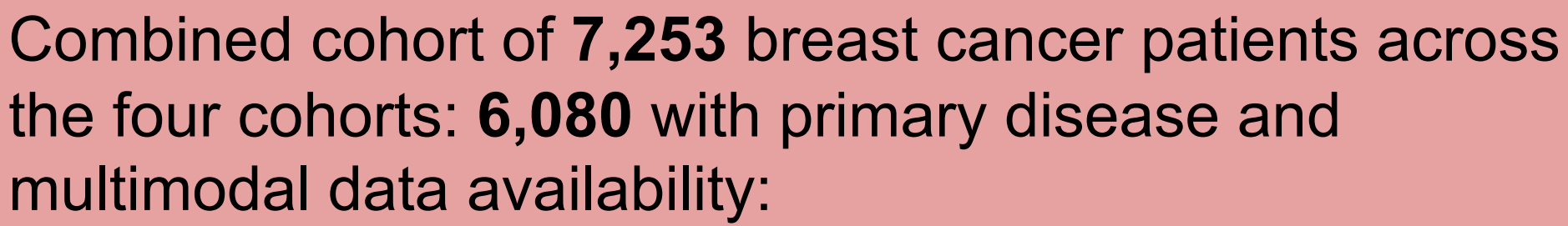


Thorn GJ^{1†}, Gadaleta E^{1*}, Dayem Ullah AZM¹, James LGE¹, Abdollahyan M¹, Barrow-McGee R², Jones LJ², Chelala C¹

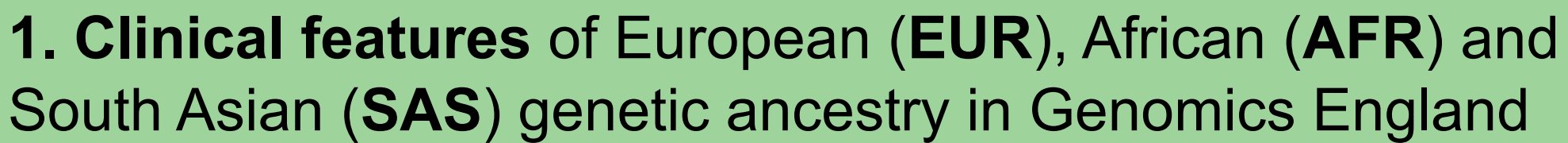
2. Centre for Tumour Biology, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, UK.

Thorn GJ*, Gadaleta E* et al. *Nat Commun* **16**, 4237 (2025)

Addressing existing racial disparity in breast cancer is crucial to ensure equitable benefit across diverse communities. We evaluate the molecular and clinical effects of genetic ancestry in African and South Asian women compared to European using a combined cohort of 7,253 breast cancer patients. We find that non-European patients present significantly earlier and die at a younger age. The African group has an increased prevalence of higher grade and hormone receptor negative disease. The South Asian group shows tendency towards lower stage at diagnosis and tumour mutational burden. We observe differences and similarities in the somatic mutational landscape, and differences in germline mutation rates relevant to genetic testing and breast cancer predisposition. Potential therapeutic candidates are identified, with a higher propensity for homologous recombination deficiency serving as a therapy response indicator. We harness breast cancer multimodal data to improve understanding of ancestry-associated differences and highlight opportunities to advance health equity.



- **2,781** from **Genomics England** 100K GP
- **1,895** from **BCN Biobank**
- **1,064** from **TCGA**
- **340** from **Genes & Health**



Descriptive characteristics:

- **AFR/SAS:** Earlier age at diagnosis, younger age at death
- **AFR:** Higher grade
- **AFR:** More ER-/PR- disease
- **AFR/SAS:** More commonly from more deprived quintiles
- **SAS:** Lower tumour mutational burden

Age at diagnosis:

- **AFR/SAS:** Peak at around 50 years old
- **EUR:** Bimodal distribution across 50-70 age range

Screening coverage:

- Current window (50-70) could miss cancers developing earlier in **non-EUR** patients
- Shifting window to earlier age would reduce inequality
 - **AFR**: ages 47-69 (coverage 61.31%)
 - **SAS**: ages 45-68 (coverage 59.35%)



Somatic signatures:

- **AFR:** more SBS1 (age-related), SBS3 (HR deficiency), RefSig R4 (clustered translocations), RefSig R5 (<10kb deletions)
- **SAS:** more SBS2 (APOBEC)

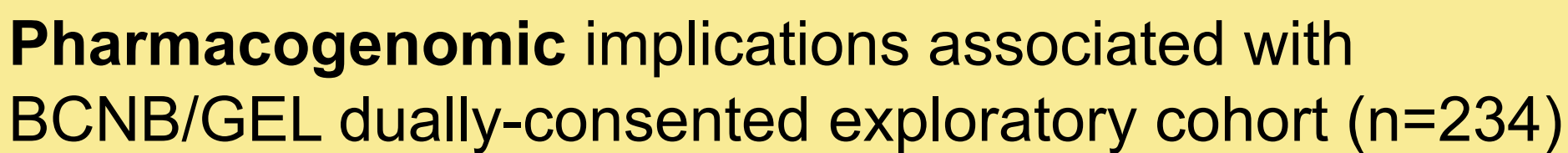
Homologous recombination deficiency patterns:

- **AFR:** More SBS3/RefSig R5
- **SAS:** More deletions with microhomology

Germline mutations:

Genes associated with DNA damage more frequently mutated in AFR compared to EUR in Genomics England and TCGA:

- **BRCA1** and **BRCA2**
- **PALB2**
- Fanconi anaemia genes (**FANCB**, **FANCI**, **FANCL**)
- Mismatch repair genes (**MSH2**, **MSH6**)



Somatic:

- **Homologous recombination deficient** patients:
 - Progression of disease of taxane-treated patients predicted by the pharmacogenomic analysis

Germline:

- Patients within the exploratory cohort that may have benefitted from PARP inhibitor treatment include:
 - 12.5% **BRCA1/2**-mutated
 - 31.3% **BRCA1/2** and/or **PALB2** mutated