Surveillance genome sequencing reveals multiple SARS-CoV-2 variants circulating in central Texas, USA, with a predominance of delta variant and review of vaccine breakthrough cases

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Abstract
As surges in the COVID-19 pandemic have continued worldwide, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has mutated, spawning several new variants, and impacting, to various degrees, transmission, disease severity, diagnostics, therapeutics, and natural and vaccine-induced immunity. Baylor Scott & White Health has implemented, along with laboratory diagnosis, SARS-CoV-2 sequencing to identify variants in its geographical service area. We analyzed virus sequencing results of specimens collected across Central Texas and found dramatic changes in variant distribution in the first half of 2021. The alpha variant (B.1.1.7) became predominant at week 13 and continued dominance until week 25. A growth rate of 1.20 ($R^2 = 0.92$) for the first 15 weeks was noted and this growth gradually declined to $-0.55$ ($R^2 = 0.99$) for the final 13 weeks. Currently, B.1.1.7 is being displaced with B.1.617.2 at a 0.58 growth rate ($R^2 = 0.97$). We also investigated vaccine breakthrough cases (VBCs) within our healthcare system and present clinical data on 28 symptomatic patients.

KEYWORDS
coronavirus, disease control, genetic variation, genetics, vaccines/vaccine strains, virus classification

1 | INTRODUCTION

As of July 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 4.1 million deaths worldwide, more than 600,000 in the United States of America, and more than 51,000 in the state of Texas alone.1 As the pandemic continues to surge in countries that have not yet received meaningful supplies of vaccines and in communities that remain resistant to vaccination, genetic variants are emerging that have different characteristics in terms of transmissibility, the severity of disease they cause, and, potentially, their susceptibility to the treatments and vaccines developed based on the wild-type virus.2 Of particular concern are emerging variants that include mutations in the S gene, coding for the viral spike protein, which has been the primary target of the most effective vaccines and passive antibody treatments authorized and deployed against COVID-19.3 Variants with mutations in the S gene are potential threats to their continued efficacy.4,5 These concerns have provided an impetus to increase testing and sequencing of viral DNA in infected persons to understand the transmissibility, virulence, and ability of variants to evade current vaccines.6
RNA viruses exist as a swarm or "quasispecies" of genome sequences around a core consensus sequence. Under conditions of selection, such as those imposed by neutralizing antibodies or drugs, variants of the swarm can escape genetically and become resistant. To date, 4150 mutations have been identified in the S gene of SARS-CoV-2 isolated from humans (CoV-GLUE, 2021; GISAID, 2021). These mutations give rise to 1246 amino acid changes including 187 substitutions in the receptor-binding domain (RBD). The abundance of many variants in the human population suggests they are not accompanied by a fitness loss. Multiple mechanisms likely account for the emergence of such substitutions including host adaptation, immune selection during natural infection, and possibly recombination of individuals with incomplete or waning immunity.

Most clinical laboratories performing diagnostic testing for SARS-CoV-2 are not equipped to detect genetic variants unless additional resources are made available for genomic sequencing of suspected cases and false negatives caused by mutations in the targeted genes. The lack of funding for technology, clinical utility, and regulatory oversight may have contributed to nonavailability of sequencing methods in the clinical laboratories. Epidemiological investigations are not part of the diagnostic laboratory routine workflow; however, the widespread nature of the SARS-CoV-2 pandemic necessitates clinical laboratories be prepared—through funding, technology acquisition, appropriate staffing, and technical competency—to perform genetic sequencing to aid in the control measures.

To assist public health officials involved in tracking and tracing the SARS-CoV-2 variants in the Central Texas community, the Baylor Scott & White Health (BSWH) molecular microbiology laboratory participated in genotyping of previously confirmed SARS-CoV-2 specimens. The reports generated were not released to patients' electronic health records (EHR) but were provided to public health officials for necessary interventions when a variant of concern (VOC) or variant of interest (VOI) was identified. Similarly, VBCs were identified and reported according to Centers for Disease Control and Prevention (CDC) definitions.

In this report, we present the evolution of SARS-CoV-2 lineages in the Central Texas area, and their association with VBCs, along with a clinical history of those breakthrough cases. In large, randomized-controlled trials, each vaccine was found to be safe and efficacious in preventing symptomatic, laboratory-confirmed COVID-19. In this report, we present the evolution of SARS-CoV-2 lineages in the limited geography of Central Texas and their association with vaccine breakthrough along with a clinical history of vaccinated patients exposed to variants.

2 | MATERIALS AND METHODS

This study was reviewed and approved by the Baylor Scott & White Research Institute Institutional Review Board (IRB # 021-144) with a waiver of the requirement of informed consent for the use of residual specimens for sequencing and epidemiological studies.

2.1 | Specimen selection for sequencing

Since the beginning of the pandemic, our laboratory has archived all the positive specimens confirmed by one of the nucleic acid amplification methods that were deployed for the diagnosis of SARS-CoV-2 infections. Since the implementation of sequencing, both retrospective and prospective specimens have been selected for variant identification in our community. The BSWH molecular pathology laboratory has conducted approximately 400,000 tests and SARS-CoV-2 and reported a 10.8% overall positivity rate for the Central Texas geography. These tests include both symptomatic and surveillance specimens since the beginning of the pandemic, March 2020. However, surveillance testing resulted in 1.8% and symptomatic 15.8% positivity rates (Data accessed on May 27, 2021). Genome sequencing was introduced to detect SARS-CoV-2 variants from the beginning of the year, 2021.

Specimens (nasopharyngeal swabs) positive for SARS-CoV-2 by emergency use authorization (EUA)-cleared nucleic acid amplification methods, performed at the Department of Pathology and Laboratory Medicine, Baylor Scott & White Hospital, Temple, TX, from January 1, 2021, to July 7, 2021, were identified for sequencing. Specimens for sequencing were selected based on $C_t < 30$ on a polymerase chain reaction (PCR) method, or relative light units (RLU) > 1000 on a transcription-mediated amplification (TMA) method. With this approach, our laboratory has successfully sequenced 87% of the confirmed cases. We randomly selected 1% of the positive specimens for sequencing when positivity rates were higher than 5% and all positive specimens when positivity rates were <5%, to identify the variants in circulation.

2.2 | Vaccine breakthrough cases

An electronic query was set up in the EHR to identify patients with a COVID-19 vaccination history. If patients were tested multiple times postvaccination, they were distinctly counted, and the first positive was counted for statistical purposes. Retrospective data collection for VBTs was done from the beginning of the year 2021; however, many clinical specimens were not available for sequencing. Among 72 VBTs, we were able to salvage 33 specimens for sequencing. Among the 33 VBTs, we collected clinical data for 28 patients from BSWH, EHR. The remaining five patients may have used the BSWH system for vaccination and testing purposes only and BSWH, EHR did not have any relevant clinical data. In Figure 3, specimens excluded from sequencing due to unavailability and low virus load have been shown, 39 specimens in total were excluded from sequencing.

2.3 | Library preparation and sequence data analysis

Nucleic acid was purified from each specimen and subjected to reverse transcription, next-generation sequencing library preparation, sequencing, and data analysis according to the manufacturer’s recommendation using two different platforms.
2.4 | Sequencing on Ion Torrent (ThermoFisher) S5 system

Extracted RNA was subject to reverse transcription using the SuperScript VILO cDNA Synthesis Kit Chef (ThermoFisher Scientific). Library preparation and subsequent templates were performed using the AmpliSeq SARS-CoV-2 Research Panel, DL8 kit, and the Ion S50 & Ion 520 & Ion 530 Kit on the Ion Chef. Sequencing was performed on the Ion Torrent S5. Data were manually uploaded to the Next-Clade bioinformatics pipeline for analysis.

2.5 | Sequencing on Illumina COVIDSeq system

Extracted RNA was subject to reverse transcription and library preparation using the Illumina COVIDSeq Test protocol and reagents (Illumina, Inc.). Libraries were pooled per manufacturer instruction and sequenced on the Illumina NextSeq. Data were analyzed using the Illumina BaseSpace application/bioinformatics pipeline, DRAGEN COVID Lineage v3.5.1.

2.6 | Data collection

Epidemiological, demographic, clinical, and laboratory data were extracted from EHR and the laboratory information system.

2.7 | Statistical analysis

Descriptive analysis was performed to present demographics factors (age, gender, and ethnicity), clinical presentation, clinical outcome, and molecular studies on SARS-CoV-2 specimens. Growth rate statistical analyses were performed in SAS 9.4. All graphs were created in R version 3.5.1. To calculate growth curves, the Verhulst growth model, also known as the logistic growth model, was used to model population growth with constraints. The formula for the Verhulst growth model is:

\[
Y(t) = \frac{K}{1 + e^{r(t-b)}}
\]

where \(Y(t)\) = The population size at a given time, \(K\) = The upper limit of the population size (in our case, 1), \(r\) = the rate of maximum growth, \(b\) = the time at which the quantity is half its maximum value, \(t\) = time

3 | RESULTS

3.1 | Evolution of Central Texas variants and rapid displacement of B.1.1.7 with B.1.617.2

Since the beginning of the pandemic, our laboratory has archived all the positive specimens confirmed by one of the nucleic acid amplification methods that were deployed for the diagnosis of SARS-CoV-2 infections. Since the implementation of sequencing, both retrospective and prospective specimens have been selected for variant identification in our community. The BSWH molecular Microbiology laboratory has conducted approximately 400,000 tests and SARS-CoV-2 and reported a 10.8% overall positivity rate for the Central Texas geography. These tests include both symptomatic and surveillance specimens since the beginning of the pandemic, March 2020. However, surveillance testing resulted in 1.8% and symptomatic 15.8% positivity rates (Data accessed on May 27, 2021). Genome sequencing was introduced to detect SARS-CoV-2 variants from the beginning of the year, 2021. We randomly selected 1% of the positive specimens for sequencing during the initial weeks when positivity rates were higher than 5% and once the overall positivity rate was below 5% all positive specimens were in the pipeline for sequencing to identify the variants in circulation.

Figure 1 shows the distribution of variants in circulation by the week of collection during the study period. Data presented in Figure 1 do not reflect every sample sequenced as there is a process lag. Among the variants of interest, epsilon and iota were detected starting Week 5 through Week 18 and Weeks 14 and 22, respectively. Epsilon had the highest presence during Week 10, 4 (14.29%), and iota peaked during Week 19, 3 (7.14%). Other variants, such as B.1.621, B1.1.318, B.1.1.519 were also found circulating in central Texas at <5% of the total sequenced specimens. B.1.621 has been designated as Mu VOI while this manuscript went into the press.

Among the VOC, the alpha variant (B.1.1.7) became the predominant variant at Week 13 and continued dominance until Week 25 (Figure 2A). A growth rate of 1.20 \((R^2 = 0.92)\) for the first 15 weeks was noted and this growth gradually declined to -0.55 \((R^2 = 0.99)\) for the final 13 weeks. Currently, B.1.1.7 is being displaced by the delta variant (B.1.617.2) at 0.58 growth rate \((R^2 = 0.97)\) (Figure 2B).

3.2 | Vaccine breakthrough studies

BSWH tested 96,357 patients for SARS-CoV2 by nucleic acid amplification testing (NAAT) between January 1, 2021, and May 31, 2021. Patients tested multiple times were distinctly counted once. In the event a patient was tested multiple times with both detected and not detected results, only the first detected result was counted for capturing the vaccine breakthrough on the earliest day of detection.

Among the 96,357 patients, 3925 (4%) were fully vaccinated with the BNT162b2, mRNA-1273, or Janssen COVID-19 vaccine, and were at least 14 days post the final dose. An additional 3164 (3.2%) patients were partially vaccinated either with BNT162b2 or mRNA-1273. Patients were considered partially vaccinated if their second dose (or the single dose for Janssen COVID-19) was <14 days before the specimen collection being investigated.

According to the established criteria (https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html), we detected 72 (1.8%) VBCs out of 3925 fully vaccinated individuals.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant distribution nucleic acid amplification confirmed SARS-CoV-2 specimens were frozen until sequenced. Data presented in the bar graph show the variant distribution for the respective weeks and the trend lines for alpha and delta variants.

**FIGURE 1** Growth curves for alpha and delta variants. Growth rate statistical analyses were performed in SAS 9.4. All graphs were created in R version 3.5.1. To calculate growth curves, the Verhulst growth model, also known as the logistic growth model was used to model population growth with constraints. Data presented in (A) show growth curves for both alpha and delta variants from the beginning of the year 2021 and (B) rates for both variants for the final 13 weeks.
Of these 72 cases, 33 (45.8%) specimens had <30 Ct value or >1000 RLU on the TMA method and so were suitable for sequencing. In the partially vaccinated patients, 207 VBCs were detected for a 6.54% positivity rate, while among the 90,898 unvaccinated individuals, 10,503 (11.5%) were positive for SARS-CoV-2 infection.

Data presented in Figure 3 show the weekly distribution of VBCs and the variants involved. The vaccine breakthrough investigation was begun at Week 10. The alpha variant (B.1.1.7) caused 16 (22.2%) out 72 VBCs, while the delta variant (B.1.617.2) contributed 11 (15.2%) VBCs, all during the final 4 weeks of the study period (Weeks 24–27), as this variant gained more prevalence.

### 3.3 | Clinical presentation of vaccine breakthrough cases

We performed a review of EHR of patients who were fully vaccinated and experienced vaccine breakthroughs (Table 1). Among the 33 VBCs that were sequenced, 28 were included in the VBT study as their clinical data existed in BSWH, EHR. Of the 28 VBT cases reviewed, 17 (60%) were females, and the mean age of these 28 patients was 54.9 (20–88 years).

**Abbreviations:** CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HTN, hypertension.

Most of the vaccine breakthrough patients (96%) had comorbid conditions, hypertension being the most common (39.3%). Other common comorbid conditions were determined and included diabetes mellitus (28.6%), asthma (17.9%), and chronic obstructive pulmonary disease (7.1%). Approximately 45% of the patients reported being either active (10%) or former smokers (35%).

Table 1 shows the symptoms associated with breakthrough under each vaccine brand in our sample. However, direct comparisons between brands cannot be made with our data, given both the small numbers and the complexities related to the different dosing schedules and different rates of use in the population, and conclusions about the relative effectiveness of the different brands overall or against specific variants should not be inferred from these results. Two (2.1%) VBCs were hospitalized with shortness of breath. Despite the existence of comorbidities among VBCs, the majority of them had mild symptoms and did not require hospitalization.

### 4 | DISCUSSION

In this study, we examined the SARS-CoV-2 variant distribution in the Central Texas region in the first half of 2021, finding firstly growing dominance by the alpha (B.1.1.7) variant, with a maximum growth rate of 1.20 in the first 15 weeks, followed by rapid displacement by the delta (B1.617.2) variant at a 0.58 growth rate. We also identified 207 VBCs among the 3164 partially vaccinated individuals, and 72 among the 3925 fully vaccinated individuals for whom we had testing samples, including 28 for whom the variant with which they were infected was able to be determined. Similar to the overall pattern of various distribution among COVID cases in this study population, the sequenced VBCs showed a predominance of the alpha (B.1.1.7) variant being rapidly replaced by the delta (B.1.617.2) variant in the last few weeks of the study period.
Our findings regarding the distribution of circulating variants in Central Texas are similar to those observed for the United States as a whole. The alpha (B.1.1.7) variant became the predominant variant across the United States by April 2021, followed by rapid displacement by the delta (B.1.617.2) variant, which became the dominant strain early in July 2021. By July 3, 2021, the delta (B.1.617.2) variant accounted for an estimated 61.7% of COVID-19 cases nationally, which is similar to the 64% we observed in the final week of our study period (ending on July 7, 2021). Such rapid, widespread changes in variant distribution underscore the critical need for robust and timely genomic surveillance. A growth rate of 1.20 for the first 15 weeks was noted for the alpha variant and this growth gradually declined to −0.55 for the final 13 weeks. Currently, B.1.1.7 is being displaced with B.1.617.2 at a 0.58 growth rate. Our data collected from Central Texas reflect the national trend that delta is rapidly becoming a prevalent variant.

Questions raised with each new variant spreading include whether the variant will "escape" the protection conferred by either natural immunity following infection with a different strain of the virus or acquired immunity from one of the authorized vaccines, all of which were developed based on the version of SARS-CoV-2 originally detected in Wuhan, China. Of particular interest in the United States, currently, is whether the predominance of the delta (B.1.617.2) variant will cause an increased rate of VBCs. In the spring of 2021, the alpha (B.1.1.7) variant plateaued at a relatively low level in the many US regions in the context of increasing vaccination while mask mandates and social distancing measures implemented by local and state governments, as well as many private businesses, remained effective. However, as the delta variant spread rapidly, these measures may need to be reevaluated to ensure continued suppression of transmission.

### Table 1: Demographic, comorbidity, symptoms, and other social and past medical history of BSWH vaccine breakthrough cases

| Baseline characteristics (total n = 28) |
|----------------------------------------|
| **Demographics**                        |
| Gender % (n)                           |
| Male: 39% (11)                         |
| Female: 60% (17)                      |
| Age (years)                            |
| Mean: 54.9                             |
| Range: 20–88                           |
| **Comorbid conditions**                |
| Type 2 diabetes mellitus               |
| 28.6% (8)                              |
| Asthma % (n)                           |
| 17.9% (5)                              |
| COPD % (n)                             |
| 7.1% (2)                               |
| CHF % (n)                              |
| 3.6% (1)                               |
| HTN % (n)                              |
| 39.3% (11)                             |
| Current smokers                       |
| 10.7 (3)                               |
| Former smokers                        |
| 35.7% (10)                             |

| **Subjective symptoms**                |
|----------------------------------------|
| BNT162b2                               |
| Total 17                               |
| Asymptomatic, 28.6% (8)                |
| 41.2% (7)                              |
| Fever/chills, 25% (7)                  |
| 17.6% (3)                              |
| Headache, 28.6% (8)                    |
| 23.5% (4)                              |
| Rhinorrhea, 21.4% (6)                  |
| 5.9% (1)                               |
| Cough, 46.4% (13)                      |
| 23.5% (4)                              |
| Otyalgia/pressure, 3.6% (1)            |
| 0% (0)                                 |
| Odynophagia, 17.9% (5)                 |
| 17.6% (3)                              |
| SOB/severe dyspnea, 14.3% (4)          |
| 5.9% (1)                               |
| Diarrhea, 7.1% (2)                     |
| 5.9% (1)                               |
| Loss of taste and smell, 14.3% (4)     |
| 5.9% (1)                               |

| Janssen COVID-19 vaccine               |
| Total 11                               |
| Asymptomatic, 28.6% (8)                |
| 41.2% (7)                              |
| Fever/chills, 25% (7)                  |
| 17.6% (3)                              |
| Headache, 28.6% (8)                    |
| 23.5% (4)                              |
| Rhinorrhea, 21.4% (6)                  |
| 5.9% (1)                               |
| Cough, 46.4% (13)                      |
| 23.5% (4)                              |
| Otyalgia/pressure, 3.6% (1)            |
| 0% (0)                                 |
| Odynophagia, 17.9% (5)                 |
| 17.6% (3)                              |
| SOB/severe dyspnea, 14.3% (4)          |
| 5.9% (1)                               |
| Diarrhea, 7.1% (2)                     |
| 5.9% (1)                               |
| Loss of taste and smell, 14.3% (4)     |
| 5.9% (1)                               |

| mRNA-1273                              |
| Total 0                                |
| Asymptomatic, 28.6% (8)                |
| 9.1% (1)                               |
| Fever/chills, 25% (7)                  |
| 36.4% (4)                              |
| Headache, 28.6% (8)                    |
| 36.4% (4)                              |
| Rhinorrhea, 21.4% (6)                  |
| 45.5% (5)                              |
| Cough, 46.4% (13)                      |
| 81.8% (9)                              |
| Otyalgia/pressure, 3.6% (1)            |
| 9.1% (1)                               |
| Odynophagia, 17.9% (5)                 |
| 18.2% (2)                              |
| SOB/severe dyspnea, 14.3% (4)          |
| 27.3% (3)                              |
| Diarrhea, 7.1% (2)                     |
| 9.1% (1)                               |
| Loss of taste and smell, 14.3% (4)     |
| 27.3% (3)                              |
in place. Texas, which ended government-ordered mask mandates and other pandemic-related restrictions in March 2021, has seen a rapid rise in COVID-19 cases and hospitalizations again in July 2021 concomitant with the rising dominance of the delta (B.1.617.2) variant. Our results examining the variant distribution in VBCs show that both the alpha (B.1.1.7) and delta (B.1.617.2) variants caused a small number of breakthrough cases, with predominance patterns appearing to mirror those of the broader cases of COVID-19. The number of samples suitable for sequencing in our study is too small, and the portion of our study period in which the delta (B.1.617.2) variant held dominance too short, to make any comparisons regarding the risk for vaccine breakthrough these two variants carry.

Almost all (96%) of the fully vaccinated patients who experienced vaccine breakthroughs in our study had comorbid chronic conditions. Little evidence is currently available regarding risk factors for vaccine breakthrough infection, but our results are consistent with such evidence as is available. One study conducted using data from the Veterans Health Administration reported that increasing age, multiple comorbid conditions, and non-Black race were associated with confirmed breakthrough infection. A systematic review of studies reporting serious adverse effects, SARS-CoV-2 infection and deaths after COVID-19 vaccination, identified comorbidities, VOCs, and casual attitude toward COVID appropriate behaviors among the most important factors contributing to risk for vaccine breakthrough infection.

We also examined the symptoms the 28 fully vaccinated patients with breakthrough infections experienced. Cough was most commonly reported (46.4%), but four (14.3%) had shortness of breath, and 2 (7%) required hospitalization. In terms of serious illness requiring hospitalization, these results are similar to those reported by the CDC from 46 US states and territories as for January 1 to April 30, 2021, in which 10% of patients with breakthrough infections required hospitalization. Likewise, similar percentages of breakthrough cases were asymptomatic in our sample (28.6%) and in the national data reported by the CDC (27%).

Our study design was not intended to deduce vaccine effectiveness against any particular variant, but the small numbers of vaccine breakthrough infections we identified add to the growing evidence that the greatest remaining risks for COVID-19 in the United States are almost entirely isolated to the unvaccinated. Equally important is the substantially higher positivity rate we observed in partially vaccinated individuals. It is to be hoped that continued accumulation of such evidence will encourage the 40% of eligible Texans who remain entirely unvaccinated, and the 9% who have not completed their vaccination schedule to take this important step in protecting themselves, their families, and their communities. Continued monitoring will, of course, be needed, particularly given the current overall rise in the case of numbers in Texas, and the recent shift in dominance from the alpha (B.1.1.7) to the delta (B.1.617.2) variant. A second limitation that must be kept in mind when interpreting the results reported here is that, while clinical manifestation data for the 28 VBCs for which sequencing was possible are presented by vaccine brand, they cannot support comparisons of effectiveness between the brands, as there was an unequal distribution of vaccine brands in the Central Texas community.

In conclusion, our results show that, in early 2021, Central Texas experienced rapid growth of the alpha (B.1.1.7) variant, which then maintained dominance for several weeks, but toward the end of the study period (June/July 2021) was itself rapidly displaced by the delta (B.617.2) variant. Examination of vaccine breakthrough infections showed small numbers overall and with each of these variants, with the distribution of the variants among breakthrough cases following a similar pattern to the distribution in the overall COVID-19 cases in our study population. Continued monitoring is needed, both to assess the longer-term impact of the delta (B.1.617.2) variant’s dominance on risk for vaccine breakthrough infections, and to identify any new variants, or variants altering the distribution in circulating strains, that might impact risks for disease and/or effectiveness of vaccines and therapeutics.

Finally, the findings in this report are subject to at least two limitations. First, the number of reported COVID-19 vaccine breakthrough cases is likely a substantial undercount of all SARS-CoV-2 infections among fully vaccinated persons. This study relied on the EHR of patients within our healthcare system and data might not be complete or representative. Many persons with vaccine breakthrough infections, especially those who are asymptomatic or who experience mild illness, might not seek testing. Second, SARS-CoV-2 sequence data are available for only a small proportion of the reported cases.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Manohar B. Mutnal, Arundhati Rao, and Alejandro C. Arroliga conceived and designed the study. Shelby Johnson, Linden Morales, Marcus Volz, and Kimberly Walker performed the experiments, data collection, and analysis. Manohar B. Mutnal, Nada Mohamed, and Rasha Abdelgader helped in EHR data retrieval, analysis, and IRB submissions. Manohar B. Mutnal wrote the paper. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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