Table 1. Input parameters and disease risk estimates following testing for all case study scenarios.

*Parameter ascertainment is comprehensively described within Supplementary Materials 3. HD = Huntington's disease; ALS = amyotrophic lateral sclerosis; PKU = phenylketonuria. SNV = single nucleotide variant; STRE = short tandem repeat expansion. §Estimates are based on populations of predominantly European ancestry – 95% confidence intervals shown for newly derived estimates in the ALS case study; *includes FUS variants classified as pathogenic or likely pathogenic for ALS in the ClinVar database and recorded within ALS population databases (see Table S3, Table S4); ¶defined by variant calling performance benchmarks of tools for genotyping in sequencing data by variant type (see Table S1) and, where marked †, by aggregate laboratory accuracy for genotyping C9orf72 STRE with repeat-primed polymerase chain reaction and amplicon-length analysis (45). ΩRisk following positive results in primary screening and confirmatory tests relative to a negative screening result (probability of PKU given a negative metabolic screening result is approximated as 1×10^{-6}). Probabilities are defined in the methods.*

Case study	Gene containing marker (case study scenario)	Variant type	Pre-test disease probability§	Marker frequency in people affected§	Penetrance§	Test sensitivity ¶	Test specificity ¶	Disease risk after positive test	Disease risk after negative test	Relative disease risk after positive rather than negative test
-	-	-	P(D)	P(M|D)	P(D|M)	P(T|M)	P(T'|M')	P(D|T)	P(D|T')	-
1: HD	*HTT* (screening)	STRE	0.000410	1.000	1.000	0.990	0.900	0.00404	0.00000456	887
	HTT (targeted)	STRE	0.500	1.000	1.000	0.990	0.900	0.908	0.011	82.7
2: ALS	*SOD1* (all)	SNV	0.00333	0.0188 (0.0138, 0.0238)	0.701 (0.491, 0.926)	0.9996	0.9995	0.109	0.00327	33.3
	SOD1 (A5V)	SNV	0.00333	0.000529 (4.43×10^{-5}, 0.00101)	0.91	0.9996	0.9995	0.00683	0.00333	2.05
	FUS (all)	SNV	0.00333	0.00425 (0.0023, 0.0062)	0.579 (0.291, 0.884)	0.9996	0.9995	0.0302	0.00332	9.09
	FUS (ClinVar*)	SNV	0.00333	0.00251 (0.00125, 0.00377)	0.536 (0.211, 0.877)	0.9996	0.9995	0.0194	0.00333	5.84
	C9orf72	STRE	0.00333	0.0635 (0.0538, 0.0732)	0.439 (0.358, 0.520)	0.990	0.900	0.00519	0.00313	1.66
	C9orf72 (positive sequencing screening confirmation)	STRE	0.0052	0.0635 (0.0538, 0.0732)	0.439 (0.358, 0.520)	0.95†	0.98†	0.0198	0.00489	4.06 (6.35 Ω)
3: PKU	*PAH* (screening)	SNV	0.000100	0.743	0.892	0.9996	0.9995	0.127	0.0000257	4,961
	PAH (positive metabolic screening confirmation)	SNV	0.167	0.743	0.892	0.9996	0.9995	0.889	0.0497	17.9 (889,000 Ω)