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Actionable Genotypes and Their Association with Life Span in Iceland

B.O. Jensson, G.A. Arnadottir, H. Katrinardottir, R. Fridriksdottir, H. Helgason, A. Oddsson, G. Sveinbjornsson, H.P. Eggertsson, G.H. Halldorsson, B.A. Atlason, H. Jonsson, G.R. Oskarsson, A. Sturluson, S.A. Gudjonsson, G.A. Thorisson, F. Zink, K.H.S. Moore, G. Palsson, A. Sigurdsson, Adalbjorg Jonasdottir, Aslaug Jonasdottir, M.K. Magnusson, A. Helgadottir, V. Steinthorsdottir, J. Gudmundsson, S.N. Stacey, R. Hilmarsson, I. Olafsson, O.T. Johannsson, D.O. Arnar, J. Saemundsdottir, O.T. Magnusson, G. Masson, B.V. Halldorsson, A. Helgason, H. Stefansson, I. Jonsdottir, H. Holm, T. Rafnar, U. Thorsteinsdottir, D.F. Gudbjartsson, K. Stefansson, and P. Sulem

ABSTRACT

BACKGROUND

In 2021, the American College of Medical Genetics and Genomics (ACMG) recommended reporting actionable genotypes in 73 genes associated with diseases for which preventive or therapeutic measures are available. Evaluations of the association of actionable genotypes in these genes with life span are currently lacking.

METHODS

We assessed the prevalence of coding and splice variants in genes on the ACMG Secondary Findings, version 3.0 (ACMG SF v3.0), list in the genomes of 57,933 Icelanders. We assigned pathogenicity to all reviewed variants using reported evidence in the ClinVar database, the frequency of variants, and their associations with disease to create a manually curated set of actionable genotypes (variants). We assessed the relationship between these genotypes and life span and further examined the specific causes of death among carriers.

RESULTS

Through manual curation of 4405 sequence variants in the ACMG SF v3.0 genes, we identified 235 actionable genotypes in 53 genes. Of the 57,933 participants, 2306 (4.0%) carried at least one actionable genotype. We found shorter median survival among persons carrying actionable genotypes than among noncarriers. Specifically, we found that carrying an actionable genotype in a cancer gene was associated with survival that was 3 years shorter than that among noncarriers, with causes of death among carriers attributed primarily to cancer-related conditions. Furthermore, we found evidence of association between carrying an actionable genotype in certain genes in the cardiovascular disease group and a reduced life span.

CONCLUSIONS

On the basis of the ACMG SF v3.0 guidelines, we found that approximately 1 in 25 Icelanders carried an actionable genotype and that carrying such a genotype was associated with a reduced life span. (Funded by deCODE Genetics–Amgen.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. K. Stefansson can be contacted at kstefans@decode.is or at deCODE Genetics–Amgen, Sturlugata 8, Reykjavik 102, Iceland. Dr. Sulem can be contacted at patrick.sulem@decode.is or at deCODE Genetics–Amgen, Sturlugata 8, Reykjavik 102, Iceland.

Mr. Jensson, Ms. Arnadottir, Ms. Katrinardottir, Ms. Fridriksdottir, and Dr. H. Helgason and Drs. K. Stefansson and Sulem contributed equally to this article.

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The number of sequenced exomes and genomes is increasing quickly as a result of technological advances and reductions in cost. In addition to clinical contexts in which exomes and genomes are sequenced, research initiatives involving exome and genome sequencing are recruiting very large patient cohorts. The exomes[1] or genomes[2] of half a million participants in the U.K. Biobank study have been obtained, and the All of Us[3] and Our Future Health[4] programs intend to perform sequencing in 1 million and 5 million participants, respectively. The data generated in these programs will include pathogenic genotypes carried by the participants.

The American College of Medical Genetics and Genomics (ACMG) provides guidelines for the reporting of secondary findings in clinical exome and genome sequence analyses. In May 2021,[5] the ACMG introduced a list of 73 genes considered to be medically actionable because they harbor variants that are highly penetrant for monogenic diseases for which preventive or therapeutic measures are established and known to be effective. The genes are categorized into cardiovascular, cancer, metabolic, and miscellaneous groups on the basis of associated diseases. The gene list is updated annually: the most recent version (ACMG Secondary Findings [SF], version 3.2) was published in June 2023.[6]

According to the ACMG SF, version 3.0 (ACMG SF v3.0), recommendations, the detection of actionable genotypes should be reported only to persons who undergo exome or genome sequencing in a clinical context and for the purposes of obtaining a diagnosis.[7,8] However, returning incidental actionable genotypes could also benefit participants in large-scale studies that involve exome and genome sequencing,[9,10] as well as participants in biobanks[11] and clinical trials.[12] Some research groups have constructed systems for returning such findings to participants,[13,14] whereas others have not.[15] With several large-scale sequencing initiatives already under way, the importance of efficient and appropriate return of results to participants of research programs increases. Evaluating the association between actionable genotypes and mortality can assist in prioritizing the return of the genotypes most relevant to survival.

We have previously described the genomes of 58,000 Icelanders (1 in 6 Icelanders) and imputed variants in 166,000 Icelanders who had undergone chip genotyping (1 in 2 Icelanders) and reported the association of variants with diseases and other traits.[16-21] These data have allowed us to assess the pathogenicity of variants found in genes on the ACMG SF v3.0 list on the basis of their frequency and disease associations in the Icelandic population. The frequency of rare variants in Iceland is influenced by a founder effect, and therefore that of certain rare variants is relatively high,[22] which facilitates their classification.

Using a manual review of variants and their associated evidence, we assessed the fraction of 57,933 Icelanders with whole-genome sequencing data who carried an actionable genotype in one or more of the ACMG SF v3.0 genes. We then assessed the relationships between actionable genotypes and both survival and causes of death and used genotype–phenotype associations in Iceland to search for additional actionable genes.

Methods

Study Population

We conducted a study involving 57,933 Icelanders who had undergone whole-genome sequencing and 108,348 Icelanders who had undergone chip genotyping, all of whom were participating in disease projects at deCODE Genetics. Participants or their guardians provided written informed consent. The National Bioethics Committee provided approval of these studies after evaluation by the Icelandic Data Protection Authority.

Genome Sequencing, Sequence Analysis, and Genotype Filtering

Genome sequencing and sequence alignment were performed as described previously.[22,23] Paired-end sequencing by synthesis was performed on Illumina sequencers to a target depth of 30×. Reads were aligned to human genome assembly GRCh38 with the use of the Burrows–Wheeler Aligner, version 0.7.10.[24] Variants were called with the use of the Genome Analysis Toolkit, version 2014.4-2-g9ad6aa8.[25] The effects of variants were annotated with the Variant Effect Predictor (VEP-Ensembl), release 80.[26]

We included all genotypes with a sequence depth greater than or equal to 6×, a genotype

quality score greater than or equal to 20 (on the Phred scale, with 20 equal to a 1% probability of an incorrect genotype call), and an alternative-allele fraction greater than or equal to 0.20 for heterozygous genotypes. For hemizygous and homozygous genotypes, the alternative-allele fraction was restricted to 0.95 or higher.

ASSOCIATION WITH LIFE SPAN AND CAUSES OF DEATH

To determine whether actionable genotypes are associated with life span, we performed two types of analyses: survival analysis and analysis of the association with the number of years lived as a quantitative trait. We also analyzed the causes of death among carriers of actionable genotypes.

Survival curves were based on the Kaplan–Meier estimator. Comparison of the survival times between carriers and noncarriers was based on the log-rank test. The Cox proportional-hazards model was used for analyses stratified according to sex. The confidence intervals reported here were not adjusted for multiplicity and cannot be interpreted as hypothesis tests.

We regressed life span against allele counts at each variant. We calculated the expected life span of persons who were still alive and at least 65 years of age on the basis of their sex and year of birth. We assumed that the overall death rate has not changed over time.

To evaluate the causes of death among persons with actionable genotypes, we analyzed data from the Icelandic Death Registry. To assess the association between carrying an actionable genotype that confers a predisposition to a particular disease or condition and dying from that same disease or condition, we performed a logistic regression, assuming a binomial model for the two carrier-status groups (carriers vs. noncarriers). The "glm" and the "confint" functions in R software were used to perform the logistic regression and calculate 95% confidence intervals (with the use of profile log-likelihood). A more detailed description of all these analyses is provided in the Supplementary Methods section of Supplementary Appendix 1, available with the full text of this article at NEJM.org.

CURATING A SET OF ACTIONABLE GENOTYPES

We retrieved all 4405 coding and splice variants in the ACMG SF v3.0 genes for the 57,933 Icelanders who had undergone whole-genome sequencing (Fig. S1 in Supplementary Appendix 1 [all supplementary figures, tables, and sections are available in Supplementary Appendix 1 unless otherwise indicated]). To assess pathogenicity, we cross-referenced those variants with ClinVar.[27] We also annotated the variants with their association with the respective disease in Iceland. Carriers of actionable genotypes were defined as persons who carried at least one copy of a pathogenic or likely pathogenic variant in an ACMG SF v3.0 gene with autosomal dominant inheritance (i.e., heterozygotes), two copies of a pathogenic or likely pathogenic variant in an ACMG SF v3.0 gene with autosomal recessive inheritance (i.e., homozygotes), or one copy (male participants) or at least one copy (female participants) of a pathogenic or likely pathogenic variant in an ACMG SF v3.0 gene with X-linked inheritance. We grouped the genotypes in two ways. First, we determined a set of genotypes defined by narrow criteria.[15] Second, we determined a set of genotypes made up of variants classified as pathogenic or likely pathogenic on the basis of our manual curation.

The genotype set defined by the narrow criteria[15] contains variants classified as pathogenic or likely pathogenic in ClinVar with a high aggregate review status and all predicted loss-of-function variants in genes in which loss of function is a known cause of disease (see Supplementary Methods).[15] For manual curation of pathogenicity, each of the 4405 variants identified in the ACMG SF v3.0 genes was manually reviewed by at least one of five reviewers. The variant review included an assessment of evidence in ClinVar, the minor-allele frequency in Iceland and other populations, and support for an association with disease in Iceland. We assessed all variants described as pathogenic or likely pathogenic in ClinVar. We manually reviewed all variants that had conflicting interpretations of pathogenicity in ClinVar for which at least 40% of the individual submissions classified the variant as pathogenic or likely pathogenic. In addition, we assessed each predicted loss-of-function variant in genes in which loss of function is a known cause of a disease. We assigned pathogenicity to all 4405 variants according to the ACMG–Association for Molecular Pathology five-tier classification system: pathogenic, likely pathogenic, variant of uncertain significance, likely benign,

Table 1. Actionable Genotypes in ACMG SF v3.0 Genes Detected among Icelanders Who Had Undergone Whole-Genome Sequencing or Chip Genotyping.*

Disease Group and Gene	No. of Variants	Persons with WGS (N=57,933)	Persons with Chip Genotyping and Imputation (N=108,348)	Disease	Inheritance
		no. of actionable genotype carriers (%)			
Cancer					
BRCA2	16	447 (0.77)	746 (0.69)	Hereditary breast and ovarian cancer	AD
BRCA1	7	161 (0.28)	255 (0.24)	Hereditary breast and ovarian cancer	AD
PALB2	9	129 (0.22)	189 (0.17)	Hereditary breast cancer	AD
MSH6	8	61 (0.11)	92 (0.08)	Lynch syndrome	AD
PMS2	4	57 (0.10)	93 (0.09)	Lynch syndrome	AD
Other	54	127 (0.22)	83 (0.08)		
Total	98	982 (1.70)	1458 (1.35)		
Cardiovascular					
KCNQ1	8	311 (0.54)	533 (0.49)	Long QT syndrome, types 1 and 2	AD
MYBPC3	5	239 (0.41)	356 (0.33)	Hypertrophic cardiomyopathy	AD
PKP2	2	138 (0.24)	168 (0.16)	Arrhythmogenic right ventricular dysplasia or cardiomyopathy	AD
LDLR	9	81 (0.14)	62 (0.06)	Familial hypercholesterolemia	AD
TTN	27	68 (0.12)	61 (0.06)	Dilated cardiomyopathy	AD
Other	62	192 (0.33)	164 (0.15)		
Total	113	1029 (1.78)	1344 (1.24)		
Metabolic					
GLA	3	13 (0.02)	1 (<0.01)	Fabry's disease	XL
GAA	1	1 (<0.01)	1 (<0.01)	Pompe's disease	AR
Total	4	14 (0.02)	2 (<0.01)		
Miscellaneous					
HFE	1	264 (0.46)	446 (0.41)	Hereditary hemochromatosis	AR
RYR1	9	31 (0.05)	31 (0.03)	Malignant hyperthermia	AD
HNF1A	4	18 (0.03)	105 (0.10)	Maturity-onset diabetes of the young	AD
Other	6	10 (0.02)	5 (<0.01)		
Total	20	323 (0.56)	587 (0.54)		
Overall†	235	2348 (4.05)	3391 (3.13)		

* The table lists the top genes ranked according to the highest number of carriers per disease category. We detected actionable genotypes in 53 of the 73 genes in the list from the American College of Medical Genetics and Genomics Secondary Findings, version 3.0 (ACMG SF v3.0). The full list of genes and the corresponding counts of detected genotypes are provided in Table S1. AD denotes autosomal dominant, AR autosomal recessive, and XL X-linked.

† The overall totals reflect 2306 unique carriers, including 42 persons carrying two actionable variants, who had undergone whole-genome sequencing (WGS) and 3320 unique chip-genotyped carriers, including 71 persons carrying two actionable variants.

and benign.[7] The manually curated set consisted of all reviewed variants assigned a classification of pathogenic or likely pathogenic. A more detailed description of our methods is provided in Supplementary Methods.

RESULTS

ACTIONABLE GENOTYPE ASSESSMENT

On the basis of our manual curation of 4405 variants in the 73 ACMG SF v3.0 genes, we iden-

tified 235 actionable genotypes in 53 genes in 2306 of 57,933 Icelanders (4.0%, or 1 in 25) who had undergone whole-genome sequencing (Table 1, Table S1, and Table S18 in Supplementary Appendix 2). In comparison, using the previously defined narrow criteria,[15] we found only 213 actionable genotypes among 1650 Icelanders who had undergone whole-genome sequencing (2.9%) (Table S17 in Supplementary Appendix 2). Actionable genotypes in two genes were found in 42 persons. The p.Asn257LysfsTer17 founder variant in *BRCA2* (previously termed 999del5)[28] was responsible for the greatest number of actionable genotypes (421 carriers). Of the 235 variants, 67 (in 33 genes) were used to impute the genotypes of an additional 108,348 Icelanders who had undergone chip genotyping (Table 1).

When we compared our results with those of other groups,[13,15,29] using the same gene list that they had used (ACMG, version 2.0) and narrow criteria,[15] we detected actionable genotypes in 2.3% of Icelanders who had undergone whole-genome sequencing (Table S8). This percentage is consistent with those observed in Qatar, the United Kingdom, and the United States, where 2.3%, 2.0%, and 2.8%, respectively, of persons who had undergone sequencing were found to carry an actionable genotype.

GENOTYPE, LIFE SPAN, AND CAUSE OF DEATH

We assessed the association of actionable genotypes with survival (Fig. 1). We found shorter median survival among carriers of actionable genotypes (pathogenic or likely pathogenic variants) than among noncarriers, with a median survival of 86 years (95% confidence interval [CI], 85 to 87) among carriers and 87 years among noncarriers. This difference is even more evident for early death: 10% of carriers died before reaching the age of 69 years, whereas 10% of noncarriers died before reaching the age of 73 years. When persons were stratified according to disease group, median survival among carriers of actionable genotypes in the cancer group of genes was shorter than that among noncarriers by 3 years (84 years [95% CI, 82 to 85], vs. 87 years [95% CI, 87 to 87] among noncarriers), and the difference in the lowest decile of life span was 8 years (65 years for carriers and 73 years for noncarriers) (Fig. 1D and Table S5). We assessed whether the observed difference in median survival times between carriers and noncarriers of variants within cancer genes was driven mainly by carriers of variants in *BRCA1* or *BRCA2*. Median survival among carriers of variants in cancer genes other than *BRCA1* and *BRCA2* was 85 years (95% CI, 82 to 87), and that among noncarriers was 87 years (95% CI, 87 to 87) (Fig. S6 and Table S6). We found no meaningful difference in survival between carriers and noncarriers of actionable genotypes in genes in the cardiovascular disease group (Fig. 1E) or the miscellaneous disease group (Fig. 1F).

Given that the Icelandic p.Asn257LysfsTer17 founder variant in *BRCA2* is responsible for the greatest number of actionable genotypes, carried by 18% of carriers of actionable genotypes in any disease group of genes and 43% of such carriers in the cancer group, we performed a survival analysis with these carriers excluded. We again found shorter median survival, by 1 year, among carriers of actionable genotypes in all groups combined than among noncarriers (Fig. S3). Median survival among carriers of actionable genotypes in cancer group genes (but not including carriers of the founder variant) was 3 years shorter than among noncarriers (Fig. S7). Analogous calculations of life span yielded differences of 3 and 8 years for the combined groups and the cancer group, respectively (Tables S4 and S7).

To assess the association of individual actionable variants with life span, we tested the 67 imputed variants for associations with time to death among persons who lived to be at least 50 years of age (Table 2, Table S11, and Supplementary Methods). These 67 imputed variants accounted for 90% of the actionable genotypes detected through genome sequencing (Table S12).

Of these 67 variants, 13 showed evidence of association with shorter life span. The Icelandic p.Asn257LysfsTer17 founder variant in *BRCA2* (effect of the variant, −7.11 years; 95% CI, −8.01 to −6.21) was associated with a shorter time to death for both female carriers (effect of the variant, −9.34 years; 95% CI, −10.61 to −7.99) and male carriers (effect of the variant, −4.60 years; 95% CI, −5.77 to −3.43). We observed associations between eight other cancer-group variants and shorter time to death. Taken together, carriers of these nine variants accounted for 73% of all carriers of actionable genotypes in the cancer group. We found an association with shorter time to death among carriers of four variants in

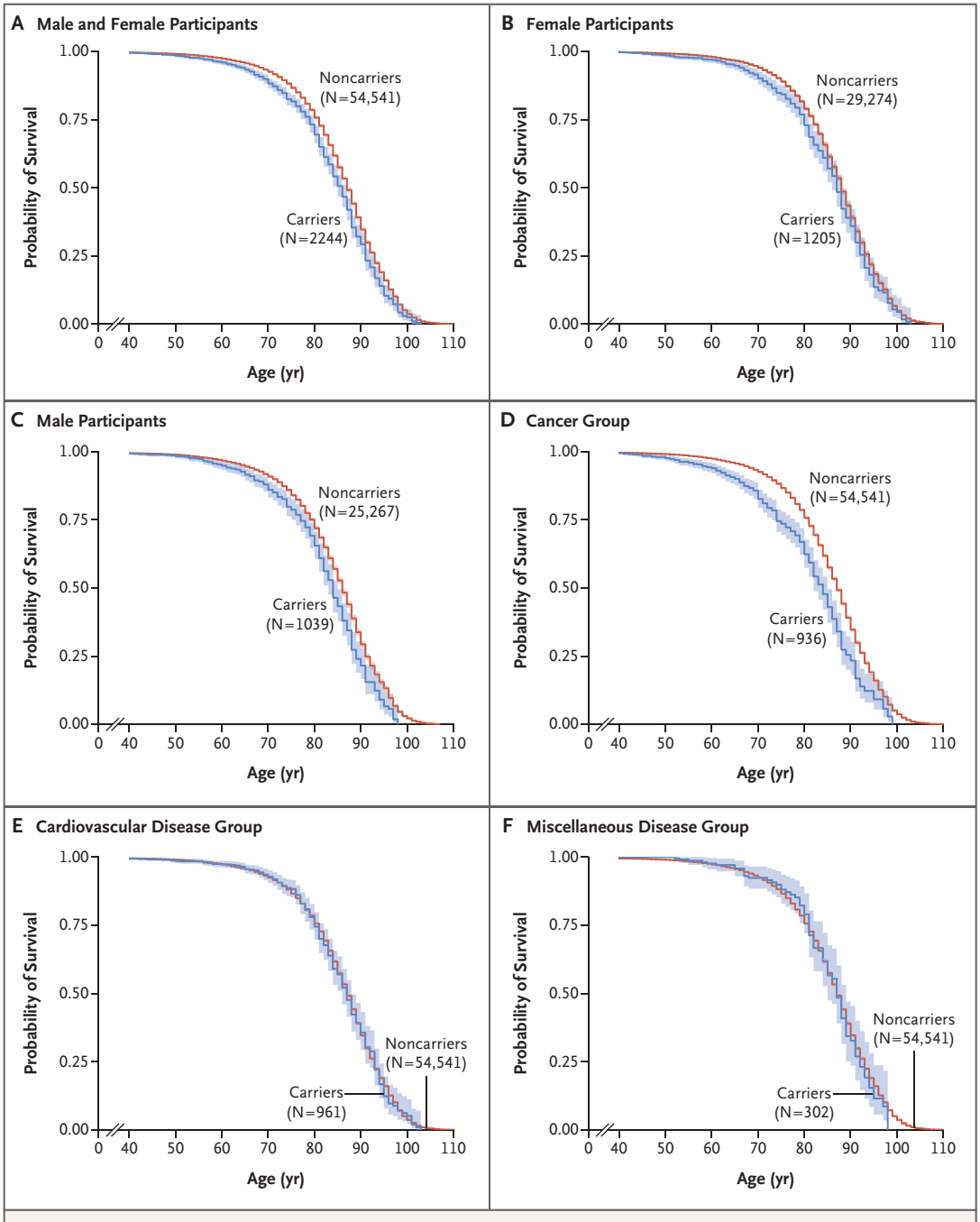

Figure 1. Kaplan–Meier Survival Curves for Carriers of Actionable Genotypes (Pathogenic or Likely Pathogenic Variants) and Noncarriers among Icelanders Who Have Undergone Whole-Genome Sequencing.

The cancer group included carriers of variants in cancer-associated genes, the cardiovascular disease group carriers of variants in cardiovascular-associated genes, and the miscellaneous group carriers of variants in genes associated with other diseases. Confidence intervals (shading) for the kth quantile for the survival curves were based on the intersection of the horizontal line at height P=1−k with the upper and lower confidence limit for the survival curve.

genes from the other disease groups (Table 2). Two of these variants were in the cardiovascular group of genes: *LDLR* (effect of the variant, −6.47 years; 95% CI, −9.91 to −3.03) and *MYBPC3* (effect of the variant, −2.18 years; 95% CI, −3.44 to −0.92). Only 25% of all carriers of actionable genotypes in genes in the cardiovascular group carried one of these two variants. We found no

association between life span and the most common actionable genotypes in the cardiovascular, miscellaneous, or metabolic disease groups (Table S11).

To evaluate the causes of death among persons with actionable genotypes, we examined data obtained from the Icelandic Death Registry (see Supplementary Methods). When we restricted the analysis to genes for which we had information on the causes of death in at least six carriers, we identified seven genes that showed evidence of association with the respective disease or condition, listed as either an underlying cause of death, a direct cause, or a contributing factor in the death certificates (Table S15 in Supplementary Appendix 2). Among these genes, four were related to cancer (*BRCA2*, *BRCA1*, *PALB2*, and *MSH6*), two belonged to the cardiovascular group (*TGFBR2* and *KCNQ1*), and one was from the miscellaneous group (*HFE*). We observed the strongest association for *BRCA2*: 22% of persons with an actionable genotype in *BRCA2* had a *BRCA2*-related disease (breast, ovarian, or pancreatic cancer) indicated on the death certificate, as compared with 4% of noncarriers (odds ratio, 6.82; 95% CI, 4.01 to 11.62).

We also found an association between actionable genotypes in *PALB2* — a relatively recent addition to the ACMG list — and death attributed to breast cancer. Among carriers of these genotypes who were deceased, 18.5% had breast cancer indicated on the death certificate, as compared with 2.4% of noncarriers (odds ratio, 9.27; 95% CI, 3.48 to 24.65).

The death certificates of 10.4% of persons carrying an actionable genotype in *MYBPC3* indicated the presence of cardiomyopathy, whereas those of 0.8% of noncarriers indicated cardiomyopathy (odds ratio, 14.04; 95% CI, 5.44 to 36.23). The effect was diluted in a test of association with a combination of all *MYBPC3*-associated conditions, including cardiomyopathy, sudden cardiac death, atrial fibrillation, and heart failure (odds ratio, 1.34; 95% CI, 0.74 to 2.42). These findings indicate that selecting the relevant diseases or conditions associated with each of the ACMG genes is an important aspect of analyzing causes of death in persons carrying actionable genotypes.

VARIANT CLASSIFICATION IN A LARGE-SCALE STUDY

We have listed five examples (variants in *BRCA1*, *PCSK9*, *MSH6*, *KCNQ1*, and *DSG2*) that illustrate the effectiveness of using a local genotypic and phenotypic data set to manually curate the pathogenicity of variants (Table S9). One of these examples is a splice-site variant in *BRCA1*, c.4096+3A→G, which is classified as a variant of uncertain significance in ClinVar on the basis of a review by an expert panel. The variant is observed in approximately 1 in 500 Icelanders but in only 1 of 132,000 persons who have undergone whole-genome sequencing in the U.K. Biobank, a finding consistent with a founder effect in Iceland. This variant was associated with breast cancer (odds ratio, 3.13; 95% CI, 1.90 to 5.16) and ovarian cancer (odds ratio, 8.49; 95% CI, 3.99 to 18.10) in the current study, although its penetrance has been reported to be incomplete.[30,31] We found a shorter life span among carriers of this variant than among noncarriers (effect of the variant, −2.68 years; 95% CI, −4.34 to −1.02) (Table 2). We assessed RNA sequence data from 42 persons who were heterozygous for the variant and 17,551 noncarriers and concluded that c.4096+3A→G is associated with omission of *BRCA1* exon 10 mRNA (effect of the variant on exon 10 RNA level, −1.45 SD; 95% CI, −1.81 to −1.09) (Fig. S8), a finding consistent with a damaging effect on protein function. We therefore conclude that the c.4096+3A→G variant should be classified as pathogenic.

EXPANDING THE LIST OF ACTIONABLE GENES

The ACMG has announced an annual update of the list of actionable genes.[5] We have identified 10 genotypes in 10 genes in Iceland that could be considered for inclusion in this list. Pathogenic variation in each of these genes is associated with diseases for which interventions are available to improve outcomes (Table 3). Pathogenic variation in five of the genes (*PKD2*, *APRT*, *PKD1*, *MYL4*, and *F5*) is associated with a shorter life span (Table S13).

Among the 10 genotypes that we identified are the *F5* (factor V) Leiden thrombophilia missense variant p.Arg534Gln and the *F2* (factor II) 3′ untranslated region variant c.*97G→A. These two genotypes in *F2* and *F5* are common causes of venous thromboembolism among White, Hispanic, and Black persons in the United States.[32] Persons who are homozygous for the *F5* Leiden variant have a greater than 80% lifetime risk of venous thromboembolism; in contrast, persons who are heterozygous have a 10% lifetime risk.[32]

Table 2. Genotypes Associated with Time to Death among Persons Who Lived to Be at Least 50 Years of Age.*

Gene	Consequence of Sequence Variant	Persons with WGS	Persons with Imputation	Effect on Life Span (95% CI)†		Death Registry Data among Persons with WGS‡			
						Carriers with Associated Condition	Noncarriers with Associated Condition	Odds Ratio (95% CI)	Persons in Registry
		no. with genotype		*SD*	*yr*	*percent*			*no.*
ATP7B	NP_000044.2: p.Tyr670Ter	4§	7§	−1.46 (−2.70 to −0.22)	−15.72 (−29.12 to −2.32)	—	—	—	4
BRCA1	NM_007294.4: c.4096+3A→G	118	313	−0.25 (−0.41 to −0.09)	−2.68 (−4.34 to −1.02)	17.9	4.0	5.19 (1.96 to 13.72)	28
BRCA1	NP_009225.1: p.Asp1692Asn	26	70	−0.51 (−0.84 to −0.18)	−5.46 (−9.04 to −1.88)	33.3	4.0	11.94 (2.98 to 47.89)	9
BRCA1	NP_009225.1: p.Gly129AlafsTer34	9	24	−0.57 (−1.12 to −0.02)	−6.16 (−12.07 to −0.25)	—	—	—	2
BRCA2	NP_000050.2: p.Asn257LysfsTer17	421	1161	−0.66 (−0.74 to −0.58)	−7.11 (−8.01 to −6.21)	22.1	4.0	6.77 (3.92 to 11.69)	77
HNF1A	NP_000536.6: p.Pro291GlnfsTer51	10	55	−0.55 (−0.98 to −0.12)	−5.96 (−10.67 to −1.25)	—	—	—	2
LDLR	NM_000527.5: c.694+2T→C	41	80	−0.60 (−0.92 to −0.28)	−6.47 (−9.91 to −3.03)	—	—	—	4
MSH2	NM_000251.3: c.792+1G→C	2	2	−1.99 (−3.88 to −0.10)	−21.51 (−41.96 to −1.06)	—	—	—	1
MSH6	NP_000170.1: p.Leu585Pro	34	102	−0.31 (−0.56 to −0.06)	−3.39 (−6.13 to −0.65)	14.3	4.5	3.56 (0.43 to 29.64)	7
MSH6	NP_000170.1: p.Arg1172LysfsTer5	13	32	−0.47 (−0.87 to −0.07)	−5.02 (−9.34 to −0.70)	—	—	—	4
MYBPC3	NM_000256.3: c.927−2A→G	218	561	−0.20 (−0.32 to −0.08)	−2.18 (−3.44 to −0.92)	37.2	29.0	1.45 (0.78 to 2.69)	43
PALB2	NP_078951.2: p.Trp906Ter	88	239	−0.32 (−0.50 to −0.14)	−3.48 (−5.41 to −1.55)	10.5	2.4	4.80 (1.10 to 20.86)	19
TP53	NP_000537.3: p.Pro152Leu	2	1	−1.80 (−3.52 to −0.08)	−19.50 (−38.18 to −0.82)	—	—	—	1

* Shown are actionable genotypes associated with time to death in Icelanders who lived to be at least 50 years of age and their association with causes of death. All associations with time to death are under the additive model, with the exception of the association of the variant in *ATP7B*, which is under the recessive model. The association with causes of death is listed only for genotypes for which information from the death registry was available for at least six carriers. In cases in which death registry information was available only for five or fewer carriers, a dash is shown in the corresponding column.

† Data on life span were based on persons who had undergone chip genotyping and their first- and second-degree relatives who had not been directly genotyped (see Supplementary Methods).

‡ Data from the death registry were based on persons who had undergone whole-genome sequencing and for whom death registry data were available (see Supplementary Methods).

§ These persons were homozygotes.

We identified, in our data set, 83 persons who were homozygous for the *F5* Leiden variant and 5 who were homozygous for the *F2* variant (Table 3). Both genotypes were associated with an increased risk of venous thromboembolism in our study: the odds ratio for venous thromboembolism among persons homozygous for the *F5* Leiden variant was 7.61 (95% CI, 3.99 to 14.47), and that among persons homozygous for the *F2* variant was 11.92 (95% CI, 1.27 to 111.42). In addition, we found a shorter life span among persons homozygous for the *F5* Leiden variant than among noncarriers (effect of the variant, −4.47 years; 95% CI, −8.94 to −0.01) (Table S13).

DISCUSSION

On the basis of manual curation of a set of variants from 57,933 Icelanders who had undergone whole-genome sequencing, with the use of a local genotypic and phenotypic database and reported evidence, we found that 4.0% of Icelanders (1 in 25) carry an actionable genotype in at least one of the ACMG SF v3.0 genes. We found shorter survival (i.e., a shorter time to death) among carriers of actionable genotypes than among noncarriers, and we found that the majority of variants in cancer genes were associated with a reduced life span when tested either as a group or individually. We found that the most common actionable cancer genotype, the Icelandic p.Asn257LysfsTer17 founder variant in *BRCA2*, does not entirely explain the difference in survival between carriers of actionable genotypes and noncarriers. We did not find a difference in survival between carriers and noncarriers of actionable genotypes in the cardiovascular and miscellaneous disease groups of genes. In these two groups, we did find an association between carrying an actionable genotype and having a reduced life span, but only for variants that were present in a minority of carriers of such genotypes. It is possible that some of the risk conferred by the genotypes may be mitigated through treatment. Some of the genotypes, such as the C282Y homozygous genotype in *HFE*, although not associated with mortality, are associated with morbidity, including liver cirrhosis and liver cancer,[33] which underscores the value of reporting such genotypes. Variants with incomplete penetrance may still lead to serious disease, and in these scenarios, the benefit–risk ratio between interventions and disease outcomes must be evaluated. For example, the normalization of iron levels in persons who are homozygous for C282Y is obtained by phlebotomy, an easily accessible intervention with a low risk of adverse effects.

The results of our analysis of causes of death are consistent with those of the analyses of survival and life span. We identified several genes with variants that showed evidence of association with mortality, with the underlying or contributing cause of death related to the relevant disease. Of particular note was the association with cancer-related genotypes. However, these observations are sensitive to the selection of conditions associated with each gene, as exemplified by *MYBPC3*, for which we observed a clear association with cardiomyopathy but not with heart failure as a cause of death. This finding could potentially be explained by the fact that heart failure is a prevalent condition in the general population.

The Centers for Disease Control and Prevention Office of Public Health Genomics has prioritized 10 genes ("tier 1")[34] on the basis of a predicted positive effect on public health in the event that pathogenic or likely pathogenic variants in these genes are detected at an early age. The fact that 7 of these genes, when variant, are associated with cancer aligns with our observation that carrying an actionable genotype in a cancer-associated gene was associated with a shortened life span. Furthermore, among noncancer tier 1 genes, we observed an association between the c.694+2T→C variant in *LDLR*, which confers a predisposition to cardiovascular disease, and a shortened life span.

The survival rate among Icelanders in this cross-sectional study is certainly overestimated because persons who die prematurely are less likely to participate in research studies. However, the calculated reduction in survival among carriers of actionable genotypes is probably underestimated because carriers of such genotypes who have severe disease or an early death are relatively unlikely to have entered the study.

Ongoing large-scale sequencing efforts, such as the All of Us and Our Future Health projects, highlight the need for reaching a consensus on the return of genomic results to participants in research studies, biobanks, and

Table 3. Potentially Actionable Genotypes in Genes Currently Not on the ACMG List Detected through Icelandic Population Studies.*

Gene	Consequence of Sequence Variant	Disease in Literature (MOI)	Clinical Significance (ClinVar ID)	Persons with WGS/Persons with Imputation†	Associated Action	Manually Curated Clinical Significance‡	Disease Association in Iceland§	
							Phenotype	Odds Ratio (95% CI)
				no. with genotype				
APRT	NP_000476.1: p.Asp65Val	CKD (AR)	Pathogenic (18297)	11/33¶	Treatment with allopurinol or febuxostat, prevention of CKD progression	LP	Kidney stones, CKD	28.31 (12.15 to 65.99) for kidney stones 38.40 (11.11 to 132.68) for CKD
F2	NM_000506.4: c.*97G→A	VTE (AD and AR)	Conflicting interpretations of pathogenicity, risk factor (13310)	2/3¶	Hormonal treatment selection and antithrombotic prophylaxis	LP	DVT	11.92 (1.27 to 111.42)
F5	NP_000121.2: p.Arg534Gln	VTE (AD and AR)	Pathogenic, risk factor (642)	38/45¶	Hormonal treatment selection and antithrombotic prophylaxis	LP	DVT	7.61 (3.99 to 14.47)
F8	NP_000123.1: p.Arg2178Cys	Hemophilia A (XLR)	Pathogenic (10318)	7/17‖	Replacement therapy	P	Factor 8 deficiency	91.69 (36.76 to 228.67)
GCK	NP_000153.1: p.Gln219Ter	MODY type 2 (AD)	NA	6/8	Insulin treatment during pregnancy, diet and exercise	P	MODY and T1D	157.67 (21.16 to 1174.73)
MYL4	NP_002467.1: p.Cys78TrpfsTer29	AF (AR)	NA	9/0¶	Antiarrhythmic drug therapy	P	Early-onset AF, ischemic stroke**	101.36 (27.51 to 373.52) for early-onset AF 93.63 (15.17 to 578.04) for ischemic stroke
NEUROD1	NP_002491.2: p.Glu110Lys	MODY type 6 (AD)	NA	9/7	Diet, oral antibiotics, insulin	LP	T1D	74.28 (19.92 to 276.94)
NKX2–5	NP_004378.1: p.Phe145Leu	DCM (AD)	NA	15/7	Drug therapy, surgically implanted device	P	DCM	121.78 (32.00 to 463.85)
PKD1	NP_000287.4: p.Trp1839Arg	PKD (AD)	NA	7/2	Surveillance and prevention of complications, treatment selection	P	PKD	215.12 (48.68 to 951.57)
PKD2	NM_000297.3: c.596–12_599del	PKD (AD)	NA	31/17	Surveillance and prevention of complications, treatment selection	P	PKD	237.40 (85.78 to 657.03)

* AF denotes atrial fibrillation, CKD chronic kidney disease, DCM dilated cardiomyopathy, DVT deep-vein thrombosis, LP likely pathogenic, MODY maturity-onset diabetes of the young, MOI mode of inheritance, NA not applicable (variant absent from ClinVar database), P pathogenic, PKD polycystic kidney disease, T1D type 1 diabetes, VTE venous thromboembolism, and XLR X-linked recessive.

† Data are from the 57,933 Icelanders with whole-genome sequencing data and from the 108,348 Icelanders with chip-genotyping and imputed data (but no whole-genome sequencing data).

‡ Information on the ACMG–Association for Molecular Pathology criteria used in the determination of manually curated clinical significance is provided in Table S20.

§ All disease associations for AR genes are under the recessive model.

¶ These persons were homozygotes.

‖ These persons were hemizygotes.

** Early-onset AF is defined as AF with an onset in a patient younger than 60 years of age.

clinical trials, as has been done for patients seeking a diagnosis through clinical exome and genome sequencing.[9] The fraction of the half million participants in the U.K. Biobank who carry actionable genotypes is similar to that observed in the Icelandic population,[2] but there exists no plan to return these results to the participants. To provide a mechanism through which participants can be notified of genetic risk, we established a Web interface through which they can request *BRCA2* p.Asn257LysfsTer17 genotype status. We have reported 450 positive, technically validated results in response to 39,267 requests.

We have found evidence of an association between actionable genotypes in the Icelandic population and a shortened life span. The identification and disclosure of actionable genotypes to participants holds considerable potential to mitigate the disease burden on individual persons as well as on society in general.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Brynjar O. Jensson, M.Sc., Gudny A. Arnadottir, M.Sc., Hildigunnur Katrinardottir, M.Sc., Run Fridriksdottir, M.Sc., Hannes Helgason, Ph.D., Asmundur Oddsson, Ph.D., Gardar Sveinbjornsson, M.Sc., Hannes P. Eggertsson, Ph.D., Gisli H. Halldorsson, M.Sc., Bjarni A. Atlason, B.A., Hakon Jonsson, Ph.D., Gudjon R. Oskarsson, Ph.D., Arni Sturluson, Ph.D., Sigurjon A. Gudjonsson, B.Sc., Gudmundur A. Thorisson, Ph.D., Florian Zink, Ph.D., Kristjan H.S. Moore, M.A., Gunnar Palsson, Ph.D., Asgeir Sigurdsson, B.Sc., Adalbjorg Jonasdottir, B.Sc., Aslaug Jonasdottir, M.Sc., Magnus K. Magnusson, M.D., Anna Helgadottir, Ph.D., Valgerdur Steinthorsdottir, Ph.D., Julius Gudmundsson, M.Sc., Simon N. Stacey, Ph.D., Rafn Hilmarsson, M.D., Isleifur Olafsson, M.D., Ph.D., Oskar T. Johannsson, M.D., David O. Arnar, M.D., Ph.D., M.P.H., Jona Saemundsdottir, B.Sc., Olafur T. Magnusson, Ph.D., Gisli Masson, Ph.D., Bjarni V. Halldorsson, Ph.D., Agnar Helgason, Ph.D., Hreinn Stefansson, Ph.D., Ingileif Jonsdottir, Ph.D., Hilma Holm, M.D., Thorunn Rafnar, Ph.D., Unnur Thorsteinsdottir, Ph.D., Daniel F. Gudbjartsson, Ph.D., Kari Stefansson, M.D., Ph.D., and Patrick Sulem, M.D.

The authors' affiliations are as follows: deCODE Genetics–Amgen (B.O.J., G.A.A., H.K., R.F., H. Helgason, A.O., G.S., H.P.E., G.H.H., B.A.A., H.J., G.R.O., A. Sturluson, S.A.G., G.A.T., F.Z., K.H.S.M., G.P., A. Sigurdsson, Adalbjorg Jonasdottir, Aslaug Jonasdottir, M.K.M., A. Helgadottir, V.S., J.G., S.N.S., D.O.A., J.S., O.T.M., G.M., B.V.H., A. Helgason, H.S., I.J., H. Holm, T.R., U.T., D.F.G., K.S., P.S.), the Faculty of Medicine, School of Health Sciences (G.A.A., M.K.M., R.H., D.O.A., I.J., U.T., K.S.), the Department of Anthropology (K.H.S.M., A. Helgason), and the School of Engineering and Natural Sciences (H. Helgason, G.H.H., D.F.G.), University of Iceland, the Departments of Urology (R.H.), Clinical Biochemistry (I.O.), Oncology (O.T.J.), Medicine (D.O.A.), and Immunology (I.J.), Landspitali–the National University Hospital of Iceland, and the School of Science and Engineering, Reykjavik University (B.V.H.) — all in Reykjavik, Iceland.

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