# Genetics Plays a Limited Role in ESA-Hyporesponsiveness and Haemoglobin Outcomes in End-Stage Renal Disease Patients on Haemodialysis

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**Disclosures and Funding:**

- **SG** is an employee of Parexel International; **AYC, JLA, MGE and RKI** are employees of and shareholders in GlaxoSmithKline; **DJF and LDC** are employees of Parexel International and shareholders in GlaxoSmithKline; **GM** is an employee of and shareholder in DaVita; **JC** reports consultancy agreements and research funding with GlaxoSmithKline, ownership interest in DaVita Inc., and is a scientific advisor to GlaxoSmithKline
- This study was funded by GlaxoSmithKline
- Medical writing support (in the form of collating author comments and grammatical editing) was provided by Joanna Wilson, PhD, of Ashfield MedComms, Glasgow, UK, and was funded by GlaxoSmithKline

# Introduction and Methodology

## Study Population:

- ESRD patients on HD from DaVita Inc., a large dialysis organization in the US
- African Americans: 1380 patients; European Americans: 1410 patients

## Objective:

To determine if genetic variation, as measured by genetic risk score (GRS) is associated with anaemia outcomes in the ESRD population. GRS is calculated as a sum of the individual variant effects on hemoglobin concentration.

## Method:

- A logistic regression model was used to study association between exposure variables and ESA* hyporesponsiveness† and iron replete status‡ outcomes
- A linear regression model was used to study association between exposure variables and Hgb concentration§ outcome

## Exposures

- Genetic instruments:
  - Hgb Trans-ethnic GRS
  - Hgb European GRS
  - Hgb *EGLN* 1,2,3 GRS
- Demographics
- Prior treatments
- Baseline labs

## Anaemia Outcomes of Interest

- ESA Hyporesponsiveness
- Time-weighted mean Hgb
- Iron replete status

## Results

- Ancestry-specific baseline differences
- GRS, clinical variables association with outcomes

Epoetin alfa thresholds for ESA hyporesponsiveness = ERI ≥2.0 U/kg/wk/g/L (IV) or ≥1.33 U/kg/wk/g/L (SC), or Dose ≥450 U/kg/wk epoetin alfa (IV) or ≥300 U/kg/wk (SC). Darbepoetin thresholds for ESA hyporesponsiveness = ERI ≥0.008 µg/kg/wk/g/L (SC or IV), or Dose ≥1.5 µg/kg/wk (SC or IV). *SC or IV administration; †Identified either by the ERI (calculated as the dry weight adjusted weekly mean ESA dose divided by Hgb concentration) or by a very high dose of ESA; ‡Replete = ferritin >=100 ng/<L and TSAT >=20%, not replete Ferritin <100 ng/mL OR mean TSAT <20%; §Defined as time-weighted mean Hgb conc averaged over 1-year observational period.
Conc, concentration; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; GRS, genetic risk score; HD, haemodialysis; Hgb, haemoglobin; IV, intravenous; SC, subcutaneous

# Population-Level Differences of Baseline Variables Between African and European Americans

| Variable | AA vs EA mean/proportion diff: mean (95% CI) | P-value |
|---|---|---|
| Age, years | -6.93 (5.87 – 7.99) | $3.35 \times 10^{-36}$ |
| Sex, % female | 5.80 (1.74 – 9.86) | 0.0062 |
| Time on dialysis, years | 1.92 (1.56 – 2.30) | $5.07 \times 10^{-24}$ |
| Baseline albumin, g/L | 0.39 (0.11 – 0.67) | 0.0066 |
| Baseline ferritin, ng/mL | 80.01 (49.38 – 110.64) | $3.24 \times 10^{-7}$ |
| Baseline creatinine, µmol/L | 214.58 (194.85 – 234.31) | $7.24 \times 10^{-92}$ |
| Baseline sys BP status, mmHg | | $1.78 \times 10^{-4}$ |
| High [≥160mmHg], % | 7.70 (3.78 – 11.62) | NA |
| Low [<120mmHg], % | -2.8 (-5.12 to -0.48) | NA |

## Summary of observed differences

1. At enrolment AAs were on an average 6.93 years younger than EAs
2. The % of females in AA were 5.8% higher than the % in EA
3. AAs were 1.92 years longer on dialysis than EAs
4. Baseline differences in labs were also observed (see table)
5. AAs had higher % of patients with high BP (7.70% higher) and lower % of patients with low BP (2.8% lower) compared to EAs
6. Results indicate that population-level baseline variable differences need to be accounted for when designing clinical trials or providing clinical care

# Clinical Variable Associations With Anaemia Outcomes

| Clinical characteristic | Outcome | | |
|---|---|---|---|
| | ESA (HypoR vs responsive)* OR, p-value | Hgb concentration† estimate, p-value | Iron outcome (not replete vs replete) OR, p-value |
| Age, years | 0.98, p<0.01‡ | NS | 1.01, p<0.05‡¶ |
| Sex [ref=female] | 1.21, p<0.01‡<br>1.14, p<0.05§¶ | NS | NS |
| Time on dialysis, months | 1.01, p<0.01‡ | $8.33 \times 10^{-4}$, p<0.01§ | NS |
| ARB/ACEi status [ref=no baseline use] | 0.79, p<0.01‡ | -0.09, p<0.05‡¶<br>-0.11, p<0.01§ | NS |
| BMI, kg/m² | 0.93, p<0.0001 | NS | 1.03, p<0.01§ |
| Hgb, g/L | 0.93, p<0.0001‡<br>0.95, p<0.0001§ | 0.03, p<0.0001 | 0.97, p<0.0001‡ |
| TSAT, % | 0.97, p<0.0001‡<br>0.99, p<0.01§ | NS | 0.89, p<0.0001 |
| Albumin, g/L | 0.93, p<0.001§ | NS | 0.91, p<0.0001§ |

*When a single OR/estimate and p-value are shown without designating a particular population, the result applies to both the AA and EA populations. *ESA hypoR vs responsive status during 1-year period post-enrolment; †Time weighted mean Hb concentration per day measured during 1-year period post-enrolment; ‡In EA population; §In AA population; ¶Nominal association*

AA, African American; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; EA, European American; ESA, erythropoiesis-stimulating agent; Hgb, haemoglobin; HypoR, hyporesponsive; NA, not applicable; NS, not significant; sys, systolic; OR, odds ratio; TSAT, transferrin saturation

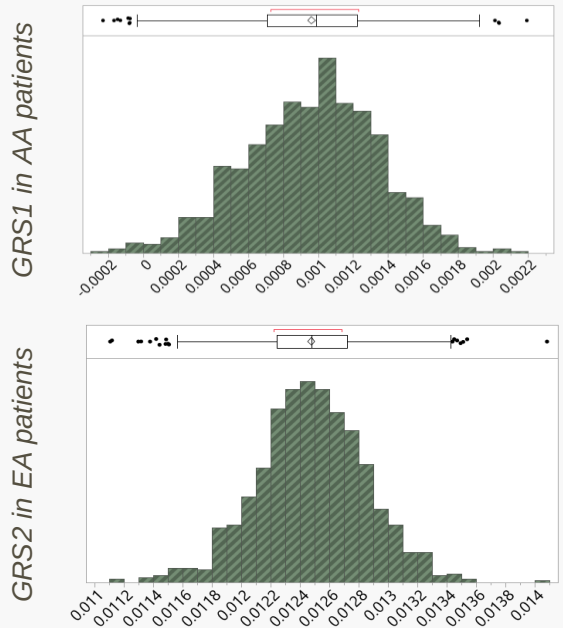
# Genetic Risk Scores Were not Associated With Outcomes of Interest

GRS

1. Hgb trans-ethnic GRS, constructed using variants from 5 ancestry-specific analyses with ~750K participants[1] (GRS1: only for AA patients)
2. Hgb European GRS, constructed using variants from UK biobank cohort with ~408K participants[2] (GRS2: only for EA patients)
3. Hgb GRS3 constructed from variants overlapping EGLN 1, 2, 3 and using beta/effect size from Vuckovic et al. 2020[2] (GRS3 used in both AA and EA patients)

| | ESA (HypoR vs responsive) p-value | | Hgb concentration p-value | | Iron outcome (not replete vs replete) p-value | |
|---|---|---|---|---|---|---|
| | EA | AA | EA | AA | EA | AA |
| **GRS1** | NA | p>0.1 | NA | p>0.1 | NA | p>0.5 |
| **GRS2** | p>0.1 | NA | p>0.1 | NA | p>0.1 | NA |
| **GRS3** | p<0.05‡ | p>0.05 | p>0.5 | p<0.01* | p>0.5 | p>0.5 |

## Distribution of GRS in cohort from this study



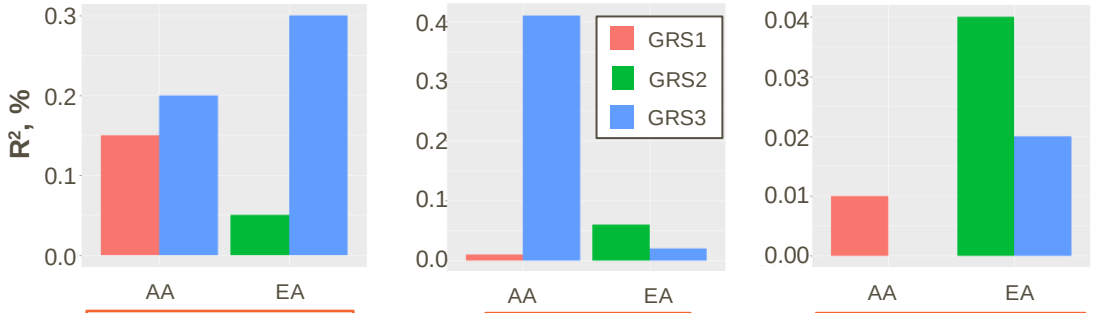

1. Chen M-H et al. Trans-ethnic and ancestry-specific blood-cell genetics in 746,667 individuals from 5 global populations. Cell. 2020; 182: 1198-1213;
2. Vuckovic et al. The Polygenic and Monogenic Basis of Blood Traits and Diseases. Cell. 2020 Sep 3;182(5):1214-1231.e11.

*Low beta squared effect size =0.005; ‡High mean OR with high variability

AA, African American; EA, European American; ESA, erythropoiesis-stimulating agent; GRS, genetic risk score; Hgb, haemoglobin; HypoR, hyporesponsive; NA, not applicable; OR, odds ratio

# Genetic Risk Scores Have no Clinically Meaningful Associations With Outcomes

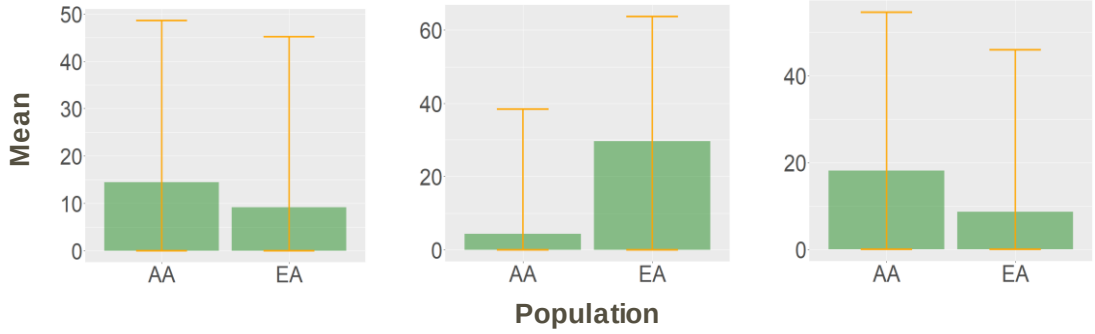
**$R^2$ coefficient of determination for GRS: A measure of variance captured. High $R^2$ means high ability to explain variation in outcomes**




**Summary**

For the statistically significant associations, the $R^2$ indicated that none of the GRSs evaluated explained clinically meaningful variation in outcomes of interest

**GCTA heritability estimates with SE**




**Summary**

GCTA analysis showed moderate heritability with high SE, indicating inconclusive evidence for significant genetic component for outcomes

AA, African American; Conc, concentration; EA, European American; ESA, erythropoiesis-stimulating agent; GCTA, genome-wide complex trait analysis; GRS, genetic risk score; Hgb, haemoglobin; $R^2$, correlation coefficient; SE, standard error

# Acknowledgements


- Sandra Stinnett (Parexel) for assistance with genetic sample genotyping
- Charles Cox (Pharmacogenetics, GlaxoSmithKline) for project support and insightful review and interpretation of results
- Alex Cobitz (Daprodustat team, GlaxoSmithKline) for input into protocol and data interpretation