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# Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis

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## ABSTRACT

**Objective** We sought to test the hypothesis that Polygenic Risk Scores (PRSs) have strong capacity to discriminate cases of ankylosing spondylitis (AS) from healthy controls and individuals in the community with chronic back pain.

**Methods** PRSs were developed and validated in individuals of European and East Asian ethnicity, using data from genome-wide association studies in 15 585 AS cases and 20 452 controls. The discriminatory values of PRSs in these populations were compared with other widely used diagnostic tests, including C-reactive protein (CRP), *HLA-B27* and sacroiliac MRI.

**Results** In people of European descent, PRS had high discriminatory capacity with area under the curve (AUC) in receiver operator characteristic analysis of 0.924. This was significantly better than for *HLA-B27* testing alone (AUC=0.869), MRI (AUC=0.885) or C-reactive protein (AUC=0.700). PRS developed and validated in individuals of East Asian descent performed similarly (AUC=0.948). Assuming a prior probability of AS of 10% such as in patients with chronic back pain under 45 years of age, compared with *HLA-B27* testing alone, PRS provides higher positive values for 35% of patients and negative predictive values for 67.5% of patients. For PRS, in people of European descent, the maximum positive predictive value was 78.2% and negative predictive value was 100%, whereas for *HLA-B27,* these values were 51.9% and 97.9%, respectively.

**Conclusions** PRS have higher discriminatory capacity for AS than CRP, sacroiliac MRI or *HLA-B27* status alone. For optimal performance, PRS should be developed for use in the specific ethnic groups to which they are to be applied.

### Key messages

**What is already known about this subject?**

► *HLA-B27* testing is widely used in the diagnostic pathway in ankylosing spondylitis (AS), but only captures a moderate proportion (~20%) of the overall genetic risk for the disease.

**What does this study add?**

► Polygenic Risk Scores (PRSs) for AS perform better than *HLA-B27* testing and other standard diagnostic tests employed in AS including C-reactive protein measurement and MRI scanning.

**How might this impact on clinical practice or future developments?**

► PRS for AS should be used to assist diagnosing AS among patients with chronic back pain.

## INTRODUCTION

Ankylosing spondylitis (AS) affects approximately 0.2%–0.6% of individuals of European descent and Chinese.[1 2] Early treatment with biologic therapies in those with more severe forms of the disease achieves more effective clinical responses[3] and probably reduces the rate joint fusion in the long term.[4] However, other causes of chronic back pain are common in the community, and AS is responsible for only a minority of these cases. It can be difficult to distinguish AS from other causes of back pain, particularly early in the disease with the consequence that the diagnosis of AS is often significantly delayed; many surveys undertaken in a variety of different health systems suggest an average delay of 6–10 years.[5–7] A recent North American survey reported that fewer than half (37.1%) of patients with AS reported that they were correctly diagnosed within 1 year of seeking medical attention, and 32.8% waited more than a decade to receive the diagnosis.[7] Population surveys suggest that as many as 80% of cases in the community remain

undiagnosed[8] and therefore may not receive appropriate effective treatment. There is thus a great need for improved testing to improve early accurate diagnosis.

Currently, the most widely used tests for AS in those with chronic back pain are measurements of acute phase reactants, such as erythrocyte sedimentation rate and C-reactive protein (CRP), genetic testing for *HLA-B27* and imaging—either plain radiographs or MRI of the sacroiliac joints.[9] However, each of these tests has limitations. In brief, acute phase reactants and MRI are only positive after disease develops and are therefore not useful for predicting disease risk. Acute phase reactants have only moderate sensitivity and specificity, particularly in early disease. MRI is expensive and is not universally available. Genetic factors are the major determinants of the risk of developing AS, with heritability assessed in twins of >90%.[10 11] Although *HLA-B27* alone contributes 20% of the variation in disease risk,[12] the remainder of the genetic risk is determined by thousands of common genetic variants, each of which has only a very small effect. Polygenic Risk Scores (PRS) use combinations of hundreds to thousands of genetic variants to quantify an individual's genetic risk of disease. Unlike *HLA-B27* testing which is categorical or dichotomous in outcome, PRS are continuous measures. They are of particularly strong predictive value for low-frequency diseases with high heritability,[13] such as AS. Here, we describe the development and validation of PRS for AS in two different ethnic groups and compare its performance to standard screening or diagnostic tests.

## METHODS

### Study population

AS was defined according to the modified New York criteria.[14] Following genotyping quality control, there were 8244 cases and 14 274 controls of western European descent; 6001 cases and 4493 controls of East Asian (Chinese) descent; and 1340 cases and 1685 controls of Turkish and Iranian origin, respectively. Written informed consent was obtained from all cases, with approval from the relevant research ethics authorities at each participating centre. Cohort details are provided in online supplemental table S1.

### Genetic data

Samples were genotyped using the Illumina Core-Exome SNP genotyping microarray, according to the manufacturer's recommendations (chip versions used per cohort are provided in online supplemental table S1). Bead intensity data were processed and normalised for each sample, and genotypes called, using Genome Studio V.2.0 software (GenomeStudio Software Downloads (illumina.com)). Standard quality control measures as outlined in the Supplementary Methods were applied including identification and exclusion of cryptic-related samples, exclusion of samples with an outlying heterozygosity rate (3 SD from the mean in each cohort) or excess missingness (>5%). Single nucleotide polymorphisms (SNPs) with genotyping missing rate >2%, p value of Hardy-Weinberg equilibrium test $<1\times10^{-6}$, or with allele frequency <1% were removed. Population stratification was accessed using Shellfish (http://www.stats.ox.ac.uk/~davison/software/shellfish/shellfish.php). PRS analyses were performed with and without inclusion of principal components and gender as covariates. Results including principal components and gender as covariates are reported in online supplemental table S2 and are very similar to the results not including these covariates.

*HLA-B27* imputation was performed using SNP2HLA, using a deep sequencing Chinese reference panel (n=10 689)[15] for East Asian samples and Type 1 Diabetes Genetics Consortium (n=5225) panel of combined HLA types and MHC SNP genotypes for all other subjects.[16]

PRS were calculated for each individual using the adaptive MultiBLUP algorithm (implemented in the software LDAK V.5.0).[17] LDAK first divides the genetic data into chunks of size 75 000 bp and then performs association test for all the chunks and thinned out SNPs in strong linkage disequilibrium. The significant chunks with p value $<1\times10^{-5}$ and all adjacent chunks with p value <0.01 are merged into regions. Then the variance components and effect size of SNPs are estimated, and the effect size of the SNPs used to calculate the PRS. A 10-fold cross-validation analysis was performed as internal validation; a separate external validation was performed in the British and North American subjects, as well as through comparison of performance of PRS trained in either European descent or East Asian subjects, then validated in a separate ethnic group. In regard to cross-validation studies, the case–control cohort being studied is divided into 10 equal folds randomly with same case–control ratio. Nine folds of samples were used as a training set and the remaining fold of samples was retained as the validation data for testing the model generated by the training set. The process was repeated 10 times, with each of the 10-folds used only once as the validation data. The out-of-fold predictions based on the effect sizes of the selected SNPs were obtained for the test fold. All the predictions of 10 test folds were merged, after which statistical analysis was performed using all out-of-fold test set predictions to maximise sample size for internal testing. The resulting weighted predictors were then applied to the test cohort to obtain per sample scores from which the area under the curve (AUC) was obtained using receiver operator characteristic (ROC) analysis. R package pROC was used to calculate the 95% CI of the AUC and also compare AUCs from two models.[18] Positive (PPV) and negative predictive values (NPV) were then calculated for PRS centiles, assuming different prior probabilities of AS. The continuous net reclassification improvement (NRI),[19] a statistic that aims to quantify differences in classification performance of different models, was calculated using the R package PredictABEL[20] and used to compare accuracy of diagnostic assignment by *HLA-B27* testing and PRS.

## RESULTS

ROC analyses of test discriminatory capacity are summarised in table 1. In 10-fold cross-validation in this case–control cohort, the PRS had AUC of 0.924 (95% CI 0.920 to 0.928) (figure 1). The AUC of *HLA-B27* testing alone was 0.869 (95% CI 0.865 to 0.874), which was statistically significantly less discriminatory than the PRS ($p<2.2\times10^{-16}$). Additionally, the NRI was positive (0.717, 95% CI 0.692 to 0.743), confirming that the PRS is an improvement on *HLA-B27* alone. A PRS including only non-MHC SNPs performed less well (AUC 0.782), as did a PRS including only 103 (genotyped or imputed) loci previously reported to have achieved genome-wide significance in AS (AUC=0.659).[21] MRI has a reported sensitivity of 85% and specificity of 92% in AS,[22] which correlates with an AUC of 0.885. CRP has a reported sensitivity of 50% and specificity of 80% for the disease (AUC=0.7).[23]

To test the performance of the PRS using external validation, the European descent cases were divided into British and North American cohorts, and controls divided in the same proportion as the two case cohorts. PRS was then

**Table 1** ROC analysis findings (AUC) of genetic risk scores in different populations

| | Population tested in | | | |
|---|---|---|---|---|
| **Predictors** | **European** | **East Asian** | **Iranian** | **Turkish** |
| HLA-B27 alone | 0.869 (0.865–0.874) | 0.901 (0.895–0.906) | 0.831 (0.807–0.854) | 0.821 (0.804–0.838) |
| European non-MHC PRS | 0.782 (0.776–0.788)* | 0.594 (0.539–0.560) | 0.534 (0.500–0.569) | 0.568 (0.542–0.595) |
| European overall PRS | 0.924 (0.920–0.928)* | 0.788 (0.779–0.796) | 0.852 (0.826–0.879) | 0.854 (0.836–0.872) |
| East Asian non-MHC PRS | 0.555 (0.547–0.563) | 0.731 (0.722–0.741)* | 0.565 (0.531–0.598) | 0.554 (0.528–0.581) |
| East Asian overall PRS | 0.880 (0.875–0.887) | 0.948 (0.943–0.952)* | 0.872 (0.848–0.895) | 0.840 (0.821–0.860) |
| MRI EUR | 0.885 | | | |
| MRI CH[41] | 0.62 | | | |
| CRP | 0.7 | | | |

*10-fold cross-validation. All other PRS AUC values are external validation statistics.
AUC, area under the curve; CRP, C-reactive protein; PRS, Polygenic Risk Score; ROC, receiver operator characteristic .

developed in the British training set (n=6499 cases, 12 163 controls) and externally validated in the North American case–control cohort (n=1128 cases, 2111 controls). The PRS in the North American cohort had AUC of 0.928 (95% CI 0.918 to 0.939), significantly higher than *HLA-B27* alone (0.895, 95% CI 0.883 to 0.906, $p=1.73\times10^{-5}$) (online supplemental figure S1). These findings are very similar to the cross-validation analysis of the overall dataset reported above.

The PRS developed in all the European descent subjects, with 3994 SNPs (including 2244 major histocompatibility complex (MHC) SNPs), had moderate discriminatory capacity in East Asian, Iranian and Turkish cases and controls (AUC=0.788, 0.852 and 0.854, respectively), better than the performance of HLA-B27 alone in the Iranian and Turkish cohorts, but not in East Asians. In contrast, the PRS developed in East Asian subjects, then tested by cross-validation (i.e. also in East Asian subjects), had much better discriminatory capacity (AUC=0.948, 95% CI 0.943 to 0.952) than did the PRS developed in European descent subjects when tested in East Asian subjects. The PRS involving 8659 SNPs (including 2417 MHC SNPs) developed with all the East Asian subjects also performed well in European descent subjects (AUC=0.880, online supplemental figure S2), better than the discriminatory performance of HLA-B27 in each of the other three populations tested.

In clinical practice, the utility of all such tests depends on the prior probability of the disease concerned. The PPV and NPV of the PRS and *HLA-B27* in European subjects are presented in figure 2 in the setting of a patient under 45 years of age, attending a physician with a history of back pain for 3 months or more. Published studies report that in this setting the prior probability of AS is ~30%,[24–26] but as this may vary according to referral patterns, we have additionally provided findings for prior probabilities of 10% and 20% (online supplemental figures S5 and S6; East Asian specific findings are presented in online supplemental figures S7-S9). Assuming a prior probability for AS of 30%,

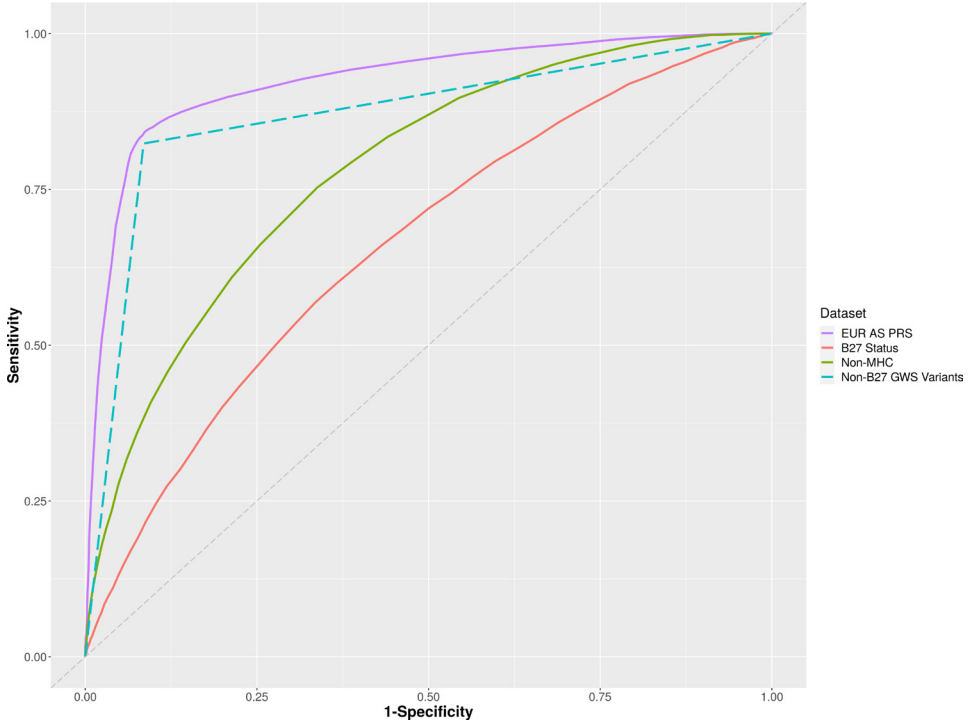


**Figure 1** Receiver operating characteristic curve plot of performance of Polygenic Risk Scores (PRS) (purple dashes, area under the curve (AUC)=0.924), HLA-B27 (aqua dashes, AUC=0.869), PRS less major histocompatibility complex (MHC) (green line, AUC=0.782) and genome-wide significant loci only (red line, AUC=0.659).

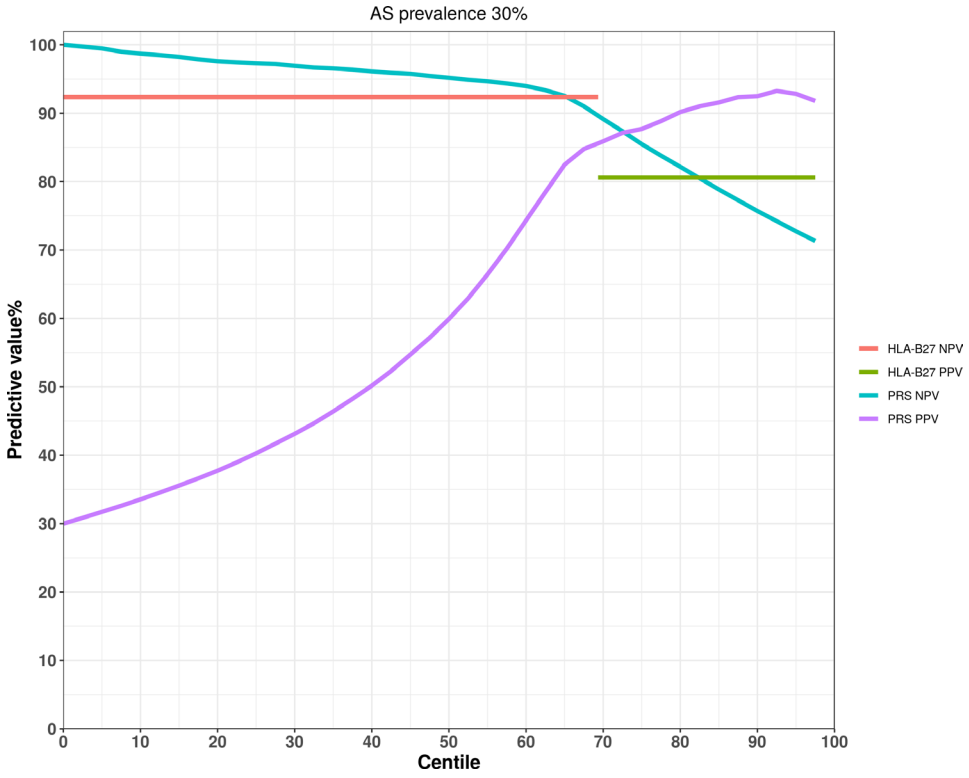


**Figure 2** Positive (PPV) and negative predictive values (NPV) of Polygenic Risk Scores (PRS) and HLA-B27 for ankylosing spondylitis (AS), assuming prior probability of AS of 30%, among Europeans. Centiles refer to the population distribution of the PRS.

an *HLA-B27* test will be positive in 31% of those tested with a PPV of 80.6%, and in the 69% of those with a negative test, the NPV is 92.4%. Using the PRS, the PPV is >80.6% for top 35% of those screened, and achieves a higher maximum value (93.3%) than does *HLA-B27* (80.6%) (figure 2). The PRS NPV will be >92.4% for 65% of those screened, and also achieves a higher maximum value (99.6%) than does *HLA-B27* (92.4%). Considering the situation where only 10% of screened patients have AS, then *HLA-B27* will be positive in 16% of those tested. In this group, *HLA-B27* positivity has a PPV of 51.9%, and a negative result (seen in 84% of screened patients) has an NPV of 97.9%. Using the PRS, the PPV is >51.9% for 35% of patients and has a much higher maximum value (78.2% vs 51.9%). The NPV for the PRS is >97.9% for 65% of patients and achieves a slightly higher maximum value than *HLA-B27* testing (100% vs 97.9%).

Considering general population screening, at least 8% of the European population carry *HLA-B27*,[27] yet only 5% of carriers of this allele will develop AS[28]; as such, no higher PPV can be achieved using *HLA-B27* testing alone. In contrast, for the PRS, the PPV for the top 8% of the population is three times higher (15.1%), and it is higher than 5% for the top 35% of the population. The NPV for *HLA-B27*-negative status is 99.9%, which is exceeded by the PRS for 62.5% of the population.

## DISCUSSION

Distinguishing AS from other causes of chronic back pain remains an important issue in rheumatology. *HLA-B27* testing can have a valuable PPV for AS, particularly in clinical settings where the pretest probability of the disease is relatively high compared with the general population. It is therefore included in the Assessment of Spondyloarthritis International Study Group (ASAS) axial spondyloarthritis (axSpA) classification criteria and is an essential criterion for those with no available imaging evidence of disease. *HLA-B27* testing has also been recommended for screening patients with chronic back pain to identify those at higher risk of AS or the related group of diseases axSpA, for referral to specialist services.[23 25] However, *HLA-B27* only contributes ~20% of the overall heritability of AS, which is estimated to be ≥90% overall, indicating a substantial non-MHC component.[29] This suggests that PRS, which capture the common-variant component of heritability, are likely to be much more informative than *HLA-B27* tests alone. Our study confirms this, with the PRS performing better than *HLA-B27* testing in both AUC and continuous NRI analyses, irrespective of the prevalence of AS among those being tested. We confirm these findings both by internal cross-validation and by external validation. For 35% of the population, the PPV is higher for the PRS than for *HLA-B27* testing, and the NPV is higher for >65%. In particular, the peak PPV is substantially higher for the PRS than for *HLA-B27* and is informative for a far higher proportion of patients, as it is a continuous variable whereas HLA-B27 is dichotomous. PRS testing also has higher discriminatory capacity for AS than MRI, and far higher than CRP. Accurate interpretation of MRI scans is known to be dependent on training and experience, and particularly in inexperienced, untrained hands may perform worse than the average reported performance, in which setting PRS may be particularly valuable.

Chronic back pain of >3 months' duration has previously been shown to have very low heritability attributable to common genetic variants (minor allele frequency >0.01) such as those included in our AS PRS (common variant heritability=6.43%[30]–7.6%[31]) and not to be genetically correlated with AS. Therefore, it is unlikely that the AS

PRS will prove less discriminatory in practice in the clinical setting of patients presenting with chronic back pain than the estimates presented here. A limitation of this study is that the performance of the PRS has not been formally tested in this setting, where it will require further evaluation.

axSpA refers to a spectrum of diseases. Patients with radiographic sacroiliitis are classified as having AS, whereas those without X-ray changes are classified as having non-radiographic (nr)-axSpA. The current PRS may have prognostic value in distinguishing the 16%–24% of nr-axSpA cases that are likely to go on to develop AS.[32 33] Whether the PRS we report here will prove more informative than *HLA-B27* testing alone in patients with nr-axSpA itself is unknown. The ASAS have previously demonstrated that patients meeting the ASAS classification criteria for axSpA who do not yet have AS have a much lower average genetic risk score than patients with AS, using only genome-wide significant AS loci.[34] Whether this is because nr-axSpA is actually genetically distinct from AS, or reflects the greater clinical and likely aetiopathogenic heterogeneity of nr-axSpA,[35] will require further study.

As with the use of PRS in the screening of individuals with chronic back pain, its performance in nr-axSpA will also require further study. Similarly, the performance of the PRS in males compared with females, in subjects with environmental risk factors for the disease such as cigarette smoking,[36] and in subsets of patients such as those with extraskeletal manifestations of AS requires further study. In that regard, the excellent performance of a PRS in patients with acute anterior uveitis complicating AS (AUC=0.96; 95% CI 0.955 to 0.966) suggests that at least in some AS subsets the performance of the PRS will be even better than reported here.[37]

PRS testing can be performed using data from any dense SNP microarray. Indeed, the performance of the PRS reported here was high despite our use of a relatively low density SNP microarray—the Illumina Core-Exome chip (>520 000 variants, including many rare and non-polymorphic variants that do not contribute to the PRS). The performance of PRS testing would be likely to improve further with use of microarrays with better SNP coverage, or with whole genome sequencing. It has been estimated that up to 12 million Americans have had SNP microarray testing performed by commercial services such as 23andMe and Ancestry.[38] At little additional cost, these data would probably prove suitable for the calculation of the AS PRS we report, as well as enabling PRS for many other diseases in which they have been shown to be informative. The cost-effectiveness of the PRS we report here needs to be confirmed in further studies. As the genetic profile of AS becomes better understood, the discriminatory capacity of these tests is also likely to increase. For example, it is likely that many of the SNPs included in the PRS at present are not truly associated with AS, but just add noise to the test.

As there is no preventive therapy yet for AS, general population screening to identify patients at high risk of the disease is not recommended except, perhaps, for those at increased risk, such as the relatives of those with AS (given the high sibling recurrence risk of 8.2%).[39] PRS performs significantly better than *HLA-B27* testing alone in the general population, with the PPV of the ~8% of the general population who carry *HLA-B27* being 5%, compared with the peak PPV of the PRS of 15.1%. Similarly, the NPV for the PRS exceeds that of *HLA-B27* testing for most of the population. Although the PPV for PRS testing for general population screening is modest, the test performs well compared with other widely used screening tests. For example, the PPVs for 10-year risk of coronary heart disease of a high total cholesterol (≥240 mg/dL)—a threshold above which many patients will be prescribed cholesterol-lowering therapy—are 10.3% in women and 18.6% in men,[40] similar to the top 20% of PPVs of PRS for AS in general population screening. Among those who have already had SNP microarray testing performed, knowledge of a high AS-PRS even in the absence of symptoms may heighten clinician awareness of the possible diagnosis, reduce delay and assist with earlier appropriate and effective treatment, given the current long diagnostic delays.

Our study shows that the performance of the PRS varies between ethnic groups, although it remains moderately high even when a PRS developed in subjects of (western) European descent is tested in eastern European/west Asian subjects such as Turks and Iranians. The PRS developed specifically for East Asians performed far better in that population than did the European PRS, indicating that at least for populations that are remotely related, ethnic-specific PRSs are preferable.

We conclude that PRS testing for AS has greater discriminatory capacity than *HLA-B27* testing, MRI scanning or CRP testing, either alone or in combination. PRS could be used to screen patients with chronic back pain to identify subjects at increased risk of the disease for referral to secondary care and to assist in diagnosing the condition.

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**Contributors** Study design was performed by ZL, XW, PL, MHW, LG, MMW, MHR, JDR, BPW, HX and MAB. Case recruitment was performed by XW, NA, MA, GM, MM, HMO, CTC, AAH, SS, GTJ, SYB, GW, AJ, EF, JS, LL, ML, JCCW, NM, MJW, MJL, YW, JZ, JSZ, XW, JZB, MHW, LG, MMW, MHR, LD, THK, JDR, BPW, HX and MAB. Genotyping and/or analysis were performed by ZL,XW, ML PL, GW, EDG, LA, LW, XH and MAB. The manuscript was prepared by ZL, JDR, BPW, XH and MAB. All authors were involved in completion of, and approved, the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Written informed consent was obtained from all cases, with approval from the relevant research ethics authorities at each participating centre. The overall programme was reviewed and approved by Metro South Hospital Research Ethics Committee (approval reference HREC/05/QPAH/221).

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Details of the polygenic risk scores will be made available depending on completion of data transfer agreements with King's College London.

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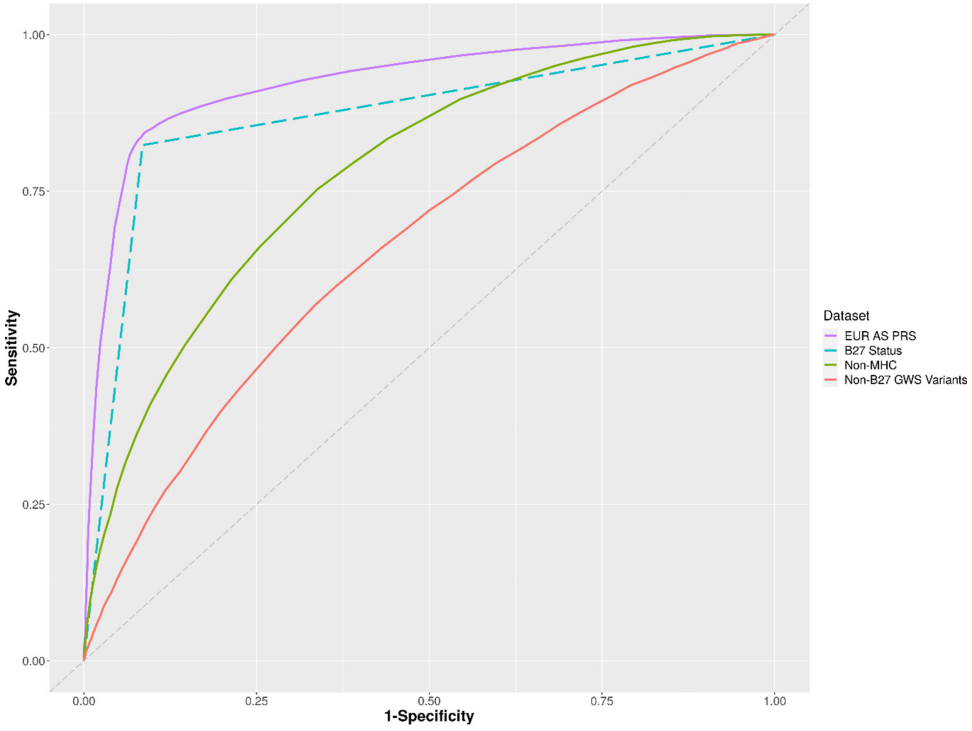
# Correction: *Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis*

Li Z, Wu X, Leo PJ, *et al*. Polygenic Risk Scores have high diagnostic capacity in ankylosing spondylitis. *Ann Rheum Dis* 2021;80:1168–74.

An error occurred in figure 1. The key for the figure has swapped the colours of the lines for 'B27 status' and 'non-MHC GWS variants'. The numbers for these are given in the text but the figure is wrong and should be:



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