Improving reporting standards for polygenic scores in risk prediction studies

Polygenic risk scores (PRSs), which often aggregate results from genome-wide association studies, can bridge the gap between initial discovery efforts and clinical applications for the estimation of disease risk using genetics. However, there is notable heterogeneity in the application and reporting of these risk scores, which hinders the translation of PRSs into clinical care. Here, in a collaboration between the Clinical Genome Resource (ClinGen) Complex Disease Working Group and the Polygenic Score (PGS) Catalog, we present the Polygenic Risk Score Reporting Standards (PRS-RS), in which we update the Genetic Risk Prediction Studies (GRIPS) Statement to reflect the present state of the field. Drawing on the input of experts in epidemiology, statistics, disease-specific applications, implementation and policy, this comprehensive reporting framework defines the minimal information that is needed to interpret and evaluate PRSs, especially with respect to downstream clinical applications. Items span detailed descriptions of study populations, statistical methods for the development and validation of PRSs and considerations for the potential limitations of these scores. In addition, we emphasize the need for data availability and transparency, and we encourage researchers to deposit and share PRSs through the PGS Catalog to facilitate reproducibility and comparative benchmarking. By providing these criteria in a structured format that builds on existing standards and ontologies, the use of this framework in publishing PRSs will facilitate translation into clinical care and progress towards defining best practice.
Box 1

Definitions of relevant genetic risk prediction terms

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

Integrated risk model. a risk model for the outcome of interest which combines PRS with other risk factors, such as demographics (often age and sex), anthropometrics, biomarkers, and clinical measurements.

Categories of use for PRS and/or integrated risk models

The addition of PRSs to existing risk models has several potential applications, summarized below. Each aims to improve individual or subgroup classification such that there is clinical benefit.

- Disease risk prediction — estimate an individual's risk of developing a disease, on the basis of certain genetic and/or clinical variables.
- Disease diagnosis — classify whether an individual has a disease, or a disease subtype, on the basis of certain genetic and/or clinical variables
- Disease prognosis — estimate the risk of further adverse outcome(s) subsequent to the diagnosis of disease
- Therapeutic — predict the response of a patient or subgroup to a particular treatment

Box 2

Current CHD PRSs and their potential uses

Many PRSs have been developed for CHD, which vary in the computational methods used, number of variants included (50–6,000,000) and cohorts used for PRS training. For example, many of the latest CHD PRSs use GWAS summary statistics from the CardiogramPlusC4D study26, and differ by the method of selecting and weighting individual variants (including LDpred41,42, lassosum43 and meta-scoring approaches44) and how they are used in an integrated risk model. These PRSs may provide useful information for predicting the risk of CHD that is largely orthogonal to conventional risk factors (age, sex, hypertension, cholesterol, BMI, diabetes and smoking) as well as family history. Clinical applications may include:

- Improved risk prediction for future adverse cardiovascular events when added to conventional risk models (such as the Framingham risk score35, pooled cohort equations36,44 and QRISK45).
- Reclassification of risk categories often leading to recommendations for risk-reducing treatments like statins46–48.

Although the data for these clinical applications strongly suggest CHD PRSs may improve patient outcomes, clinical use through randomized clinical trials has yet to be established; however, a number of clinical trials are underway (https://clinicaltrials.gov).

The capacity of PRSs to quantify genetic predisposition for many clinically relevant traits and diseases has begun to be established, with many potential clinical uses in settings related to disease risk stratification as well as proposed prognostic uses (for example, predicting responses to intervention or treatment). Readiness for implementation varies by outcome, and mature PRSs with potential clinical utility are available for only a few diseases—for example, coronary heart disease (CHD) and breast cancer (Boxes 2 and 3, respectively). There has also been a rapid rise of direct-to-consumer assays and for-profit companies (23andMe, Color, MyHeritage, and so on) that provide PGS and PRS results to customers outside of the traditional patient–provider framework. These concomitant developments have resulted in both methodological development and applications of PRSs that further compound the heterogeneity in reporting; for example, using PRSs as tools for testing gene–environment interactions or shared aetiology between diseases23–26. The rapid evolution in both methodological development and applications of PRSs make it challenging to compare or reproduce claims about the predictive performance of a PRS for a specific outcome when studies are not properly documented. These deficiencies are barriers to PRSs being interpreted, compared, and reproduced, and must be addressed to enable the application of PRSs to improve clinical practice and public health.

Frameworks have been developed to establish standards around the transparent, standardized, accurate, complete and meaningful reporting of scientific studies. In 2011, an international working group published the Genetic Risk Prediction Studies (GRIPS) Statement—a set of reporting guidelines for risk prediction models that include genetic variants, from genetic mutations to gene scores29. These guidelines are analogous to those developed for observational epidemiological studies (STROBE30) and genome-wide association studies (STREGA31), and are in line with the reporting guidelines for multivariate prediction models (TRIPOD32). Adherence to reporting statements has been low, and the same holds for GRIPS. One reason might be that researchers feel that the GRIPS Statement inadequately addresses PRSs. Researchers
**Box 3**

**Current breast cancer PRSs and their potential uses**

Many of the most recent and most predictive PRSs for breast cancer include a smaller number of variants (usually hundreds to thousands), possibly owing to a less polygenic architecture and more low-frequency variants having greater effect; however, scores composed of millions of variants also exist. PRS construction typically includes GWAS summary statistics and data from the Breast Cancer Association Consortium (BCAC), then variants passing genome-wide significance (lead SNPs), stepwise regression, penalized regression on individual-level genotypes, clumping and thresholding or Bayesian methods. In contrast to CHD, genetics is commonly used to measure breast cancer risk vis-à-vis testing for BRCA1 and BRCA2 mutations; however, routine screening for breast cancer is often performed in older women using non-genetic risk prediction tools, such as mammography. Research into PRSs for breast cancer includes multiple potential clinical uses and considerations:

- **Multiple PRSs exist to predict risk for subtypes of breast cancer** (for example, ER-positive or -negative, luminal, and triple-negative[48,59]), which could be used to stratify patients according to prognosis or for more beneficial treatments.
- **Integrated risk models which combine PRSs with non-genetic risk factors** (such as age, family history, mammographic density, hormone replacement therapy)[60,61].
- **PRSs can provide important stratification of risk among carriers of pathogenic variants in genes that are already screened in clinical practice** (for example, BRCA1, BRCA2, PALB2, CHEK2 and ATM)[69] and thus could improve clinical decision-making[42,48,50-52].

Indeed, the BOADICEA breast cancer risk prediction model includes the effects of common variants (PRS[31]; ref. 48) as well as other rare pathogenic genetic variants[52] and has been implemented in the CanRisk Tool (www.canrisk.org), which has been approved for use by healthcare professionals in the European Economic Area. The utility of PRSs has been studied in simulations[74] and is being evaluated in risk-based breast cancer screening trials in the US[60] and Europe (MyPeBS; https://mypebs.eu).

PRSs are frequently uncertain as to what precisely should be reported for a PRS study to be assessed as rigorous, reproducible and ultimately translatable, especially with the increased push for data availability and transparency. Most PRS studies follow a prototypical process (Fig. 1) that can be used as a template for standardizing reporting and benchmarking in the field.

Here, the Clinical Genome Resource (ClinGen) Complex Disease Working Group and the Polygenic Score (PGS) Catalog (Supplementary Note 1) jointly present the Polygenic Risk Score Reporting Standards (PRS-RS), an expanded and updated set of reporting standards for PRSs that addresses current research environments with advanced methodological developments to inform clinically meaningful reporting on the development and validation of PRSs in the literature, with an emphasis on reproducibility and transparency throughout the development process. Additional methods are detailed in Supplementary Note 2.

**The PRS-RS**

The PRS-RS is a set of standard items specifying the minimal criteria that need to be described in a manuscript to accurately interpret a PRS and reproduce results throughout the PRS development process[31] (see Fig. 1f for a brief summary). It applies to PRS development and validation studies that aim to predict disease onset, diagnosis and prognosis, as well as response to therapies; however, other research uses of PRSs have overlapping steps that should be reported in a similar manner. Table 1 presents the full PRS-RS, with reporting items organized into key components along the developmental pipeline of PRSs for clear interpretation and to encourage their documentation from the inception of the study, well before publication.

**Reporting on the background of risk scores**

The development and validation of a PRS tests a specific hypothesis with a defined outcome and study population. Therefore, authors should define a priori (note that in the next few sections, inverted commas are used to refer to each of the Reporting Standards referred to in Table 1) the ‘study type’ (for example, development and/or validation), ‘risk model purpose’ (for example, risk prediction versus prognosis) and ‘predicted outcome’ (for example, CHD) in enough detail to understand why the study population and risk model selected are relevant (for example, the value for CHD risk stratification and primary prevention is highest in younger individuals compared to those over 80 with lifetime accumulated risk). As the PRS-RS is focused on clinical validity and implementation, authors must outline the study and appropriate outcomes to understand what risk is measured, what the purpose of measuring risk would be and why this purpose may be of clinical relevance. To establish the internal validity of a study, authors should use the appropriate data for the intended purpose (for example, prediction of incident disease versus prognosis), with adequate documentation of dataset characteristics to understand nuances in measured risk.

**Reporting on study populations**

The applicability of any risk prediction to an external target population (the who, where, and when) depends on its similarity to the original study populations that were used to derive the risk model. Therefore, authors need to define and characterize the details of their study population (‘study design and recruitment’), and describe study ‘participant demographics’ for key variables (most often age and sex) and ancestry. Notably, there are often inconsistent definitions and levels of detail associated with ancestry, and the transferability of genetic findings between different racial and ethnic groups can be limited[18-20].

It is therefore essential for authors to provide a detailed description of the genetic ‘ancestry’ of participants—including how ancestry was determined—using a common controlled vocabulary where possible (for example, the standardized framework developed by the NHGRI-EBI GWAS Catalog[7]). Authors should provide a sufficient level of detailed criteria for defining all of the factors relevant to the ‘outcome of interest’, including but not limited to those used in the risk model (‘non-genetic variables’). These details should accompany information about how the population was genotyped (‘genetic data’), including assays and all quality control measures.

**Reporting on the development of risk models**

At present there are several commonly used methods to select variants that constitute the PRS and fine-tune their weights[7,18-31]. Methods using GWAS summary statistics should clearly cite the relevant GWAS, preferably using unique and persistent study identifiers from the GWAS Catalog (GCSTs)[31]. As the performance and limitations of the combined risk model are dependent on methodological considerations, authors must provide complete details including the method used and how variants are combined into a single PRS (‘PRS construction and estimation’). Apart from genetic data, authors should also describe the defining criteria for other demographic and non-genetic predictors (‘non-genetic variables’) included in the model. Often authors will iterate through numerous models to find the optimal fit. In addition to the estimation methods, it is important to detail the ‘integrated risk model(s) fitting’
Table 1 | Polygenic Risk Score Reporting Standards (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 PRSs or integrated risk models, include identifier(s) of original PRS (PMID, PGS Catalog ID). |
| **Risk model purpose and predicted outcome** | Specify what the risk model is intended to predict and the purpose. This includes intended use (risk prediction, diagnostic, prognostic, or therapeutic modalities), predicted outcome (if a clinical feature or endpoint within a specific disease) and the current models available for that outcome. |
| **Study population and data** 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 (for example, training, validation and subgroup analysis samples) in the manuscript should be defined using this common set of descriptors. | **Study design and recruitment** For each of the datasets describe the study design (for example, cohort, case–control, cross-sectional), eligibility criteria, recruitment period and setting (for example, 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 demographics and clinical characteristics** | Include the distribution of demographic information in each dataset (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 (including those from any GWAS summary statistics that were included), and the data source of this ancestry information (for example, self-report, genotyping). Ancestry information should be reported using the standardized framework developed by the NHGRI-EBI GWAS Catalog with 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. |
| **Genetic data** | Provide the method for acquiring genetic information (for example, sequencing, genotyping) in each sample, including information about genome build and technical assay details. If imputed, specify the imputation panel and give ancestry information. 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 (for example, assay, ICD codes, e-phenotyping algorithms, chart review, self-report). Indicate the scale of each variable, for example, dichotomous, continuous, categorical or ordinal. Explicitly state which variables are included in the final model. |
| **Outcome of interest** | Define the predicted outcome(s) of interest and report distribution. If the predicted outcome is a clinical feature or end-point within a specific disease, provide the criteria used to define that disease membership. Include details on how information was ascertained (for example, ICD codes, e-phenotyping algorithms, chart review, self-report). Transformation of continuous data into binary, ordinal, or categorical outcomes should be detailed with justification. State whether the predicted phenotype of the polygenic score is the same as or different from the predicted outcome of the risk model. Provide justification for differences, if applicable. |
| **Missing data** | State explicitly how missing data were handled for all variables included in the model. If imputation was used, include detailed of the approach used and any subsequent filtering or post-processing. |
| **Risk model development and application** | **PRS construction and 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 whether risk is cumulative or cross-sectional, with appropriate comparison groups if relative risk is presented. Report time until predicted risk (for example, 5 years, 10 years, lifetime). In an absolute risk model, state the time until the predicted event and the prevalence or incidence of the predicted outcome in the general population. |
| **Integrated risk model(s) description and fitting** | State the procedure used 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. |

Continued
| Reporting standard                  | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Risk model evaluation**          | Outline results and procedures used to evaluate the risk model, specifying internal or external validation. Performance results should be described for both development and validation samples. Specify if the application of the risk model differs between the development and the validation samples.                                                                                              |
| **PRS distribution**               | Include a general description of the distribution of the PRS. This details the continuous distribution output directly from the risk score calculation.                                                                                                                                                                                                                                                                                       |
| **Risk model predictive ability**  | Describe and report 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 and non-genetic variables included in the analysis.                                                                                                      |
| **Risk model discrimination**      | Describe and report metrics (such as AUROC, AUPRC, and—for survival models—the C-index) used to assess the discrimination of evaluated risk models and whether any non-genetic variables were included beyond a PRS in this analysis. Evaluation of the potential clinical utility of models requires evaluating tail-based measures, such as proportions of populations and cases that exceed specified clinically relevant thresholds and measures of reclassifications (for example, NRI) at such thresholds for comparison of models. |
| **Risk model calibration**         | Describe and report metrics used to assess the calibration of evaluated risk scores and models. Describe the set of genetic and non-genetic variables included in the analysis.                                                                                                                                                                                                                                         |
| **Subgroup analyses**              | Subgroup size, demographics and clinical characteristics should be given. Relevant evaluation methods and measures (distribution, predictive ability, discrimination and calibration) should be described for each subgroup analysis.                                                                                                                                                                      |
| **Limitations and clinical implications** | Discuss the broader context of the study and risk model.                                                                                                                                                                                                                                                                                                                                                                                                                               |
| **Risk model interpretation**      | Summarize the risk models in terms of what they predict, how well and in whom. Explicitly mention the incremental performance of the PRS and/or combined risk model in comparison to conventional risk models, as well as the performance of the PRS and risk model alone. Conventional risk models might include demographic (age, sex), disease-specific risk factors and/or family history of disease. |
| **Limitations**                    | Outline limitations of the study with relevance to the results, discuss the effects 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 or specificity of outcome data, and any statistical considerations. Note and discuss the effects of any unknown reporting items from previous sections. |
| **Generalizability**               | 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.                                                                                   |
| **Risk model intended uses**       | 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 compares with current standards of care or other published work (such as existing PRSs) on predicting the outcome of interest.                                           |
| **Data transparency and availability** | 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 (for example, rsID, chromosomal location, effect allele and the effect weight) that comprise the score; PRSs with this information should be deposited in the PGS Catalog for findability and to promote reuse and comparison with other established scores. Weights for non-genetic variables should also be provided to make the risk model calculable. |

Further reporting considerations beyond the minimal reporting for PRS-RS items can be found in Supplementary Note 3. A reference of relevant manuscript sections for each item is provided in Supplementary Table 4. ICD, International Classification of Diseases; PMID, PubMed ID; rsID, reference SNP cluster ID; SNP, single-nucleotide polymorphism.

procedure, including the measures that were used for the selection of the final model. Translating the continuous PRS distribution to a risk estimate, whether absolute or relative, is highly dependent on assumptions and limitations that are inherent to the specific dataset used. When describing the ‘risk model type’, authors should detail the timescale used for prediction, or the study period and follow-up time for a relative hazard model. Furthermore, if relative risk is estimated, the reference group should be well described. These details should be described for the training set, as well as for validation and sub-group analyses.

**Reporting on the evaluation of risk models**
Authors should report estimates for all evaluated models (including the methods used to derive them) to equip readers with the information necessary to evaluate the relative value of an increase in performance against other trade-offs. We recommend that authors provide summary information of the ‘PRS distribution’ to aid in model interpretation. The ‘predictive ability’, ‘calibration’, and ‘discrimination’ of the risk model should also be assessed and detailed with common descriptions including the risk score effect size, variance explained ($R^2$), reclassification indices and metrics like sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The risk model ‘calibration’ and ‘discrimination’ should be described for all analyses, although their estimation and interpretation are most relevant for the PRS validation sample. It is imperative for the PRS and integrated risk models to be evaluated on a population that is external (independent, non-overlapping) to the individuals in the study population. The ability
of the risk model to classify individuals of interest (‘risk model discrimination’) is commonly described and presented in terms of the area under the receiver operating characteristic (AUROC) or precision-recall curve (AUPRC), or the concordance statistic (C-index). Any differences in variable definitions or performance discrepancies between the training and validation sets should be described.

**Reporting on interpretation**

By explicitly describing the ‘risk model interpretation’ and outlining potential ‘limitations’ to the ‘generalizability’ of their model, authors will empower readers and the wider community to better understand the risk score and its relative merits. Authors should justify the clinical relevance and the ‘intended uses’ of the risk model, such as how the performance of their PRS compares to other commonly used risk models, or previously published PRSs. This may also include comparisons to other genetic predictors of disease (for example, mutations in high or moderate risk genes associated with Mendelian forms of the disease), family history, simple demographic models or conventional risk calculators (see Boxes 2 and 3 for disease-specific examples). What indicates a ‘good’ prediction can differ between outcomes and intended uses, but should be reported with similar metrics to those described in the evaluation section.

**Reporting on model parameters**

The underlying PRS (variant alleles and derived weights) should be made publicly available, preferably through direct submission to an indexed repository such as the PGS Catalog, to enable others to reuse existing models (with known validity) and to facilitate direct benchmarking between different PRSs for the same trait (thus promoting ‘data transparency and availability’). The current mathematical form of most PRSs—a linear combination of allele counts—facilitates clear model description and reproducibility. Future genomic risk models may have more complex forms; for example, allowing for explicit non-linear epistatic and gene–environment interactions, or deep neural networks of lesser clarity. It will be important to describe these models in sufficient detail to allow their implementation and evaluation by other researchers and clinical groups.

Supplementary Note 3 provides explanations of reporting considerations in addition to the minimal reporting framework in Table 1. Authors intending downstream clinical implementation should aim for the level of transparent and comprehensive reporting covered in both Table 1 and Fig. 1 | Prototype of PRS development and validation process. The prototypical steps for PRS construction, risk model development and validation of performance are displayed with select aspects of the PRS-RS guidelines (labelled in bold). During PRS development, variants associated with an outcome of interest, typically identified from a GWAS, are combined as a weighted sum of allele counts. Methods for optimizing variant selection (PRS construction and estimation) are not shown. To predict the outcome of interest the PRS is added to a risk model and may be combined with non-genetic variables (for example, age, sex, ancestry or clinical variables; collectively referred to as risk model variables). After fitting procedures to select the best risk model, this model is validated in an independent sample. The PRS distribution should be described, and the performance of the risk model demonstrated in terms of its discrimination, predictive ability and calibration. Though not displayed in the figure, these same results should also be reported for the training sample for comparison to the validation sample. In both training and validation cohorts, the outcome of interest criteria, demographics, genotyping and non-genetic variables should be reported (Table 1) HLA, human leukocyte antigen; HR, hazard ratio; IDI, integrated discrimination improvement; IQR, interquartile range; NRI, net reclassification improvement; OR, odds ratio; β, effect estimate from linear regression.
Improving PRS research and translation

We surveyed 30 publications (selecting for a range of disease domains, risk score categories and populations) to understand how the information in the PRS-RS is presented and displayed as part of the larger iterative process to clarify and improve minimal reporting item descriptions. For 10 of these publications, we provide detailed annotations using the final minimal reporting requirements (Supplementary Table 3) and use these annotations to illustrate the detail necessary for each PRS-RS item (further described in Supplementary Note 3). The heterogeneity in the PRS reporting we observed in this pilot highlights a series of challenges. Critical aspects of PRS studies—including ancestry, predictive ability, and transparency or availability of information needed to reproduce PRSs—were frequently absent or reported in insufficient detail. This underscores the need for the PRS-RS to clearly and specifically define meaningful aspects of PRS development, testing and intended clinical use. However, these deficits in reporting are not unique to PRSs; previous reports of underreporting have found that 77% of GWAS publications in 2017 did not share summary statistics14 and 4% of GWASs do not report any relevant ancestry information1. In line with the push towards a culture of reproducibility and open data in genomics, we as the ClinGen Complex Disease Working Group and PGS Catalog joined to create this set of reporting standards (Table 1), which is specifically tailored to PRS research and adapts the previous standards on the basis of the opinions of multidisciplinary and international experts.

Researchers using the PRS-RS may identify fringe cases that are inadequately captured by these reporting items, as we have modelled our guidelines on prototypical steps for PRS development (Fig. 1). Although we anticipate that the field may change further as novel methods and technologies are generated, the PRS-RS items can be expanded and adapted to encompass new considerations. By updating previous standards, drawing on the knowledge of leaders in the field and tailoring the framework to common barriers observed in recent literature, we aim to provide a comprehensive and pragmatic perspective on the topic. In line with previous standards, the PRS-RS includes elements related to understanding the clinical validity of PRSS and consequent risk models. Items such as ‘predicted outcome’ and ‘intended use’ bookend our guidelines with the intended clinical framing of PRS reporting. In addition, we have modelled the guidelines by steps in experimental design—from hypothesis to interpretation—to more clearly emphasize the importance of considering the risk model’s intended purpose in defining what needs to be reported and to inform documentation throughout the process. As a reference, we have included a guide to where PRS-RS items should be reported in a manuscript in Supplementary Table 4. These expansions will further facilitate the curation and expert annotation of published PRSs as we move towards widespread clinical use.

Although the scope of our work encompasses clinical validity, it does not address the additional requirements that are needed to establish the clinical or public health utility of a PRS, such as randomized trials with clinically meaningful outcomes, health economic evaluations or feasibility studies34. In addition, the translation of structured data elements into useful clinical parameters may not be direct. One example is the case definitions used in training or validation in any particular PRS study may deviate (sometimes substantially) from those used in any specific health system. CHD symptoms commonly include angina (chest pain), whereas PRSs are frequently trained on stricter definitions excluding angina. Another example is that the definitions used for race or ancestry as outlined in the PGS Catalog and the GWAS Catalog may differ from structured terms used to document ancestry information in the clinic. Consistent mappings and potentially parallel analyses may be necessary to translate from genetically determined ancestries to those that are routinely used in clinical care. Such translation issues potentially limit generalizability to target populations and warrant further discussion, and we reiterate the need for authors to be mindful of their intended purpose and target audience when discussing their findings. Authors’ understanding of potential translational barriers can be aided by considering the current CAP and CLIA analytical and clinical validity evidence requirements of peer-reviewed literature to ensure that the PRS-RS has value in informing later steps of the clinical translation spectrum, including clinical utility (Supplementary Table 1). Finally, although the principles of this work are clear, its scope does not include the complex commercial restrictions—such as intellectual property—that may be placed on published studies with regard to the reporting or distribution of PGSS or the data that underlie them. We hope that our work will inform downstream regulation and transparency standards for PRSs as a commercial clinical tool.

The coordinated efforts of the ClinGen Complex Disease Working Group and PGS Catalog provide a set of compatible resources for researchers to deposit PGSS and PRS-related information. The PGS Catalog (www.PGSCatalog.org) provides an informatics platform, with data integration and harmonization to other PGSSs as well as the source GWAS study through its sister platform, the GWAS Catalog134. In addition, it provides a structured database of scores (variants and effect weights) that can be reused, along with metadata requested in the PRS-RS. With these tools, the PRS-RS can be mandated by leading peer-reviewed journals and, consequently, the quality and rigour of PRS research will be increased to a level that facilitates clinical implementation. We encourage readers to visit the ClinGen website (https://clinicalgenome.org/working-groups/complex-disease/) for any future changes or amendments to our reporting standards.

Although we have provided explicit recommendations on how to acknowledge study design limitations and their effects on the interpretation and generalizability of a PRS, future research should attempt to establish best practices to guide the field. Moving forward, supplementary frameworks should be developed for the reporting of new methods, such as deep learning, as well as requirements for clinical utility and readiness. Together, the PRS-RS enables the rapid development of PRSs as potentially powerful tools for the translation of genomic discoveries into clinical and public health benefits, and provides a framework for PRSS to transform multiple areas of research in human genetics.

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