drugs of abuse screening in intracerebral hemorrhage

Laura M. Tormoehlen, MD
Ashley D. Blatsioris, MPA
Elizabeth A.S. Moser, MS
Ravan J.L. Carter, BS
Alec Stevenson, BS
Susan Ofner, MS
Abigail L. Hulin, BA
Darren P. O'Neill, MD
Aaron A. Cohen-Gadol, MD
Thomas J. Leipzig, MD
Linda S. Williams, MD
Jason Mackey, MD, MS

Correspondence to Dr. Mackey: jsmackey@iupui.edu

ABSTRACT

Objective: To characterize the pattern of urine drug screening in a cohort of intracerebral hemorrhage (ICH) patients at our academic centers.

Methods: We identified cases of primary ICH occurring from 2009 to 2011 in our academic centers. Demographic data, imaging characteristics, processes of care, and short-term outcomes were ascertained. We performed logistic regression to identify predictors for screening and evaluated preguideline and postguideline reiteration screening patterns.

Results: We identified 610 patients with primary ICH in 2009–2011; 379 (62.1%) were initially evaluated at an outside hospital. Overall, 142/610 (23.3%) patients were screened, with 21 positive for cocaine and 3 for amphetamine. Of patients <55 years of age, only 65/140 (46.4%) were screened. Black patients <55 years of age were screened more than nonblack patients <55 years of age (38/61 [62.3%] vs 27/79 [34.2%]; $p = 0.0009$). In the best multivariable model, age group ($p = 0.0001$), black race ($p = 0.4529$), first Glasgow Coma Scale score ($p = 0.0492$), current smoking ($p < 0.0001$), and age group × black race ($p = 0.0097$) were associated with screening. Guideline reiteration in 2010 did not improve the proportion <55 years of age who were screened: 42/74 (56.8%) were screened before and 23/66 (34.9%) after ($p = 0.01$).

Conclusions: We found disparities in drugs of abuse (DOA) screening and suboptimal guideline adherence. Systematic efforts to improve screening for DOA are warranted. Improved identification of sympathomimetic exposure may improve etiologic classification and influence decision-making and prognosis counseling. *Neurology*® 2017;88:252–258

GLOSSARY

AHC = academic health centers; **CI** = confidence interval; **DOA** = drugs of abuse; **GCS** = Glasgow Coma Scale; **ICD-9** = *International Classification of Diseases–9*; **ICH** = intracerebral hemorrhage; **INPC** = Indiana Network for Patient Care; **IVH** = intraventricular hemorrhage; **NIHSS** = NIH Stroke Scale; **NSDUH** = National Survey on Drug Use and Health; **OR** = odds ratio; **OSH** = outside hospital; **UDS** = urine drug screen.

Substance abuse is increasingly detected in stroke populations.[1] Intracerebral hemorrhage (ICH) has the highest morbidity and mortality of all stroke subtypes[2] and sympathomimetic drugs have previously been associated with poorer outcomes in ICH.[3] The ICH guidelines in 2007[4] and 2010[5] recommended toxicology screening in young or middle-aged patients to detect cocaine and other sympathomimetic drugs of abuse (DOA), but guideline adherence data are scarce, particularly outside of academic centers. We therefore sought to characterize the prevalence and predictors of screening for DOA in our primary ICH cohort as well as the effect of guideline reiteration on screening patterns.

METHODS

Standard protocol approvals, registrations, and patient consents. This study was approved by the Indiana University institutional review board, the Wishard Hospital review board, and the board of directors of the Indiana Network for Patient Care (INPC).

We performed a retrospective study of primary ICH in patients presenting to our 2 academic health centers (AHC). We queried all patients ≥18 years of age in the INPC database[6] (http://www.ihie.org/) between January 1, 2009, and December 31, 2011, with ICD-9 codes of 431 and 432.9. ICD-9 codes 431 and 432.9 have been demonstrated to have >85% sensitivity for the identification of patients with ICH.[7] The database was additionally queried until February 29, 2012, to identify patients who were admitted to

Supplemental data at Neurology.org

From the Departments of Neurology (L.M.T., A.D.B., A.S., A.L.H., L.S.W., J.M.), Emergency Medicine (L.M.T.), Biostatistics (E.A.S.M., S.O.), Radiology (D.P.O.), and Neurosurgery (A.A.C.-G., T.J.L.), Indiana University School of Medicine; Regenstrief Institute (R.J.L.C., L.S.W., J.M.); and Richard L. Roudebush VA Medical Center (L.S.W.), Indianapolis, IN.

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a participating hospital during the study period but discharged from the hospital in the following months. A vascular neurologist (J.M.) reviewed the entire chart and imaging scans of all potential cases to ensure correct case ascertainment. Patients with suspected ICH etiologies of trauma, aneurysm, encephalitis, or tumor were excluded. Patients with suspected hemorrhagic transformation of an ischemic infarct or hemorrhage due to venous sinus thrombosis, carotid endarterectomy, or thrombolytic administration for ischemic stroke were also excluded.

Abstractors ascertained via chart review demographic data, vascular risk factors (including hypertension, diabetes mellitus, history of smoking, and dyslipidemia), and other comorbidities including modified Charlson score and process of care variables under the close supervision of the vascular neurologist. All clinical data were recorded in Research Electronic Data Capture (REDCap).[8] Referring hospital data and all transfer data were reviewed. If an NIH Stroke Scale (NIHSS) score was not explicitly calculated, we used a validated method to estimate NIHSS.[9] The neurologist reviewed the initial imaging scan from the academic center as well as the initial imaging scan from the referring hospital, if available. Hematoma volume was calculated via the ABC/2 method[10] and the intraventricular volume was calculated via a previously reported method.[11]

We ascertained whether urine drug screen (UDS) was performed as well as results for cocaine or amphetamine/methamphetamine at both the referring hospitals and academic centers. We analyzed performance of UDS by race, sex, age, and hospital presentation (outside hospital [OSH] vs academic center). The guidelines did not specify an age cutoff for young or middle-aged patients; we selected age 55 for analysis purposes. We also dichotomized the study time period into preguideline and postguideline publication (online July 22, 2010) to assess if guideline reiteration changed screening patterns.

Outcome measures included modified Rankin Scale score at discharge and date, time, and cause of death for patients who died during the hospitalization. We determined vital status via present-day chart review and obituary query. We then performed a National Death Index query for the vital status of all patients for whom we still could not account.

Statistical methods. Patient characteristics were compared between those screened and not by χ^2, Fisher exact, analysis of variance, or Wilcoxon rank-sum tests where appropriate. Modeling of UDS began with bivariate logistic regressions. Each continuous candidate variable was assessed for linearity of the logit, and those with evidence of nonlinearity were converted to categorical variables. Variables with bivariate statistical significance of ≤ 0.30 were eligible for inclusion in a multivariable logistic model. A stepwise variable selection method was utilized to find the best model, with a significance level for remaining in the model of 0.05. Bivariate results are not presented. β Coefficients from the resulting multivariable model were used to calculate odds ratios (OR) and 95% confidence intervals (CIs). Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS We identified 610 patients with primary ICH in 2009–2011; 379 (62.1%) were initially evaluated at an OSH. Patients presenting initially to OSH vs directly to the AHC were older (67.0 years vs 63.2 years, $p = 0.002$) and less likely to be black (6.9% vs 59.7%, $p < 0.0001$). Patients presenting initially to an OSH also had a lower NIHSS (7 vs 12, $p = 0.0002$), lower systolic blood pressure (176.7 vs 189.9 mm Hg, $p < 0.0001$) and diastolic blood pressure (96.1 vs 105.0 mm Hg, $p < 0.0001$), lower Charlson score (1 [0–2] vs 1 [0–3], $p = 0.003$), lower rate of tracheostomy (5.5% vs 10.4%, $p = 0.03$), and a shorter length of stay (7 days [4–12] vs 8 days [5–16], $p = 0.004$).

The baseline characteristics stratified by screening status are shown in table 1. Overall, 142/610 (23.3%) patients had UDS performed, with 21 positive screens for cocaine and 3 for amphetamine, with an overall yield of 16.9% (24/142). Patients screened for DOA were younger; were more likely to be male, black, and current smokers; were clinically more severe (lower Glasgow Coma Scale [GCS] score, higher NIHSS, more intraventricular hemorrhage [IVH], and a longer length of stay); and had higher systolic and diastolic blood pressure than those not screened. Of patients <55 years of age, only 65/140 (46.4%) were screened. There was a difference in screening between nonblack and black patients <55 years of age (27/79 [34.2%] vs 38/61 [62.3%], $p = 0.0009$). Of the 74 patients <55 years of age presenting to an OSH, only 27 (36.5%) were screened: 10 at the OSH only, 15 at the academic center only, and 2 at both the OSH and the academic center. The proportion of patients <55 years of age screened who presented to our centers initially was 38/66 (57.6%). The oldest patient with a positive cocaine or amphetamine screen was 63 years of age and the oldest screened was 95 years of age. A total of 9 of 24 (37.5%) patients with a positive screen were older than 55 years, and 18 of 24 (75%) were older than 45 years.

The best multivariable model (table 2) included age group ($p = 0.0001$), black race ($p = 0.4529$), first GCS score ($p = 0.0492$), current smoking ($p < 0.0001$), and the interaction between age group and black race ($p = 0.0097$), with an area under the curve of 0.79 and no significant lack of fit (Hosmer-Lemeshow goodness-of-fit: $p = 0.96$). The frequencies of those screened stratified by age group and race are shown in table 3. The proportion screened decreased in every ascending age group, but in all age strata <65 years, black patients were screened more than nonblack patients. The most striking differences in screening between black and nonblack patients were in the 45–54 years of age stratum (OR 6.93, 95% CI 2.50–19.20, black vs nonblack, $p = 0.0002$) and the 55–64 years of age stratum (OR 3.85, 95% CI 1.70–8.71, black vs nonblack, $p = 0.0012$).

Among those screened, we also performed a secondary analysis of cocaine-positive and cocaine-negative patients (table 4); to minimize potential heterogeneity of the groups, we excluded the 3 amphetamine-positive patients from this analysis. The cocaine-positive patients were more likely to be black and to have a higher diastolic blood pressure at

Table 1 Baseline characteristics by screening status

	Not screened (n = 468)	Screened (n = 142)	p Value
Age group, y, n (%)			<0.0001
<45	18 (3.8)	30 (21.1)	
45–54	57 (12.2)	35 (24.7)	
55–64	107 (22.9)	45 (31.7)	
65+	286 (61.1)	32 (22.5)	
Black, n (%)	99 (21.2)	65 (45.8)	<0.0001
Female, n (%)	234 (50.0)	55 (38.7)	0.02
GCS, median (IQR)	14 (11–15)	14 (7–15)	0.004
NIHSS, median (IQR)	8 (3–17)	12 (4–25)	0.009
Charlson, median (IQR); max	1 (0–2); 8	1 (0–2); 6	0.01
ICH score, median (IQR)	1 (1–2)	2 (0–3)	0.16
ICH volume, median (IQR)	10.5 (2.5–27.0)	9.4 (2.5–24.8)	0.65
IVH presence, n (%)	208 (44.4)	78 (54.9)	0.03
IVH volume, median (IQR)	6.0 (2.2–16.4)	7.4 (2.2–16.4)	0.61
First SBP, mm Hg, mean (SD)	178.6 ± 37.4	191.4 ± 43.4	0.0007
First DBP, mm Hg, mean (SD)	96.6 ± 25.7	108.8 ± 26.3	<0.0001
Current smoker, n (%)[a]	93 (20.1)	73 (55.7)	<0.0001
Anticoagulant use, n (%)	85 (18.2)	12 (8.5)	0.0056
Presentation at OSH, n (%)	314 (67.1)	65 (45.8)	<0.0001

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; NIHSS = NIH Stroke Scale; OSH = outside hospital; SBP = systolic blood pressure.
[a] Missing smoking data for 16 patients (denominators: 463 screened, 131 not screened).

presentation. There was no difference in ICH location or presence of IVH. There was no difference in the rate of tracheostomy (2/21 vs 13/118, $p = 1.0$), percutaneous endoscopic gastrostomy tube (3/21 vs 27/118, $p = 0.57$), discharge home (5/17 vs 22/91, $p = 0.76$), or decision for comfort care only (1/21 vs 12/118, $p = 0.69$). With regard to outcomes, we did not find a difference in discharge modified Rankin Scale score (4 [3–4] vs 4 [3–5], $p = 0.66$) or case-fatality at any time point (inpatient [4/21 vs 27/118, $p = 1.0$], 30 days [4/21 vs 36/118, $p = 0.29$], or 1 year [6/21 vs 49/118, $p = 0.26$]).

Prior to guideline reiteration, 76/328 (23.2%) patients were screened, compared to 66/282 (23.4%) after guideline reiteration ($p = 0.95$). For the <55 years of age group, 42/74 (56.8%) were screened before and 23/66 (34.9%) were screened after ($p = 0.01$).

DISCUSSION We found low overall rates of screening for DOA in our ICH cohort, with fewer than half of patients <55 years of age undergoing screening and with opportunities for improvement at both OSHs and academic centers. We also found that younger age, black race, lower initial GCS score, current smoking, and the interaction between age group and black race were associated with screening. The relationship between race and screening was modified by age; black patients were screened more frequently at all ages <65 years, but the biggest disparity was in middle age (age 45–64 years). We did not find an improvement in rates of screening after reiteration of the guidelines; in fact, in patients <55 years of age, the proportion screened after guideline reiteration was lower. (That screening of young patients did not improve in the year and a half following guideline reiteration is not surprising, given well-documented lags in dissemination.[12]) In contrast to a previous study of cocaine-associated ICH, which reported higher frequency of nonlobar locations, higher risk of IVH, and poorer prognosis,[3] we did not find differences in location, intraventricular extension, or short-term outcomes compared with cocaine-negative ICH. Though we excluded the 3 amphetamine/methamphetamine-positive patients from the analysis to minimize potential heterogeneity, the pathophysiology of cocaine and amphetamine/methamphetamine-associated ICH is substantially similar. A previous study of 25 patients with methamphetamine-associated ICH also reported a higher frequency of nonlobar locations, but did not find a difference in rates of IVH or short-term outcomes.[13] The reasons for the differences in findings are not clear, but may be secondary to small cohort size.

A previous study of urine drug screening in an urban stroke center from 2005 to 2007 of more than 1,000 patients included 133 ICHs, of whom 57 (42.9%) patients were screened and 14 (24.6%) were cocaine-positive. These investigators also found a higher rate of screening in black patients and men.[14] Disparities in screening may be partly related to a provider expectation that the rate of sympathomimetic drug use is higher in these particular subgroups. However, the observed disparities in this study exceed the differences seen in the 2011 National Survey on Drug Use and Health (NSDUH). In that study, past-month illicit drug use (age 12 years and older) was higher in black or African American respondents (10%) than for white (8.7%), Hispanic or Latino (8.4%), and Asian (3.8%) respondents. Current illicit drug use was higher for men (11.1%) than women (6.5%) for overall illicit use, as well as for cocaine specifically (men 0.7% vs women 0.4%). In addition, current illicit drug use was higher in large metropolitan counties (9.2%) than in nonmetropolitan, rural counties (5.7%).[15] Further, use of sympathomimetic drugs is not limited to young patients. In fact, the 2011 NSDUH reported increasing rates of overall illicit drug use in the age 50 to 59 years cohort—6.3% in 2011 compared to 2.7% in 2002.[15] The authors note that this may be related to

Table 2 Multivariable model

Parameter	Parameter estimate	Standard error	Type 3 test (overall p value)	p Value	Odds ratio (95% CI)
Intercept	0.3772	0.5003	—	0.4509	—
Age group, y					
<45 (referent)	0	0		—	—
45–54	−2.0355	0.5716	0.0001	0.0004	0.13 (0.04–0.40)
55–64	−1.7293	0.4940		0.0005	0.18 (0.07–0.47)
65+	−2.0750	0.4673		<0.0001	0.13 (0.05–0.31)
Race					
Nonblack (referent)	0	0		—	—
Black	0.5233	0.6973	0.4529		—
Age-race interaction					
<45, White (referent)	0	0		—	—
45–54, Black	1.4129	0.8687	0.0097	0.1038	4.11 (0.75–22.54)
55–64, Black	0.8251	0.8110		0.3089	2.28 (0.47–11.19)
65+, Black	−1.0381	0.9005		0.2490	0.35 (0.06–2.07)
First GCS	−0.0550	0.0280	0.0492	0.0492	0.95 (0.90–1.00)
Current smoker					
No (referent)	0	0		—	—
Yes	1.2885	0.2475	<0.0001	<0.0001	3.63 (2.23–5.89)

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale.
Area under the curve = 0.79.

the advancing age of the baby boom generation, who have always had higher rates of illicit drug use.[15] While the disparities in screening may be driven by these patterns of drug use, the result is a missed opportunity for a comprehensive etiologic evaluation in all patients.

Not all illicit drugs associated with increased risk of ICH will be identified on routine UDS. Standard urine drug screening is a set of immunoassays that evaluate for classes of drugs of abuse by structural similarity to the reference drug. Urine screening for cocaine is an immunoassay for benzoylecgonine, a metabolite of cocaine that is formed rapidly after exposure. This assay is typically highly sensitive and specific for use of cocaine within the past 3 days.

Table 3 Screening by race within age strata

	Overall	Not screened	Screened	p Value	Odds ratio (95% CI)
Under 45 years old, n (%)	n = 48	18 (37.5)	30 (62.5)		
Black	19 (39.6)	6 (31.6)	13 (68.4)	0.4529	1.69 (0.43–6.62)
Nonblack	29 (60.4)	12 (41.4)	17 (58.6)		(referent)
45–54 years old, n (%)	n = 92	57 (62.0)	35 (38.0)		
Black	42 (45.7)	17 (40.5)	25 (59.5)	0.0002	6.93 (2.50–19.20)
Nonblack	50 (54.3)	40 (80.0)	10 (20.0)		(referent)
55–64 years old, n (%)	n = 152	107 (70.4)	45 (29.6)		
Black	50 (32.9)	27 (54.0)	23 (46.0)	0.0012	3.85 (1.70–8.71)
Nonblack	102 (67.1)	80 (78.4)	22 (21.6)		(referent)
65+ years old, n (%)	n = 318	286 (89.9)	32 (10.1)		
Black	53 (16.7)	49 (92.5)	4 (7.5)	0.3654	0.60 (0.20–1.82)
Nonblack	265 (83.3)	237 (89.4)	28 (10.6)		(referent)

Abbreviation: CI = confidence interval.

Table 4 Cocaine-positive vs cocaine-negative on urine drug screen

	Cocaine-positive (n = 21)	Cocaine-negative (n = 118)	*p* Value
Age group, y, n (%)			0.01
<45	4 (19.0)	24 (20.3)	
45–54	9 (42.9)	26 (22.0)	
55–64	8 (38.1)	36 (30.5)	
65+	0 (0)	32 (27.1)	
Black, n (%)	20 (95.2)	45 (38.1)	<0.0001
Female, n (%)	8 (38.1)	47 (39.8)	0.88
GCS, median (IQR)	13 (9.5–15)	13.5 (6–15)	0.67
NIHSS, median (IQR)	12 (7–18)	12.5 (3–27)	0.99
Charlson, median (IQR)	1 (0–2) [max: 5]	1 (0–2) [max: 6]	0.21
ICH score, median (IQR)	2 (1–2)	2 (0–3)	0.80
ICH volume, mL, median (IQR)	9.0 (1.9–26.3)	10.0 (2.9–24.6)	0.68
IVH presence, n (%)	12 (57.1)	65 (55.1)	0.86
IVH volume, mL, median (IQR)	10.0 (3.7–16.4)	7.4 (2.2–30.0)	0.65
First SBP, mm Hg, mean (SD)	206.7 ± 32.4	189.3 ± 43.4	0.09
First DBP, mm Hg, mean (SD)	124.1 ± 21.1	106.8 ± 26.2	0.006
Current smoker, n (%)[a]	15 (83.3)	55 (50.0)	0.008
Anticoagulant use, n (%)	1 (4.8)	11 (9.3)	0.69
OSH, n (%)	2 (9.5)	60 (50.9)	0.0004
ICH location, n (%)			0.49
Deep	14 (66.7)	65 (55.1)	
Lobar	3 (14.3)	35 (29.7)	
Brainstem	2 (9.5)	10 (8.5)	
Cerebellar	2 (9.5)	8 (6.8)	

Abbreviations: DBP = diastolic blood pressure; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; NIHSS = NIH Stroke Scale; OSH = outside hospital; SBP = systolic blood pressure.
Three amphetamine-positive patients not included.
[a] Missing smoking data for 11 patients (denominators: 18 positive, 110 negative).

Urine screening for amphetamines is less sensitive for substances that would be typically regarded as amphetamines, specifically a rate of detection for methylenedioxymethamphetamine that is 50% lower than for amphetamine and methamphetamine. It is also less specific in that there is a large number of over-the-counter and prescription drugs that can cross-react with this assay.[16] More importantly, neither the cocaine nor the amphetamines assay will reliably detect some of the emerging DOA with sympathomimetic effects. This includes both cathinone (Khat, from the plant *Catha edulis*) and synthetic cathinones (e.g., bath salts) within the phenethylamine category of DOA. In addition, the standard marijuana immunoassay will be negative in patients with synthetic cannabinoid (e.g., K2/Spice) use. ICH has been reported in association with Khat,[17] Spice,[18] and the stimulant1,3-dimethylethylamine (DMAA).[19] None of these substances would produce a positive result on a standard UDS. This is especially relevant because Indiana Poison Center data, which record real-time data on exposures for the same geographic area as the INPC data in this study, show that there was a peak of reported new sympathomimetics and synthetic cannabinoid use in central Indiana in 2011 (personal communication with James Mowry, PharmD, September 25, 2015; see appendix e-1 at Neurology.org).

Strengths of this work include a large and well-characterized ICH cohort, data on UDS screening from OSHs, inclusion of a preguideline and postguideline publication timeframe, and 1-year outcomes data. Limitations of our study include its retrospective cohort design that is academic center–based and not population-based, so the findings may not be applicable to all patient populations. We reviewed all available records, but it is possible that some OSH records were not included in the transfer records. Detailed social history was not available, so we cannot draw conclusions about the effect on screening of a focused drug abuse history. The UDS results are limited by the immunoassay technique, as discussed above, and no confirmatory testing was performed to exclude cross-reactivity with non-DOA substances. The secondary analysis pertaining to cocaine use is limited to a relatively small sample size. There may be other factors for which we cannot account that played a role in selecting patients for screening. Finally, these data are from 2009 to 2011, and screening patterns might have changed.

There are several important implications of this work for the care of ICH patients. Given the disparities in screening and incongruence between patient behavior and physician perceptions noted in this study and others,[14,20] we advocate for DOA screening in most ICH patients presenting in the appropriate timeframe. While an analysis of the cost-effectiveness of screening is beyond the scope of the present work, we found a yield of at least 4% in our ICH cohort (if all unscreened patients were in fact negative), which is similar to a previous report.[21] Screening for DOA is also relatively inexpensive (see below) compared to other common investigations in stroke patients. Screening should include an immunoassay for cocaine and amphetamines, as well as a targeted social history. While there may be other indications to perform a complete UDS, sympathomimetics are the drugs of interest in terms of potential ICH etiology. At our institution, the price of a routine UDS panel is $670, while selected testing of sympathomimetics is $192 (personal communication, Jim McGown, Indiana University Health Laboratory, May 23, 2016), so unless the full panel is otherwise warranted, limited testing is preferred. The targeted social history should be performed at a time when the patient or family is

capable of a thoughtful history and include language directed at use of any sympathomimetic, which may be accomplished by the interviewer mentioning bath salts and K2/Spice (in addition to cocaine and amphetamines) as examples of DOA. The interview should also include an open-ended question about any other substance use in order to identify the next category of emerging substances.

We found marked disparities in sympathomimetic DOA screening and identified a substantial opportunity for screening improvements. Improved identification of sympathomimetic exposure may improve ICH etiologic classification with the potential to influence therapeutic decision-making and prognosis counseling. Future investigations should include a prospective assessment of DOA across different geographic settings to better understand patterns of use and their relation to ICH and development of larger cohorts of sympathomimetic-related ICH to more fully evaluate the effect of these drugs on patient outcomes. Future studies should also examine trends in screening several years after guideline publication to assess degree of implementation.

AUTHOR CONTRIBUTIONS

Dr. Tormoehlen: study concept and design, preparation of the manuscript. A.D. Blatsioris: acquisition of data. E.A.S. Moser: analysis and interpretation of the data. R.J.L. Carter: acquisition of data. A. Stevenson: acquisition of data. S. Ofner: analysis and interpretation of the data. A.L. Hulin: acquisition of data. Dr. O'Neill: critical review of the manuscript. Dr. Cohen-Gadol: critical review of the manuscript. Dr. Leipzig: critical review of the manuscript. Dr. Williams: study concept and design, critical review of the manuscript. Dr. Mackey: study concept and design, study supervision, preparation of the manuscript, critical review of the manuscript, manuscript guarantor.

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