ClinicoEconomics and Outcomes Research

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ORIGINAL RESEARCH

Real World Evaluation of Next-Day Molecular Respiratory Infectious Disease Testing on Healthcare Resource Utilization and Costs

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Purpose: Advancements in pathogen identification by diagnostic testing may improve patient outcomes. This study evaluated healthcare utilization and costs following diagnostic testing for acute oropharyngeal and respiratory tract infections (RTIs).

Patients and Methods: Healthcare utilization and costs were evaluated in patients with acute oropharyngeal infections (n=1,172,693), and RTIs (n=4,005,228) who received a syndromic panel-based PCR test with next-day results (HealthTrackRx, Denton, TX), or no test in the IQVIA PharMetrics® Plus adjudicated claims database.

Results: Statistically significant differences were observed between patients who received the PCR test compared to those who received no test. The PCR test cohort had lower total healthcare costs (mean = $5,601±$29,170, median = $807) versus the no test cohort (mean = $7,460±$40,817, median = $1,163) (p = 0.0014) over 6 months, and fewer outpatient visits, other medical service visits, emergency room visits, and inpatient stays (p<0.0001). Similarly, those who received the PCR test for oropharyngeal infection trended towards lower total healthcare costs (mean = $4,393±$13,524, median=$844) than those who received no test (mean = $5,503 ±$34,141, median = $956) (p=0.0525) and had fewer outpatient and other medical services (p<0.0001).

Conclusion: Next-day molecular testing for respiratory and oropharyngeal infection lowers healthcare utilization and costs, suggesting improved patient care through reduced need for healthcare resources.

Keywords: PCR, NAAT, syndromic multiplex testing, respiratory virus, influenza viruses, respiratory tract infection, pharyngitis, diagnostics, healthcare utilization

Introduction

Acute respiratory tract infections (RTIs) present a costly and prevalent burden on the United States healthcare system, accounting for $12.6 Billion in annual spending and ~120 million annual outpatient visits in the United States.[1] Most of the costs are attributed to outpatient care (58.1%), emergency department services (21.7%), general admission (10.0%), inpatient care (6.3%), and pharmacy (3.6%).[2] As the clinical signs and symptoms of acute RTIs are not pathogen specific, insufficient diagnostic tools to identify the pathogen causing the RTI within a reasonable time frame to influence clinical decision-making have contributed to inappropriate antibiotic prescribing.[3–5] Thus, RTIs contribute a significant cost burden on families and society,[6] including detrimental long-term impacts to population health due to overuse of antibiotics.[7–9]

Accurate and timely diagnosis of respiratory pathogens is necessary for optimal patient care by informing appropriate treatment and infection control practices.[5,10] Molecular tests have recently emerged as superior to traditional methods for the diagnosis of RTIs due to improvements in test sensitivity and specificity, reduced turnaround time, and an expanded range of detectable pathogens.[10] Several molecular testing methods that amplify specific sequences of nucleic acids are available including conventional, reverse transcription, broad-range, real-time, digital and multiplex polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), nicking endonuclease amplification reaction, recombinase polymerase amplification, and clustered regularly interspaced short palindromic repeats.[11–13] Multiplex molecular

Received: 25 September 2024
Accepted: 22 January 2025
Published: 11 February 2025

PCR panels (also known as 'syndromic panels') have improved the diagnosis of infectious diseases by enabling the detection of several pathogens associated with similar symptomatology simultaneously in a single sample.

Molecular syndromic panels are now considered a "powerful decision-making tool for patient management."[14] Their improved ability to identify and differentiate viral and bacterial pathogens,[15] has led to some evidence of improved patient outcomes.[16,17] Thus, recent guidelines from the Infectious Disease Society of America have acknowledged applications of molecular testing over culture and rapid antigen tests for the detection of respiratory pathogens.[18] Moreover, as molecular testing for pathogens causing respiratory illness has become more accessible for inpatient and outpatient care through clinical laboratories, expanded use has been recommended by others.[10] Taken together, emerging research on the clinical utility of molecular diagnostics for RTIs has suggested that limiting use of the tests is not considered the best clinical practice.[10]

Diagnostic testing for respiratory symptoms is used somewhat sparingly in clinical settings due to relatively long turnaround times to generate test results with send-out tests. While traditional culture tests can offer a range of pathogen detection, results require up to a week to identify the pathogen, often resulting in interim empiric antibiotic treatment. Rapid antigen tests are available for a limited set of pathogens: influenza virus, SARS-CoV-2 (COVID-19), respiratory syncytial virus (RSV), and Streptococcus pyogenes (Group A Strep). These tests also suffer from limited sensitivity. Although point-of-care testing allows onsite detection, they are limited in the pathogens that can be detected and are insufficient for complex treatment decision-making when results are negative.[19] Thus, clinicians may opt to forgo testing. Yet to improve patient outcomes, comprehensive diagnostic testing should be available in a time frame that can affect patient management such as the initiation or discontinuation of antiviral and antibiotic treatments.[10] Ideally, accurate test results should be available within 24 hours to positively influence patient care,[10] which has presented a logistical challenge for clinical laboratories with central operations.

Despite improved test performance, there is a lack of real-world population-based economic research that has examined healthcare resource utilization and costs from patients receiving novel syndromic-based molecular testing for respiratory illness. Some evidence has shown cost-effectiveness for molecular testing for influenza.[20] Yet, in order to evaluate the potential value of new syndromic panel molecular tests with next-day results, the real-world impact on healthcare utilization and the subsequent cost of patient care needs to be determined. Such costs include the total cost of care, inpatient and outpatient visits and costs, pharmacy costs, hospitalizations, length of hospital stay, and additional testing and services due to the lack of a diagnosis. Thus, the purpose of this observational investigation was to evaluate the impact of next-day PCR testing for acute respiratory and oropharyngeal infections on healthcare utilization and healthcare costs through retrospective analysis of a large real-world population-level healthcare claims dataset.

Materials and Methods

This study aimed to understand the healthcare cost and utilization impact when utilizing a syndromic, next-day PCR test for diagnosis of acute oropharyngeal infections or upper respiratory tract infections compared to no test.

The real-world impact of PCR testing on healthcare claims outcomes related to oropharyngeal and upper respiratory tract infections (RTI) were retrospectively evaluated across the IQVIA PharMetrics® Plus adjudicated claims database from July 1, 2020, to October 31, 2023 (study period) representing more than 210 million commercially insured patients.

Patients in the analysis included those with an initial claim with an ICD-10 CM code for diagnosis or relevant symptom for acute oropharyngeal infections or RTIs in outpatient setting. Patients included in the analysis were required to have continuous health plan enrollment during the 6 months prior to their index date (baseline period), and the 6 months after the index date (follow-up period). Patients with missing or invalid data including year of birth, sex, region, or health plan enrollment dates were excluded from the analysis. Laboratory tests performed on the index visit date were excluded from the analysis.

All clinical samples were collected and tested via real-time PCR, at HealthTrackRx Laboratories. Nucleic acid extraction was performed following manufacturer's instructions using Kingfisher Flex automated extraction system with MagMax™ Viral/Pathogen II (MVP II) Nucleic Acid Isolation Kit (ThermoFisher, California, USA).

Subsequent real-time PCR analysis was conducted using the QuantStudio™ 12K Flex Real-Time PCR system as per the manufacturer's instructions (ThermoFisher, California, USA) and as previously described[27], targeting syndrome-based viral and bacterial pathogen targets.

Acute Oropharyngeal Infections

Healthcare costs across a total of n=4,131,631 with acute oropharyngeal infection (see Supplemental Table 1 for ICD codes) were evaluated over 6 months of follow-up. Of those, 3,558 had a next-day, syndromic PCR test for pharyngitis, and 1,169,135 had no test (Figure 1A). Patients in the next-day, syndromic PCR test group may have received a rapid antigen test prior to sending for the PCR. The no test group consisted of patients with claims that did not include CPT codes for culture (see Supplemental Table 1), or rapid antigen tests.

To understand the clinical utilization of these test modalities, this study examined unmatched cohorts. The mean age for the PCR Test cohort was 30.1± 18.2 years and 35.5 ±19.1 years for the No Test cohort. More than a fifth of the

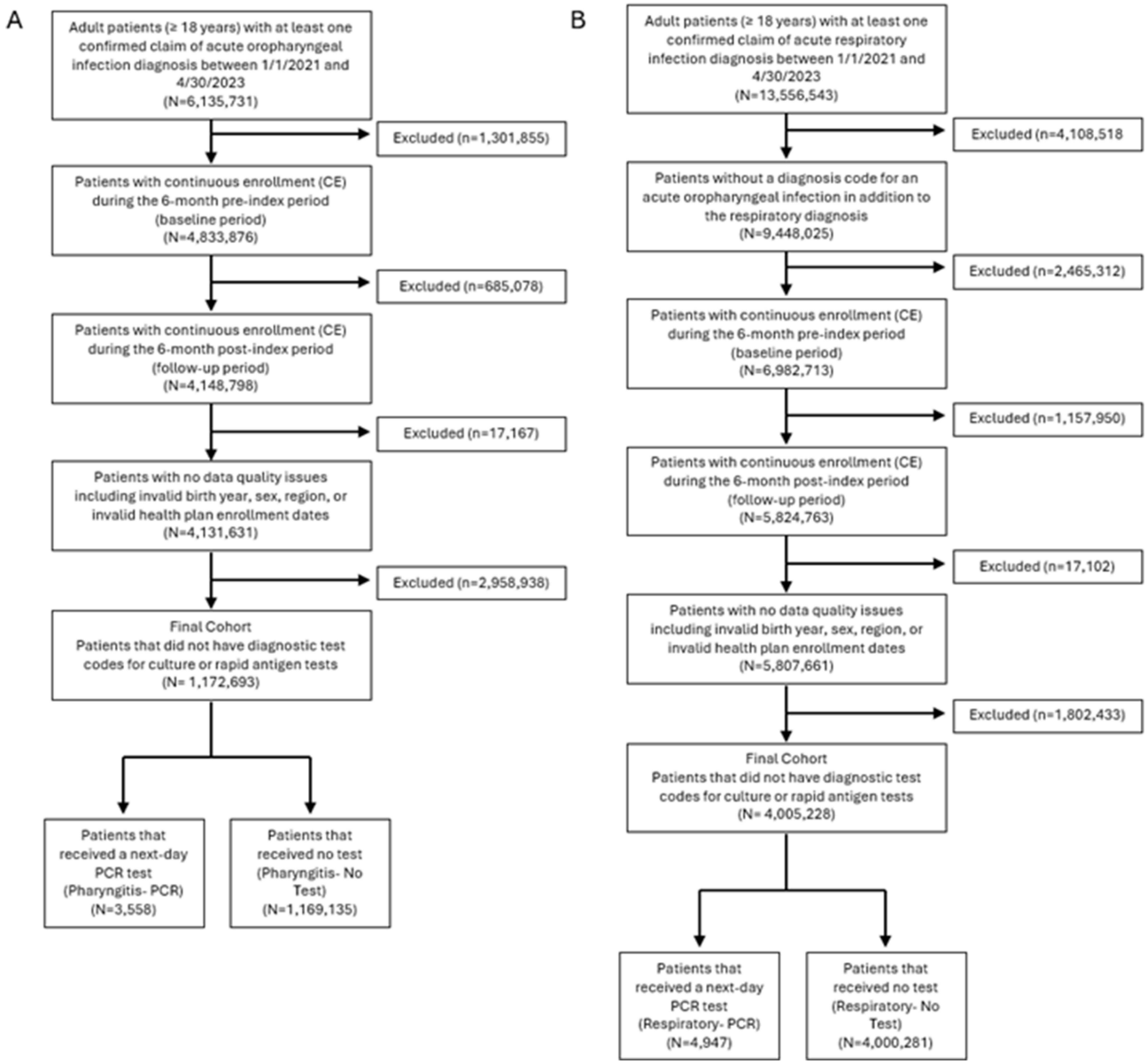

Figure 1 Attrition flow chart of adult patients with acute oropharyngeal infections or acute respiratory infection. Patients in the study cohorts for (**A**) acute oropharyngeal infections or (**B**) acute respiratory infections were identified by age, diagnosis codes, complete data sets, and billing codes for diagnostic tests.

https://doi.org/10.2147/CEOR.S497838

Table 1 Baseline Characteristics of Patients With Acute Oropharyngeal Infection

Baseline Characteristics	Syndromic Pharyngitis PCR		No Test		P-value
Age at study index date					
Mean	30.1		35.5		<0.0001
SD	18.2		19.1		
Median	28		35		<0.0001
Age group (n, %)					
<18	1,048	29.5%	244,449	20.9%	<0.0001
18–24	531	14.9%	139,673	11.9%	
25–34	576	16.2%	182,240	15.6%	
35–44	594	16.7%	198,746	17.0%	
45–54	380	10.7%	176,508	15.1%	
55–64	314	8.8%	171,646	14.7%	
65–74	89	2.5%	39,037	3.3%	
≥75	26	0.7%	16,836	1.4%	
Geographic region: (n, %)					
Northeast	187	5.3%	161,016	13.8%	<0.0001
Midwest	967	27.2%	276,335	23.6%	
South	2,262	63.6%	581,466	49.7%	
West	142	4.0%	150,318	12.9%	
Gender (n,%)					
Male	1375	38.6%	471,173	40.3%	0.0444
Female	2183	61.4%	697,962	59.7%	
Charlson Comorbidity Index (CCI), CDMF adaptation					
Mean	0.3		`0.5		<0.0001
SD	1.2		1.4		
Median	0		0		<0.0001
CCI categories (n,%)					
0	3,013	84.7%	951,733	81.4%	<0.0001
1	341	9.6%	123,427	10.6%	
2	75	2.1%	36,005	3.1%	
3	29	0.8%	14,346	1.2%	
4	9	0.3%	5,255	0.4%	
5+	91	2.6%	38,369	3.3%	

patients in each subcohort were <18 years of age (PCR test 29.5%; No test: 20.9%), and more than half were women (PCR test: 61.4%; No test: 59.7%) (Table 1). At baseline, most patients in each subcohort had a Charleston Comorbidity Index (CCI)[21] category of 0 (PCR Test: 84.7%; No test: 81.4%).

Respiratory Tract Infections

Healthcare costs across a total of n=5,807,661 with respiratory tract infection (see Supplemental Table 1 for ICD codes) were evaluated over 6 months of follow-up. Of those n=4,947 (0.1%) had a syndromic, next-day PCR test and 4,000,281 had no test (68.9%). The no test group consisted of patients with claims that did not include CPT codes for culture (see Supplemental Table 1)), or rapid antigen tests. Patients who had another test (n=1,802,433, 31.0%) such as culture or rapid antigen test were excluded from the analysis (Figure 1B).

Table 2 Baseline Demographic Characteristics of Patients With Upper Respiratory Infections

Baseline Characteristics	Syndromic Respiratory PCR		No Test		P-value
Age at study index date					
Mean	38.7		40.9		<0.0001
SD	18.8		21.3		
Median	40		44		<0.0001
Age group (n, %)					
<18	749	15.1%	731,548	18.3%	<0.0001
18–24	494	10.0%	258,355	6.5%	
25–34	795	16.1%	428,404	10.7%	
35–44	842	17.0%	594,955	14.9%	
45–54	872	17.6%	713,373	17.8%	
55–64	905	18.3%	874,754	21.9%	
65–74	216	4.4%	253,429	6.3%	
≥75	74	1.5%	145,463	3.6%	
Geographic region: (n, %)					
Northeast	94	1.9%	613,716	15.3%	<0.0001
Midwest	833	16.8%	1,064,573	26.6%	
South	3,672	74.2%	1,792,038	44.8%	
West	348	7.0%	529,954	13.2%	
Gender (n,%)					
Male	2212	44.7%	1,820,085	45.5%	0.2679
Female	2735	55.3%	2,180,196	54.5%	
Charlson Comorbidity Index (CCI), CDMF adaptation					
Mean	0.4		0.6		<0.0001
SD	1.2		1.5		
Median	0		0		<0.0001
CCI categories (n,%)					
0	4,114	83.2%	3,063,436	76.6%	<0.0001
1	478	9.7%	490,481	12.3%	
2	153	3.1%	181,930	4.5%	
3	53	1.1%	81,561	2.0%	
4	31	0.6%	34,647	0.9%	
5+	118	2.4%	148,226	3.7%	

The mean age for the PCR test cohort was 38.7± 18.8 years and 40.9 ±21.3 years for the No Test cohort. The largest proportion of patients in both test groups was 55–64 years old (PCR: 18.3%; No Test: 21.9%) and more than half were women (PCR test: 55.3%; No test: 54.5%) (Table 2). At baseline, most patients in each subcohort had a CCI category of 0 (PCR Test: 83.2%; No test: 76.6%).

Outcomes

Outcomes were evaluated over 6-months for each patient beginning the day after the index date (index visit+1 day to index+180 days). Healthcare cost outcomes included total (medical and outpatient pharmacy) costs, outpatient services costs (including physician office visits, ER visit, other medical services, and overall all-cause outpatient medical services. Inpatient costs and laboratory or pathology costs (both total and condition-specific) were also evaluated. Computations of costs used the "allowed amount" recorded on the respective claims from the IQVIA PharMetrics® Plus adjudicated

claims database. Healthcare resource utilization is reported as the proportion of patients utilizing each service and number of visits for each service per patient.

Statistical Analysis

Descriptive statistics were reported for patient demographic and baseline clinical characteristics for all subcohorts (Tables 1 and 2). Statistical testing was applied to evaluate differences in baseline characteristics and outcomes for the unmatched PCR and No Test subcohorts as follows. Parametric *t*-tests were used to evaluate statistical differences in mean values of continuous variables. Chi-Square tests were used to compare proportions for the categorical variables and Fisher's Exact tests were used when more than 20% of categories had expected frequencies less than 5. A p-value of < 0.05 was considered statistically significant.

Due to skewness of the claims data, Wilcoxon Rank-Sum tests were also evaluated to statistically compare the median values. Median values were considered to represent the realistic middle value of the population with less impact by outlier claims. As analysis of medians revealed similar outcomes to analysis of means, for real world applications and applications to population health management and total costs in a population, mean costs were reported.

De-Identification

The data were de-identified and certified to be fully compliant with US Patient Confidentiality Requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Institutional Review Board approval was not required.

Results

Oropharyngeal Infection

Of 4,131,631 patients with acute oropharyngeal infection and complete datasets, n=1,169,135 (28.3%) received no diagnostic test. Only n=3,558 (0.1%) received the syndromic next-day PCR test (Figure 1A). Patients receiving a PCR test for oropharyngeal infections were younger (30.1±18.2y, median = 28, vs 35.5±19.1y, median = 35, p<0.0001), and more likely to live in the south than those receiving no test (p<0.0001) (Table 1). Additionally, patients receiving a PCR test had fewer comorbidities as measured by the CCI (PCR: 0.3±1.2 vs No Test: 0.5±1.4; p<0.0001) than those receiving no test (Table 1).

Total Cost of Care Trended Lower With Use of PCR for Oropharyngeal Infection Diagnosis Compared to No Test

The mean total healthcare (medical + pharmacy) costs per patient trended lower for those who received a PCR test for acute oropharyngeal infection compared to those who received no test (PCR: $4,393±$13,524 vs No Test: $5,503± $34,141; p=0.0525), a mean difference of $1,110 per patient over 6-months (Table 3).

These decreased costs corresponded to significantly fewer patients utilizing outpatient services (PCR: 87.5% vs No Test: 89.0%; p=0.0029) and other medical services (PCR: 70.0% vs No Test: 74.4%; p<0.0001) (Figure 2A). However, there were no differences in the proportion of patients utilizing physician office visits, ER visits, or inpatient services (Figure 2A). Patients receiving a next-day PCR test for pharyngitis had slightly increased utilization of all laboratory services (PCR: 66.3% vs No Test: 63.0%; p<0.0001) and condition-specific laboratory services (PCR: 33.4% vs No Test: 18.5%; p<0.0001) (Figure 2B).

To better understand resource utilization, the number of utilizations per patient and associated costs were also examined. Those who received the PCR test had significantly fewer total outpatient medical services (PCR: 11.9±18.5 vs No Test: 13.8±22.6; p<0.0001), outpatient pharmacy fills per patient (PCR: 7.8±14.3 vs No Test: 8.7±13.8; p=0.0004), physician office visits per patient (PCR: 5.4±8.6 vs No Test: 5.8±9.3; p=0.0090), and other medical services per patient (PCR: 6.3±12.2 vs No Test: 7.8±16.4; p<0.0001) than those who received no test (Table 4). However, there were no differences in the number of ER visits either among all patients or among patients with at least one ER visit (Table 4). Consequently, patients that received a PCR test had lower mean total outpatient medical service costs (PCR: $2,384 ±6,802 vs No Test: $2,945±11.488; p=0.0036), which consisted of similar costs for physician office visits and ER visits, but lower costs of other medical services (PCR: $1,444±5,940 vs No Test: $1,962±10,218; p=0.0025) (Table 3).

Table 3 Post-Index Healthcare Costs for Patients With Oropharyngeal Infections

Cost Measures	Mean	SD	Median	IQR	P-value
Total Healthcare Costs					
Syndromic Pharyngitis PCR	$4,393	$13,514	$844	$2,801	
No Test	$5,503	$34,141	$956	$3,100	0.0525
Total Outpatient Medical Services					
Syndromic Pharyngitis PCR	$2,384	$6,802	$586	$1,727	
No Test	$2,945	$11,488	$652	$1,977	
Total Outpatient Cost Savings	$561				0.0036
Physician office visits					
Syndromic Pharyngitis PCR	$649	$1,213	$308	$595	
No Test	$713	$2,992	$328	$632	0.1998
ER visit					
Syndromic Pharyngitis PCR	$292	$1,243	$0	$0	
No Test	$270	$1,495	$0	$0	0.3843
Other medical services					
Syndromic Pharyngitis PCR	$1,444	$5,940	$100	$695	
No Test	$1,962	$10,218	$141	$849	0.0025
Outpatient Pharmacy					
Syndromic Pharyngitis PCR	$1,258	$7,534	$68	$311	
No Test	$1,390	$8,725	$80	$366	0.3681
Inpatient Costs					
Syndromic Pharyngitis PCR	$751	$7,321	$0	$0	
No Test	$1,168	$28,935	$0	$0	0.3903
Laboratory/Pathology Services					
For all laboratory/pathology services					
Syndromic Pharyngitis PCR	$263	$698	$51	$256	
No Test	$226	$1,121	$40	$172	0.0522
For condition-specific laboratory/pathology services					
Syndromic Pharyngitis PCR	$73	$200	$0	$33	
No Test	$19	$90	$0	$0	<0.0001

Inpatient utilization per patient analysis showed that patients that received a PCR test had shorter average length of stays both among all patients (PCR: 0.1±0.9 vs No Test: 0.2±1.7; p=0.0304) and among patients with at least one stay (PCR: 4.5±3.4 vs No Test: 5.9±7.4; p=0.0445) (Table 5). In addition, patients receiving a PCR test had fewer hospitalization days among all patients (PCR: 0.2±1.9 vs No Test: 0.3±3.4; p=0.0379), and there was a trend toward fewer hospitalization days among patients with at least one inpatient stay (PCR: 6.4±9.6 vs No Test: 9.5±16.7; p=0.0613) (Table 5). However, there were no significant differences observed in the number of inpatient stays between the two groups. Inpatient costs were similar between the two groups, potentially due to the large variability (PCR: $751±7,321 vs No Test: $1,168±28,935; p=0.3903) (Table 3).

Patients who received the PCR test had significantly higher mean laboratory/pathology events for all services (7.1±12 vs 5.9±12.1; p<0.0001) and condition-specific tests (1.3±2.9, vs 0.4±1.1; p<0.0001) than those who received no test (Table 6). Patients who received the PCR test had higher mean costs for condition-specific laboratory/pathology services (PCR test; $73±$200 vs No Test: $19±$90; p<0.0001) (Table 3).

https://doi.org/10.2147/CEOR.S497838

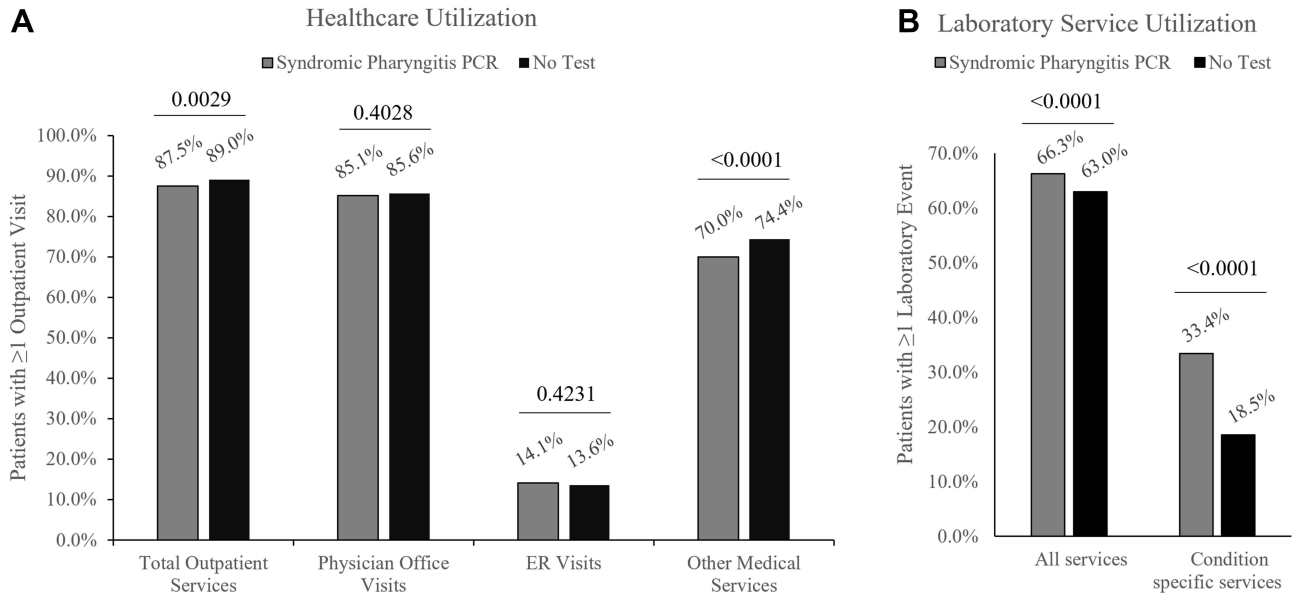

Figure 2 Healthcare utilization for patients receiving a next-day PCR or no test for acute oropharyngeal infections. Percentage of patients receiving (**A**) care for each service type and (**B**) additional laboratory services, not including the PCR test.

Respiratory Tract Infections

Of 5,807,661 patients with respiratory infection but not oropharyngeal infection and complete datasets, n= 4,000,281 (68.9%) received no diagnostic test. Only n= 4,947 (0.1%) received the syndromic next-day PCR test (Figure 1A). Patients receiving a PCR test for RTIs were younger (38.7±18.8y, median = 40, vs 40.9±21.3y, median = 44, p<0.0001),

Table 4 Post-Index Outpatient Healthcare Resource Utilization for Patients With Oropharyngeal Infections

Total Outpatient Medical Services Per Patient	Mean	SD	Median	IQR	P-value
Syndromic Pharyngitis PCR	11.9	18.5	14	23	
No Test	13.8	22.6	7	14	<0.0001
Outpatient pharmacy fills per patient					
Syndromic Pharyngitis PCR	7.8	14.3	4	9	
No Test	8.7	13.8	4	10	0.0004
Physician office visits per patient					
Syndromic Pharyngitis PCR	5.4	8.6	3	5	
No Test	5.8	9.3	3	6	0.0090
ER visits per patient					
Number of ER visits (among all patients)					
Syndromic Pharyngitis PCR	0.2	1.0	0	0	
No Test	0.2	0.9	0	0	0.4284
Number of ER visits (among patient with ≥1 ER)					
Syndromic Pharyngitis PCR	1.6	2.2	1	1	
No Test	1.6	1.8	1	1	0.7149
Other medical services per patient					
Syndromic Pharyngitis PCR	6.3	12.2	2	7	
No Test	7.8	16.4	3	9	<0.0001

https://doi.org/10.2147/CEOR.S497838

Table 5 Post-Index Inpatient Healthcare Resource Utilization for Patients With Oropharyngeal Infections

Total Inpatient Utilization Per Patient	Mean	SD	Median	IQR	P-value
Average length of stay (among all patients)					
Syndromic Pharyngitis PCR	0.1	0.9	0	0	
No Test	0.2	1.7	0	0	0.0304
Average length of stay (among patients with ≥1 inpatient stay)					
Syndromic Pharyngitis PCR	4.5	3.4	3	2	
No Test	5.9	7.4	4	3	0.0445
Number of inpatient stays (among all patients)					
Syndromic Pharyngitis PCR	0.0	0.2	0	0	
No Test	0.0	0.3	0	0	0.1206
Number of inpatient stays (among patients with ≥1 inpatient stay)					
Syndromic Pharyngitis PCR	1.2	0.8	1	0	
No Test	1.4	1.0	1	0	0.2255
Number of hospitalization days per patient (among all patients)					
Syndromic Pharyngitis PCR	0.2	1.9	0	0	
No Test	0.3	3.4	0	0	0.0379
Number of hospitalization days per patient (among patient with ≥1 inpatient stay)					
Syndromic Pharyngitis PCR	6.4	9.6	4	3	
No Test	9.5	16.7	4	5	0.0613

Table 6 Post-Index Laboratory/Pathology Healthcare Resource Utilization for Patients With Oropharyngeal Infections

Laboratory/Pathology Utilization	Mean	SD	Median	IQR	P-value
Laboratory/pathology (For all laboratory/pathology services)					
Syndromic Pharyngitis PCR	7.1	12.0	3	9	
No Test	5.9	12.1	2	7	<0.0001
Laboratory/pathology (For condition-specific tests)					
Syndromic Pharyngitis PCR	1.3	2.9	0	1	
No Test	0.4	1.1	0	0	<0.0001

and more likely to live in the south than those receiving no test (Table 2). Additionally, patients receiving a PCR test had fewer comorbidities as measured by the CCI (PCR: 0.4±1.2 vs No Test: 0.6±1.5; p<0.001) than those receiving no test (Table 2).

Use of PCR for Upper Respiratory Tract Infection Diagnosis Results in Reduced Total Cost of Care Compared to No Test.

Over 6-months of follow-up, the mean total healthcare (medical ± pharmacy) costs were lower for patients who received a PCR test for RTIs than those who received no test (PCR: $5,601±$29,170 vs No Test: $7,460±$40,817; p=0.0014), a mean difference of $1,859 over 6 months (Table 7).

These decreased costs corresponded to decreased utilization of total outpatient services (PCR: 85.1% vs No Test: 89.1%; p<0.0001), physician office visits (PCR: 81.4% vs No Test: 85.5%; p<0.0001), ER visits (PCR: 12.0% vs No Test: 13.3%; p=0.0057), other medical services (PCR: 71.6% vs No Test: 76.8%; p<0.0001), and inpatient services (PCR: 3.4% vs No Test: 6.2%; p<0.0001) (Figure 3A). While there was no difference in the percentage of patients receiving all laboratory services, a greater percentage of patients that received the PCR test received additional condition-specific tests (PCR: 12.9% vs No Test: 7.8%; p<0.0001) (Figure 3B).

When looking at number of utilizations, those who received a PCR test for respiratory tract infection had significantly fewer total outpatient medical services (PCR: 11.5±19.8 vs No Test:15.1±24.8; p<0.0001), outpatient pharmacy fills per

Table 7 Post-Index Healthcare Costs for Patients With Acute Respiratory Infections

Cost Measures	Mean	SD	Median	IQR	P-value
Total Healthcare Costs					
Syndromic Respiratory PCR	$5,601	$29,170	$807	$2,780	
No Test	$7,460	$40,817	$1,163	$4,061	0.0014
Total Outpatient Medical Services					
Syndromic Respiratory PCR	$2,475	$8,803	$509	$1,611	
No Test	$3,573	$30,051	$736	$2,284	0.0102
Total Outpatient Cost Savings	$1,098				
Physician office visits					
Syndromic Respiratory PCR	$515	$917	$268	$526	
No Test	$778	$4,723	$337	$645	<0.0001
ER visit					
Syndromic Respiratory PCR	$263	$1,373	$0	$0	
No Test	$249	$1,294	$0	$0	0.4425
Other medical services					
Syndromic Respiratory PCR	$1,697	$8,189	$109	$710	
No Test	$2,547	$29,160	$202	$1,171	0.0405
Outpatient Pharmacy					
Total outpatient pharmacy costs					
Syndromic Respiratory PCR	$1,456	$7,795	$81	$362	
No Test	$1,763	$9,729	$103	$538	0.0266
Inpatient					
Syndromic Respiratory PCR	$1,669	$25,257	$0	$0	
No Test	$2,124	$22,354	$0	$0	0.1532
Laboratory/Pathology Services					
For all laboratory/pathology services					
Syndromic Pharyngitis PCR	$200	$659	$37	$155	
No Test	$224	$1,129	$33	$157	0.1437
For condition-specific laboratory/pathology services					
Syndromic Pharyngitis PCR	$24	$103	$0	$0	
No Test	$9	$62	$0	$0	<0.0001

patient (PCR: 8.1±12.4 vs No Test:10.1±15.2; p<0.0001), outpatient physician office visits (PCR: 4.5±7.3 vs No Test: 5.9 ±10.0; p<0.0001), ER visits among all patients (PCR: 0.2±0.6 vs No Test: 0.2±0.7; p=0.0051), and other medical services per patient (PCR: 6.8±15.4 vs No Test: 9.0±18.3; p<0.0001) (Table 8). Costs for total outpatient medical services (PCR: $2,475±$8,803 vs No Test: $3,573±$30,051; p=0.0102), physician office visits (PCR: $515±917 vs No Test: $778±4,723; p<0.0001), and other medical services (PCR: $1,697±8,189 vs No Test: $2,547±29,160; p=0.0405), and total outpatient pharmacy costs (PCR: $1,456±7,795 vs No Test: $1,763±9,729; p=0.0266) were lower for those who received a PCR test than those who received no test (Table 7).

Patients that received a PCR test also had fewer average length of impatient stay among all patients (PCR: 0.2±1.4 vs No Test: 0.4±2.4, p<0.001), number of inpatient stays among all patients (PCR: 0.0±0.3 vs No Test: 0.1±0.4; p<0.0001), and number of hospitalization days per patient (PCR: 0.3±3.7 vs No Test: 0.7±5.2; p<0.0001) than those who received no

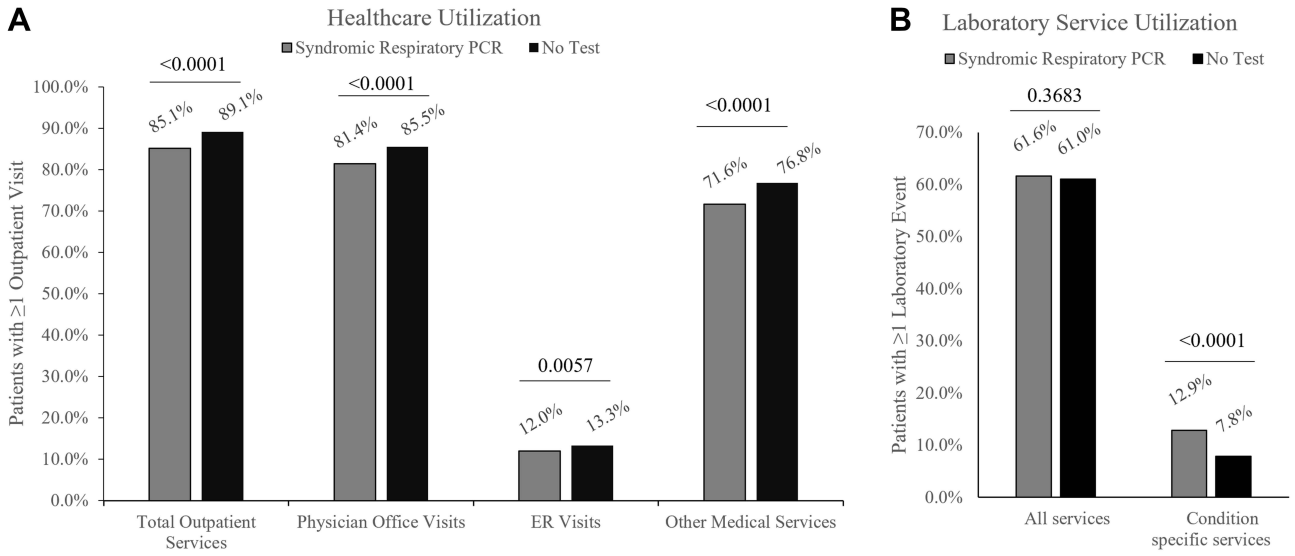

Figure 3 Healthcare utilization for patients receiving a next-day PCR or no test for acute respiratory infections. Percentage of patients receiving (**A**) care for each service type and (**B**) additional laboratory services, not including the PCR test.

test over 6-months (Table 9). There were no significant differences in total inpatient costs, potentially due to the large variability (PCR: $1,669±$25,257 vs No test: $2,124±$22,354; p=0.1532) (Table 7).

Patients who received the PCR test had similar mean laboratory/pathology events for all services (PCR: 6.1±11.2 vs No Test: 6.0±12.6; p=0.4655), but higher condition-specific laboratory/pathology events (PCR: 0.5±1.6 vs No

Table 8 Post-Index Outpatient Healthcare Resource Utilization for Patients With Acute Respiratory Infections

Total Outpatient Medical Services Per Patient	Mean	SD	Median	IQR	P-value
Syndromic Respiratory PCR	11.5	19.8	6	12	
No Test	15.1	24.8	8	15	<0.0001
Outpatient pharmacy fills per patient					
Syndromic Respiratory PCR	8.1	12.4	4	10	
No Test	10.1	15.2	5	12	<0.0001
Physician office visits per patient					
Syndromic Respiratory PCR	4.5	7.3	2	4	
No Test	5.9	10.0	3	6	<0.0001
ER visits per patient					
Number of ER visits (among all patients)					
Syndromic Respiratory PCR	0.2	0.6	0	0	
No Test	0.2	0.7	0	0	0.0051
Number of ER visits (among patient with ≥1 ER)					
Syndromic Respiratory PCR	1.5	1.0	1	1	
No Test	1.5	1.4	1	1	0.2032
Other medical services per patient					
Syndromic Respiratory PCR	6.8	15.4	3	8	
No Test	9.0	18.3	4	9	<0.0001

https://doi.org/10.2147/CEOR.S497838

Table 9 Post-Index Inpatient Healthcare Resource Utilization for Patients With Acute Respiratory Infections

Total Inpatient Utilization Per Patient	Mean	SD	Median	IQR	P-value
Average length of stay (among all patients)					
Syndromic Respiratory PCR	0.2	1.4	0	0	
No Test	0.4	2.4	0	0	<0.0001
Average length of stay (among patient with ≥1 inpatient stay)					
Syndromic Respiratory PCR	5.6	5.2	4	3	
No Test	6.3	7.3	4	4	0.2641
Number of inpatient stays (among all patients)					
Syndromic Respiratory PCR	0.0	0.3	0	0	
No Test	0.1	0.4	0	0	<0.0001
Number of inpatient stays (among patients with ≥1 inpatient stay)					
Syndromic Respiratory PCR	1.3	1.1	1	0	
No Test	1.4	1.0	1	0	0.1931
Number of hospitalization days per patient (among all patients)					
Syndromic Respiratory PCR	0.3	3.7	0	0	
No Test	0.7	5.2	0	0	<0.0001
Number of hospitalization days per patient (among patient with ≥1 inpatient stay)					
Syndromic Respiratory PCR	9.1	18.4	4	4	
No Test	10.7	18.3	5	7	0.2529

Table 10 Post-Index Laboratory/Pathology Healthcare Resource Utilization for Patients With Acute Respiratory Infections

Laboratory/Pathology Utilization	Mean	SD	Median	IQR	P-value
Laboratory/pathology (For all laboratory/pathology services)					
Syndromic Respiratory PCR	6.1	11.2	2	8	
No Test	6.0	12.6	2	7	0.4655
Laboratory/pathology (For condition-specific tests)					
Syndromic Respiratory PCR	0.5	1.6	0	0	
No Test	0.2	0.9	0	0	<0.0001

Test: 0.2±0.9; p<0.0001) than those who received no test (Table 10). Those who received the PCR test had similar mean costs for all laboratory/pathology services but higher costs for condition-specific tests (PCR: $24±$103 vs No Test: $9±$62; p<0.0001) (Table 7).

Discussion

This real-world observational analysis of healthcare resource utilization and costs claims across more than 5 million patients with RTIs or oropharyngeal infections demonstrated that patients that received the PCR test for RTI had lower total healthcare costs ($1,859 lower mean costs per patient), 3.6 fewer outpatient visits, other medical service visits, fewer emergency room visits, and 0.1 fewer inpatient stays over 6 months compared to those who received no test. Similarly, those who received the PCR test for oropharyngeal infection trended towards lower total healthcare costs

($1,110 lower mean costs per patient) and had 1.9 fewer outpatient and 1.5 fewer other medical services than those who received no test over 6 months.

Another key finding was that among nearly 5 million patients, most did not receive a diagnostic test to identify the causal pathogen. Patients who received a next-day syndromic panel-based PCR test were younger with fewer comorbidities than those who received no test. For the cohort of patients receiving a PCR test for an oropharyngeal infection, the younger average age may reflect the CDC recommendations for confirmatory testing in patients older than 3 years of age.[22] Although RTIs and oropharyngeal infections may not require a diagnostic test when considered mild and self-limiting,[23] low testing rates may also suggest low awareness of the test or low perceived value of available diagnostics for RTIs or oropharyngeal infections. Given limitations of previous diagnostic tests such as lower sensitivity, low specificity, and limited pathogen detection capacities of rapid antigen tests and long turnaround time of traditional culture tests, clinical preference for empiric treatments without diagnostic testing has become standard.[4]

Reasons why younger and healthier patients received the next-day syndromic PCR panel compared to no testing on older patients with comorbid conditions are unclear. Coverage and reimbursement policies may play a factor in test ordering in different patient populations.[24] Yet, it would be expected that older patients with higher risk would receive testing, as many guidelines, including the pneumonia severity index (PSI), use age as a factor for determining low-risk patients eligible for hospital discharge.[25] Given the primary utilization of next-day syndromic PCR testing in the outpatient space, patients receiving these tests may represent healthier patients.

Observations of this large real-world population-based claims analysis provide preliminary evidence on the clinical utility of improvements in diagnostics for RTIs and oropharyngeal infections. Fewer outpatient visits for those receiving the PCR test for both conditions imply better management, treatment, and symptom resolution for those who received the test vs those who did not benefit from diagnostic testing. Moreover, overall outpatient services were significantly lower in patients who received the test, further implicating the role of diagnostic testing in preventing the need for downstream care. Among contributors to cost of care in the 6-month post-index period, fewer and shorter inpatient stays imply testing may have mediated progression of the severity of the infection, preventing the need for escalated levels of care. Yet, further study is needed to explore symptom duration with early and accurate diagnosis in a prospective study design with a focus on clinical outcomes.

Not all categories reflected decreased utilization for patients receiving a PCR test. The differences in number of total outpatient pharmacy prescriptions observed for patients receiving PCR tests for oropharyngeal or respiratory tract infections may reflect impacts to appropriateness of antibiotic prescribing but further real-world data analysis is required to understand the suitability of the prescriptions for each patient. For both infection types, patients that received the PCR test had greater costs for condition-specific laboratory/pathology services, which may reflect costs for confirmatory testing in patients where providers are new to using PCR for bacterial causes of infection.

This study builds on prior research by evaluating an innovative test in a real-world setting of a large patient population. Although prior research has shown the clinical potential of PCR testing for patient care,[26] prior research has not evaluated a laboratory test that overcomes the logistical challenges of PCR testing in a central clinical laboratory. Our study reports for the first time the impact of a molecular syndromic-based PCR test with next-day results. Accurate, next-day results overcome the previous limitation of prior diagnostic methods. Unlike prior research on the use of PCR testing for RTIs and oropharyngeal infection, the PCR test evaluated in this investigation is novel and unique because the test result is delivered in one day versus 2–3 days with the high sensitivity and accuracy of PCR testing from clinical laboratory settings.[27] Additionally, the syndromic test evaluates viral and bacterial pathogens simultaneously in contrast to the limited test menus available with other modalities. Moreover, the large patient syndrome-specific sample sizes provide preliminary evidence of impact with real world applications.

Despite reported observations, our analysis had several limitations. Interpretation of medical claims can be complicated by variability and skewness in the data.[28,29] Outlier claims were not excluded from the analysis in order to provide a complete and valid view of the results. This approach maintains high variability in the data and makes statistical significance more difficult to achieve. Although data transformation can be implemented to decrease skewness, limitations remain, including that healthcare costs do not allow for conclusions about patient outcomes.[28] Further, retrospective analysis of medical and pharmacy data is challenged by data review that was collected without the study aims in mind,

creating limitations in data utility and completeness. Additionally, the data presented here represents observational cohorts with different characteristics, thereby constraining the strength of the conclusions. However, this comprehensive study is necessary to understand the setting of next-day PCR and the subsequent healthcare costs associated with these patients. To more confidently attribute observations to the test, future research may utilize prospective and matched designs. Moreover, while testing is believed to contribute to more targeted treatments, future research should evaluate the impact of testing on appropriate antibiotic utilization.

Conclusion

In summary, this real-world observational report demonstrated that syndromic panel-based PCR testing for respiratory and oropharyngeal infections may contribute to lower healthcare utilization and costs across 6-months of follow up. Implications of these results support broader adoption of next-day PCR testing in clinical practice to improve diagnosis and treatment of respiratory and oropharyngeal infection in outpatient settings. Additionally, results may inform policy makers in reimbursement decisions regarding coverage policies for use of these diagnostic tools in outpatient settings. As the clinical benefits of more timely diagnostic testing are demonstrated, coverage policy for these tests in the outpatient setting should align with improved patient outcomes. These findings support recent guidelines from the Infectious Disease Society of America on molecular testing for respiratory infections for more accurate diagnoses and favorable healthcare outcomes including directed therapy.[18] Furthermore, these real-world results provide justification for further study and implementation of these innovations in molecular diagnostics to improve patient care for infectious disease.

Acknowledgments

We are grateful to the IQVIA team for data curation.

Disclosure

All authors are employed by HealthTrackRx. The authors report no other conflicts of interest in this work.

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