

 Open access • Posted Content • DOI:10.1101/2020.04.23.20077099

Improving reporting standards for polygenic scores in risk prediction studies

— [Source link](#) 

Hannah Wand, Samuel A. Lambert, Cecelia P. Tamburro, Michael A. Iacocca ...+30 more authors

Institutions: [Stanford University](#), [National Institutes of Health](#), [Mayo Clinic](#), [Harvard University](#) ...+12 more institutions

Published on: 23 Sep 2020 - [medRxiv](#) (Cold Spring Harbor Laboratory Press)

Related papers:

- [Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations](#)
- [Does standardised structured reporting contribute to quality in diagnostic pathology? The importance of evidence-based datasets.](#)
- [A genetic test registry: bringing credible and actionable data together.](#)
- [Review of study reporting guidelines for clinical studies using artificial intelligence in healthcare](#)
- [An update on statistical modeling for quality risk assessment of clinical trials](#)

Share this paper:    

View more about this paper here: <https://typeset.io/papers/improving-reporting-standards-for-polygenic-scores-in-risk-2r5mipkia6>

1 Improving reporting standards for polygenic scores in 2 risk prediction studies

3
4 Hannah Wand^{#1,2}, Samuel A. Lambert^{#3-7}, Cecelia Tamburro⁸, Michael A. Iacocca¹, Jack W. O'Sullivan^{1,2},
5 Catherine Sillari⁸, Iftikhar J. Kullo⁹, Robb Rowley⁸, Jacqueline S. Dron^{10,11}, Deanna Brockman¹⁰, Eric Venner¹²,
6 Mark I. McCarthy^{13,14}, Antonis C. Antoniou¹⁵, Douglas F. Easton¹⁵, Robert A. Hegele¹¹, Amit V. Khera¹⁰, Nilanjan
7 Chatterjee^{16,17}, Charles Kooperberg¹⁸, Karen Edwards¹⁹, Katherine Vlessis²⁰, Kim Kinnear²⁰, John N. Danesh^{5,6},
8 ²¹, Helen Parkinson^{6,7}, Erin M. Ramos⁸, Megan C. Roberts²², Kelly E. Ormond^{20,23}, Muin J. Khoury²⁴, A. Cecile
9 J.W. Janssens²⁵, Katrina A.B. Goddard^{26,27}, Peter Kraft²⁸, Jaqueline A. L. MacArthur⁷, Michael Inouye^{§3-6,21,29},
10 Genevieve Wojcik^{§30}

11 #Shared first authorship

12 §Shared senior authorship

- 13 1. Stanford University School of Medicine, Stanford, CA, USA
- 14 2. Stanford Center for Inherited Cardiovascular Disease, Stanford, CA, USA
- 15 3. Cambridge Baker Systems Genomic Initiative, University of Cambridge, Cambridge, UK
- 16 4. Cambridge Baker Systems Genomic Initiative, Baker Heart and Diabetes Institute, Melbourne, AUS
- 17 5. BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of
18 Cambridge, Cambridge, UK
- 19 6. Health Data Research UK-Cambridge, Wellcome Genome Campus, Hinxton, UK
- 20 7. European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome
21 Campus, Hinxton, UK
- 22 8. National Human Genome Research Institute, Bethesda, MD, USA
- 23 9. Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA
- 24 10. Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
- 25 11. Western University, London, ON, Canada
- 26 12. Baylor College of Medicine, Houston, TX, USA
- 27 13. Department of Human Genetics, Genentech, South San Francisco, CA, USA
- 28 14. Wellcome Centre for Human Genetics, Oxford, UK
- 29 15. University of Cambridge, Cambridge, United Kingdom
- 30 16. Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
- 31 17. Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD, USA
- 32 18. Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
- 33 19. Department of Epidemiology, University of California, Irvine, CA, USA
- 34 20. Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA
- 35 21. National Institute for Health Research Cambridge Biomedical Research Centre, University of
36 Cambridge and Cambridge University Hospitals, Cambridge, UK
- 37 22. Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, Chapel Hill,
38 NC, USA
- 39 23. Stanford Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, CA, USA
- 40 24. Centers for Disease Control and Prevention, Atlanta, GA, USA
- 41 25. Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA
- 42 26. Department of Translational and Applied Genomics, Kaiser Permanente Northwest, Portland, OR, USA
- 43 27. Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA
- 44 28. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
- 45 29. The Alan Turing Institute, London, UK
- 46 30. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

47 *Corresponding author: Dr. Genevieve L. Wojcik, gwojcik1@jhu.edu

51 Abstract

52 Polygenic risk scores (PRS), often aggregating the results from genome-wide association studies, can bridge
53 the gap between the initial discovery efforts and clinical applications for disease risk estimation. However, there
54 is remarkable heterogeneity in the reporting of these risk scores. This lack of adherence to reporting standards
55 hinders the translation of PRS into clinical care. The ClinGen Complex Disease Working Group, in a
56 collaboration with the Polygenic Score (PGS) Catalog, have updated the Genetic Risk Prediction (GRIPS)
57 Reporting Statement to the current state of the field and to enable downstream utility. Drawing upon experts in
58 epidemiology, statistics, disease-specific applications, implementation, and policy, this 22-item reporting
59 framework defines the minimal information needed to interpret and evaluate a PRS, especially with respect to
60 any downstream clinical applications. Items span detailed descriptions of the study population (recruitment
61 method, key demographic and clinical characteristics, inclusion/exclusion criteria, and outcome definition),
62 statistical methods for both PRS development and validation, and considerations for potential limitations of the
63 published risk score and downstream clinical utility. Additionally, emphasis has been placed on data availability
64 and transparency to facilitate reproducibility and benchmarking against other PRS, such as deposition in the
65 publicly available PGS Catalog. By providing these criteria in a structured format that builds upon existing
66 standards and ontologies, the use of this framework in publishing PRS will facilitate translation of PRS into
67 clinical care and progress towards defining best practices.

68 Summary

69 In recent years, polygenic risk scores (PRS) have increasingly been used to capture the genome-wide liability
70 underlying many human traits and diseases, hoping to better inform an individual's genetic risk. However, a
71 lack of adherence to existing reporting standards has hindered the translation of this important tool into clinical
72 and public health practice; in particular, details necessary for benchmarking and reproducibility are
73 underreported. To address this gap, the ClinGen Complex Disease Working Group and Polygenic Score (PGS)
74 Catalog have updated the Genetic Risk Prediction (GRIPS) Reporting Statement into the 22-item Polygenic
75 Risk Score Reporting Statement (PRS-RS). This framework provides the minimal information expected of
76 authors to promote the validity, transparency, and reproducibility of PRS by encouraging authors to detail the
77 study population, statistical methods, and potential clinical utility of a published score. The widespread adoption
78 of this framework will encourage rigorous methodological consideration and facilitate benchmarking to ensure
79 high quality scores are translated into the clinic.

80 Main Text

81 The predisposition to common diseases and traits arises from a complex interaction between genetic and
82 nongenetic factors. In the past decade there has been enormous success at discovering the landscape of
83 disease-associated genetic variants as a result of the many collaborative consortia and large cohorts of well-
84 phenotyped individuals and matched genetic information.¹⁻⁵ In particular, genome-wide association studies
85 (GWAS) have emerged as a powerful approach to identify disease- or trait-associated genetic variants and
86 yielded summary statistics that describe the magnitude (effect size) and statistical significance of association
87 between an allele and the outcome of interest.^{4,6} GWAS have been applied to a wide range of complex human
88 traits and diseases, including height, blood pressure, cardiovascular disease, cancer, obesity, and Alzheimer's
89 disease.

90 The associations identified via GWAS can be combined to quantify genetic predisposition to a heritable
91 trait, and this information can be used to conduct disease risk stratification or predict prognostic outcomes and
92 response to therapy.^{7,8} Typically, information across many variants is used to form a weighted sum of allele
93 counts, where the weights reflect the relative magnitude of association between variant alleles and the trait or
94 disease. These weighted sums can include up to millions of variants, and are frequently referred to as
95 **polygenic risk score(s) (PRS)**, or **genetic or genomic risk score(s) (GRS)**, if they refer to risk estimates of
96 disease outcomes; or, more generally, **polygenic score(s) (PGS)** when referring to any outcome (see [Box 1](#)
97 *for further discussion of nomenclature*). While there is active development of algorithms to decide how many
98 and which variants to include and how to weigh them so as to maximize the proportion of variance explained
99 or disease discrimination, there is an emerging consensus that the inclusion of variants beyond those meeting
100 stringent GWAS significance levels can boost predictive performance.^{9,10} Methodological research has also
101 established theoretical limits of PGS/PRS performance based on the trait's genetic architecture and
102 heritability.¹¹⁻¹⁵

103 In the last decade, the landscape of genetic prediction studies has transformed. There have been over
104 900 publications mentioning PGS/PRS with significant developments in how PGS are constructed and
105 evaluated, as well as many new proposed uses. The data available in the current era of biomedical research is
106 larger and more consolidated than ever before. Biobanks and large-scale consortia have become dominant,
107 yet frequently researchers have limited access to individual-level data. Since individual data is unavailable,
108 most PRS risk predictions are developed from summary-level data (e.g. GWAS summary statistics) in
109 secondary datasets, each of which come with their own specific methodological considerations.¹⁶⁻¹⁸ At the same
110 time, there has been a push towards open data sharing as outlined in the FAIR (Findable, Accessible,
111 Interoperable and Reusable) Data Principles^{3,19}, with an emphasis on ensuring that research is reproducible
112 by all.

Box 1. Definitions of relevant genetic risk prediction terms

Polygenic Score(s) (PGS): a single value that quantifies an individual's genetic predisposition to a trait. Typically calculated by summing the number of trait-associated alleles in an individual weighted by per-allele effect sizes from a discovery GWAS, and normalized using a relevant population distribution. Sometimes referred to as a genetic score.

Polygenic Risk Score(s) (PRS): a subset of PGS which is used to estimate risk of disease or other clinically relevant outcomes (binary or discrete). Sometimes referred to as a genetic or genomic risk score (GRS). See categories of PRS below.

Integrated Risk Model: a risk model combining PRS with other established risk factors for the outcome of interest, such as demographics (often age and sex), anthropometrics, biomarkers, and clinical measurements to estimate a specific disease risk.

Categories of use for PRS and/or integrated risk models

The addition of PRS to existing risk models has several potential applications, summarized below. In each, the aim of PRS integration is to improve individual or subgroup classification to the extent that there is meaningful clinical benefit.

Disease Risk Prediction – used to estimate an individual's risk of developing a disease, based on the presence of certain genetic and/or clinical variables.

Disease Diagnosis – used to classify whether an individual has a disease, or a disease subtype, linked to a certain etiology based on the presence of certain genetic and/or clinical variables.^{9,20}

Disease Prognosis – used to estimate the risk of further adverse outcome(s) *subsequent to* diagnosis of disease.²¹

Therapeutic – used to predict a patient or subgroup's response to a particular treatment.²²

113

114 The capacity of PRS to quantify genetic predisposition for many clinically relevant traits and diseases
115 has begun to be established, with multiple potential clinical uses in settings related to disease risk stratification
116 as well as proposed prognostic uses (e.g., predicting response to intervention/treatment). The readiness of PRS
117 for implementation varies among outcomes, with only a few diseases, like coronary heart disease (CHD) and
118 breast cancer, having mature PRS with potential clinical utility (**Boxes 2 and 3**, respectively). There has also
119 been a rapid rise of direct-to-consumer assays and for-profit companies (23andMe, Color, MyHeritage, etc.)
120 providing PGS/PRS results to customers outside of the traditional patient-provider framework. These
121 concomitant advances have resulted in healthcare systems developing new infrastructures to deliver genetic
122 risk information.²³ These advances, individually and combined, have raised significant challenges for PRS
123 reporting standards; from the very basic (e.g. reporting performance metrics on an external validation dataset)
124 to the complicated (e.g. making the raw variant and weight information for a PRS available), necessitating the
125 updating of existing standard for reporting genetic risk prediction studies to convey the increased scope of PRS
126 and complexity for their clinical applications.

Box 2: Current CHD PRS and their potential uses

Many PRS have been developed for CHD, varying in the computational methods used, the number of variants included (50–6,000,000), and the GWAS and cohorts used for PRS training. For example, the latest and currently most predictive CHD PRS use GWAS summary statistics from the CardiogramPlusC4D study²⁴, and mainly differ by the computational methods used to select and weight individual variants (including LDpred^{25,26}, lassosum²⁷, and meta-scoring approaches²⁸, and how they are combined into risk models with conventional risk factors. These PRS may provide useful information for predicting risk of CHD that is largely orthogonal to conventional risk factors (age, sex, hypertension, cholesterol, BMI, diabetes, smoking) as well as family history. Clinical applications may include:

- Improved prediction of risk for future adverse cardiovascular events when added to conventional risk models (such as the Framingham Risk Score²⁹, Pooled Cohort Equations^{27,28}, QRISK²⁷).
- Reclassification of risk categories often leading to recommendations related to risk-reducing treatments like statins.^{29–31}

While the data strongly suggest CHD PRS, by refining risk estimates, may improve patient outcomes, clinical utility through randomized clinical trials has yet to be conclusively established. We anticipate this is the future direction of PRS studies, and a number of clinical trials are underway.³²

127

Box 3: Current breast cancer PRS and their potential uses

Many of the most recent and most predictive PRS for breast cancer include a smaller number of variants (usually in the 100-1,000s), possibly owing to a less polygenic architecture and more low-frequency variants having greater effect; however, scores composed of millions of variants also exist. Most of the latest PRS have been developed using GWAS summary statistics and data from the Breast Cancer Association Consortium (BCAC), using variants passing genome-wide significance (lead SNPs) or methods including stepwise or penalized regressions on individual-level genotypes³³, Pruning + Thresholding²⁵, and LDpred²⁶. In contrast to CHD, genetics is commonly used to measure and understand breast cancer risk vis-a-vis *BRCA1/2* mutation testing; however, routine screening for breast cancer is often performed in older women using mammography and non-genetic risk prediction tools already exist. As such there has been active research into the value of capturing the polygenic risk of common variation on breast cancer, with multiple potential clinical uses and considerations:

- Multiple PRS exist to predict risk for specific subtypes of breast cancer (e.g. ER positive/negative, luminal, and triple negative^{33,34}), which could be used to stratify patients for more beneficial treatments, and may have prognostic implications.
- PRS can be combined with existing non-genetic risk prediction models (combining risk factors such as age, family history, mammographic density, hormone replacement therapy) and improve the prediction of incident breast cancer risk.^{35–42}
- Breast cancer has been linked to several rare high-or moderate-risk penetrant genes (e.g. *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *ATM*) and screening for pathogenic variants in these genes is part of clinical practice.⁴³ It has been shown that PRS can provide important stratification of risk among carriers of such pathogenic variants and thus could be further useful for clinical decision making.^{26,40,44–48}

Indeed, the BOADICEA breast cancer risk prediction model includes the effects of common variants (PRS313³³) as well as of other rare pathogenic genetic variants⁴⁰ and has been implemented in the CanRisk Tool (www.canrisk.org) that has been approved for use by healthcare professionals in the European Economic Area. PRS information has been studied via simulation⁴⁹ and is being tested in risk-based breast cancer screening trials in the US⁵⁰ and Europe (MyPeBS; <https://mypebs.eu>).

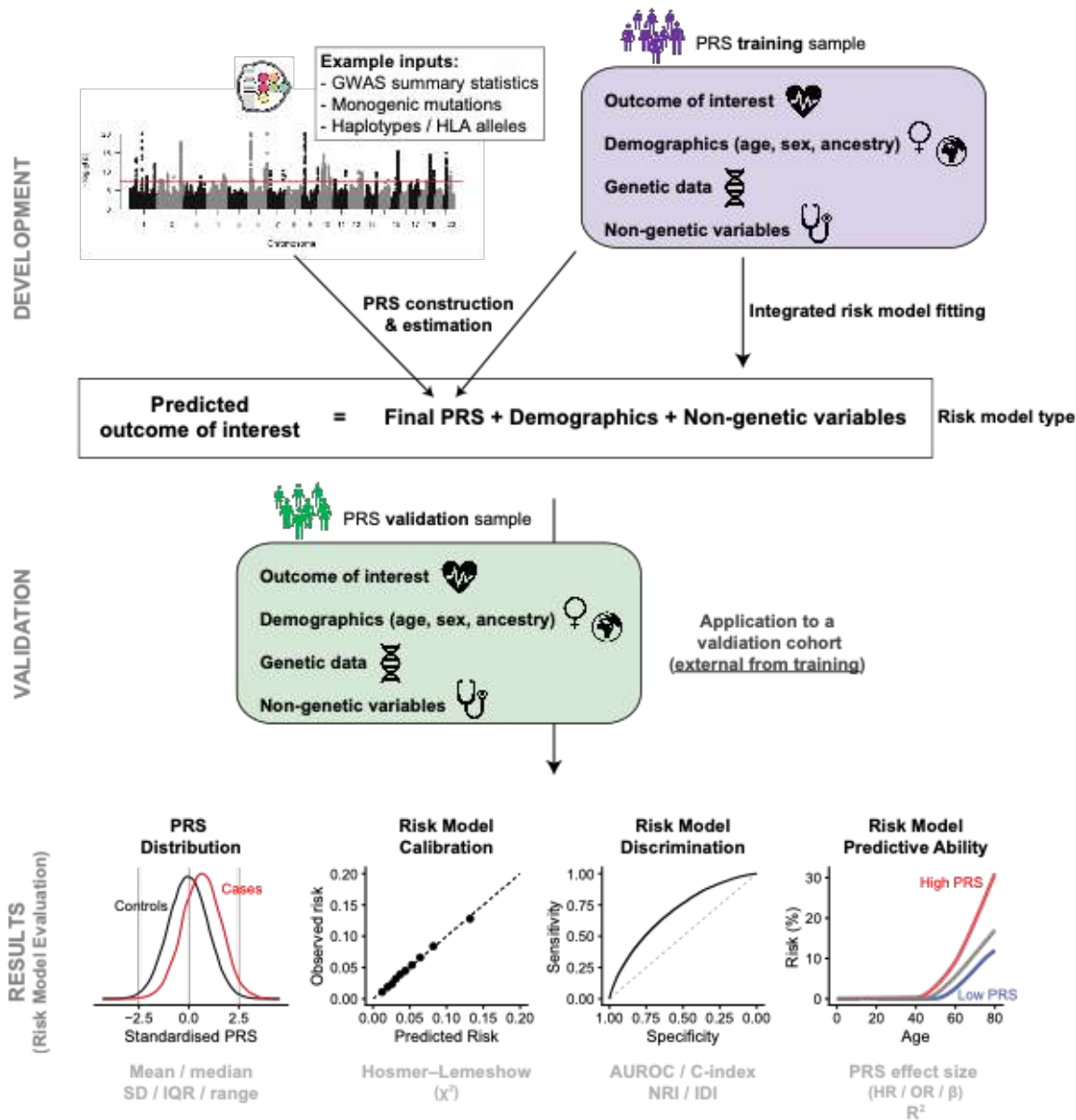
128

129 Poorly designed or described studies call into question the validity of some PRS to predict their target
130 outcome^{51,52}, and relatively few studies have benchmarked multiple scores performance externally. At present,
131 there are no uniformly agreed best practices for developing PRS, nor widely adopted standards or regulations
132 sufficiently tailored to assess the eventual clinical readiness of a PRS. There are rapidly emerging applications
133 of PRS that further compound the heterogeneity in reporting, e.g. using PRS as tools for testing gene x
134 environment interactions or shared etiology between diseases.^{53–56} This in itself is not an issue, but the rapid
135 evolution in both the methodological development and applications of PRS make it challenging to compare or
136 reproduce claims about the predictive performance of a PRS for a specific outcome when studies are not
137 properly documented. These deficiencies are barriers to PRS being interpreted, compared, and reproduced,
138 and must be addressed to enable the application of PRS to improve clinical practice and public health.

139 Frameworks have been developed to establish standards around the transparent, standardized,
140 accurate, complete, and meaningful reporting of scientific studies. In 2011, an international working group
141 published the Genetic Risk Prediction Studies (GRIPS) Statement, a reporting guideline for the study of risk
142 prediction models that include genetic variants, from genetic mutations to gene scores.⁵⁷ This guideline is
143 analogous to guidelines developed for observational epidemiological studies (STROBE⁵⁸) and genome-wide
144 association studies (STREGA⁵⁹), and is in line with the reporting guideline for multivariate prediction models
145 (TRIPOD⁶⁰). Adherence to reporting statements has been low, and the same holds for GRIPS. One of the
146 reasons might be that researchers feel that GRIPS inadequately addresses PRS, where there has been rapid
147 evolution in score development methodology in recent years. Researchers are frequently uncertain as to what
148 precisely should be reported for a PRS study to be assessed as rigorous, reproducible, and ultimately
149 translatable, especially with the increased push for data availability and transparency. Most PRS studies follow
150 a prototypical process to PRS development evaluation (**Figure 1**) that can be used as a template for
151 standardizing reporting and benchmarking in the field.

152 Here, the Clinical Genome Resource (ClinGen) Complex Disease Working Group and the Polygenic
153 Score (PGS) Catalog (**Supplemental Note 1**) jointly present the Polygenic Risk Score Reporting Standards
154 (PRS-RS), a synthesis of an expanded reporting standard for PRS that addresses current research
155 environments with advanced methodological developments to inform clinically meaningful reporting on PRS
156 development and validation in the literature with an emphasis on reproducibility and transparency throughout
157 the development process. Additional methods are detailed in **Supplemental Note 2**.

158



159

160 **Figure 1: Prototype of PRS development and validation process.** Figure 1 displays prototypical steps for
 161 PRS construction, risk model development, and validation of performance with select aspects of the PRS-RS
 162 guideline labeled in bold text throughout. In PRS development, variants associated with an outcome of interest,
 163 typically identified from a GWAS, are combined as a weighted sum of allele counts across variants. Methods
 164 for optimizing variant selection for a PRS (PRS construction & estimation) are not shown. The PRS is tested in
 165 a risk model predicting the outcome of interest and may be combined with other non-genetic variables (e.g.
 166 age, sex, ancestry, clinical variables); collectively these are referred to as risk model variables. After fitting
 167 procedures to select the best risk model, this model is validated in an independent sample. The PRS distribution
 168 should be described, and the performance of the risk model demonstrated in terms of its discrimination,
 169 predictive ability, and calibration. Though not displayed in the figure, these same results should also be reported
 170 for the training sample for comparison to the validation sample. In both training and validation cohorts, the
 171 outcome of interest criteria, demographics, genotyping, and non-genetic variables should be reported (**Table**
 172 **1**).

173

174 **The ClinGen-PGS Catalog Polygenic Risk Score Reporting Standards (PRS-RS)**

175 The PRS-RS is a set of standard items specifying the minimal criteria that need to be described in a manuscript
176 in order to accurately interpret a PRS and reproduce results throughout the PRS development process, briefly
177 illustrated in **Figure 1**.⁶¹ It applies to both PRS development and validation studies that aim to predict disease
178 onset and prognosis, as well as response to therapies; however, other research uses of PRS have overlapping
179 steps that should be reported similarly. **Table 1** presents the full PRS-RS, in which criteria are organized into
180 key components along the developmental pipeline of PRS for clear interpretation and to encourage their
181 documentation from the inception of the study well before publication.

182

183 **Reporting on risk score background:** The development and validation of a PRS tests a specific hypothesis
184 with a defined outcome and study population. Therefore, authors should define *a priori* the *study type* (e.g.
185 development and/or validation), *purpose* (e.g. risk prediction vs. prognosis) and *predicted end outcome* (e.g.
186 CHD) in enough detail to understand why the study population and risk model selected are relevant (e.g. the
187 value for CHD risk stratification and primary prevention is highest in younger individuals compared to those
188 over 80 who have accumulated risk over a lifetime). As the PRS-RS is focused on clinical validity and
189 implementation, authors must outline the study and appropriate outcomes to understand what risk is measured,
190 what the purpose of measuring risk would be, and why this purpose may be of clinical relevance. In order to
191 establish the internal validity of a study, authors should use the appropriate data needed to address the intended
192 purpose (e.g. prediction of incident disease vs. prognosis), with adequate documentation of dataset
193 characteristics to understand nuances in measured risk.

194

195 **Reporting on study populations:** The applicability of any risk prediction to an external target population (the
196 “who, where, and when”) depends on its similarity to the original study populations used to derive the risk model.
197 Therefore, authors need to define and characterize the details of their study population (e.g. *study design and*
198 *recruitment*), and describe *participant demographics* for key variables (such as age and sex) and *ancestry*.
199 Importantly, there are often inconsistent definitions and levels of detail associated with ancestry, and the
200 transferability of genetic findings between different racial/ethnic groups can be limited.^{1,9,62} It is therefore
201 essential for authors to provide a detailed description of participants’ genetic ancestry - including how ancestry
202 was determined – using a common controlled vocabulary where possible (e.g. tables 1 and 2 of the
203 standardized framework developed by the NHGRI-EBI GWAS Catalog¹). While age, sex and ancestry are the
204 most universally relevant characteristics, authors should provide a sufficient level of detailed criteria for defining
205 all the relevant factors used in the risk model (*non-genetic variable(s)*) and the *outcome of interest*. This is
206 particularly important if they are included in the final risk model and should accompany information about how
207 the population was genotyped (*genetic data*).

208

209 **Reporting on risk model development:** There are currently several methods that are commonly used to select

210 variants and fine-tune weights that constitute the PRS.^{7,16–18,61} For methods using individual-level genomic
211 data, the original source study should be cited or the assays and quality control described in detail. Methods
212 using GWAS summary statistics should clearly cite the relevant GWAS(s) (preferably using unique and
213 persistent study identifiers from the GWAS Catalog (GCSTs;⁶³). As the performance and limitations of the
214 combined risk model are dependent on methodological considerations, authors must provide complete details
215 including the method used and how variants are selected and combined into a single PRS (*PRS construction*
216 & *estimation*). Apart from the genetic data in the model, authors should also describe the defining criteria for
217 other demographic and non-genetic predictors (*non-genetic variables*) included in the model. Often authors will
218 iterate through numerous models to find the optimal fit. In addition to the estimation methods, it is important to
219 detail the *integrated risk model fitting* procedure, including the measures used for final model selection.
220 Translating the continuous PRS distribution to a risk estimate, whether absolute or relative, is highly dependent
221 on assumptions and limitations inherent to the specific data set utilized. When describing the *risk model type*,
222 authors should detail the time scale employed for prediction or the study period/follow-up time for a relative
223 hazard model. Additionally, if relative risk is estimated, the reference group should be well described. These
224 details should be described for the training set, as well as validation and sub-group analyses.

225

226 **Reporting on model parameters:** Authors should report estimates for all evaluated models, not only the
227 methods behind decision-making, equipping readers with the information necessary to gauge the relative value
228 of an increase in performance against other trade-offs (*data transparency and availability*). The underlying PRS
229 (variant alleles and derived weights) should be made publicly available, preferably through direct submission to
230 an indexed repository such as the PGS Catalog, to enable others to reuse existing models (with known validity)
231 and facilitate direct benchmarking between different PRS for the same trait. The current mathematical form of
232 most PRS—a linear combination of allele counts—facilitates clear model description and reproducibility. Future
233 genomic risk models may have more complex forms, e.g. allowing for explicit non-linear epistatic and gene-
234 environment interactions, or deep neural networks of lesser clarity. It will be important to describe these models
235 in sufficient detail to allow their implementation and evaluation by other researchers and clinical groups.

236

237 **Reporting on risk model evaluation:** We recommend that authors provide summary information of the *risk*
238 *score distribution* to aid in model interpretation. The *risk model's predictive ability, calibration, and discrimination*
239 should also be assessed and described with common descriptions including the risk score effect size, variance
240 explained (R^2), reclassification indices, and metrics like sensitivity, specificity, positive predictive value (PPV),
241 and negative predictive value (NPV). The *risk model calibration and discrimination* should be described for all
242 analyses, although their estimation and interpretation are most relevant for the PRS validation sample. It is
243 imperative for the PRS and expanded risk models to be evaluated on a population that is external (e.g.
244 independent, non-overlapping) to the individuals in the study population. The ability of the risk model to classify
245 individuals of interest (*risk model discrimination*) can commonly described and presented in terms of the
246 AUROC, AUPRC or C-index. Any differences in variable definitions or performance discrepancies between the

247 training and validation sets should be described.

248

249 **Reporting on interpretation:** By explicitly describing the *risk model's interpretation* and outlining potential
250 *limitations* to the *generalizability* of their model, authors will empower readers and the wider community to better
251 understand the risk score and its relative merits. Authors should justify the clinical relevance and *risk model*
252 *intended uses*, such as how the performance of their PRS compares to other commonly used risk models, or
253 previously published PRS. This may also include comparisons to other genetic predictors of disease (e.g.
254 mutations in high/moderate risk genes associated with Mendelian forms of the disease), family history, simple
255 demographic models, or conventional risk calculators (see Box 2 and 3 for disease-specific examples). What
256 indicates a “good” prediction can differ between outcomes and *intended uses*, but should be reported with
257 similar metrics to what is described in the evaluation section.

258

259 **Supplemental Note 3** provides reporting considerations in addition to the minimal reporting framework
260 in **Table 1**. Authors intending downstream clinical implementation should aim for the level of transparent and
261 comprehensive reporting covered in both **Table 1** and **Supplemental Notes**, especially those related to
262 discussing the interpretation, limitations, and generalizability of results. The proper reporting of PRS
263 development and performance can also have implications for seeking regulatory approval of the PRS as a
264 clinical test. Though not a comprehensive list of regulatory requirements, we highlight aspects of PRS-RS that
265 would be considered evidence of analytical and clinical validity from the College of American Pathologists (CAP)
266 and the Clinical Laboratory Improvement Amendments (CLIA) perspective (**Supplemental Table 1**). CAP and
267 CLIA approvals are additional incentives for reporting adherence of researchers wishing to translate their work,
268 as well as a caution for researchers wishing to avoid unintended uses of their findings. Lastly, we reiterate the
269 need for both methodological and data transparency and encourage deposition of PRS (variant-level
270 information necessary to recalculate the genetic portion of the score) in the PGS Catalog
271 (www.PGSCatalog.org; ⁶⁴), which provides an invaluable resource for widespread adoption and distribution of
272 a published PRS. The PGS Catalog provides access to PGS and related metadata to support the FAIR
273 principles of data stewardship ¹⁹, enabling subsequent applications and assessments of PGS performance and
274 best practices (see **Supplemental Table 2** for a description of the metadata captured in the Catalog and it's
275 overlap with the PRS-RS).

276

277 **Using the PRS-RS and PGS Catalog to improve PRS research and translation:** 278 **transparency and open data**

279 We surveyed 30 publications (selecting for a diversity of disease domains, risk score categories, and
280 populations) to understand how the information in the PRS-RS is presented and displayed as part of the larger
281 iterative process to clarify and improve field definitions. For 10 of these publications, we provide detailed
282 annotations using the final field definitions (**Supplemental Table 3**) and use these annotations to illustrate the

283 detail necessary for each PRS-RS item (further described in **Supplemental Note 3**). The heterogeneity in the
284 PRS reporting we observed in this pilot highlights a series of challenges. Critical aspects of PRS studies,
285 including ancestry, predictive ability, and transparency/availability of information needed to reproduce PRS,
286 were frequently absent or reported in insufficient detail. This underscores the need for PRS-RS to clearly and
287 specifically define meaningful aspects of PRS development, testing, and intended clinical use. However, these
288 deficits in reporting are not unique to PRS; previous reports of underreporting have found that 77% of GWAS
289 publications in 2017 did not share summary statistics⁶⁵ and 4% of GWAS do not report any relevant ancestry
290 information¹. In line with the push towards a culture of reproducibility and open data in genomics, we as the
291 ClinGen Complex Disease Working Group and PGS Catalog joined to create a set of reporting standards (**Table**
292 **1**) specifically tailored to PRS research based on multidisciplinary and international expert opinion for tailoring
293 previous standards.

294 Researchers using PRS-RS may identify fringe cases that are inadequately captured by these reporting
295 items, as we have modeled our guideline on prototypical steps for PRS development (**Figure 1**) for flexibility.
296 While we anticipate the field may further change as novel methods and technologies are generated, the PRS-
297 RS items can be further expanded and adapted to encompass novel considerations. By updating previous
298 standards, drawing upon current leaders in the field, and tailoring the framework to common barriers observed
299 in recent literature, we aim to provide a comprehensive and pragmatic perspective on the topic. In line with
300 previous standards, PRS-RS includes elements related to understanding the clinical validity of PRS and
301 consequent risk models. Items such as *predicted end outcome* and *intended use* bookend our guideline with
302 the intended clinical framing of PRS reporting. In addition, we have modeled the guideline by steps in
303 experimental design, from hypothesis to interpretation, to more clearly emphasize the significance of the
304 intended use case in defining what needs reported and inform documentation throughout the process. As a
305 reference, we have also included a guide to where PRS-RS items should be reported in a manuscript in
306 **Supplemental Table 4**). These expansions will further facilitate the curation and expert annotation of published
307 PRS as we move towards widespread clinical use.

308 While the scope of our work encompasses clinical validity, it does not address the additional
309 requirements needed to establish the clinical or public health utility of a PRS, such as randomized trials with
310 clinically meaningful outcomes, health economic evaluations, or feasibility studies.⁶⁶ In addition, the translation
311 of structured data elements into useful clinical parameters may not be direct. A relevant example is that the
312 disease case definitions utilized in training or validation in any particular PRS study may deviate (sometimes
313 substantially) from those utilized in any specific health system, for example CHD symptoms commonly include
314 angina (chest pain), whereas PRS are frequently trained on stricter definitions excluding angina. In addition,
315 the definitions used for race/ancestry as outlined in the PGS and GWAS Catalog¹ may also differ from structured
316 terms used to document ancestry information in clinical care, in which case consistent mappings, and potentially
317 parallel analyses, may be necessary to translate from genetically determined ancestries to those routinely used
318 in clinical care. Such translation issues potentially limit generalizability to target populations and warrant further
319 discussion, and we reiterate the need for authors to be mindful of their intended purpose and target audience

320 when discussing their findings. Nevertheless, we have aided authors' understanding of potential translational
321 barriers by considering current CAP/CLIA analytical and clinical validity evidence requirements of peer-
322 reviewed literature to ensure PRS-RS has value in informing later steps of the clinical translation spectrum,
323 including clinical utility (**Supplemental Table 1**). Finally, while the principles of this work are clear, its scope
324 does not include the complex commercial restrictions, such as intellectual property, that may be placed on
325 published studies regarding the reporting or distribution of PGS, or the underlying data thereof. We hope this
326 work will inform downstream regulation and transparency standards for PRS as a commercial clinical tool.

327 The coordinated efforts of the ClinGen Complex Disease Working Group and PGS Catalog provide a
328 set of compatible resources for researchers to deposit PGS/PRS information. The PGS Catalog
329 (www.PGSCatalog.org) provides an informatics platform with data integration and harmonization to other PGS
330 as well as the source GWAS study through its sister platform, the GWAS Catalog.⁶⁴ In addition, it provides a
331 structured database of scores (variants and effect weights) that can be reused, along with metadata requested
332 in the PRS-RS. With these tools, PRS-RS can be mandated by leading peer-reviewed journals and,
333 consequently, the quality and rigor of PRS research will be elevated to a level which facilitates clinical
334 implementation. We encourage readers to visit the ClinGen complex disease website
335 (<https://clinicalgenome.org/working-groups/complex-disease/>) for any future changes or amendments to the
336 reporting guideline.

337 While we have provided explicit recommendations on how to acknowledge study design limitations and
338 their impact on the interpretation and generalizability of a PRS, future research should attempt to establish best
339 practices to guide the field. Moving forward, supplemental frameworks should be developed for the reporting of
340 new methods, such as deep learning, as well as requirements for clinical utility and readiness. Taken together,
341 PRS-RS facilitates the rapid emergence of polygenic risk scores as potentially powerful tools for the translation
342 of genomic discoveries into clinical and public health benefits, and provides a framework for PRS to transform
343 multiple areas of human genetic research.

344 Acknowledgements

345 We would like to acknowledge the input of the ClinGen Complex Disease Working Group members, including
346 Carlos D. Bustamante, Michelle Meyer, Frank Harrell, David Kent, Peter Visscher, Tim Assimes, Sharon Plon,
347 and Jonathan Berg. We would also like to thank Diane Durham for her editorial support and Angela Paolucci
348 for her administrative support in the preparation and submission of this manuscript.

349

350 ClinGen is primarily funded by the National Human Genome Research Institute (NHGRI), through the following
351 three grants: U41HG006834, U41HG009649, U41HG009650. ClinGen also receives support for content
352 curation from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
353 through the following three grants: U24HD093483, U24HD093486, U24HD093487. The content is solely the
354 responsibility of the authors and does not necessarily represent the official views of the National Institutes of
355 Health. Additionally, the views expressed in this article are those of the author(s) and not necessarily those of
356 the NHS, the NIHR, or the Department of Health. Research reported in this publication was supported by the
357 National Human Genome Research Institute of the National Institutes of Health under Award Number
358 U41HG007823 (EBI-NHGRI GWAS Catalog, PGS Catalog). In addition, we acknowledge funding from the
359 European Molecular Biology Laboratory. Individuals were funded from the following sources: MIM was a
360 Wellcome Investigator and an NIHR Senior Investigator with funding from NIDDK (U01-DK105535); Wellcome
361 (090532, 098381, 106130, 203141, 212259). MI, SAL, and JD were supported by core funding from: the UK
362 Medical Research Council (MR/L003120/1), the British Heart Foundation (RG/13/13/30194; RG/18/13/33946)
363 and the National Institute for Health Research (Cambridge Biomedical Research Centre at the Cambridge
364 University Hospitals NHS Foundation Trust). SAL is supported by a Canadian Institutes of Health Research
365 postdoctoral fellowship (MFE-171279). JD holds a British Heart Foundation Personal Chair and a National
366 Institute for Health Research Senior Investigator Award. This work was also supported by Health Data
367 Research UK, which is funded by the UK Medical Research Council, Engineering and Physical Sciences
368 Research Council, Economic and Social Research Council, Department of Health and Social Care (England),
369 Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care
370 Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British
371 Heart Foundation and Wellcome.

372 Author Contributions

373 HW, CT, MAI, IJK, CS, RR, KV, KK, KABG, PK, and GLW conducted the literature review of reporting practices.
374 HW, SAL, CT, MIA, JWO, IJK, RR, DB, EV, MIM, ACA, DFE, RAH, AVK, NC, CK, KE, EMR, MCR, KEO, MJK,
375 ACJWJ, KABG, PK, JALM, MI, and GLW provided feedback on the reporting framework. HW, SAL, CT, MAI,
376 JWO, IJK, AVK, JND, HP, EMR, MR, ACJWJ, KABG, PK, JALM, MI, and GLW wrote and edited the manuscript

377 text and items.

378 Competing Interests

379 MIM is on the advisory panels Pfizer, Novo Nordisk, and Zoe Global; Honoraria: Merck, Pfizer, Novo Nordisk,
380 and Eli Lilly; Research funding: Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo
381 Nordisk, Pfizer, Roche, Sanofi Aventis, Servier & Takeda. As of June 2019, he is an employee of Genentech
382 with stock and stock options in Roche. No other authors have competing interests to declare.

383

384 Bibliography

- 385 1. Morales, J. *et al.* A standardized framework for representation of ancestry data in genomics studies, with
386 application to the NHGRI-EBI GWAS Catalog. *Genome Biol.* **19**, 21 (2018).
- 387 2. MacArthur, J. *et al.* The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS
388 Catalog). *Nucleic Acids Res.* **45**, D896–D901 (2017).
- 389 3. Claussnitzer, M. *et al.* A brief history of human disease genetics. *Nature* (2020).
- 390 4. Visscher, P. M., Brown, M. A., McCarthy, M. I. & Yang, J. Five years of GWAS discovery. *Am. J. Hum.*
391 *Genet.* **90**, 7–24 (2012).
- 392 5. Visscher, P. M. *et al.* 10 years of GWAS discovery: biology, function, and translation. *Am. J. Hum. Genet.*
393 **101**, 5–22 (2017).
- 394 6. Pasaniuc, B. & Price, A. L. Dissecting the genetics of complex traits using summary association statistics.
395 *Nat. Rev. Genet.* **18**, 117–127 (2017).
- 396 7. Lambert, S. A., Abraham, G. & Inouye, M. Towards clinical utility of polygenic risk scores. *Hum. Mol. Genet.*
397 **28**, R133–R142 (2019).
- 398 8. Torkamani, A., Wineinger, N. E. & Topol, E. J. The personal and clinical utility of polygenic risk scores.
399 *Nat. Rev. Genet.* **19**, 581–590 (2018).
- 400 9. Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat.*
401 *Genet.* **51**, 584–591 (2019).
- 402 10. Chatterjee, N., Shi, J. & García-Closas, M. Developing and evaluating polygenic risk prediction models for
403 stratified disease prevention. *Nat. Rev. Genet.* **17**, 392–406 (2016).
- 404 11. Wray, N. R., Yang, J., Goddard, M. E. & Visscher, P. M. The genetic interpretation of area under the ROC
405 curve in genomic profiling. *PLoS Genet.* **6**, e1000864 (2010).
- 406 12. Dudbridge, F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet.* **9**, e1003348 (2013).
- 407 13. Pharoah, P. D. P. *et al.* Polygenic susceptibility to breast cancer and implications for prevention. *Nat.*
408 *Genet.* **31**, 33–36 (2002).
- 409 14. Zhang, Y., Qi, G., Park, J.-H. & Chatterjee, N. Estimation of complex effect-size distributions using

- 410 summary-level statistics from genome-wide association studies across 32 complex traits. *Nat. Genet.* **50**,
411 1318–1326 (2018).
- 412 15. Chatterjee, N. *et al.* Projecting the performance of risk prediction based on polygenic analyses of genome-
413 wide association studies. *Nat. Genet.* **45**, 400–5, 405e1 (2013).
- 414 16. Mak, T. S. H., Porsch, R. M., Choi, S. W., Zhou, X. & Sham, P. C. Polygenic scores via penalized
415 regression on summary statistics. *Genet. Epidemiol.* **41**, 469–480 (2017).
- 416 17. Choi, S. W. & O'Reilly, P. F. PRSice-2: Polygenic Risk Score software for biobank-scale data. *Gigascience*
417 **8**, (2019).
- 418 18. Vilhjálmsson, B. J. *et al.* Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am.*
419 *J. Hum. Genet.* **97**, 576–592 (2015).
- 420 19. Wilkinson, M. D. *et al.* The FAIR Guiding Principles for scientific data management and stewardship. *Sci.*
421 *Data* **3**, 160018 (2016).
- 422 20. Huo, D. *et al.* Comparison of breast cancer molecular features and survival by african and european
423 ancestry in the cancer genome atlas. *JAMA Oncol.* **3**, 1654–1662 (2017).
- 424 21. Choi, J. *et al.* The associations between immunity-related genes and breast cancer prognosis in Korean
425 women. *PLoS One* **9**, e103593 (2014).
- 426 22. Marston, N. A. *et al.* Predicting benefit from evolocumab therapy in patients with atherosclerotic disease
427 using a genetic risk score: results from the FOURIER trial. *Circulation* **141**, 616–623 (2020).
- 428 23. Ganguly, P. & National Human Genome Research Institute. NIH funds centers to improve the role of
429 genomics in assessing and managing disease risk. (2020). at <[https://www.genome.gov/news/news-](https://www.genome.gov/news/news-release/NIH-funds-centers-to-improve-role-of-genomics-in-assessing-and-managing-disease-risk)
430 [release/NIH-funds-centers-to-improve-role-of-genomics-in-assessing-and-managing-disease-risk](https://www.genome.gov/news/news-release/NIH-funds-centers-to-improve-role-of-genomics-in-assessing-and-managing-disease-risk)>
- 431 24. Nikpay, M. *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of
432 coronary artery disease. *Nat. Genet.* **47**, 1121–1130 (2015).
- 433 25. Khera, A. V. *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk
434 equivalent to monogenic mutations. *Nat. Genet.* **50**, 1219–1224 (2018).
- 435 26. Mars, N. *et al.* Polygenic and clinical risk scores and their impact on age at onset and prediction of
436 cardiometabolic diseases and common cancers. *Nat. Med.* **26**, 549–557 (2020).
- 437 27. Elliott, J. *et al.* Predictive Accuracy of a Polygenic Risk Score-Enhanced Prediction Model vs a Clinical
438 Risk Score for Coronary Artery Disease. *JAMA* **323**, 636–645 (2020).
- 439 28. Inouye, M. *et al.* Genomic risk prediction of coronary artery disease in 480,000 adults: implications for
440 primary prevention. *J. Am. Coll. Cardiol.* **72**, 1883–1893 (2018).
- 441 29. Abraham, G. *et al.* Genomic prediction of coronary heart disease. *Eur. Heart J.* **37**, 3267–3278 (2016).
- 442 30. Ganna, A. *et al.* Multilocus genetic risk scores for coronary heart disease prediction. *Arterioscler. Thromb.*
443 *Vasc. Biol.* **33**, 2267–2272 (2013).
- 444 31. Kullo, I. J. *et al.* Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates: Effect
445 on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial). *Circulation* **133**, 1181–1188
446 (2016).

- 447 32. U.S. National Library of Medicine. Home - ClinicalTrials.gov. at <<https://clinicaltrials.gov/>>
- 448 33. Mavaddat, N. *et al.* Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am.*
449 *J. Hum. Genet.* **104**, 21–34 (2019).
- 450 34. Zhang, H. *et al.* Genome-wide association study identifies 32 novel breast cancer susceptibility loci from
451 overall and subtype-specific analyses. *Nat. Genet.* **52**, 572–581 (2020).
- 452 35. Zhang, X. *et al.* Addition of a polygenic risk score, mammographic density, and endogenous hormones to
453 existing breast cancer risk prediction models: A nested case-control study. *PLoS Med.* **15**, e1002644
454 (2018).
- 455 36. Lakeman, I. M. M. *et al.* Addition of a 161-SNP polygenic risk score to family history-based risk prediction:
456 impact on clinical management in non-BRCA1/2 breast cancer families. *J. Med. Genet.* **56**, 581–589
457 (2019).
- 458 37. Wilcox, A. N. *et al.* Prospective Evaluation of a Breast Cancer Risk Model Integrating Classical Risk
459 Factors and Polygenic Risk in 15 Cohorts from Six Countries. *medRxiv* (2019). doi:10.1101/19011171
- 460 38. Pal Choudhury, P. *et al.* Comparative validation of the BOADICEA and Tyrer-Cuzick breast cancer risk
461 models incorporating classical risk factors and polygenic risk in a population-based prospective cohort.
462 *medRxiv* (2020). doi:10.1101/2020.04.27.20081265
- 463 39. Maas, P. *et al.* Breast cancer risk from modifiable and nonmodifiable risk factors among white women in
464 the united states. *JAMA Oncol.* **2**, 1295–1302 (2016).
- 465 40. Lee, A. *et al.* BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and
466 nongenetic risk factors. *Genet. Med.* **21**, 1708–1718 (2019).
- 467 41. Garcia-Closas, M., Gunsoy, N. B. & Chatterjee, N. Combined associations of genetic and environmental
468 risk factors: implications for prevention of breast cancer. *J. Natl. Cancer Inst.* **106**, (2014).
- 469 42. Kapoor, P. M. *et al.* Combined associations of a polygenic risk score and classical risk factors with breast
470 cancer risk. *J. Natl. Cancer Inst.* (2020). doi:10.1093/jnci/djaa056
- 471 43. Easton, D. F. *et al.* Gene-panel sequencing and the prediction of breast-cancer risk. *N. Engl. J. Med.* **372**,
472 2243–2257 (2015).
- 473 44. Muranen, T. A. *et al.* Genetic modifiers of CHEK2*1100delC-associated breast cancer risk. *Genet. Med.*
474 **19**, 599–603 (2017).
- 475 45. Kuchenbaecker, K. B. *et al.* Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction
476 in BRCA1 and BRCA2 mutation carriers. *J. Natl. Cancer Inst.* **109**, (2017).
- 477 46. Mars, N. *et al.* Polygenic risk, susceptibility genes, and breast cancer over the life course. *medRxiv* (2020).
478 doi:10.1101/2020.04.17.20069229
- 479 47. Fahed, A. C. *et al.* Polygenic background modifies penetrance of monogenic variants conferring risk for
480 coronary artery disease, breast cancer, or colorectal cancer. *medRxiv* (2019). doi:10.1101/19013086
- 481 48. Barnes, D. R. *et al.* Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of
482 BRCA1 and BRCA2 pathogenic variants. *Genet. Med.* (2020). doi:10.1038/s41436-020-0862-x
- 483 49. van den Broek, J. J. *et al.* Personalizing breast cancer screening based on polygenic risk and family history.

- 484 *J. Natl. Cancer Inst.* (2020). doi:10.1093/jnci/djaa127
- 485 50. Esserman, L. J. & WISDOM Study and Athena Investigators. The WISDOM Study: breaking the deadlock
486 in the breast cancer screening debate. *NPJ Breast Cancer* **3**, 34 (2017).
- 487 51. Martens, F. K., Tonk, E. C. M. & Janssens, A. C. J. W. Evaluation of polygenic risk models using multiple
488 performance measures: a critical assessment of discordant results. *Genet. Med.* **21**, 391–397 (2019).
- 489 52. Janssens, A. C. J. W. Validity of polygenic risk scores: are we measuring what we think we are? *Hum.*
490 *Mol. Genet.* **28**, R143–R150 (2019).
- 491 53. Warriar, V. *et al.* Polygenic scores for intelligence, educational attainment and schizophrenia are
492 differentially associated with core autism features, IQ, and adaptive behaviour in autistic individuals.
493 *medRxiv* (2020). doi:10.1101/2020.07.21.20159228
- 494 54. Matoba, N., Love, M. I. & Stein, J. L. Evaluating brain structure traits as endophenotypes using polygenicity
495 and discoverability. *BioRxiv* (2020). doi:10.1101/2020.07.17.208843
- 496 55. Coleman, J. R. I. *et al.* Genome-wide gene-environment analyses of major depressive disorder and
497 reported lifetime traumatic experiences in UK Biobank. *Mol. Psychiatry* **25**, 1430–1446 (2020).
- 498 56. Kraft, P. & Aschard, H. Finding the missing gene-environment interactions. *Eur J Epidemiol* **30**, 353–355
499 (2015).
- 500 57. Janssens, A. C. J. W. *et al.* Strengthening the reporting of genetic risk prediction studies (GRIPS):
501 explanation and elaboration. *Eur. J. Hum. Genet.* **19**, 18 p preceding 494 (2011).
- 502 58. von Elm, E. *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)
503 statement: guidelines for reporting observational studies. *BMJ* **335**, 806–808 (2007).
- 504 59. Little, J. *et al.* STrengthening the REporting of Genetic Association Studies (STREGA): an extension of
505 the STROBE statement. *PLoS Med.* **6**, e22 (2009).
- 506 60. Moons, K. G. M. *et al.* Transparent Reporting of a multivariable prediction model for Individual Prognosis
507 or Diagnosis (TRIPOD): explanation and elaboration. *Ann. Intern. Med.* **162**, W1-73 (2015).
- 508 61. Choi, S. W., Mak, T. S.-H. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk score analyses.
509 *Nat. Protoc.* **15**, 2759–2772 (2020).
- 510 62. Wojcik, G. L. *et al.* Genetic analyses of diverse populations improves discovery for complex traits. *Nature*
511 **570**, 514–518 (2019).
- 512 63. Buniello, A. *et al.* The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted
513 arrays and summary statistics 2019. *Nucleic Acids Res.* **47**, D1005–D1012 (2019).
- 514 64. Lambert, S. A. *et al.* The Polygenic Score Catalog: an open database for reproducibility and systematic
515 evaluation. *medRxiv* (2020). doi:10.1101/2020.05.20.20108217
- 516 65. Thelwall, M. *et al.* Is useful research data usually shared? An investigation of genome-wide association
517 study summary statistics. *PLoS One* **15**, e0229578 (2020).
- 518 66. Burke, W. & Zimmern, R. *Moving Beyond ACCE: An Expanded Framework for Genetic Test Evaluation.*
519 (PHG Foundation, 2007).

Table 1. Polygenic Risk Score Reporting Statement (PRS-RS)

| Reporting Standard | | Description |
|--|---|---|
| Background | Study Type | Specify whether the study aims to develop and/or validate a PRS. When externally validating or combining previously published PRS or integrated risk model, include identifier(s) of original PRS (PMID, PGS Catalog ID). |
| | Risk Model Purpose & Predicted End Outcome | Specify what the risk model is intended to predict and the purpose: <ul style="list-style-type: none"> • Will it be used in risk prediction, diagnostic, prognostic, or therapeutic modalities? • What is the end outcome predicted by the risk model? If the predicted outcome is a clinical feature or endpoint within a specific disease, state the disease. • What current models for risk prediction are available, if pertinent? |
| Study Population and Data <i>Many risk score studies involve multiple populations and cohorts that can be used in different stages of PRS and risk score development and evaluation. Each of the populations used (e.g. training, validation, subgroup analysis samples) in the manuscript should be defined using this common set of descriptors.</i> | Study Design & Recruitment | For each of the data sets describe the study design (e.g., cohort, case-control, cross-sectional), eligibility criteria, recruitment period and setting (e.g. method and years), and follow-up. State whether the data are primary or secondary data. If secondary analysis, include the full reference to the original study. |
| | Participant Demographic and Clinical Characteristics | Include the distribution of demographic information in each data set (and the combined total if relevant) used to generate a single risk model (whether a single sample set, or the summary of combined samples) including the mean, standard deviation and range. This should at minimum include age, sex and any other characteristics relevant to describe the study population or the performance of the model. Provide demographics stratified by case/control status, if applicable. |
| | Ancestry | Include the ancestral background distribution of each sample population used during PRS development and validation, and the data source of this ancestry information (e.g., self-report, genotyping). Ancestry information should be reported using the standardized framework developed by the NHGRI-EBI GWAS Catalog and ideally include detailed information beyond this when available. When combining samples from multiple studies, aggregate ancestral distribution information is sufficient. The method of ancestry inference should be provided. Genomic methods are preferred, such as principal component analysis. |
| | Genetic Data | Provide method for acquiring genetic information (e.g. sequencing, genotyping) in each sample, including information about genome build and technical details of the assay. If imputing, specify the imputation panel and give ancestry information if not a standard imputation panel. Report any relevant quality control, including imputation quality filters to exclude low quality imputed SNPs. If parameters were selected from another study, include reference (PMID, GWAS Catalog ID). |
| | Non-Genetic Variables | Define any non-genetic variables that were included in the risk model, provide variable definitions and measurement (e.g., assay, ICD codes, e-phenotyping algorithms, chart review, self-report). Indicate the scale of each variable, e.g. dichotomous, continuous, categorical, or ordinal. Explicitly state which variables are included in the final model. |
| | Outcome of Interest | Define the predicted outcome of interest. If the predicted outcome is a clinical feature or endpoint within a specific disease, provide the criteria used to define that disease membership. Include details on how information was ascertained (e.g., ICD codes, e-phenotyping algorithms, chart review, self-report). Transformation of continuous data into binary, ordinal, or categorical outcomes should be detailed with justification. Authors should explicitly state the number of cases and controls. |
| | Missing Data | State explicitly how missing data were handled for all variables included in the model. If imputation was utilized, include detailed of the approach used and any subsequent filtering or post-processing. |
| Risk Model Development & Application <i>Describe the relevant methods used to form the final PRS and/or risk model. Samples used in</i> | Polygenic Risk Score Construction & Estimation | Describe how genetic data were included in the PRS. Authors should detail criteria used to determine inclusion in the model for all variants. Define how the variants were selected, weighted and combined into a single score. If the PRS was derived from another study include the reference (PMID, PGS Catalog Score ID). |
| | Risk Model Type | Detail statistical methods used to estimate risk, either relative or absolute, from the continuous risk score distribution. Detail if risk is cumulative or cross-sectional, as well as the appropriate comparison groups if relative risk presented. Report time until predicted risk (e.g. 5-year, 10-year, lifetime). In a relative hazard model, the study period or follow up |

| | | |
|---|--|--|
| <p><i>this stage of the analysis should be referred to as "Score Development" or "Training" samples, and be described according to the items in the <u>Study Populations</u> section.</i></p> | | time may be used. In an absolute risk model, state the time until predicted event and the prevalence/incidence of the predicted outcome in the general population. |
| | <p>Integrated Risk Model(s) Description and Fitting</p> | State the procedure utilized to develop the risk models that includes non-genetic and/or genetic variables other than the PRS. If the model(s) was selected for optimal performance, describe measures used to assess performance. Explicitly state all variables used in each risk model. |
| <p>Risk Model Evaluation <i>Outline the results and procedures utilized to evaluate the risk model, specifying internal or external validation. Performance results should be described for both the development and validation samples. Specify if the application of the risk model differs between the development and validation samples.</i></p> | <p>PRS Distribution</p> | Include a general description of the distribution of the PRS. This details the continuous distribution output directly from the risk score calculation. |
| | <p>Risk Model Predictive Ability</p> | Describe and report any metrics of overall performance (proportion of variance explained; R^2) and estimates of risk (such as odds or hazards ratios from regression models) used to evaluate the PRS and/or risk models. Describe the set of genetic/non-genetic variables included in the analysis. |
| | <p>Risk Model Discrimination</p> | Describe and report metrics used to assess the discrimination of evaluated risk models and whether any non-genetic variables were included beyond a PRS in this analysis. Common metrics include the area under the ROC or Precision-Recall (AUROC/AUPRC) and the Concordance statistic (C-index) for survival models. Evaluation of potential clinical utility of models requires also evaluating tail-based measures, such as proportions of populations and cases exceeding specified clinically relevant risk thresholds and measures of reclassifications (e.g. NRI) at such thresholds for comparison of models. |
| | <p>Risk Model Calibration</p> | Describe and report metrics used to assess the calibration of evaluated risk scores and models. Describe the set of genetic/non-genetic variables included in the analysis. |
| | <p>Subgroup Analyses</p> | Subgroup size, demographics and clinical characteristics should be given. Relevant evaluation methods and measures (distribution, predictive ability, discrimination, calibration) should be described for each subgroup analysis. |
| <p>Limitations and Clinical Implications <i>Discuss the broader context of the study and risk model.</i></p> | <p>Risk Model Interpretation</p> | Summarize the risk models in terms of what they predict, how well, and in whom. Explicitly mention the performance of the PRS and/or combined risk model in comparison to conventional risk models. Conventional risk models might include demographic (age, sex), disease-specific risk factors, and/or family history of disease. |
| | <p>Limitations</p> | Outline limitations of the study with relevance to the results, discuss the impact of these limitations on the interpretation of the risk model and any downstream replication efforts needed. Common considerations include: study design restrictions, use of a surrogate outcome, ascertainment biases, the distribution of participant-level traits (ancestry, age, comorbidities), accuracy/specificity of outcome data, and any statistical considerations. Make note of and discuss the impact of any unknown reporting items from previous sections. |
| | <p>Generalizability</p> | Discuss the intended target groups or populations this score may be applied to and explicitly address any issues with generalizability beyond the included populations. Discuss whether the study externally validates the score and/or model, or if the sample is limited with respect to ancestry, age, or other variables. |
| | <p>Risk Model Intended Uses</p> | Discuss whether there is an intended clinical use or utility to the risk model. If so, discuss the "clinic readiness" and next steps with respect to the interpretation, limitations, and generalizability of the model. Discuss how the predictive ability of the model is compared against current standard of care or other published work (such as existing PRS) on predicting the outcome of interest. |
| <p>Data Transparency and Availability</p> | | Information sufficient to calculate the PRS and the risk model(s) on external samples should be made freely available. For genetic variables this would include information about the variants (e.g., rsID, chromosomal location, effect allele, and the effect weight) that comprise the score; PRS with this information should be deposited in the PGS Catalog for findability and to promote re-use and comparison with other established scores. Weights for non-genetic variables should also be provided to make the risk model calculable. |

Further reporting considerations can be found in **Supplemental Note 3**. A reference of relevant manuscript sections for each item is provided in **Supplemental Table 4**.