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Prevalence of clinically significant incidental findings by whole-body FDG-PET/CT scanning in moderate-to-severe psoriasis patients participating in clinical trials

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Abstract

Objective: Determine the prevalence of incidentalomas and rate of malignancy identified by FDG-PET/CT imaging in clinical trial patients with moderate-to-severe psoriasis.

Methods: Cross-sectional secondary analysis of moderate-to-severe psoriasis patients who underwent FDG-PET/CT scans at the baseline visit, prior to randomization, for three phase 4 vascular inflammation in psoriasis clinical trials. Only patients without active infection, malignancy or uncontrolled comorbidities were eligible for the clinical trials.

Results: 259 healthy patients with moderate-to-severe psoriasis underwent an FDG-PET/CT scan as part of study procedures. Thirty-one patients (11.97% [95% Confidence Interval (CI):8.28–16.56]) had clinically significant incidentalomas on the baseline FDG-PET/CT scan. Univariate logistic regression demonstrated that with every increase in 10 years of age, there was an approximate 30% increased risk of discovering an incidentaloma (Odds Ratio 1.30 [95%CI:1.01–1.68]). Of the findings suspicious for malignancy (n=28), cancer was confirmed in 6 patients resulting in a 2.31% (95%CI:0.9–5.0) prevalence of malignancy. Positive predictive value of a true cancer was 31.58% (range 21%–54%).

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We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. Data for this project was collected under approved IRB protocols: 814278, 820124, and 824648.

Limitations: Generalizability and lost to follow-up.

Conclusion: Incidentalomas on FDG-PET/CT imaging are common in otherwise healthy, asymptomatic clinical trial patients with moderate-to-severe psoriasis. Our results can help inform clinical trials safety data interpretation and emphasizes the importance of compliance with cancer screening recommendations.

Capsule Summary

- The prevalence of serious medical problems not detected by routine history, physical, and laboratory studies in patients with moderate-to-severe psoriasis presenting for clinical trials is not known.
- About 12% of patients had clinically significant incidental findings on FDG-PET/CT imaging, and 2.31% of patients had cancer.

Keywords

psoriasis; randomized controlled trials; biologics; FDG-PET/CT; incidental findings

Introduction

Psoriasis is a chronic, systemic, inflammatory disease that affects approximately 125 million people worldwide. About 20% of patients with psoriasis have moderate-to-severe skin disease, and may be candidates for treatment with phototherapy or oral or injectable (e.g., biologic) medications.¹ Patients with psoriasis, particularly when disease is severe, have an increased incidence and prevalence of major comorbidities including cardiovascular disease, metabolic disease, and malignancy.^{2–5} There has been a revolution in the treatment of moderate-to-severe psoriasis over the last two decades with multiple novel agents being investigated in clinical trials. In clinical research, some medical conditions may not be diagnosed at the start of the study but seemingly appear during the course of the study or follow-up which can affect assessments of drug safety. Therefore, it is of special interest to understand what types of major medical problems may be undiagnosed at the start of a clinical trial that may become identified during follow-up as incident medical conditions.

We have been conducting a series of clinical trials to determine the impact of several different psoriasis treatments on markers of cardiovascular disease using ¹⁸F-fluorodeoxyglucose (FDG) uptake detected and measured on positron emission tomography/computed tomography. This technique was used as a primary endpoint as it allows for measurement of aortic vascular inflammation that is reliable, predictive of cardiovascular events, and rapidly responsive (e.g., within 4–12 weeks) to treatments that are known to lower cardiovascular risk, such as statins.⁶ FDG-PET/CT imaging is also highly sensitive, but not necessarily specific, for conditions characterized by increased metabolic activity, such as cancer.⁷ As a result, the use of FDG-PET/CT for research purposes may give rise to “incidentalomas” which are findings that are unexpected in an asymptomatic patient or findings in a symptomatic patient that are unrelated to the reason for which the investigation was ordered.^{8–10} Incidentalomas are estimated to impact tens of thousands of human subjects involved in imaging research annually in the United States,⁸ but little research has

reported the rates and types of incidentalomas found in clinical trials of patients with chronic inflammatory disease such as psoriasis. Therefore, the aim of this study is to evaluate the prevalence of previously unfound clinically significant medical problems identified by baseline FDG-PET/CT imaging in clinical trial patients with moderate-to-severe psoriasis.

Methods

Study design and Patient Selection

This was a cross-sectional secondary analysis of patients with moderate-to-severe psoriasis who were screened and underwent baseline FDG-PET/CT scans for three phase 4 clinical trials: Vascular Inflammation in Psoriasis (VIP, conducted at nine sites), VIP-Secukinumab (VIP-S, conducted at twelve sites), and VIP-Ustekinumab (VIP-U, conducted at one site). Adult patients with moderate-to-severe plaque psoriasis, defined by 10 percent body surface area involvement and Psoriasis Area and Severity Index (PASI) score of 12, were screened for eligibility. Only healthy patients were eligible for the three clinical trials. Patients with medically significant, uncontrolled comorbidities (e.g., unstable ischemic heart disease, congestive heart failure, uncontrolled hypertension, recent cerebrovascular accidents, diabetes mellitus, psychiatric disease requiring frequent hospitalization) were excluded for the primary purpose of the clinical trial. Furthermore, patients with a history of demyelinating disease or systemic lupus erythematosus, hematological or solid malignancy within the past five years (except successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma, or cervical carcinoma in situ) were also excluded. To determine eligibility for the trial, recruited patients attended a screening visit whereby baseline demographics, a thorough clinical history, a full physical examination, and laboratory testing (for blood count, kidney and liver function, and screening for human immunodeficiency virus (HIV), hepatitis B and C, and tuberculosis infections) were obtained. Specifically, required laboratory values were: hemoglobin >10 g/dL in females or >12 g/dL in males, white blood cell count between $2.5\text{--}15 \times 10^9/\text{L}$ (if white blood cell count $<2.5 \times 10^9/\text{L}$, subject could be included as long as absolute neutrophil count was $>1000 \text{ cells}/\text{mm}^3$), platelet count $>100 \times 10^9/\text{L}$, creatinine $<1.6 \text{ mg}/\text{dL}$ ($<141 \mu\text{mol}/\text{L}$), aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 upper limits of normal, and total bilirubin $<2 \text{ mg}/\text{dL}$ ($<26 \mu\text{mol}/\text{L}$). Further details of the primary outcomes and methodology have been previously published¹¹ and reported on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01553058, NCT02690701, NCT02187172).^{12–14} Study approval for the clinical trials was obtained from the Institutional Review Board (IRB) at the University of Pennsylvania (UPenn) or the respective local IRB when indicated. All study participants provided written informed consent. This manuscript was prepared according to the STROBE statement.¹⁵

Outcomes and Classification

Incidental findings, the outcome of interest, were defined as observations of potential clinical significance that were discovered and unrelated to the purpose or beyond the aims of the research studies in healthy, asymptomatic subjects or symptomatic patients with seemingly unsuspecting symptoms. This definition of incidentalomas is similar to definitions described in previous research studies^{8,10} and clinical practice.⁹ In our study, an incidentaloma was considered as “clinically significant” when the board-certified radiologist

recommended further work-up with additional laboratory testing, imaging, or invasive procedures (e.g., biopsy). If a patient had more than one incidentaloma, the incidentaloma was classified based on the one with the most severe category because that would dictate whether or not the patient required further workup. As a sensitivity analysis, a separate classification method proposed by Lumberas *et al.* was also utilized. Each “clinically significant” incidental finding was categorized as: “major” (may cause mortality), “moderate” (may cause morbidity), “minor” (hardly relevant and likely no follow-up needed), and “unclassified” (not categorized in the aforementioned classification system).¹⁶

Data Collection

All patients who met the screening criteria underwent a whole-body (i.e., skull vertex to toes) FDG-PET/CT scan ~60–120 minutes (range of delay: 48 to 146 minutes) following intravenous administration of ~15 mCi of FDG (or weight-based dosing for the VIP-S study) during the baseline visit at the respective medical centers in the United States. Radiological images were interpreted by a board-certified radiologist experienced in the interpretation of FDG-PET/CT scan imaging. Patients without “clinically significant” incidental findings on FDG-PET/CT were randomized and started the intervention phase of the respective study. We reviewed the reports for all patients with “clinically significant” incidental findings. As part of the study procedures, these patients underwent additional evaluation and were randomized if the clinically significant incidental finding was not deemed to be relevant to the safety of the treatments being studied. Subsequent recommendation for workup was categorized as clinical correlation, additional laboratory testing, imaging, or invasive procedures (e.g., biopsy). Available research visit notes and pathology reports were reviewed to confirm neoplastic status.

Data Analysis

The exposure was FDG-PET/CT baseline imaging. Some patients underwent baseline imaging for multiple VIP studies, so we only included findings from each patient’s first baseline scan for our analyses. The outcomes of interest were (1) the prevalence of “clinically significant” incidentalomas and (2) the rate of malignancy. Of the patients who underwent baseline imaging, we evaluated the number of patients who had a confirmed cancer diagnosis to find the rate of malignancy.

$$\text{Prevalence} = \frac{\# \text{ of patients with } \geq 1 \text{ incidentaloma}}{\text{Total } \# \text{ of patients who underwent baseline imaging}}$$

$$\text{Malignancy Rate} = \frac{\# \text{ of patients with } \geq 1 \text{ malignancy}}{\text{Total } \# \text{ of patients who underwent baseline imaging}}$$

From the extracted data, we summarized ranges for continuous data, calculated proportions, and percentages for categorical data with 95% Confidence Interval (95%CI). Logistic regression was performed to identify baseline characteristics that may predict a “clinically significant” incidental finding. Data management and statistical analyses were performed using STATA 15.1 (StataCorp, College Station, Texas, USA).

Results

Two hundred and fifty-nine patients with moderate-to-severe psoriasis with no evidence of active or poorly controlled medical conditions and who had a physical examination and laboratory evaluation without clinically significant findings, underwent an initial FDG-PET/CT scan at the baseline visit as part of the screening phase for the three clinical trials. Baseline characteristics of the study population are summarized in Table 1. The majority of patients were Caucasian males, with an average body mass index of 31.83(SD 7.47), and a mean age of approximately 45 years (SD 14.70).

Thirty-one patients of the 259 (11.97% [95%CI: 8.28–16.56]) with a mean age of 50.61 years (SD 14.71) had “clinically significant” incidental findings in the baseline FDG-PET/CT scan. Fifteen patients (5.79% [95%CI: 3.27–9.37]) had “major” findings, 10 patients (3.86% [95%CI: 1.87–6.99]) had “moderate” incidentalomas, and 4 patients (12.90% [95%CI: 3.63–29.83]) had “minor” incidentalomas according to the classification system developed by Lumberas *et al.* An additional 2 patients (6.45% [95%CI: 0.79–21.42]) had benign incidentalomas which could not be categorized by the aforementioned system (Table 2).¹⁶ The “major” and “moderate” category corresponded to our study definition of “clinically significant” incidentalomas as diagnoses in those categories were likely to require further work-up. Univariate logistic regression demonstrated that with every increase in 10 years of age (decile), there was an approximately 30% increased risk of discovering a “clinically significant” incidentaloma as determined by both classification methods (OR 1.30 [95%CI: 1.01–1.68]). No association was seen with sex, smoking, alcohol use, history of oral systemic or biologic treatment use, body mass index, or psoriasis severity as measured by PASI.

The clinical suspicion and course of the patients with “clinically significant” incidental findings are described in Table 3. Of the 31 patients with incidentalomas, 7 (22.58% [95%CI: 9.59–41.10]) were found in the lungs, 6 (19.35% [95%CI: 7.45–37.47]) in the head and neck region, 5 (16.13% [95%CI: 5.45–33.73]) in the colon, and 3 (9.68% [95%CI: 2.04–25.75]) in the pelvis. There was 1 (3.2% [95%CI: 0.08–16.70]) incidentaloma each found in the adrenal glands, bone, esophagus, inguinal area, kidney, liver, mediastinum, prostate gland, rectum, and stomach, respectively. Of the 31 patients with “clinically significant” incidentalomas, further investigation was needed for one patient due to the suspicion of an arachnoid cyst, and two patients had findings suspicious of infection. Overwhelmingly, most findings were suspicious for malignancy (n=28). Cancer was confirmed in 6 patients (gastrointestinal stromal tumor of the small bowel, oropharyngeal adenocarcinoma, uterine leiomyosarcoma, lymphoma, papillary thyroid carcinoma, non-small cell lung adenocarcinoma), yielding an overall prevalence of malignancy in the study population of 2.31% (95%CI: 0.9–5.0). The 6 patients with confirmed cancer had a mean age of 66.5 years (SD 9.29). Nine patients with findings concerning for cancer were lost to follow-up. The positive predictive value (PPV) of a “clinically significant” neoplastic incidental finding for being a true cancer was 31.58%. The PPV ranged from 21% (assuming that all nine patients in whom follow-up information was unobtainable did not have cancer) to 54% (if all patients lost to follow-up, in fact, had cancer).

Discussion

To our knowledge, this is the first large multi-center study to report the frequency and outcomes of incidental findings with the use of non-invasive imaging in patients with psoriasis. The results of our study demonstrate that there is an approximately 12% prevalence of clinically significant imaging findings in a population of patients with moderate-to-severe psoriasis who are asymptomatic and have an unremarkable history, physical examination, and laboratory work-up. In total, 6 patients (2.3%) had a serious underlying cancer that necessitated further follow-up or work-up. The true rate of cancer in this population may be as high as 6% (total N=15) if all suspected neoplasms that we were unable to obtain follow-up information for were true malignancies. These findings have important implications for clinical trials and clinical practice. For example, we identified one case of lung adenocarcinoma in a patient with a history of smoking, which, in daily clinical practice, could have been potentially identified by routine screening in accordance with US Preventive Services Task Force recommendations, emphasizing the importance of encouraging patients to be up-to-date with age-appropriate cancer screening recommendations.¹⁷ While the lung adenocarcinoma may have been detected by recommended screening, it is possible that the other cancers (gastrointestinal stromal tumor of the small bowel, oropharyngeal adenocarcinoma, uterine leiomyosarcoma, lymphoma, papillary thyroid carcinoma) may not have been detected based on current cancer screening recommendations.

In a survey of healthy research volunteers,¹⁸ most individuals reported a desire to be informed if clinically significant health-related research findings were discovered and its likelihood of discovery, despite potential medical, insurance, and employment implications. Our results provide a foundation for clinical trialists to help guide the discussion during the informed consent process on what otherwise healthy patients with moderate-to-severe psoriasis can expect (i.e., frequency of incidentalomas) should any “clinically significant” incidentalomas be found if undergoing comprehensive radiological imaging during a clinical trial.

Though there are differing views on the handling of incidentalomas,^{10,19} we encourage clinicians and researchers to develop procedures that are suitable within their framework such as collaborating with local hospitals or conferring with other specialists for further evaluation and management (i.e., developing a procedure to disclose findings to patients and discussions of next steps). As part of our process, we developed a systematic procedure of managing “clinically significant” incidentalomas whereby we internally track and discuss “clinically significant” incidentalomas within our research team, which includes a radiologist, and subsequently relay information to the patient and the relevant clinical service in a timely manner. Several research bodies and teams have reported different methods of managing incidentalomas²⁰ such as incorporating a dedicated section in the electronic medical record to prompt whether or not an incidentaloma was found,²¹ or creating a closed feedback loop with the patients’ research team and primary care physician.^{22,23}

Our findings can also be used to inform interpretation of safety data of novel therapies as there are numerous reports of malignancy in clinical trials of immune modulating treatments for psoriasis.²⁴ For example, in a phase 3 trial of 666 patients with moderate-to-severe plaque psoriasis patients receiving tofacitinib, three patients had malignancies: colon cancer (59 days post-initiation), prostate cancer (84 days post-initiation), and pancreatic cancer (138 days post-initiation).²⁵ Given the statistical rarity of cancer, investigators, regulators, and others may interpret a false safety signal when cancers are observed in a clinical trial. However, our data provide an estimate for what the prevalent rate of cancer is in the moderate-to-severe psoriasis population and therefore should help inform interpretation of these safety results.

As with all studies, there are limitations to consider. These results may not be generalizable to the non-US population of patients with moderate-to-severe psoriasis. However, our patient characteristics (age, sex, duration of psoriasis, PASI) are quite similar to most large phase 3 programs and thus are likely generalizable to the US population. The clinical trial population may falsely inflate signals discovered through imaging as it may include uninsured individuals with limited access to health care and therefore may have prior undiagnosed diseases.²⁶

Conclusion

In summary, clinically significant findings on FDG-PET/CT imaging are common in otherwise healthy asymptomatic patients with moderate-to-severe psoriasis participating in clinical trials. Of special importance is that at least 2.3% of patients had serious unrecognized cancers. These findings can help inform the interpretation of safety data from clinical trials and further emphasizes the importance of encouraging psoriasis patients with moderate-to-severe disease to be compliant with current, age-appropriate cancer screening recommendations.

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Disclosures:

Dr. Gelfand served as a consultant for BMS, Boehringer Ingelheim, GSK, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologic and Novartis. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr. Gelfand is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology.

Dr. Mehta is a full-time US Government Employee and receives research grants to the National Heart, Lung, and Blood Institute (NHLBI) from AbbVie, Janssen, Celgene, and Novartis.

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Dr. Torigian is a co-founder of Quantitative Radiology Solutions LLC.

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Table 1.

Baseline characteristics of patients with psoriasis.

	Total (n=259)
Gender, N (%)	
Female	82 (31.66%)
Male	177 (68.34%)
Mean Age, Year (SD)	45.31 (14.70)
Age Range, Year	19–83
Race, N (%)	
American Indian/Native	1 (0.39%)
Asian	18 (6.95%)
African American	21 (8.11%)
White	202 (77.99%)
Other	17 (6.56%)
Ethnicity, N (%)	
Hispanic/Latino	54 (20.85%)
Non-Hispanic/Non-Latino	202 (77.99%)
<i>Missing</i>	<i>3 (1.16%)</i>
BMI, kg/m ²	
Mean (SD)	31.83 (7.47)
Range	18.00–58.72
<i>Missing, N (%)</i>	<i>3 (1.16%)</i>
Smoking, N (%)	
Never	126 (48.65%)
Current	57 (22.01%)
Former	73 (28.19%)
<i>Missing</i>	<i>3 (1.16%)</i>
Alcohol units consumed per week, Median (IQR)	1 (1–7)
History of Biologic treatment, N (%)	84 (32.43%)
History of Phototherapy, N (%)	74 (28.57%)
History of Oral Systemic Treatment, N (%)	71 (27.41%)
Body Surface Area, Mean (SD)	24.80 (16.33)
Psoriasis Area and Severity Index, Mean (SD)	19.22 (9.15)

Table 2.

Rates of clinically significant incidental findings* in the VIP trials.

Total No. of baseline scans	No. of patients with Clinically Significant Incidental Findings %	British Journal of Radiology Classification**						
		Major		Moderate		Minor		Unclassified (Benign)
		15	5.79%	10	3.86%	4	1.54%	2
259	31 (11.97%)	Malignancy Status						
		Confirmed malignancy			Unknown		Benign	
		6	2.32%	9	3.47%	16	6.18%	

* Clinically significant as defined by requiring workup from the radiologist or dermatologist.

** Major findings (that may cause mortality), moderate findings (may cause morbidity), minor findings (hardly relevant and no follow-up needed), unclassified (benign findings that were not mentioned in the classification system). If a patient had more than one incidentaloma, the incidentaloma that was classified as the most severe category as that would dictate whether or not the patient required further workup.

Table 3.

Clinical course of patients with clinically significant incidental findings.

Age	Sex	Race	Clinical Suspicion/Differential Diagnosis	Related Past Medical History	Recommendation	Additional Work-Up That Was Undertaken	Diagnosis (Last Known Clinical Course)	Randomized*	Study Course**
Diagnosed with Malignancy									
55	F	White	Underlying malignancy (e.g., SCC of soft palate, cancer of minor salivary gland, infectious or inflammatory etiologies)	No history of cancer	Biopsy	Endoscopic correlation	Polymorphous low-grade adenocarcinoma (T1N0M0)	No	Discontinued
57	F	White	Post-menopausal endometrial thickening from degenerated leiomyoma or uterine malignancy	PCP previously investigated - biopsy showed non-cycling endometrium	Pelvic MRI	Hysterectomy for ongoing symptoms	Pathology of the uterus revealed leiomyosarcoma contained within the uterus	Yes	Discontinued
65	M	White	Adrenal metastasis, small bowel (lymphoma, GIST, carcinoid tumor)	N/A	Abdominal MRI	MRI; f/u with specialist	GIST of the small bowel - Stage T2N0M0G1, 1A, KIT exon 11 (Excision and radiation of neoplasms)	No	Discontinued
69	M	White	Bilateral inguinal and obturator chain lymphoma	N/A	Biopsy	Biopsy	Bilateral inguinal and obturator chain lymphoma	No	Discontinued
76	M	White	Thyroid nodule	Basal cell carcinoma, SCC, prostate cancer	Biopsy	Biopsy	Papillary thyroid carcinoma (unknown Stage)	No	Discontinued
77	M	African American	Lung carcinoma (vasculitis, lymphoma, and cryptogenic organizing pneumonia)	Denies any toxic, asbestos or TB exposures. Smoke 1 cigarette pack/day for 50 years	Clinical correlation and scan	Bronchoscopy, then Chemotherapy	Non-small cell lung adenocarcinoma (Stage IV T2N0M1a with pleural metastases, EGFR/ALK wild-type)	No	Discontinued
Not diagnosed with Malignancy (Benign or Unknown findings)									
21	M	White	Pulmonary nodule	No prior smoking history or family history of lung cancer	Chest CT	f/u imaging	Resolved; "most likely benign"	Yes	Continued
30	F	Black	Fibroid	Denies excessive pain with menstrual cycles or heavy bleeding	Follow-up PET/CT imaging or Pelvic Ultrasound	f/u imaging	Fibroids	Yes	Continued
30	M	White	Lymphoma, adenosis in nasopharynx/oropharynx	N/A	Endoscopy	Endoscopy	Unknown (lost to f/u)	No	Discontinued
31	F	Black	Underlying inflammation; right palatine tonsil, nonspecific	Eyes, Ears, Nose, Mouth, Throat Exam: Negative.	Follow-up PET/CT imaging	f/u imaging	Unchanged; "non-specific"	Yes	Continued
31	M	Hispanic White	Lung neoplasm in left hemithorax	N/A	Follow-up PET/CT imaging, chest CT, chest MRI, or tissue sampling	Unknown	Unknown (lost to f/u)	No	Discontinued
34	M	Unknown	Inflammation of cervical lymph node, nonspecific	N/A	Follow-up PET/CT imaging	f/u imaging	Unchanged; "non-specific most likely inflammatory"	Yes	Continued
38	M	Hispanic White	Cirrhosis	Consumed 2 drinks daily	Clinical and/or laboratory correlation	f/u with PCP	Cirrhosis	Yes	Continued
39	M	Unknown	Pulmonary nodule	N/A	Follow-up PET/CT imaging or Chest CT	f/u imaging	"nonspecific"	Yes	Continued
42	F	White	Ovarian neoplasm (complex left ovarian cyst with inflammation, endometrioma)	Family history of breast and fallopian tube cancer	Pelvic MRI	Elective bilateral salpingo-oophorectomy	Ovarian cyst	Yes	Continued
43	F	Black	Superior cerebellar cistern (or arachnoid cyst)	N/A	Clinical correlation and/or brain MRI	None	Resolved	Yes	Continued
48	M	Hispanic White	Pulmonary nodule	N/A	Chest CT	f/u with specialist; chest CT	Latent TB	Yes	Continued
48	M	White	Thial sclerosis	N/A	Follow-up PET/CT imaging	f/u imaging	Unchanged; "most likely benign"	Yes	Continued
48	M	Hispanic White	Renal Mass	N/A	Abdominal ultrasonography or MRI	f/u with PCP	Unknown (lost to f/u)	Yes	Continued
48	M	White	Small hiatal hernia	GERD intermittently, managed by diet and Tums as needed. Never Smoker.	Upper endoscopy or esophagography	Upper endoscopy	Barrett's esophagus; resolved with medication	Yes	Continued
49	M	White	Mosaic attenuation of the lungs	Smoker	Chest CT	f/u imaging	Not malignant or infectious	Yes	Continued
50	M	White	Rectal neoplasm	N/A	Follow-up PET/CT imaging or pelvic MRI or colonoscopy	Unknown	Unknown (lost to f/u)	Yes	Continued
51	M	White	Distal esophagus uptake, nonspecific	N/A	Upper endoscopy	Upper endoscopy	GERD	Yes	Continued

Age	Sex	Race	Clinical Suspicion/Differential Diagnosis	Related Past Medical History	Recommendation	Additional Work-Up That Was Undertaken	Diagnosis (Last Known Clinical Course)	Randomized*	Study Course**
53	M	White	Colorectal carcinoma	N/A	Colonoscopy	Unknown	Unknown (lost to f/u)	No	Discontinued
53	F	Hispanic White	Sigmoid colon adenoma or carcinoma	N/A	Colonoscopy	colonoscopy	Benign adenoma	Yes	Continued
54	M	White	Prostatitis	Normal annual physical exam	Serum PSA levels	f/u with PCP	f/u with PCP	Yes	Continued
60	F	White	Pulmonary nodule and emphysema	N/A	Chest CT	f/u imaging; f/u with pulmonologist	Unchanged; "most likely benign"	Yes	Continued
62	M	White	Colonic polyp	Colitis (proctitis) episode previously	Colonoscopy	Seen by gastrointestinal specialist	Benign	No	Discontinued
64	M	White	Mediastinal tumor - lymphoma, thymoma, or germ cell tumor	GERD	Biopsy	Biopsy	Thymoma	No	Discontinued
68	F	White	Colonic polyp	No family history of colon cancer	Colonoscopy	f/u with gastroenterology	Unknown (lost to f/u)	Yes	Continued
75	M	White	Primary malignancy or large colonic polyp	N/A	Colonoscopy	Unknown	Unknown (lost to f/u)	No	Discontinued

Note: All patients were asymptomatic at presentation. Abbreviations: computed tomography (CT), follow-up (f/u), gastroesophageal reflux disease (GERD), gastrointestinal stromal tumor (GIST), magnetic resonance imaging (MRI), not applicable (N/A), primary care physician (PCP), squamous cell carcinoma (SCC), tuberculosis (TB).

* Randomized and received active therapy or placebo

** Study course: "continued" means continued on study protocol and "discontinued" means discontinued or withdrew from study protocol