Cognition and Education Benefits of Increased Hemoglobin and Blood Oxygenation in Children

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Disclosures

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- Current employment in Genesis Research and former employee of PRECISIONheor, a life sciences research consulting firm paid by GBT to conduct this study
- Research funding: NHLBI, HRSA, PCORI, and ASH

Allison A. King

- Research funding: Global Blood Therapeutics

Andy Nguyen

- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

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- Current employee of PRECISIONheor, a life sciences research consulting firm paid by GBT to conduct this study. He owns no equity in PRECISIONheor

Irene Agooda

- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics

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- Current employment and current equity holder in a publicly traded company: Global Blood Therapeutics
Introduction

- Chronic anemia in individuals with sickle cell disease (SCD) has been associated with impaired intellectual functioning and lower academic achievement.\textsuperscript{1-4}

- Among these individuals, decreased hemoglobin (Hb) is associated with increased risk of stroke and lower oxygen saturation (SpO2), which are both associated with lower intelligence quotient (IQ) scores.\textsuperscript{5,6}

- Thus, increasing Hb and SpO2 in individuals with SCD may increase IQ and educational attainment.


Hb, hemoglobin; IQ, intelligence quotient; SpO2, oxygen saturation.
Objectives

- To model the link between increased hemoglobin/oxygenation and improvements in cognitive function, educational attainment, and incidence of stroke as a result of improved treatment for SCD.
Methods
Model Design

- A cohort simulation model was built to reflect the pediatric SCD population and used to estimate how improvements in pediatric cognitive function, as measured by IQ, generated from randomized treatment for SCD, affect academic performance and educational attainment.

- The model contained two key stages: childhood (preschool and school age, <10 years) and adolescence (≥10 years). The model framework is shown in Figure 1.
  - In the first stage, children in the treated group had a mean Hb increase of 1.1 g/dL and increased SpO2, which impacted IQ by directly increasing it and preventing deterioration of IQ over time. Hb increase also decreased the risk of stroke.
  - In the second stage, adolescence, IQ was a determinant of academic performance, as measured by the Armed Forces Qualification Test scores.¹
  - These scores and other individual characteristics, including pre-school attendance, parental educational attainment, and noncognitive skills (social skills, motivation, self-esteem, and self-control) were employed to model years of education completed.²

- Key model parameters were identified in the literature and are summarized in Table 1.

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IQ, intelligence quotient; SCD, sickle cell disease; SpO2, oxygen saturation.
Figure 1. Model Diagram

Hb, hemoglobin; IQ, intelligence quotient; SCD, sickle cell disease.
Table 1. Key model parameters

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Value</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment effect on hemoglobin</strong></td>
<td>1.10 g/dL increase (95% CI: 0.9-1.4)</td>
<td>Vichinsky et al. (2019)¹</td>
</tr>
<tr>
<td><strong>Treatment effect on oxygen saturation</strong></td>
<td>3.10 percentage point increase per 1 g/dL increase in Hb</td>
<td>Blyden et al. (2018)²</td>
</tr>
<tr>
<td><strong>Relative stroke risk (infarctive)</strong></td>
<td>1.85 (95% CI: 1.32-2.59) per 1 g/dL decrease in Hb</td>
<td>Ohene-Frempong et al. (1998)³</td>
</tr>
<tr>
<td><strong>Reduction in IQ score in stage 1 resulting from stroke</strong></td>
<td>−15.86</td>
<td>Kawadler et al. (2014)⁴</td>
</tr>
<tr>
<td><strong>Reduction in IQ score in untreated state between stages 1 and 2 independent of stroke/infarct status</strong></td>
<td>−5.00</td>
<td>Wang et al. (2001),⁵ King et al. (2014)⁶</td>
</tr>
<tr>
<td><strong>Increase in IQ score per 1 percentage point increase in SpO₂</strong></td>
<td>0.75</td>
<td>King et al. (2014)⁶</td>
</tr>
<tr>
<td><strong>Baseline initial IQ</strong></td>
<td>Mean 89.18 (95% CI: 86.36-92.00)</td>
<td>Kawadler et al. (2014)⁴</td>
</tr>
<tr>
<td><strong>Baseline initial stroke risk</strong></td>
<td>Mean 7.20% (SD 0.7)</td>
<td>DeBaun et al. (2014)⁷</td>
</tr>
<tr>
<td><strong>Probability of being female</strong></td>
<td>52.00%</td>
<td>Farber et al (1985)⁸</td>
</tr>
</tbody>
</table>


Hb, hemoglobin; IQ, intelligence quotient; SpO₂, oxygen saturation.
Model Scenarios

• **Baseline**
  – Individuals in the treated group receive a boost in Hb and SpO2, which affects IQ both directly—increasing it and preventing the deterioration of IQ over time—and indirectly, by decreasing the risk of stroke.

• **Only treatment varies between cohorts**
  – All individuals in the cohort had the same baseline levels of socioeconomic variables including noncognitive skills, mother’s education, father’s education, and preschool attendance.
  – Isolates the impact of cognitive skills on educational attainment.

• **Treatment impacts noncognitive skill development as well as**
  – Explores the potential impact of allowing treatment to affect noncognitive skills, which in turn impact educational outcomes.
  – Treatment increased the probability that the socialization, self-concept, and motivation noncognitive skills were present by 10%.

Hb, hemoglobin; IQ, intelligence quotient; SpO2, oxygen saturation.
Results
44.4% Lower Incidence of Stroke Among Treated Group in Model

- The model predicted that 4.5% of the treated group would have a stroke versus 8.1% of the untreated group.
Average IQ 9.9% Higher Among Treated Group in Model

- Average IQ was estimated to be 91.1 in the treated group vs 82.8 in the untreated group

IQ, intelligence quotient.
High School Completion 64.7% Higher Among Treated Group in Model

- 76.1% of the treated group were projected to complete 12+ years of school vs 46.2% of the untreated group
## Model Results

<table>
<thead>
<tr>
<th>Predicted Outcome</th>
<th>Group</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Treated</td>
<td>Absolute</td>
<td>Relative</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Panel A: Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>8.1%</td>
<td>4.5%</td>
<td>−3.6%</td>
<td>−44.4%</td>
<td>0.001</td>
</tr>
<tr>
<td>IQ score</td>
<td>82.85</td>
<td>91.08</td>
<td>8.23</td>
<td>9.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.87</td>
<td>12.53</td>
<td>0.65</td>
<td>5.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% completing ≥12 years of education</td>
<td>46.2%</td>
<td>76.1%</td>
<td>29.9%</td>
<td>64.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Panel B: Scenario 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>8.3%</td>
<td>4.3%</td>
<td>−4.0%</td>
<td>−48.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IQ score</td>
<td>82.72</td>
<td>91.03</td>
<td>8.30</td>
<td>10.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.50</td>
<td>12.17</td>
<td>0.66</td>
<td>5.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% completing ≥12 years of education</td>
<td>18.7%</td>
<td>65.0%</td>
<td>46.3%</td>
<td>247.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Panel C: Scenario 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>6.9%</td>
<td>4.9%</td>
<td>−2.0%</td>
<td>−29.0%</td>
<td>0.058</td>
</tr>
<tr>
<td>IQ score</td>
<td>82.96</td>
<td>90.94</td>
<td>7.99</td>
<td>9.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.86</td>
<td>12.55</td>
<td>0.69</td>
<td>5.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% completing ≥12 years of education</td>
<td>44.9%</td>
<td>75.2%</td>
<td>30.3%</td>
<td>67.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQ, intelligence quotient.
Limitations

The model does not capture the following impacts/relationships:

• Improved cognitive function on noncognitive function

• Improved cognitive function and increased educational attainment on employment

• Improved cognitive function and increased educational attainment on life expectancy

• Stroke on educational attainment and academic achievement (only captured indirectly through IQ)

IQ, intelligence quotient.
Conclusions

In this simulation model, children with SCD with increased Hb and SpO2 were estimated to have better cognitive function (IQ) and lower risk of stroke.

Our model predicts that an average 1.1 g/dL improvement in Hb may be associated with improved neurocognition and educational outcomes.

These improvements may also generate benefits not captured by our model, including improved quality of life, employment, and income among individuals with SCD.

Hb, hemoglobin; IQ, intelligence quotient; SCD, sickle cell disease; SpO2, oxygen saturation.
Acknowledgments

- This study was supported by Global Blood Therapeutics.