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Transcranial Doppler Screening in a Current Cohort of Children with Sickle Cell Anemia: Results from the DISPLACE Study

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Abstract

Stroke prevention guidelines for sickle cell anemia (SCA) recommend transcranial Doppler (TCD) screening to identify children at stroke risk; however, TCD screening implementation remains poor. This report describes results from Part 1 of the 28-site **DISPLACE** (**D**issemination and **I**mplementation of **S**troke **P**revention **L**ooking **a**t the **C**are **E**nvironment) study, a baseline assessment of TCD implementation rates. This report describes TCD implementation by consortium site characteristics; characteristics of TCDs completed; and TCD results based on age. The cohort included 5247 children with SCA, of whom 5116 were eligible for TCD implementation assessment for at least one study year. The majority of children were African American or Black, non-Hispanic and received Medicaid. Mean age at first recorded TCD was 5.9 years and 10.5 years at study end. Observed TCD screening rates were unsatisfactory across geographic regions (mean 49.9%; range 30.9–74.7%) independent of size, institution type, or previous stroke prevention trial participation. The abnormal TCD rate was 2.9%, with a median age of 6.3 years for first abnormal TCD result. Findings highlight real-world TCD screening practices and results from the largest SCA cohort to date. Data informed the Part 3 implementation study for improving stroke screening and findings may inform clinical practice improvements.

Keywords

pediatrics; sickle cell anemia; transcranial Doppler screening

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Introduction

Stroke is a devastating complication of sickle cell disease (SCD). Ischemic stroke is more common in the first decade of life while hemorrhagic stroke is more common in the 2nd-3rd decades. Although stroke can occur in all genotypes, ischemic stroke is more common in sickle cell anemia (SCA). In 1998, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated that a high risk group of children with SCA could be identified using transcranial Doppler ultrasound (TCD) and that chronic red cell transfusion (CRCT) could reduce risk of first ischemic stroke by over 90%.[1] The STOP protocol was further validated in follow-up studies which demonstrated a persistent, significantly reduced rate of ischemic stroke.[2, 3] Prior to STOP protocol implementation, the estimated chance of overt stroke by age 20 was 11%.[4]

The STOP protocol has been incorporated into several SCD-related treatment recommendations, including endorsement from the National Heart, Lung, and Blood Institute (NHLBI) following the STOP study, health supervision recommendations from the American Academy of Pediatrics in 2002, recommendations from the 2014 NHLBI Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, and the recently published 2020 American Society of Hematology (ASH) cerebrovascular guidelines.[5–7] The STOP protocol recommends children with SCA, ages 2–16, undergo an annual TCD to identify those individuals with abnormal (high) blood flow who are at high risk of stroke. The protocol then recommends initiating CRCT therapy for children with abnormal TCD. This is one of few endorsements designated as a “Strong Recommendation, High-Quality Evidence” in the NHLBI’s graded report.

Despite this recommendation, a retrospective study using Medicaid Claims Data and the recent Post-STOP study, as well as single-center projects, show poor implementation.[8–12] Although a few institutions have conducted quality improvement projects for TCD screening at their institutions,[9, 13, 14] a systematic, multi-site assessment of implementation of TCD screening in a nationally-representative sample of institutions caring for children with SCA has not been undertaken. A real-world assessment of TCD implementation overcomes limitations of prior studies that rely on successfully billed TCD screenings and do not capture unbillable screenings, such as those conducted in the clinic setting and those not conducted by a certified ultrasonographer. In addition, studies conducted only with Medicaid databases do not capture screenings for children with all types of third-party payers. In 2016, the **DISPLACE** (**D**issemination and **I**mplementation of **S**troke **P**revention **L**ooking **a**t the **C**are **E**nvironment) study was funded by NHLBI to evaluate implementation of TCD screening, assess barriers and facilitators to evidence-based stroke prevention for children with SCA, and test novel implementation strategies to overcome barriers across a large, multicenter consortium of 28 sites. DISPLACE was divided into three parts:

Part 1: Retrospective cohort study using rigorous chart review to assess the gap between current and recommended evidence-based stroke prevention practices (both risk identification and preventive intervention) as an assessment of current practice.

Part 2: Quantitative and qualitative multilevel assessment of barriers and facilitators to stroke prevention practices.

Part 3: A novel implementation multi-level trial to enhance implementation of stroke screening.

This report describes findings from DISPLACE Part 1, highlighting real-world implementation of stroke screening practices and TCD results from the largest SCA cohort to date. Specifically, this report describes a baseline (retrospective) assessment of TCD implementation rates among the consortium. The report also describes site characteristics in relation to TCD implementation and characteristics of completed TCDs. In addition, we examined age at first abnormal TCD to determine whether a specific age cohort of children could be identified as the focus of the Part 3 implementation trial.

Materials and Methods

Study Design Overview

This retrospective medical record review study was designed to identify current stroke screening practices including rates of TCD implementation in a nationally representative, diverse cohort of children with SCA. Parts 1 and 2 are registered in ClinicalTrials.gov under NCT03621826.

Consortium Selection

Potential site investigators from Pediatric Hematology/Oncology departments were recruited to represent tertiary academic medical centers and community-based SCD centers of varying sizes, locations, and experience in clinical research. Thirty-five sites were approached for the study. Five sites felt they did not have the resources to complete the study. Two sites who had previously undertaken quality improvement projects did not want to be included as they had recently made changes to their screening process. Twenty-eight sites agreed to participate.

Patient Identification

Each consortium institution (CI) identified patients in several steps. Initially, sites were instructed to use their local SCD databases and perform a broad electronic medical record search for patients with SCA ICD-9/10 codes, born between 1996–2014. Patient cohorts were then assessed for the following inclusion criteria: 1.) SCA diagnosis (HbSS, HbSB0, HbSOarab, HbSD) by HPLC newborn screening or hemoglobin electrophoresis; 2.) documented outpatient visit at CI between study years 2012–2016, assuring patients were followed by that institution; and 3.) at least two episodes of care (inpatient or outpatient) between 2012–2016. The final cohort included children with SCA, aged 2–16 years who should have undergone TCD screening, including patients who might have missed appointments or were “lost to follow-up.” Patients were considered to “belong” to an institution if they were seen for acute or outpatient care at least twice during a study year. In rare cases, patients seen for two or more acute visits could be excluded if pinpointed by the principal investigator (for example if a patient was identified as “visiting” from another state, they were not included in the analysis). For institutions with large patient populations (>300), patients were listed in alphabetical order and then entered into the database alphabetically. This systematic method of entry was undertaken to prevent bias,

in case larger institutions did not complete the extensive data collection (as opposed to the most frequently seen or compliant patients being entered first). Only 4 sites were unable to enter all identified patients into the database and used the above protocol. One site was unable to enter more than 10% of their patient population and was excluded from TCD implementation analysis.

Data Collection

Institutional Review Board and Data Use Agreements—Institutional Review Board approval was obtained at each CI using a common protocol. Data use agreements between the sponsoring institution and each CI were also obtained. All data were de-identified at time of entry; thus, consent was not required from individual patients.

Electronic Database Description—DISPLACE Part 1 patients were enrolled into the custom-designed electronic database, WebDCU™ from 2017 – 2018. WebDCU™ was created by The Data Coordination Unit (DCU) at the Medical University of South Carolina. WebDCU™ is a comprehensive clinical trial management system established in 2005. The database provides regulatory document tracking, central adjudication, query generation, and electronic case report form (CRF) data capture. Secure data entry occurred at CI via an online, user-friendly data-entry interface. The DCU provided training and technical support to all users, including study team members and coordinators.

Overview of Data Collection Procedures—Once eligibility was confirmed by CI, each patient was registered in the database; all data were obtained through intensive chart review of the patient's medical record by trained coordinators or site PIs. The initial patient CRF included demographics, SCD genotype, and history of abnormal TCD or MRI results prior to study years (i.e., before 2012). Demographic information included gender, birth date, ethnicity, insurance type (last recorded), and race. After the initial CRF, annual data were entered for each of the study years (2012–2016). The annual CRFs included: SCD-related complications, baseline laboratory values, vital signs and anthropometric values, TCD results, MRI results, echocardiogram results, medications, and previous or concurrent treatment with hydroxyurea (HU) or CRCT. For patients started on CRCT during the years of 2012–2016, the TCD/patient rates were included prior to start of CRCT but excluded once the patient started CRCT.

TCD Data Collection Methods—The TCD CRF captured: 1.) if TCD was completed for that year, 2.) TCD results (as classified by the CI), and 3.) follow up actions after TCD or 4.) reasons TCD was not completed. Per NHLBI guidelines, expectations were that each patient, ages 2–16 would have an annual TCD. For patients with more than one TCD in a study year, all TCDs were documented. For patients >2 years of age at study entry (2012), additional data were captured to include any TCD performed prior to first study year. TCD data were not required once patients reached 16 years of age. The TCD CRF was completed per patient even if the TCD had not been done. If a TCD was not completed for a study year, data were collected regarding causation of the missed exam (appointment not scheduled, appointment scheduled but not attended, etc.). However, due to the retrospective nature of these data, sites could not always locate these answers. Thus, barriers to TCD were obtained

through additional qualitative and quantitative analyses during Part 2 of the study (please see Discussion).

The TCD CRF also included where the study was performed (radiology, SCD clinic, etc.), TCD type (dedicated Doppler, TCD imaging aka TCDi, or unknown), and results as classified by the CI (low, normal, conditional, abnormal, or inadequate). For those with results other than normal, the CRF captured when/if the TCD was repeated. If not repeated, additional data were captured regarding why it was not repeated (provider choice, patient lost to follow up, technical issues, appointment cancellation or no-show, refusal, or unknown). Data collected on patients with abnormal TCD included treatment recommendations (repeat TCD, initiation of HU, CRCT, hematopoietic stem cell transplant or unknown).

Definition of Optimal TCD Implementation and Results Classification— Guideline-based implementation was defined as annual TCD for all patients ages 2–16 with SCA who were not receiving CRCT. Each individual should have had at least one TCD/calendar year to be considered “on time”. This minimum TCD schedule could include more than one assessment/year if the result fell in the conditional or abnormal range (and TCD was repeated). TCD results were classified as normal, conditional, abnormal, or inadequate as per the CI’s report. TCD images were not centrally reviewed; assumptions were made that TCDs were performed and results were read according to standard of care. (Consortium practices and TCD results classification were collected and published separately.[15]) This consideration is important because 12 sites (42.9%) were using TCDi to classify results.

Variables

The primary outcome of this study was to calculate the current, real-world TCD screening rate at each institution (calculated as patient/year/site over all study years). Implementation rates were calculated as the ratio of number of eligible years at least one TCD was completed to number of eligible years TCDs should have been completed. A TCD eligible year was defined as any study year during which a patient was 2–16 years of age and not on CRCT. Implementation rates were calculated on a per site basis in order to identify the lowest performing sites for the subsequent implementation study (Part 3). Secondary outcomes included CI assessments, TCD results, and per patient results.

Site characteristics included institution size based on estimated number of total patients with SCD being treated prior to data capture and previous participation in the STOP I/II trials. For institutional size, the 27 CI included in the implementation analyses were classified as small (<200 total patients; n = 7), medium (201–400 total patients; n = 12), or large (>400 total patients; n = 8) based on sites’ estimated numbers of patients followed (not based on number of patients with SCA entered into the database). Analyses were conducted for sites overall and by comparing the top 3 and bottom 3 sites in terms of TCD implementation rates.

Information about current TCD results per patient and in aggregate included current rates of abnormal and conditional TCD; age of child at first abnormal TCD; TCD type (dedicated

Doppler versus TCDi); and location of and timing of TCD (same day as clinic visit or separate day).

Statistical Methods

Data cleaning was performed to ensure reported numerical outcomes (e.g., vital signs, laboratory values) were in physiologic ranges and consistent with patient age, removing duplicate patients, and adjudicating abnormal TCD results with each site. Records with insufficient data relevant to study outcomes were removed (e.g., vital signs but no other data) and TCD CRFs were deleted if the test date was unknown. TCD data were analyzed for 27 CI; analyses not involving TCD implementation included all 28 sites.

Analyses were carried out in two distinct ways: 1.) demographic, screening, treatment, and clinical characteristics were determined *by patient*, and 2.) information on TCD results and characteristics was analyzed *by TCD.* For example, for individual patient outcomes (i.e., did a patient receive a TCD/year), analyses were done per patient. For TCD implementation outcomes (i.e., if a TCD was abnormal), analyses were performed per TCD, as patients could have multiple TCDs per year. Similarly, data for pre-study year periods (pre-2012) are highly relevant in the per patient analysis, but not for the implementation analysis. Institution size and number of patients in relation to TCD implementation rates were assessed using Kruskal-Wallis and Pearson correlation, respectively. Patients who died during study years were excluded from analyses (n=24). All statistical analyses were conducted using SAS Software Version 9.4 (Copyright © 2016 by SAS Institute Inc., Cary, NC, USA).

Results

Demographics

The final consortium comprised 28 institutions across the United States with various sizes and locations. There were 5247 patients entered into WebDCU™ making this the largest cohort of children with SCA ever investigated. Patient demographics for the 5116 patients eligible for at least 1 TCD during study years are reported in Table 1. The majority of children were African American or Black, non-Hispanic and received Medicaid insurance. Not all questions were answered for each patient.

Primary Outcomes: TCD implementation

The primary goal of DISPLACE Part 1 was to assess current TCD screening implementation at CIs. This intensive evaluation was necessary as only the lowest performing 16 sites would participate in the subsequent implementation trial (Part 3). The final dataset included 5247 children ages 2–16 years. Of these, 5116 were eligible for TCD implementation assessment (for at least one study year). Patients were deemed ineligible if they had started CRCT or received stem cell transplant prior to 2012 (n=22). Patients from the site with <10% of total patients entered were removed from TCD implementation assessment due to potential bias (n=33). Twenty-four patients who died during the study window were excluded.

TCD implementation was measured for study years 2012–2016. TCD screening rates were collected per patient/year/institution and the mean and median were calculated for better representation of overall screening rates. Overall TCD screening rates varied widely among institutions ranging from 30.9–74.7% (mean 49.9%, median 48.6%; Table 2). No trends in TCD rates were observed across the study years. During this time, 3655 patients registered in the database had at least one TCD during the study period (71.4%) and 1461 (28.6%) did not have a single TCD. Among patients who were eligible for at least four study years and should have had at least four TCDs, 601 patients (18.0%) did not have a single TCD (Table 3).

Secondary Outcomes

Site Characteristics—Screening variation both within site (from year to year) and between sites was high. Institution size and number of patients were not statistically significantly related to TCD implementation rates (Chi-square=0.22, p=0.895 obtained from Kruskal-Wallis Test for non-parametric distributions; r=−.20, p=0.313 from Pearson correlation, respectively). No difference in implementation of TCD by participation in STOP I and/or II trials was noted (all sites: 48.4%; STOP I/II sites: 46.4%; non-STOP sites: 51.2%). A comparison of the 3 sites with the highest implementation rates and the 3 sites with the lowest implementation rates by size and participation in STOP trials indicated no trends by size. Specifically, the lowest three sites included two small sites and one large site as well as one site that participated in STOP I and/or II. The highest three sites included one small, one medium, and one large site and no sites that participated in STOP I and/or II.

TCD Characteristics—Assessment of TCD results included patients studied from 2012–2016 who had at least one TCD and were not on CRCT. There were 104 (2.8%) patients with abnormal TCD and 495 (13.5%) patients with a conditional TCD during this time period (Table 3). Mean age at time of first abnormal TCD during study years was 6.3 years (median 6, interquartile range of 4–8 years). Of note, the oldest patient to develop a new, abnormal TCD was 16 years old. More TCDs were conducted using dedicated Doppler (66.2%) compared to TCDi (32.8%). There was no difference in abnormal results seen with TCD vs. TCDi. Nearly all TCDs were conducted at the study hospital (96.9%) and the majority were conducted at the same time as a clinic appointment (67.3%).

Discussion

The STOP study dramatically changed stroke prevention practices for children with SCA, offering a preventive strategy to a devastating complication.[2] Results from DISPLACE Part 1 highlight real-world stroke screening practices and TCD results in the modern era in the largest SCA cohort to date. This real-world assessment of TCD implementation overcomes limitations in prior studies conducted with administrative datasets and illustrates the need for a clinical longitudinal registry for more accurate monitoring of clinical care and patient outcomes. Unfortunately, findings demonstrate wide variability in TCD screening implementation not due to geographic location, institution size, number of patients, or prior participation in the STOP trials.

Barriers and facilitators to TCD implementation occur at multiple levels (patient level, provider level, and system level). We previously reported data from qualitative interviews performed during Part 2 of DISPLACE that reveal predominant barriers and facilitators that likely explain the variability observed in TCD rates. These results showed that predominant barriers included patient/caregiver logistical difficulties and competing life demands and gaps in scheduling, communication, and coordination. Predominant facilitators included coordination, scheduling, and reminders (especially when there was a single identified coordinator) and education and information (patient/caregiver knowledge of TCD).[16] These results suggest that a combination of patient-, provider-, and systems-level issues are involved in TCD implementation, consistent with previous, single center studies,[10–12, 17–24] and suggest that targeted multi-level interventions are likely needed to improve TCD screening rates.

Overall, the abnormal TCD rate is considerably lower in this large, real-world sample of children with SCA compared to the STOP study.[1] STOP was a prospective study to assess CRCT for patients with abnormal TCD. Thus, the findings in this retrospective, real-world study cannot be directly compared to those in STOP. However, the incidence of abnormal TCD in this cohort is lower than seen during the STOP study. This difference is likely multifactorial and may be due to improvements in overall SCD management, including use of HU.[25] During the STOP study, the majority of HU use was in adults.[26] Further, because the STOP screening protocol has been implemented in care for >10 years, many who had abnormal TCD are no longer in the screening pool as they are now on CRCT. Despite improvements in care, many children continue to have abnormal TCD and remain at high risk of ischemic stroke.

The average age at abnormal TCD was only slightly higher in DISPLACE compared to the STOP study although direct statistical comparisons could not be made.[1] The mean age at the time of first abnormal TCD during study years was 6.3 years (range 2–16). The majority of abnormal TCDs (75%) were before or at 7 years of age. However, 25% of abnormal TCD occurred in older patients (>9 years) in this cohort. Additional characterization of those with abnormal TCD and findings relative to use of HU will be presented in a separate paper. It is important to characterize which older children (>9 years) remain at high risk of developing abnormal TCD and whether a clinically defined group could stop screening before 16 years of age. We used these data to guide the enrollment age group for the Part 3 implementation trial. To reduce the number of patients enrolled at each site, we chose to focus data collection on ages 2–8, as these children would be the most likely to have an abnormal TCD during the trial.

In the STOP study, only dedicated Doppler was used. However, in DISPLACE, almost half of sites used TCDi.[15] Previous studies have compared results using dedicated Doppler versus TCDi in SCA and recent guidelines from ASH have formally recommended the use of lower velocities for identifying abnormal results when using TCDi (compared to dedicated Doppler).[27–31] More specifically, these guidelines recommend using the STOP criterion of ≥200 time average mean of the maximum (TAMM) velocity for dedicated Doppler versus ≥185 TAMM time for TCDi. Our previous paper on practice patterns for TCD screening in the consortium suggested variation in how TCDi studies were categorized

as there were no clear guidelines during the time of data collection[15]; however, there was no clinically significant difference in the number of abnormal TCD results between methods. Nonetheless, it is possible that the rate of abnormal TCDs was affected by variation in practices.

Limitations

DISPLACE is a real-world evaluation of current practice in 28 centers in the US. There was potential bias in the site selection. First, most CI were academic centers; however, the majority of children with SCD receive care in the US at academic institutions.[32] Thus, screening rates were likely representative of typical care. Second, 7 of the original 35 sites approached chose not to participate in the study. Two of these sites had already conducted single center quality improvement projects and had new screening processes in place. Five others did not have sufficient research staff. While the two sites who had previously undertaken projects to improve screening rates now have better rates, these were not likely representative screening rates. The sites that did not participate might have had lower screening rates as their ability to participate and track these outcomes was limited. TCDs were conducted according to institutional practice and not per a single study protocol, and only abnormal TCD were adjudicated by the PI and confirmed to meet the “STOP protocol” definition. Thus, data reported are based on institutional judgement, which may be regarded as a limitation but is consistent with real-world practice. All data were collected by intensive chart review, but testing was not performed prospectively for this study. Thus, it is possible that TCD classifications in DISPLACE would not be consistent with STOP protocol definitions.

Conclusion

TCD screening was one of the most strongly recommended practices by the NHLBI SCD guidelines.[6] Despite being the most common inherited blood disorder in the US, SCD is still affected by multiple health disparities, including a lack of funding, well-defined quality metrics and assessments, and novel drug development that exists in other life-limiting conditions, such as cystic fibrosis.[33] Further, there are limited treatment guidelines or oversight for individuals with SCD compared to other conditions.[34, 35]

Current TCD implementation is lacking. Findings in DISPLACE likely reflect other areas of profound gaps between guidelines and practice. DISPLACE seeks to optimize implementation of stroke risk screening in SCD as one means for improving care. New SCD guidelines have recently been published by ASH,[7, 36, 37] and new therapies have been approved. Lessons learned from the DISPLACE implementation study are expected to provide new strategies to improve quality of care and reduce health outcome inequities for this at-risk population.

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Table 1:

Subject Demographics

Characteristic	N	n	%
BASELINE CHARACTERISTICS			**5116**
Age[a] mean (sd), median, IQR			
First recorded TCD in study years	5.9 (4.1)	5.0	(2–9)
End of Study (31Dec2016)	10.5 (5.3)	10.0	(6–15)
Sex [a]	5116		
Male		2575	50.3
Female		2541	49.7
Ethnicity [a]	5116		
Hispanic or Latino		124	2.4
Not Hispanic/Latino		4661	91.1
Unknown		331	6.5
Race [*,a]	5116		
Native American		13	0.3
Asian		8	0.2
African-American or Black		4850	94.8
Pacific Islander		8	0.2
White		64	1.3
Unknown		188	3.7
Insurance [b]	3972		
Medicaid		2505	63.1
CHIP		43	1.1
Tricare		62	1.6
Private		782	19.7
Local		88	2.2
None		52	1.3
Unknown		545	13.7
Genotype [a,c]	5106		
Hb SS or sickle cell anemia		4782	93.7
Hb s beta thalassemia		273	5.4
Hb S + Hb FH[d]		37	0.7
Hb SE		4	0.1
Hb SD		5	0.1
Hb SO		5	0.1
TREATMENT			

Characteristic	N	n	%
Hydroxyurea [a]	5116	3009	58.8

[*] Not mutually exclusive

[a] Rates per subject (Subjects are only represented once but Hydroxyurea use could be at any time from 2012–2016)

[b] Baseline rates per subject (Subjects are only represented once)

[c] Missing 10

[d] Included at the discretion of the local CI (not genetically defined)

Table 2:

TCD Implementation Rates Across the 27 DISPLACE Consortium Institutions by Institution Size

			Year									
	Overall		2012		2013		2014		2015		2016	
Site	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Small												
1	173	104 (60.1%)	29	15 (51.7%)	32	15 (46.9%)	36	21 (58.3%)	38	28 (73.7%)	38	25 (65.8%)
2	197	126 (64.0%)	40	19 (47.5%)	36	26 (72.2%)	39	23 (59.0%)	43	30 (69.8%)	39	28 (71.8%)
3	304	94 (30.9%)	60	12 (20.0%)	59	19 (32.2%)	58	25 (43.1%)	62	22 (35.5%)	65	16 (24.6%)
4	478	272 (56.9%)	93	47 (50.5%)	98	57 (58.2%)	98	48 (49.0%)	95	66 (69.5%)	94	54 (57.4%)
5	531	177 (33.3%)	90	35 (38.9%)	97	32 (33.0%)	104	39 (37.5%)	112	26 (23.2%)	128	45 (35.2%)
6	584	268 (45.9%)	108	27 (25.0%)	119	49 (41.2%)	117	58 (49.6%)	115	65 (56.5%)	125	69 (55.2%)
7	919	371 (40.4%)	186	50 (26.9%)	183	73 (39.9%)	184	81 (44.0%)	179	78 (43.6%)	187	89 (47.6%)
Medium												
8	244	132 (54.1%)	48	23 (47.9%)	42	26 (61.9%)	45	23 (51.1%)	51	31 (60.8%)	58	29 (50.0%)
9	312	213 (68.3%)	60	42 (70.0%)	59	42 (71.2%)	61	40 (65.6%)	67	39 (58.2%)	65	50 (76.9%)
10	324	175 (54.0%)	63	32 (50.8%)	62	33 (53.2%)	63	37 (58.7%)	69	36 (52.2%)	67	37 (55.2%)
11	475	197 (41.5%)	77	24 (31.2%)	93	35 (37.6%)	98	41 (41.8%)	101	50 (49.5%)	106	47 (44.3%)
12	506	267 (52.8%)	98	54 (55.1%)	95	50 (52.6%)	103	47 (45.6%)	107	57 (53.3%)	103	59 (57.3%)
13	592	260 (43.9%)	123	48 (39.0%)	123	54 (43.9%)	123	51 (41.5%)	115	52 (45.2%)	108	55 (50.9%)
14	650	360 (55.4%)	129	74 (57.4%)	132	72 (54.5%)	131	64 (48.9%)	124	74 (59.7%)	134	76 (56.7%)
15	658	284 (43.2%)	123	52 (42.3%)	130	63 (48.5%)	131	60 (45.8%)	136	60 (44.1%)	138	49 (35.5%)
16	707	442 (62.5%)	141	82 (58.2%)	149	79 (53.0%)	146	111 (76.0%)	136	93 (68.4%)	135	77 (57.0%)
17	752	428 (56.9%)	150	80 (53.3%)	148	79 (53.4%)	151	85 (56.3%)	152	94 (61.8%)	151	90 (59.6%)
18	769	267 (34.7%)	155	41 (26.5%)	151	55 (36.4%)	154	60 (39.0%)	155	50 (32.3%)	154	61 (39.6%)
19	785	353 (45.0%)	164	79 (48.2%)	160	70 (43.8%)	159	81 (50.9%)	149	70 (47.0%)	153	53 (34.6%)
Large												
20	615	199 (32.4%)	124	26 (21.0%)	137	26 (19.0%)	122	44 (36.1%)	120	54 (45.0%)	112	49 (43.8%)
21	644	360 (55.9%)	93	46 (49.5%)	117	64 (54.7%)	128	68 (53.1%)	151	77 (51.0%)	155	105 (67.7%)

			Year									
	Overall		2012		2013		2014		2015		2016	
Site	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
22	738	551 (74.7%)	141	98 (69.5%)	147	105 (71.4%)	151	113 (74.8%)	149	111 (74.5%)	150	124 (82.7%)
23	1040	651 (62.6%)	217	101 (46.5%)	211	119 (56.4%)	207	138 (66.7%)	210	143 (68.1%)	195	150 (76.9%)
24	1128	529 (46.9%)	237	106 (44.7%)	238	100 (42.0%)	221	99 (44.8%)	221	117 (52.9%)	211	107 (50.7%)
25	1369	622 (45.4%)	270	93 (34.4%)	275	101 (36.7%)	285	102 (35.8%)	270	180 (66.7%)	269	146 (54.3%)
26	2016	768 (38.1%)	391	136 (34.8%)	401	140 (34.9%)	405	155 (38.3%)	408	175 (42.9%)	411	162 (39.4%)
27	2205	1072 (48.6%)	426	191 (44.8%)	439	210 (47.8%)	449	228 (50.8%)	453	206 (45.5%)	438	237 (54.1%)

N=total number of TCDs needed per eligible patient per year eligible

Table 3:

TCD Implementation Based on Years of Eligibility with Rates of Abnormal and Conditional Results

	2012–2016	
	Eligible 1+ year[b] (n=5116)	**Eligible 4+ years[c] (n=3354)**
Unique Patients who DID NOT HAVE A TCD	1461 (28.6%)	601 (17.9%)
Unique patients who only had ONE TCD	917 (17.9%)	456 (13.6%)
Unique Patients who had a TCD total	3655 (71.4%)	2753 (82.1%)
Unique Patients with abnormal TCD[a]	102 (2.8%)	80 (2.9%)
Unique Patients with conditional TCD[a]	495 (13.5%)	406 (14.8%)

[a]Denominator = Unique patients who had a TCD total

[b]Of the 5,116 patients eligible to receive a TCD for at least 1 year during the study years

[c]Of the 3,354 patients eligible to receive a TCD for at least 4 (of the 5) years during the study years