Towards responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps

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Summary

Polygenic risk scores (PRS) aggregate the many small effects of alleles across the human genome to estimate the risk of a disease or disease-related trait for an individual. The potential benefits of PRS include cost-effective enhancement of primary disease prevention, more refined diagnoses and improved precision when prescribing medicines. However, these must be weighed against the potential risks, such as uncertainties and biases in PRS performance, as well as potential misunderstanding and misuse of these within medical practice and in wider society. By addressing key issues including gaps in best practices, risk communication and regulatory frameworks, PRS can be used responsibly to improve human health. Here, the International Common Disease Alliance's PRS Task Force, a multi-disciplinary group comprising expertise in genetics, law, ethics and more, highlights recent research to provide a comprehensive summary of the state of polygenic score research as well as the needs and challenges as PRS move closer to widespread use in the clinic.

Introduction

Polygenic risk scores (PRS) provide an estimate of an individual's germline genetic risk for a specific disease or trait, and recent studies have shown that they may have clinical utility in a variety of settings. While not diagnostic *per se,* PRS generally provide information that can be used to enhance or guide, but not replace, risk prediction models and diagnostic pathways. In essence, apart from being based on an individual's germline genome, a PRS may be treated as any other risk predictor. Because of recent advances in PRS research, it is timely to consider how to appropriately and responsibly use PRS in the clinic and in society.

The International Common Disease Alliance (ICDA) aims to improve prevention, diagnosis, and treatment of common diseases across the world, in part through understanding how genetics can be leveraged to improve health. There is a spectrum of potential benefits that the use of PRS could have in research, clinical care, clinical trial design, and public health. There are also known risks and limitations of PRS, and gaps in knowledge related to their use, highlighting the need for additional research and debate to ensure responsible use. To this end, the ICDA has established the PRS Task Force, which has initially focused on the potential use of PRS in clinical care and population health while also recognizing their potential utility to enhance efficacy of clinical trials.

The PRS Task Force interprets "responsible use" as use of a PRS where there are clear benefits that outweigh risks, and where effort is taken towards a goal of equitable benefit for all. The potential benefits and risks remain incompletely quantified at present but will vary by clinical context, healthcare system, and population. Ideally, all people have equal opportunity to benefit from PRS and it is important that researchers and healthcare professionals (HCPs) are supported to enable this. Equitable opportunity is not just about known issues for PRS development, e.g. PRS performance differences between ancestries, but also the real-world impact PRS will ultimately have, and on whom.

In working towards responsible use, a prerequisite is to understand the gaps in knowledge that prevent responsible use, as well as potential risks and benefits. Academic discourse can initiate the gathering of new evidence or development of best practices, which are needed to ensure responsible use. In this Perspective, we therefore outline the Task Force's understanding of the current state of knowledge regarding benefits, risks and gaps regarding PRS, and provide an overview of key objectives (**Table 1**) in order to maximize responsible use of PRS in clinical settings.

Benefits

PRS have the potential to enhance disease risk prediction[1] and diagnostic refinement; predict progression and recurrence of disease; deploy precision therapeutics; and improve the efficiency of population-level screening. Furthermore, a single genetic test per individual (~£25 or $35 for a genome-wide array with automated bioinformatics) provides raw genetic information that could be used to generate many polygenic risk scores (e.g. for heart disease, diabetes,

breast cancer, etc.) based on approaches that exist now, or that could be developed in the future from existing genetic data.

Disease risk prediction

PRS are constructed based on inherited genetic variation, which is set at conception, and can therefore be utilized earlier in life than many lifestyle, age-related and other non-genetic risk factors. PRS provide the opportunity to estimate risk trajectories across a lifetime, rather than for 5 or 10 years, as is the case for most clinical risk scores. Importantly, PRS often capture risk that is substantially independent from and thus complementary to traditional risk factors and clinical risk scores. Furthermore, elevated genetic risk can be associated with earlier onset of disease, even in the absence of traditional risk factors. Thus, PRS hold the potential to improve the accuracy of both early and targeted primary prevention, particularly for chronic diseases that develop over decades.

Multiple studies of coronary artery disease (CAD) show that disease prediction algorithms that jointly model the effects of clinical risk factors and PRS perform better than those of only clinical risk factors[2-6]. Thus, adding CAD PRS to existing screening protocols and prevention strategies may more accurately identify individuals at high risk of developing disease. Particularly for cardiovascular disease, PRS facilitate lifetime risk prediction beyond current 5-10 year risk models, which are typically optimized for middle-aged individuals.

There is also growing evidence that PRS substantially improve disease risk estimates in people who carry high-impact disease-causing genetic variants (e.g. for familial hypercholesterolemia (FH)[7] or breast cancer[8]). As such, an elevated PRS may augment the risk conferred by a high-impact mutation, or a protective PRS may compensate for the pathogenic mutation and bring the individual's risk closer to the population average[9]. However, it should be noted that providing PRS based on common variants but not considering or testing for rare high-impact variants may give a substantially incomplete risk estimate for individuals, especially those with a family history (e.g. breast cancer).

While most evidence suggests clinical utility may be maximal when PRS are combined with non-genetic risk factors, there is also evidence that PRS alone may have utility for those with extremely high polygenic scores. For example, persons in the top 8% of a CAD PRS distribution have risk comparable to those with a monogenic familial hypercholesterolemia mutation[10], whereas women in the top 10% of a breast cancer PRS distribution have a 30% lifetime breast cancer risk, comparable to those with pathogenic mutations in *CHEK2* and *ATM* genes[8]. Based on equivalent risk principles, it can be argued that an individual with a PRS-based risk similar to a monogenic risk should qualify for a similar level of preventative therapies.

The clinical benefit of utilizing PRS for disease risk prediction also depends on the availability of preventive interventions and/or medicines. For example, while CAD PRS improves risk stratification for future cardiovascular disease, individuals with high clinical risk factors and an elevated CAD PRS may derive more benefit (an increased reduction in risk) from statin

treatment than individuals at low polygenic risk[11,12]. Based on cross-sectional studies, a favorable lifestyle appears to compensate for the increased risk of a high CAD PRS[13]. Given that the practical implications for disease prevention will be disease specific, it is clear that further studies are warranted to elucidate the proper mode of prevention for each disease and any relevant subgroups.

Diagnostic refinement

PRS may improve diagnosis accuracy. For example, clinical differentiation between type 1 and type 2 diabetes (T1D and T2D) can be complex as the presenting symptoms are similar and laboratory results often overlap. Diagnostic accuracy is currently imperfect; improved diagnosis can influence treatment plans (e.g. whether insulin is prescribed) and improve outcomes (e.g. reduced risk of diabetic ketoacidosis)[14]. Further, recent evidence suggests that approximately 40% of individuals who develop T1D during their lifetime present with symptoms after the age of 30 years[15]. A PRS for differentiating T1D and T2D achieved reasonably high predictive capacity - while not a metric of clinical utility, the area under the receiver operator curve (AUROC; a composite of sensitivity and specificity with maximum value of 1.0) was 0.88. When integrated with other clinical risk factors, the resulting model achieved an improved AUROC of 0.96[16]. T1D PRS have shown further promise in prioritizing newborns for autoantibody screening[17] and as part of integrated models to predict disease prior to symptom onset, which may prevent T1D and complications throughout early childhood[18].

Diagnostic refinements using PRS have also been evaluated for other autoimmune diseases. A celiac disease PRS improves upon HLA typing alone[19-21] and pilot clinical studies indicate improved effectiveness and cost-efficiency for celiac diagnosis, potentially reducing invasive diagnostic procedures[22]. For juvenile idiopathic arthritis and its subtypes, PRS may substantially improve upon clinical diagnosis, potentially reducing long waiting periods[23]. Furthermore, a PRS for ankylosing spondylitis has been shown to have high diagnostic capacity (AUROCs of 0.92 and 0.94 in European and East Asian ancestries, respectively) and potential clinical utility for earlier and cost-effective diagnosis if combined with MRI imaging[24].

Disease progression and recurrence

Recent studies have assessed the potential clinical utility of PRS for slowing disease progression and recurrence, and reducing the need for deployment of new (sometimes costly) therapeutics. Amongst those with acute coronary syndrome, elevated lipids and optimized statin treatment, a high CAD PRS was associated with elevated risk for recurrent cardiovascular events as well as larger absolute and relative risk reduction with recently-developed PCSK9 inhibitors[25,26]. Similarly, a high T2D PRS has been associated with earlier disease onset, increased risk of progression to an insulin-dependent stage and a low response to glucose-lowering drugs[27]. PRS screening could identify individuals at a preclinical stage of T2D to allow earlier control of glycemia and identify personalized treatments. This could motivate a regime of diet and exercise to potentially avoid pharmacologic interventions to manage T2D[28].

Prompting risk-reducing behaviors

PRS information could motivate risk-reducing health behavior, for example by prompting initiation of medication, screening, or lifestyle changes[29]. Although not focused on PRS specifically, research on inherited cancer syndromes have shown improved screening adherence following disclosure of genetic test results[30]. Additionally, a recent study suggested that providing people with personal genetic results about obesity risk can alter cardiorespiratory and satiety physiologies, including perceived exertion and running endurance during exercise, and perceived fullness after food consumption[31].

There is still limited data on whether disclosure of PRS information motivates health behavior changes across a spectrum of common diseases, but emerging evidence suggests a potentially beneficial behavioral impact for CAD risk. Studies of disclosure of CAD PRS found increased perception of personal control and increased information seeking[32], favorable health behaviors[33], and increased shared decision-making resulting in more statin prescriptions[34]. Nonetheless, given that multiple factors besides the disclosure of genetic risk can impact health behaviors[35], future disease risk communication strategies should carefully consider the relative and combined effects of all relevant types of information.

Improving population screening

The purpose of population-level screening is to identify individuals at sufficiently elevated risk of disease that they would benefit from intervention. However, a key barrier to population-level screening is that the pre-test probability of any single individual in the population having the disease is low, and the number of false positives resulting from screening can be very high. In addition, the vast majority of individuals completing population-level screening are told that their risk of disease is too low to warrant an intervention; thus, most expenditures in screening programs lead to no change in clinical care.

Despite these in-built inefficiencies, population level screening could be improved in several ways using PRS. For example, PRS may improve the identification of individuals who would benefit from inclusion in screening intervention programs, the timing of screening initiation, the frequency of screening, and/or the tools (e.g. non-genetic clinical risk scores) used as part of screening. We provide three examples of screening strategies utilizing PRS.

While osteoporosis screening has rarely been implemented at population-level, recent trials have demonstrated a reduction in hip fracture rates by screening for elderly women at risk, predominantly using bone mineral density assessments. However, most women are deemed to be at insufficient risk to merit intervention after screening. By applying a PRS to screen individuals at risk for low bone density (the main metric for therapeutic interventions), the number of people requiring bone density evaluations may be reduced by ~40%, with high sensitivity (~93%) and specificity (~98%) to identify those requiring clinical care[36].

For breast cancer, PRS can be used to more accurately quantify 10-year risk. For women aged 40-50 years with unknown family history of disease, the average population risk of breast cancer is 1.7%. Using questionnaire-based risk factors and mammographic density, the BOADICEA risk prediction algorithm identifies 9.2% of the women in the population who would be classified at moderate or high risk of developing breast cancer (based on the UK's NICE guidelines[37]). A breast cancer PRS alone identifies 10%. As such, a PRS for breast cancer risk could be used to optimize the screening initiation and frequency of mammograms. An integrated model with PRS, questionnaire-based risk factors and mammographic density identifies 13% of women with a moderate or high risk. BOADICEA v5 (as implemented in the CanRisk tool) already implements a 313-variant PRS and currently supports hundreds of thousands of women, doctors and genetic counsellors annually in >90 countries making treatment decisions[37,38]. PRS-guided mammographic screening is also being tested in the WISDOM and PERSPECTIVE I&I studies[39,40].

The benefits of a CAD PRS could be sufficient to justify an update to population level screening. By adding PRS to existing risk prediction models, multiple large studies have shown improved individual risk reclassification across a population, and thus may improve targeted therapeutic interventions (e.g. statins[41,42]). PRS-guided lipid-lowering treatment, particularly for those at intermediate risk, has shown promise in decreasing cardiovascular disease events[2,43,44]. With a safe, effective and inexpensive preventative therapeutic, cardiovascular disease screening strategies which consider PRS and conventional risk factors jointly (e.g. in a primary care population of at least 40 years of age[43]) or which take a 2-stage approach (screening first with PRS then with conventional risk factors, or vice versa[44,45]) appear to robustly provide clinical benefit; however, further refinement regarding who and when to treat is still necessary.

Risks

Despite the potential, and in some cases demonstrated, benefits of PRS there are potential risks to both individual patients and the general population from clinical use of PRS which should be acknowledged and mitigated[46].

Risks arising from 'incorrect' information

If a PRS is used as a standalone tool, a key risk relates to delivering substantially incorrect risk estimates to the individual. 'False positive' results (e.g. wrongly categorizing an individual as 'high risk' based on their PRS) could lead to inappropriate clinical actions and unnecessary emotional harms. The clinical implications of a substantially incorrect polygenic score are dependent on disease severity, the relative contribution of non-genetic risk factors, and the cost or harm of recommended or missed interventions[46-48]. It is important to emphasize to individuals that PRS are estimates with a level of uncertainty around them that could affect risk stratification due to statistical imprecision[49] and the use of discrete cut-offs[50]. Notably, these concerns

regarding incorrect or imprecise risk estimates are the same for all risk factors and not specific to PRS.

PRS are also susceptible to the same biases as other prediction models in that their performance (whether classification accuracy, short term or long-term prediction) can be substantially attenuated if the individual is not adequately represented by the original study population. A major source of error for individuals of non-European ancestries is the lack of representation in genotyped cohort studies. As with many areas of medical research, the majority of genetic research has been conducted in European ancestries (~88% of participants in published GWAS[51,52] to date), which often leads to reduced predictive performance for PRS in individuals from other ancestries[53-55]. PRS performance can vary widely in admixed individuals[53], or for other demographic groups by age and sex[56]. These differences could in turn exacerbate existing demographic disparities in access to healthcare and clinical outcomes[57].

Inequities in performance of biomarkers and interventions across demographic characteristics are pervasive in medicine. Examples include glomerular filtration rate estimation across ethnicities and interventions for chronic kidney disease (such as renal transplantation); risk prediction for atherosclerotic cardiovascular disease and adverse side effects of statins in Black patients; and body mass index thresholds and risk of diabetes in Asian individuals[58,59]. While some tolerance of differential performance is necessary, how much should be tolerated is an important question which must consider a wide range of issues, including specific clinical context, healthcare system and economics, as well as ethics and the ramifications of withholding or modifying the performance/treatment.

Risks arising from 'correct' information

Risks remain for PRS based on ‘correct’ information — that which is informative, well-calibrated and minimally biased. These risks are primarily related to the communication of the PRS information to the individual, and require careful consideration as they may be incorrectly conflated with return of monogenic results, which are more diagnostic in nature. Risks include failure to convey the uncertainty in the estimate, and deliver timely counsel regarding approaches to reduce overall risk (not just that attributable to the PRS). Improper risk communication may result in physical or financial harm from unnecessary lifestyle or clinical interventions as well as unwarranted negative psychosocial effects such as anxiety or depression[60].

In the US, the current standard for ethical return of monogenic results requires health care professionals trained in genetics (e.g. genetic counselors), typically working together with a physician who is an expert in preventing, screening for, or treating the disease under discussion. This approach typically involves genetic counseling before and after the genetic test, followed by a physician visit. For population-level screening, it is not feasible to scale this process for the return of PRS results to many individuals for many diseases, particularly since

genetic counselors are in short supply in many countries[61,62]. However, there are existing models for successful large-scale return of genomic results in the primary care setting[63] even when those HCPs report average levels of genetics training and comfort with genetic information[64].

Communication of PRS results to patients or their primary care physicians are being trialed using a wide variety of formats, including indicating the individual's position on a bell curve, their percentile, and categorical risks (e.g. "slightly increased risk"). For individuals from diverse ancestries and cultures, researchers are only just beginning to investigate which display formats optimize comprehension of PRS[49].

The majority of studies to date have found little evidence of lasting negative psychosocial effects of providing monogenic results to individuals who choose to receive them[65]. However, a few studies have found negative effects; in one, informing participants of the APOE genotype for Alzheimer's disease risk impacted their objective and subjective performance on subsequent memory tests[66]. While there is a relatively large body of literature on the psychosocial effects of returning monogenic results to patients and families in clinical settings, the research assessing the impact of PRS on individuals is still in the very early stages. This is understandable given the relatively nascent stage of PRS discovery research compared to rare high penetrance variants, but it is vital that these translational studies are now conducted given the potentially widespread use of PRS in the near future. At present, little is known about the potential harms of PRS such as anxiety, stress or misunderstanding, nor about how these harms can be best avoided via careful communication and delivery of the results and appropriate support before and after.

Mitigating societal risks

PRS are becoming more widely available for a broad range of common conditions, which strengthens the case for stronger protections against genetic discrimination. History has shown that marginalized groups are especially vulnerable to both racism and genetic discrimination, as exemplified by mandatory sickle cell screening in the US in the 1970s[67,68]. In that case, discriminatory practices denied education opportunities, employment, and insurance based on carrier status - which primarily affected individuals of African ancestries[68]. This and other historical injustices have been reported as causes of hesitancy in undergoing predictive genetic testing for African Americans[69]. Failure to strengthen and enforce anti-discrimination regulations is particularly pertinent as we seek to increase research participation from underrepresented groups[67,70], who may be suspicious of medical research or healthcare more generally[71].

Without appropriate communication of the uncertainty around PRS estimates, large-scale deployment of PRS could potentially reinforce and amplify false genetic determinism attitudes. If healthcare professionals adopt these attitudes, it may influence what type of care will be offered to whom. Widespread and irresponsible use of PRS risks may systematically downplay the role

of the environment in an individual's health. Not only would this be inaccurate, but it could potentially offset the work that has been done to highlight social determinants of health and work against interventions that help eliminate health disparities[72]. Ultimately, best practices for PRS delivery will need to be done in close consultation with behavioral and social scientists so that both the social and genetic determinants of health, and their respective interventions, are considered.

Human genetic information, and the language of geneticists themselves, can be easily misunderstood by the public and cause harm[73]. A particularly concerning risk for minority groups is the comparison of PRS distributions between populations (including ancestries). Any difference in mean value of a PRS between populations could be used in a potentially racist or sexist attempt to explain observed group differences in health outcomes, behaviors, wealth and other traits. Such inferences would be both harmful and incorrect because differences in mean PRS value between populations are typically due to allele frequency differences and biases in the genetic discovery data, and thus unrelated to differences in phenotype[74].

The availability and ease of developing PRS may also lead to inappropriate use. For example, some companies are offering PRS for embryo selection of non-clinical traits under the rationale that PRS are used in medicine[75]. However, the clinical value of using PRS for embryo selection is likely to be limited[75], and the ethics of parents selecting non-clinical traits or incompletely understood clinical traits in offspring is ethically dubious[76].

Direct-to-consumer companies make genetic tests available to anyone who submits a sample, and they may also return PRS results for a wider variety of diseases and phenotypes. The mode of communication may be via email or web portal and may have only limited or no capacity to offer genetic counseling. Traits that are behavioral or have a stigma attached may be particularly distressing to the consumer[77]. For preventable diseases, follow-up with a physician may be less likely to happen than when results are returned in a clinical setting. For diseases with no available intervention, the potential for psychosocial stress or harm must be considered, and the potential benefits (family planning or altered life goals) weighted against the stresses of receiving the result.

Gaps

Deployment of PRS holds both promises and risks which may improve or detract from patient and population health. However, even for diseases with a large potential benefit and minimal risk of clinical PRS application, consistent and equitable implementation must remain a priority. Prior to large-scale deployment, there are gaps in PRS research which need to be filled for there to be confidence that PRS will be used responsibly.

Polygenic risk score development and evaluation

PRS development typically involves selecting a set of genetic variants and corresponding weights, then testing the constructed PRS performance in an independent dataset. Reporting of PRS and their resultant performance in external datasets has been historically lacking and inconsistent[78]. Data sharing is critical to PRS development, in particular full GWAS summary statistics which underpin the selection and weighting of genetic variants for a particular trait. Comprehensive databases of GWAS summary statistics, such as the pioneering NHGRI-EBI GWAS Catalog[79], are widely utilized by the community but still only a minority of published GWAS share their full summary statistics[80]. This is a critical gap which hampers the development, robustness and generalizability of PRS. The GWAS research community, global biobank collaborations and private direct-to-consumer companies should require public sharing of summary statistics, and utilize standardized formats, to avoid exacerbating global health disparities[70].

As noted above, some PRS have reduced performance in non-European ancestries which may exacerbate health inequities[70,81]. Breast cancer patients of non-European ancestries are offered less genetic testing and breast cancer PRS are frequently relevant for women of European ancestries only[82]. The historic focus of cohort studies, and medical research more broadly, on European ancestries is a key factor in this bias and the lack of study recruitment of non-European ancestries together with corresponding genomic and health data is a critical gap. For GWASs and thus PRS to represent non-European ancestries[70], we must prioritize resources for recruitment of and data generation for individuals of African, Asian, Indigenous, and other underrepresented ancestries in both wealthy and low-middle income countries. So far, there are positive signs that human genetics and polygenic score research in particular are working to address ancestry biases, including large-scale diverse cohort recruitment and sharing of ancestry-specific GWAS summary statistics. We hope these continue and intensify to the point where PRS are a model for other epidemiological and medical research areas where ethnic and ancestral diversity still lags behind.

Beyond current ancestry biases, there remain gaps in study design and analysis for PRS. Cryptic substructure within a population or within an ancestry group, potentially related to geography or participation bias, may induce inaccuracies in PRS[83,84]. If these differences are related to confounders, such as differences in social environment, or gene–environment interactions then care is needed to ensure PRS performance estimates are accurate and fit to inform clinical practice. Multi-morbidity structures and correlations amongst PRS also should be considered. PRS methods vary in multiple ways; there is a need for clarity on the optimal number of variants to use, how to utilize ancestry information[85], how to incorporate high impact rare variants[86], and reliable metrics for selecting the best performing PRS. Recent analyses have shown that improved imputation reference panels, fine-mapping procedures, and GWASs that include even a small amount of non-European ancestries can ameliorate differential PRS performance[87,88]. The centralization of well-documented PRS studies as well as free and open provision of PRS models (genetic variants and weights), for example via the Polygenic Score Catalog[89], are also vital. Further improvements will enable comprehensive PRS performance comparisons and will increase the transparency, reproducibility, and public trust in PRS.

Gaps in translation

Although there is largely consensus that PRS should be used alongside other informative non-genetic risk factors, gaps remain in determining precisely how this should be done. Even once comprehensive models are constructed (whether joint or two-stage), it is not yet clear how best to communicate individual PRS from laboratories and bioinformatics teams to HCPs, although work towards this is ongoing by eMERGE Network investigators[90], Our Future Health[91], and many others. There are similar gaps in best practices regarding results reports for patients. Notably, there is wide diversity and no standards or agreement for clinical reports that include PRS[92].

There are gaps regarding how HCPs interpret and adjust clinical decisions with additional PRS information. There is some evidence to suggest that the use of PRS influence HCPs' behavior in terms of clinical recommendations and prescribing, but this is largely limited to a handful of disease areas, most notably cardiovascular disease[93]. Very few clinical guidelines support HCPs in helping patients make informed choices or shared decisions about their health care based on PRS results. For example, in England, HCPs have clear guidelines provided by the National Institutes of Clinical and Healthcare Excellence (NICE) on strategies for patients with cardiovascular disease risk greater than the 10-year risk threshold of 10%[94] (or 7.5% in the US). However, what should the HCP recommend if a patient has high risk based on a PRS alone? What are the potential risks of stigmatization or discrimination, particularly if early in life? What are the implications of parents having this information for their children early in life (prior to the child giving informed consent)? Additionally, effective counselling should take into account cultural beliefs[95] and other social factors (e.g. access to risk-reducing interventions). Training programs for genetic counsellors and HCPs may need to be adapted to appropriately cover PRS-derived risk estimates for common diseases.

Finally, it is unclear whether the use of PRS in specific health care systems will be cost-effective if the benefits outweigh the risks. While the technology needed to generate PRS (genome-wide genotyping array) is relatively inexpensive, other costs associated with deployment of PRS at scale (e.g. genetic counseling time, training and educational resources for other HCPs, etc) may not be. Early intervention and corresponding healthcare cost reductions is especially important in resource-challenged settings around the world. Addressing this translational gap is a priority that will require studies that consider both economic factors and health care management that vary across clinical settings and regions.

Regulation of PRS

PRS need a process for demonstrating and refining clinical utility; preferably, this would be dynamic, adaptive, and mainly focused on using real world data. An ideal regulatory approach would allow for PRS to be updated as the science evolves.

Existing regulatory frameworks ensure medical devices brought to market are safe and effective by evaluating their quality, effectiveness, accuracy and safety; and the same must be done for

PRS. The timelines, costs, supporting documentation, and rigor under which medical devices are evaluated depend on the assigned risk class[96]; yet, the rapid pace of software tool development (which may encompass PRS) makes it difficult to determine regulatory needs, timing, and terms[97]. Current regulations recognize that software used for "medical purposes" can, if certain conditions are met, be deemed and regulated as Software as a Medical Device (SaMD), for example those used for diagnosis, treatment or prevention of disease[98,99]. In some jurisdictions, risk prediction models and PRS have expanded the definition of medical purposes to also include prediction, monitoring, and screening[100].

With PRS research rapidly iterating between basic and clinical, and subsequent clinical validity and utility constantly evolving, the scientific and technical limitations complicate their current definition within the regulatory frameworks[101]. Likewise, PRS use for medical purposes is currently uncertain under most legislation[101].

This uncertainty is exacerbated because, despite increasing efforts[102], medical device regulatory frameworks are not internationally harmonized. The regulatory processes (requirements, costs, timelines, risk classes) as well as their applicability to the specific device vary across jurisdictions. The International Medical Device Regulators Forum SaMD guidelines provide inclusion and exclusion criteria and examine the significance of the information provided by the software for health decisions as well as the seriousness of the healthcare condition for which the software is intended[100,103-106]. Yet, there is significant variation in definitions and examples provided in guidelines. While legal classifications are not settled, Canada[107] for example seems to exclude PRS from the definition of a medical device, however the US could consider them falling outside the technical definition of clinical decision support tools and oversee them as medical devices. The EU SaMD guidelines on the other hand, focus on the specific intended uses, examples of software excluded from regulation, and whether it is stand-alone software or an accessory to an *in vitro* medical device. In the EU, PRS could be an accessory SaMD depending on the accuracy with which they can predict the risk of developing a medical condition. In fact, the BOADICEA risk prediction model itself, which incorporates the use of a PRS, carries a CE (Conformitè Europëenne) marking as an *in vitro* medical device in the EU[108]. Where PRS are not regulated as SaMD, they would be considered non-device clinical decision support tools. Manufacturers in this case are not obligated to comply with any of the medical device regulations but are encouraged to follow best practices of validation and quality assurance. Efforts are also needed in other regions of the world outside of the EU and North America regarding regulations to anticipate future implementation of PRS in a globally equitable way.

The costs of complying with medical device regulations are likely an important but unknown factor for implementation, access or use of PRS. These costs will be higher than those associated with following best practices, and high costs may create inequitable access between populations, countries and subgroups within countries. Furthermore, improving the clinical utility and validity of PRS greatly depends on global collaboration. Burdensome or uncertain regulations can hinder this collaboration by discouraging, complicating, or increasing the

costs[40]. Hence, it is crucial to address regulatory uncertainty and strike a balance between ensuring safety, improving health, and equitable use.

Conclusions

When estimating clinical risk, HCPs typically consider age, sex, ethnicity/ancestry, past medical history, family history, and biomarkers. Incorporating genomic risk information, which can be generated for hundreds of diseases with one DNA test, would mean these risk estimates could be more personalized, more accurate, and utilized earlier in life. While many risk reduction strategies (e.g. healthy diet, exercise, reduced consumption of alcohol and tobacco) are most effective when applied to the whole population, some strategies are not suitable for population-level intervention due to factors like financial cost and adverse treatment effects. Some strategies (e.g. statin use) should be prioritized for high-risk individuals for preventive interventions to effectively balance risk, benefit and cost. Furthermore, genetically-informed clinical tools can enhance diagnosis of subtypes of disease, predict progression and recurrence, and potentially guide treatment regimes. Early results suggest that genetic risk information may motivate patients to make behavioral lifestyle changes to reduce their disease risk.

There are also risks of PRS deployment that should be considered. Patients or physicians may misunderstand the uncertainty in a PRS-informed risk estimate. Individuals with non-European ancestry may have inaccurate risk estimates due to a relative lack of large prospective cohorts with genomic data from these ancestries, potentially exacerbating inequities in health care. We advocate for effective and clear risk communication by trained professionals to minimize potential psychosocial effects.

As noted above, a current example of a PRS in clinical use is the 313-variant PRS for breast cancer[109] implemented as part of the multi-factorial BOADICEA/CanRisk tool[37], which itself carries CE marking for use in the European Economic Area. BOADICEA/CanRisk is part of a first wave of PRS moving into clinical practice, and it signifies the urgency of the clinical and research communities to develop responsible use frameworks more broadly across many clinical pathways.

Although many inequities in access to health care are evident across nations as well as demographic and socioeconomic groups, PRS do also have the potential to improve equitable access to preventive care, hopefully serving as a model which aligns with and stimulates other equity initiatives in medicine. The International Common Disease Alliance's PRS Task Force will continue to support research enabling the responsible and equitable use of PRS for the betterment of human health. We look forward to working with cognate groups worldwide to ensure that medical insights from the human genome, exemplified by PRS, are effective, transparent and available to all.

Table 1. Future objectives for responsible use of PRS by communities, researchers and clinicians.

	Short term (current - 5 years)	**Long term (>5 years)**
Establish Benefits	Determine clinical utility for diagnostic refinement, risk prediction	Adopt standards within professional societies that make PRS risk information actionable
	Quantify cost effectiveness for specific-use cases and across health systems	Create internationally federated informatic platform for PRS implementation to standardize data workflows and clinical pathways
	Complement clinical-based lifestyle recommendations	
Mitigate Risks	Incorporate context and cultural competence into return of PRS	Minimize PRS-related stigmas via broad, persistent public engagement
	Improve ancestral representation to decrease existing disparities	Monitor and enforce accountability of the use of PRS to support racist and eugenic ideologies
	Ameliorate societal risk with interdisciplinary expertise and anti-discrimination regulations	
Close Gaps	Advance analytic methods and study design	Educate medical students & HCPs-in-training in application and bioethics
	Focus on equity and inclusion	Promote translation and build research capacity in low-middle income countries or other settings which lack resources
	Train specialists and public stakeholders	
	Enable translational applicability and HCP communication	
	Develop clear, flexible, and interoperable regulatory frameworks	

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The ICDA Polygenic Risk Score Task Force

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