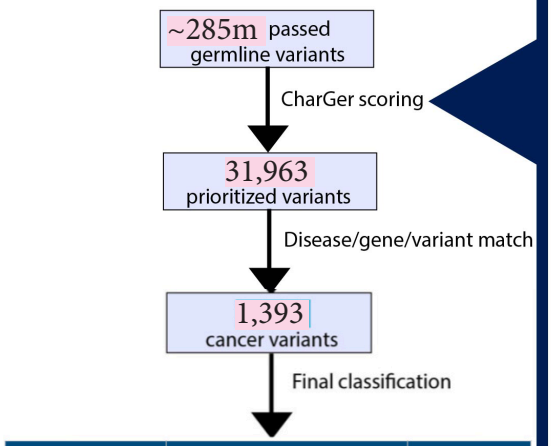
A

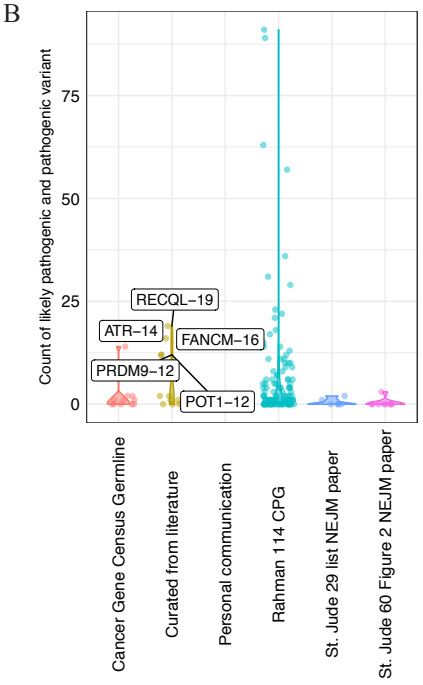


Classification	Evidence	Variant count
Pathogenic	Known pathogenic in ClinVar/ curated databases	435
Likely Pathogenic	CharGer score > 8	418
Prioritized VUS	CharGer score > 4	540

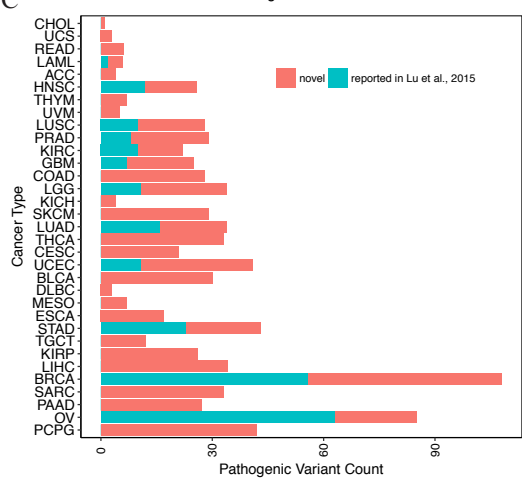
CharGer Scoring Scheme

Module Name	Desription	Database/tools	Points
PVS1	Truncations in susceptibility genes where LOF is a known mechanism and harbor variants with a dominant mode of inheritance.	152 cancer predisposition genes	8
PS1	Same peptide change as a previously established pathogenic variant.	ClinVar/compiled gene-specific databases	7
PSC1	Truncations in susceptibility genes where LOF is a known mechanism and harbor variants with a recessive mode of inheritance.	152 cancer predisposition genes	4
PMC1	Truncations when no susceptibility gene list provided	None	2
PM1	Variants located in a somatic mutation hotspot as determined by HotSpot3D clustering analysis of TCGA (MC3).	TCGA/HotSpot3D	2
PM2	Absent or extremely low frequency in the general population (MAF < 0.0005).	ExAC	2
PM4	Protein length changes due to inframe indels or nonstop variant of genes that harbor variants with a dominant mode of inheritance.	152 cancer predisposition genes	2
PM5	Different peptide change of a pathogenic variant at the same amino acid residue.	ClinVar/compiled gene-specific databases	2
PP2	Missense variant in the susceptibility genes.	152 cancer predisposition genes	1
PP3	Multiple lines (>1) of in silico evidence of deleterious effect.	SIFT/PolyPhen/ Blosum62/Compara/ VEPImpact/ MaxEntScan/ GeneSplicer	1
PPC1	Protein length changes due to inframe indels or nonstop variant of genes that harbor variants with a recessive mode of inheritance.	152 cancer predisposition genes	1
PPC2	Protein length changes due to inframe indels or nonstop variant when no susceptibility gene list provided	None	1
BP4	Multiple lines (>1) of in silico evidence of none deleterious effect.	SIFT/PolyPhen/ Blosum62/Compara/ VEPImpact/ MaxEntScan/ GeneSplicer	-1
BMC1	Peptide change is at the same location of a known benign change	ClinVar/compiled gene-specific databases	-2
BSC1	Peptide change is known to be benign	ClinVar/compiled gene-specific databases	-6
BA1	High allele frequency in the general population (MAF > 0.05).	ExAC	-8

B



C



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