OBJECTIVE: Pulse oximetry is commonly used in Neonatology, however recent adult data suggest racial disparity in accuracy, with overestimation of oxygen saturation for Black patients.

STUDY DESIGN: Black and White infants <32 weeks gestation underwent simultaneous arterial blood gas and pulse oximetry measurement. Error by race was examined using mean bias, A_{max} Bland–Altman, and linear/non-linear analysis.

RESULTS: A total of 294 infants (124 Black, 170 White) were identified with mean GA of 25.8 ± 2.1 weeks and mean BW of 845 ± 265 grams, yielding 4387 SaO2–SpO2 datapoints. SpO2 overestimation, measured by mean bias, was 2.4-fold greater for Black infants and resulted in greater occult hypoxemia (SpO2 > 90% when SaO2 < 85%; 9.2% vs. 7.7% of samples). Sensitivity and specificity for detection of true hypoxemia were similar between groups (39 vs. 38%; 81 vs. 78%).

CONCLUSION: There is a modest but consistent difference in SpO2 error between Black and White infants, with increased incidence of occult hypoxemia in Black infants.

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INTRODUCTION
Continuous pulse oximetry has been a valuable tool for Neonatologists since the early 1980s [1, 2]. Titration of supplemental oxygen to maintain a narrow window of oxygen saturation is essential to reduce the risk of retinopathy of prematurity [3, 4], bronchopulmonary dysplasia [5, 6], and death [7, 8]. Continuous pulse oximetry (SpO2) is superior to clinical observation alone; without it, desaturation can only be detected once arterial saturation (SaO2) has dropped below 80% and cyanosis develops [9, 10]. Pulse oximetry also avoids frequent phlebotomy for blood gas analysis, which is painful and causes iatrogenic anemia.

Oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) absorb red (660 nm) and infrared (940 nm) light differently—saturated blood permits increased transmission of red light but decreased transmission of infrared light. Accordingly, a pulse oximeter consists of red and infrared light emitters and a photoreceiver positioned on opposite sides of an arterial bed and measures the quantity of light transmitted through tissue. As oxygen saturation is the ratio of oxyhemoglobin to total hemoglobin, arterial saturation (SaO2) can be derived from variation in light absorption [11–13].

Melanin is a secondary absorber of near-infrared light and may impact pulse oximeter accuracy. A recent comparison of oxygen saturation determined by pulse oximeter and arterial blood gas (ABG) in adults, demonstrated a notable overestimation of oxygen saturation in patients self-identified as Black [14] and an increased incidence of occult hypoxemia. Another recent study of adults admitted to the ICU with COVID-19 [15] identified suboptimal pulse oximeter accuracy. As this study used a cohort with nearly 70% of individuals identified as Black, Asian or Minority Ethnic, the authors speculated that greater melanin concentration may have contributed to increased inaccuracy [16]. Given the link between hypoxemia and adverse outcomes in preterm infants, over-estimation of oxygenation may be problematic.

For this study, we identified a cohort of preterm infants born before 32 weeks gestation who had a simultaneous collection of timed ABG samples and pulse oximetry. We hypothesized that differences in secondary light absorption between Black and White infants will lead to systematic error in pulse oximeter-based determination of arterial oxygen saturation.

METHODS
Cohort development
All preterm infants born between 2012 and 2019 with a gestational age of less than 32 weeks, birth weight less than 1500 g, and admitted to the St. Louis Children’s Hospital Neonatal Intensive Care Unit (SLCH NICU) were eligible for inclusion.

Infants admitted to the SLCH NICU undergo continuous vital sign monitoring including pulse oximetry. Patient monitors were either Philips IntelliVue MP70 or MX800 (Philips Medical, Andover, MA), but both use a common pulse oximeter, the Nellcor SpO2 Module (Medtronic, Minneapolis, MN) with the Neonatal-Adult MAX-N adhesive SpO2 sensor (Covidien, Mansfield, MA). Vital sign data are automatically captured in an electronic database (BedMasterEX, Excel Medical, Jupiter, FL) sampled once per second (1 Hz). During the study period, all infants had standardized oxygen saturation targets to maintain SpO2 between 90 and 95% with alarm limits set between 88 and 96%. After infants reached 35 weeks post-menstrual age (PMA), the target range was changed to 90–100% with the desaturation alarm set to 88%.

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Infants were included in the study if they met gestational age and birth weight criteria, had valid vital sign data, and at least one ABG performed during hospitalization. Standard clinical variables were collected including gestational age, birth weight, sex, antenatal steroid exposure, method of delivery, and Apgar scores. Infants were classified as Black or White based on parental identification on birth certificates. Infants of Hispanic, Asian, or unspecified descent made up a small proportion of admissions to the SLCH NICU and were excluded as there would be an insufficient number for a representative sample. The study was reviewed and approved by the IRB at Washington University under waiver of consent.

**ABG analysis**

Invasive arterial lines are placed for frequent blood sampling and/or arterial blood pressure monitoring. ABG analysis was performed in a consistent manner across all patients—the line was accessed and cleared and a minimum sample volume of 0.5 mL was obtained and immediately brought to the clinical laboratory where it was run on a gas analyzer (ABL800 Flex, Radiometer America, Brea, CA) yielding a measurement of arterial oxygen saturation (SaO₂). For each patient in the cohort, the measured SaO₂ and the date/time of sample acquisition were recorded.

**SpO₂ processing and bias calculation**

Raw recording files were converted to MATLAB format (The MathWorks, Natick, MA) using conversion software (University of Virginia, Charlottesville, VA). A processing script identified the location corresponding to the date/time of the ABG and extracted a time-matched 60-second window of SpO₂ data centered on the ABG timepoint (30 s before and after) which was then averaged. This average of over 60 s was employed to reduce the impact of transient fluctuations in the SpO₂ and to mimic the typical length of time taken to draw an arterial sample for the SaO₂.

**Accuracy measurements**

The accuracy of pulse oximetry to estimate arterial oxygen saturation can be evaluated in several different ways. The primary methods used in FDA practice are mean bias and accuracy root mean squared, however, we performed an expanded analysis of pulse ox accuracy across six different metrics including:

1. **Mean bias (B)** – Mean bias is the average difference between SaO₂ and SpO₂, and is calculated using the formula:

   \[ B = \frac{\sum (S_{aO₂} - S_{PO₂})}{n} \]

   Positive values resulting from this calculation indicate an overestimation of SaO₂ by the pulse oximeter while negative values indicate an underestimate.

2. **Accuracy root mean squared (Arms)** – Arms is a related measure of the average difference between SaO₂ and SpO₂, and is calculated using the formula:

   \[ \text{Arms} = \sqrt{\frac{\sum (S_{aO₂} - S_{PO₂})^2}{n}} \] [17].

   Given the quadratic nature of this calculation, Arms is always a positive value and ranges from 0 (no error at all) and increases as the number of errors increase.

3. **Proportional bias** – Also called Bland–Altman analysis, this method was developed to quantify differences between measurement methods. Like B and Arms, the mean difference between the two methods is first calculated. From these differences, the 95% limits of agreement can be computed as the average difference ± 1.96 standard deviations. Bland–Altman can be used to identify the relationship of discrepancies between two measurement methods, also called proportional bias. The presence of proportional bias indicates that the degree of disagreement varies over the range of measurements.

4. **Prevalence of occult hypoxemia** – The occult hypoxemia definition of Spjoding et al. was adapted to the preterm population. In this case, occult hypoxemia was defined as a true SaO₂ < 85% when SpO₂ reads a value in the normal range (SpO₂ ≥ 95%).

5. **Sensitivity/specificity for detection of occult hypoxemia** – The sensitivity of the pulse oximeter to detect true hypoxemia (SpO₂ < 90% when SaO₂ < 85%) was calculated as:

   \[ \text{Sensitivity} = \frac{\text{True positive}}{\text{True negative} + \text{False positive}} \]

   Sensitivity and specificity calculations were made for the overall cohort and within racial groups.

   While B and Arms were calculated across the entire range of SpO₂ values, an evaluation of local bias was also conducted on the “clinically relevant” SpO₂ range of 85–100%. An additional limited investigation was performed to study the impact of post-menstrual age (PMA) at the time of sampling on measurement error.

**Statistical approach**

Infant characteristics underwent univariate comparison using non-parametric methods including Fisher’s Exact Test for categorical variables and Mann–Whitney U test for continuous variables. The proportion of samples where occult hypoxemia occurred was compared between Black and White infants using Fisher’s Exact Test.

The relationship between SpO₂ and SaO₂, bias, and PMA were modeled using the Pearson correlation coefficient and conventional linear regression. Non-linear regression was performed using a conditional mean function, where the outcome variable (e.g., SaO₂ bias score) was modeled as a function of SpO₂. In this approach, a larger dataset is convoluted or broken into smaller subsets, in which low-order polynomials are fit. For these analyses, the length of the sampling was four days (IQR 2-7), reflecting our typical clinical practice of obtaining an arterial blood gas every 8 h from an arterial catheter in place for an average of four days following birth for VLBW infants. Most of the samples were obtained within the first week of life (75% within seven days, Supplemental Fig. 1).

Of the 294 included infants, 42% were Black and 58% were White, consistent with the general demographic profile of infants admitted to the SLCH NICU (40% Black, 50% White, 10% Asian, Hispanic, or not listed). The two groups of infants were similar except for slightly lower birth weight (805 g vs. 875 g, p = 0.02) and median one-minute Apgar score (2 vs. 3, p < 0.01) in the Black infants. All other characteristics were not statistically different. A complete descriptive summary of the cohort can be found in Table 1.

**Occult hypoxemia**

The number of data samples was balanced between the two groups, with 2044 samples for Black infants and 2342 samples for White infants. True hypoxemia (defined as SaO₂ < 85%) was noted slightly more often in Black infants, being identified in 312/2044 (15.2%) of samples as compared to 293/2342 (12.5%) of samples for White infants. Occult hypoxemia, (defined as SaO₂ < 85% when SpO₂ ≥ 90%) was more common in Black infants, occurring in 188/2044 (9.2%) of samples compared to 181/2343 (7.7%) of samples for White infants, although this difference did not meet statistical significance (p = 0.08).

**Sensitivity and specificity for detection of hypoxemia**

Of the 4387 SpO₂-SaO₂ pairs collected in this study, 605/4387 (13.7%) were noted to have true hypoxemia. Overall, the sensitivity of the pulse oximeter for detecting true hypoxemia (defined as SpO₂ < 90% when SaO₂ < 85%) was 38% while the specificity was 89%. In subgroup analysis by race, sensitivity and
Table 1. Cohort descriptive statistics.

|                      | Black infants, n = 124 | White infants, n=170 | P value |
|----------------------|------------------------|-----------------------|---------|
| Gestational age, mean (SD), weeks | 25.6 (1.9)            | 25.9 (2.1)            | 0.09    |
| Birth weight, mean (SD), grams    | 805 (260)             | 875 (268)             | 0.02*   |
| Female sex, n (%)                  | 64 (52)                | 74 (44)               | 0.19    |
| Apgar score one-minute, median (range) | 2 (0–8)              | 3 (0–10)              | <0.01*  |
| Apgar score five-minutes, median (range) | 6 (0–9)              | 6 (0–9)               | 0.09    |
| Received antenatal steroids, n (%) | 87 (70)               | 127 (74)              | 0.49    |
| Vaginal delivery, n (%)             | 35 (28)                | 42 (23)               | 0.68    |

* denotes significance at p < 0.05.

DISCUSSION
These data reveal a complex relationship between pulse oximetry-based estimation of arterial oxygen saturation and race. Over this collection of SaO2–SpO2 pairs, Black infants were noted to have true hypoxemia more often than White infants. Pulse oximetry overestimated the true arterial oxygen saturation of Black VLBW infants by 1% more on average compared to White infants. The direction of error also varies by SpO2, with overestimation of the true saturation when SpO2 is greater than 90% and underestimation at saturations of 90% or below. The greater degree of
imprecision for Black infants is well-summarized by the difference in \( A_{\text{rms}} \) values (9.5\% vs. 8.9\%). The aggregate impact of each of these small differences was an increased incidence of occult hypoxemia in Black infants, occurring in 9.2\% of samples compared to 7.7\% of samples for White infants.

Although the difference in measurement bias between Black and White infants is small, these one-minute samples represent only a small fraction of each infant’s NICU hospitalization. There are many examples in the literature of the association between hypoxia and severe outcomes including an increased incidence of intraventricular hemorrhage (IVH) \([19, 20]\) and death \([7, 8]\). In a previous publication, we identified that the difference in time spent with severe hypoxia between infants with severe IVH and those without severe IVH was less than 3\% of the total recording.

**Fig. 2** Scatterplot of oxygen saturation measured by pulse oximeter (x-axis) and ABG (y-axis). Black infants are shown as gray dots, White infants are shown as white dots. Regression lines are shown for each race group. The line of unity is shown as a diagonal gray line.

**Fig. 3** Measurement bias (SpO\textsubscript{2} saturation–ABG saturation) is shown, clustered by SpO\textsubscript{2} saturation and race. Black infants are shown as gray dots, White infants are shown as white dots. Non-linear regression lines are shown for each group (solid for Black infants, dashed for White infants). Shaded areas represent 95\% CI.
distribution of higher SpO2 values while also a greater number of infants in this study are compared, Black infants have a greater degree of separation generated by the algorithm was small, on lower SaO2 values (Supplemental Fig. 3). In a recent manuscript, the absorption spectra of fetal and adult hemoglobin with estimates ranging between 10 and 20% [24, 25]. In some investigations, the absorption spectra of fetal and adult hemoglobin were found to be identical [26, 27], however, there is some evidence that an admixture of HbF and HbA results in impaired pulse oximetry accuracy (underestimation) by 3–4% [28, 29], although this effect occurs primarily at lower oxygen saturation [30]. Although not measured, the slightly lower gestational age of Black infants in this cohort may have a higher proportion of HbF contributing to greater SpO2 error.

Skin pigmentation may also play a role in pulse oximeter accuracy. Melanin is a pigment produced by melanocytes located in the basal epidermis after exposure to ultraviolet radiation (UV, 280–315 nm) [31]. Although melanogenesis accelerates during periods of increased UV-B exposure (suntan), different amounts of basal melanin production result in varying skin tones [32]. Although the peak absorption frequency of melanin is between 400 and 600 nm (ultraviolet band), it also absorbs light across visible and infrared frequencies and is a particularly strong absorber in the near-infrared range [33]. As light absorption in the near-infrared spectrum is used by the pulse oximeter to identify the quantity of oxy- and deoxyhemoglobin, additional absorption by a secondary chromophore (melanin) disrupts the expected relationship. This potential problem has been borne out in experimental data demonstrating that increasing amounts of melanin lead to increasing error in spectroscopic measurements of hemoglobin species [33]. Melanocytes can be identified in the embryonic epidermis in the first trimester [34]. There has been limited examination of the developmental trajectory of melanin by melanocytes at different gestational ages, although a small study suggests that significant differences in skin reflectance (indicative of sufficient melanin to alter light absorption) between White and Black patients do not occur until 32 weeks corrected gestational age [35].

Complicating this analysis is the frequency with which these infants receive phototherapy for jaundice. Phototherapy lamps are engineered to generate light in the same frequency range that unconjugated bilirubin maximally absorbs light (340–540 nm) [34]. This spectral range overlaps with the band which activates melanocytes including UV-A and B (290–400 nm) [36]. There are a number of reports of an increase in melanin production following typical clinical phototherapy treatment in Black and Asian infants [37]. Increased melanin production in response to phototherapy may accelerate the change in skin reflectance beyond what might
be expected for gestational age, introducing the possibility of pulse oximetry error at younger than expected gestational ages.

The results of this study raise important questions about the utility and reliability of pulse oximetry in critical care. The modest correlation between $\text{SaO}_2$ and $\text{SpO}_2$ has been noted in other studies of infants and children [38–40], especially at lower saturation, and is likely the result of using healthy volunteers for calibration which may not be representative of the sick infant [11]. The impact of skin pigmentation has been investigated in several previous studies of adults and older children, although not in preterm infants. Studies of adults have reported mixed findings; some have identified overestimation of oxygen saturation by 2–10% in participants with greater skin pigmentation [41, 42]. Other studies [43, 44] have failed to replicate this difference, although both studies noted lower $\text{SpO}_2$ signal quality in adults with greater skin pigmentation. There has been only a single investigation of racial differences in pulse oximeter performance for infants [45] and it did not demonstrate a difference between infants with light and dark pigment. However, this study had a small sample size and strict inclusion criteria (term infants, no anemia or hypotension, stable $\text{SpO}_2$ for 2 minutes prior to sample) which are not typical for premature infants.

Although the validation data for the pulse oximeter used in this study is not publicly available, there are several other published neonatal validation studies using Nellcor-based pulse oximeters. Unfortunately, the race of the study population is either not provided in these reports [46–52] or Black infants are under-represented in the study cohort [29]. Without intentional oversampling of Black infants or stratified analysis of infants by race, disparities in device performance are not apparent. Infants in this study received a race classification based on self-report in birth certificate documentation. This binary approach does not capture the continuum of skin pigmentation, which likely has a variable impact on pulse oximeter accuracy. Several different systems for quantifying skin color have been suggested including the Fitzpatrick Skin Phototype [53], which uses a combination of visual appearance and response to ultraviolet light (burning vs. tanning). An alternative approach is the individual typology angle (ITA) which utilizes digital photography of a skin sample under highly controlled lighting conditions to quantify the amount of red-green, yellow-blue, and lightness-darkness ($L^*a^*b^*$ color) using software [54]. Although considerably more complex, melanin levels can also be quantified spectrally. Indeed, there are research near-infrared spectroscopy devices, tissue oxygen monitors which operate on similar physics principles to pulse oximetry, which utilize algorithms to quantify [55] and remove the influence of melanin in measurements [56, 57]. Notably, none of these approaches have been evaluated in the neonate.

There are several limitations of this study. First, blood gas samples can be contaminated by the accidental introduction of air into the syringe. This is a known problem in all blood gas analyses and samples are carefully examined (and potentially discarded) before the assay is run, minimizing this risk [58].

Second, the $\text{SpO}_2$ sensor placement is rotated every twelve hours to prevent skin injury. In positions other than the right upper extremity, the probe is in a post-ductal position. For preterm infants with a patent ductus arteriosus, there is the possibility of a mismatch between pre- and post-ductal measurements. Sensor placement is not routinely charted in the medical record and PDA screening is not universal, thus it is impossible to reconstruct when or how often this occurred.

Finally, infants in this study were assigned a binary race classification based on birth certificate data. The retrospective nature of this study prevents qualitative or quantitative assessment of skin tone for further interrogation. Future prospective studies should quantify melanin content, ideally spectrally, for a more granular understanding of the relationship between skin tone and device performance disparity. It is essential that preterm neonates are not excluded from correction algorithms investigation.

In conclusion, we find a small but consistent racial disparity in oxygen saturation measurement by pulse oximetry and an increased incidence of occult hypoxemia in Black preterm infants. There is increasing awareness of racial disparities in outcomes of preterm infants, particularly the risk of mortality [59–61]. Knowledge of the potential for occult hypoxemia may lead to changes in oxygen saturation targeting, with more attention paid to the avoidance of low-normal saturations to reduce the risk of adverse outcomes.

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AUTHOR CONTRIBUTIONS
ZAV and HVW developed the research idea. AT, HL, and NL performed chart reviews, analyzed the data, and wrote the manuscript. All of the authors have approved of the final manuscript, as submitted.

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Dr. Vesoulis provides independent consulting for Medtronic plc in an unrelated capacity. This project was not discussed with Medtronic during any stage of design, analysis, or writing. None of the authors have any other real or perceived conflicts of interest to disclose.

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