Delivery of Monogenic and Polygenic Results to Inform Prostate Cancer Screening: The Prostate Cancer, Genetic Risk and Equitable Screening Study (ProGRESS)

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G2V GENOMES TO VETERANS

P068

Background

- Prostate cancer (PCa) is a leading cause of death in the U.S., partially due to the lack of optimal screening strategies.
- Prostate-specific antigen (PSA) testing does not differentiate men with low-grade PCa from those with clinically significant PCa.
- Tailoring screening strategies to an individual's specific genetic profile may improve PCa screening effectiveness.
- ProGRESS is an ongoing national pragmatic randomized controlled trial of precision PCa screening.
- The Prostate CAncer integrated Risk Evaluation (P-CARE) model was derived from Million Veteran Program data and consists of a 601-SNP polygenic risk score, family history, and genetic principal components of ancestry (PMID: 41588240).
- Testing is performed using Broad Clinical Labs' Blended Genome- Exome (BGE) Sequencing.

Methods

Eligibility: men aged 55-69 without PCa and no prior prostate MRI or biopsy.

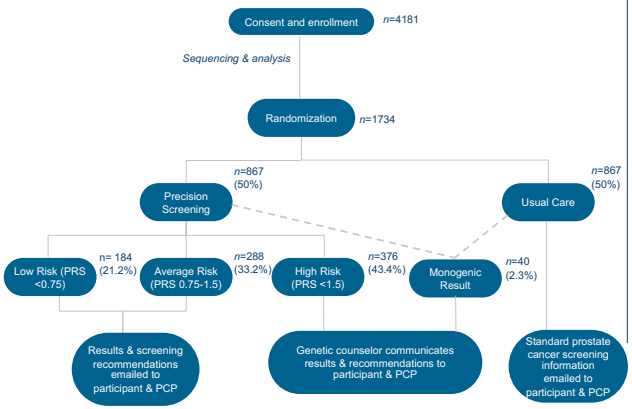

Figure 1. ProGRESS recruitment and enrollment to date.

Results as of 2/01/26

PRS result (precision screening arm)			
Low		184 (21.2%)	
Average		288 (33.2%)	
High		376 (43.4%)	
Monogenic result		40 (2.3%)	
ATM	10	*MLH1*	0
BRCA1	0	*MSH2*	0
BRCA2	5	*MSH6*	2
CHEK2	9	*PALB2*	2
EPCAM	0	*PMS2*	4
HOXB13	8	*TP53*	0

Table 1. ProGRESS trial participants results to date.

A third of the monogenic results were recurrent variants (*HOXB13* p.Gly84Glu and *CHEK2* c.1100delC). Another third were rare variants (gnomAD v4 filtering allele frequency < 1/100,000). The remaining third were established pathogenic/likely pathogenic variants, reported in gnomAD at a frequency above 1/100,000.

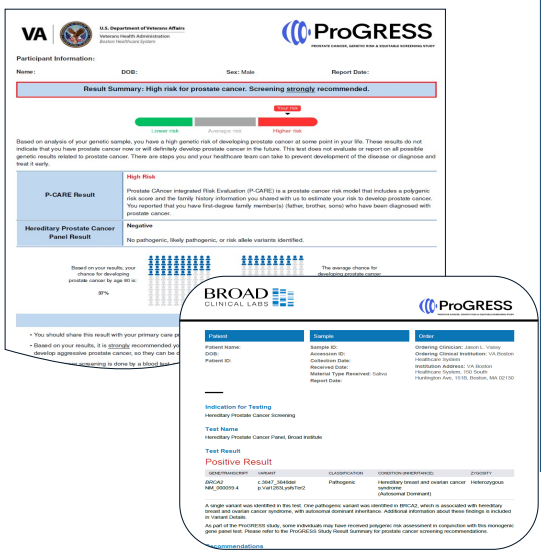

Figure 2. ProGRESS high risk result report.

Results as of 2/01/26

We have received genetic results for and randomized 1734 participants across 49 U.S. states, Puerto Rico, and Guam.

- Not surprised to learn their result
- Discussion of prior and future PSA screening
- Intention to discuss with PCP
- Elaboration of family cancer history
- Curious about difference between monogenic and polygenic testing
- Conflated colonoscopy and PSA screening

Figure 2. Frequent comments from phone conversations with participants with a monogenic finding (7-15 minutes) or high risk PRS (2-10 minutes).

Conclusion

Novel approaches to generating sequencing data at scale, like BGE, enables population-based genomic screening. The ongoing ProGRESS trial will determine if genetic-informed screening maintains the benefits of screening while minimizing the harms of unnecessary procedures by delivering a precision PCa screening intervention of monogenic testing for rare variants, a PRS, and screening recommendations delivered to participants and their PCPs.

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