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## Evaluating Approaches for Constructing Polygenic Risk Scores for Prostate Cancer in Men of African and European Ancestry

Burcu F. Darst<sup>1,2\*</sup>, Jiayi Shen<sup>1\*</sup>, Ravi K. Madduri<sup>3</sup>, Alexis A. Rodriguez<sup>3</sup>, Yukai Xiao<sup>3</sup>, Xin Sheng<sup>1</sup>, Edward J. Saunders<sup>4</sup>, Tokhir Dadaev<sup>4</sup>, Mark N. Brook<sup>4</sup>, Thomas J. Hoffmann<sup>5</sup>, Kenneth Muir<sup>6</sup>, Peggy Wan<sup>1</sup>, Loic Le Marchand<sup>7</sup>, Lynne Wilkens<sup>7</sup>, Ying Wang<sup>8</sup>, Johanna Schleutker<sup>9</sup>, Robert J. MacInnis<sup>10,11</sup>, Cezary Cybulski<sup>12</sup>, David E. Neal<sup>13,14,15</sup>, Børge G. Nordestgaard<sup>16,17</sup>, Sune F. Nielsen<sup>16,17</sup>, Jyotsna Batra<sup>18,19</sup>, Judith A. Clements<sup>18,19</sup>, Australian Prostate Cancer BioResource<sup>19,20</sup>, Henrik Grönberg<sup>21</sup>, Nora Pashayan<sup>22,23</sup>, Ruth C. Travis<sup>24</sup>, Jong Y. Park<sup>25</sup>, Demetrius Albanes<sup>26</sup>, Stephanie Weinstein<sup>26</sup>, Lorelei A. Mucci<sup>27</sup>, David J. Hunter<sup>28</sup>, Kathryn L. Penney<sup>29</sup>, Catherine M. Tangen<sup>30</sup>, Robert J. Hamilton<sup>31,32</sup>, Marie-Élise Parent<sup>33,34</sup>, Janet L. Stanford<sup>2,35</sup>, Stella Koutros<sup>26</sup>, Alicja Wolk<sup>36,37</sup>, Karina D. Sørensen<sup>38,39</sup>, William J. Blot<sup>40,41</sup>, Edward D. Yeboah<sup>42,43</sup>, James E. Mensah<sup>42,43</sup>, Yong-Jie Lu<sup>44</sup>, Daniel J. Schaid<sup>45</sup>, Stephen N. Thibodeau<sup>46</sup>, Catharine M. West<sup>47</sup>, Christiane Maier<sup>48</sup>, Adam S. Kibel<sup>49</sup>, Géraldine Cancel-Tassin<sup>50,51</sup>, Florence Menegaux<sup>52</sup>, Esther M. John<sup>53,54,55</sup>, Eli Marie Grindedal<sup>56</sup>, Kay-Tee Khaw<sup>57</sup>, Sue A. Ingles<sup>58</sup>, Ana Vega<sup>59,60,61</sup>, Barry S. Rosenstein<sup>62,63</sup>, Manuel R. Teixeira<sup>64,65</sup>, NC-LA PCaP Investigators<sup>66,67,68</sup>, Manolis Kogevinas<sup>69,70,71,72</sup>, Lisa Cannon-Albright<sup>73,74</sup>, Chad Huff<sup>75</sup>, Luc Multigner<sup>76</sup>, Radka Kaneva<sup>77</sup>, Robin J. Leach<sup>78</sup>, Hermann Brenner<sup>79,80,81</sup>, Ann W. Hsing<sup>82</sup>, Rick A. Kittles<sup>83</sup>, Adam B. Murphy<sup>84</sup>, Christopher J. Logothetis<sup>85</sup>, Susan L. Neuhausen<sup>86</sup>, William B. Isaacs<sup>87</sup>, Barbara Nemesure<sup>88</sup>, Anselm J. Hennis<sup>88,89</sup>, John Carpten<sup>90</sup>, Hardev Pandha<sup>91</sup>, Kim De Ruyck<sup>92</sup>, Jianfeng Xu<sup>93</sup>, Azad Razack<sup>94</sup>, Soo-Hwang Teo<sup>95</sup>, Canary PASS Investigators<sup>2,96</sup>, Lisa

F. Newcomb<sup>2,96</sup>, Jay H. Fowke<sup>97</sup>, Christine Neslund-Dudas<sup>98</sup>, Benjamin A. Rybicki<sup>98</sup>, Marija Gamulin<sup>99</sup>, Nawaid Usmani<sup>100,101</sup>, Frank Claessens<sup>102</sup>, Manuela Gago-Dominguez<sup>103,104</sup>, Jose Esteban Castela<sup>105</sup>, Paul A. Townsend<sup>106,107</sup>, Dana C. Crawford<sup>108</sup>, Gyorgy Petrovics<sup>109</sup>, Graham Casey<sup>110</sup>, Monique J. Roobol<sup>111</sup>, Jennifer F. Hu<sup>112</sup>, Sonja I. Berndt<sup>26</sup>, Stephen K. Van Den Eeden<sup>113,114</sup>, Douglas F. Easton<sup>23</sup>, Stephen J. Chanock<sup>26</sup>, Michael B. Cook<sup>26</sup>, Fredrik Wiklund<sup>21</sup>, John S. Witte<sup>115</sup>, Rosalind A. Eeles<sup>116,117</sup>, Zsafia Kote-Jarai<sup>116</sup>, Stephen Watya<sup>118</sup>, John M. Gaziano<sup>119,120,121</sup>, Amy C. Justice<sup>122,123</sup>, David V. Conti<sup>1</sup>, Christopher A. Haiman<sup>1</sup>

<sup>1</sup>Center for Genetic Epidemiology, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

<sup>2</sup>Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA, USA

<sup>3</sup>Argonne National Laboratory, Lemont, IL, USA

<sup>4</sup>The Institute of Cancer Research, London, UK

<sup>5</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA

<sup>6</sup>Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

<sup>7</sup>Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA

<sup>8</sup>Department of Population Science, American Cancer Society, Atlanta, GA, USA

<sup>9</sup>Institute of Biomedicine, University of Turku, Finland

<sup>10</sup>Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia

<sup>11</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia

<sup>12</sup>International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

<sup>13</sup>Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Headington, Oxford, UK

<sup>14</sup>University of Cambridge, Department of Oncology, Addenbrooke's Hospital, Cambridge, UK

<sup>15</sup>Cancer Research UK, Cambridge Research Institute, Li Ka Shing Centre, Cambridge UK

<sup>16</sup>Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

<sup>17</sup>Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Copenhagen, Denmark

<sup>18</sup>Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and School of Biomedical Sciences, Queensland University of Technology, Brisbane, Australia

<sup>19</sup>Translational Research Institute, Brisbane, Queensland, Australia

<sup>20</sup>Australian Prostate Cancer Research Centre-Qld, Queensland University of Technology, Brisbane; Prostate Cancer Research Program, Monash University, Melbourne; Dame Roma Mitchell Cancer Centre, University of Adelaide, Adelaide; Chris O'Brien Lifehouse and The Kinghorn Cancer Centre, Sydney, Australia

<sup>21</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institute,

Stockholm, Sweden

<sup>22</sup>University College London, Department of Applied Health Research, London, UK

<sup>23</sup>Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK

<sup>24</sup>Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

<sup>25</sup>Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, USA

<sup>26</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, USA

<sup>27</sup>Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

<sup>28</sup>Nuffield Department of Population Health, University of Oxford, Oxford, UK

<sup>29</sup>Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

<sup>30</sup>SWOG Statistical Center, Fred Hutchinson Cancer Center, Seattle, WA, USA

<sup>31</sup>Dept. of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, Canada

<sup>32</sup>Dept. of Surgery (Urology), University of Toronto, Canada

<sup>33</sup>Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, Laval, QC, Canada

<sup>34</sup>Department of Social and Preventive Medicine, School of Public Health, University of Montreal, Montreal, QC, Canada

<sup>35</sup>Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, USA

<sup>36</sup>Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

<sup>37</sup>Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

<sup>38</sup>Department of Molecular Medicine, Aarhus University Hospital, Aarhus N, Denmark

<sup>39</sup>Department of Clinical Medicine, Aarhus University, Aarhus N, Denmark

<sup>40</sup>Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.

<sup>41</sup>International Epidemiology Institute, Rockville, MD, USA

<sup>42</sup>University of Ghana Medical School, Accra, Ghana

<sup>43</sup>Korle Bu Teaching Hospital, Accra, Ghana

<sup>44</sup>Centre for Biomarkers and Biotherapeutics, Barts Cancer Institute, Queen Mary University of London, John Vane Science Centre, London, UK

<sup>45</sup>Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA

<sup>46</sup>Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

<sup>47</sup>Division of Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, Radiotherapy Related Research, The Christie Hospital NHS Foundation Trust, Manchester, UK

<sup>48</sup>Humangenetik Tuebingen, Tuebingen, Germany

<sup>49</sup>Division of Urologic Surgery, Brigham and Womens Hospital, Boston, MA, USA

<sup>50</sup>CeRePP, Tenon Hospital, Paris, France

<sup>51</sup>Sorbonne Universite, GRC 5 Predictive Onco-urology, Tenon Hospital, Paris, France

<sup>52</sup>"Exposome and Heredity", CESP (UMR 1018), Faculté de Médecine, Université Paris-Saclay, Inserm, Gustave Roussy, Villejuif, France

<sup>53</sup>Department of Epidemiology & Population Health, Stanford University School of Medicine, Stanford, CA, USA

<sup>54</sup>Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA, USA

<sup>55</sup>Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA

<sup>56</sup>Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

<sup>57</sup>Clinical Gerontology Unit, University of Cambridge, Cambridge, UK

<sup>58</sup>Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

<sup>59</sup>Fundación Pública Galega Medicina Xenómica, Santiago De Compostela, Spain

<sup>60</sup>Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago De Compostela, Spain

<sup>61</sup>Centro de Investigación en Red de Enfermedades Raras (CIBERER), Spain

<sup>62</sup>Department of Radiation Oncology and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>63</sup>Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>64</sup>Department of Genetics, Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal

<sup>65</sup>Biomedical Sciences Institute (ICBAS), University of Porto, Porto, Portugal

<sup>66</sup>Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

<sup>67</sup>Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill,

NC, USA

<sup>68</sup>Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

<sup>69</sup>ISGlobal, Barcelona, Spain

<sup>70</sup>IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

<sup>71</sup>Universitat Pompeu Fabra (UPF), Barcelona, Spain

<sup>72</sup>CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

<sup>73</sup>Division of Epidemiology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA

<sup>74</sup>George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, Utah, USA

<sup>75</sup>Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

<sup>76</sup>Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), Rennes, France

<sup>77</sup>Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University of Sofia, Sofia, Bulgaria

<sup>78</sup>Department of Urology, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio Texas, USA

<sup>79</sup>Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>80</sup>German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany



<sup>81</sup>Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

<sup>82</sup>Department of Medicine and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA

<sup>83</sup>Division of Health Equities, Department of Population Sciences, City of Hope, Duarte, CA, USA

<sup>84</sup>Department of Urology, Northwestern University, Chicago, IL, USA

<sup>85</sup>The University of Texas M. D. Anderson Cancer Center, Department of Genitourinary Medical Oncology, Houston, TX, USA

<sup>86</sup>Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte, CA, USA

<sup>87</sup>James Buchanan Brady Urological Institute, Johns Hopkins Hospital and Medical Institution, Baltimore, MD, USA

<sup>88</sup>Department of Family, Population and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA

<sup>89</sup>Chronic Disease Research Centre and Faculty of Medical Sciences, University of the West Indies, Bridgetown, Barbados

<sup>90</sup>Department of Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

<sup>91</sup>Faculty of Health and Medical Sciences, The University of Surrey, Guildford, Surrey, UK

<sup>92</sup>Ghent University, Faculty of Medicine and Health Sciences, Basic Medical Sciences, Gent, Belgium

<sup>93</sup>Program for Personalized Cancer Care and Department of Surgery, NorthShore University HealthSystem, Evanston, IL, USA

<sup>94</sup>Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

<sup>95</sup>Cancer Research Malaysia (CRM), Outpatient Centre, Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia

<sup>96</sup>Department of Urology, University of Washington, Seattle, WA, USA

<sup>97</sup>Division of Epidemiology, Department of Preventive Medicine, The University of Tennessee Health Science Center, TN, USA

<sup>98</sup>Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA

<sup>99</sup>Department of Oncology, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia

<sup>100</sup>Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada

<sup>101</sup>Division of Radiation Oncology, Cross Cancer Institute, Edmonton, Alberta, Canada

<sup>102</sup>Molecular Endocrinology Laboratory, Department of Cellular and Molecular Medicine, Leuven, Belgium

<sup>103</sup>Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, Servicio Galego de Saúde, SERGAS, Santiago de Compostela, Spain

<sup>104</sup>University of California San Diego, Moores Cancer Center, La Jolla, CA, USA

<sup>105</sup>Genetic Oncology Unit, CHUVI Hospital, Complexo Hospitalario Universitario de

Vigo, Instituto de Investigación Biomédica Galicia Sur (IISGS), Vigo (Pontevedra),  
Spain

<sup>106</sup>Division of Cancer Sciences, Manchester Cancer Research Centre, Faculty of  
Biology, Medicine and Health, Manchester Academic Health Science Centre, NIHR  
Manchester Biomedical Research Centre, Health Innovation Manchester, University of  
Manchester, UK

<sup>107</sup>The University of Surrey, Guildford, Surrey, UK

<sup>108</sup>Case Western Reserve University, Department of Population and Quantitative Health  
Sciences, Cleveland Institute for Computational Biology, Cleveland, OH, USA

<sup>109</sup>Center for Prostate Disease Research, Uniformed Services University, Bethesda,  
MD, USA

<sup>110</sup>Center for Public Health Genomics, Department of Public Health Sciences, University  
of Virginia, Charlottesville, VA, USA

<sup>111</sup>109 Department of Urology, Erasmus University Medical Center, Cancer Institute,  
Rotterdam, The Netherlands

<sup>112</sup>The University of Miami School of Medicine, Sylvester Comprehensive Cancer  
Center, Miami, FL, USA

<sup>113</sup>Division of Research, Kaiser Permanente, Northern California, Oakland, CA, USA

<sup>114</sup>Department of Urology, University of California San Francisco, San Francisco, CA,  
USA

<sup>115</sup>Department of Epidemiology and Population Health, Department of Biomedical Data  
Science, Stanford Cancer Institute, Stanford, CA, USA

<sup>116</sup>The Institute of Cancer Research, Sutton, London, UK

<sup>117</sup>Royal Marsden NHS Foundation Trust, London, UK

<sup>118</sup>School of Public Health, Makerere University College of Health Sciences, Kampala  
Uganda

<sup>119</sup>VA Boston Healthcare System, Boston, MA, USA

<sup>120</sup>Department of Medicine, Harvard Medical School, Boston, MA, USA

<sup>121</sup>Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

<sup>122</sup>VA Connecticut Healthcare System, West Haven, CT, USA

<sup>123</sup>Yale School of Medicine, New Haven, CT, USA

¥ Co-first authorship

\*Corresponding Author

Burcu F. Darst

1100 Fairview Ave N

Seattle, WA 98109

1-206-667-1036

[bdarst@fredhutch.org](mailto:bdarst@fredhutch.org)

## Abstract

Genome-wide polygenic risk scores (GW-PRS) have been reported to have better predictive ability than PRS based on genome-wide significance thresholds across numerous traits. We compared the predictive ability of several GW-PRS approaches to a recently developed PRS of 269 established prostate cancer risk variants from multi-ancestry GWAS and fine-mapping studies (PRS<sub>269</sub>). GW-PRS models were trained using a large and diverse prostate cancer GWAS of 107,247 cases and 127,006 controls used to develop the multi-ancestry PRS<sub>269</sub>. Resulting models were independently tested in 1,586 cases and 1,047 controls of African ancestry from the California/Uganda Study and 8,046 cases and 191,825 controls of European ancestry from the UK Biobank and further validated in 13,643 cases and 210,214 controls of European ancestry and 6,353 cases and 53,362 controls of African ancestry from the Million Veteran Program. In the testing data, the best performing GW-PRS approach had AUCs of 0.656 (95% CI=0.635-0.677) in African and 0.844 (95% CI=0.840-0.848) in European ancestry men and corresponding prostate cancer OR of 1.83 (95% CI=1.67-2.00) and 2.19 (95% CI=2.14-2.25), respectively, for each SD unit increase in the GW-PRS. However, compared to the GW-PRS, in African and European ancestry men, the PRS<sub>269</sub> had larger or similar AUCs (AUC=0.679, 95% CI=0.659-0.700 and AUC=0.845, 95% CI=0.841-0.849, respectively) and comparable prostate cancer OR (OR=2.05, 95% CI=1.87-2.26 and OR=2.21, 95% CI=2.16-2.26, respectively). Findings were similar in the validation data. This investigation suggests that current GW-PRS approaches may not improve the ability to predict prostate cancer risk compared to the multi-ancestry PRS<sub>269</sub> constructed with fine-mapping.

## Main Text

Prostate cancer is the second leading cause of cancer deaths among men in the US, with incidence rates being highest in men of African ancestry<sup>1,2</sup>. Earlier identification of men with increased risk of prostate cancer across diverse populations has the potential to reduce the stark health disparities of this disease. We recently performed a large and diverse genome-wide association (GWAS) of prostate cancer in men from African, European, East Asian, and Hispanic populations<sup>3</sup>. By performing ancestry-specific and multi-ancestry GWAS and fine-mapping analyses, this investigation revealed 269 GWAS-defined prostate cancer risk variants used to develop a multi-ancestry polygenic risk score (PRS<sub>269</sub>). The PRS<sub>269</sub> was highly predictive of prostate cancer risk across populations<sup>3</sup> and has since been validated in additional independent multi-ancestry studies<sup>4</sup>. However, genome-wide PRS (GW-PRS) approaches, which include variants across the genome that do not reach genome-wide statistical significance thresholds, have been reported to have better predictive performance than standard pruning and thresholding PRS of known variants across numerous complex traits, including schizophrenia, coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, breast cancer, and colorectal cancer<sup>5-9</sup>.

In this investigation, we compared the predictive ability of GW-PRS for prostate cancer to the multi-ancestry PRS<sub>269</sub> of established prostate cancer risk variants. GW-PRS models were trained using summary statistics from the studies used to construct the multi-ancestry PRS<sub>269</sub>, which included 107,247 cases and 127,006 controls from European (85,554 cases and 91,972 controls), African (10,368 cases and 10,986 controls), East Asian (8,611 cases and 18,809 controls), and Hispanic (2,714 cases and

5,239 controls) populations<sup>3</sup>. Three recent GW-PRS approaches were evaluated: LDpred2<sup>10</sup>, PRS-CSx<sup>11</sup>, and EB-PRS<sup>12</sup>, using the 1.1 million HapMap3 panel variants<sup>13</sup> recommended by these approaches, which included 44 of the 269 variants, with all other autosomal prostate cancer risk variants being within 800 kb and correlated with a median  $r=0.99$  (ranging from 0.31-1.00 in any given population) of at least one of the 1.1 million HapMap3 variants (**Supplemental Methods** and **Tables S1-S2**). For comparison, each model was trained using previously estimated multi-ancestry weights and population-specific weights from the GWAS summary statistics<sup>3</sup>. GW-PRS models were tested in African ancestry men from the California/Uganda Study (CA/UG Study; 1,586 cases and 1,047 controls) and European ancestry men from the UK Biobank (8,046 cases and 191,825 controls; **Supplemental Methods**). Additional validation was performed in 6,353 cases and 53,362 controls of African ancestry and 13,643 cases and 210,214 controls of European ancestry from the Million Veteran Program<sup>14</sup> (MVP; **Supplemental Methods**).

In the CA/UG and UK Biobank testing datasets, the best performing GW-PRS approach was PRS-CSx with multi-ancestry weights, with an area under the curve (AUC) of 0.656 (95% CI=0.635-0.677) in African and 0.844 (95% CI=0.840-0.848) in European ancestry men (**Supplemental Methods, Figure 1, and Table S3**). Each SD unit increase in PRS was associated with 1.83-fold higher odds of prostate cancer (95% CI=1.67-2.00) in men of African ancestry and 2.19-fold higher odds of prostate cancer (95% CI=2.14-2.25) in men of European ancestry (**Supplemental Methods, Figure 1, and Table S4**). However, compared to PRS-CSx, the PRS<sub>269</sub> had higher or nearly identical AUCs in both African (0.679, 95% CI=0.659-0.700) and European (0.845, 95%

CI=0.841-0.849) ancestry men, and the PRS<sub>269</sub> was associated with 2.05-fold higher odds (95% CI=1.87-2.26) and 2.21-fold higher odds (95% CI=2.16-2.26) of prostate cancer in African and European ancestry men, respectively (**Figure 1, Table S3, and Table S4**). Findings were consistent when investigating extreme PRS distributions, with similar prostate cancer OR observed for the PRS<sub>269</sub> and the best performing GW-PRS (PRS-CSx) when comparing African and European ancestry men in the highest PRS decile (90-100%) to those in the average 40-60% PRS category (**Supplemental Methods, Figure S1, and Table S5**).

Similarly, in the validation MVP study, the best performing GW-PRS approach was PRS-CSx with multi-ancestry weights; however, the PRS<sub>269</sub> performed either better or similarly with regards to AUC (AUC=0.656 [95% CI=0.649-0.663] versus AUC=0.624 [95% CI=0.617-0.632] in African ancestry men; AUC=0.694 [95% CI=0.690-0.699] versus AUC=0.692 [95% CI=0.687-0.696] in European ancestry men; **Figure 2 and Table S3**). Likewise, the PRS<sub>269</sub> was associated with prostate cancer OR that were comparable or larger than OR estimated with PRS-CSx (OR=1.77, 95% CI=1.72-1.82 versus OR=1.59, 95% CI=1.54-1.63 in African ancestry men; OR=1.99, 95% CI=1.95-2.02 versus OR=1.97, 95% CI=1.93-2.01 in European ancestry men; **Figure 2 and Table S4**). OR calculated for African and European men in the top PRS decile were also comparable across the PRS<sub>269</sub> and PRS-CSx (**Figure S2 and Table S5**). In the testing and validation datasets, model performance was similar for both PRS<sub>269</sub> and GW-PRS approaches when using either multi-ancestry or population-specific weights (**Figures 1-2, Figures S1-S2, and Tables S3-S5**).



Findings from this investigation suggest that current GW-PRS approaches do not outperform the multi-ancestry PRS<sub>269</sub> for overall prostate cancer risk prediction. For several other disease examples, GW-PRS have been shown to perform better than PRS of known variants<sup>5-9</sup>; however, these PRS are typically constructed from a pruning and thresholding approach within European ancestry individuals rather than a fine-mapping approach across diverse populations. As such, the performance observed for our prostate cancer PRS<sub>269</sub> may be due to identifying GWAS risk variants from a multi-ancestry GWAS and fine-mapping study, along with the use of the same multi-ancestry GWAS to construct the GW-PRS<sup>3</sup>. It is also possible that the unique genetic architecture of prostate cancer contributes to the high performance of the PRS<sub>269</sub> across populations, as prostate cancer is one of the most heritable cancers<sup>15,16</sup> and has been estimated to display a greater distribution of variants with larger effect sizes than other cancers with similar GWAS sample sizes<sup>9</sup>.

We have previously shown that GW-PRS including variants with weaker statistical evidence of association in both European and African ancestry men (based on lenient P-value thresholds down to  $1.0 \times 10^{-5}$ ) resulted in lower PRS performance<sup>3</sup>. Likewise, it was recently reported that a GW-PRS constructed from 1 million variants most strongly associated with prostate cancer risk led to comparable results as a GW-PRS based on HapMap3 variants<sup>17</sup>, further suggesting that GW-PRS approaches may not be improved by selecting a large number of variants weakly associated with prostate cancer risk. Last, a European-ancestry derived PRS of 110 established literature-curated prostate cancer risk variants was previously found to perform better than a GW-PRS in addition to a standard pruning and thresholding PRS<sup>18</sup>. These findings in

conjunction with the present study suggest that the current multi-ancestry and fine-mapped PRS<sub>269</sub> is optimal, which has important clinical implications. While genotyping a few hundred versus millions of variants to construct PRS is currently logistically easier and more cost-effective, genome-wide genotyping may be optimal in the future to enable the evaluation of PRS across many traits. However, our findings do not imply that the multi-ancestry PRS<sub>269</sub> has reached optimal performance; increasing the sample size of non-European ancestry men in the discovery GWAS, particularly African ancestry men, where we and others have observed that the PRS has lower performance than in other populations<sup>3,4</sup>, will be important to improve genetic risk prediction of prostate cancer. The multi-ancestry PRS<sub>269</sub> is an effective risk stratification tool for prostate cancer, and its clinical utility in screening and early detection warrants investigation.

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## Author Contributions

Study conception/design: BFD, DVC, CAH; Provided data: RKM, XS, EJS, TD, MNB, TJH, KM, PW, LLM, LW, YW, LS, RJM, CC, DEN, BGN, SFN, JB, JAC, APCB, HG, NP, RCT, JYP, DA, SW, LAM, DJH, KLP, CMT, RJH, MP, JLS, SK, AW, KDS, WJB, EDY, JEM, YL, SNT, CMW, CM, ASK, GC, FM, EMJ, EMG, KK, SAI, AV, BSB, MRT, NCPI, MK, LC, CH, LM, RK, RJL, HB, AWH, RAK, ABM, CJL, SLN, WBI, BN, AJH, JC, HP, KDR, JX, AR, ST, CPI, LFN, JF, CN, BAR, MG, NU, FC, MG, JEC, PAT, DCC, GP, GC, MFR, JFH, SIB, SKVDE, DFE, SJC, MBC, FW, JSW, RAE, AK, SW, JMG, ACJ, DVC, CAH; Data analysis: BFD, JS, YX, AAR; Bioinformatics support: XS, RKM;

Interpretation of data: BFD, DVC, CAH; Drafted the manuscript: BFD; Contributed to manuscript revisions: BFD, JS, XS, EJS, EMJ, DJS, NP, DVC, CAH; All authors approved of the final manuscript.

### Competing Interests Statement

The authors have no conflicts of interest to disclose.

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## Figures

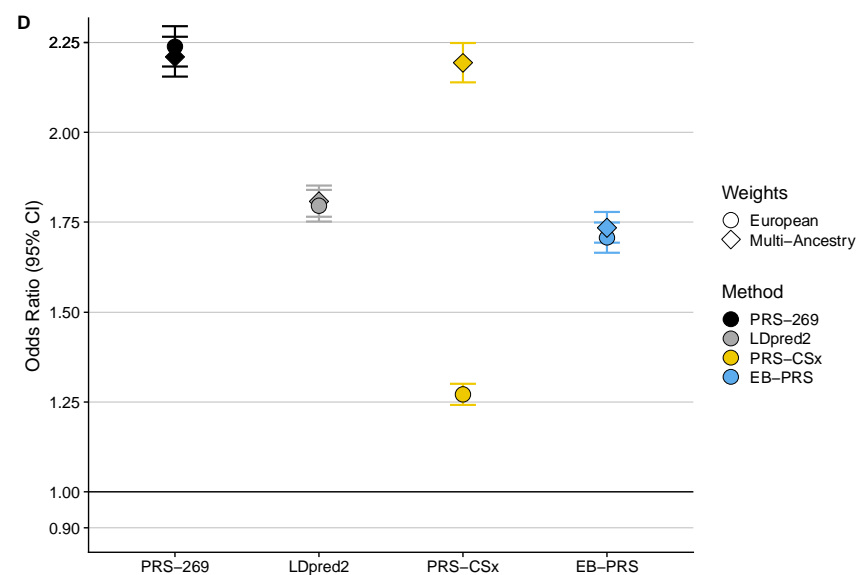
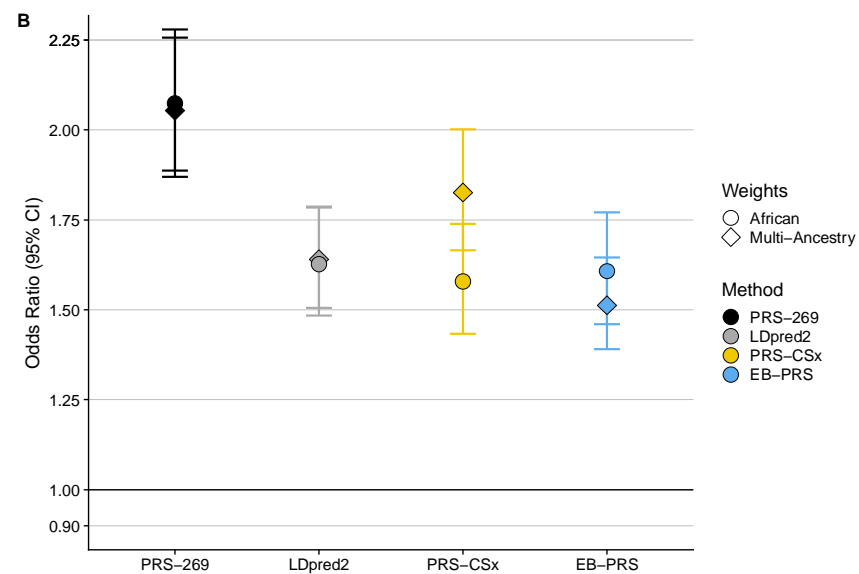
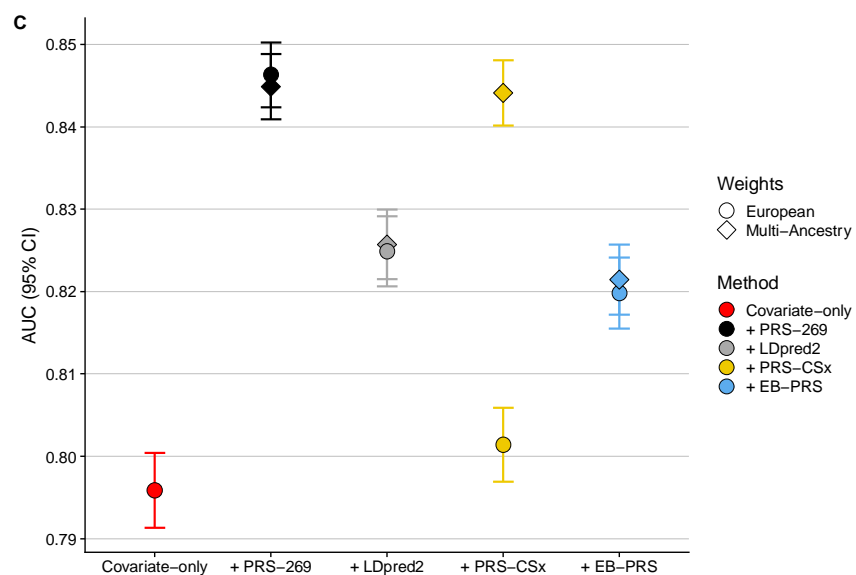
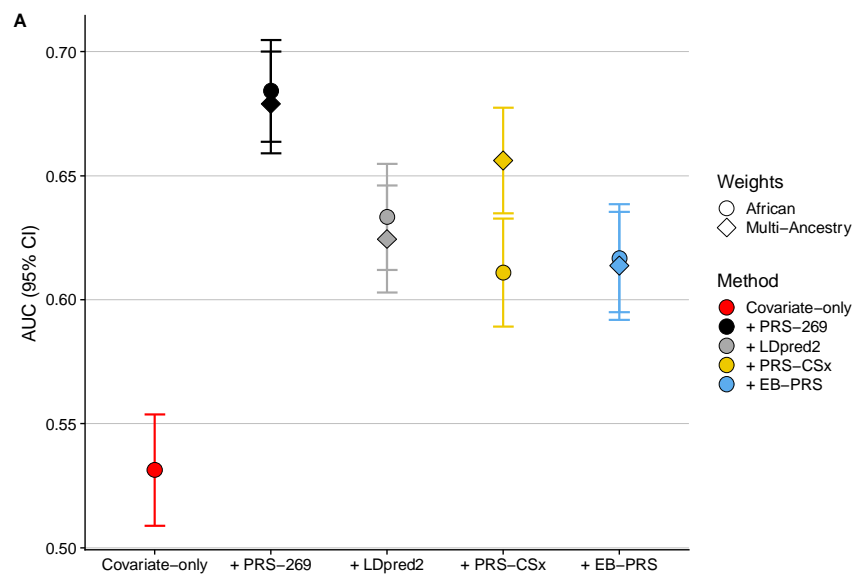




Figure 1. Comparison of PRS performance in the CA UG Study and the UK Biobank testing data. PRS performance is evaluated using area under the curve (AUC) estimated in men of A) African and C) European ancestry and OR of prostate cancer for each SD increase in PRS in men of B) African and D) European ancestry.

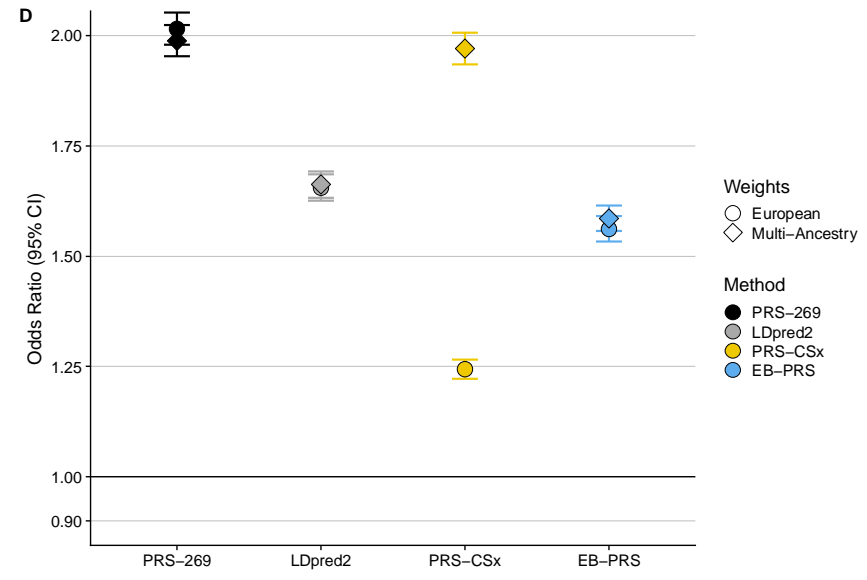
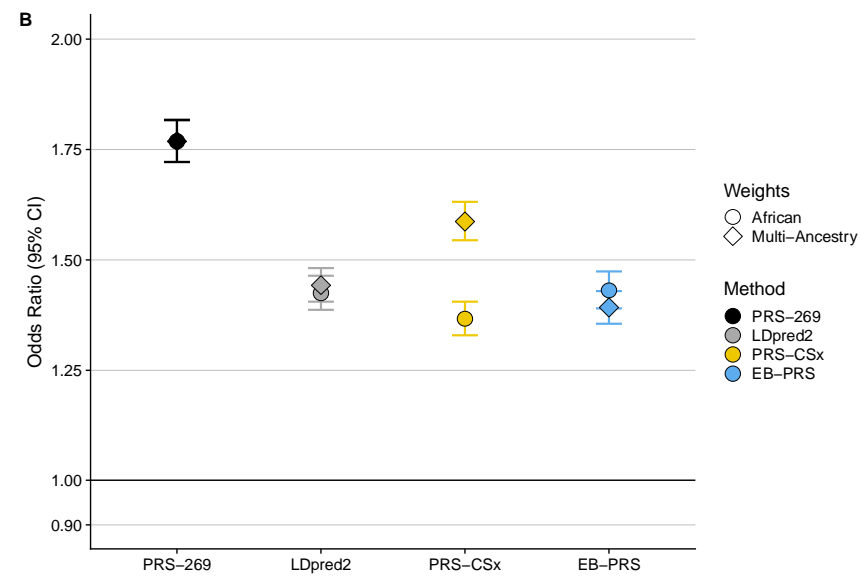
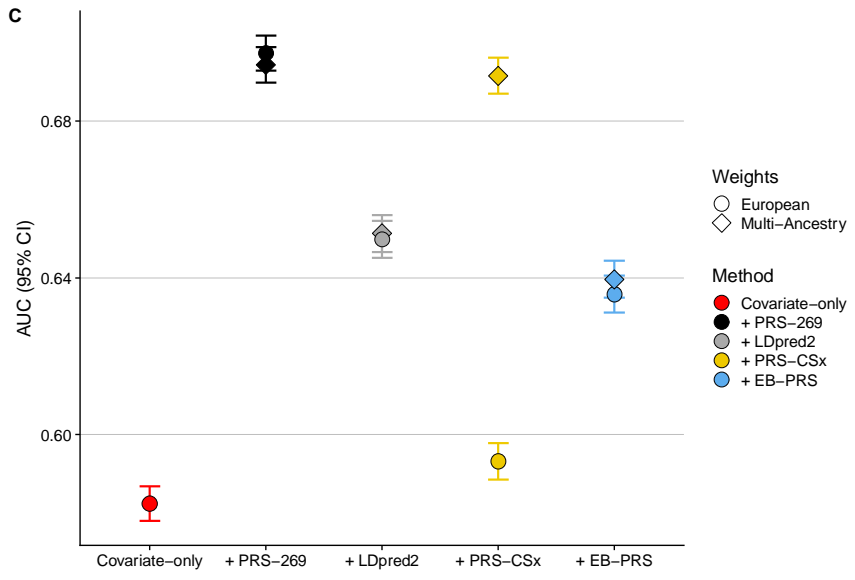
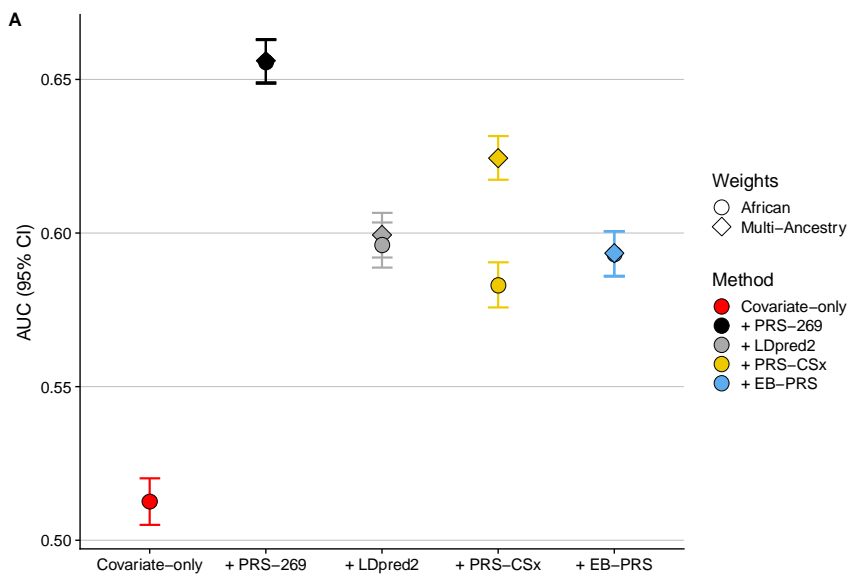


Figure 2. Comparison of PRS performance in the MVP validation data. PRS performance is evaluated using area under the curve (AUC) estimated in men of A) African and C) European ancestry and OR of prostate cancer for each SD increase in PRS in men of B) African and D) European ancestry.