Diagnostic Performance of Pulmonary Embolism Imaging in Patients with History of Asthma

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Asthma and pulmonary embolism (PE) can present with overlapping symptoms, and distinguishing between these 2 conditions can be challenging. Asthma may limit imaging for PE because of either worsened ventilation defects on ventilation–perfusion scanning (VQ) or increased motion artifacts on CT pulmonary angiography (CTPA). **Methods:** We identified adults evaluated for PE with VQ or CTPA from 2012 to 2016. Patients with chronic lung disease (other than asthma) were excluded. Studies were classified as negative, positive, or nondiagnostic. Follow-up of negative cases was reviewed to determine the rate of repeat exams (within 1 wk) and the false-negative rate (defined as diagnosis of venous thromboembolism within 90 d). **Results:** We reviewed 19,412 adults (aged 52 ± 18 y, 70% women) evaluated for PE (60% with VQ, 40% with CTPA); 23% had a history of asthma. Nondiagnostic results were comparable for those with and without asthma for both VQ (asthma, 3.3%; nonasthma, 3.8%; $P = 0.223$) and CTPA (asthma, 1.6%; nonasthma, 1.5%; $P = 0.891$). A history of asthma was not associated with a higher rate of repeat exams after negative imaging for VQ (asthma, 1.9%; nonasthma, 2.1%; $P = 0.547$) or CTPA (asthma, 0.6%; nonasthma, 0.6%; $P = 0.796$), nor was a history of asthma associated with a higher false-negative rate for VQ (asthma, 0.4%; nonasthma, 0.9%; $P = 0.015$) or CTPA (asthma, 1.9%; nonasthma 1.5%; $P = 0.347$). **Conclusion:** A history of asthma in the preceding 10 y was not associated with impaired diagnostic performance of PE imaging for either VQ or CTPA.

Key Words: pulmonary embolism; asthma; ventilation–perfusion scan; CT pulmonary angiography

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Asthma and pulmonary embolism (PE) have overlapping clinical presentations, and distinguishing these 2 entities is an ongoing challenge, particularly in the emergency department (*1,2*). Additionally, asthmatic patients are prone to development of PE (*3,4*), which may further complicate evaluation.

The presence of PE is frequently assessed with an imaging study, either ventilation–perfusion scanning (VQ) or CT pulmonary angiography (CTPA). In our institution, we have adopted an algorithm in which patients with a clear chest radiograph preferentially undergo VQ in order to reduce radiation exposure (*5*). Since asthma is a chronic disease and is frequently encountered in young adults (*6*), these patients often undergo repeated imaging evaluations and may therefore benefit from efforts to reduce diagnostic radiation exposure (*7–9*).

Unfortunately, for both VQ and CTPA, asthma has potential limitations, which have not previously been characterized. Bronchoconstriction from asthma can cause multiple ventilation (*10*) and matched-perfusion defects (*11*), which can complicate interpretation and may lead to an increased rate of nondiagnostic or false-negative interpretations on VQ. Respiratory motion is known to result in nondiagnostic CTPA exams (*12*) and may be more prevalent in acutely dyspneic asthmatic patients.

A previous series in pregnant women at our institution suggested that the subgroup of patients with asthma may have higher rate of nondiagnostic perfusion-only scans (no ventilation portion) or CTPA (*13*). This result motivated our research question—is the performance of PE imaging impaired by a history of asthma? This is a particularly important consideration for underserved populations, and with the overall increasing asthma prevalence in the United States (*14*). Our patient population has a high rate of asthma (13% of Medicaid enrollees (*15*)), as well as the highest rate of emergency department visits for asthma in New York State, with 35,000 visits in the Bronx during 2016 (244 per 10,000 people) (*16*). Because of our high patient volume, and our imaging algorithm with high VQ use in our emergency department, we have performed a large number of both VQ and CTPA studies. These factors give us the opportunity to assess whether the reliability of VQ or CTPA is impaired in the setting of asthma.

MATERIALS AND METHODS

Setting and Patient Selection

We performed a retrospective cohort study of patients evaluated for PE at Montefiore Medical Center, a multisite urban academic medical center with 3 inpatient sites and 4 emergency rooms. The Institutional Review Board approved this retrospective study, and the requirement to obtain informed consent was waived. A search of adult patients (≥18 y old) who underwent VQ or CTPA from 2012 through 2016 was performed using Looking Glass Clinical Analytics (Streamline Health), a data-mining tool designed to interact with our institution's electronic health records. CTPA exams were identified as any contrast-enhanced CT chest exam that contained the abbreviation "PE" in the report—this expression is used in the exam title, technique description, or clinical indication for most CTPA exams. Patient age, self-reported race and ethnicity, and Charlson Comorbidity Index (*17*) at the time of the exam were recorded. The clinical setting of the exam (emergency department, inpatient, or outpatient) was also recorded.

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Patients were excluded if a diagnosis of a chronic lung disease within the preceding 10 y was identified by our search method. Chronic lung diseases were defined as interstitial pneumonia, fibrotic lung disease, chronic bronchitis, emphysema, bronchiectasis, pneumoconiosis, and sarcoidosis. Perfusion-only lung scans (usually performed on pregnant patients), incomplete CTPA or VQ, or exams that did not address PE were excluded. Patients with an International Classification of Diseases (ICD) diagnosis of asthma within the preceding 10 y formed the asthmatic group. The remaining patients formed the control group. A subset of asthmatic patients was also identified by whether asthma medication had been prescribed in the preceding year (rescue medications, inhaled corticosteroids, leukotriene modifiers, or biologics).

Study Classification and Follow-up Review

All studies were classified as negative, nondiagnostic, or positive. We use this trinary interpretation scheme for VQ in our clinical practice (*18*), and this is reflected in the exam reports. CTPA was classified as negative if this was explicitly stated in the report. If an exam stated there was no central PE but was described as limited, this was also considered negative (*19*). Exams that were described as nondiagnostic or could exclude embolus only in the main, right, or left pulmonary arteries were counted as nondiagnostic. Exams describing acute or chronic PE were counted as positive. Reports were classified as negative, nondiagnostic, or positive on the basis of text searches; remaining cases unable to be classified in this way were reviewed and classified manually.

Follow-up care after PE imaging was reviewed. We determined the rate of repeat examination within 1 wk. False-negative cases were defined as the development of PE or deep-vein thrombosis within 90 d after an initial negative PE imaging study. To identify false-negative cases, patients with a negative exam who had documentation of an ICD 9 or 10 diagnosis of PE or deep-vein thrombosis within the 90-d follow-up period were identified, and these medical charts were reviewed to confirm development of PE or deep-vein thrombosis. The denominator for determining false-negative rate was the number of patients with follow-up in our system beyond 90 d (determined as documentation of an ICD code) plus the number of patients with confirmed PE or deep-vein thrombosis diagnosis within 90 d.

The cohort data were sampled and reviewed manually to determine accuracy. Review of the exam report for every 10th case demonstrated 99.5% accuracy for classifying exam result (10/1,940 misclassification rate). Review of the medical chart for every 100th case demonstrated an overall accuracy of 95% (9 errors in 194 reviewed cases: 1 erroneous exam result, 1 missed repeat exam, 4 misclassifications of asthmatic as nonasthmatic, and 3 misclassifications of nonasthmatic as asthmatic). Review of every 100th CTPA exam demonstrated that 78 of 78 exams were tailored to or performed for PE diagnosis.

Statistical Analysis

Categoric variables were compared with χ^2 testing, and continuous variables were compared with Student *t* testing. The significance level was set at a 2-tailed *P* value of less than 0.05.

RESULTS

We identified 23,586 adults who were evaluated for PE with either VQ or CTPA during the 5-y study period from 2012 through 2016. Of these, 3,608 patients carried an ICD diagnosis of a chronic lung disease within the preceding 10 y and were excluded. Of the remaining 19,978 patients, 566 were excluded (418 patients had a perfusion-only exam for pregnancy, 75 had an incomplete VQ, 58 had CT not performed for PE or not addressing PE, and 15 had incomplete CTPA).

The study cohort comprised 19,412 patients (aged 52 ± 18 y). The study population was predominantly women (70.0%; 13,590/19,412). A large portion self-identified as African-American (38%; 7,443/19,412) or Hispanic (37%; 7,267/19,412). VQ was used to evaluate 11,598 patients (60%), and CTPA was used to evaluate 7,814 patients (40%). Asthma was present in 23% (4,515/19,412) of the cohort, 25% (2,926/11,598) of patients evaluated with VQ, and 20% (1,589/7,814) of patients evaluated with CTPA (Fig. 1).

The populations undergoing VQ and CTPA were distinctly different (Table 1). Patients who underwent CTPA were older (CTPA, 56 y ± 18; VQ, 50 y ± 18; $P < 0.001$) and less predominantly women (CTPA, 65% [5,106/7,814] women; VQ, 73% [8,484/11,598] women; $P < 0.001$). Patients who underwent CTPA also tended to be sicker, as quantified by the Charlson Comorbidity Index (CTPA, 2.0 ± 2.9; VQ, 1.2 ± 2.3; $P < 0.001$). These differences were observed in patients with and without asthma. Patients with asthma were slightly younger (asthma, 51 ± 17 y; nonasthma, 52 ± 19 y; $P < 0.001$) and more predominantly women (asthma, 80% [3,625/4,515] women; nonasthma, 67% [9,965/14,897] women; $P < 0.001$). Patients with asthma had a higher Charlson Comorbidity Index (asthma, 2.0 ± 2.6; nonasthma, 1.4 ± 2.5; $P < 0.001$)—not surprising since asthma contributes 1 point to the Charlson Comorbidity Index.

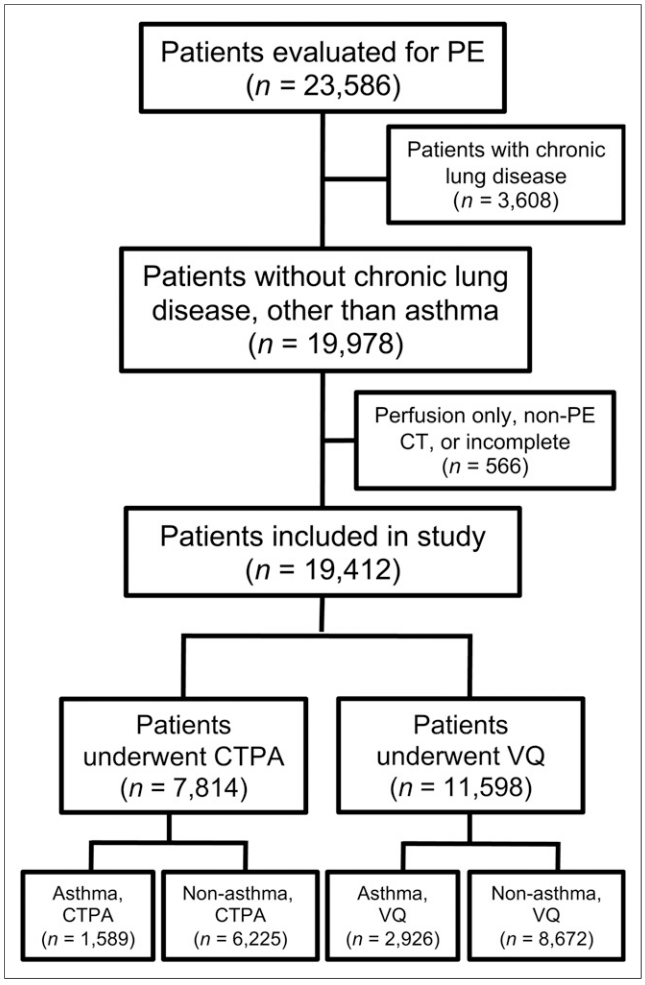

FIGURE 1. Flowchart of study design with patient sample sizes.

TABLE 1
Patient Characteristics and Exam Settings by Modality and Presence or Absence of Asthma

Characteristic	All (n = 19,412)	VQ group (n = 11,598)	CTPA group (n = 7,814)	P	Asthmatic (n = 4,515)	Nonasthmatic (n = 14,897)	P
Age (y)	52 ± 18	50 ± 18	56 ± 18	<0.001	51 ± 17	52 ± 19	<0.001
Sex (female)	70%	73%	65%	<0.001	80%	67%	<0.001
CCI	1.5 ± 2.6	1.2 ± 2.3	2.0 ± 2.9	<0.001	2.0 ± 2.6	1.4 ± 2.5	<0.001
Exam setting				<0.001			<0.001
Emergency department	60%	66%	51%		61%	60%	
Inpatient	30%	23%	42%		32%	30%	
Outpatient	4%	5%	2%		5%	4%	
Unavailable	5%	6%	5%		2%	6%	

CCI = Charlson Comorbidity Index.

The most common clinical setting for PE evaluation was the emergency department (60%, 11,724/19,412), followed by the inpatient setting (30%, 5,904/19,412). PE was rarely evaluated in the outpatient setting (4%, 768/19,412), and information about the clinical setting was not available for 5% (1,016/19,412) of cases. VQ was more commonly used in the emergency department (VQ, 66% [7,702/11,598]; CT, 51% [4,022/7,814]; $P < 0.001$) and less commonly used in an inpatient setting (VQ, 23% [2,638/11,598]; CT, 42% [3,266/7,814]; $P < 0.001$).

The rate of nondiagnostic results did not significantly differ between asthmatic and nonasthmatic populations for either VQ (asthma, 3.3% [97/2,926]; nonasthma, 3.8% [330/8,672]; $P = 0.223$) or CTPA (asthma, 1.6% [25/1,589]; nonasthma, 1.5%; [95/6,225] $P = 0.891$). Asthmatic patients had a lower rate of positive PE studies for both VQ (asthma, 5.5% [162/2,926]; nonasthma, 6.9% [596/8,672]; $P = 0.010$) and CTPA (asthma, 12.0% [191/1,589]; nonasthma, 16.3% [1,012/6,225]; $P < 0.001$; Table 2).

The presence of asthma was not associated with a higher rate of repeat PE imaging within 1 wk after an initial negative exam (Table 3). This finding was observed for both VQ (asthma, 1.9% [51/2,667]; nonasthma, 2.1% [163/7,746]; $P = 0.547$) and CTPA (asthma, 0.6% [8/1,373]; nonasthma, 0.6% [33/5,118]; $P = 0.796$). Patients with a negative VQ were more likely than patients with a negative CTPA to have a repeat exam (VQ, 2.1% [214/10,413]; CTPA, 0.6% [41/6,491]; $P < 0.001$). A history of asthma was associated with a lower rate of false-negative VQ (asthma, 0.4% [10/2,463]; nonasthma, 0.9% [57/6,273]; $P = 0.015$). A history of asthma was not associated with a different rate of false-negative CTPA (asthma, 1.9% [23/1,190]; nonasthma, 1.5% [59/3,838]; $P = 0.348$).

The subgroup of asthmatic patients who had a documented medication prescription in our health system in the preceding year consisted of 2,626 patients (58% of the asthma group), of whom 1,666 had VQ and 960 had CTPA. The exam result, a repeat exam after a negative result, and a false-negative result were similar to the broader asthma cohort; there was also a similar comparison to the nonasthmatic group, with the exception that the difference in the positivity rate for VQ between asthmatic patients with documented medication and nonasthmatic patients was not statistically significant (Table 4).

DISCUSSION

A history of asthma was not associated with impaired diagnostic ability for either VQ or CTPA when evaluating for PE. Any additional artifact or limitation in these exams that might be attributed to asthma is therefore unlikely to alter the reliability or accuracy of PE imaging.

The rate of nondiagnostic exams did not differ between asthmatic and nonasthmatic patients for either VQ or CTPA. This finding is important for managing asthmatic patients with dyspnea or chest pain—we can be assured that a history of asthma does not change the likelihood that the patient will have a diagnostic exam. We interpret VQ using a trinary approach (positive, negative, or

TABLE 2
Exam Results by Modality and Presence or Absence of Asthma

Group	Negative	P	Nondiagnostic	P	Positive	P
VQ						
Asthma (n = 2,926)	2,667 (91.1%)	0.005	97 (3.3%)	0.223	162 (5.5%)	0.010
Nonasthma (n = 8,672)	7,746 (89.3%)		330 (3.8%)		596 (6.9%)	
CTPA						
Asthma (n = 1,589)	1,373 (86.4%)	<0.001	25 (1.6%)	0.891	191 (12.0%)	<0.001
Nonasthma (n = 6,225)	5,118 (82.2%)		95 (1.5%)		1,012 (16.3%)	

TABLE 3
Outcomes After Initial Negative Exam

Group	Initial exam negative	Repeat exam within 1 wk	*P*	False-negative result or follow-up beyond 90 d	False-negative result	*P*
VQ						
Asthma	2,667	51 (1.9%)	0.547	2,463	10 (0.4%)	0.015
Nonasthma	7,746	163 (2.1%)		6,273	57 (0.9%)	
CTPA						
Asthma	1,373	8 (0.6%)	0.796	1,190	23 (1.9%)	0.347
Nonasthma	5,118	33 (0.6%)		3,838	59 (1.5%)	

nondiagnostic) rather than probability terminology (*18*). The probability terminology can be ambiguous to both exam readers (*20*) and clinicians (*21*). The trinary approach clearly communicates results to clinicians without increasing the possibility of false-negative exams. This approach provides a concise positive or negative result, keeping in line with interpretation strategies for other diagnostic studies.

With the trinary approach, the occurrence of VQ studies interpreted as nondiagnostic is low, at less than 4% for both asthmatic and nonasthmatic populations. Furthermore, the rate of false-negative VQ is also low, at less than 1% in this series. The false-negative rate was not significantly higher in asthmatic patients for either VQ or CTPA. Overall, the negative predictive value was greater than 98% for both VQ and CTPA, for patients with and without a history of asthma. Asthmatic patients demonstrated a statistically significant lower rate of false-negative VQ exams; however, the baseline numbers are small and the clinical significance is unclear. The need for a follow-up exam after an initial negative exam also did not differ between asthmatic and nonasthmatic patients, indicating that a history of asthma does not alter the need to further evaluate for PE.

Interestingly, asthmatic patients were slightly less likely to have a PE than nonasthmatic patients. Asthmatic patients in general are reported be at increased risk for venous thromboembolism (*3,4*). However, in the acute setting where patients' symptoms have already brought them to medical attention, it is not surprising that asthmatic patients are less likely to have PE—as they have an alternative diagnosis at presentation that may explain their symptoms.

Asthma is a common disease in patients presenting with alarming symptoms of chest pain or dyspnea, which overlap with symptoms of PE. Asthma may be the cause of the episode or a comorbidity. PE is a frequent and concerning differential diagnosis in these patients. The initial workup for PE is based on clinical and laboratory assessment; however, the diagnosis is ultimately dependent on imaging, usually VQ or CTPA. Both of these modalities use ionizing radiation and have limitations regarding sensitivity and specificity. VQ has the potential for false-negative results for smaller PEs, which may or may not be clinically significant (*22*), or false-positives due to nonembolic causes of pulmonary artery narrowing (*23*). CTPA has the possibility of false-positive results due to motion artifacts, heterogeneous contrast filling, or beam-hardening artifacts (*24,25*). On the basis of prior data from asthmatic pregnant patients (*13*), we were concerned that a history of asthma—with ventilation defects, air trapping, and increased respiratory motion—might increase the limitations for either of these exams.

Our practice setting provided us a good opportunity to address concerns regarding asthma in both CTPA and VQ exams. First, asthma is particularly prevalent in our practice, present in 13% of Medicaid enrollees in Bronx, NY (*15*), and was even higher in our cohort (23%, similar to the prior cohort of pregnant patients studied in our medical system (*13*)). Second, our practice algorithm recommends VQ when the chest radiography results are normal and the patient is stable enough to tolerate the exam (*5*)—this provided us with a large sample size of VQ studies to review

TABLE 4
Asthmatic Patients with Documented Asthma Medication Prescription in Preceding Year, Compared with Nonasthmatic Patients

Group	Negative	Nondiagnostic	*P*	Positive	*P*	Repeat exam after negative	*P*	False-negative	*P*
VQ									
Asthma with medication (n = 1,666)	1,511 (90.7%)	60 (3.6%)	0.689	95 (5.7%)	0.072	27 (1.8%)	0.634	4/1430 (0.3%)	0.015
Nonasthma (n = 8,672)	7,746 (89.3%)	330 (3.8%)		596 (6.9%)		163 (2.1%)		57/6273 (0.9%)	
CTPA									
Asthma with medication (n = 960)	833 (86.8%)	15 (1.6%)	0.932	112 (11.7%)	<0.001	6 (0.7%)	0.944	18/716 (2.5%)	0.063
Nonasthma (n = 6,225)	5,118 (82.2%)	95 (1.5%)		1,012 (16.3%)		33 (0.6%)		59/3838 (1.5%)	

and accounts for the older age and higher Charlson Comorbidity Index in the CTPA group. The CTPA group was also less predominantly women, likely due to the additional benefit of reducing radiation to the chest (breast tissue) in women (*7,9*).

Asthmatic patients in our cohort were found to be slightly younger and more often women; these are the patients who are most susceptible to radiation from chest imaging. Although the continued development of modern CT scanners may narrow the radiation dose difference between VQ and CTPA (*26–28*), use of VQ may be beneficial for young patients in certain practice settings and will perform reliably regardless of the diagnosis of asthma.

This analysis is limited by the limited ability to assess the acuity of a patient's asthma. Asthma exacerbation is likely in the differential for most patients presenting with shortness of breath or chest pain, especially if there is any documented history of asthma. Patients may be empirically treated for multiple conditions, including asthma, and it is therefore difficult to know the true etiology of a patient's symptoms. In fact, it is our standard practice for patients who are wheezing to recommend bronchodilator therapy before performing VQ, and our results reflect that practice. VQ is advised to be performed after bronchospasm has resolved, in order to decrease ventilatory defects (*29*). We addressed this issue with our subgroup analysis, restricted to the patients with a documented prescription for asthma medication in the preceding year. This accounted for a slight majority of the asthmatic cohort (58%). The characteristics of this subgroup were similar to the broader asthmatic cohort and compared similarly to the nonasthmatic group, indicating that our results hold for patients with more active or more recent history of asthma.

Additional limitations of this study primarily stem from its retrospective nature performed in one medical system and its dependence on medical record keeping. ICD codes were used to classify patients as asthmatic or nonasthmatic, to determine the presence of underlying chronic lung disease, and to identify the development of venous thromboembolism. The development of venous thromboembolism was likely underestimated in this study, primarily because of dependence on ICD coding to identify potential false-negative cases and incomplete follow-up of all patients within our system. However, these limitations should not bias results toward asthmatic or nonasthmatic patients. Differences between the asthmatic and nonasthmatic groups, with a higher proportion of women and a slightly younger age in the asthmatic group, are an additional limitation of this study.

There were important differences between patients evaluated with VQ or CTPA—including age, sex, and exam setting—which reflect our clinical practice and preclude comparison between VQ and CTPA in this study. CTPA had a higher rate of positive exams and false-negative exams than VQ—however, both of these findings likely reflect the older age and higher rate of comorbidities in patients who underwent CTPA. The higher positivity rate for CTPA also reflects the higher sensitivity of CTPA for small PE (*30,31*).

CONCLUSION

The decision to image for PE is complex and must take into consideration the benefits and limitations of VQ and CTPA. A history of asthma does not impair the diagnostic performance of either of these modalities.

DISCLOSURE

Leonard Freeman is a consultant for Jubilant Pharma. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Does a history of asthma impair the diagnostic performance of imaging for PE?

PERTINENT FINDINGS: Asthmatic patients did not demonstrate a higher rate of nondiagnostic studies or false-negative results for either VQ or CTPA.

IMPLICATIONS FOR PATIENT CARE: Our results should assure physicians that a history of asthma will not impair the diagnostic performance of either VQ or CTPA.

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Errata

In the article "Biodistribution and Dosimetry of Intraventricularly Administered ^{124}I-Omburtamab in Patients with Metastatic Leptomeningeal Tumors," by Pandit-Taskar et al. (*J Nucl Med.* 2019;60:1794–1801), information for Kim Kramer was inadvertently left out of the Disclosure section. The Disclosure should have additionally stated: *Kim Kramer is a paid consultant for Y-mAbs Therapeutics, Inc.* The authors regret the error.

In the article "Immune-Checkpoint Blockade Enhances ^{225}Ac-PSMA617 Efficacy in a Mouse Model of Prostate Cancer," by Czernin et al. (*J Nucl Med.* 2021;62:228–231), the Disclosure section should have included the following information: *The study was supported in part by a Broad Stem Cell Research Center (BSCRC) Innovation Award*. The authors regret the error.