Supplementary Information

**Supplementary Table 1.** SNP identifier, chromosome, effect allele, reference allele, and position (based on version 37), and beta (model weight) for the 290 SNPs used in the calculation of PHS290. The effect-allele-frequency (EAF) was estimated from controls in the training dataset with age less than 70 years. The HGNC identifier and Variant Consequence for each SNP were extracted from dbSNP.

| SNP ID       | Chr | Effect | Ref | Position    | beta  | EAF       | HGNC          | Variant Consequence                                      |
|--------------|-----|--------|-----|-------------|-------|-----------|----------------|----------------------------------------------------------|
| rs12262998   | 10  | C      | T   | 104428716   | 0.0254| 0.6792    |                |                                                          |
| rs10885396   | 10  | T      | C   | 114711755   | 0.0095| 0.5434    | TCF7L2         | intron_variant                                           |
| rs4558107    | 10  | A      | G   | 122794926   | 0.0227| 0.3932    |                |                                                          |
| rs140783917  | 10  | C      | T   | 122834482   | 0.1275| 0.9989    |                |                                                          |
| rs10788167   | 10  | T      | A   | 123054018   | 0.0249| 0.7674    |                |                                                          |
| rs10749415   | 10  | A      | G   | 123185303   | 0.0602| 0.9469    |                |                                                          |
| rs12769682   | 10  | C      | G   | 126697494   | 0.0358| 0.2720    | CTBP2          | intron_variant;non_coding_transcript_variant             |
| rs7075427    | 10  | A      | C   | 46104943    | 0.0069| 0.9209    |                |                                                          |
| rs11599847   | 10  | T      | C   | 47599029    | -0.0171| 0.9629   | TCF7L2         | intron_variant                                           |
| rs10993994   | 10  | A      | G   | 51549496    | 0.0227| 0.3932    |                |                                                          |
| rs12781100   | 10  | T      | C   | 838636      | 0.0543| 0.1600    |                |                                                          |
| rs11817544   | 10  | C      | A   | 80236999    | 0.0338| 0.9413    | LINC00856      | non_coding_transcript_variant;intron_variant             |
| rs12412705   | 10  | C      | T   | 80835998    | 0.0180| 0.0692    | ZMIZ1          | intron_variant                                           |
| rs1935581    | 10  | C      | T   | 90195149    | 0.0323| 0.6297    | RNLS           | intron_variant;non_coding_transcript_variant             |
| rs11568818   | 11  | T      | C   | 102401661   | 0.0333| 0.5494    |                |                                                          |
| rs74911261   | 11  | A      | G   | 108357137   | 0.0598| 0.0245    | KDEL2          | missense_variant;NMD_transcript_variant;non_coding_transcript_exon_variant |
| rs138466039  | 11  | T      | C   | 125054793   | 0.0801| 0.0103    | PKNOX2         | intron_variant;non_coding_transcript_variant             |
| rs878987     | 11  | G      | A   | 134266372   | 0.0241| 0.1460    | B3GAT1         | intron_variant;non_coding_transcript_variant             |
| rs1881502    | 11  | T      | C   | 1507512     | 0.0107| 0.1903    | MOB2           | intron_variant;non_coding_transcript_variant             |
| rs72853963   | 11  | A      | G   | 2224664     | 0.0190| 0.1822    |                |                                                          |
| rs11043143   | 11  | T      | C   | 2234093     | 0.0735| 0.1948    |                |                                                          |
| rs68010938   | 11  | T      | TA  | 47428209    | 0.0186| 0.3047    | non_coding_transcript_variant;intron_variant             |
| rs1048374    | 11  | G      | A   | 58902679    | -0.0747| 0.0037   | non_coding_transcript_variant                            |
| rs2277283    | 11  | C      | T   | 61908440    | 0.0356| 0.3045    | INCENP         | missense_variant;non_coding_transcript_exon_variant      |
| rs12785905   | 11  | C      | G   | 66951965    | 0.0247| 0.0389    | KDM2A          | intron_variant                                           |
| rs3018690    | 11  | T      | C   | 68882926    | 0.0297| 0.4431    |                |                                                          |
| rs11825796   | 11  | A      | G   | 68980788    | -0.0164| 0.2625   |                |                                                          |
| rs12275055   | 11  | G      | A   | 68981359    | 0.0453| 0.1652    |                |                                                          |
| chr11_68985583 | 11  | C      | T   | 68985583    | -0.0531| 0.4928   |                |                                                          |
| rsID          | Chromosome | Position | p-value | q-value | Gene/Variant Description                                    |
|--------------|------------|----------|---------|---------|-------------------------------------------------------------|
| rs11228580   | 11         | 69002342 | 0.0094  | 0.1655  | intron_variant;non_coding_transcript_variant                 |
| rs3918298    | 11         | 69463273 | 0.0824  | 0.0274  | CCND1 intron_variant                                        |
| rs61890184   | 11         | 7547587  | 0.0334  | 0.1179  | PPFIBP2 intron_variant                                      |
| rs56159348   | 11         | 76267331 | 0.0259  | 0.6783  |                                                           |
| rs77121786   | 12         | 102446675 | 0.0341 | 0.1981  | CCDC53 NMD_transcript_variant;intron_variant;non_coding_transcript_variant |
| rs1270884    | 12         | 114685571 | 0.0239 | 0.4816  | non_coding_transcript_variant;intron_variant;missense_variant;non_coding_transcript_variant;intron_variant;coding_sequence_variant |
| rs2066827    | 12         | 12871099 | 0.0348  | 0.7603  | CDKN1B intron_variant                                       |
| rs77216612   | 12         | 12877983 | 0.0030  | 0.7240  |                                                            |
| rs7295014    | 12         | 133067989 | 0.0243 | 0.3349  | FBRSL1 intron_variant                                      |
| rs10845938   | 12         | 14416918 | 0.0315  | 0.5489  |                                                            |
| rs80130819   | 12         | 48419618 | 0.0519  | 0.9104  |                                                            |
| rs56222401   | 12         | 49672714 | 0.0180  | 0.2499  |                                                            |
| rs10875943   | 12         | 49676010 | 0.0178  | 0.2810  |                                                            |
| rs113925811  | 12         | 53308932 | 0.0789  | 0.1267  | KRT8 intron_variant                                        |
| rs187809440  | 12         | 53329231 | 0.2268  | 0.0003  | KRT8 intron_variant                                        |
| rs7968403    | 12         | 65012824 | 0.0265  | 0.6390  | RASSF3 intron_variant;NMD_transcript_variant;intron_variant;NMD_transcript_variant |
| rs4842687    | 12         | 90156377 | 0.0303  | 0.7122  |                                                            |
| rs1327653    | 13         | 51076440 | 0.0295  | 0.2546  | DLEU1 non_coding_transcript_variant;intron_variant          |
| rs7489409    | 13         | 73716861 | 0.0414  | 0.1847  |                                                            |
| rs7336001    | 13         | 73995877 | 0.0554  | 0.9055  | LINC00393 intron_variant;non_coding_transcript_variant      |
| rs1004030    | 14         | 23305649 | 0.0146  | 0.5830  |                                                            |
| rs6571758    | 14         | 37136194 | 0.0324  | 0.6195  | PAX9 intron_variant;NMD_transcript_variant                  |
| rs11849126   | 14         | 38144592 | 0.0026  | 0.6944  | TTC6 intron_variant;NMD_transcript_variant                 |
| rs4901313    | 14         | 53387109 | 0.0401  | 0.8151  | FERMT2 intron_variant;NMD_transcript_variant               |
| rs8005621    | 14         | 61106699 | 0.0385  | 0.0947  |                                                            |
| rs79133931   | 14         | 64687926 | -0.1985 | 0.0010  | SYNE2 intron_variant;NMD_transcript_variant;intron_variant  |
| rs2093202    | 14         | 68923908 | 0.0160  | 0.6143  | RAD51B intron_variant;non_coding_transcript_variant         |
| rs767127     | 14         | 69134264 | 0.0238  | 0.4978  | RAD51B intron_variant;non_coding_transcript_variant         |
| rs17565772   | 14         | 70756333 | 0.0246  | 0.4595  |                                                            |
| rs11561564   | 15         | 40965044 | 0.0262  | 0.8413  |                                                            |
| rs33984059   | 15         | 56385868 | 0.0808  | 0.9754  | RFX7 missense_variant;NMD_transcript_variant                |
| rs74634457   | 15         | 66835704 | 0.0380  | 0.2563  | ZWILCH intron_variant                                       |
| SNP          | Chromosome | Position | Minor Allele | Major Allele | Minor Allele Frequency | Major Allele Frequency | Gene          | Annotation                                                                 |
|--------------|------------|----------|--------------|--------------|------------------------|------------------------|--------------|----------------------------------------------------------------------------|
| rs12913603   | 15         | 70668824 | C            | A            | 0.0195                 | 0.4757                 |              | intergenic; coding: non coding transcript variant; NMD transcript variant   |
| rs7188897    | 16         | 54469331 | C            | T            | 0.0145                 | 0.3503                 |              | coding: coding: coding: intron variant; coding: intron variant             |
| rs13380763   | 16         | 54678305 | T            | C            | 0.0265                 | 0.8116                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs11863709   | 16         | 57654576 | A            | C            | 0.0594                 | 0.9467                 | GPR56        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs28709974   | 16         | 79847632 | T            | C            | 0.0517                 | 0.5028                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs8052913    | 16         | 82166181 | T            | C            | 0.0315                 | 0.3854                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs72811270   | 17         | 12585459 | G            | A            | 0.0382                 | 0.1155                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs4795646    | 17         | 30092898 | C            | T            | 0.0294                 | 0.7716                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs718961     | 17         | 36077099 | C            | G            | 0.0145                 | 0.2274                 | HNF1B        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs11649743   | 17         | 36074979 | G            | A            | 0.0482                 | 0.8100                 | HNF1B        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs11651052   | 17         | 36102381 | C            | G            | 0.0153                 | 0.4697                 | HNF1B        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs11863709   | 17         | 36103565 | G            | A            | 0.0816                 | 0.5295                 | HNF1B        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| chr17_4682067 | 17  | 46820676 | C            | T            | 0.0944                 | 0.0410                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs2960158    | 17         | 47380305 | C            | T            | 0.0114                 | 0.7714                 | ZNF652       | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs565189650  | 17         | 47398245 | C            | T            | 0.0493                 | 0.0755                 | ZNF652       | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs1293538    | 17         | 56426027 | C            | T            | 0.0172                 | 0.5631                 | BZRAP1-AS1   | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs684232     | 17         | 618965   | T            | C            | 0.0538                 | 0.3546                 | VPS53        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs9889335    | 17         | 69115146 | T            | G            | 0.0288                 | 0.4817                 | CASC17       | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs148511027  | 17         | 69117532 | G            | T            | 0.0585                 | 0.4745                 | CASC17       | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs78378222   | 17         | 7571752  | T            | G            | 0.1025                 | 0.0107                 | TP53         | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs28441558   | 17         | 7803118  | C            | T            | 0.0623                 | 0.0568                 | CHD3         | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs8089411    | 18         | 51771322 | C            | T            | 0.0161                 | 0.4421                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs35283980   | 18         | 56745999 | C            | G            | 0.0131                 | 0.3023                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs533722308  | 18         | 60961193 | C            | T            | 0.0244                 | 0.3634                 | BCL2         | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs11876000   | 18         | 73035513 | C            | T            | 0.0228                 | 0.4137                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs9959454    | 18         | 76770820 | A            | G            | 0.0489                 | 0.7318                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs10412482   | 19         | 17228554 | C            | T            | 0.0338                 | 0.7162                 | MYO9B        | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs17501397   | 19         | 32168343 | C            | T            | 0.0217                 | 0.9097                 |              | coding: coding: coding: coding: coding: coding: coding: coding: coding:   |
| rs | Chrs | Genotype | Position | P-value | MAF | Gene | Description |
|----|------|----------|----------|---------|-----|------|-------------|
| rs59710626 | 19 | G T | 38548094 | 0.0094 | 0.8637 | SIPA1L3 | intron_variant;non_coding_transcript_variant |
| rs4802297 | 19 | G C | 38738130 | 0.0368 | 0.4976 | SPINT2 | intron_variant |
| chr19_41985587 | 19 | A G | 41985587 | -0.0470 | 0.2589 | intron_variant;non_coding_transcript_variant |
| rs11673591 | 19 | T A | 41985931 | 0.0036 | 0.7391 | intron_variant;non_coding_transcript_variant |
| rs2659051 | 19 | G C | 51345568 | 0.0421 | 0.7945 | intron_variant;non_coding_transcript_variant |
| rs61752561 | 19 | G A | 51361382 | 0.1099 | 0.9565 | KLK3 | missense_variant;3_prime_UTR_variant;NMD_transcript_variant;intron_variant;non_coding_transcript_exon_variant;coding_sequence_variant;3_prime_UTR_variant;NMD_transcript_variant;non_coding_transcript_exon_variant |
| rs61752561 | 19 | C T | 51361757 | -0.1912 | 0.0735 | KLK3 | missense_variant;3_prime_UTR_variant;NMD_transcript_variant;non_coding_transcript_variant |
| rs2847344 | 1 | A G | 10564675 | 0.0167 | 0.6902 | PEX14 | non_coding_transcript_variant;intron_variant |
| rs1811698 | 1 | C T | 150772613 | 0.0468 | 0.8913 | CTSK | intron_variant |
| rs607518 | 1 | A G | 150954671 | 0.0242 | 0.2100 | ANXA9 | 5_prime_UTR_variant |
| rs10127983 | 1 | T C | 153923276 | 0.0390 | 0.3115 | CRTC2 | intron_variant;NMD_transcript_variant;non_coding_transcript_variant |
| rs56103503 | 1 | T C | 154980351 | 0.0347 | 0.3841 | ZBTB7B | intron_variant;non_coding_transcript_variant |
| rs147847496 | 1 | C T | 155118588 | 0.0829 | 0.9783 | intron_variant;intron_variant;non_coding_transcript_variant |
| rs184104770 | 1 | A C | 155690186 | -0.0083 | 0.0100 | MSTO1 | intron_variant;non_coding_transcript_variant |
| rs80237341 | 1 | C G | 157119915 | 0.0593 | 0.0127 | intron_variant;non_coding_transcript_variant;NMD_transcript_variant |
| rs6660538 | 1 | A C | 163295678 | 0.0168 | 0.3681 | NUF2 | intron_variant;non_coding_transcript_variant;NMD_transcript_variant |
| rs10803412 | 1 | C T | 163295678 | 0.0133 | 0.1711 | CLCNKB | intron_variant |
| rs4075646 | 1 | T A | 167135941 | 0.0405 | 0.0372 | intron_variant;non_coding_transcript_variant |
| rs507603 | 1 | A C | 179897070 | 0.0044 | 0.1580 | intron_variant |
| rs34295433 | 1 | CTAAG C | 183032447 | 0.0250 | 0.5325 | LAMC1 | intron_variant |
| rs138638958 | 1 | TTTTG T | 204030362 | 0.0173 | 0.5364 | 3_prime_UTR_variant;non_coding_transcript_exon_variant;intron_variant;3_prime_UTR_variant;non_coding_transcript_exon_variant;intron_variant |
| rs4245739 | 1 | A C | 204518842 | 0.0379 | 0.7297 | MDM4 | intron_variant |
| rsID          | Chrom | Allele 1 | Allele 2 | Position | Minor Allele Frequency | Major Allele Frequency | Gene(s)                        | Variant Type                      |
|--------------|-------|----------|----------|----------|------------------------|------------------------|-------------------------------|-----------------------------------|
| rs708723     | 1     | C        | T        | 205739266 | 0.0268                 | 0.4366                 | RAB7L1                        | 3_prime_UTR_variant;NMD_transcript_variant |
| rs544780844  | 1     | T        | C        | 46251655  | 0.0301                 | 0.1424                 |                               |                                   |
| rs7542260     | 1     | T        | C        | 5743196   | -0.0044                | 0.0533                 |                               |                                   |
| rs56391074    | 1     | AT       | A        | 88210715  | 0.0170                 | 0.3664                 |                               |                                   |
| rs11480453    | 20    | C        | CA       | 31347512  | 0.0280                 | 0.6164                 |                               |                                   |
| rs6141551     | 20    | C        | T        | 34006970  | 0.0111                 | 0.6137                 |                               |                                   |
| rs73909841    | 20    | T        | C        | 49548807  | 0.0352                 | 0.9278                 |                               |                                   |
| rs6126986     | 20    | C        | T        | 52464719  | 0.0388                 | 0.4825                 |                               |                                   |
| rs381331      | 20    | A        | G        | 62229989  | 0.0178                 | 0.6224                 |                               |                                   |
| chr20_6223363| 20    | G        | A        | 62233638  | -0.0118                | 0.4016                 | GMEB2                         | intron_variant                    |
| rs3787099     | 20    | A        | G        | 62307517  | 0.0800                 | 0.9156                 |                               |                                   |
| rs1058319     | 20    | C        | T        | 62374389  | 0.0392                 | 0.8611                 |                               |                                   |
| rs11701433    | 21    | C        | T        | 40296411  | 0.0187                 | 0.3265                 |                               |                                   |
| rs61735792    | 21    | A        | G        | 42866332  | 0.1249                 | 0.0139                 |                               |                                   |
| rs9978557     | 21    | C        | T        | 42882462  | 0.0600                 | 0.9001                 |                               |                                   |
| rs1978060     | 22    | G        | A        | 19749525  | 0.0290                 | 0.6086                 |                               |                                   |
| rs9625483     | 22    | A        | G        | 28888939  | 0.0625                 | 0.0247                 |                               |                                   |
| rs138708      | 22    | G        | A        | 39138332  | 0.0418                 | 0.9795                 |                               |                                   |
| rs34584683    | 22    | T        | A        | 40499107  | 0.0246                 | 0.2073                 |                               |                                   |
| rs6003062     | 22    | G        | A        | 43499741  | 0.0026                 | 0.9308                 |                               |                                   |
| rs5759167     | 22    | G        | T        | 43500212  | 0.0631                 | 0.5003                 |                               |                                   |
| chrX_66751555 | 22    | A        | G        | 66751555  | -0.0108                | 0.4232                 |                               |                                   |
| rs9615099     | 22    | T        | A        | 45698149  | 0.0191                 | 0.7483                 |                               |                                   |
| rs17321482    | 23    | C        | T        | 11482634  | 0.0249                 | 0.8710                 |                               |                                   |
| rs5972255     | 23    | T        | C        | 30896320  | 0.0085                 | 0.2403                 |                               |                                   |
| rs4907775     | 23    | G        | A        | 51263200  | 0.0484                 | 0.3575                 |                               |                                   |
| rs5943724     | 23    | G        | A        | 52695895  | 0.0081                 | 0.6578                 |                               |                                   |
| rs4826594     | 23    | A        | G        | 54454406  | -0.0046                | 0.0586                 |                               |                                   |
| chrX_66751555 | 23    | G        | A        | 66751555  | -0.0288                | 0.1555                 |                               |                                   |
| rs5919393     | 23    | T        | C        | 66825357  | 0.0141                 | 0.8457                 |                               |                                   |
| rs11795627    | 23    | T        | C        | 69957441  | -0.0138                | 0.4819                 |                               |                                   |
| rs371707439   | 23    | A        | G        | 70139908  | 0.0217                 | 0.1969                 |                               |                                   |
| rsID       | Chromosome | Base | Alteration | Position   | MAF | Allele Frequency | Gene   | Variant Type                                      |
|------------|------------|------|------------|------------|-----|------------------|--------|--------------------------------------------------|
| rs960417   | 23         | A    | G          | 9811095    | 0.0214 | 0.7182           | SHROOM2| intron_variant                                   |
| rs73913932 | 23         | G    | A          | 10094526   | 0.0591 | 0.0742           | GRHL1  | intron_variant;non_coding_transcript_variant    |
| rs1990613  | 23         | T    | C          | 10781975   | 0.0401 | 0.5153           | NOL10  | intron_variant                                   |
| rs2165108  | 23         | A    | T          | 111861993  | 0.0385 | 0.0420           |        | intron_variant;non_coding_transcript_variant;intron_variant |
| rs11691517 | 23         | T    | G          | 111893096  | 0.0336 | 0.7489           | BCL2L11| intron_variant;NMD_transcript_variant           |
| rs111595856| 23         | C    | G          | 121003598  | 0.0639 | 0.0676           |        | non_coding_transcript_variant                   |
| rs10206072 | 23         | A    | T          | 121173466  | 0.0457 | 0.9009           |        | non_coding_transcript_variant                   |
| rs7602028  | 23         | C    | A          | 16016503   | 0.0135 | 0.7221           |        | intron_variant;non_coding_transcript_variant;intron_variant |
| rs164594905| 23         | T    | C          | 169012955  | 0.0198 | 0.9921           | STK39  | intron_variant                                  |
| rs77167534 | 23         | C    | T          | 173319930  | 0.1191 | 0.9411           | ITGA6  | intron_variant                                  |
| rs34925593 | 23         | C    | T          | 174234547  | 0.0205 | 0.4899           |        | intron_variant;non_coding_transcript_variant;intron_variant |
| rs1861270  | 23         | G    | A          | 202126615  | 0.0202 | 0.7350           | CASP8  | non_coding_transcript_variant                   |
| rs12621900 | 23         | C    | T          | 208118301  | 0.0236 | 0.7631           |        | non_coding_transcript_variant                   |
| rs9306894  | 23         | G    | A          | 20878105   | 0.0148 | 0.3690           |        | intron_variant;non_coding_transcript_variant;intron_variant |
| rs74001374 | 23         | C    | T          | 238411293  | 0.1019 | 0.9926           | MLPH   | intron_variant                                  |
| rs2292884  | 23         | G    | A          | 238443226  | 0.0354 | 0.2415           | MLPH   | intron_variant;missense_variant;splice_region_variant;intron_variant |
| rs77559646 | 23         | A    | G          | 242135265  | 0.1676 | 0.0227           | ANO7   | non_coding_transcript_variant                   |
| rs77482050 | 23         | G    | A          | 242139600  | 0.2496 | 0.9892           | ANO7   | missense_variant;stop_gained                    |
| rs2074840  | 23         | C    | T          | 242141719  | 0.0210 | 0.3041           | ANO7   | splice_region_variant;synonymous_variant        |
| rs76832527 | 23         | A    | G          | 242157241  | 0.0458 | 0.1740           | ANO7   | missense_variant                                |
| rs6738169  | 23         | C    | G          | 43064555   | 0.0286 | 0.7073           |        | intron_variant                                  |
| rs7591218  | 23         | A    | G          | 43637998   | 0.0307 | 0.3130           | THADA  | intron_variant;NMD_transcript_variant           |
| rs28541770 | 23         | C    | G          | 43851282   | 0.0139 | 0.7124           |        | missense_variant                                |
| rs11125927 | 23         | G    | A          | 62752975   | 0.0327 | 0.1139           |        | intron_variant                                  |
| rs58235267 | 23         | G    | C          | 63277843   | 0.0203 | 0.4733           | OTX1   | intron_variant                                  |
| chr2_63301164| 23       | A    | G          | 63301164   | -0.0327| 0.4982           |        | non_coding_transcript_variant                   |
| rs139283528| 23         | G    | A          | 63938756   | 0.1070 | 0.9882           | WDPCP  | intron_variant                                  |
| SNP          | chrom | ref | alt | position | MAF 1 | MAF 2 | Gene        | Variant                        |
|--------------|-------|-----|-----|----------|-------|-------|-------------|--------------------------------|
| rs74702681   | 2     | T   | C   | 66652885 | 0.0564| 0.0225| MAT2A       | intron_variant;non_coding_transcript_variant |
| rs2028900    | 2     | C   | T   | 85767735 | 0.0384| 0.5539|            |                                |
| rs11686272   | 2     | T   | G   | 8598444  | 0.0180| 0.4473|            |                                |
| rs1283104    | 3     | G   | C   | 106962521| 0.0154| 0.3755| LINC00883  | intron_variant;non_coding_transcript_variant |
| rs151038334  | 3     | C   | T   | 107193337| 0.0431| 0.9157|            |                                |
| rs2271494    | 3     | A   | T   | 113300183| 0.0182| 0.6146|            |                                |
| rs78416326   | 3     | G   | C   | 127898501| 0.0384| 0.5539|            |                                |
| rs4857841    | 3     | A   | G   | 128046643| 0.0427| 0.2779| EEFSEC     | intron_variant;non_coding_transcript_variant |
| rs577952184  | 3     | C   | T   | 128213994| 0.0182| 0.6146|            |                                |
| rs6550597    | 3     | A   | G   | 141147414| 0.0135| 0.4413| ZBTB38     | intron_variant                  |
| rs2293607    | 3     | T   | C   | 169482335| 0.0284| 0.7525| TERC       | non_coding_transcript_exon_variant;non_coding_transcript_exon_variant |
| rs35006112   | 3     | G   | A   | 137562823| 0.0182| 0.6146|            |                                |
| rs1457063    | 3     | A   | G   | 137562823| 0.0182| 0.6146|            |                                |
| rs7650602    | 3     | C   | T   | 141147414| 0.0135| 0.4413|            |                                |
| rs6853490    | 4     | G   | A   | 95544718 | 0.0218| 0.4364| PDLIM5     | intron_variant;non_coding_transcript_variant;NMD_transcript_variant |
| chr4_95562877| 4     | T   | C   | 95562877 | -0.0317| 0.3507|            |                                |
| rs2242652    | 5     | G   | A   | 1280028 | 0.0198| 0.8007| TERT       |                                |
| rs    | pos | ref | alt | effect | odds_ratio | P_value | gene       | transcript variant |
|------|-----|-----|-----|--------|------------|----------|------------|-------------------|
| rs7725218 | 5   | A   | G   | -0.0393 | 0.3501     | TERT     | intron_variant | non_coding_transcript_variant;intron_variant;NMD_transcript_variant;intron_variant |
| rs71595003 | 5   | A   | G   | 0.0815  | 0.0285     | TERT     | intron_variant;NMD_transcript_variant;intron_variant |
| rs2736098  | 5   | T   | C   | 0.0348  | 0.2626     | TERT     | intron_variant;NMD_transcript_variant;intron_variant |
| rs2736108  | 5   | T   | C   | 0.0173  | 0.2944     | TERT     | intron_variant;NMD_transcript_variant;intron_variant |
| rs10793821 | 5   | T   | C   | 0.0195  | 0.5760     | TERT     | intron_variant;NMD_transcript_variant;intron_variant |
| rs71599622 | 5   | T   | G   | 0.0136  | 0.2826     | TRIO     | intron_variant;NMD_transcript_variant;non_coding_transcript_variant |
| rs76551843 | 5   | A   | G   | 0.1520  | 0.9913     | DOCK2    | intron_variant;NMD_transcript_variant;non_coding_transcript_variant |
| rs9686557  | 5   | C   | A   | 0.0216  | 0.4429     | COL2A3   | missense_variant |
| rs61739424 | 5   | G   | A   | 0.0495  | 0.9624     | COL2A3   | intron_variant |
| rs2672843  | 5   | G   | A   | 0.0207  | 0.4090     | COL2A3   | intron_variant |
| rs4975758  | 5   | G   | C   | 0.0254  | 0.4757     | GDNF     | intron_variant |
| rs10941370 | 5   | T   | C   | 0.0811  | 0.4452     | GDNF     | intron_variant |
| rs1482675  | 5   | T   | C   | 0.0054  | 0.3113     | FGF10    | intron_variant |
| rs9292122  | 5   | A   | G   | 0.0181  | 0.7106     | RGS17    | intron_variant |
| rs2038542  | 6   | C   | T   | 0.0352  | 0.1455     | RGS17    | intron_variant;non_coding_transcript_variant |
| rs2018336  | 6   | T   | C   | 0.0415  | 0.7696     | RGS17    | intron_variant;non_coding_transcript_variant;intron_variant;NMD_transcript_variant |
| rs339351   | 6   | C   | A   | 0.0409  | 0.6990     | RFX6     | intron_variant |
| rs3910736  | 6   | T   | C   | -0.0212 | 0.3242     | RGS17    | intron_variant |
| rs13215045 | 6   | C   | T   | 0.0202  | 0.6868     | RGS17    | intron_variant;non_coding_transcript_variant |
| rs963800   | 6   | C   | T   | 0.0285  | 0.7868     | SOD2     | intron_variant;non_coding_transcript_variant |
| rs4646284  | 6   | TG  | T   | 0.0942  | 0.2974     | SOD2     | intron_variant;non_coding_transcript_variant |
| rs7769879  | 6   | C   | G   | 0.0325  | 0.3645     | SLC2A3   | intron_variant |
| rs2814811  | 6   | A   | G   | 0.0187  | 0.4043     | GMDS     | intron_variant;non_coding_transcript_variant |
| rs6927369  | 6   | C   | T   | 0.0333  | 0.8084     | GMDS     | intron_variant |
| rs4269363  | 6   | G   | A   | 0.0167  | 0.5721     | GMDS     | intron_variant |
| rs12665509 | 6   | A   | C   | 0.0150  | 0.4603     | CASC15   | intron_variant;non_coding_transcript_variant |
| rs62407547 | 6   | C   | T   | 0.0212  | 0.2467     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs9275160  | 6   | A   | G   | 0.0371  | 0.3525     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs9469899  | 6   | A   | G   | 0.0333  | 0.3648     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs4714485  | 6   | G   | T   | 0.0384  | 0.2754     | FOXP4    | intron_variant |
| rs9472120  | 6   | C   | T   | 0.0173  | 0.4902     | FOXP4    | intron_variant |
| rs3910736  | 6   | T   | C   | 0.0212  | 0.3242     | FGF10    | intron_variant |
| rs13215045 | 6   | C   | T   | 0.0202  | 0.6868     | RGS17    | intron_variant |
| rs963800   | 6   | C   | T   | 0.0285  | 0.7868     | SOD2     | intron_variant |
| rs4646284  | 6   | TG  | T   | 0.0942  | 0.2974     | SOD2     | intron_variant |
| rs7769879  | 6   | C   | G   | 0.0325  | 0.3645     | SLC2A3   | intron_variant |
| rs2814811  | 6   | A   | G   | 0.0187  | 0.4043     | GMDS     | intron_variant;non_coding_transcript_variant |
| rs6927369  | 6   | C   | T   | 0.0333  | 0.8084     | GMDS     | intron_variant |
| rs4269363  | 6   | G   | A   | 0.0167  | 0.5721     | GMDS     | intron_variant |
| rs12665509 | 6   | A   | C   | 0.0150  | 0.4603     | CASC15   | intron_variant;non_coding_transcript_variant |
| rs62407547 | 6   | C   | T   | 0.0212  | 0.2467     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs9275160  | 6   | A   | G   | 0.0371  | 0.3525     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs9469899  | 6   | A   | G   | 0.0333  | 0.3648     | HCG17    | intron_variant;non_coding_transcript_variant |
| rs4714485  | 6   | G   | T   | 0.0384  | 0.2754     | FOXP4    | intron_variant |
| rs9472120  | 6   | C   | T   | 0.0173  | 0.4902     | FOXP4    | intron_variant |
| SNP          | Chromosome | Position | MAF | Effect Allele | Gene | Variant Type                  |
|--------------|------------|----------|-----|--------------|------|------------------------------|
| rs9443189    | 6          | 76495882 | 0.0116 | G            | MYO6 | intron_variant               |
| rs4513875    | 7          | 1928159  | 0.0240 | T            | MAD1L1| intron_variant               |
| rs11452686   | 7          | 20414110 | 0.0005 | C            | ITGB8| intron_variant;non_coding_transcript_variant |
| rs9655205    | 7          | 20999211 | 0.0448 | C            | LINC01162| intron_variant;non_coding_transcript_variant |
| rs35389879   | 7          | 21812043 | 0.0238 | G            | DNAH11| intron_variant               |
| rs6956484    | 7          | 27564862 | 0.0335 | C            | MYO6 | intron_variant;NMD_transcript_variant |
| rs10486567   | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs4513875    | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs11452686   | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs9655205    | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs35389879   | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs6956484    | 7          | 2797653 | 0.0240 | C            | JAZF1| intron_variant;non_coding_transcript_variant |
| rs          | pos | ref | alt | freq | odds | p-value | Gene       | Annotation                                                                 |
|------------|-----|-----|-----|------|------|---------|------------|--------------------------------------------------------------------------------|
| rs11467    | 8   | A   | G   | 0.0178 | 0.6294 | TACC1    | intron_variant;non_coding_transcript_variant;5_prime_UTR_variant |
| rs870167   | 8   | G   | A   | 0.0256 | 0.0648 |          |            |                                                                         |
| rs4451364  | 9   | A   | G   | 0.0281 | 0.7642 |          |            |                                                                         |
| rs817872   | 9   | C   | T   | 0.0298 | 0.2772 |          |            |                                                                         |
| rs143655302| 9   | G   | A   | 0.1524 | 0.9855 |          |            |                                                                         |
| rs2241167  | 9   | A   | G   | 0.0244 | 0.5134 | STXBP1   | intron_variant |                                                                       |
| rs12634    | 9   | T   | G   | 0.0342 | 0.2361 | TOR1B    | 3_prime_UTR_variant |                                                                   |
| rs34540271 | 9   | C   | T   | 0.0132 | 0.6956 | ADAMTS1  | intron_variant |                                                                       |
| rs10122990 | 9   | C   | A   | 0.0190 | 0.3753 | HAUS6    | intron_variant |                                                                       |
| rs17694493 | 9   | G   | C   | 0.0260 | 0.1366 | CDKN2B-AS1| non_coding_transcript_variant;intron_variant |                                                                 |
| rs10122495 | 9   | T   | A   | 0.0032 | 0.2858 |          |            |                                                                         |
| rs139135938| 20  | TGGCA| GTGG| CAGC | 0.0250 | 0.6818 | RBBP8NL  | intron_variant |                                                                       |
| rs555607708| 22  | A   | AG  | 0.1694 | 0.0024 | CHEK2    | frameshift_variant;intron_variant;3_prime_UTR_variant;NMD_transcript_variant |                                                                 |
| rs145053401| 3   | C   | CAT | 0.0435 | 0.8924 | MBNL1    | non_coding_transcript_variant;intron_variant |                                                                 |
| rs150184171| 6   | G   | GT  | 0.0231 | 0.5643 | TBPL1    | intron_variant |                                                                       |
| rs57588856 | 8   | C   | CA  | 0.0221 | 0.6435 |          |            |                                                                         |
| rs142727307| 9   | T   | TG  | 0.0178 | 0.1115 |          |            |                                                                         |
| rs11338635 | 23  | GA  | G   | 0.0032 | 0.3563 |          | intron_variant;non_coding_transcript_variant |                                                                 |
| rs141811748| 8   | C   | AAA | 0.0487 | 0.1442 |          |            |                                                                         |
Harrell’s concordance index

Conventional area under the curve (AUC) and optimal operating points are appropriate for analyses of binary discrimination. The present study used a survival analysis approach to evaluate association with age at diagnosis of clinically significant prostate cancer. Moreover, the survival analysis includes censoring, which conventional AUC cannot account for.

One proposed metric for survival analyses is the Harrell’s concordance index\(^1\). Briefly, individuals in the dataset are compared in pairs, and the concordance is the percentage of pairs for which the earlier time to event (in this study, age at diagnosis of clinically significant prostate cancer) occurs in the individual with higher score (in this study, PHS46 or PHS290). Where censoring in one or both individuals in a given pair interferes with assessing concordance, that pair is excluded from the index. There are limitations to the interpretation of the Harrell’s concordance index\(^2,3\), and it may not be ideal for situations like polygenic risk, where the extremes of genetic risk are of more clinical interest than the scores of individuals within, say, the 30\(^{\text{th}}\)-70\(^{\text{th}}\) percentiles.

Nevertheless, we calculated the Harrell’s concordance index for PHS46 and PHS290 in each testing dataset to evaluate whether PHS290 represented an improvement in concordance index for the endpoint of age at diagnosis of clinically significant prostate cancer. As before, 1,000 bootstrap samples were generated to yield 95% confidence intervals.

The concordance index improved in each testing dataset. In the ProtecT dataset, concordance index was 0.63 [95% CI: 0.60-0.65] for PHS46 and 0.67 [0.64-0.69] for PHS290. Corresponding concordance index results for the other datasets were as follows. African dataset: 0.62 [0.58-0.65] for PHS46 and 0.69 [0.63-0.74] for PHS290. Asian dataset: 0.62 [0.58-0.65] for PHS46 and 0.66 [0.63-0.69] for PHS290. COSM dataset: 0.58 [0.57-0.60] for PHS46 and 0.63 [0.62-0.65] for PHS290.

References for Supplemental Information

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