**S1 Table 1**.

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| --- | --- | --- | --- | --- | --- | --- |
| **Diseases** | **Range of general population prevalence estimates** | **Maximum estimated pathogenic variants per person** | **Exome Sequencing Project (n=6,501)** | | **1000 Genomes**  **(n=1,092)** | |
| Predicted number of pathogenic variants (event rate) | Number of variants exceeding the 95th cumulative probability percentile | Predicted number of pathogenic variants (event rate) | Number of variants exceeding the 95th cumulative probability percentile |
| *BRCA1* and *BRCA2* Hereditary Breast and Ovarian Cancer | 1:400-1:800 | 0.00125 | 16.25 | 23 | 2.73 | 6 |
| Li-Fraumeni Syndrome | 1:5,000-1:20,000 | 0.00010 | 1.30 | 3\* | 0.22 | 1\* |
| Peutz-Jeghers syndrome | 1:25,000-1:300,000 | 0.00002 | 0.26 | 1\* | 0.04 | 1\* |
| Lynch Syndrome | 1:440 | 0.00114 | 14.78 | 21 | 2.48 | 5 |
| Familial adenomatous polyposis; APC-Associated Polyposis Conditions | 1:7,000-1:44,000 | 0.00007 | 0.93 | 3 | 0.16 | 1\* |
| MUTYH-associated polyposis | 1:20,000-1:40,000 | 0.01414 | 91.94 | 108 | 15.44 | 22 |
| Von Hippel-Lindau Disease | 1:36,000 | 0.00001 | 0.18 | 1\* | 0.03 | 1\* |
| Multiple Endocrine Neoplasia Type 1 | 1:30,000 | 0.00002 | 0.22 | 1\* | 0.04 | 1\* |
| Multiple Endocrine Neoplasia Type 2 | 1:35,000 | 0.00001 | 0.19 | 1\* | 0.03 | 1\* |
| *PTEN* Hamartoma Tumor Syndrome | 1:200,000 | 0.00000 | 0.03 | 1\* | 0.01 | 1\* |
| Retinoblastoma | 1:15,000-1:20,000 | 0.00003 | 0.43 | 2\* | 0.07 | 1\* |
| Hereditary paraganglioma- pheochromocytoma syndrome | 1:1,000,000 | 0.00000 | 0.01 | 1\* | 0.00 | 1\* |
| Tuberous sclerosis complex | 1:5,800-1:6,000 | 0.00009 | 1.12 | 3\* | 0.19 | 1\* |
| *WT1*-related Wilms tumor | 1:8,000-1:10,000 | 0.00000 | 0.01 | 1\* | 0.00 | 1\* |
| Neurofibromatosis type 2 | 1:60,000 | 0.00001 | 0.11 | 1\* | 0.02 | 1\* |
| Ehlers-Danlos syndrome, vascular type | 1:50,000-1:200,000 | 0.00001 | 0.13 | 1\* | 0.02 | 1\* |
| Marfan syndrome | 1:5,000-1:10,000 | 0.00010 | 1.30 | 3\* | 0.22 | 1\* |
| Hypertrophic cardiomyopathy | 1:500 | 0.00100 | 13.00 | 19 | 2.18 | 5 |
| Catecholaminergic polymorphic ventricular tachycardia | 1:10,000 | 0.00005 | 0.65 | 2\* | 0.11 | 1\* |
| Arrhythmogenic right-ventricular cardiomyopathy | 1:1000-1:1250 | 0.00050 | 6.50 | 11 | 1.09 | 3\* |
| Long QT syndrome; Romano-Ward Syndrome | 1:3000-1:7000 | 0.00017 | 2.17 | 5 | 0.36 | 2\* |
| Familial hypercholesterolemia | 1:200-1:500 | 0.00250 | 32.51 | 42 | 5.46 | 10 |
| Malignant hyperthermia susceptibility | 1:3000-1:70000 | 0.00017 | 2.17 | 5 | 0.36 | 2\* |