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From Basic Science to Clinical Application of Polygenic Risk Scores
A Primer

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IMPORTANCE Polygenic risk scores (PRS) are predictors of the genetic susceptibilities of individuals to diseases. All individuals have DNA risk variants for all common diseases, but genetic susceptibility differences between people reflect the cumulative burden of these. Polygenic risk scores for an individual are calculated as weighted counts of thousands of risk variants that they carry, where the risk variants and their weights have been identified in genome-wide association studies. Here, we review the underlying basic science of PRS, providing a foundation for understanding the potential clinical utility and limitations of PRS.

OBSERVATIONS Polygenic risk scores can be calculated for a wide range of diseases from a saliva or blood sample using genotyping technologies that are inexpensive. While genotyping only needs to be done once for each individual in their lifetime, the PRS can be recalculated as identification of risk variants improves. On their own, PRS will never be able to establish or definitively predict future diagnoses of common complex conditions because genetic factors only contribute part of the risk, and PRS will only ever capture part of the genetic contributions. Nonetheless, just as clinical medicine uses a multitude of other predictive measures, PRS either on their own or as part of multivariable predictive algorithms could play a role.

CONCLUSIONS AND RELEVANCE Utility of PRS in clinical medicine and ethical issues related to their use should be evaluated in the context of realistic expectations of what PRS can and cannot deliver. For different diseases, PRS could have utility in community settings (stratification to better triage people into established screening programs) or could contribute to clinical decision-making for those presenting with symptoms but where formal diagnosis is unclear. In principle, PRS could contribute to treatment choices, but more data are needed to allow development of PRS in this context.

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Supplemental content

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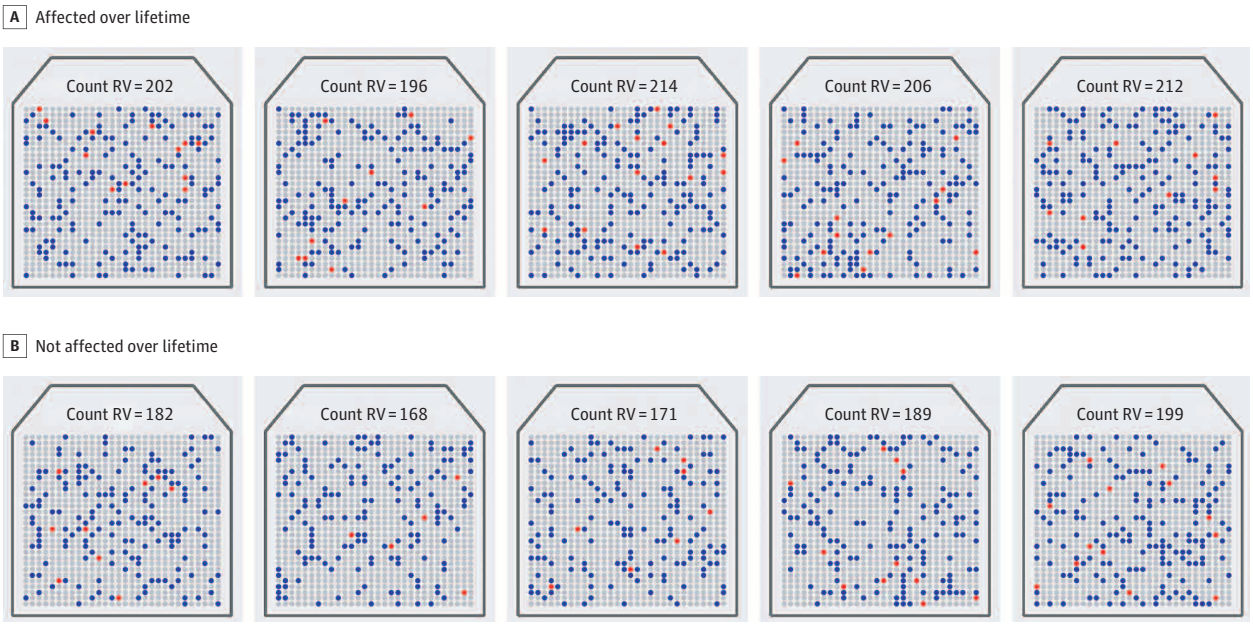
In some medical disorders, a single genetic variant is sufficient to directly cause illness. However, common conditions are multifactorial in etiology, influenced by both genetic and nongenetic factors. Genome-wide association studies have shown that common diseases are polygenic, ie, thousands of DNA variants contribute to risk, and most of these have very small effect.[1-3] In spite of this complexity, it is now possible to estimate the degree to which an individual is at risk of common illnesses owing to their genetic makeup. The so-called polygenic risk scores[4,5] (PRS) are generated from DNA taken from a saliva or blood sample with DNA variants measured using genotyping technologies that are inexpensive (< US $100 per person). From these data, PRS can be calculated for a wide range of diseases (by multiplying count of DNA variants with trait-specific, predetermined effect sizes). The DNA collection is only needed once, but the PRS can be recalculated from the genetic data if new information to improve PRS for a given disease becomes available. As with many risk factors used in health care (eg, cholesterol levels[6]), these risk scores have limited predictive accuracy (ie, they cannot confidently predict the clinical outcome of interest with precision at the individual patient level). Even if the risk DNA variants were identified with perfect accuracy, imperfect prediction by PRS is expected for 2 key reasons. First, genetic factors are not the only risk factors for common disorders. Second, the risk scores currently only provide data about part of the genetic contribution (that associated with common DNA variants, which typically each have small effect). Moreover, in real applications, other factors contribute to the accuracy with which risk variants and their weights are estimated (eAppendix in the Supplement).

Accepting that PRS are never going to be able to definitively predict complex conditions, the natural question for a physician, the patient, or their family, is "can PRS be useful in clinical practice, now or ever?" While a single test can generate risk scores for many diseases simultaneously, the utility of those scores varies between conditions. Here, we highlight some aspects of the basic science underpinning PRS that are relevant to considerations of clinical applications.

While the costs of generating PRS are low, we do not consider downstream associated costs in a health system nor implications for health insurance. This is outside of our expertise, but evaluation of these topics needs to be informed by an understanding of what PRS

Figure 1. A Visualization of Genetic Profiles of Individuals for Polygenic Disease



A toy example to visualize the genetic profiles for 10 individuals for a polygenic disease. Each block represents the genetic profile of an individual for 900 common DNA locations that contribute to risk of disease. Each dot is the genotype of the individual at a risk variant. The dots are colored gray if the person carries nonrisk (or protective) variants on both chromosomes, blue if they carry 1 risk and 1 nonrisk variant, and red if they carry 2 risk variants. The count at the top of the box is the sum of the total number of risk variants. For simplicity, each risk variant has frequency 0.1 and each contributes equal risk to disease. See the eAppendix in the Supplement for more detail. RV indicates DNA risk variants.

can and cannot deliver. In particular, it is important to dispel the dogma that equates a genetic test with high levels of accuracy of current/future diagnosis. We hope this article will contribute to this understanding. We also do not consider deeply the way in which risk should be communicated to the general public or to those presenting with current or past clinical symptoms, ie, genetic risk literacy. This is an important topic, and we recognize that the interrelationship between genetic test information and mental health may be complex[7,8]; we refer readers to some thoughtful commentaries.[9-11] We do note that return of PRS to patients is already undergoing research trials in health systems around the world. Moreover, commercial genotyping is now available in the public domain from a number of private companies by mailing in a saliva sample. Some direct-to-consumer companies report PRS for a number of diseases and traits. Consumers can also download their genotype (genetic variant) data and upload them into online PRS calculators.[12] Clinicians may wish to consider the possibility of a patient (and/or family member or future spouse) attending their consultation in the near future armed with their own, commercially derived, individual disease-specific PRS in the expectation that the clinician will interpret them. Our goal is to present an understandable narrative about the utility of PRS for the general reader (there are many other useful review articles[13-19]), and we plan to provide a psychiatry-specific evaluation in a future article.

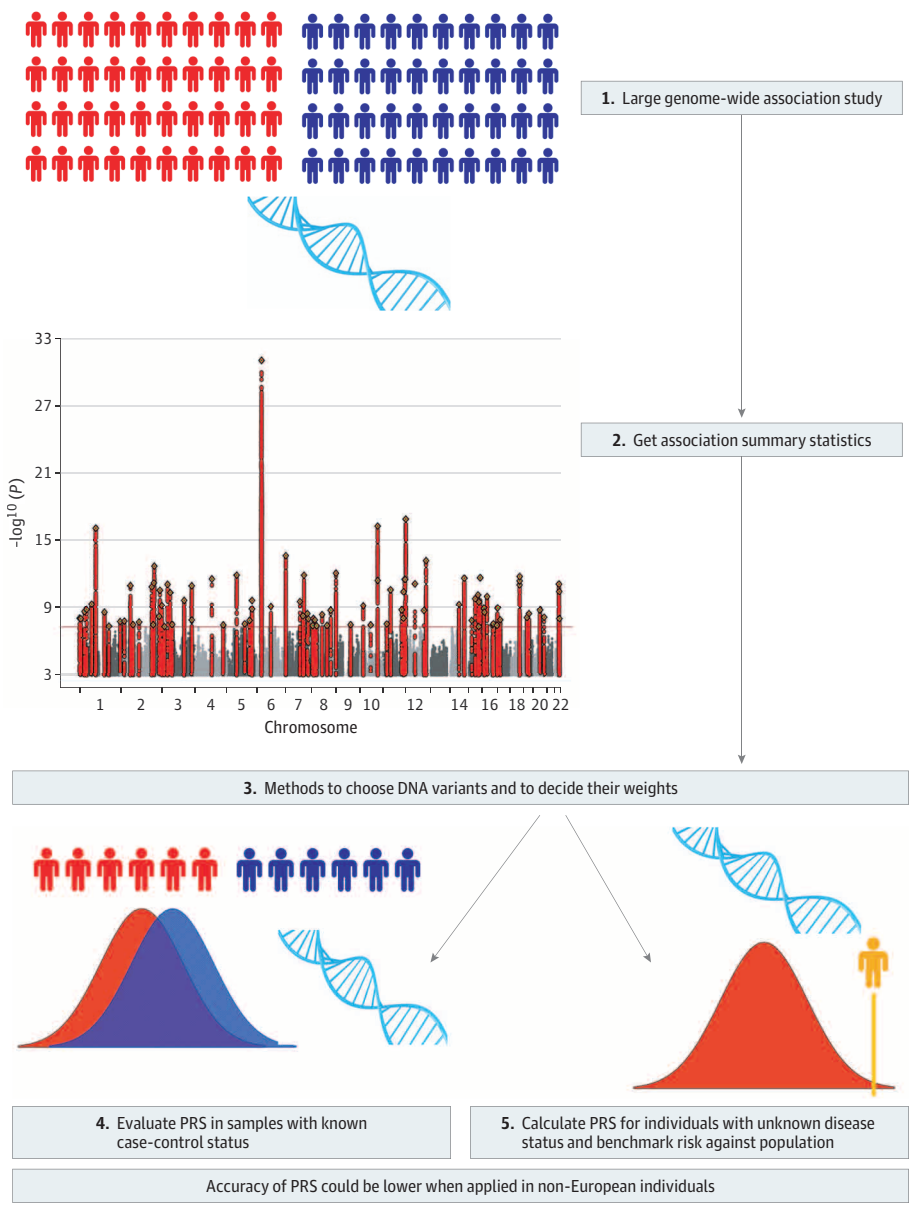
What Does "Polygenic" Mean for Individuals?

Common diseases and disorders are recognized to be polygenic.[3] This means that thousands of DNA variants contribute to genetic risk, where a variant is defined as a difference in DNA code at a particular location between people. Given we each carry 2 versions of each chromosome, at each DNA variant location, individuals can have 2 risk-associated variants (variants are often called alleles), 2 protective variants, or 1 of each (where risk and protective are relative terms). So when we say common diseases are polygenic, it means each of us have some risk variants in our DNA for all diseases, but those who carry a higher burden of risk variants for a particular disease have increased risk for that disease (**Figure 1** provides a visualization of this) or are more vulnerable to developing a condition in the context of other risk factors, and chance. In fact, we expect manyfold more rare variants to contribute to disease risk than common variants. However, rare variants are difficult to identify with confidence. There are so many of them that testing for their association with disease massively increases the multiple testing burden; therefore, very large samples are needed to identify those associated with disease. When so many risk loci contribute to disease etiology, it is likely that each person has a unique combination of risk variants (Figure 1), which, together with an individual's unique combination of life experiences, generates the variable presentation and life course that characterize common disorders, such as heart disease, type 2 diabetes, cancers, immune disorders, and mental health disorders.

What Are PRS?

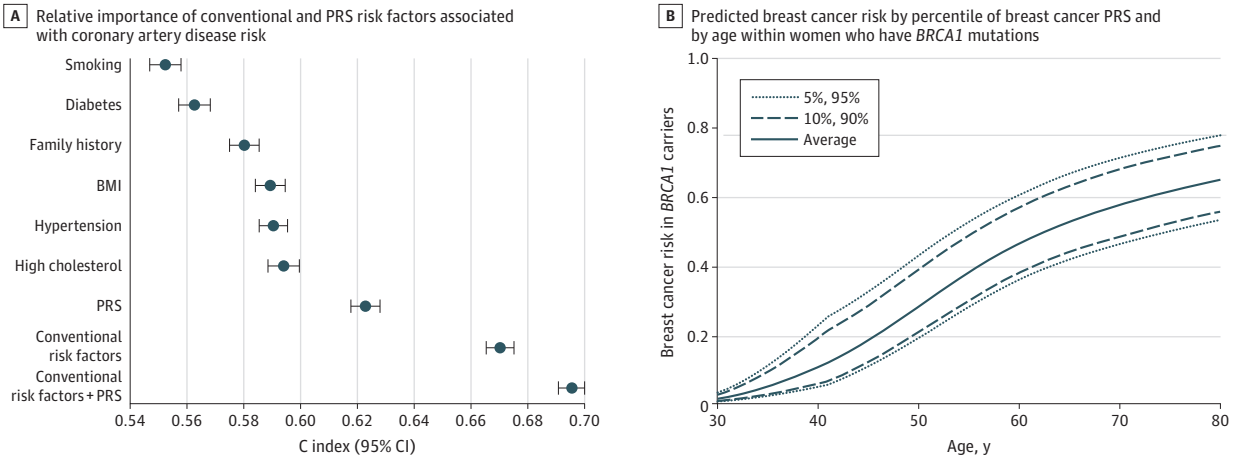
Polygenic risk scores for a disorder are calculated as weighted sums of risk variants for that disorder (**Figure 2**). Polygenic risk

Figure 2. Schematic of the Steps Needed to Generate and Validate Polygenic Risk Scores (PRS)



scores can be calculated from an individual's DNA sample for all disorders for which risk variants have been identified and are essentially a count of the number of the risk variants present in the person's DNA, weighted so that the presence of some risk variants is considered more important than others. The identities of the specific risk variants, and the basic information about how to weigh them, comes from the allele frequency differences between cases and controls identified in genome-wide association studies (GWAS).[5] The optimal selection of variants and the weights associated with them is an active area of research (eAppendix in the Supplement). Notably, risk prediction does not need knowledge of causal variants and can tolerate inclusion of some false-positive variants. Polygenic risk scores are validated by application in cohorts with already known case/control status. If the PRS are found to be predictive of the disease, then the PRS can be applied to an individual with unknown disease status, with the score benchmarked against a large group of ancestry-matched individuals. Ideally, at this stage, the PRS should be further validated for utility through formal clinical trials. Although the acronym *PRS* is currently the most widely used nomenclature, other acronyms are used (eAppendix in the Supplement). There are many statistics to evaluate PRS and they are interrelated (eAppendix in the Supplement). Most GWAS to date have been conducted in those of European ancestry; therefore, while some predictive ability is expected for individuals from other ancestral populations, the prediction is expected to be attenuated particularly into those with African ancestry[20,21] (eAppendix in the Supplement). There is considerable effort to increase GWAS sample collection across worldwide population groups to address this concern.[20,21]

Figure 3. Examples of Polygenic Risk Scores (PRS) Applications in Heart Disease and Breast Cancer



A, Relative importance of conventional and PRS risk factors associated with coronary artery disease risk.[26] The y-axis can be interpreted as the probability that a person who went on to have coronary artery disease ranked higher on the risk predictor than someone who did not get the disease. Results from Cox regression of incident coronary artery disease in the UK Biobank for conventional risk factors individually and in combination with the PRS, including covariates (sex-stratified age-as-timescale). B, Predicted breast cancer risk by percentile of breast cancer PRS and by age within women who have *BRCA1* mutations.[27] See the eAppendix in the Supplement for more detail.

Applications and Evaluations of PRS

To demonstrate why there is considerable discussion about implementation of PRS into health systems, we consider the application in cardiovascular medicine because it was highlighted[22] that PRS provide a level of predictive information that can be considered similar to the risk of specific single rare variants that are currently clinically actionable. In standard practice, the detection of such rare variants (often investigated in families that have multiple affected individuals) can lead to changes in clinical management (eg, surveillance or prophylactic measures).[22] In this retrospective study, it was shown that those in the top 1% of cardiovascular PRS had lifetime risk of greater than 10%, which is equivalent to the risk faced by those carrying single rare genetic variants that, when detected, can inform changes in clinical management. On the flip side, approximately 90% of people in this top 1% would not go on to have heart disease, but encouraging this subgroup of the population to consider prevention strategies could be worthwhile in reducing risk. Use of risk information in this way is sometimes referred to as precision prevention genomics, where the precision focus is a population stratum.

Risk prediction for heart disease is already well established around the world.[23-25] These predictors can be found in online tools and combine information associated with clinical risk factors, such as sex, age, blood pressure, smoking status, family history of cardiovascular disease, total and high-density lipoprotein cholesterol, diabetes, and electrocardiogram measures, into a total risk score. None of the individual contributing factors is a useful risk predictor alone, but the combination of factors is used to inform prescription of statins and other lifestyle preventive interventions. Another study[26] using prospective, longitudinal data from the UK Biobank[26] showed that while coronary artery disease PRS were a less accurate predictor of a subsequent coronary artery disease event than the other clinical risk predictors when they were combined, it was more accurate than any of the other individual clinical risk factors (**Figure 3**A).[27] Additionally, when PRS were added to the existing combination of clinical risk predictors, the accuracy increased. Extrapolating the UK Biobank results to 13 million UK residents aged 40 to 55 years, it is estimated that incorporating PRS into the QRISK algorithm[23] could lead to many hundreds of thousands of people changing risk category: more than 500 000 could move from less than the threshold for statin prescription to greater than the risk threshold, while more than 200 000 people could move from greater than the risk threshold for statin prescription to less than the threshold.[28] Although application of PRS in prediction of cardiovascular risk is an ongoing topic of discussion,[29,30] incorporating genetic data into such risk algorithms used routinely in primary care could have significant public health implications.

Global interest in using PRS is most notable for diseases that already have population-based screening and prevention programs. Because screening programs carry both benefits and risks (eg, unnecessary invasive test and/or treatments), additional information with which to stratify risk could result in screening being focused on a more restricted group, which could potentially decrease risks associated with screening for the population overall, and lead to cost savings.[31] Hence, PRS-based risk stratification could be of potential utility in other contexts such as colorectal cancer (where screening kits are posted biannually to those older than 50 years and where resources to encourage kit return could focus on those at highest PRS-based risk[32]) or breast cancer (where PRS could personalize age at first breast screening[33]). Another example is application to common eye disorders, such as glaucoma, where those with high-glaucoma PRS[34] could be particularly encouraged to take up the ophthalmological screening because intervention on early detection of increased intraocular pressure can prevent otherwise irreversible blindness.

For some common diseases, there are known rare variants of large effect. For example, about 2% of breast cancers in women

of European ancestry are associated with variants in the *BRCA1* gene. These variants are individually rare in the population but are associated with massively increased risk in the families in which they segregate. In women with these *BRCA1* variants, high PRS for breast cancer (derived from nonfamilial breast cancer GWAS) are associated with earlier age at breast cancer diagnosis[27] (Figure 3B). Similar results using disease-specific PRS have been reported for *BRCA2* breast cancer, *BRCA1/2* ovarian[27] and prostate cancer,[35] familial (MYOC p.Gln368Ter) glaucoma,[34] and familial (Lynch syndrome) colorectal cancer risk.[36]

Together, these examples demonstrate that risk prediction from PRS will be combined with other risk information for an individual. While predicted risk from both PRS and rare genetic variants of large effect are available from birth, lifestyle risk factors used to generate predictors of absolute risk will change with age.

Will People With Known Family History Have High PRS?

People with known family history of a common disease are likely to have higher than average PRS, but may not. Why not? First, because family history encompasses both genetic and nongenetic risk factors shared by family members, although the genetic contribution is on average larger.[37] Second, the risk variants included in the PRS only capture part of the genetic contribution, and so those with family history are not guaranteed to have high PRS. Third, an individual may share fewer risk variants than expected with their affected family members because of the random segregation of risk variants from parents to offspring. In fact, PRS have the potential to differentiate risk between family members who have the same family history information. In the clinical context, if people present with relevant family history of a disorder but low PRS, then the clinician should make any clinical decisions in a manner guided by the family history. Such patients could be prioritized for testing of other genetic risk factors not included in the PRS, such as chromosomal rearrangements or structural variants.[38]

Could People Have High PRS But No Family History?

It is fully expected that many of those with high PRS for a specific disease will have no family history of that disease. From polygenic theory, the only way to reconcile both the polygenic nature of common disease and the frequency of a disease in the population is that most people presenting with common disease have no known affected family members.[39] This is consistent with the risk of disease being highly nonlinear with the genetic contribution to liability of disease (or "true" PRS).[40] For example, for a disease of lifetime risk of 1% and heritability 70% (approximately representative of a range of common diseases/disorders such as rheumatoid arthritis, schizophrenia, bipolar disorder, and colon cancer), just based on idealized families without the additional vagaries associated with real-life knowledge of family history, about 75% of those affected are expected to have no first-degree, second-degree, or third-degree relatives with the condition.[39,40] These perhaps nonintuitive but observationally endorsed results reflect that important genetic differences occur between family members as a result of the segregation of variants from parents to children at meiosis. While each child receives half their DNA complement from their mother and half from their father, there are more than 8 million ways that the chromosomes of each parent can be split. For polygenic disorders, the genetic variance between siblings in a family is expected to be half of the genetic variance in liability between all individuals in the population[41] (Figure 1). For this reason, although the PRS of 2 family members will be more similar than the PRS of 2 people selected randomly, the PRS will vary between family members. As PRS become more accurate, the variation in PRS between full siblings will increase and will differentiate the risk between them despite having the same family history. Hence, a high polygenic risk for a condition is simply a consequence of the genetic lottery of life.

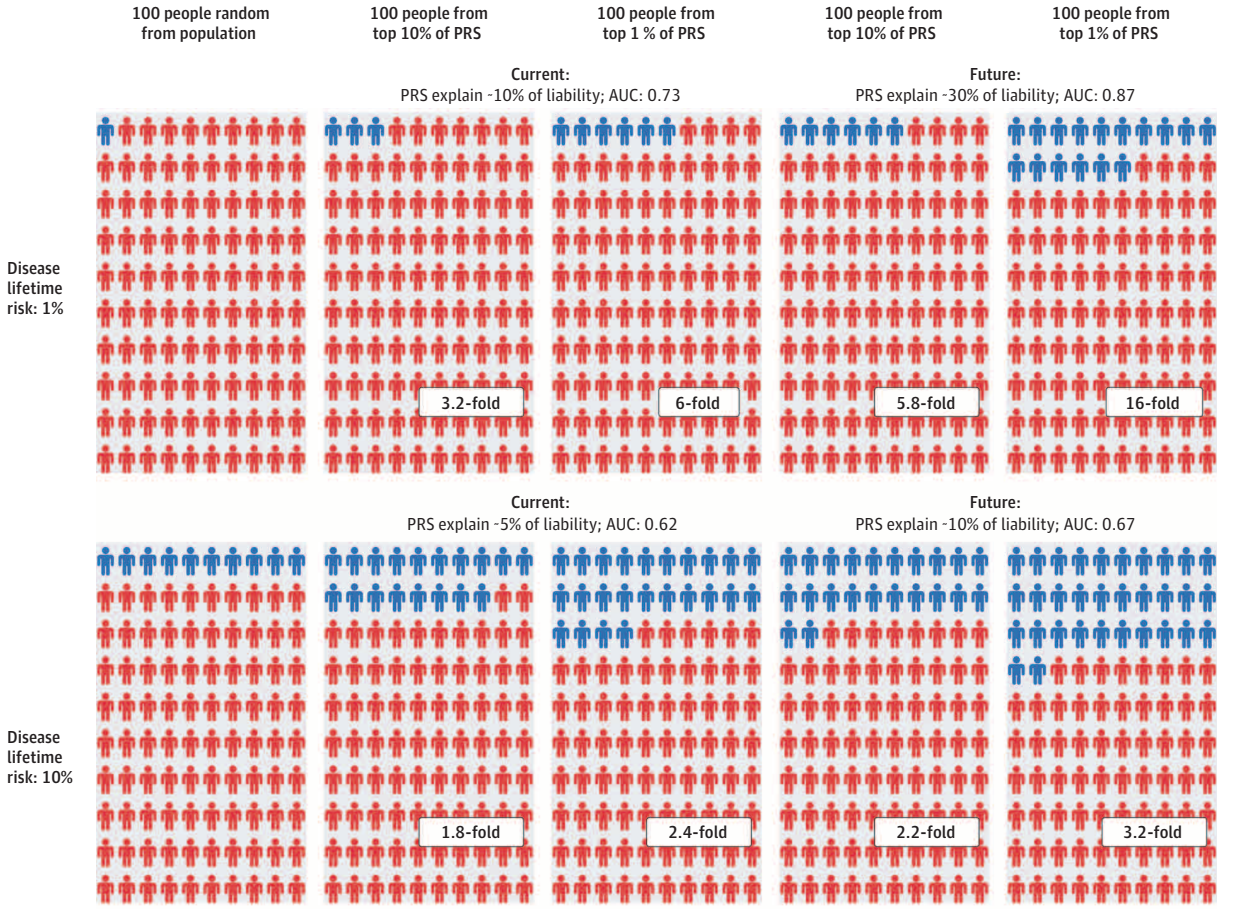
What Is the Maximum Expected Future Accuracy of PRS?

Polygenic risk scores can only explain part of the genetic aspect of a condition. Because nongenetic factors also contribute to risk, the maximum accuracy of genetic predictor is limited by the heritability of the disorder, where heritability is the proportion of the variance between people in their liability to a disease that is attributed to genetic factors.[42] However, construction of PRS is, to date, limited to DNA risk variants that have frequency of at least 1% in the population (and in some applications, variants are only included if they have a frequency of more than 10%[43,44] owing to greater instability in PRS using low frequency variants [currently]). Hence, PRS are not designed to capture all genetic variation only tagged by common single nucleotide variants (SNVs). Therefore, the so-called SNV-based heritability gives the upper limit of the variance between people in their liability to a disease that can be explained by PRS and represents the variance explained by common DNA variants. As GWAS sample sizes increase, the variance explained by PRS will also increase and approach the SNV-based heritability. The SNV-based heritability estimates vary across diseases, but an approximate upper limit is approximately 30%. Although in principle, use of whole-genome sequence data could increase the variance explained by PRS (because more variance would be tagged by measured markers, ie, the SNV-based heritability approaches the heritability), it is unlikely (at least in the short term) to improve PRS (eAppendix in the Supplement). Risk stratification based on current and future PRS is illustrated in **Figure 4**.

Conclusions

Polygenic risk scores are not and never will be stand-alone predictors of common diseases. The expected role for PRS across medical applications is partly predicated on the fact that the genotyping needed for calculation of PRS is cheap, that a one-off generation of genome-wide genotypes can provide PRS for multiple conditions, and that even small changes in health outcomes can have a large effect on health economics because polygenic diseases are common

Figure 4. Using Polygenic Risk Score (PRS) for Population Stratification



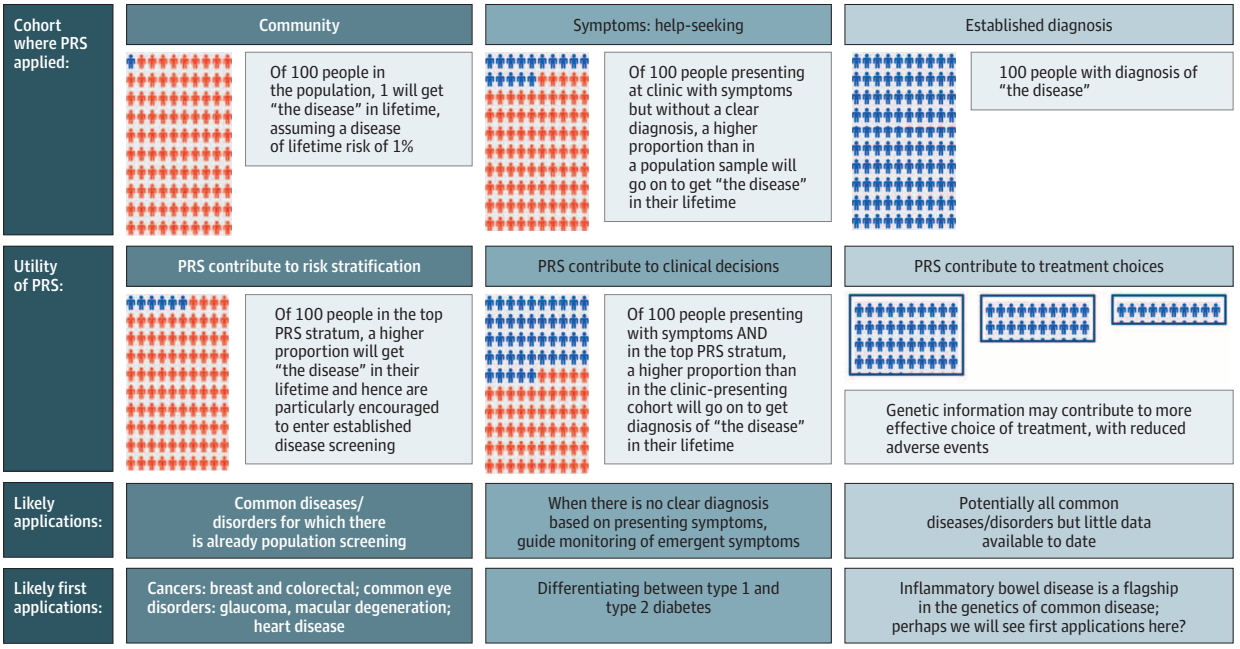
Rates of disease in the general population and those in the top 10% or top 1% of the PRS distribution. Top row: a disease with lifetime risk of 1%, where PRS explain 10% of liability variance now and 30% in the future. Bottom row: a disease with lifetime risk of 10% where PRS explain 5% of the variance in liability now and 10% in the future. These examples are selected to approximate results from real data for diseases of these frequencies. AUC indicates area under the receiver operating characteristic curve, which can be interpreted as the probability that a person with disease ranks higher on PRS than a person without disease. See the eAppendix in the Supplement for more detail.

diseases of society. Polygenic risk scores are already available to those who have undertaken direct-to-consumer testing or through the upload of genome-wide genotypes received through ancestry testing into PRS calculating online tools.[12] Therefore, it seems likely that PRS will become available; the question then becomes, if we have PRS, do we use them?

Polygenic risk scores could be used at 3 key stages (**Figure 5**). First, PRS could be applied in healthy populations. In principle, PRS could be available for an individual for all common diseases from birth. The genetic data would be held as part of the health record, with the latest score accessed for a specific disease at a point relevant to that disease. As described previously, PRS could easily be integrated into health systems for diseases where population screening programs and preventive health management strategies are already available. It is notable that if PRS were available for 20 different (and uncorrelated) diseases/disorders, while only 1% of the population is at high risk (defined as in top 1%) for any one of them, up to 20% of the population is expected to be in the high-risk category for one of them. It is the ability of the same genetic data to provide multidisease results that are important for health economic evaluations.

Second, PRS could be used in the early phase of illness, when patients present with very general and nonspecific symptoms that do not fit a specific diagnosis. For many diseases/disorders, presentation with clinical symptoms is sufficient together with biomarker testing (such as electrocardiogram for heart arrhythmia[45]) to confirm diagnosis. For diabetes, although a blood glucose test confirms diagnosis, 15% of adults presenting with type 1 diabetes are misdiagnosed as the more common type 2 diabetes, an impactful misdiagnosis given differences in treatment and care.[46] Within those with type 1 diabetes, high PRS for type 1 diabetes could be used to trigger more frequent monitoring of insulin levels because type 1 diabetes PRS were found to predict progression to the critical phenotype of insulin deficiency.[15,46] In some circumstances, PRS could be used to predict time to event.[47] For example, prediction of age at onset of breast cancer for those carrying causal variants in *BRCA1* could contribute to advice on timing of mastectomy.[27] We also propose that PRS could help with the triage and clinical staging of young

Figure 5. An Overview of the Population Cohorts Where Polygenic Risk Scores (PRS) Could Be Applied



The cohort in which PRS are applied will be disease/disorder dependent.

adults when they first present to services with very general and nonspecific symptoms (eg, anxiety, depression, or suicidal thoughts or behaviors), contributing to clinical decision-making.

Third, it is possible that in the future, PRS could contribute to treatment choices, because responses to treatment, including development of adverse health outcomes (such as weight gain), are likely complex genetic traits. However, investigating the utility of PRS in the context of choice of drug treatments requires larger data sets than are currently available. Compared with a decade ago, we now have the tools to develop models to predict treatment response, but are limited by data to develop and validate predictors. Large cohorts of patients treated with different medications must be followed up and responders contrasted with nonresponders to generate genetic predictors of response or recovery. To date, the inflammatory bowel diseases research has been the flagship for translation of genetic associations into new treatments, and identification of treatment responding subtypes is an active area of research.[48]

We conclude that the PRS available currently may have clinical utility for some diseases for which investigation in clinical settings is already justified. The breadth of applications will increase as genetic data become increasingly available as part of routine health records. Key to making this happen is to extinguish the dogma that equates a genetic test with a result of very high predictive value for current or future diagnosis and accept PRS to have an inherently limited accuracy, as do to many other tests routinely used in health care.[6,49]

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Author Contributions: Drs Wray and Hickie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Wray, Austin, McGrath, Hickie, Murray, Visscher.
Acquisition, analysis, or interpretation of data: Wray, Lin.
Drafting of the manuscript: Wray, McGrath, Hickie, Murray.
Critical revision of the manuscript for important intellectual content: Wray, Lin, Austin, Visscher.
Statistical analysis: Wray, Lin, Hickie, Visscher.
Obtained funding: Wray, Visscher.
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Supervision: Wray.

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Camperdown under contract to headspace. Dr Hickie had previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, and AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a Board Member of Psychosis Australia Trust and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to and a 5% equity shareholder in InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 million Australian Government–funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. No other disclosures were reported.

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