Rapidity of Coccidioidomycosis Diagnosis and Its Effect on Healthcare Utilization

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Abstract

Background: Coccidioidomycosis is an infection caused by the fungal Coccidioides species common to Central and South America, and the southwestern United States, with Arizona claiming the vast majority of U.S.-based cases. Recognizing and diagnosing coccidioidomycosis is often difficult, with the wide range of symptoms being commonly misdiagnosed as a bacterial community-acquired pneumonia. Misdiagnosis and a delay in true diagnosis leads to ineffective, costly, and burdensome ramifications. Data investigating the diagnostic delay of Coccidioidomycosis could provide means for future changes in clinical practice.

Methods: This is a two-phase study: phase one assessed disease markers and symptomatology, and phase two analyzing healthcare utilization based on electronic medical record data extraction of 139 patients.

Results: The mean and median for 0-30 days of delay was $6,273 and $770 respectively; this increased at 151-183 days of diagnostic delay to $57,724 and $8,917 respectively. Small final population size precluded meaningful statistical analysis.

Conclusion: Demonstrating diagnostic delay characteristics for patients with coccidioidomycosis is possible, however due to small final population size and difficulties encountered due to the innate properties of the electronic medical record, future investigation and optimization will be necessary for more powerful analysis.

Abbreviation List

CAP: Community Acquired Pneumonia

CT scan: Computed Tomography scan

PET scan: Positron-Emission Tomography scan

EMR: Electronic Medical Record

ICD-9: International Classification of Diseases 9th Revision

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Introduction

Coccidioidomycosis, also known as Valley Fever or “desert rheumatism”, is an infection caused by the fungal Coccidioides species.[1] The fungus is common to parts of Mexico, Central and South America, and the arid southwestern United States, with Arizona claiming nearly 70% of yearly reported cases (Figure 1.).[2]

The Coccidioides genus is comprised of two species: *C. immitus* and *C. posadasii*, with their most important difference being geographical predilection with no known clinical implications.[1] A dimorphic fungus, Coccidioides species (spp.) survive as mycelia in the soil, growing and forming into brittle, easily distributed arthroconidium that can be inhaled and establish an infection.[2,3]

Recognizing and diagnosing Coccidioidomycosis is often difficult; of those exposed 60% never have symptoms. Those who do typically develop a mild range including fatigue, cough, fever, shortness of breath, headache, night sweats, muscle-joint aches, rash, etc.[1] Symptoms are often nonspecific and confused for either a viral or bacterial respiratory illness. Indeed, a significant amount of cases of community-acquired pneumonia (CAP) in these regions are likely to be caused by Coccidioides spp.[4,5] In Arizona's Valley Fever corridor—consisting of Maricopa, Pinal, and Pima counties, at least 25% of all CAP diagnoses in ambulatory patients are primary respiratory disease caused by Coccidioides spp. Despite Arizona Department of Health Services recommendations to test CAP patients for Coccidioidomycosis, fewer than 13% of these patients are evaluated for possible Coccidioides spp. infection via serologic testing.[2] In most circumstances, a positive serologic test for coccidioidal antibodies is highly presumptive of a current infection; however, a negative serologic test never excludes the presence of a coccidioidal infection.[2,6]

Figure 1. *Shaded areas indicate suspected coccidioidomycosis distribution in the Western Hemisphere.*[2]

If a patient is given a presumptive diagnosis of CAP while truly suffering from a Coccidioides spp. infection, a multitude of negative resultant and ongoing issues occurs. Primarily, this causes a delay in true diagnosis—sometimes for several months. Moreover, misdiagnosis of CAP can lead to management with empiric antibacterial treatments, which are ineffective against the fungal Coccidioides spp. In one study, 81% of patients with Coccidioidomycosis pneumonia received at least one course, and 31% received multiple courses of antibacterial treatment for their illness.[2] In an attempt to identify the true etiology, unnecessary and further testing can extend over a similar timeline. Overall, incorrect management exposes patients to the risk and side-effects of a myriad of items: diagnostic blood tests, chest X-rays, CT scans, PET scans, bronchoscopies, percutaneous fine needle aspirations, and even thoracotomies. Patients' fear of the unknown, increased community antibacterial resistance due to incorrect therapies, and the increased cost of healthcare are all additional factors to consider. Ongoing research is critical to ensuring timely, affordable, and if necessary, effective treatment for Coccidioidomycosis.

Diagnostic delay is a major issue; a review of the literature, including cancer and Tuberculosis diagnostic delay, shows at least fifteen distinct definitions of this issue.[7] Common among these definitions is the differentiation between two main components of total delay: patient and health system delay, shown in Figure 2.[8]

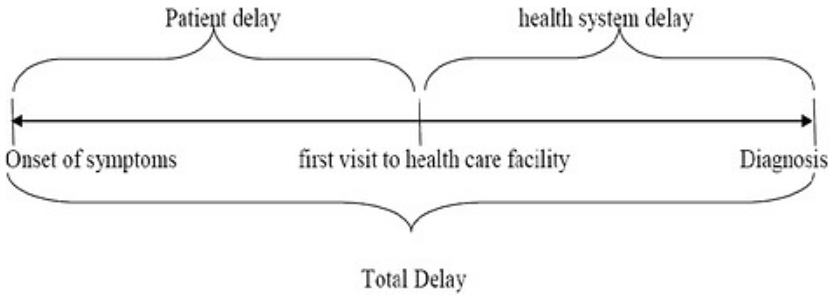

Figure 2. *Illustration of patient, health system and total delay*[8]

Patient delay describes the time from true onset of disease to when a patient first seeks medical care; and health system delay which describes the time from the initial healthcare visit to a formal, correct diagnosis. Patient delay, especially in the ambulatory setting, is difficult to evaluate, as symptoms are reported by the patient rather than observed formally in a clinical setting. Due to emphasis reliance on programmatic chart analysis in this study, focus is placed on health system delay. This study will refer to and define the health system delay portion as diagnostic delay.

In this study, we aimed to investigate the clinical decision-making, diagnostic delay and related healthcare utilization surrounding the diagnosis of Coccidioidomycosis. A two-phase project was designed: phase one focused on manual chart review to identify disease markers and symptom-diagnosis onset; phase two revolved around programmatically pulling and analyzing data from a hospital-based electronic medical record (EMR) to assess total healthcare utilization. Emphasis will be placed on phase two of this project, although phase one will be briefly touched upon.

Methods

Setting

Banner Health is a non-profit health system operating 28 hospitals and numerous ambulatory facilities across six states in the western United States—headquartered in Phoenix, Arizona.[9] The facilities, physicians, and researchers are uniquely placed to research and optimize Coccidioidomycosis care. Banner Health serves the population most commonly diagnosed with Coccidioidomycosis and with its large network of physicians and connected EMR, advanced analytics of this large population is possible.

Phase One[10]

The initial phase of this project aimed to identify symptoms associated with Coccidioides spp. infection in patients seeking care at Arizona-based Banner ambulatory clinics. From a pool of 495 patients found to be formally diagnosed with Coccidioidomycosis between the January 1st, 2014 and December 31st, 2014, a random selection of 50 patients was chosen to be manually evaluated by an expert medical team. This team consisted of resident physicians and medical students, examining each patient to determine specific characteristics. Patients were excluded if they were under 18, diagnosed with Coccidioidomycosis prior to the year 2014, or if their chart was only reviewed by only one member of the expert medical team. 37 patients met inclusion criteria with their symptoms and date of symptom onset recorded and cross-examined against at least one independent reviewer on the expert medical team. An attending physician assessed inter-rater reliability and oversaw final data evaluation. Symptom results from phase one were then used to inform phase two regarding Coccidioidomycosis symptoms and their corresponding ICD-9 codes.

Phase Two

Patients for phase two were found through programmatic extraction of Banner Health ambulatory clinics' EMR database. Inclusion criteria for this new group of patients was separate to those of phase one and is described in Figure 3.

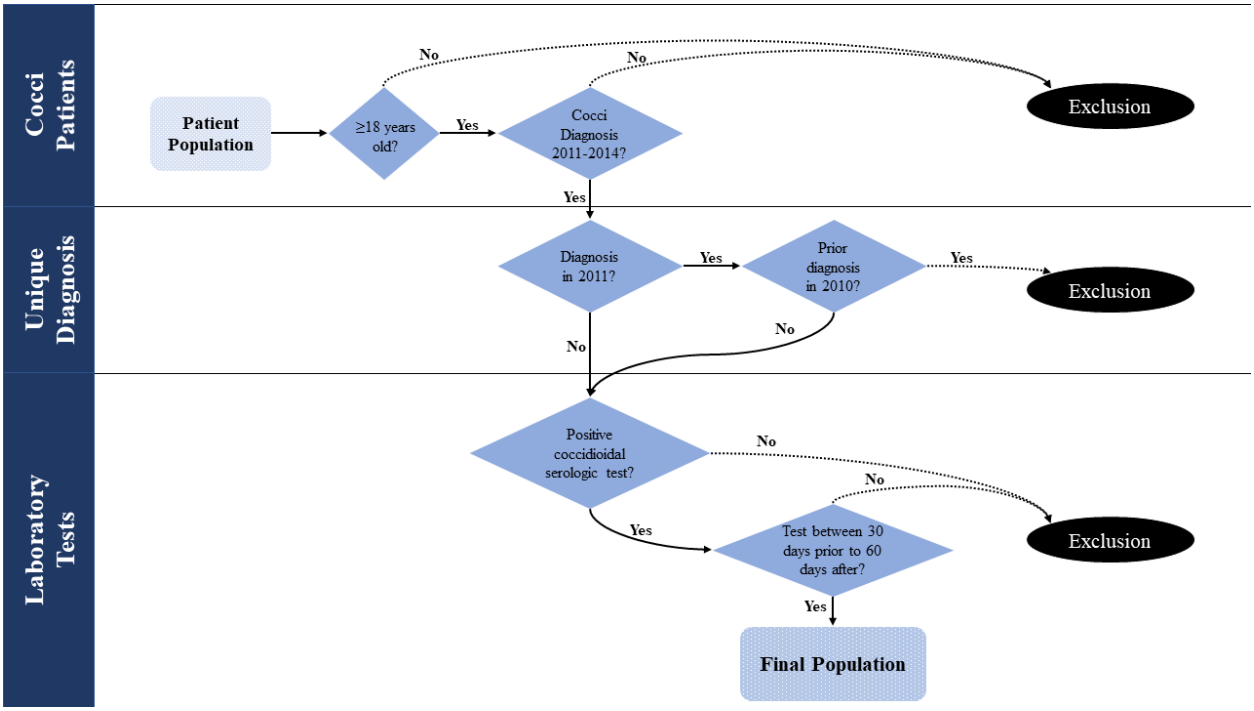

Figure 3. *Inclusion and Exclusion Criteria for Final Population*

Briefly, patients of at least 18 years of age with a Coccidioidomycosis diagnosis from January 1st, 2011 to December 31st, 2014 were included, and the earliest diagnosis date was used. Patients were excluded if they did not have a positive coccidioidal serologic test 30 days prior to or 60 days after diagnosis date. To authenticate the first date or "index date" at which a diagnosis was made, patients were excluded if they had a prior Coccidioidomycosis diagnosis recorded within one year of the index date—as far back as January 1st, 2010. The final population consisted of 139 patients with the above inclusion and exclusion criteria.

To calculate the previously described diagnostic delay, patient records were searched for compatible symptoms occurring within 6 months of the index date. The symptom list used was influenced by, but not the same as, the phase one study. Due to phase one's small sample size and broad, nonspecific symptom list, there existed significant overlap between other disease processes. The entire record of symptoms for all patients 6 months prior to their index date was retrieved from the EMR database. An expert medical team consisting of attending physicians and medical students manually reviewed this record for clinical and physiologic similarity within the context of phase one's symptom list. Each potential symptom and corresponding ICD-9 code was given final arbitration by an Infectious Disease physician specializing in Coccidioidomycosis. A larger list, as compared to that of phase one, of specific symptoms and their corresponding ICD-9 codes was constructed via this method and the final symptom list is presented in Appendix 1.

To assess healthcare utilization, healthcare charges was used to represent this measure. Billing data was available both in the ambulatory EMR as well as Banner Health's associated hospital-based EMR. By cross-referencing patient identifiers, 66 patients of the 139 were found to have billing data from the hospital-based EMR. We defined healthcare utilization as the total charges from the earliest symptom date recorded to 6 months after the index date. If no symptom was recorded for the patient, then the index date itself was used as the first-time point. A visual representation of this definition is demonstrated in Figure 4.

This study utilized the specialized software for both custom data retrieval and advanced analytics on the records gathered.

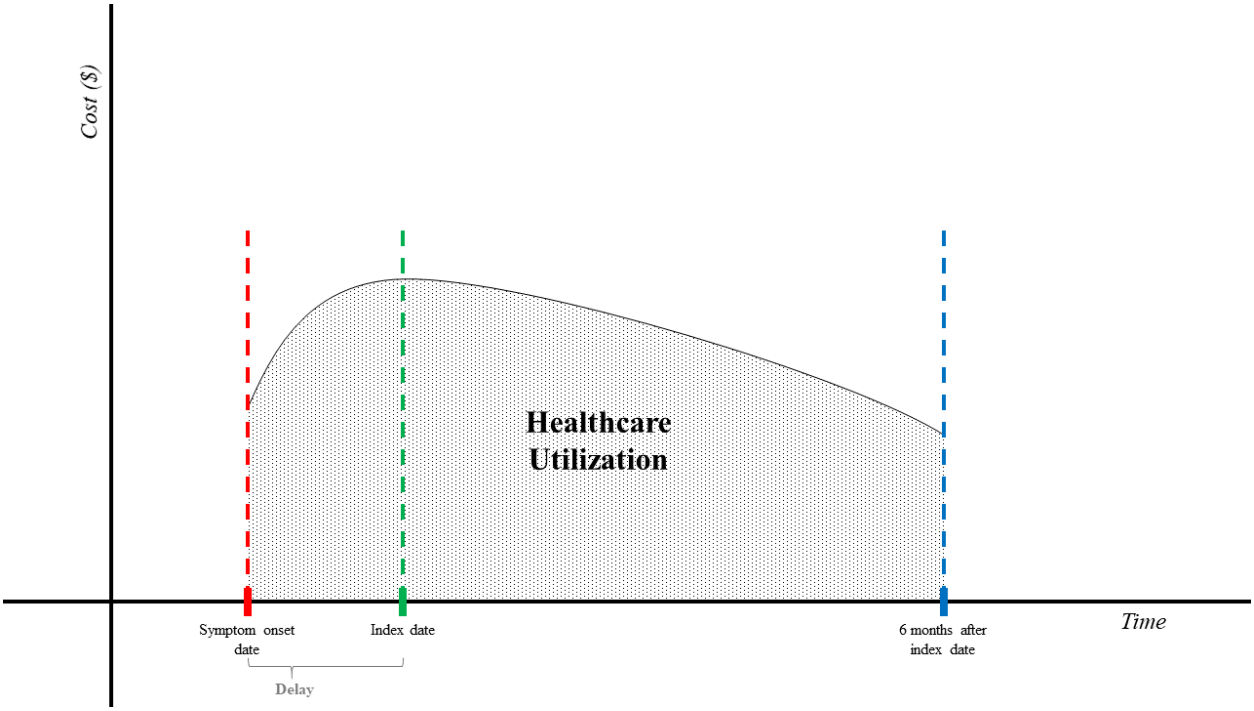

Figure 4. *Example distribution of healthcare utilization; utilization expected to increase during delay and decrease given appropriate medical attention.*

Results

Of the 139 patients in the final population, the age distribution was relatively normal and both genders were represented fairly equally: female 52% and male 48%. Of this population, only one patient died within the study period.

Seven unique diagnoses and their corresponding ICD-9 codes were used to formally indicate a Coccidioides spp. infection. These seven diagnostic definitions and their relative frequencies are shown in Figure 5.

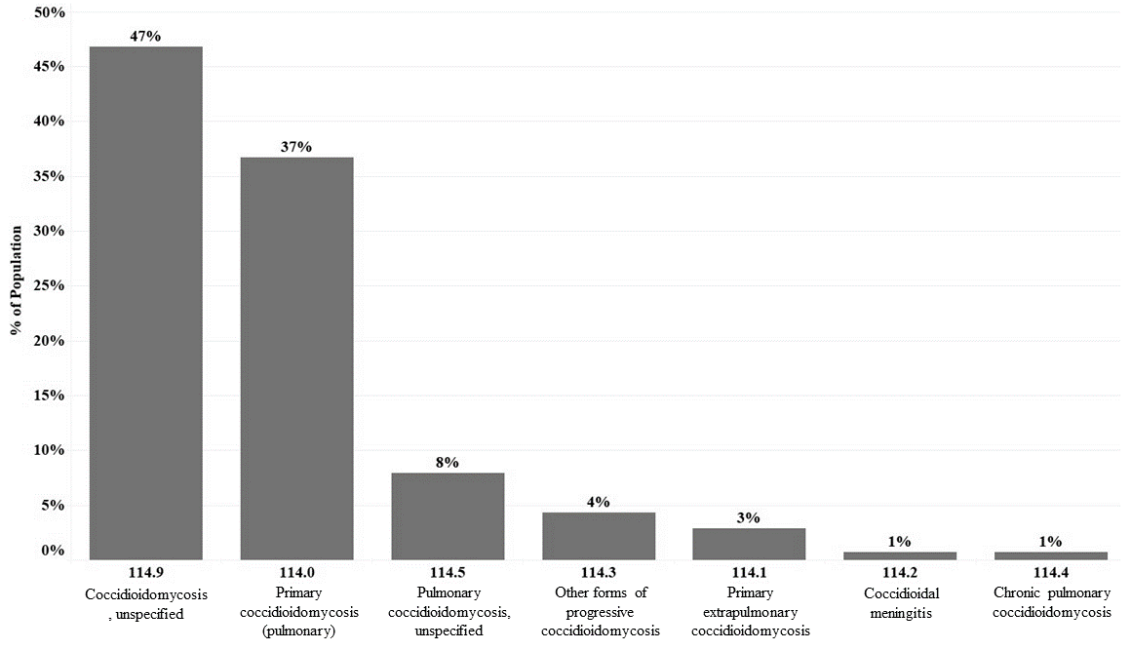

Figure 5. *Distribution of patients by diagnostic category and related ICD-9 code.*

With regard to the positive coccidioidal serologic confirmation test, the vast majority of these tests were conducted and reported before or on the index date. A graphical representation of the days prior to, after the, or on the index date are presented in Figure 6.

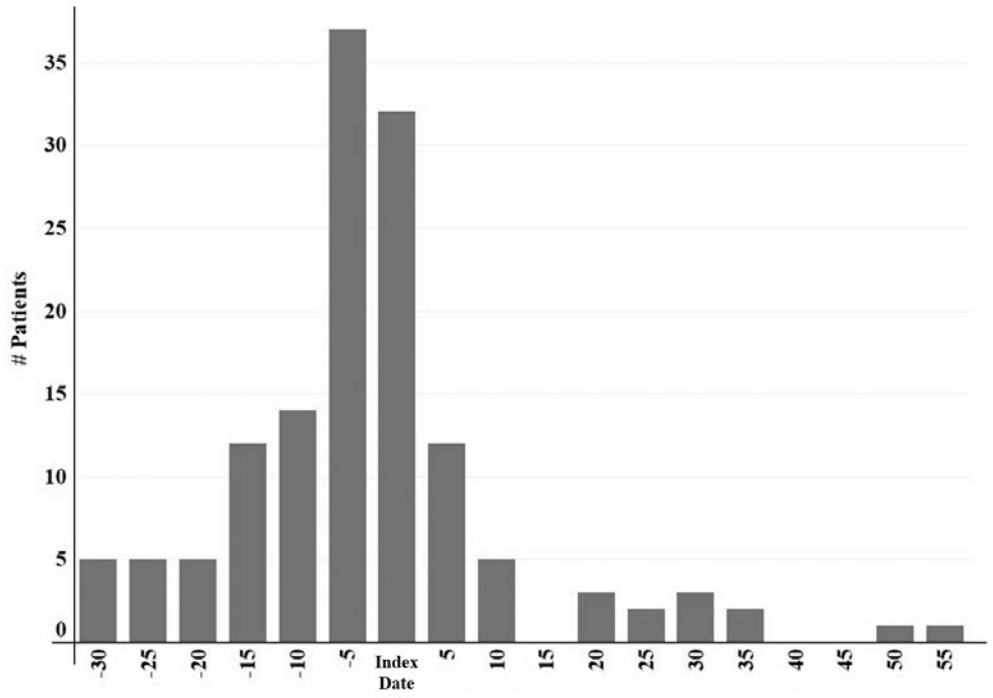

Figure 6. *Distribution of positive coccidioidal confirmation dates as compared to the index date.*

The set of symptoms assembled through phase one influence and subsequent expert review expanded the symptom list and the relevant ICD-9 codes from 23 to 89 overall. This expanded list allowed for 120 out of the 139 selected population to have a coded symptom onset date before the index date (please refer to Figure 4. for more detail). 19 patients did not have a symptom code in their record, and programmatically their initial onset date was equivalent to the index date. This group differs from 16 other patients that had a symptom recorded on the same day of their diagnostic index date. The full expanded list of symptoms can again be found in Appendix 1.

Diagnosis delay and healthcare utilization measures were arranged by periods of thirty days and showed a trend of the mean toward increasing total charges as the number of delay days increased. The 95% confidence intervals however intersected between the time period categories, with upper cost values nearing at in some instances seven-times the mean. Additionally, the median healthcare cost mimicked the progression seen when examining the mean values, albeit with narrower variation. Most time periods included less than 30 patients with the exception of the time period of diagnostic delay between 0 and 30 days. These results and respective categories are displayed in Table 1.

Diagnosis Delay Days	Mean	*95% Lower CI (Mean)**	*95% Upper CI (Mean)**	*# Patients*	Median	*Min*	*Max*
no symptom	$41,386	$14,720	$68,052	19	$2,751	$209	$432,049
0-30	$6,273	$0	$21,806	56	$770	$150	$81,541
31-60	$14,342	$0	$39,124	22	$1,572	$384	$96,353
61-90	$22,558	$0	$52,570	15	$9,667	$629	$83,310
91-120	$6,501	$0	$40,055	12	$2,167	$446	$28,974
121-150	$78,896	$26,914	$130,878	5	$4,293	$463	$360,378
151-183	$57,724	$20,967	$94,480	10	$8,917	$223	$437,221

Table 1. *Data arranged by time groups with respect to diagnostic delay days.*
**assumes normal distribution*

Discussion

Overall the small final population size and difficulties encountered due to the innate properties of the electronic medical record preclude robust and meaningful statistical analysis. Firstly, little demographic information such as race, household income, insurance coverage, zip code, etc. was available from the EMR which does not allow for more descriptive analysis. Due to the one death present in our study, a potentially useful marker would be mortality—more appropriate in larger population studies.

The majority of confirmatory, positive coccidioidal serologic tests taking place before or on the index date may represent a clinician's suspicion that the underlying disease process may very well be Coccidioidomycosis, but there is a logical level of unwillingness to label the patient's disease before laboratory confirmation. Additionally, the presence of these positive tests being recorded after the index date may represent a diagnosis of Coccidioidomycosis by other means: whether that be radiologic evidence, lumbar puncture, aspiration, biopsies or even highly consistent and classic patient history or compatible exposure. The billing aspect of the EMR need also be considered here, as laboratory test orders may need to be justified by a formal diagnosis—perhaps explaining partially the substantial number of positive tests on the index date itself.

Demonstrating diagnostic delay for Coccidioidomycosis is possible, as shown in Table 1. Although no statistically significant comparisons can be made due to the limitations of patient numbers, mean and median healthcare utilization did somewhat increase as delay diagnosis times increased. The mean and median for 0-30 days delay was $6,273 and $770 respectively; this increased at 151-183 days of diagnostic delay to $57,724 and $8,917 respectively. Patients with no recorded symptom, as seen in Table 1., could have had a significant delay which may have simply not been captured by the database. Additionally, if they were seen at a non-Banner Health facility, that information would not be in the Banner Health EMR. A confounding factor in this study was that all costs were included—potentially including costs completely unrelated to Coccidioidomycosis. Therefore, with increasing delay diagnosis times, there is simply more time to accumulate healthcare related charges and costs. This would make high utilization due to

increased Coccidioides spp. infection progression less likely. Future investigations should consider this factor.

The EMR itself also has innate difficulties that any investigation will have to uniquely address. With Banner Health, the data connection between the ambulatory and hospital-based systems is imperfect. Though all 139 patients had ambulatory diagnoses and billing data, supplementation was attempted with hospital level data to acquire a more complete view of utilization. However, this was not possible for all patients due to reasons described above, with only 66 of the 139 patients possessing identifiable hospital billing data. In summary, these issues could very well have affect the results presented, however with a larger sample size and increased control, it may be less impactful.

To the best of our knowledge, this is the first study of its kind to investigate healthcare utilization by assessing Coccidioidomycosis related diagnostic delays based on programmatic analysis. The study's methodology is novel and will be helpful for future improvements and endeavors. Using a two-phase study to first discern regional markers for a disease process and then expand the resultant set of ICD-9 codes with expert medical reviewers is an innovative approach. This approach is needed when computationally extracting symptom codes from medical databases, which vary widely depending on the type of diagnostic code used. Future prospects may include looking at utilization from an inpatient-only perspective, prospectively following patients with Coccidioidomycosis, recording related expenditures, and applying this approach to a larger patient population database.

References

1. Fungal Diseases - Valley Fever (Coccidioidomycosis). Centers for Disease Control and Prevention. https://www.cdc.gov/fungal/diseases/coccidioidomycosis/index.html. Published May 22, 2017.

2. Galgiani JN, Thompson III GR. Valley Fever (Coccidioidomycosis), Tutorial for Primary Care Professionals. Valley Fever Center for Excellence, The University of Arizona. 2016.

3. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis, Clinical Infectious Diseases, Volume 63, Issue 6, 15 September 2016, Pages e112–e146

4. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community acquired pneumonia. Emerg Infect Dis. 2006;12(6):958-962.

5. Chang DC, Anderson S, Wannemuehler K, et al. Testing for coccidioidomycosis among patients with community-acquired pneumonia. Emerg Infect Dis. 2008;14(7):1053-1059.

6. Yozwiak ML, Lundergan LL, Kerrick SS, Galgiani JN. Symptoms and routine laboratory abnormalities associated with coccidioidomycosis. West J Med. 1988;149(4):419-421.

7. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. Br J Cancer 2015;112(Suppl 1):S92–S107.

8. Getnet F, Demissie M, et al. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. BMC Pulm Med. 2017 Dec 13;17(1):202.

9. About Banner Health. Health care made easier in AZ, CO, WY, NE, NV, CA. https://www.bannerhealth.com/about.

10. Narasimhan S, Goodsell J, et al. Rapidity of Coccidioidomycosis Diagnosis and Its Effect on Healthcare Utilization - Phase One. Banner Health. 2016.