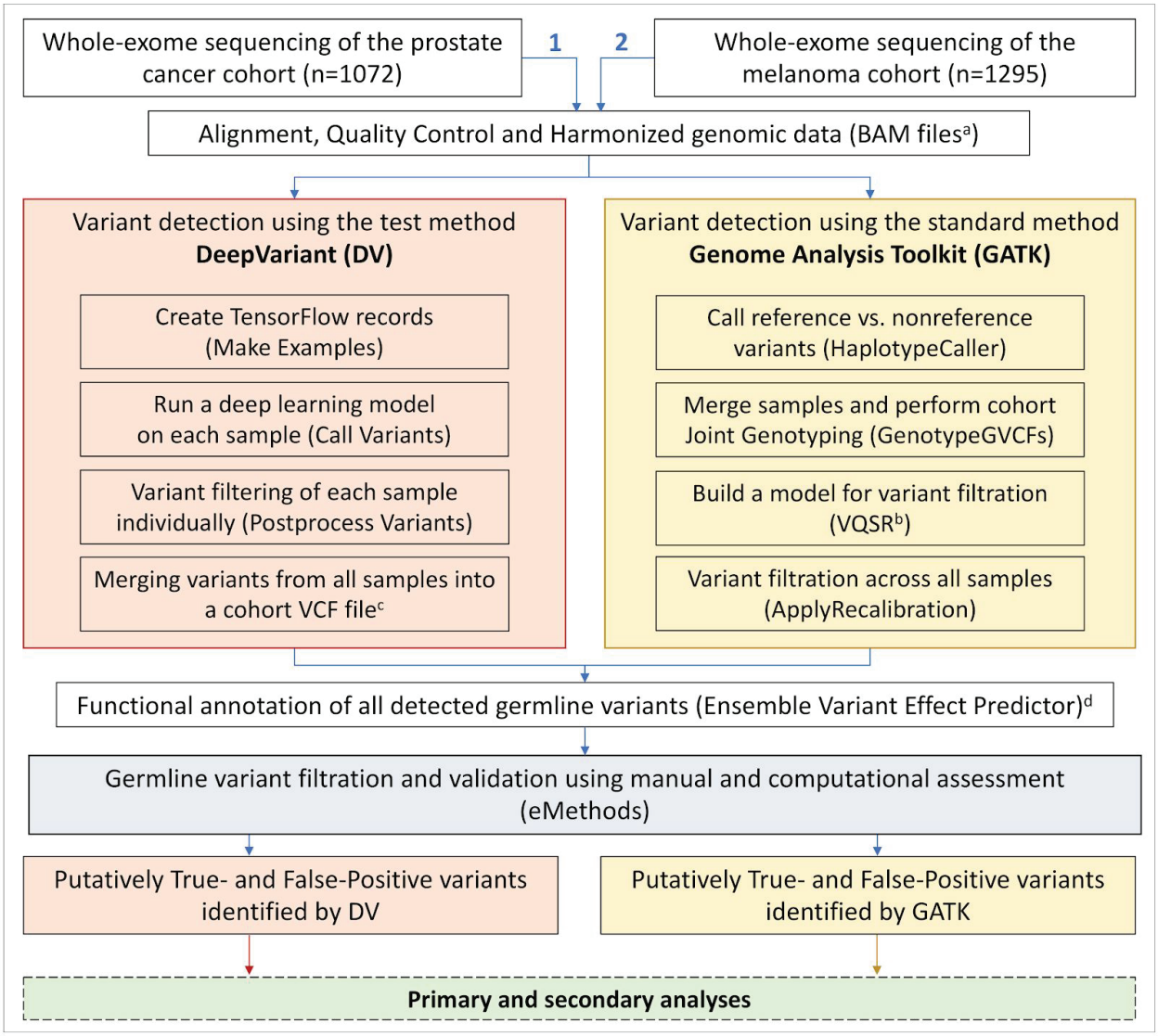
The false-positive rate is calculated as the number of false positives divided by the sum of the number of false positives and the number of true negatives:

```
False Positive Rate (FPR)= False Positives (FP) / (False
Positives(FP) + True Negatives (TN))
```

The Receiver Operator Curve (ROC) is reported by plotting the false positive rate (FPR) on the X-axis and the true positive rate (TPR) on the Y-axis. The area under the ROC curve (AUC) is calculated for both DV and GATK models.

eFigures:

eFigure 1: Technical overview of the preprocessing, variant calling, and variant analysis steps.



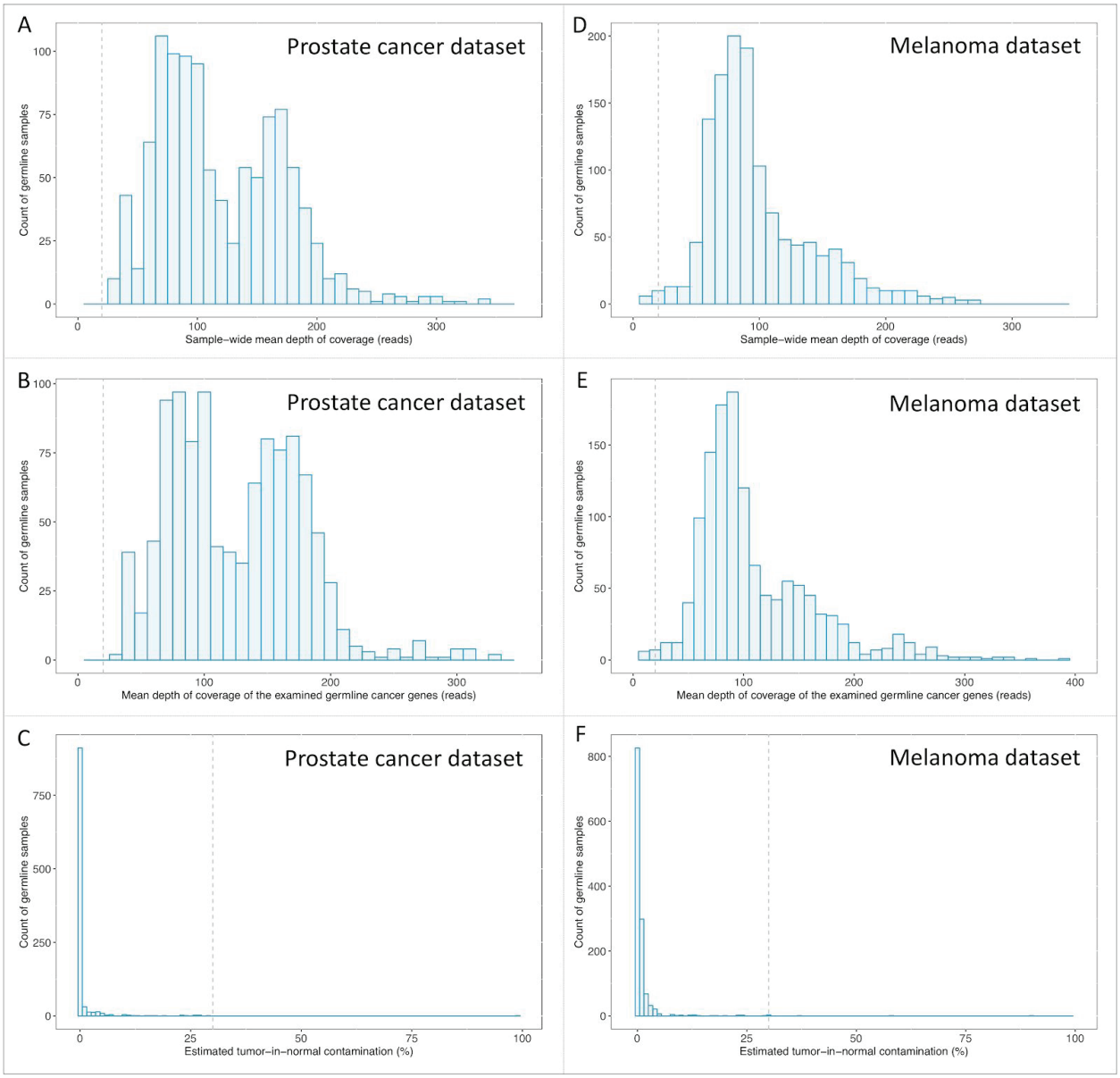
[a] Binary Alignment Map (BAM) files are highly compressed files that are used to represent aligned sequencing reads. They are the most commonly used input format for variant detection and other downstream analyses

[b] Variant Quality Score Recalibration (VQSR) is a step in GATK, the standard germline variant detection pipeline, that determines the quality of each identified variant. The generated quality scores are subsequently used for downstream variant filtration

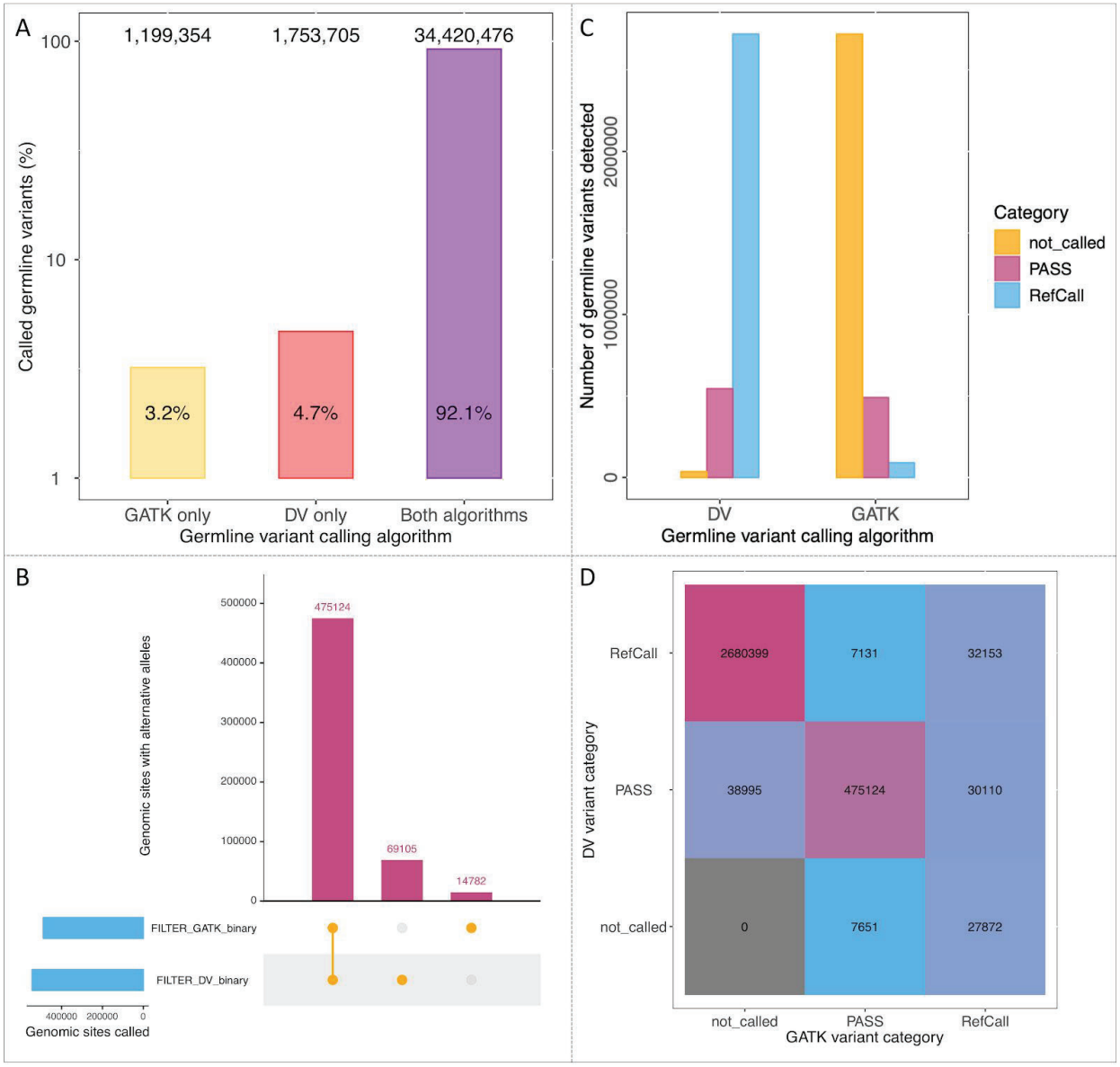
[c] Variant Call Format (VCF) files are the most widely used files to store variants and their functional annotations for sequenced individual samples and cohorts of samples

[d] Ensemble Variant Effect Predictor (VEP) is an annotation tool that provides the functional impact, the conservation scores, and the population level minor allele frequency of each identified germline variant

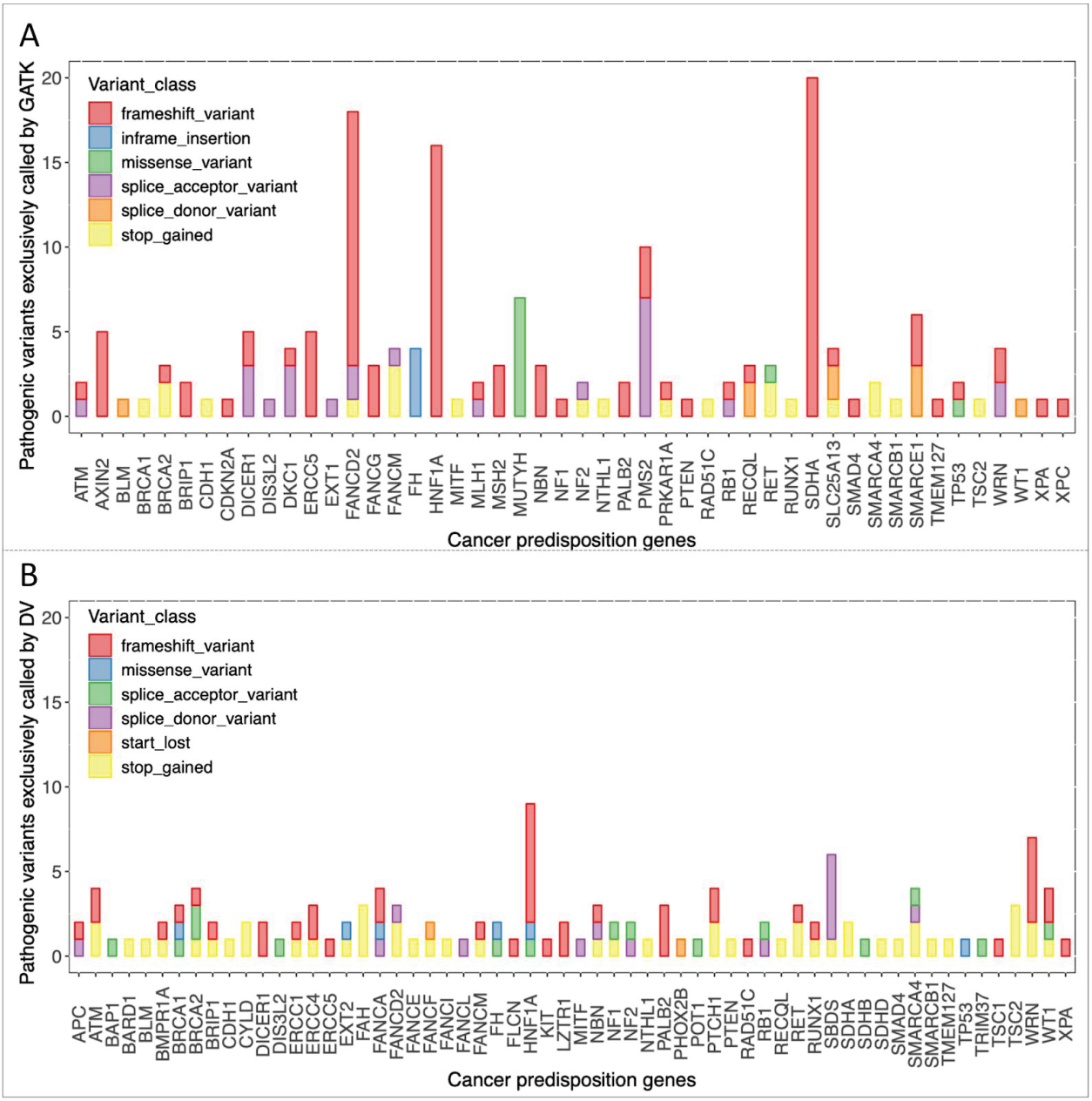
eFigure 2: Sequencing and quality control (QC) metrics of the prostate cancer (A, B, and C) and melanoma (D, E, and F) cohorts. A; The exome-wide depth of coverage for germline WES of the prostate cancer cohort was 105.78X (interquartile range: 78.00-162.64). B; The average coverage of the cancer predisposition genes in patients with prostate cancer was 122.78X. C: The mean tumor-in-normal contamination of the prostate cancer germline data was 0.7%. D&E; The sample-wide and cancer gene average depth of coverage in the melanoma cohort were 86.85X (interquartile range: 70.55-115.90) and 92.07X, respectively. F; The mean tumor-in-normal contamination of the melanoma cohort samples was 1.0%.



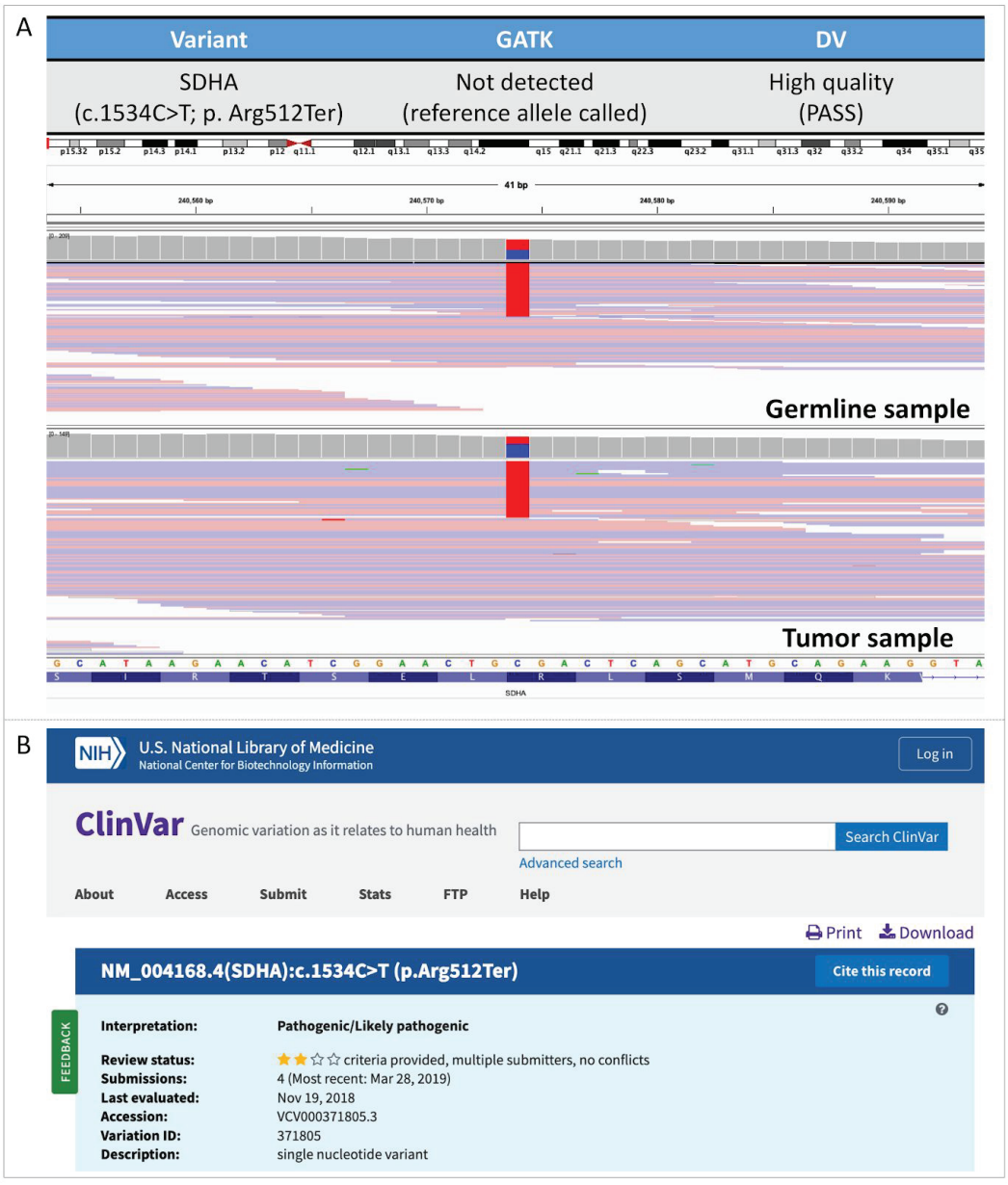
eFigure 3: Exome-wide germline variant detection in 1072 germline samples of patients with prostate cancer. A; only 92.1% of all detected germline variants were called by both the standard (GATK) and deep learning (DV) methods, while 2,953,059 variants were exclusively detected by one of these approaches. B; Of 559,011 unique genomic sites with potential variants that were detected by one or both methods, only 475,124 (85.0%; 95% CI:84.9-85.1) of these genomic sites were concordant between both variant detection tools. C; Number of genomic sites evaluated by the high-sensitivity initial variant detection step of each algorithm ("HaplotypeCaller" for GATK and "Call Variants" for DV). Although both tools aim to flag any site suspected of having a non-reference variant for downstream analysis, most of the sites included for further analysis by DV were not flagged by GATK HaplotypeCaller for further assessment, suggesting multiple modes for variant underdetection. D; Compared to 7,651 unique genetic variant sites exclusively detected by the standard method, nearly 40,000 unique genetic variant sites were exclusively detected by deep learning.



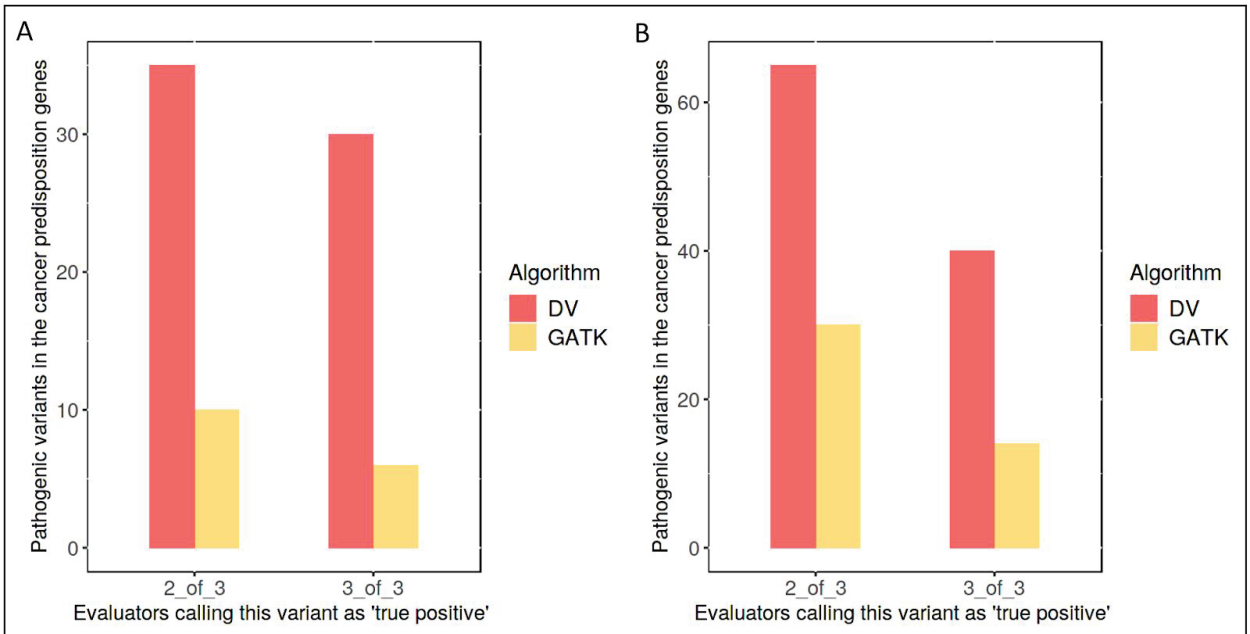
eFigure 4: Pathogenic cancer-predisposition variants discovered in 1295 patients with melanoma. A; A total of 209 pathogenic cancer-risk variants were only identified by the standard method, GATK, in 118 cancer predisposition genes in the melanoma dataset. However, only 32 of these were validated true positive variants. B; A total of 171 pathogenic variants were identified exclusively by deep learning in the cancer-predisposition genes, 51 of which were validated true positive variants.



eFigure 5: A representative pathogenic predisposition variant in the succinate dehydrogenase complex, subunit A (SDHA) gene that was only detected by deep learning but not standard variant calling methodology. A; An IGV snapshot of the variant showed adequate sequencing coverage and a balanced variant allelic fraction (VAF) in both the germline sample (top panel) and the tumor sample (bottom panel). B; This truncating variant in *SDHA* (c.1534C>T; p. Arg512Ter) introduces a stop codon leading to the termination of the gene transcript at codon 512 and is known to be pathogenic in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000371805.3 [accessed Sept. 3, 2019]). In addition, this variant has been frequently seen in patients with paraganglioma, pheochromocytoma, and gastrointestinal stromal tumors (PMIDs: 22955521, 371805, 25720320).



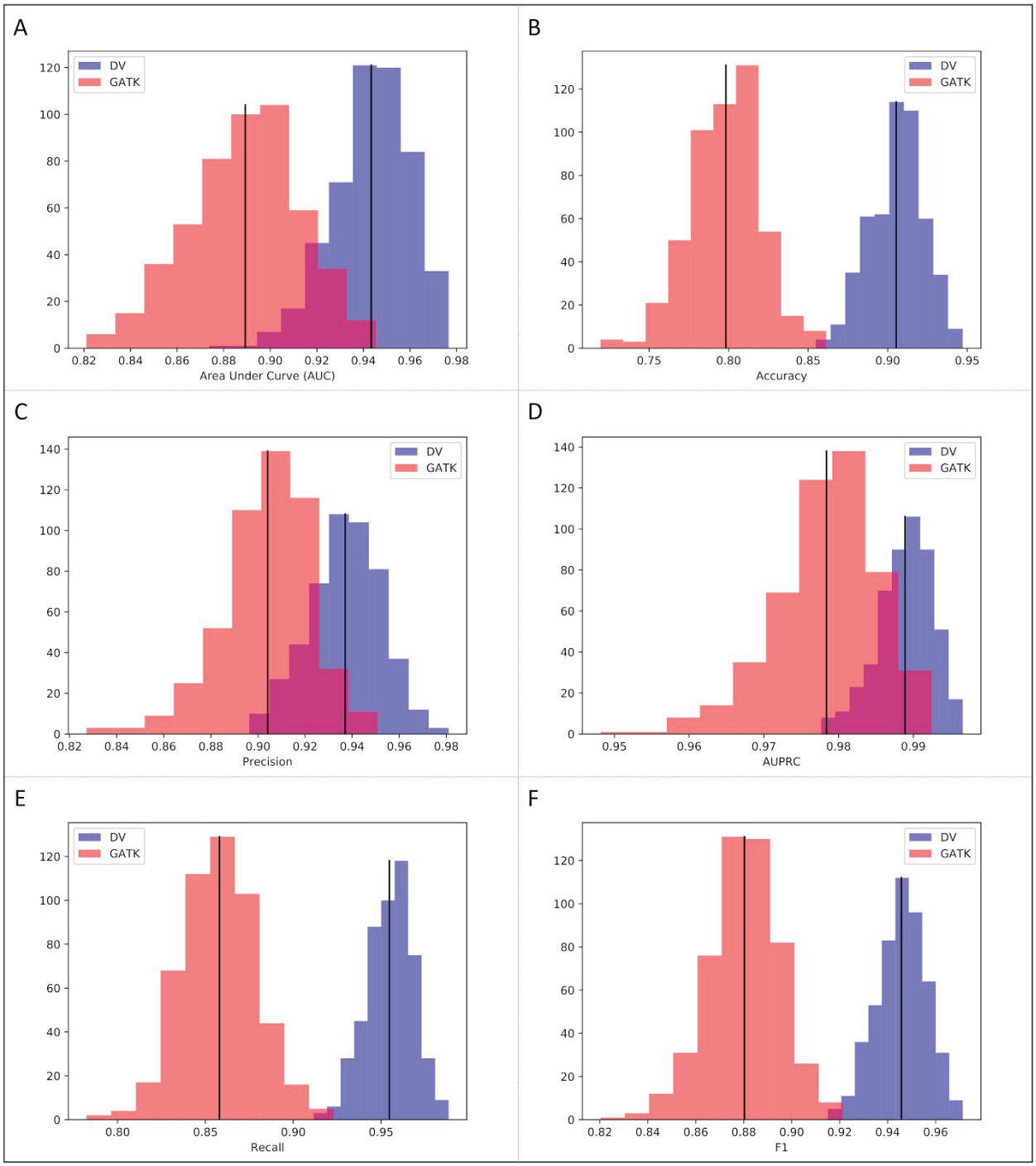
eFigure 6: Effect of considering true positive variants as variants that were considered "valid" by all three examiners. This post hoc analysis showed that although the absolute number and fraction of true positive variants dropped when adopting a more stringent criterion for true positive calls, DV still detected more "true-positive" variants compared to GATK across all cohorts.



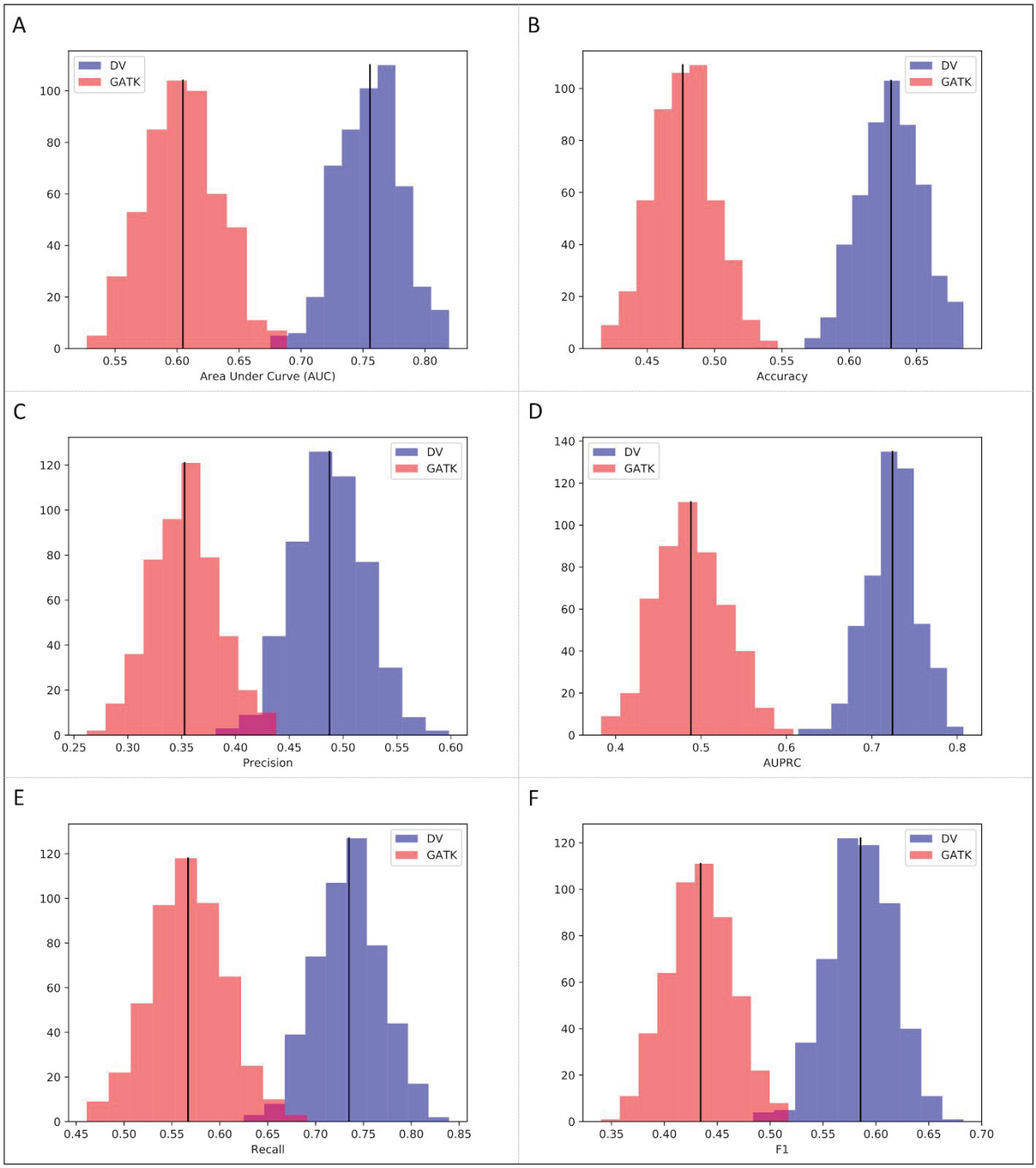
C

Cohorts	True Positive: At least 2 of 3 observers to call the variant "real"			True Positive: All 3 observers to call the variant "real"		
	DV (% of total)	GATK (% of total)	DV vs. GATK	DV (% of total)	GATK (% of total)	DV vs. GATK
PC	35 (72.9)	10 (33.3)	Difference: 39.5%; 95% CI:18.5-60.6; **p<0.001**	30 (62.5)	6 (20%)	Difference: 42.5%; 95% CI:22.7-62.3; **p<0.001**
MEL	65 (37.6)	30 (18.2)	Difference: 19.3%; 95% CI:10.1-28.7; **p<0.001**	40 (23.1)	14 (8.48)	Difference: 14.6%; 95% CI:7.1-22.2; **p<0.001**

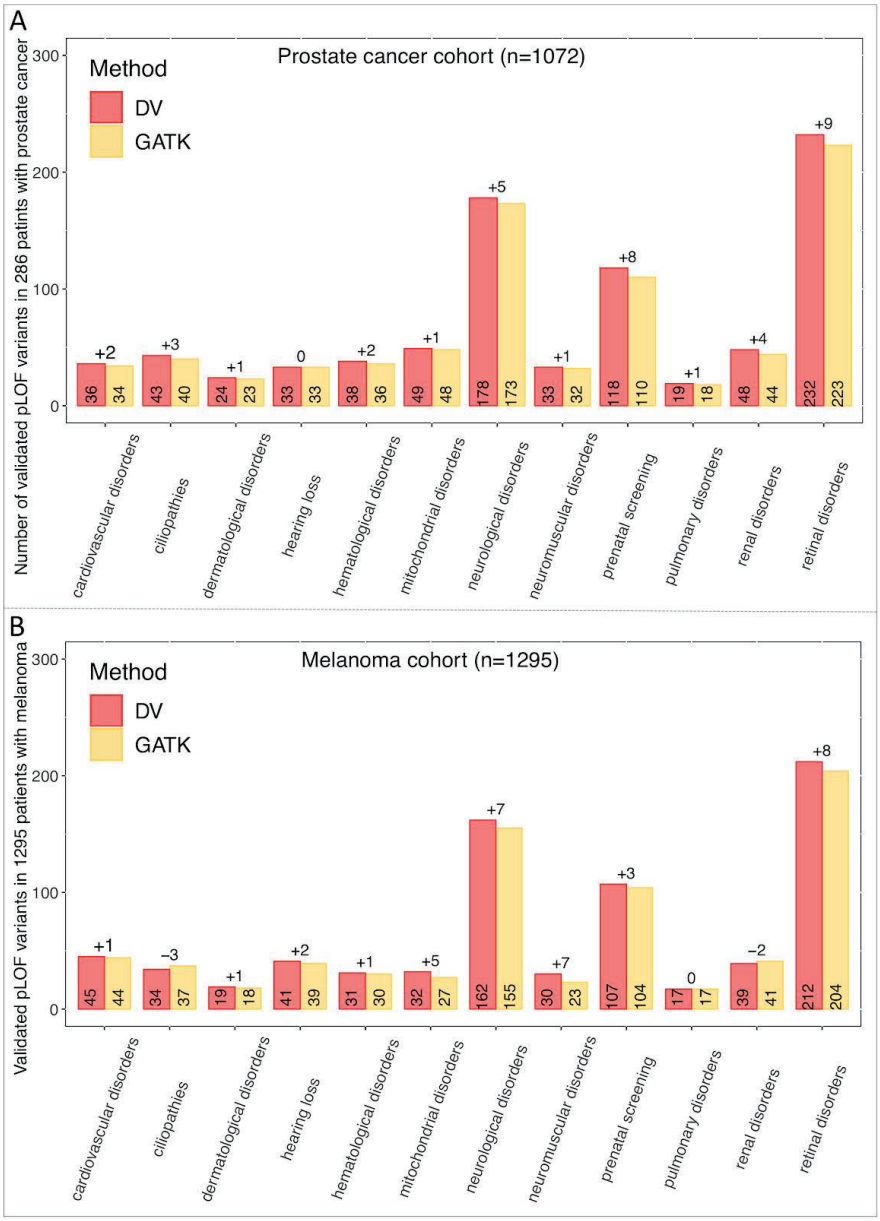
eFigure 7: Performance of GATK and DV models to detect pathogenic variants in 151 cancer predisposition and ACMG genes in 1072 patients with prostate cancer. (AUC: Area under the curve, AuPR: Area under precision-recall)



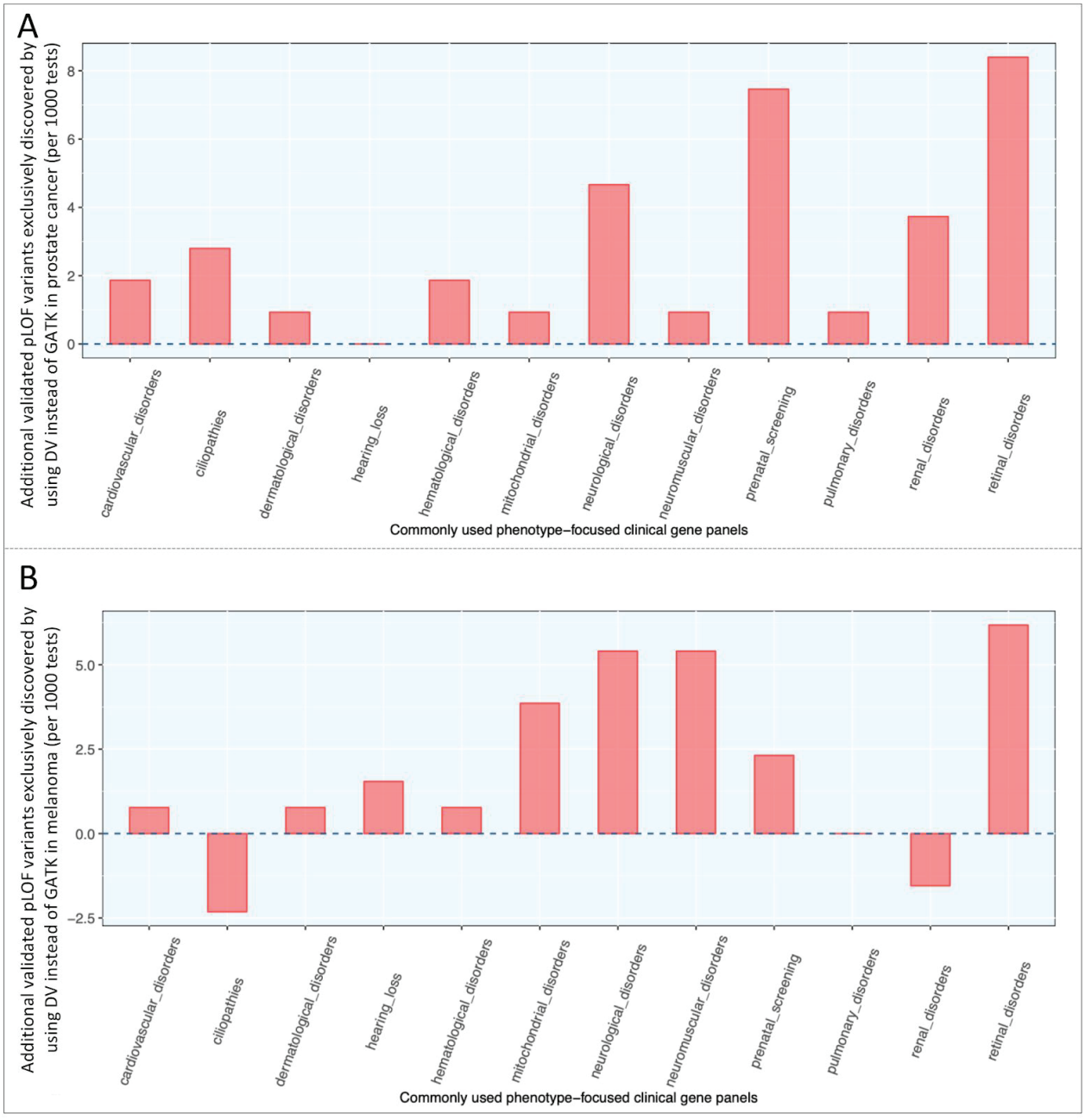
eFigure 8: Performance of GATK and DV models to detect pathogenic variants in 151 cancer predisposition and ACMG genes in 1295 patients with melanoma. (AUC: Area under the curve, AuPR: Area under precision-recall)



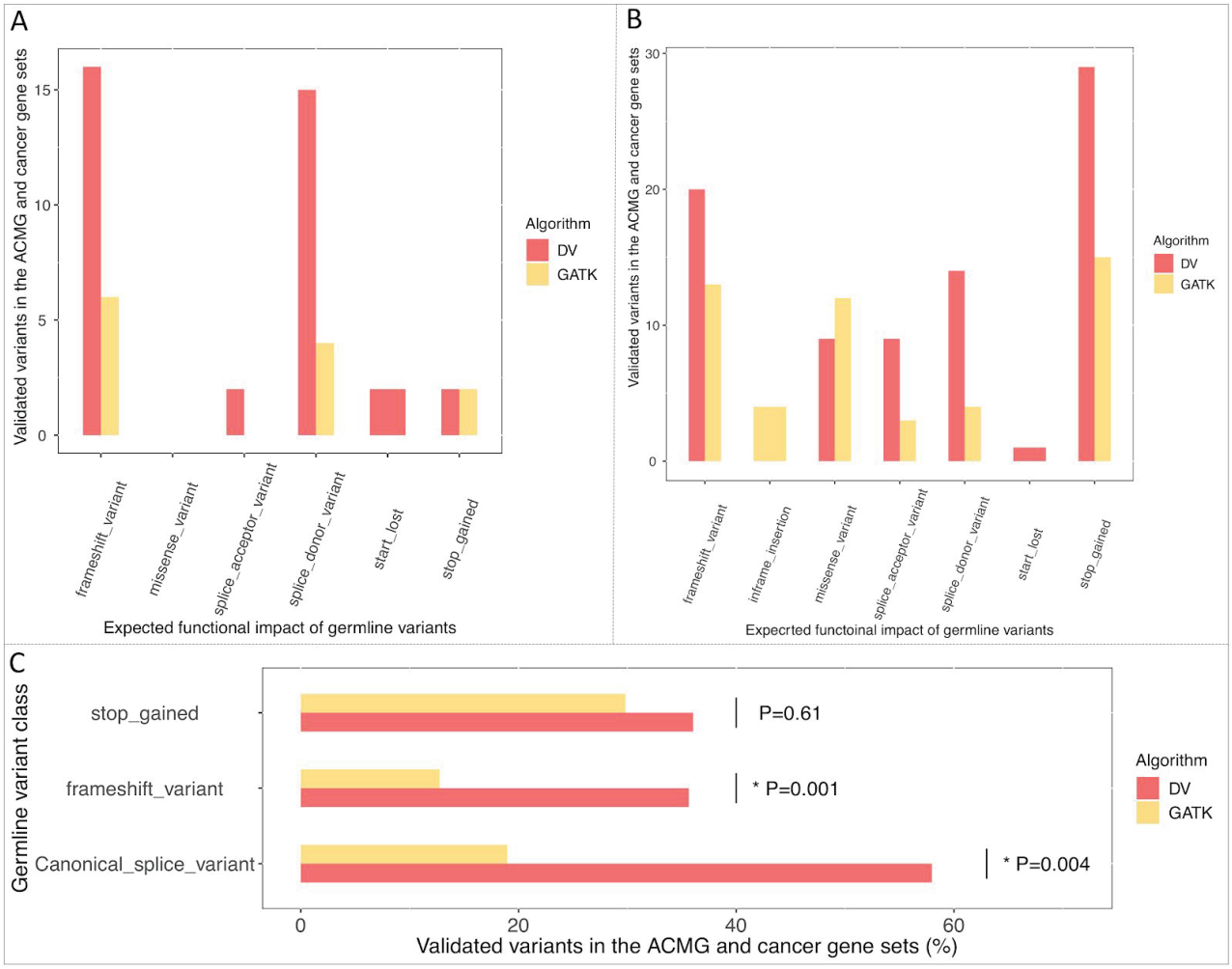
eFigure 9: Performance of the deep learning and standard methods to detect pLOF variants that were judged to be valid in 12 clinically oriented multi-gene panels. A; Analysis of 286 patients with prostate cancer using the deep learning method, DV, identified more pLOF variants that were judged valid (Method) in 11 (91.7%; 95% CI: 61.5-99.8) of the 12 phenotype-targeted multi-gene panels that were evaluated. DV and GATK, the standard method, detected the same number of pLOF variants in one multi-gene panel (8.3%; 95% CI: 0.21-38.5). B; Similarly, analysis of these multi-gene panels in 1295 patients with melanoma showed that the deep learning method identified more pLOF variants, that were judged valid, in 9 panels (75.0%; 95% CI: 42.8-94.5) compared with 2 (16.7%; 95% CI: 2.1-48.4) panels where the standard method detected more pLOF variants that were judged valid while both methods had equal performance in one panel (8.3%; 95% CI: 0.21-38.5). Full names of these clinical multi-gene panels are listed in eTable 2. (DV: DeepVariant, GATK: The Genome Analysis Toolkit, and pLOF: putative loss-of-function)



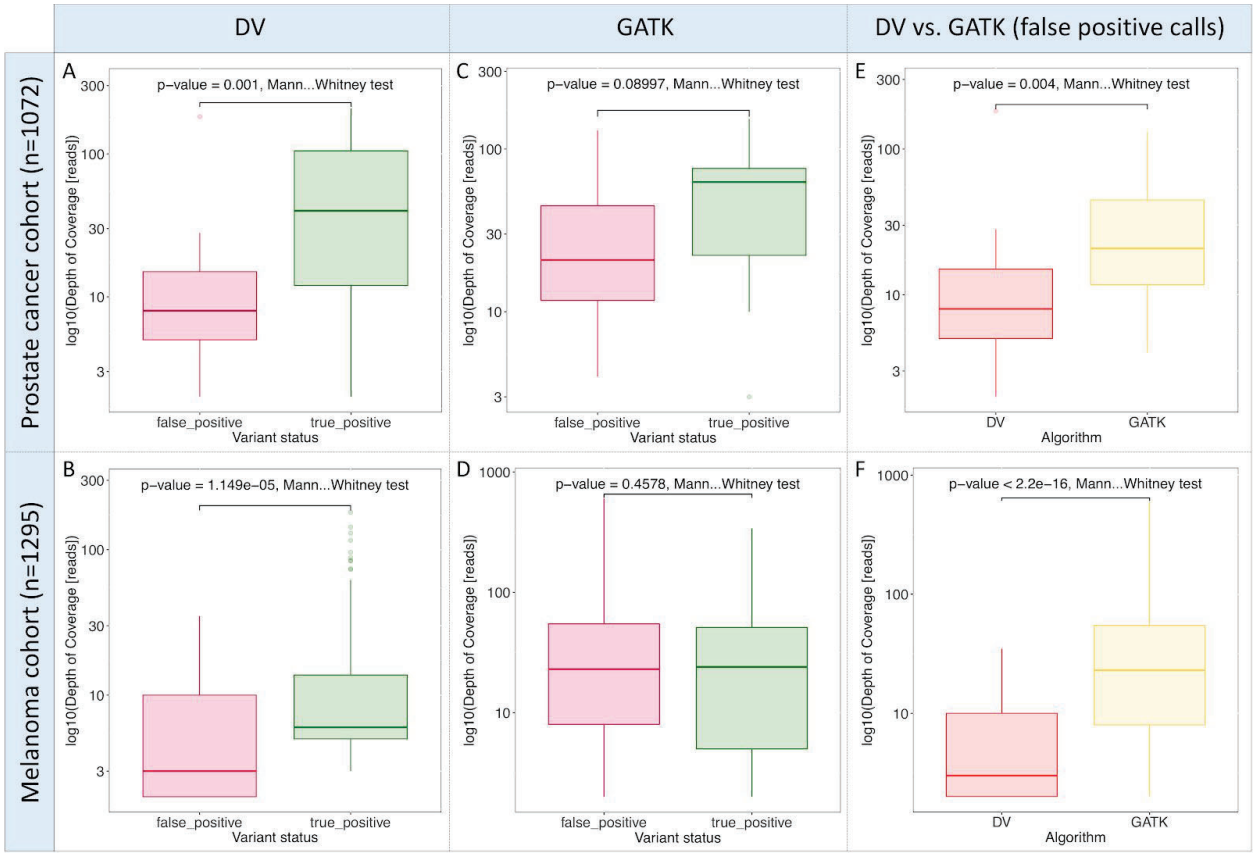
eFigure 10: Analysis of the molecular diagnostic yield of the current standard method and deep learning, towards detecting putative LOF variants in 12 phenotype-based multi-gene panels. A systematic analysis of commonly used clinical multi-gene panels showed superior performance of deep learning across most of the examined gene panels in 286 patients with prostate cancer (A) and 1295 patients with melanoma (B).



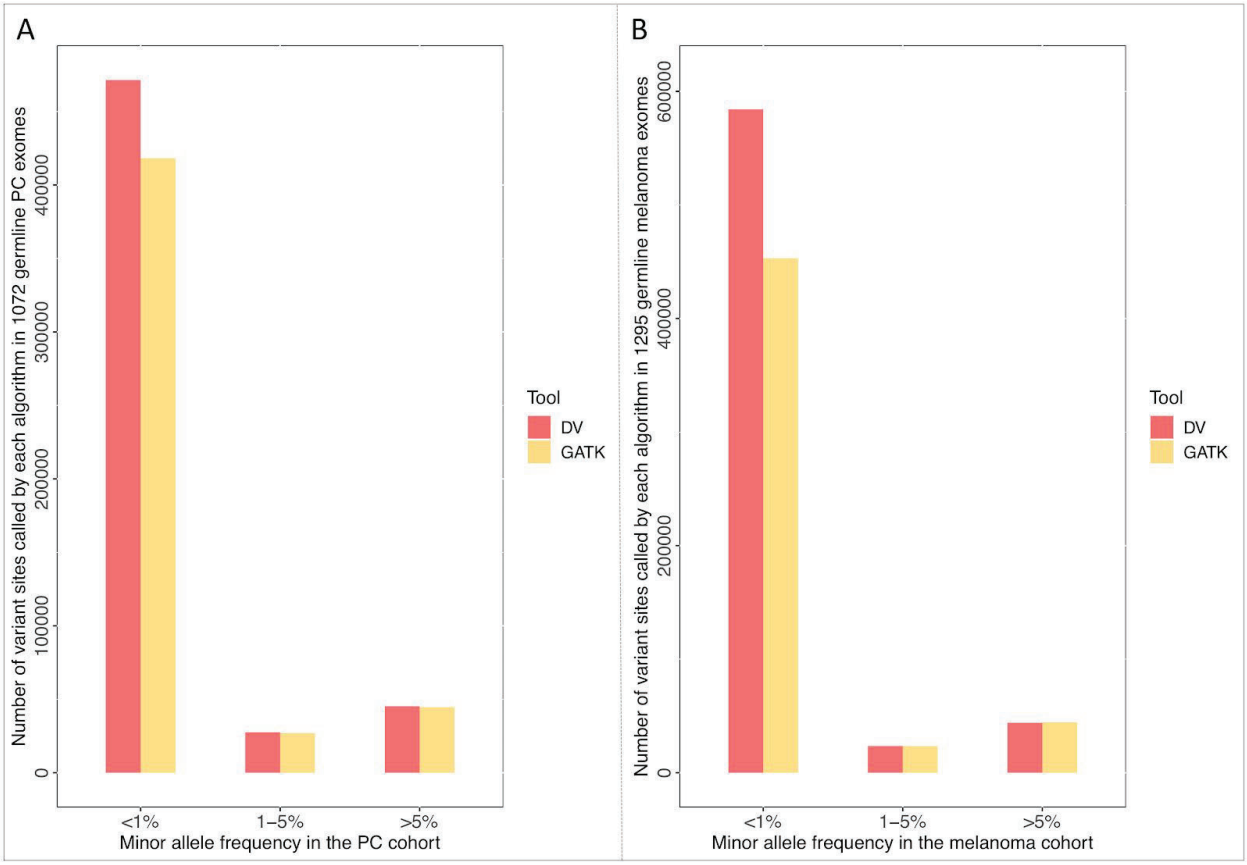
eFigure 11: Characteristics of validated germline pathogenic variants in 151 ACMG and cancer predisposition genes. Regardless of the functional class of the germline pathogenic variants in these genes, DV identified more manually validated pathogenic variants in patients with prostate cancer (A) and those with melanoma (B). C; Validated pathogenic frameshifts and splice variants, exclusively detected by deep learning in both cohorts, were more likely to be deemed "valid" variants upon manual evaluation compared to those exclusively called by the standard method (OR=2.79; 95%CI:1.47-5.29; P=0.001 and OR=3.04; 95%CI:1.39-6.73; P=0.004 for frameshifts and splice variants respectively; two-sided Fisher's exact).



eFigure 12: Depth of sequencing coverage of pathogenic variants exclusively called by deep learning and the gold-standard method in 151 cancer predisposition and ACMG genes. False-positive variants exclusively called by deep learning were in significantly lower coverage genomic regions compared with DV-only validated true positive variants (A & B). However, false-positive variants exclusively called by the standard method had sufficient sequencing coverage which was comparable to the sequencing coverage of the GATK-only true positive calls (C & D), raising concern about additional sources of false-positive calls. E & F; Comparison of the sequencing depth of coverage of false-positive variants exclusively called by deep learning and those exclusively called by the standard method.



eFigure 13: Performance of the standard method, GATK, and deep learning, DV, for detecting common, uncommon, and rare variants (minor allele frequency (MAF) of >5%, 1-5%, and <1% respectively). A; Our analysis shows that deep learning called 1.3% and 2.1% more common (MAF>5%) and uncommon variants (MAF:1-5%), respectively, than the standard method in 1072 germline prostate cancer exomes. However, deep learning identified 53,161 (12.7%) more rare variants (MAF<1%) than the standard approach in this dataset, suggesting a substantially higher performance of deep learning towards detecting this variant subset which is highly enriched for Mendelian disease-causing variants. B; A similar pattern of substantially higher detection rate of rare variants was also seen when analyzing germline WES data of 1295 patients with melanoma.



Supplementary Tables:

eTable 3: Definition of the performance metrics and other terms used in this study

Term	Definition
Valid pathogenic variants	Pathogenic variants were considered valid if they were determined by at least 2 (out of 3) computational biologists to be present in the raw genomic data using a genome visualization tool such as the Integrative Genomics Viewer (IGV). No functional validation using orthogonal methods such as sanger sequencing was conducted in this study.
Valid pLOF variants	Germline putative loss-of-function (pLOF) variants were considered valid if they were also present in the tumor whole-exome sequencing data which was independently generated for that participant. No functional validation using orthogonal methods such as sanger sequencing was conducted in this study.
True-positive	Germline variants were considered true-positive by a particular the germline variant detection method if 1) they were **detected** by that method and 2) were judged to be **valid** (i.e. present in the raw genomic data)
False-positive	Germline variants were considered false-positive by a particular the germline variant detection method if 1) they were **detected** by that method and 2) were judged to be **invalid** (i.e. not present in the raw genomic data)
True-negative	Germline variants were considered true-negative if they were not detected by either of the computational methods OR 1) they were **detected by only the other** method and 2) were **judged to be invalid** (i.e. not present in the raw genomic data)
False-negative	Germline variants were considered false-negative if 1) they were **detected by only the other** method and 2) were **judged to be valid** (i.e. present in the raw genomic data)
The reference variant set	In this study, the combined variant callset, derived from GATK and DV, and their validation status (see above) were considered the "reference variant set" against which the relative performance (relative sensitivity, relative specificity, positive predictive value, and negative predictive value) of GATK and DV were assessed
Relative sensitivity	Relative sensitivity represents the proportion of true-positive variants (i.e. Called and valid) detected by that method to the total number of true-positive variants in the combined variant callset, derived from GATK and DV (i.e. the reference variant set) in that gene set
Relative specificity	Relative specificity represents the proportion of true-negative variants (i.e.called by the other method but invalid) detected by that method to the total number of true-negative variants in the combined variant callset, derived from GATK and DV (i.e. the reference variant set) in that gene set
Positive predictive value (PPV)	This represents the probability of a participant with **a variant** detected by one of the germline variant detection methods, in the examined gene set, **to actually have the molecular genetic change** (i.e. to be a true-positive variant). In this study, PPV does not inform the probability of the patient to develop the clinical disease
Negative predictive value (NPV)	This represents the probability of a participant with **a negative result** in the examined gene set **to not have the molecular genetic change** (i.e. to be a true-negative result). In this study, NPV does not inform the probability of the patient to develop the clinical disease

eTable4: Pathogenic and likely pathogenic variants exclusively detected by deep learning in the cancer predisposition genes in 1072 prostate cancer patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER binary	FILTER updated DV	Manual validation	Pathogenicity classification
11	108175459	ATM	C	T	stop_gained	ENST00000278616.4 :c.5554C>T	ENSP00000278616.4 :p.Gln1852Ter	VQSRTranche SNP99.80to99.90	RefCall	PASS	true_positive	Likely Pathogenic
11	22646871	FANCF	CAG	C	frameshift_variant	ENST00000327470.3 :c.484_485del	ENSP00000330875.3 :p.Leu162AspfsTer103	VQSRTranche INDEL99.40to99.50	RefCall	PASS	true_positive	Pathogenic
16	2103446	TSC2	A	AG	frameshift_variant	ENST00000219476.3 :c.333dup	ENSP00000219476.3 :p.Gln112AlafsTer14	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	2121933	TSC2	CA	C	frameshift_variant	ENST00000219476.3 :c.2096del	ENSP00000219476.3 :p.Gln699ArgfsTer8	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	2133695	TSC2	G	T	splice_acceptor _variant	ENST00000219476.3 :c.3884-1G>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic
16	68771321	CDH1	G	A	start_lost	ENST00000261769.5 :c.3G>A	ENSP00000261769.4 :p.Met1?	not_called	not_called	PASS	true_positive	Likely Pathogenic
17	29557859	NF1	G	A	splice_acceptor _variant	ENST00000358273.4 :c.3114-1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
17	33434123	RAD51D	CT	C	frameshift_variant	ENST00000590016.1 :c.423del	ENSP00000466399.1 :p.Ala142GlnfsTer14	VQSRTranche INDEL99.40to99.50	RefCall	PASS	true_positive	Pathogenic
17	56770093	RAD51C	CG	C	frameshift_variant	ENST00000337432.4 :c.93del	ENSP00000336701.4 :p.Phe32SerfsTer8	not_called	not_called	PASS	false_positive	Pathogenic
19	45922431	ERCC1	TG	T	frameshift_variant	ENST00000013807.5 :c.449del	ENSP00000013807.4 :p.Pro150GlnfsTer26	not_called	not_called	PASS	false_positive	Likely Pathogenic
21	36164503	RUNX1	T	TG	frameshift_variant	ENST00000300305.3 :c.1371dup	ENSP00000300305.3 :p.Ser458GlnfsTer142	not_called	not_called	PASS	false_positive	Likely Pathogenic
21	36164503	RUNX1	T	TG	frameshift_variant	ENST00000300305.3 :c.1371dup	ENSP00000300305.3 :p.Ser458GlnfsTer142	not_called	not_called	PASS	false_positive	Likely Pathogenic
21	36164503	RUNX1	T	TG	frameshift_variant	ENST00000300305.3 :c.1371dup	ENSP00000300305.3 :p.Ser458GlnfsTer142	not_called	not_called	PASS	true_positive	Likely Pathogenic
21	36164503	RUNX1	T	TG	frameshift_variant	ENST00000300305.3 :c.1371dup	ENSP00000300305.3 :p.Ser458GlnfsTer142	not_called	not_called	PASS	true_positive	Likely Pathogenic
22	21348449	LZTR1	T	TG	frameshift_variant	ENST00000215739.8 :c.1510dup	ENSP00000215739.8 :p.Ala504GlyfsTer165	not_called	not_called	PASS	false_positive	Likely Pathogenic
22	21348449	LZTR1	T	TG	frameshift_variant	ENST00000215739.8 :c.1510dup	ENSP00000215739.8 :p.Ala504GlyfsTer165	not_called	not_called	PASS	true_positive	Likely Pathogenic
3	14201258	XPC	T	A	stop_gained	ENST00000285021.7 :c.973A>T	ENSP00000285021.7 :p.Lys325Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor

7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
7	66459197	SBDS	A	G	splice_donor _variant	ENST00000246868.2 :c.258+2T>C	-	VQSRTranche SNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5 :c.659dup	ENSP00000298139.5 :p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5 :c.659dup	ENSP00000298139.5 :p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5 :c.659dup	ENSP00000298139.5 :p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5 :c.659dup	ENSP00000298139.5 :p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5 :c.659dup	ENSP00000298139.5 :p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic

eTable5: Pathogenic and likely pathogenic variants exclusively detected by the standard method, GATK, in the cancer predisposition genes in 1072 prostate cancer patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER updated GATK	FILTER binary	FILTER updated DV	Manual validation	Pathogenicity classification
10	89711926	PTEN	TTAA	T	stop_gained	ENST00000371953.3 :c.545_547del	ENSP00000361021.3 :p.Leu182_Lys183del insTer	PASS	PASS	not_called	false_positive	Pathogenic
10	89711943	PTEN	T	TCC	frameshift_variant	ENST00000371953.3 :c.561_562insCC	ENSP00000361021.3 :p.Tyr188ProfsTer12	PASS	PASS	not_called	false_positive	Likely Pathogenic
11	108198394	ATM	C	*	frameshift_variant	ENST00000278616.4 :c.6998del	ENSP00000278616.4 :	PASS	PASS	not_called	true_positive	Likely Pathogenic
12	21624569	RECQL	T	*	frameshift_variant	ENST00000444129.2 :c.1460del	ENSP00000416739.2 :p.Lys487ArgfsTer3	PASS	PASS	not_called	true_positive	Likely Pathogenic
13	32912964	BRCA2	TGAAA	*	frameshift_variant	ENST00000544455.1 :c.4472_4476del	ENSP00000439902.1 :p.Leu1491ArgfsTer21	PASS	PASS	not_called	true_positive	Pathogenic
15	89858542	FANCI	C	*	frameshift_variant	ENST00000310775.7 :c.3846del	ENSP00000310842.7 :p.Ser1282ArgfsTer13	PASS	PASS	not_called	true_positive	Likely pathogenic
15	91312795	BLM	TGAAG	T	frameshift_variant	ENST00000355112.3 :c.2535_2538del	ENSP00000347232.3 :p.Lys846PhefsTer9	PASS	PASS	not_called	false_positive	Likely Pathogenic
16	68772290	CDH1	G	T	stop_gained	ENST00000261769.5 :c.139G>T	ENSP00000261769.4 :p.Glu47Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
17	17119766	FLCN	C	A	stop_gained	ENST00000285071.4 :c.1228G>T	ENSP00000285071.4 :p.Glu410Ter	PASS	PASS	RefCall	true_positive	Pathogenic
17	29677337	NF1	G	GCAG ATGA GTC	splice_donor _variant	ENST00000358273.4 :c.7457+1_7457+2ins CAGATGAGTC	-	PASS	PASS	not_called	false_positive	Likely pathogenic
17	41226441	BRCA1	G	GA	frameshift_variant	ENST00000471181.2 :c.4644_4645insT	ENSP00000418960.2 :p.Leu1549SerfsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226442	BRCA1	CTCCT CTTGA GATGG	C	frameshift_variant	ENST00000471181.2 :c.4630_4643del	ENSP00000418960.2 :p.Pro1544AlafsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226464	BRCA1	CT	C	frameshift_variant	ENST00000471181.2 :c.4621del	ENSP00000418960.2 :p.Arg1541GlufsTer28	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226466	BRCA1	AT	A	frameshift_variant	ENST00000471181.2 :c.4619del	ENSP00000418960.2 :p.Asn1540IlefsTer29	PASS	PASS	not_called	false_positive	Likely Pathogenic
19	11106905	SMARCA4	G	GGTA ATAC GACT CACT ATAG GCAG	stop_gained	ENST00000429416.3 :c.1613_1614insATA CGACTCACTATAGGC AGATGAGTCTACGTA	ENSP00000395654.1 :p.Gly537_Tyr538insTer	PASS	PASS	not_called	false_positive	Likely Pathogenic

				ATGAGTCTAC								
22	21348433	LZTR1	C	CCGGCGTGGCTGCTGGTG	frameshift_variant	ENST00000215739.8:c.1491_1507dup	ENSP00000215739.8:p.Gly503AlafsTer59	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	215609853	BARD1	A	AT	frameshift_variant	ENST00000260947.4:c.1840_1841insA	ENSP00000260947.4:p.Val614AspfsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	48030639	MSH6	A	AC	frameshift_variant	ENST00000234420.5:c.3261dup	ENSP00000234420.4:p.Phe1088LeufsTer5	PASS	PASS	PASS	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5:c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	58388727	FANCL	C	CGACTCACTATAGGCAGATGAGTCTA	frameshift_variant	ENST00000402135.3:c.964_965insTAGACTCATCTGCCTATAGTGAGTC	ENSP00000385021.3:p.Gly322ValfsTer13	PASS	PASS	not_called	false_positive	Likely Pathogenic
6	35427467	FANCE	C	*	frameshift_variant	ENST00000229769.2:c.1246del	ENSP00000229769.2:p.Gln416LysfsTer9	PASS	PASS	not_called	true_positive	Likely Pathogenic
7	6029587	PMS2	C	*	splice_acceptor_variant	ENST00000265849.7:c.989-1del	-	PASS	PASS	not_called	false_positive	Pathogenic

eTable6: Pathogenic and likely pathogenic variants exclusively detected by the standard method in the cancer predisposition genes in 1295 melanoma patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER Binary GATK	FILTER updated DV	Manual validation	Pathogenicity classification
10	43572713	RET	A	T	stop_gained	ENST00000355710.3:c.7A>T	ENSP00000347942.3:p.Lys3Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
10	43609097	RET	G	T	missense_variant	ENST00000355710.3:c.1853G>T	ENSP00000347942.3:p.Cys618Phe	PASS	PASS	RefCall	false_positive	Likely Pathogenic
10	43615074	RET	G	T	stop_gained	ENST00000355710.3:c.2488G>T	ENSP00000347942.3:p.Gly830Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
10	89692886	PTEN	TG	T	frameshift_variant	ENST00000371953.3:c.371del	ENSP00000361021.3:p.Cys124LeufsTer10	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	108114676	ATM	TAAGA	T	splice_acceptor_variant	ENST00000278616.4:c.497-2_498del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
11	108199892	ATM	A	AAC	frameshift_variant	ENST00000278616.4:c.7236_7237dup	ENSP00000278616.4:p.Lys2413ThrfsTer6	PASS	PASS	not_called	false_positive	Likely Pathogenic
11	32438034	WT1	A	T	splice_donor_variant	ENST00000332351.3:c.1001+2T>A	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432116	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.863_864insC	ENSP00000257555.4:p.Pro289AlafsTer28	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic

12	121432117	HNF1A	G	GC	frameshift_variant	ENST00000257555.6:c.872dup	ENSP00000257555.4:p.Gly292ArgfsTer25	PASS	PASS	PASS	false_positive	Likely Pathogenic
12	21624358	RECQL	ATACT	A	splice_donor_variant	ENST00000444129.2:c.1667_1667+3del	-	PASS	PASS	PASS	true_positive	Pathogenic
12	21624358	RECQL	ATACT	A	splice_donor_variant	ENST00000444129.2:c.1667_1667+3del	-	PASS	PASS	PASS	true_positive	Pathogenic
12	21626569	RECQL	G	*	frameshift_variant	ENST00000444129.2:c.1363del	ENSP00000416739.2:p.Arg455ValfsTer3	PASS	PASS	not_called	true_positive	Likely pathogenic
13	103524611	ERCC5	GA	G	frameshift_variant	ENST00000355739.4:c.2751del	ENSP00000347978.4:p.Lys917AsnfsTer65	PASS	PASS	PASS	false_positive	Likely Pathogenic
13	103524611	ERCC5	GA	G	frameshift_variant	ENST00000355739.4:c.2751del	ENSP00000347978.4:p.Lys917AsnfsTer65	PASS	PASS	PASS	false_positive	Likely Pathogenic
13	103524611	ERCC5	GA	G	frameshift_variant	ENST00000355739.4:c.2751del	ENSP00000347978.4:p.Lys917AsnfsTer65	PASS	PASS	PASS	true_positive	Likely Pathogenic
13	103524611	ERCC5	GA	G	frameshift_variant	ENST00000355739.4:c.2751del	ENSP00000347978.4:p.Lys917AsnfsTer65	PASS	PASS	PASS	false_positive	Likely Pathogenic
13	103524611	ERCC5	GA	G	frameshift_variant	ENST00000355739.4:c.2751del	ENSP00000347978.4:p.Lys917AsnfsTer65	PASS	PASS	PASS	false_positive	Likely Pathogenic
13	32900703	BRCA2	C	A	stop_gained	ENST00000544455.1:c.584C>A	ENSP00000439902.1:p.Ser195Ter	PASS	PASS	RefCall	false_positive	Pathogenic
13	32912156	BRCA2	G	GA	frameshift_variant	ENST00000544455.1:c.3664_3665insA	ENSP00000439902.1:p.Ala1222AspfsTer11	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	32912157	BRCA2	C	CATGAAGA	stop_gained	ENST00000544455.1:c.3665_3666insATGAAGA	ENSP00000439902.1:p.His1223Ter	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	48955380	RB1	TAGG	T	splice_acceptor_variant	ENST00000267163.4:c.1499-1_1500del	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
13	48955383	RB1	G	GTT	frameshift_variant	ENST00000267163.4:c.1499_1500insTT	ENSP00000267163.4:p.Arg500SerfsTer2	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	45605688	FANCM	G	T	stop_gained	ENST00000267430.5:c.454G>T	ENSP00000267430.5:p.Glu152Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
14	45644273	FANCM	G	T	splice_acceptor_variant	ENST00000267430.5:c.2317-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
14	45657086	FANCM	C	A	stop_gained	ENST00000267430.5:c.4775C>A	ENSP00000267430.5:p.Ser1592Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
14	45658074	FANCM	C	T	stop_gained	ENST00000267430.5:c.4849C>T	ENSP00000267430.5:p.Gln1617Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
14	95574758	DICER1	GGT	G	frameshift_variant	ENST00000526495.1:c.2337_2338del	ENSP00000437256.1:p.Pro780PhefsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	95574761	DICER1	G	GAAAAAAAAAAAAAC	frameshift_variant	ENST00000526495.1:c.2335_2336insGTTTTTTTTTTTTT	ENSP00000437256.1:p.Thr779SerfsTer32	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	95583031	DICER1	ACCTG	A	splice_acceptor_variant	ENST00000526495.1:c.1510-3_1510del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	95583031	DICER1	ACCTG	A	splice_acceptor_variant	ENST00000526495.1:c.1510-3_1510del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	95583031	DICER1	ACCTG	A	splice_acceptor_variant	ENST00000526495.1:c.1510-3_1510del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
15	91346951	BLM	G	T	splice_donor_variant	ENST00000355112.3:c.3558+1G>T	-	PASS	PASS	PASS	false_positive	Likely Pathogenic
16	2097833	NTHL1	C	A	stop_gained	ENST00000219066.1:c.16G>T	ENSP00000219066.1:p.Glu6Ter	PASS	PASS	RefCall	true_positive	Likely pathogenic

16	2103391	TSC2	G	T	stop_gained	ENST00000219476.3:c.274G>T	ENSP00000219476.3:p.Glu92Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
16	23647191	PALB2	T	TG	frameshift_variant	ENST00000261584.4:c.675_676insC	ENSP00000261584.4:p.Thr226HisfsTer9	PASS	PASS	not_called	false_positive	Likely Pathogenic
16	23647287	PALB2	CA	C	frameshift_variant	ENST00000261584.4:c.579del	ENSP00000261584.4:p.Glu194LysfsTer2	PASS	PASS	not_called	true_positive	Likely Pathogenic
16	68845642	CDH1	C	A	stop_gained	ENST00000261769.5:c.888C>A	ENSP00000261769.4:p.Tyr296Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
17	29683982	NF1	TC	T	frameshift_variant	ENST00000358273.4:c.7744del	ENSP00000351015.4:p.Gln2582ArgfsTer42	PASS	PASS	not_called	false_positive	Likely pathogenic
17	38792180	SMARCE1	TACCA	T	splice_donor_variant	ENST00000348513.6:c.540_541+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
17	38792180	SMARCE1	TACCA	T	splice_donor_variant	ENST00000348513.6:c.540_541+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
17	38792180	SMARCE1	TACCA	T	splice_donor_variant	ENST00000348513.6:c.540_541+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
17	38792184	SMARCE1	A	ATTTT	frameshift_variant	ENST00000348513.6:c.539_540insAAAA	ENSP00000323967.6:p.Asp180GlufsTer3	PASS	PASS	not_called	false_positive	Pathogenic
17	38792184	SMARCE1	A	ATTTT	frameshift_variant	ENST00000348513.6:c.539_540insAAAA	ENSP00000323967.6:p.Asp180GlufsTer3	PASS	PASS	not_called	false_positive	Pathogenic
17	38792184	SMARCE1	A	ATTTT	frameshift_variant	ENST00000348513.6:c.539_540insAAAA	ENSP00000323967.6:p.Asp180GlufsTer3	PASS	PASS	not_called	false_positive	Pathogenic
17	41247902	BRCA1	C	A	stop_gained	ENST00000471181.2:c.631G>T	ENSP00000418960.2:p.Gly211Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
17	56774139	RAD51C	T	TAGGTATCACTAAAG	stop_gained	ENST00000337432.4:c.490_491insAGGTATCACTAAAG	ENSP00000336701.4:p.Phe164Ter	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	59934548	BRIP1	AT	A	frameshift_variant	ENST00000259008.2:c.249del	ENSP00000259008.2:p.Gln83HisfsTer18	PASS	PASS	not_called	false_positive	likely Pathogenic
17	59934548	BRIP1	AT	A	frameshift_variant	ENST00000259008.2:c.249del	ENSP00000259008.2:p.Gln83HisfsTer18	PASS	PASS	not_called	false_positive	likely Pathogenic
17	63533938	AXIN2	CCT	C	frameshift_variant	ENST00000307078.5:c.1214_1215del	ENSP00000302625.5:p.Glu405GlyfsTer56	PASS	PASS	RefCall	false_positive	Likely pathogenic
17	63533938	AXIN2	CCT	C	frameshift_variant	ENST00000307078.5:c.1214_1215del	ENSP00000302625.5:p.Glu405GlyfsTer56	PASS	PASS	RefCall	false_positive	Likely pathogenic
17	63533938	AXIN2	CCT	C	frameshift_variant	ENST00000307078.5:c.1214_1215del	ENSP00000302625.5:p.Glu405GlyfsTer56	PASS	PASS	RefCall	false_positive	Likely pathogenic
17	63533938	AXIN2	CCT	C	frameshift_variant	ENST00000307078.5:c.1214_1215del	ENSP00000302625.5:p.Glu405GlyfsTer56	PASS	PASS	RefCall	false_positive	Likely pathogenic
17	63533938	AXIN2	CCT	C	frameshift_variant	ENST00000307078.5:c.1214_1215del	ENSP00000302625.5:p.Glu405GlyfsTer56	PASS	PASS	RefCall	true_positive	Likely pathogenic
17	66522025	PRKAR1A	A	AAAAAGTTTATTTT	frameshift_variant	ENST00000589228.1:c.680_681insAAAAGTTTATTTT	ENSP00000464977.1:p.Asp227GlufsTer10	PASS	PASS	not_called	false_positive	Likely pathogenic
17	66522027	PRKAR1A	C	CTAAAGTGCAAGT	stop_gained	ENST00000589228.1:c.682_683insTAAAGTGCAAGT	ENSP00000464977.1:p.Arg228delinsLeuLysCysLysTer	PASS	PASS	not_called	false_positive	Likely pathogenic
17	7578211	TP53	C	T	missense_variant	ENST00000269305.4:c.638G>A	ENSP00000269305.4:p.Arg213Gln	PASS	PASS	RefCall	false_positive	pathogenic
17	7579546	TP53	CG	C	frameshift_variant	ENST00000269305.4:c.140del	ENSP00000269305.4:p.Pro47ArgfsTer76	PASS	PASS	RefCall	false_positive	Likely Pathogenic

18	48591912	SMAD4	G	GCTATAGGAAATAAATGGGAAAGAACATCCTCCCAT	frameshift_variant	ENST00000342988.3:c.1075_1076insCTATAGGAAATAAATGGGAAAGAACATCCTCCCAT	ENSP00000341551.3:p.Gly359AlafsTer37	PASS	PASS	not_called	false_positive	Likely Pathogenic
19	11145614	SMARCA4	G	T	stop_gained	ENST00000429416.3:c.3976G>T	ENSP00000395654.1:p.Glu1326Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
19	11145701	SMARCA4	G	T	stop_gained	ENST00000429416.3:c.4063G>T	ENSP00000395654.1:p.Glu1355Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
1	241661227	FH	A	ATTT	inframe_insertion	ENST00000366560.3:c.1431_1433dup	ENSP00000355518.3:p.Lys477dup	PASS	PASS	PASS	true_positive	Pathogenic
1	241661227	FH	A	ATTT	inframe_insertion	ENST00000366560.3:c.1431_1433dup	ENSP00000355518.3:p.Lys477dup	PASS	PASS	PASS	true_positive	Pathogenic
1	241661227	FH	A	ATTT	inframe_insertion	ENST00000366560.3:c.1431_1433dup	ENSP00000355518.3:p.Lys477dup	PASS	PASS	PASS	true_positive	Pathogenic
1	241661227	FH	A	ATTT	inframe_insertion	ENST00000366560.3:c.1431_1433dup	ENSP00000355518.3:p.Lys477dup	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	false_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3:c.1178G>A	ENSP00000361170.3:p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
21	36171600	RUNX1	G	T	stop_gained	ENST00000300305.3:c.965C>A	ENSP00000300305.3:p.Ser322Ter	PASS	PASS	RefCall	true_positive	Likely pathogenic
22	24145609	SMARCB1	G	T	stop_gained	ENST00000263121.7:c.628G>T	ENSP00000263121.7:p.Glu210Ter	PASS	PASS	RefCall	true_positive	Pathogenic
22	30070823	NF2	A	T	splice_acceptor_variant	ENST00000338641.4:c.1341-2A>T	-	PASS	PASS	RefCall	false_positive	Likely pathogenic
22	30070904	NF2	G	T	stop_gained	ENST00000338641.4:c.1420G>T	ENSP00000344666.4:p.Glu474Ter	PASS	PASS	RefCall	false_positive	Likely pathogenic
2	232894688	DIS3L2	G	T	splice_acceptor_variant	ENST00000325385.7:c.265-1G>T	-	PASS	PASS	RefCall	true_positive	Likely pathogenic
2	47635630	MSH2	A	AG	frameshift_variant	ENST00000233146.2:c.302_303insG	ENSP00000233146.2:p.Val102SerfsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	47635631	MSH2	A	ATATTACAT	frameshift_variant	ENST00000233146.2:c.303_304insTATTACAT	ENSP00000233146.2:p.Val102TyrfsTer75	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	47637485	MSH2	G	GC	frameshift_variant	ENST00000233146.2:c.620dup	ENSP00000233146.2:p.Gly208TrpfsTer24	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	96931001	TMEM127	GAC	G	frameshift_variant	ENST00000258439.3:c.117_118del	ENSP00000258439.2:p.Ser40TyrfsTer67	PASS	PASS	RefCall	true_positive	Likely pathogenic
3	10080961	FANCD2	A	T	splice_acceptor_variant	ENST00000287647.3:c.492-2A>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic

3	10080962	FANCD2	G	T	splice_acceptor_variant	ENST00000287647.3:c.492-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10088407	FANCD2	A	ATT	frameshift_variant	ENST00000287647.3:c.1278_1278+1insTT	ENSP00000287647.3:p.Val427LeufsTer21	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	10105572	FANCD2	G	T	stop_gained	ENST00000287647.3:c.1924G>T	ENSP00000287647.3:p.Glu642Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
3	10115003	FANCD2	CAGAATGTGACCCTACGCCATCTCAT	C	frameshift_variant	ENST00000287647.3:c.2676_2700del	ENSP00000287647.3:p.Cys893AlafsTer3	PASS	PASS	RefCall	true_positive	Likely Pathogenic
3	14199942	XPC	TGG	T	frameshift_variant	ENST00000285021.7:c.1439_1440del	ENSP00000285021.7:p.Ser480Ter	PASS	PASS	RefCall	true_positive	Likely pathogenic
3	37042543	MLH1	AG	A	frameshift_variant	ENST00000231790.2:c.306+1del	-	PASS	PASS	RefCall	true_positive	Likely Pathogenic
3	37067123	MLH1	TACAGAC	T	splice_acceptor_variant	ENST00000231790.2:c.1039-4_1040del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	69788762	MITF	C	A	stop_gained	ENST00000352241.4:c.14C>A	ENSP00000295600.7:p.Ser5Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic

5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
5	256483	SDHA	CTT	C	frameshift_variant	ENST00000264932.6:c.1945_1946del	ENSP00000264932.6:p.Leu649GlufsTer4	PASS	PASS	RefCall	false_positive	Pathogenic
7	6037018	PMS2	T	TCTTCACACAC	frameshift_variant	ENST00000265849.7:c.741_742insGTGTGTGAAG	ENSP00000265849.7:p.Ser248ValfsTer5	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037019	PMS2	AGGGGG	A	frameshift_variant	ENST00000265849.7:c.736_740del	ENSP00000265849.7:p.Pro246Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	T	A	splice_acceptor_variant	ENST00000265849.7:c.706-2A>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	T	A	splice_acceptor_variant	ENST00000265849.7:c.706-2A>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	TG	*	splice_acceptor_variant	ENST00000265849.7:c.706-3_706-2del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic

7	6037056	PMS2	TG	*	splice_acceptor_variant	ENST00000265849.7:c.706-3_706-2del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	6042184	PMS2	T	TGA	frameshift_variant	ENST00000265849.7:c.436_437insTC	ENSP00000265849.7:p.Lys146IlefsTer56	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	95818892	SLC25A13	C	A	splice_donor_variant	ENST00000416240.2:c.848+1G>T	-	PASS	PASS	PASS	true_positive	Likely Pathogenic
7	95818892	SLC25A13	C	A	splice_donor_variant	ENST00000416240.2:c.848+1G>T	-	PASS	PASS	PASS	true_positive	Likely Pathogenic
7	95820547	SLC25A13	T	TGTATTATTATTAGGGTGAAGAAGGCA	frameshift_variant	ENST00000416240.2:c.627_628insTGCCTTCTTCACCCTAATAATAATAC	ENSP00000400101.2:p.Thr210CysfsTer49	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	95822366	SLC25A13	C	A	stop_gained	ENST00000416240.2:c.598G>T	ENSP00000400101.2:p.Glu200Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
8	118847788	EXT1	AGCCTGAGC	A	splice_acceptor_variant	ENST00000378204.2:c.1057-6_1058del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
8	30938380	WRN	TAGGG	T	splice_acceptor_variant	ENST00000298139.5:c.840-2_841del	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
8	30938380	WRN	TAGGG	T	splice_acceptor_variant	ENST00000298139.5:c.840-2_841del	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
8	30938384	WRN	G	GTTTT	frameshift_variant	ENST00000298139.5:c.844_845insTTTT	ENSP00000298139.5:p.Ser282PhefsTer24	PASS	PASS	not_called	false_positive	Likely Pathogenic
8	30938384	WRN	G	GTTTT	frameshift_variant	ENST00000298139.5:c.844_845insTTTT	ENSP00000298139.5:p.Ser282PhefsTer24	PASS	PASS	not_called	false_positive	Likely Pathogenic
8	90983441	NBN	ATTTGT	A	frameshift_variant	ENST00000265433.3:c.657_661del	ENSP00000265433.3:p.Lys219AsnfsTer16	PASS	PASS	PASS	true_positive	Pathogenic
8	90983441	NBN	ATTTGT	A	frameshift_variant	ENST00000265433.3:c.657_661del	ENSP00000265433.3:p.Lys219AsnfsTer16	PASS	PASS	PASS	true_positive	Pathogenic
8	90983441	NBN	ATTTGT	A	frameshift_variant	ENST00000265433.3:c.657_661del	ENSP00000265433.3:p.Lys219AsnfsTer16	PASS	PASS	PASS	true_positive	Pathogenic
9	100449472	XPA	TCACAG	T	frameshift_variant	ENST00000375128.4:c.456_460del	ENSP00000364270.4:p.Asp152GlufsTer10	PASS	PASS	not_called	false_positive	Likely Pathogenic
9	21971116	CDKN2A	G	*	frameshift_variant	ENST00000498124.1:c.243del	ENSP00000418915.1:p.Val82CysfsTer64	PASS	PASS	not_called	false_positive	Likely Pathogenic
9	35075736	FANCG	AG	A	frameshift_variant	ENST00000378643.3:c.1158del	ENSP00000367910.3:p.Ser387ProfsTer16	PASS	PASS	PASS	false_positive	Pathogenic
9	35075736	FANCG	AG	A	frameshift_variant	ENST00000378643.3:c.1158del	ENSP00000367910.3:p.Ser387ProfsTer16	PASS	PASS	PASS	false_positive	Pathogenic
9	35075736	FANCG	AG	A	frameshift_variant	ENST00000378643.3:c.1158del	ENSP00000367910.3:p.Ser387ProfsTer16	PASS	PASS	PASS	false_positive	Pathogenic
X	153993171	DKC1	TA	T	splice_acceptor_variant	ENST00000369550.5:c.17-2del	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
X	153993173	DKC1	G	T	splice_acceptor_variant	ENST00000369550.5:c.17-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
X	153993173	DKC1	G	T	splice_acceptor_variant	ENST00000369550.5:c.17-1G>T	-	PASS	PASS	RefCall	true_positive	Likely Pathogenic
X	154004558	DKC1	G	GAT	frameshift_variant	ENST00000369550.5:c.1435_1436insAT	ENSP00000358563.5:p.Ala479AspfsTer32	PASS	PASS	not_called	false_positive	Likely Pathogenic

eTable7: Pathogenic and likely pathogenic variants exclusively detected by deep learning in the cancer predisposition genes in 1295 melanoma patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER Binary GATK	FILTER updated DV	Manual validation	Pathogenicity classification	Binary classification
10	43609042	RET	C	CG	frameshift_variant	ENST00000355710.3:c.1803dup	ENSP00000347942.3:p.Ile602AspfsTer2	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
10	43612074	RET	G	T	stop_gained	ENST00000355710.3:c.2179G>T	ENSP00000347942.3:p.Gly727Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
10	43623583	RET	G	T	stop_gained	ENST00000355710.3:c.3211G>T	ENSP00000347942.3:p.Gly1071Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
10	88635782	BMPR1A	CA	C	frameshift_variant	ENST00000372037.3:c.8del	ENSP00000361107.1:p.Gln3ArgfsTer33	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
10	88677032	BMPR1A	C	T	stop_gained	ENST00000372037.3:c.817C>T	ENSP00000361107.1:p.Arg273Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
10	89725102	PTEN	C	A	stop_gained	ENST00000371953.3:c.1085C>A	ENSP00000361021.3:p.Ser362Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
11	108159816	ATM	C	CTT	frameshift_variant	ENST00000278616.4:c.4224_4225dup	ENSP00000278616.4:p.Ser1409PhefsTer43	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
11	108170560	ATM	C	T	stop_gained	ENST00000278616.4:c.5125C>T	ENSP00000278616.4:p.Gln1709Ter	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
11	108172425	ATM	C	CA	frameshift_variant	ENST00000278616.4:c.5231dup	ENSP00000278616.4:p.Thr1745AspfsTer4	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
11	108175528	ATM	C	T	stop_gained	ENST00000278616.4:c.5623C>T	ENSP00000278616.4:p.Arg1875Ter	VQSRTranchSNP99.70to99.80	RefCall	PASS	true_positive	Pathogenic	pathogenic
11	111965529	SDHD	G	A	stop_gained	ENST00000375549.3:c.315G>A	ENSP00000364699.3:p.Trp105Ter	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
11	22647107	FANCF	G	A	stop_gained	ENST00000327470.3:c.250C>T	ENSP00000330875.3:p.Gln84Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
11	22647355	FANCF	A	C	start_lost	ENST00000327470.3:c.2T>G	ENSP00000330875.3:p.Met1?	VQSRTranchSNP99.70to99.80	RefCall	PASS	true_positive	Pathogenic	pathogenic
11	32410726	WT1	C	A	splice_acceptor_variant	ENST00000332351.3:c.1433-1G>T	-	VQSRTranchSNP99.60to99.70	RefCall	PASS	true_positive	Likely pathogenic	pathogenic
11	32414291	WT1	TG	T	frameshift_variant	ENST00000332351.3:c.1259del	ENSP00000331327.3:p.Pro420HisfsTer29	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
11	32456813	WT1	G	A	stop_gained	ENST00000332351.3:c.79C>T	ENSP00000331327.3:p.Gln27Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
11	32456828	WT1	GC	G	frameshift_variant	ENST00000332351.3:c.63del	ENSP00000331327.3:p.Pro22LeufsTer22	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
11	44129329	EXT2	C	T	stop_gained	ENST00000395673.3:c.166C>T	ENSP00000379032.3:p.Arg56Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
11	44129545	EXT2	C	T	missense_variant	ENST00000395673.3:c.382C>T	ENSP00000379032.3:p.Arg128Cys	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic

12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121432114	HNF1A	CG	C	frameshift_variant	ENST00000257555.6:c.864del	ENSP00000257555.4:p.Pro291GlnfsTer51	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
12	121432125	HNF1A	C	A	missense_variant	ENST00000257555.6:c.872C>A	ENSP00000257555.4:p.Pro291Gln	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
12	121434343	HNF1A	G	T	splice_acceptor_variant	ENST00000257555.6:c.1108-1G>T	-	VQSRTrancheSNP99.80to99.90	RefCall	PASS	true_positive	Likely Pathogenic	pathogenic
12	21644525	RECQL	G	A	stop_gained	ENST00000444129.2:c.142C>T	ENSP00000416739.2:p.Gln48Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
13	103515408	ERCC5	GC	G	frameshift_variant	ENST00000355739.4:c.1911del	ENSP00000347978.4:p.Val638TrpfsTer23	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
13	32893243	BRCA2	G	T	stop_gained	ENST00000544455.1:c.97G>T	ENSP00000439902.1:p.Glu33Ter	not_called	not_called	PASS	true_positive	Pathogenic	pathogenic
13	32899211	BRCA2	A	G	splice_acceptor_variant	ENST00000544455.1:c.317-2A>G	-	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
13	32928997	BRCA2	G	A	splice_acceptor_variant	ENST00000544455.1:c.7008-1G>A	-	not_called	not_called	PASS	false_positive	Pathogenic	pathogenic
13	32953607	BRCA2	TG	T	frameshift_variant	ENST00000544455.1:c.8910del	ENSP00000439902.1:p.Trp2970Ter	not_called	not_called	PASS	false_positive	Pathogenic	pathogenic
13	48953787	RB1	G	A	splice_donor_variant	ENST00000267163.4:c.1389+1G>A	-	not_called	not_called	PASS	true_positive	Pathogenic	pathogenic
13	48955381	RB1	A	G	splice_acceptor_variant	ENST00000267163.4:c.1499-2A>G	-	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
14	45620707	FANCM	GA	G	frameshift_variant	ENST00000267430.5:c.1031del	ENSP00000267430.5:p.Asn344ThrfsTer13	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
14	45645591	FANCM	G	T	stop_gained	ENST00000267430.5:c.3634G>T	ENSP00000267430.5:p.Glu1212Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
14	95574262	DICER1	G	GT	frameshift_variant	ENST00000526495.1:c.2604dup	ENSP00000437256.1:p.Pro869ThrfsTer5	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
14	95590563	DICER1	TC	T	frameshift_variant	ENST00000526495.1:c.1345del	ENSP00000437256.1:p.Glu449LysfsTer9	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
15	80464551	FAH	G	T	stop_gained	ENST00000407106.1:c.667G>T	ENSP00000385080.1:p.Glu223Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
15	80467433	FAH	G	T	stop_gained	ENST00000407106.1:c.913G>T	ENSP00000385080.1:p.Gly305Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
15	80473422	FAH	G	A	stop_gained	ENST00000407106.1:c.1101G>A	ENSP00000385080.1:p.Trp367Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
15	89807837	FANCI	G	T	stop_gained	ENST00000310775.7:c.754G>T	ENSP00000310842.7:p.Glu252Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
15	91303397	BLM	C	T	stop_gained	ENST00000355112.3:c.1108C>T	ENSP00000347232.3:p.Gln370Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic

16	14024720	ERCC4	ACG	A	frameshift_variant	ENST00000311895.7:c.947_948del	ENSP00000310520.7:p.Thr316ArgfsTer14	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	14029139	ERCC4	G	A	stop_gained	ENST00000311895.7:c.1350G>A	ENSP00000310520.7:p.Trp450Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	14029242	ERCC4	CT	C	frameshift_variant	ENST00000311895.7:c.1454del	ENSP00000310520.7:p.Leu485ProfsTer8	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	2090035	NTHL1	C	A	stop_gained	ENST00000219066.1:c.829G>T	ENSP00000219066.1:p.Glu277Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
16	2103362	TSC2	G	A	stop_gained	ENST00000219476.3:c.245G>A	ENSP00000219476.3:p.Trp82Ter	not_called	not_called	PASS	true_positive	Pathogenic	pathogenic
16	2112977	TSC2	G	T	stop_gained	ENST00000219476.3:c.1366G>T	ENSP00000219476.3:p.Glu456Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
16	2137867	TSC2	C	T	stop_gained	ENST00000219476.3:c.4993C>T	ENSP00000219476.3:p.Gln1665Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
16	23625382	PALB2	C	CT	frameshift_variant	ENST00000261584.4:c.3143dup	ENSP00000261584.4:p.Met1049AspfsTer4	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	23646813	PALB2	CTGTT	C	frameshift_variant	ENST00000261584.4:c.1050_1053del	ENSP00000261584.4:p.Thr351ArgfsTer4	VQSRTrancheINDEL99.60to99.70	RefCall	PASS	false_positive	Likely Pathogenic	pathogenic
16	23646921	PALB2	GC	G	frameshift_variant	ENST00000261584.4:c.945del	ENSP00000261584.4:p.Thr317GlnfsTer5	VQSRTrancheINDEL99.40to99.50	RefCall	PASS	false_positive	Likely Pathogenic	pathogenic
16	50783627	CYLD	G	A	stop_gained	ENST00000427738.3:c.18G>A	ENSP00000392025.3:p.Trp6Ter	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
16	50811816	CYLD	C	T	stop_gained	ENST00000427738.3:c.1102C>T	ENSP00000392025.3:p.Gln368Ter	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
16	68772254	CDH1	G	T	stop_gained	ENST00000261769.5:c.103G>T	ENSP00000261769.4:p.Glu35Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	89805889	FANCA	TA	T	frameshift_variant	ENST00000389301.3:c.4006del	ENSP00000373952.3:p.Tyr1336ThrfsTer27	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
16	89813256	FANCA	T	C	missense_variant	ENST00000389301.3:c.3391A>G	ENSP00000373952.3:p.Thr1131Ala	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
16	89849414	FANCA	C	T	splice_donor_variant	ENST00000389301.3:c.1566+1G>A	-	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Likely Pathogenic	pathogenic
16	89858926	FANCA	ACT	A	frameshift_variant	ENST00000389301.3:c.1034_1035del	ENSP00000373952.3:p.Glu345ValfsTer63	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
17	17119708	FLCN	TG	T	frameshift_variant	ENST00000285071.4:c.1285del	ENSP00000285071.4:p.His429ThrfsTer39	not_called	not_called	PASS	true_positive	Pathogenic	pathogenic
17	29586049	NF1	G	C	splice_acceptor_variant	ENST00000358273.4:c.4333-1G>C	-	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
17	29684041	NF1	C	A	stop_gained	ENST00000358273.4:c.7802C>A	ENSP00000351015.4:p.Ser2601Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
17	41215969	BRCA1	C	T	splice_acceptor_variant	ENST00000471181.2:c.5138-1G>A	-	not_called	not_called	PASS	false_positive	Pathogenic	pathogenic
17	41234460	BRCA1	C	CA	frameshift_variant	ENST00000471181.2:c.4317dup	ENSP00000418960.2:p.Glu1440Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
17	41258504	BRCA1	A	C	missense_variant	ENST00000471181.2:c.181T>G	ENSP00000418960.2:p.Cys61Gly	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Pathogenic	pathogenic
17	56772479	RAD51C	TG	T	frameshift_variant	ENST00000337432.4:c.338del	ENSP00000336701.4:p.Gly113ValfsTer5	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic

17	57161451	TRIM37	C	A	splice_acceptor_variant	ENST00000262294.7:c.282-1G>T	-	not_called	not_called	PASS	false_positive	likely Pathogenic	pathogenic
17	59761478	BRIP1	C	CA	frameshift_variant	ENST00000259008.2:c.2928_2929insT	ENSP00000259008.2:p.Ala977CysfsTer25	not_called	not_called	PASS	false_positive	likely Pathogenic	pathogenic
17	59858254	BRIP1	G	A	stop_gained	ENST00000259008.2:c.1741C>T	ENSP00000259008.2:p.Arg581Ter	VQSRTrancheSNP99.60to99.70	RefCall	PASS	true_positive	Pathogenic	pathogenic
17	7577114	TP53	C	T	missense_variant	ENST00000269305.4:c.824G>A	ENSP00000269305.4:p.Cys275Tyr	VQSRTrancheSNP99.60to99.70	RefCall	PASS	false_positive	pathogenic	pathogenic
18	48584825	SMAD4	C	A	stop_gained	ENST00000342988.3:c.903C>A	ENSP00000341551.3:p.Tyr301Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	true_positive	Likely pathogenic	pathogenic
19	11097122	SMARCA4	C	T	stop_gained	ENST00000429416.3:c.613C>T	ENSP00000395654.1:p.Gln205Ter	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
19	11098494	SMARCA4	C	T	stop_gained	ENST00000429416.3:c.1012C>T	ENSP00000395654.1:p.Gln338Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
19	11107169	SMARCA4	G	A	splice_acceptor_variant	ENST00000429416.3:c.1762-1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
19	11134308	SMARCA4	G	A	splice_donor_variant	ENST00000429416.3:c.2973+1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
19	45918159	ERCC1	TC	T	frameshift_variant	ENST00000013807.5:c.661del	ENSP00000013807.4:p.Asp221ThrfsTer3	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
19	45924501	ERCC1	C	A	stop_gained	ENST00000013807.5:c.256G>T	ENSP00000013807.4:p.Glu86Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
1	17359641	SDHB	C	T	splice_acceptor_variant	ENST00000375499.3:c.201-1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
1	241665790	FH	C	T	missense_variant	ENST00000366560.3:c.1189G>A	ENSP00000355518.3:p.Gly397Arg	not_called	not_called	PASS	true_positive	Pathogenic	pathogenic
1	241669469	FH	C	A	splice_acceptor_variant	ENST00000366560.3:c.739-1G>T	-	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
21	36164503	RUNX1	T	TG	frameshift_variant	ENST00000300305.3:c.1371dup	ENSP00000300305.3:p.Ser458GlnfsTer142	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
21	36164654	RUNX1	G	T	stop_gained	ENST00000300305.3:c.1221C>A	ENSP00000300305.3:p.Tyr407Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
22	21346004	LZTR1	CCG	C	frameshift_variant	ENST00000215739.8:c.881_882del	ENSP00000215739.8:p.Arg294ProfsTer21	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
22	21348449	LZTR1	T	TG	frameshift_variant	ENST00000215739.8:c.1510dup	ENSP00000215739.8:p.Ala504GlyfsTer165	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
22	24129447	SMARCB1	G	T	stop_gained	ENST00000263121.7:c.91G>T	ENSP00000263121.7:p.Glu31Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
22	30032739	NF2	G	A	splice_acceptor_variant	ENST00000338641.4:c.115-1G>A	-	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
22	30070931	NF2	G	T	splice_donor_variant	ENST00000338641.4:c.1446+1G>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
2	215645382	BARD1	G	A	stop_gained	ENST00000260947.4:c.1216C>T	ENSP00000260947.4:p.Arg406Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
2	233199340	DIS3L2	G	A	splice_acceptor_variant	ENST00000325385.7:c.2290-1G>A	-	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
2	58390000	FANCL	C	A	splice_donor_variant	ENST00000402135.3:c.918+1G>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic

2	96930948	TMEM127	C	A	stop_gained	ENST00000258439.3:c.172G>T	ENSP00000258439.2:p.Gly58Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
3	10085540	FANCD2	G	T	stop_gained	ENST00000287647.3:c.1126G>T	ENSP00000287647.3:p.Glu376Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
3	10115047	FANCD2	G	A	splice_donor_variant	ENST00000287647.3:c.2715+1G>A	-	VQSRTrancheSNP99.60to99.70	RefCall	PASS	true_positive	Likely Pathogenic	pathogenic
3	10127575	FANCD2	G	T	stop_gained	ENST00000287647.3:c.3304G>T	ENSP00000287647.3:p.Glu1102Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
3	52443760	BAP1	C	T	splice_acceptor_variant	ENST00000460680.1:c.38-1G>A	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	false_positive	Likely Pathogenic	pathogenic
3	69988333	MITF	G	A	splice_donor_variant	ENST00000352241.4:c.666+1G>A	-	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
4	41750625	PHOX2B	C	A	start_lost	ENST00000226382.2:c.3G>T	ENSP00000226382.2:p.Met1?	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
4	55603430	KIT	C	CAG	frameshift_variant	ENST00000288135.5:c.2791_2792dup	ENSP00000288135.5:p.Ser931ArgfsTer10	VQSRTrancheINDEL99.70to99.80	RefCall	PASS	false_positive	Likely Pathogenic	pathogenic
5	112102108	APC	GT	G	splice_donor_variant	ENST00000457016.1:c.220+2del	-	not_called	not_called	PASS	false_positive	Pathogenic	pathogenic
5	112175618	APC	CCT	C	frameshift_variant	ENST00000457016.1:c.4329_4330del	ENSP00000413133.1:p.Gln1444AsnfsTer10	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
5	240574	SDHA	C	T	stop_gained	ENST00000264932.6:c.1534C>T	ENSP00000264932.6:p.Arg512Ter	VQSRTrancheSNP99.60to99.70	RefCall	PASS	true_positive	Likely pathogenic	pathogenic
5	254520	SDHA	G	T	stop_gained	ENST00000264932.6:c.1807G>T	ENSP00000264932.6:p.Glu603Ter	not_called	not_called	PASS	false_positive	Pathogenic	pathogenic
6	35420378	FANCE	G	A	stop_gained	ENST00000229769.2:c.56G>A	ENSP00000229769.2:p.Trp19Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
7	124532436	POT1	T	A	splice_acceptor_variant	ENST00000357628.3:c.10-2A>T	-	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
7	66459197	SBDS	A	G	splice_donor_variant	ENST00000246868.2:c.258+2T>C	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor	pathogenic
7	66459197	SBDS	A	G	splice_donor_variant	ENST00000246868.2:c.258+2T>C	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor	pathogenic
7	66459197	SBDS	A	G	splice_donor_variant	ENST00000246868.2:c.258+2T>C	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor	pathogenic
7	66459197	SBDS	A	G	splice_donor_variant	ENST00000246868.2:c.258+2T>C	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor	pathogenic
7	66459197	SBDS	A	G	splice_donor_variant	ENST00000246868.2:c.258+2T>C	-	VQSRTrancheSNP99.70to99.80	RefCall	PASS	true_positive	Risk Factor	pathogenic
7	66459273	SBDS	T	A	stop_gained	ENST00000246868.2:c.184A>T	ENSP00000246868.2:p.Lys62Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	true_positive	Pathogenic	pathogenic
8	30916016	WRN	G	A	stop_gained	ENST00000298139.5:c.53G>A	ENSP00000298139.5:p.Trp18Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic

8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5:c.659dup	ENSP00000298139.5:p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5:c.659dup	ENSP00000298139.5:p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5:c.659dup	ENSP00000298139.5:p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5:c.659dup	ENSP00000298139.5:p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
8	30925776	WRN	T	TG	frameshift_variant	ENST00000298139.5:c.659dup	ENSP00000298139.5:p.Ile222TyrfsTer11	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
8	30945344	WRN	T	A	stop_gained	ENST00000298139.5:c.1484T>A	ENSP00000298139.5:p.Leu495Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
8	90965785	NBN	TTC	T	frameshift_variant	ENST00000265433.3:c.1530_1531del	ENSP00000265433.3:p.Asn511Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
8	90967509	NBN	A	T	splice_donor_variant	ENST00000265433.3:c.1397+2T>A	-	not_called	not_called	PASS	true_positive	Likely pathogenic	pathogenic
8	90995072	NBN	T	A	stop_gained	ENST00000265433.3:c.49A>T	ENSP00000265433.3:p.Arg17Ter	not_called	not_called	PASS	false_positive	Likely pathogenic	pathogenic
9	100447237	XPA	AT	A	frameshift_variant	ENST00000375128.4:c.640del	ENSP00000364270.4:p.Met214Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
9	135785963	TSC1	TG	T	frameshift_variant	ENST00000298552.3:c.1257del	ENSP00000298552.3:p.Arg420GlyfsTer20	not_called	not_called	PASS	true_positive	Likely Pathogenic	pathogenic
9	98209685	PTCH1	G	A	stop_gained	ENST00000331920.6:c.3853C>T	ENSP00000332353.6:p.Gln1285Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
9	98218591	PTCH1	GC	G	frameshift_variant	ENST00000331920.6:c.3272del	ENSP00000332353.6:p.Gly1091AlafsTer2	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
9	98229425	PTCH1	GC	G	frameshift_variant	ENST00000331920.6:c.2532del	ENSP00000332353.6:p.Trp844CysfsTer59	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic
9	98268833	PTCH1	G	A	stop_gained	ENST00000331920.6:c.250C>T	ENSP00000332353.6:p.Gln84Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic	pathogenic

eTable8: Pathogenic and likely pathogenic variants exclusively detected by the standard method in the ACMG genes in 1072 prostate cancer patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER binary GATK	FILTER updated DV	Manual validation	Pathogenicity classification
10	89711926	PTEN	TTAA	T	stop_gained	ENST00000371953.3: c.545_547del	ENSP00000361021.3 :p.Leu182_Lys183del insTer	PASS	PASS	not_called	false_positive	Pathogenic
10	89711943	PTEN	T	TCC	frameshift_variant	ENST00000371953.3: c.561_562insCC	ENSP00000361021.3 :p.Tyr188ProfsTer12	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	32912964	BRCA2	TGAAA	*	frameshift_variant	ENST00000544455.1: c.4472_4476del	ENSP00000439902.1 :p.Leu1491ArgfsTer21	PASS	PASS	not_called	true_positive	Pathogenic
17	41226441	BRCA1	G	GA	frameshift_variant	ENST00000471181.2: c.4644_4645insT	ENSP00000418960.2 :p.Leu1549SerfsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226442	BRCA1	CTCCT CTTGA GATGG	C	frameshift_variant	ENST00000471181.2: c.4630_4643del	ENSP00000418960.2 :p.Pro1544AlafsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226464	BRCA1	CT	C	frameshift_variant	ENST00000471181.2: c.4621del	ENSP00000418960.2 :p.Arg1541GlufsTer28	PASS	PASS	not_called	false_positive	Likely Pathogenic
17	41226466	BRCA1	AT	A	frameshift_variant	ENST00000471181.2: c.4619del	ENSP00000418960.2 :p.Asn1540IlefsTer29	PASS	PASS	not_called	false_positive	Likely Pathogenic
18	28671095	DSC2	G	*	frameshift_variant	ENST00000280904.6: c.370del	ENSP00000280904.6 :p.His124IlefsTer7	PASS	PASS	not_called	true_positive	Likely Pathogenic
18	29126300	DSG2	CA	C	frameshift_variant	ENST00000261590.8: c.2952del	ENSP00000261590.8 :p.Val985LeufsTer7	PASS	PASS	not_called	false_positive	Likely Pathogenic
18	29126303	DSG2	TTGTG GTCAC TGAA	T	frameshift_variant	ENST00000261590.8: c.2955_2967del	ENSP00000261590.8 :p.Val986GlufsTer2	PASS	PASS	not_called	false_positive	Likely Pathogenic
18	29126322	DSG2	A	*	frameshift_variant	ENST00000261590.8: c.2974del	ENSP00000261590.8 :p.Ile992TyrfsTer25	PASS	PASS	not_called	false_positive	Likely Pathogenic
18	29126334	DSG2	TGGGG	T	frameshift_variant	ENST00000261590.8: c.2987_2990del	ENSP00000261590.8 :p.Gly996ValfsTer20	PASS	PASS	not_called	false_positive	Likely Pathogenic
18	29126341	DSG2	GGATC GAAT	G	frameshift_variant	ENST00000261590.8: c.2993_3000del	ENSP00000261590.8 :p.Gly998AlafsTer37	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	48030639	MSH6	A	AC	frameshift_variant	ENST00000234420.5: c.3261dup	ENSP00000234420.4 :p.Phe1088LeufsTer5	PASS	PASS	PASS	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	false_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
2	48033792	MSH6	T	*	splice_donor_variant	ENST00000234420.5: c.4001+2del	-	PASS	PASS	not_called	true_positive	Pathogenic
3	38622625	SCN5A	AG	A	frameshift_variant	ENST00000413689.1: c.3024del	ENSP00000410257.1 :p.Tyr1009ThrfsTer	PASS	PASS	RefCall	false_positive	Likely Pathogenic

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7	6029587	PMS2	C	*	splice_acceptor_variant	ENST00000265849.7: c.989-1del	-	PASS	PASS	not_called	false_positive	Pathogenic
X	100653366	GLA	G	GCTGGTAATACGACTCACTATAGGCAGATGAGTCTACGT	stop_gained	ENST00000218516.3: c.990_991insACGTAGACTCATCTGCCTATAGTGAGTCGTATTACCAG	ENSP00000218516.3 :p.Leu331ThrfsTer2	PASS	PASS	not_called	false_positive	Likely Pathogenic
X	38262913	OTC	G	A	missense_variant	ENST00000039007.4: c.583G>A	ENSP00000039007.4 :p.Gly195Arg	PASS	PASS	RefCall	false_positive	Likely Pathogenic

eTable9: Pathogenic and likely pathogenic variants exclusively detected by deep learning in the ACMG genes in 1072 prostate cancer patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER binary GATK	FILTER updated DV	Manual validation	Classification
11	2466331	KCNQ1	G	T	start_lost	ENST00000155840.5:c.3G>T	ENSP00000155840.2:p.Met1?	not_called	not_called	PASS	true_positive	Likely Pathogenic
11	2466686	KCNQ1	T	TG	frameshift_variant	ENST00000155840.5:c.360dup	ENSP00000155840.2:p.Lys121GlufsTer164	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	2466686	KCNQ1	T	TG	frameshift_variant	ENST00000155840.5:c.360dup	ENSP00000155840.2:p.Lys121GlufsTer164	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47362744	MYBPC3	G	C	stop_gained	ENST00000545968.1:c.1842C>G	ENSP00000442795.1:p.Tyr614Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47371619	MYBPC3	CG	C	frameshift_variant	ENST00000545968.1:c.450del	ENSP00000442795.1:p.Asp151MetfsTer8	not_called	not_called	PASS	false_positive	Likely Pathogenic
13	52516531	ATP7B	CG	C	frameshift_variant	ENST00000242839.4:c.3402del	ENSP00000242839.4:p.Ala1135GlnfsTer13	not_called	not_called	PASS	true_positive	Pathogenic
16	2103446	TSC2	A	AG	frameshift_variant	ENST00000219476.3:c.333dup	ENSP00000219476.3:p.Gln112AlafsTer14	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	2121933	TSC2	CA	C	frameshift_variant	ENST00000219476.3:c.2096del	ENSP00000219476.3:p.Gln699ArgfsTer8	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	2133695	TSC2	G	T	splice_acceptor_variant	ENST00000219476.3:c.3884-1G>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic
1	156107464	LMNA	TG	T	frameshift_variant	ENST00000368300.4:c.1630del	ENSP00000357283.4:p.Val544CysfsTer4	not_called	not_called	PASS	false_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	false_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864566	COL3A1	A	T	splice_acceptor_variant	ENST00000304636.3:c.2230-2A>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189867789	COL3A1	G	C	splice_donor_variant	ENST00000304636.3:c.2553+1G>C	-	not_called	not_called	PASS	true_positive	Pathogenic
6	7542233	DSP	G	T	stop_gained	ENST00000379802.3:c.85G>T	ENSP00000369129.3:p.Glu29Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic
7	150644883	KCNH2	GC	G	frameshift_variant	ENST00000262186.5:c.2775del	ENSP00000262186.5:p.Pro926ArgfsTer48	not_called	not_called	PASS	false_positive	Likely Pathogenic
7	150655548	KCNH2	GC	G	frameshift_variant	ENST00000262186.5:c.514del	ENSP00000262186.5:p.Ala172ArgfsTer2	not_called	not_called	PASS	false_positive	Likely Pathogenic

eTable10: Pathogenic and likely pathogenic variants exclusively detected by the standard method in the ACMG genes in 1295 melanoma patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER binary GATK	FILTER updated DV	Manual validation	Pathogenicity classification
10	43572713	RET	A	T	stop_gained	ENST00000355710.3: c.7A>T	ENSP00000347942.3: p.Lys3Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
10	43609097	RET	G	T	missense_variant	ENST00000355710.3: c.1853G>T	ENSP00000347942.3: p.Cys618Phe	PASS	PASS	RefCall	false_positive	Likely Pathogenic
10	43615074	RET	G	T	stop_gained	ENST00000355710.3: c.2488G>T	ENSP00000347942.3: p.Gly830Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
10	89692886	PTEN	TG	T	frameshift_variant	ENST00000371953.3: c.371del	ENSP00000361021.3: p.Cys124LeufsTer10	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	2466438	KCNQ1	C	A	stop_gained	ENST00000155840.5: c.110C>A	ENSP00000155840.2: p.Ser37Ter	PASS	PASS	PASS	true_positive	Likely Pathogenic
11	2466438	KCNQ1	C	A	stop_gained	ENST00000155840.5: c.110C>A	ENSP00000155840.2: p.Ser37Ter	PASS	PASS	PASS	true_positive	Likely Pathogenic
11	2466438	KCNQ1	C	A	stop_gained	ENST00000155840.5: c.110C>A	ENSP00000155840.2: p.Ser37Ter	PASS	PASS	PASS	true_positive	Likely Pathogenic
11	32438034	WT1	A	T	splice_donor_variant	ENST00000332351.3: c.1001+2T>A	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	47353433	MYBPC3	C	T	splice_acceptor_variant	ENST00000545968.1: c.3815-1G>A	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	47357495	MYBPC3	C	T	stop_gained	ENST00000545968.1: c.2670G>A	ENSP00000442795.1: p.Trp890Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	47357495	MYBPC3	C	T	stop_gained	ENST00000545968.1: c.2670G>A	ENSP00000442795.1: p.Trp890Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	47369031	MYBPC3	C	A	splice_acceptor_variant	ENST00000545968.1: c.852-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
11	47372921	MYBPC3	TTG	T	frameshift_variant	ENST00000545968.1: c.159_160del	ENSP00000442795.1: p.Asn53LysfsTer59	PASS	PASS	RefCall	false_positive	Likely Pathogenic
12	111348898	MYL2	C	A	stop_gained	ENST00000228841.8: c.484G>T	ENSP00000228841.7: p.Gly162Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
13	32900703	BRCA2	C	A	stop_gained	ENST00000544455.1: c.584C>A	ENSP00000439902.1: p.Ser195Ter	PASS	PASS	RefCall	false_positive	Pathogenic
13	32912156	BRCA2	G	GA	frameshift_variant	ENST00000544455.1: c.3664_3665insA	ENSP00000439902.1: p.Ala1222AspfsTer11	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	32912157	BRCA2	C	CATGAAGA	stop_gained	ENST00000544455.1: c.3665_3666insATGAAGA	ENSP00000439902.1: p.His1223Ter	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	48955380	RB1	TAGG	T	splice_acceptor_variant	ENST00000267163.4: c.1499-1_1500del	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
13	48955383	RB1	G	GTT	frameshift_variant	ENST00000267163.4: c.1499_1500insTT	ENSP00000267163.4: p.Arg500SerfsTer2	PASS	PASS	not_called	false_positive	Likely Pathogenic
13	52548696	ATP7B	TC	T	frameshift_variant	ENST00000242839.4: c.659del	ENSP00000242839.4: p.Gly220AspfsTer42	PASS	PASS	RefCall	true_positive	Likely Pathogenic
13	52548696	ATP7B	TC	T	frameshift_variant	ENST00000242839.4: c.659del	ENSP00000242839.4: p.Gly220AspfsTer42	PASS	PASS	RefCall	false_positive	Likely Pathogenic

14	23889285	MYH7	C	CA	frameshift_variant	ENST00000355349.3:c.3494_3495insT	ENSP00000347507.3:p.Lys1165AsnfsTer66	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	23889285	MYH7	C	CA	frameshift_variant	ENST00000355349.3:c.3494_3495insT	ENSP00000347507.3:p.Lys1165AsnfsTer66	PASS	PASS	not_called	false_positive	Likely Pathogenic
14	23901858	MYH7	G	T	stop_gained	ENST00000355349.3:c.492C>A	ENSP00000347507.3:p.Tyr164Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
15	48755415	FBN1	G	T	stop_gained	ENST00000316623.5:c.5088C>A	ENSP00000325527.5:p.Tyr1696Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
15	48762915	FBN1	C	A	stop_gained	ENST00000316623.5:c.4375G>T	ENSP00000325527.5:p.Gly1459Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
15	48773876	FBN1	TGCCGGAGTAG	T	frameshift_variant	ENST00000316623.5:c.3930_3939del	ENSP00000325527.5:p.Tyr1311LysfsTer99	PASS	PASS	not_called	false_positive	Likely Pathogenic
15	48773886	FBN1	G	GTTTTTTTTTT	frameshift_variant	ENST00000316623.5:c.3929_3930insAAAAAAAAAA	ENSP00000325527.5:p.Tyr1311LysfsTer18	PASS	PASS	not_called	false_positive	Likely Pathogenic
15	48808525	FBN1	T	TCAAAA	frameshift_variant	ENST00000316623.5:c.1181_1182insTTTTG	ENSP00000325527.5:p.Ile395PhefsTer55	PASS	PASS	not_called	false_positive	Likely Pathogenic
16	15853586	MYH11	C	A	splice_acceptor_variant	ENST00000396324.3:c.1270-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
16	2103391	TSC2	G	T	stop_gained	ENST00000219476.3:c.274G>T	ENSP00000219476.3:p.Glu92Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
17	41247902	BRCA1	C	A	stop_gained	ENST00000471181.2:c.631G>T	ENSP00000418960.2:p.Gly211Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
17	7578211	TP53	C	T	missense_variant	ENST00000269305.4:c.638G>A	ENSP00000269305.4:p.Arg213Gln	PASS	PASS	RefCall	false_positive	pathogenic
17	7579546	TP53	CG	C	frameshift_variant	ENST00000269305.4:c.140del	ENSP00000269305.4:p.Pro47ArgfsTer76	PASS	PASS	RefCall	false_positive	Likely Pathogenic
18	28669413	DSC2	C	A	stop_gained	ENST00000280904.6:c.619G>T	ENSP00000280904.6:p.Glu207Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
18	28669422	DSC2	C	A	stop_gained	ENST00000280904.6:c.610G>T	ENSP00000280904.6:p.Glu204Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
18	48591912	SMAD4	G	GCTATAGGAAATAAATGGGAAAGAACATCCTCCCAT	frameshift_variant	ENST00000342988.3:c.1075_1076insCTATAGGAAATAAATGGGAAAGAACATCCTCCCAT	ENSP00000341551.3:p.Gly359AlafsTer37	PASS	PASS	not_called	false_positive	Likely Pathogenic
19	38974083	RYR1	G	T	stop_gained	ENST00000359596.3:c.4861G>T	ENSP00000352608.2:p.Glu1621Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
19	38974083	RYR1	G	T	stop_gained	ENST00000359596.3:c.4861G>T	ENSP00000352608.2:p.Glu1621Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
19	38990457	RYR1	G	T	stop_gained	ENST00000359596.3:c.7210G>T	ENSP00000352608.2:p.Glu2404Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
19	39056056	RYR1	C	A	stop_gained	ENST00000359596.3:c.13082C>A	ENSP00000352608.2:p.Ser4361Ter	PASS	PASS	RefCall	true_positive	Likely Pathogenic
19	39075708	RYR1	CG	C	frameshift_variant	ENST00000359596.3:c.14773del	ENSP00000352608.2:p.Val4925SerfsTer12	PASS	PASS	RefCall	false_positive	Likely Pathogenic
1	156106139	LMNA	C	A	stop_gained	ENST00000368300.4:c.1292C>A	ENSP00000357283.4:p.Ser431Ter	PASS	PASS	RefCall	true_positive	Pathogenic
1	201022716	CACNA1S	C	A	splice_acceptor_variant	ENST00000362061.3:c.3667-1G>T	-	PASS	PASS	RefCall	false_positive	likely Pathogenic

1	201060899	CACNA1S	GA	G	frameshift_variant	ENST00000362061.3: c.562del	ENSP00000355192.3: p.Ser188ProfsTer146	PASS	PASS	not_called	false_positive	likely Pathogenic
1	201060903	CACNA1S	TCAGGA	T	frameshift_variant	ENST00000362061.3: c.554_558del	ENSP00000355192.3: p.Val185GlufsTer54	PASS	PASS	not_called	false_positive	likely Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	false_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
1	45797228	MUTYH	C	T	missense_variant	ENST00000372098.3: c.1178G>A	ENSP00000361170.3: p.Gly393Asp	PASS	PASS	PASS	true_positive	Pathogenic
22	30070823	NF2	A	T	splice_acceptor_variant	ENST00000338641.4: c.1341-2A>T	-	PASS	PASS	RefCall	false_positive	Likely pathogenic
22	30070904	NF2	G	T	stop_gained	ENST00000338641.4: c.1420G>T	ENSP00000344666.4: p.Glu474Ter	PASS	PASS	RefCall	false_positive	Likely pathogenic
2	189858959	COL3A1	G	T	splice_acceptor_variant	ENST00000304636.3: c.1195-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
2	21236294	APOB	TGTCC	T	frameshift_variant	ENST00000233242.1: c.3950_3953del	ENSP00000233242.1: p.Arg1317AsnfsTer39	PASS	PASS	not_called	false_positive	Likely pathogenic
2	21236294	APOB	TGTCC	T	frameshift_variant	ENST00000233242.1: c.3950_3953del	ENSP00000233242.1: p.Arg1317AsnfsTer39	PASS	PASS	not_called	false_positive	Likely pathogenic
2	21245916	APOB	T	A	splice_acceptor_variant	ENST00000233242.1: c.2605-2A>T	-	PASS	PASS	RefCall	true_positive	Likely pathogenic
2	47635630	MSH2	A	AG	frameshift_variant	ENST00000233146.2: c.302_303insG	ENSP00000233146.2: p.Val102SerfsTer3	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	47635631	MSH2	A	ATATTACAT	frameshift_variant	ENST00000233146.2: c.303_304insTATTACAT	ENSP00000233146.2: p.Val102TyrfsTer75	PASS	PASS	not_called	false_positive	Likely Pathogenic
2	47637485	MSH2	G	GC	frameshift_variant	ENST00000233146.2: c.620dup	ENSP00000233146.2: p.Gly208TrpfsTer24	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	37042543	MLH1	AG	A	frameshift_variant	ENST00000231790.2: c.306+1del	-	PASS	PASS	RefCall	true_positive	Likely Pathogenic
3	37067123	MLH1	TACAGAC	T	splice_acceptor_variant	ENST00000231790.2: c.1039-4_1040del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
3	38662410	SCN5A	G	A	stop_gained	ENST00000413689.1: c.535C>T	ENSP00000410257.1: p.Arg179Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
6	7542306	DSP	C	A	stop_gained	ENST00000379802.3: c.158C>A	ENSP00000369129.3: p.Ser53Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
6	7542306	DSP	C	A	stop_gained	ENST00000379802.3: c.158C>A	ENSP00000369129.3: p.Ser53Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
6	7580426	DSP	C	CTAAGATTTTTGGA	frameshift_variant	ENST00000379802.3: c.4003_4004insTAAGATTTTTGGA	ENSP00000369129.3: p.Gln1335LeufsTer15	PASS	PASS	not_called	false_positive	Likely Pathogenic

6	7581284	DSP	C	CTCTTTCAG	frameshift_variant	ENST00000379802.3:c.4861_4862insTCTTTCAG	ENSP00000369129.3:p.Gln1621LeufsTer27	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	150644591	KCNH2	C	A	stop_gained	ENST00000262186.5:c.2977G>T	ENSP00000262186.5:p.Gly993Ter	PASS	PASS	RefCall	true_positive	Pathogenic
7	150644591	KCNH2	C	A	stop_gained	ENST00000262186.5:c.2977G>T	ENSP00000262186.5:p.Gly993Ter	PASS	PASS	RefCall	false_positive	Pathogenic
7	150644591	KCNH2	C	A	stop_gained	ENST00000262186.5:c.2977G>T	ENSP00000262186.5:p.Gly993Ter	PASS	PASS	RefCall	false_positive	Pathogenic
7	150655378	KCNH2	C	A	stop_gained	ENST00000262186.5:c.685G>T	ENSP00000262186.5:p.Glu229Ter	PASS	PASS	RefCall	true_positive	Pathogenic
7	150655378	KCNH2	C	A	stop_gained	ENST00000262186.5:c.685G>T	ENSP00000262186.5:p.Glu229Ter	PASS	PASS	RefCall	false_positive	Pathogenic
7	6037018	PMS2	T	TCTTCACACAC	frameshift_variant	ENST00000265849.7:c.741_742insGTGTGTGAAG	ENSP00000265849.7:p.Ser248ValfsTer5	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037019	PMS2	AGGGGG	A	frameshift_variant	ENST00000265849.7:c.736_740del	ENSP00000265849.7:p.Pro246Ter	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037055	PMS2	C	A	splice_acceptor_variant	ENST00000265849.7:c.706-1G>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	T	A	splice_acceptor_variant	ENST00000265849.7:c.706-2A>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	T	A	splice_acceptor_variant	ENST00000265849.7:c.706-2A>T	-	PASS	PASS	RefCall	false_positive	Likely Pathogenic
7	6037056	PMS2	TG	*	splice_acceptor_variant	ENST00000265849.7:c.706-3_706-2del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	6037056	PMS2	TG	*	splice_acceptor_variant	ENST00000265849.7:c.706-3_706-2del	-	PASS	PASS	not_called	false_positive	Likely Pathogenic
7	6042184	PMS2	T	TGA	frameshift_variant	ENST00000265849.7:c.436_437insTC	ENSP00000265849.7:p.Lys146IlefsTer56	PASS	PASS	not_called	false_positive	Likely Pathogenic

eTable11: Pathogenic and likely pathogenic variants exclusively detected by deep learning in the ACMG genes in 1295 melanoma patients.

CHROM	POS	SYMBOL	REF	ALT	Consequence	HGVSc	HGVSp	FILTER GATK	FILTER binary GATK	FILTER updated DV	Manual validation	Pathogenicity classification
10	43609042	RET	C	CG	frameshift_variant	ENST00000355710.3:c.1803dup	ENSP00000347942.3:p.Ile602AspfsTer2	not_called	not_called	PASS	false_positive	Likely Pathogenic
10	43612074	RET	G	T	stop_gained	ENST00000355710.3:c.2179G>T	ENSP00000347942.3:p.Gly727Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
10	43623583	RET	G	T	stop_gained	ENST00000355710.3:c.3211G>T	ENSP00000347942.3:p.Gly1071Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic
10	88635782	BMPR1A	CA	C	frameshift_variant	ENST00000372037.3:c.8del	ENSP00000361107.1:p.Gln3ArgfsTer33	not_called	not_called	PASS	false_positive	Likely Pathogenic
10	88677032	BMPR1A	C	T	stop_gained	ENST00000372037.3:c.817C>T	ENSP00000361107.1:p.Arg273Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
10	89725102	PTEN	C	A	stop_gained	ENST00000371953.3:c.1085C>A	ENSP00000361021.3:p.Ser362Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	111965529	SDHD	G	A	stop_gained	ENST00000375549.3:c.315G>A	ENSP00000364699.3:p.Trp105Ter	not_called	not_called	PASS	true_positive	Likely pathogenic
11	2592624	KCNQ1	C	T	missense_variant	ENST00000155840.5:c.674C>T	ENSP00000155840.2:p.Ser225Leu	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	2797229	KCNQ1	C	T	stop_gained	ENST00000155840.5:c.1630C>T	ENSP00000155840.2:p.Gln544Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	2797263	KCNQ1	G	A	missense_variant	ENST00000155840.5:c.1664G>A	ENSP00000155840.2:p.Arg555His	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	32410726	WT1	C	A	splice_acceptor_variant	ENST00000332351.3:c.1433-1G>T	-	VQSRTrancheSNP99.60to99.70	RefCall	PASS	true_positive	Likely pathogenic
11	32414291	WT1	TG	T	frameshift_variant	ENST00000332351.3:c.1259del	ENSP00000331327.3:p.Pro420HisfsTer29	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	32456813	WT1	G	A	stop_gained	ENST00000332351.3:c.79C>T	ENSP00000331327.3:p.Gln27Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	32456828	WT1	GC	G	frameshift_variant	ENST00000332351.3:c.63del	ENSP00000331327.3:p.Pro22LeufsTer22	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47354854	MYBPC3	A	AC	frameshift_variant	ENST00000545968.1:c.3220dup	ENSP00000442795.1:p.Val1074GlyfsTer3	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47362797	MYBPC3	T	C	splice_acceptor_variant	ENST00000545968.1:c.1791-2A>G	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47369200	MYBPC3	A	G	splice_donor_variant	ENST00000545968.1:c.851+2T>C	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
11	47369442	MYBPC3	C	A	stop_gained	ENST00000545968.1:c.787G>T	ENSP00000442795.1:p.Gly263Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Likely Pathogenic
11	47371664	MYBPC3	C	A	splice_acceptor_variant	ENST00000545968.1:c.407-1G>T	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
12	32949233	PKP2	C	A	splice_acceptor_variant	ENST00000070846.6:c.2300-1G>T	-	not_called	not_called	PASS	true_positive	Likely pathogenic
12	32994140	PKP2	C	A	splice_acceptor_variant	ENST00000070846.6:c.1511-1G>T	-	not_called	not_called	PASS	false_positive	Likely pathogenic
12	33049636	PKP2	G	C	stop_gained	ENST00000070846.6:c.30C>G	ENSP00000070846.6:p.Tyr10Ter	not_called	not_called	PASS	false_positive	Likely pathogenic

13	32893243	BRCA2	G	T	stop_gained	ENST00000544455.1:c.97G>T	ENSP00000439902.1:p.Glu33Ter	not_called	not_called	PASS	true_positive	Pathogenic
13	32899211	BRCA2	A	G	splice_acceptor_variant	ENST00000544455.1:c.317-2A>G	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
13	32928997	BRCA2	G	A	splice_acceptor_variant	ENST00000544455.1:c.7008-1G>A	-	not_called	not_called	PASS	false_positive	Pathogenic
13	32953607	BRCA2	TG	T	frameshift_variant	ENST00000544455.1:c.8910del	ENSP00000439902.1:p.Trp2970Ter	not_called	not_called	PASS	false_positive	Pathogenic
13	48953787	RB1	G	A	splice_donor_variant	ENST00000267163.4:c.1389+1G>A	-	not_called	not_called	PASS	true_positive	Pathogenic
13	48955381	RB1	A	G	splice_acceptor_variant	ENST00000267163.4:c.1499-2A>G	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
13	52516531	ATP7B	CG	C	frameshift_variant	ENST00000242839.4:c.3402del	ENSP00000242839.4:p.Ala1135GlnfsTer13	not_called	not_called	PASS	true_positive	Pathogenic
13	52516531	ATP7B	CG	C	frameshift_variant	ENST00000242839.4:c.3402del	ENSP00000242839.4:p.Ala1135GlnfsTer13	not_called	not_called	PASS	true_positive	Pathogenic
13	52516531	ATP7B	CG	C	frameshift_variant	ENST00000242839.4:c.3402del	ENSP00000242839.4:p.Ala1135GlnfsTer13	not_called	not_called	PASS	true_positive	Pathogenic
13	52520615	ATP7B	C	T	splice_acceptor_variant	ENST00000242839.4:c.2866-1G>A	-	not_called	not_called	PASS	true_positive	Likely Pathogenic
14	23896043	MYH7	G	A	missense_variant	ENST00000355349.3:c.1987C>T	ENSP00000347507.3:p.Arg663Cys	not_called	not_called	PASS	true_positive	Pathogenic
14	23900993	MYH7	TG	T	frameshift_variant	ENST00000355349.3:c.615del	ENSP00000347507.3:p.Ser205ArgfsTer59	VQSRTrancheINDEL99.90to100.00	RefCall	PASS	false_positive	Likely Pathogenic
15	48713848	FBN1	C	T	missense_variant	ENST00000316623.5:c.7606G>A	ENSP00000325527.5:p.Gly2536Arg	not_called	not_called	PASS	true_positive	Pathogenic
15	48722997	FBN1	C	A	stop_gained	ENST00000316623.5:c.6742G>T	ENSP00000325527.5:p.Glu2248Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic
15	48760294	FBN1	G	A	missense_variant	ENST00000316623.5:c.4588C>T	ENSP00000325527.5:p.Arg1530Cys	not_called	not_called	PASS	false_positive	Pathogenic
15	48787352	FBN1	G	A	missense_variant	ENST00000316623.5:c.2645C>T	ENSP00000325527.5:p.Ala882Val	not_called	not_called	PASS	true_positive	Likely pathogenic
15	48788340	FBN1	G	T	stop_gained	ENST00000316623.5:c.2376C>A	ENSP00000325527.5:p.Cys792Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
15	48807696	FBN1	G	T	stop_gained	ENST00000316623.5:c.1356C>A	ENSP00000325527.5:p.Tyr452Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
15	67459149	SMAD3	G	T	stop_gained	ENST00000327367.4:c.565G>T	ENSP00000332973.4:p.Gly189Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
15	67479834	SMAD3	G	T	stop_gained	ENST00000327367.4:c.1141G>T	ENSP00000332973.4:p.Gly381Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
15	67479845	SMAD3	C	A	stop_gained	ENST00000327367.4:c.1152C>A	ENSP00000332973.4:p.Tyr384Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	15818211	MYH11	TC	T	frameshift_variant	ENST00000396324.3:c.4192del	ENSP00000379616.3:p.Glu1398LysfsTer67	VQSRTrancheINDEL99.70to99.80	RefCall	PASS	false_positive	Likely Pathogenic
16	15917186	MYH11	TTG	T	stop_gained	ENST00000396324.3:c.426_427del	ENSP00000379616.3:p.Tyr142Ter	VQSRTrancheINDEL99.30to99.40	RefCall	PASS	false_positive	Likely Pathogenic
16	15931991	MYH11	G	T	stop_gained	ENST00000396324.3:c.119C>A	ENSP00000379616.3:p.Ser40Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic

16	2103362	TSC2	G	A	stop_gained	ENST00000219476.3:c.245G>A	ENSP00000219476.3:p.Trp82Ter	not_called	not_called	PASS	true_positive	Pathogenic
16	2112977	TSC2	G	T	stop_gained	ENST00000219476.3:c.1366G>T	ENSP00000219476.3:p.Glu456Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
16	2137867	TSC2	C	T	stop_gained	ENST00000219476.3:c.4993C>T	ENSP00000219476.3:p.Gln1665Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
17	41215969	BRCA1	C	T	splice_acceptor_variant	ENST00000471181.2:c.5138-1G>A	-	not_called	not_called	PASS	false_positive	Pathogenic
17	41234460	BRCA1	C	CA	frameshift_variant	ENST00000471181.2:c.4317dup	ENSP00000418960.2:p.Glu1440Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
17	41258504	BRCA1	A	C	missense_variant	ENST00000471181.2:c.181T>G	ENSP00000418960.2:p.Cys61Gly	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Pathogenic
17	7577114	TP53	C	T	missense_variant	ENST00000269305.4:c.824G>A	ENSP00000269305.4:p.Cys275Tyr	VQSRTrancheSNP99.60to99.70	RefCall	PASS	false_positive	pathogenic
18	28681907	DSC2	AG	A	frameshift_variant	ENST00000280904.6:c.27del	ENSP00000280904.6:p.Trp10GlyfsTer11	VQSRTrancheINDEL99.70to99.80	RefCall	PASS	false_positive	Likely Pathogenic
18	48584825	SMAD4	C	A	stop_gained	ENST00000342988.3:c.903C>A	ENSP00000341551.3:p.Tyr301Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	true_positive	Likely pathogenic
19	11213390	LDLR	C	A	missense_variant	ENST00000558518.1:c.241C>A	ENSP00000454071.1:p.Arg81Ser	not_called	not_called	PASS	true_positive	Likely Pathogenic
19	11216247	LDLR	G	T	missense_variant	ENST00000558518.1:c.665G>T	ENSP00000454071.1:p.Cys222Phe	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	38959605	RYR1	G	A	splice_acceptor_variant	ENST00000359596.3:c.3382-1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	38964317	RYR1	G	GC	frameshift_variant	ENST00000359596.3:c.4071dup	ENSP00000352608.2:p.Gly1358ArgfsTer18	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	38966022	RYR1	C	T	stop_gained	ENST00000359596.3:c.4225C>T	ENSP00000352608.2:p.Arg1409Ter	not_called	not_called	PASS	true_positive	Pathogenic
19	38983277	RYR1	G	A	splice_donor_variant	ENST00000359596.3:c.6274+1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	38995970	RYR1	G	T	stop_gained	ENST00000359596.3:c.8332G>T	ENSP00000352608.2:p.Gly2778Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Likely Pathogenic
19	39025415	RYR1	G	A	missense_variant	ENST00000359596.3:c.11315G>A	ENSP00000352608.2:p.Arg3772Gln	not_called	not_called	PASS	false_positive	Pathogenic
19	39034301	RYR1	G	T	splice_donor_variant	ENST00000359596.3:c.11907+1G>T	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	39055701	RYR1	G	T	stop_gained	ENST00000359596.3:c.12727G>T	ENSP00000352608.2:p.Glu4243Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic
19	39055726	RYR1	C	A	stop_gained	ENST00000359596.3:c.12752C>A	ENSP00000352608.2:p.Ser4251Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	39056073	RYR1	C	CA	frameshift_variant	ENST00000359596.3:c.13099_13100insA	ENSP00000352608.2:p.Leu4367HisfsTer216	not_called	not_called	PASS	false_positive	Likely Pathogenic
19	39056142	RYR1	G	T	stop_gained	ENST00000359596.3:c.13168G>T	ENSP00000352608.2:p.Glu4390Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
1	156104999	LMNA	GC	G	frameshift_variant	ENST00000368300.4:c.833del	ENSP00000357283.4:p.Ala278ValfsTer202	not_called	not_called	PASS	false_positive	Likely Pathogenic

1	17359641	SDHB	C	T	splice_acceptor_variant	ENST00000375499.3:c.201-1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
1	201010703	CACNA1S	CT	C	frameshift_variant	ENST00000362061.3:c.5062del	ENSP00000355192.3:p.Arg1688GlyfsTer35	not_called	not_called	PASS	false_positive	likely Pathogenic
1	201047043	CACNA1S	C	A	missense_variant	ENST00000362061.3:c.1583G>T	ENSP00000355192.3:p.Arg528Leu	not_called	not_called	PASS	true_positive	Pathogenic
1	201061234	CACNA1S	GT	G	frameshift_variant	ENST00000362061.3:c.406del	ENSP00000355192.3:p.Thr136ProfsTer2	VQSRTrancheINDEL99.90to100.00	RefCall	PASS	false_positive	likely Pathogenic
1	201063068	CACNA1S	G	A	stop_gained	ENST00000362061.3:c.340C>T	ENSP00000355192.3:p.Gln114Ter	not_called	not_called	PASS	false_positive	likely Pathogenic
1	237955576	RYR2	C	T	missense_variant	ENST00000366574.2:c.13735C>T	ENSP00000355533.2:p.His4579Tyr	not_called	not_called	PASS	true_positive	Likely pathogenic
1	55509580	PCSK9	C	A	stop_gained	ENST00000302118.5:c.272C>A	ENSP00000303208.5:p.Ser91Ter	not_called	not_called	PASS	false_positive	Protective allele
1	55518016	PCSK9	G	T	stop_gained	ENST00000302118.5:c.589G>T	ENSP00000303208.5:p.Glu197Ter	VQSRTrancheSNP99.80to99.90	RefCall	PASS	false_positive	Protective allele
1	55527130	PCSK9	C	A	stop_gained	ENST00000302118.5:c.1764C>A	ENSP00000303208.5:p.Cys588Ter	not_called	not_called	PASS	false_positive	Protective allele
1	55527230	PCSK9	G	A	splice_donor_variant	ENST00000302118.5:c.1863+1G>A	-	not_called	not_called	PASS	true_positive	Likely pathogenic
22	30032739	NF2	G	A	splice_acceptor_variant	ENST00000338641.4:c.115-1G>A	-	not_called	not_called	PASS	false_positive	Likely pathogenic
22	30070931	NF2	G	T	splice_donor_variant	ENST00000338641.4:c.1446+1G>T	-	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189855070	COL3A1	G	A	missense_variant	ENST00000304636.3:c.782G>A	ENSP00000304408.3:p.Gly261Asp	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189855784	COL3A1	G	A	splice_donor_variant	ENST00000304636.3:c.852+1G>A	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
2	189860480	COL3A1	TG	T	frameshift_variant	ENST00000304636.3:c.1574del	ENSP00000304408.3:p.Gly525AlafsTer11	not_called	not_called	PASS	false_positive	Likely Pathogenic
2	189861175	COL3A1	C	T	stop_gained	ENST00000304636.3:c.1714C>T	ENSP00000304408.3:p.Arg572Ter	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	false_positive	Likely Pathogenic
2	189864055	COL3A1	A	AG	frameshift_variant	ENST00000304636.3:c.2071dup	ENSP00000304408.3:p.Ala691GlyfsTer5	not_called	not_called	PASS	true_positive	Likely Pathogenic
2	21229161	APOB	G	A	missense_variant	ENST00000233242.1:c.10579C>T	ENSP00000233242.1:p.Arg3527Trp	not_called	not_called	PASS	false_positive	Pathogenic
2	21230265	APOB	TC	T	frameshift_variant	ENST00000233242.1:c.9474del	ENSP00000233242.1:p.Lys3159ArgfsTer4	not_called	not_called	PASS	true_positive	Likely pathogenic
3	38662360	SCN5A	C	T	stop_gained	ENST00000413689.1:c.585G>A	ENSP00000410257.1:p.Trp195Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
5	112102108	APC	GT	G	splice_donor_variant	ENST00000457016.1:c.220+2del	-	not_called	not_called	PASS	false_positive	Pathogenic
5	112175618	APC	CCT	C	frameshift_variant	ENST00000457016.1:c.4329_4330del	ENSP00000413133.1:p.Gln1444AsnfsTer10	not_called	not_called	PASS	false_positive	Likely Pathogenic
6	7555950	DSP	G	T	splice_acceptor_variant	ENST00000379802.3:c.171-1G>T	-	not_called	not_called	PASS	false_positive	Likely Pathogenic
7	150644432	KCNH2	G	A	stop_gained	ENST00000262186.5:c.3136C>T	ENSP00000262186.5:p.Gln1046Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic

7	150644883	KCNH2	GC	G	frameshift_variant	ENST00000262186.5:c.2775del	ENSP00000262186.5:p.Pro926ArgfsTer48	not_called	not_called	PASS	false_positive	Likely Pathogenic
7	150644935	KCNH2	C	CA	frameshift_variant	ENST00000262186.5:c.2723dup	ENSP00000262186.5:p.Leu908PhefsTer12	not_called	not_called	PASS	false_positive	Likely Pathogenic
7	150655324	KCNH2	G	A	stop_gained	ENST00000262186.5:c.739C>T	ENSP00000262186.5:p.Gln247Ter	not_called	not_called	PASS	false_positive	Likely Pathogenic
9	135785963	TSC1	TG	T	frameshift_variant	ENST00000298552.3:c.1257del	ENSP00000298552.3:p.Arg420GlyfsTer20	not_called	not_called	PASS	false_positive	Likely Pathogenic

eTable12: Performance of the standard and deep learning models in 1072 and 1295 patients with prostate cancer and melanoma using the ACMG and the cancer predisposition gene sets.

Cohort	Tool	AUC	AUC 95% CI	AUC std	accuracy	accuracy 95% CI	Accuracy std	AuPR	AuPR 95% CI	AuPR std	f1	f1 95% CI	f1 std	precision	precision 95% CI	precision std	recall	recall 95% CI	recall std
1072 PC patients	DV	0.943	0.907-0.971	0.017	0.904	0.871-0.934	0.017	0.989	0.981-0.995	0.004	0.945	0.924-0.963	0.010	0.936	0.907-0.966	0.015	0.954	0.929-0.977	0.013
	GATK	0.891	0.839-0.933	0.024	0.799	0.752-0.842	0.022	0.979	0.963-0.990	0.007	0.881	0.848-0.909	0.015	0.904	0.863-0.938	0.019	0.859	0.817-0.899	0.021
1295 melanoma patients	DV	0.755	0.709-0.806	0.025	0.630	0.589-0.676	0.023	0.723	0.667-0.779	0.030	0.585	0.528-0.643	0.030	0.486	0.427-0.555	0.034	0.735	0.669-0.803	0.034
	GATK	0.605	0.549-0.669	0.030	0.477	0.431-0.521	0.023	0.484	0.416-0.573	0.041	0.435	0.378-0.497	0.031	0.352	0.297-0.416	0.031	0.568	0.490-0.647	0.039

AUC: Area under the curve
AuPR: Area under precision-recall

eNotes:

1- Genome Analysis Toolkit (GATK) pipeline

Genome Analysis Toolkit (GATK) HaplotypeCaller (HC) pipeline (version 3.7) was used to call germline variants according to the GATK Best Practices. The following steps and commands were followed:

1. HaplotypeCaller (HC): this command is run on each sample individually:

```
java -Xmx12G  -jar ~/GenomeAnalysisTK.jar \
-nct 8 \
-T HaplotypeCaller \
-R  ~/Homo_sapiens_assembly19.fasta \
-I  [single.sample.bam] \
--dbsnp ~/dbsnp_138.hg19.vcf.gz \
--genotyping_mode DISCOVERY \
-variant_index_type LINEAR \
-variant_index_parameter 128000 \
--emitRefConfidence GVCF \
--max_alternate_alleles 6 \
--minPruning 2 \
-stand_call_conf 30.0 \
-A DepthPerSampleHC \
-A StrandBiasBySample \
-A Coverage \
-A StrandBiasBySample \
-o ~/[single.sample].gvcf.gz
```

2. Joint genotyping (GenotypeGVCFs): this step combines all the gVCFs that were generated by the previous step to do cohort-wide genotyping:

```
java -jar -Xmx32G ~/GenomeAnalysisTK.jar \
-R ~/Homo_sapiens_assembly19.fasta -T GenotypeGVCFs \
--variant ~/[list_of_all_gVCFs].list  \
-L  ~/[capture_region].interval_list \
-o  ~/[cohort].gvcf.gz
```

3. VariantRecalibration (SNPs):

```
java -Xmx24G  -jar ~/GenomeAnalysisTK.jar \
-T VariantRecalibrator \
-R ~/Homo_sapiens_assembly19.fasta \
-input ~/[cohort].gvcf.gz \
-resource:hapmap,known=false,training=true,truth=true,prior=15.
0 ~/hapmap_3.3.b37.vcf \
-resource:omni,known=false,training=true,truth=true,prior=12.0
~/1000G_omni2.5.b37.vcf \
```

```
-resource:1000G,known=false,training=true,truth=false,prior=10.
0 ~/1000G_phase1.snps.high_confidence.b37.vcf \
-resource:dbsnp,known=true,training=false,truth=false,prior=2.0
~/dbsnp_138.b37.vcf \
-an QD -an MQRankSum -an ReadPosRankSum -an FS -an MQ -an
InbreedingCoeff \
-mode SNP \
-tranche 100.0 \
-tranche 99.9 -tranche 99.9 -tranche 99.8 -tranche 99.7
-tranche 99.6 -tranche 99.5 \
-tranche 99.4 -tranche 99.3 -tranche 99.2 -tranche 99.1
-tranche 99.0 \
-tranche 98.9 -tranche 98.8 -tranche 98.6 -tranche 98.5
-tranche 98.3 \
-tranche 98.2 -tranche 98.1 -tranche 98.0 -tranche 97.9
-tranche 97.8 \
-tranche 97.5 -tranche 97.0 -tranche 95.0 -tranche 90.0 \
-recalFile ~/[cohort].SNP.recal \
-tranchesFile ~/[cohort].SNP.tranches \
-rscriptFile ~/[cohort].SNP.R \
-nt 4
```

4. Apply recalibration (SNP):

```
java -jar -Xmx24G ~/GenomeAnalysisTK.jar \
-T ApplyRecalibration \
-R ~/Homo_sapiens_assembly19.fasta \
-input ~/[cohort].gvcf.gz \
--ts_filter_level 99.6 \
-tranchesFile ~/[cohort].SNP.tranches \
-recalFile ~/[cohort].SNP.recal \
-mode SNP \
-o ~/[cohort].snp.recalibrated.vcf.gz
```

5. VariantRecalibration (INDELs):

```
java -jar -Xmx24G ~/GenomeAnalysisTK.jar \
-T VariantRecalibrator \
-R ~/Homo_sapiens_assembly19.fasta \
-input ~/[cohort].gvcf.gz \
-tranche 100.0 \
-tranche 99.9 -tranche 99.9 -tranche 99.8 -tranche 99.7
-tranche 99.6 -tranche 99.5 \
-tranche 99.4 -tranche 99.3 -tranche 99.2 -tranche 99.1
-tranche 99.0 \
```

```
-tranche 98.9 -tranche 98.8 -tranche 98.6 -tranche 98.5
-tranche 98.3 \
-tranche 98.2 -tranche 98.1 -tranche 98.0 -tranche 97.9
-tranche 97.8 \
-tranche 97.5 -tranche 97.0 -tranche 95.0 -tranche 90.0 \
-resource:mills,known=false,training=true,truth=true,prior=12.0
~/Mills_and_1000G_gold_standard.indels.b37.vcf \
-resource:dbsnp,known=true,training=false,truth=false,prior=2.0
~/dbsnp_138.b37.vcf \
-an FS -an QD -an MQRankSum -an ReadPosRankSum -an
InbreedingCoeff \
-mode INDEL \
-recalFile ~/[cohort].INDEL.recal \
-tranchesFile ~/[cohort].INDEL.tranches \
-rscriptFile ~/[cohort].INDEL.R \
-nt 4
```

6. Apply recalibration (INDELS):

```
java -jar -Xmx24G ~/GenomeAnalysisTK.jar \
-T ApplyRecalibration \
-R ~/Homo_sapiens_assembly19.fasta \
-input ~[cohort].snp.recalibrated.vcf.gz \
--ts_filter_level 99.0 \
-tranchesFile ~/[cohort].INDEL.tranches \
-recalFile ~/[cohort].INDEL.recal \
-mode INDEL \
-o ~/[cohort].snp.recalibrated.indel.recalibrated.vcf.gz
```

2- DeepVariant Pipeline

DeepVariant version 0.6.0 was used to call variants on the same sample cohorts as follows:

1. Make examples:

```
~/deepvariant/bin/make_examples \
--mode calling \
--ref ~/Homo_sapiens_assembly19.fasta \
--reads ~/[single.sample].bam \
--examples ~/[single.sample].examples.tfrecord \
--regions ~/[capture_region].interval_list
```

2. Call variants:

```
~/deepvariant/bin/call_variants \
--outfile call_variants_output.tfrecord \
--examples ~/[single.sample].examples.tfrecord \
```

```
 --checkpoint models/model.ckpt
```

3. Postprocess variants:

```
~/deepvariant/bin/postprocess_variants \
--ref ~/Homo_sapiens_assembly19.fasta \
--infile call_variants_output.tfrecord \
--outfile [single.sample].vcf
```

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