

## Background

- Whole genome sequencing (WGS) remains the **gold standard** for genetic studies, but even though it has become more affordable the relatively **high cost remains a barrier** to the feasibility of many population studies
- Whole exome sequencing (WES) is a **more affordable option**, however, the shortcomings of being **blind to significant portions of the genome** may be prohibitive for certain research questions
- Imputation from genotyping arrays** provides a bridge between affordability and information about large regions of the genome, however the limitation of only being able to capture **predefined alleles** results in **reduced applicability to diverse populations and disease characteristics**
- Blended Genome-Exome** combines **high-coverage exome** (40x) and **low-coverage whole genome** (1-3x) into one sequencing product<sup>1</sup>

## Highlights

- Imputation using blended genome-exome (BGE) achieves superior results to existing methods using GDA genotyping arrays**
- Cloud-native pipeline provides cost-effective imputation for large-scale cohorts
- Accuracy of polygenic risk scores calculated from BGE data are on-par with or superior to existing technologies**, enabling both research and clinical applications

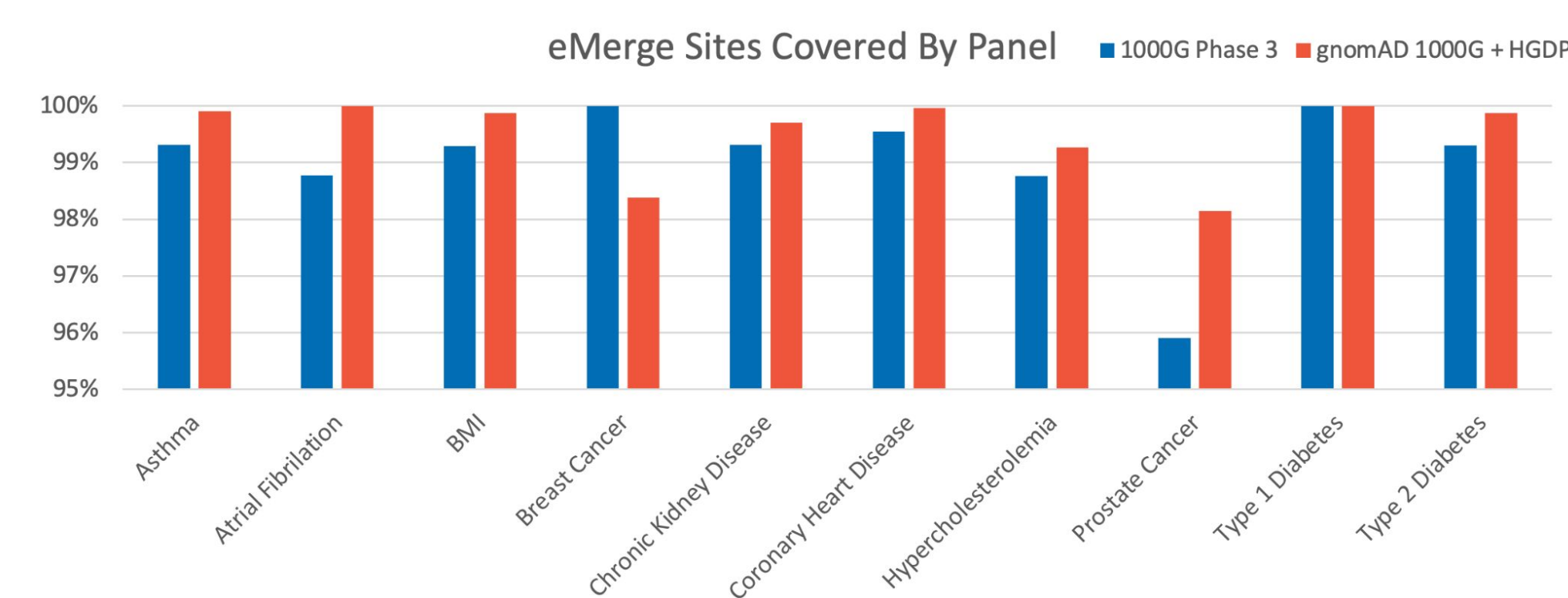
## Methods

### Imputation Pipeline

- GLIMPSE2<sup>2</sup> is optimized for low-coverage whole genome imputation, scaling sub-linearly with number of samples and markers in reference panel
- Cost-optimized cloud-native pipeline for high throughput of samples

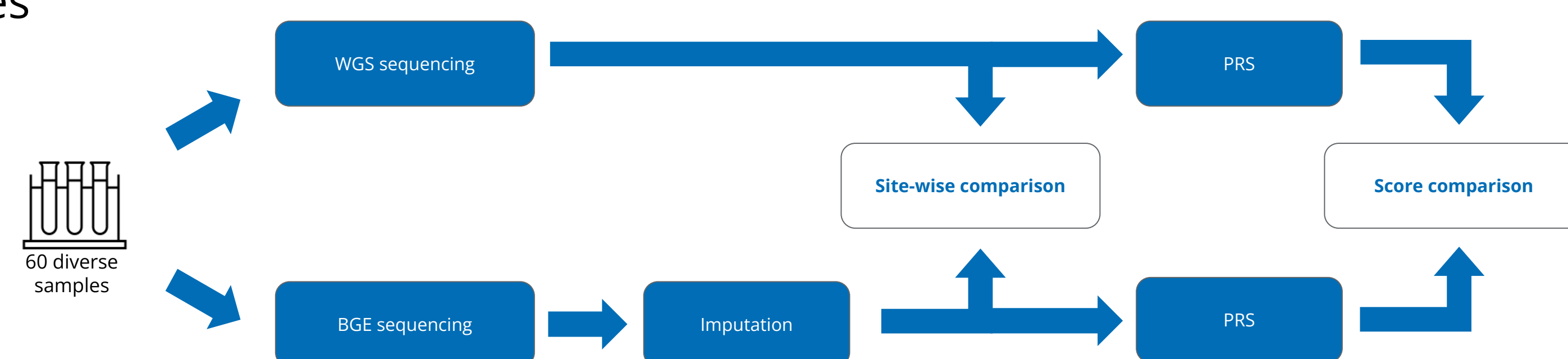
### Reference Panel

- Imputation using gnomAD 1000 Genomes + Human Genome Diversity Project (HGDP) panel<sup>3</sup>
- 2,500 samples (1000G) + 780 samples (HGDP) from > 60 distinct populations from Africa, Europe, the Middle East, South and Central and South Asia, East Asia, Oceania, and the Americas, jointly phased with entirety of gnomAD
- 91% more sites than commonly-used 1000G Phase 3 panel after removing singletons
- Increase in covered sites for 10 eMerge PRS models<sup>4</sup> from 99.3% to 99.8%



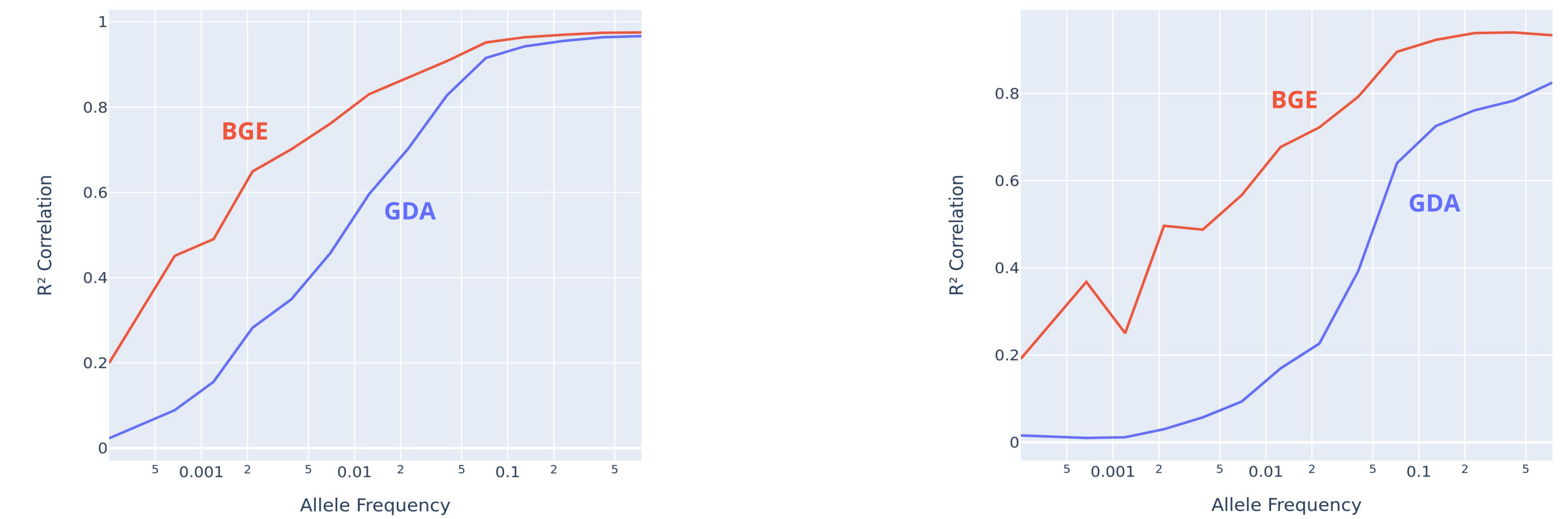
### Evaluation

- 60 samples of diverse ancestries with matched WGS, BGE, and GDA genotyping data
- Site-wise comparison of imputed (BGE/GDA) genotypes to measured (WGS) genotypes
- Calculation of eMerge Prostate Cancer PRS scores<sup>5</sup> on imputed (BGE/GDA) genotypes and measured WGS genotypes



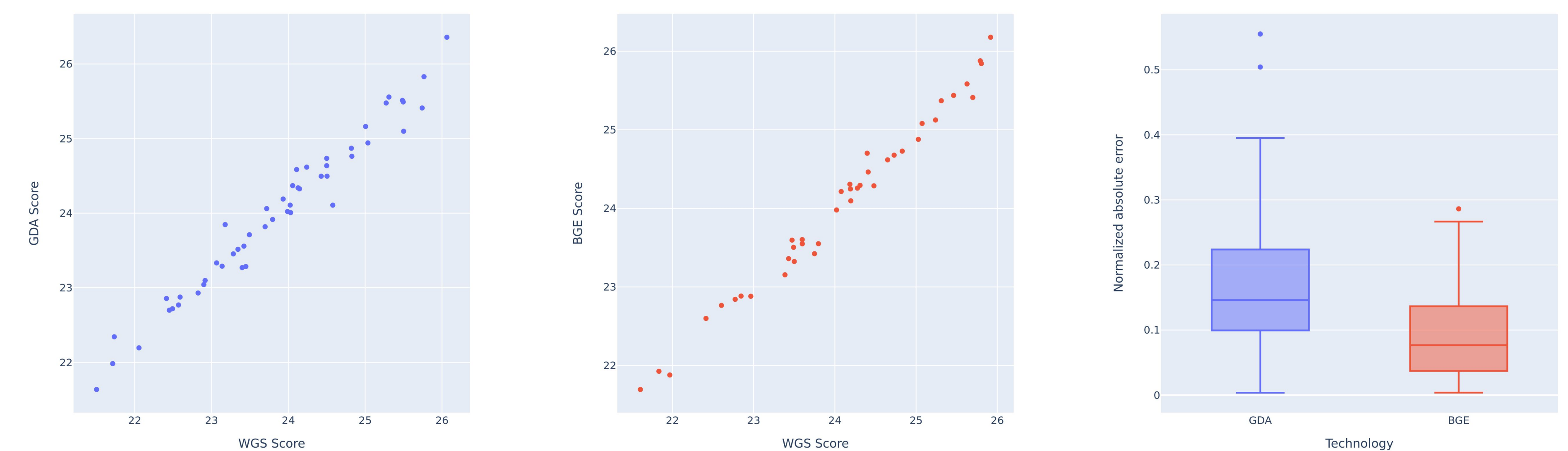
## Results

### Correlation between imputed sites and WGS sequencing



Site-wise correlation between WGS sequencing data and imputed genotypes from BGE and GDA data (chr20).

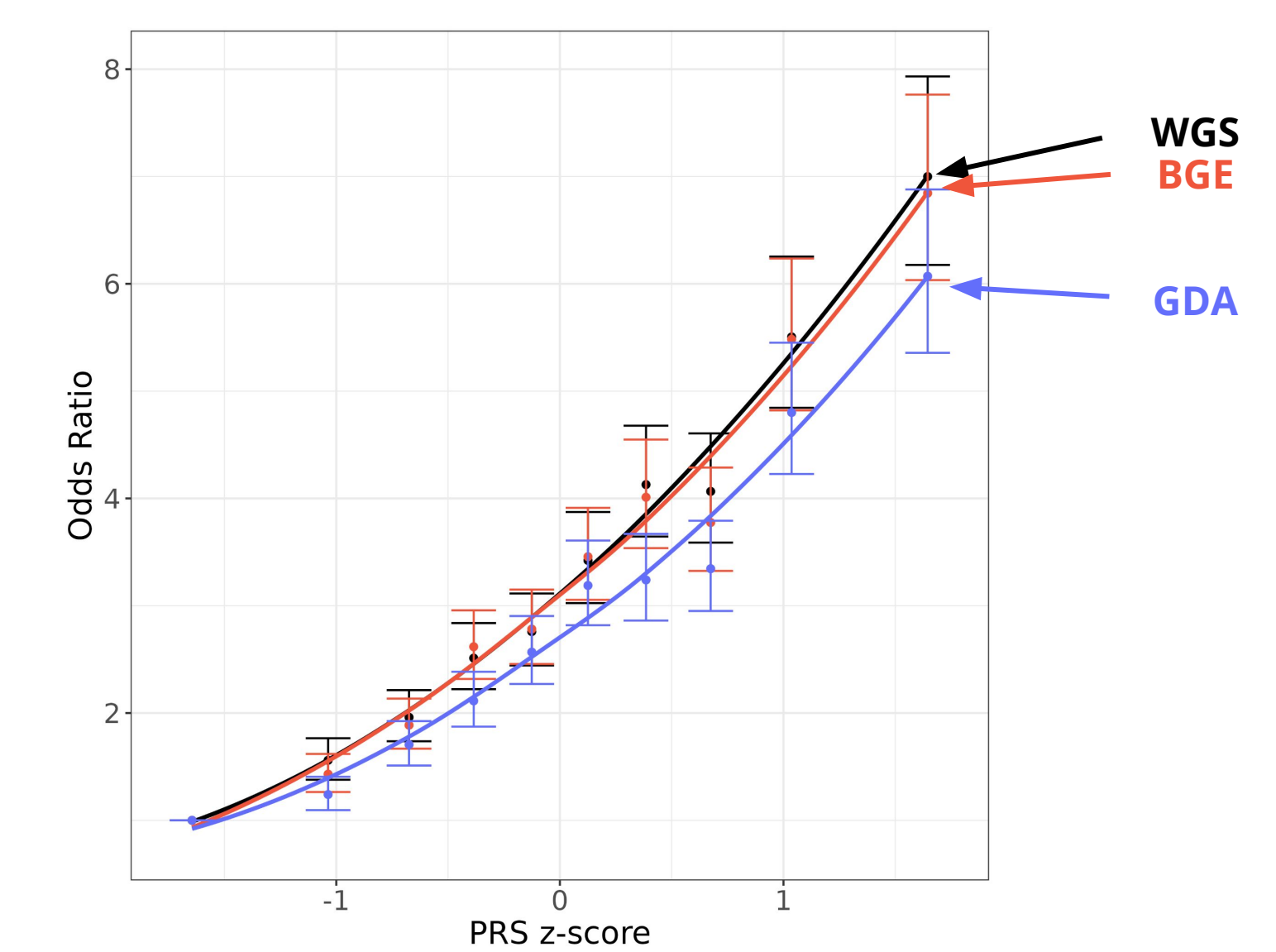
### Effect on Polygenic Risk Scores



PRS scores calculated from WGS data compared to PRS scores calculated from imputed BGE and GDA data, as well as the normalized absolute error between GDA/WGS scores and BGE/WGS scores.

### Validation of predictive power of different technologies

We calculated PRS scores (eMerge Prostate Cancer<sup>5</sup>) based on All of Us<sup>6</sup> WGS genotype data ( $n_{cases} = 4108$ ,  $n_{controls} = 4108$ ) and simulated BGE and GDA imputed data by adding the noise determined above, and validated the predictive power using corresponding phenotype data. PRS scores calculated from BGE data have better predictive power than PRS scores calculated from GDA data, and is comparable in accuracy to WGS.



## Conclusions

- The combination of Blended Genome-Exome data as an input for imputation with an improved, more diverse reference panel significantly improves the accuracy of results as compared with current approaches
- Combined with high-confidence over the exome calls for rare variants, Blended Genome-Exome provides a cost-effective and accurate solution for population genetics studies without the need for multiple analysis modalities
- The scalable cloud-native imputation pipeline enables a high throughput of samples for both research and clinical applications

## References

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 2. Rubincici, S., Hofmeister, R.J., Sousa da Mota, B. et al. Imputation of low-coverage sequencing data from 150,119 UK Biobank genomes. *Nat Genet* 55, 1088–1090 (2023)  
 3. Sivek, C., Laurent, C., Francioli, J., et al. A genome-wide mutational constraint map quantified from variation in 76,156 human genomes. *bioRxiv* 2022.03.20.485034 (2022)  
 4. Lennon, N.J., Kotlyan, L.C., Kachulis, C. et al. Selection, optimization, and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse populations. *medRxiv* 2023.05.25.23290535 (2023)  
 5. Conti, D.V., Darst, B.F., Moss, L.C. et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. *Nat Genet* 53, 65–75 (2021)  
 6. The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026558; 1 OT2 OD026559; 1 OT2 OD026560; 1 OT2 OD026561; 1 OT2 OD026562; 1 OT2 OD026563; 1 OT2 OD026564; 1 OT2 OD026565; 1 OT2 OD026566; 1 OT2 OD026567; 1 OT2 OD026568; 1 OT2 OD026569; 1 OT2 OD026570; 1 OT2 OD026571; 1 OT2 OD026572; 1 OT2 OD026573; 1 OT2 OD026574; 1 OT2 OD026575; 1 OT2 OD026576; 1 OT2 OD026577; 1 OT2 OD026578; 1 OT2 OD026579; 1 OT2 OD026580; 1 OT2 OD026581; 1 OT2 OD026582; 1 OT2 OD026583; 1 OT2 OD026584; 1 OT2 OD026585; 1 OT2 OD026586; 1 OT2 OD026587; 1 OT2 OD026588; 1 OT2 OD026589; 1 OT2 OD026590; 1 OT2 OD026591; 1 OT2 OD026592; 1 OT2 OD026593; 1 OT2 OD026594; 1 OT2 OD026595; 1 OT2 OD026596; 1 OT2 OD026597; 1 OT2 OD026598; 1 OT2 OD026599; 1 OT2 OD026600; 1 OT2 OD026601; 1 OT2 OD026602; 1 OT2 OD026603; 1 OT2 OD026604; 1 OT2 OD026605; 1 OT2 OD026606; 1 OT2 OD026607; 1 OT2 OD026608; 1 OT2 OD026609; 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