


Factors determining change in treatment for ambulatory children with pulmonary arterial hypertension: Implications for monitoring

Paul J. Critser¹ | Shane L. Collins¹ | Eleni G. Elia¹ | Julia McSweeney¹ |
Brienne Leary¹ | Lynn A. Sleeper^{1,2} | Mary P. Mullen^{1,2} 

¹Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA

²Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

Correspondence

Mary P. Mullen, Department of Cardiology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, USA.

Email: mary.mullen@cardio.chboston.org

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Abstract

While care models adapt to the COVID-19 pandemic with virtual and hybrid visits, clinical factors associated with treatment changes among ambulatory pediatric pulmonary arterial hypertension (PAH) patients are not well characterized. To understand which data critically altered treatment recommendations, we conducted a retrospective review among ambulatory children with Group 1 PAH to determine optimal visit and diagnostic strategies. Changes in management included: unplanned new treatments, dose modifications of vasodilators or diuretics, unscheduled hospitalizations, or changes to activity recommendations, catheterization schedule, or other testing. Factors prompting management changes were classified as symptoms, exam findings, or diagnostic tests. Across 398 ambulatory visits by 48 patients, 38 patients (79%) at 88 visits (22%) required change in management, most commonly in targeted PH medication. Changes were driven by symptoms alone (15%), diagnostic testing alone (47%), exam only (2%), symptoms and exam (2%), combination of testing and symptoms or testing and exam (25%), and other reasons (9%). Patients with World Health Organization functional Class IV (odds ratio [OR] 9.04 vs. Class I, $p = 0.014$) or Class III (OR 2.08 vs. Class I, $p = 0.050$) were more likely to undergo change in management. However, among Class I patients, 18% of visits generated changes in management because of test findings. While multiple factors affect management in ambulatory pediatric PH, neither symptoms nor exam was sufficient for identifying patients warranting clinical change in management. Testing accounted for most changes. Thus, in-person or hybrid surveillance including

Abbreviations: 6MWT, 6-min walk test; BNP, B-type natriuretic peptide; FC, functional class; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVRI, pulmonary vascular resistance index; RV, right ventricular; WHO, World Health Organization.

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history, exam, and diagnostic testing remains essential for optimal management of pediatric PAH.

KEYWORDS

decision making, echocardiogram, pediatric

INTRODUCTION

Pediatric pulmonary arterial hypertension (PAH) is a chronic, progressive cardiovascular disease characterized by elevated pulmonary artery pressure and vascular resistance.¹ Given the significant morbidity and mortality associated with PAH, appropriate clinical management and monitoring of disease progression is essential.¹⁻⁴ The standard of practice for managing pediatric PAH patients includes regular physical examinations (PEs) and cardiac testing to guide clinical care and evaluation. Expert guidelines from the American Thoracic Society/American Heart Association recommend that patients on active treatment medications are assessed every 3 months with history, exam, electrocardiogram, laboratory studies, and 6-min walk test (6MWT), and undergo echocardiogram evaluation every 6 months.¹

A number of classifications are available to gauge severity of pediatric pulmonary hypertension (PH) including the World Health Organization functional class (WHO FC), the Panama/pulmonary vascular resistance index (PVRI) FC, and combined composite scores.^{1,3,5,6} Each of these scales has shown prognostic success in predicting adverse outcomes among pediatric PAH patients. However, there are few data for what clinical information is most critical for making real-time patient treatment decisions in chronic management of patients with pediatric PAH, or regarding what the factors are, such as patient history, symptoms, exam, or diagnostic measurements that are most linked to changes in patient management.

This gap in management insight has taken on particular urgency during the COVID-19 pandemic.⁷ Health care providers have been adjusting clinical practice with prompt implementation of virtual telehealth visits.⁸ Providers and patients have shifted to virtual or telehealth visits in response to the pandemic, to maximize the safety of children with serious cardiopulmonary disease. The complex and variable etiology of pediatric PAH, as well as the high risk of clinical worsening,⁹ underscores the importance of establishing evidence-based guidelines when opting for virtual visits.¹⁰⁻¹² Similar to a face-to-face office visit, a virtual visit allows patients to report their symptoms and adherence to treatment. However, the lack of cardiac imaging, laboratory studies, and PE places virtual visits at variance with previous standards of care.^{11,12} It is uncertain if symptom reporting

and limited video examination are sufficient for understanding the clinical needs of the pediatric PAH patient, and there are no data to define the adequacy of telehealth for pediatric PAH patients.

To understand clinical decision making in managing pediatric PAH, we sought to characterize the critical factors contributing to change in ambulatory treatment management among pediatric PAH patients. In addition to identifying which clinical information is most likely to alter treatment plans, we specifically hoped to identify which patients might in the future be followed “virtually” and which still warrant in-person clinical assessment.

METHODS

A retrospective, cohort study was conducted among ambulatory PAH patients seen at Boston Children's Hospital between January 1, 2010 and December 31, 2019. This study was approved by our Institutional Review Board (IRB-P00036852) with the requirement to obtain informed consent waived. Demographic and clinical follow-up data were collected from patients' medical records.

Inclusion criteria included diagnosis of World Symposium Pulmonary Hypertension (WSPH) Group 1 PAH at ≤ 18 years of age, and a history of cardiac catheterization with findings of mean pulmonary artery pressure > 20 mmHg, PVRI ≥ 3 Wood Units, and pulmonary arterial wedge pressure ≤ 15 mmHg.¹³ Eligible patients were established (as opposed to new diagnoses), followed during the 2010–19 study period, seen for an in-person clinical encounter in either 2018 or 2019, had a minimum of three routine visits during the full study period, and were actively receiving treatment with a pulmonary vasodilator. For each patient, up to 10 visits were included in the analysis. If a patient had more than 10 visits during the study period, the 10 most recent visits were included. Unscheduled visits, new diagnoses/consultations, and visits following heart or lung transplant, were excluded from the analysis.

Demographic information collected included sex, age of PAH diagnosis, and subcategory of Group 1 PAH. Clinical follow-up visit data included age at visit, whether or not the patient was on parenteral prostacyclin, WHO FC, symptoms, PE, echocardiography-derived

right ventricular (RV) pressure and function, 6MWT, B-type natriuretic peptide (BNP), other PH-related tests, change in PH management, and reasons for change in PH management. Our usual protocol for follow-up is clinical evaluation with history and physical exam, electrocardiogram (EKG), 6MWT, and laboratory testing every 3 months with echocardiography added to visits every 6 months. Any reported changes in patient status may prompt earlier re-evaluation. Change of management was defined as an unplanned added or increased dose of targeted PH medication, unplanned discontinued or decreased dose of targeted PH medication, change in diuretic, scheduling or cancellation of a nonroutine catheterization or other study, change in exercise prescription, or unscheduled hospital admission. A planned increase or decrease in medication dose due to a change in the patient's weight was not considered a change of management.

Reasons for change in clinical PH management were categorized into symptoms, PE, and testing. Symptoms included dyspnea/exercise limitation/fatigue, syncope, chest pain, palpitations, side-effect of PH medication, or other symptoms. PE included peripheral edema, increased work of breathing, and decreased peripheral perfusion. Testing included RV pressure, RV function, 6MWT, BNP, heart catheterization, or other testing. In a given clinical encounter with a change in management, more than one reason could be selected. No individual physical exam finding, symptom, or test was given greater weight for decision making.

Independence of all encounters was assumed, even if multiple encounters were associated with the same patient. Categorical characteristics for the change in management and no change in management groups were compared using a Fisher exact test; continuous characteristics were compared using Student's *t* test (mean) and Wilcoxon rank sum test (median). Univariate logistic regression was used with years since diagnosis and WHO FC at clinic visit as predictors for the outcome of change versus no change in management. A *p*-value of 0.05 or less was considered statistically significant. Analyses were performed using R version 4.03 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

RESULTS

A total of 48 patients with WSPH Group I PAH, constituting 398 follow-up visits, were included in our analysis (Table 1). Among this cohort, the median age of diagnosis was 4.83 years (interquartile range: 0.43–9.64), and 34 (70.8%) were

TABLE 1 Cohort demographics and pulmonary hypertension classification

N	48
Age at diagnosis median (IQR), years	4.83 (0.43, 9.64)
Age of diagnosis range (years)	0.00–18.59
Patients with change(s) in management <i>n</i> (%)	38 (79.2%)
Sex	
Male <i>n</i> (%)	14 (29.2%)
Female <i>n</i> (%)	34 (70.8%)
Group 1 PAH classification	
Idiopathic PAH <i>n</i> (%)	18 (37.5%)
Heritable PAH <i>n</i> (%)	14 (29.2%)
Associated with congenital heart disease <i>n</i> (%)	11 (22.9%)
Associated with connective tissue disorder <i>n</i> (%)	4 (8.3%)
Associated with liver disease <i>n</i> (%)	1 (2.1%)

Note: Results are count (percentage) unless otherwise specified.

Abbreviations: IQR, Interquartile range; PAH, pulmonary arterial hypertension.

female. The most common PAH classifications among our population was idiopathic PAH (18, 37.5%), followed by heritable PAH (14, 29.2%), PAH associated with congenital heart disease (11, 22.9%), PAH associated with connective tissue disease (4, 8.3%), and PAH associated with liver disease (1, 2.1%). There were varying numbers of encounters entered for each patient. Six patients had 3 recorded visits, 1 had 4 visits, 1 had 5 visits, 3 had 6 visits, and 37 (77%) had more than 6 visits (Supporting Information: Figure 1).

Within the cohort, 38 patients (79%) experienced at least one change in clinical PH management (Supporting Information: Table 1). Each of the 398 follow-up visits was categorized as a reported change in clinical PH management (*n* = 88, 22.1%) or no change in clinical PH management (*n* = 310, 77.9%). Symptoms and exam findings during encounters that led to a change of management, as opposed to those that did not, included higher rates of PH symptoms such as new or worsening dyspnea, exercise limitation, or fatigue (*p* = 0.002); new or worse side-effects of a targeted PH medication (*p* = 0.011); findings of peripheral edema or increased work of breathing; and FC IV. For patients with an unremarkable exam, there was a lower likelihood of changing clinical management (*p* = 0.011) than if there were findings on physical exam. Encounters that led to a change in management were also significantly associated with diagnostic test findings (Supporting Information:

Table 1C), including RV pressure greater than systemic ($p = 0.032$); RV pressure higher than on previous echocardiogram ($p = 0.002$); RV function severely depressed ($p < 0.001$); and RV function worse than that on previous echocardiogram ($p = 0.002$). Change in management was not associated with performing an echocardiogram per se, nor with results from a 6MWT, or BNP measurement.

The reasons for change in clinical management were classified according to symptoms, testing, and exam (Figure 1 and Supporting Information: Table 2). A total of 13 (15%) of the 88 changes were due to symptoms alone, largely dyspnea, while 41 (47%) were due to diagnostic testing alone, 2 (2%) were due to exam alone, 2 (2%) were due to symptoms and exam, and 22 (25%) were due to a combination of testing and symptoms or testing and exam. The remaining eight changes (9%) were due to other reasons, for example, changes to increase medication compliance. Thirty-five (40%) encounters had two or more reasons selected. The most cited reasons for changing PAH management were RV pressure (58.8%) measured by echocardiogram or catheterization, dyspnea/exercise limitation/fatigue (23.9%), and RV function (22.7%), as determined by echocardiogram or catheterization (Supporting Information: Table 2). In total, the change in management in the majority (72%) of instances was attributed to diagnostic test findings themselves or in combination with symptoms or findings on exam

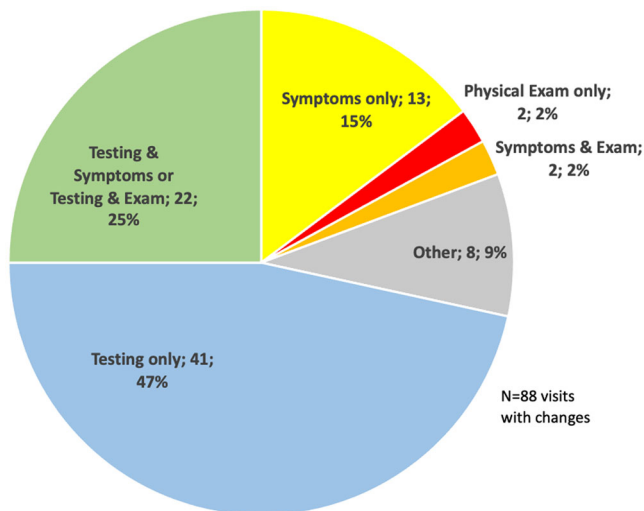


FIGURE 1 Clinical factors associated with change in pulmonary hypertension (PH) management. A total of 88 visits were associated with change in PH management. Contributing factors to recommendations for change in management were: diagnostic testing, only; symptoms, only; physical exam, only; physical exam and symptoms; diagnostic testing in combination with either symptoms or physical exam; or other. Numbers and percentages are shown.

(Figure 1), whereas symptoms and exams alone were cited as prompting 19% of management changes.

We sought to identify situations where the likelihood of a change in management was less than 10% for any given visit. However, almost none of the common clinical situations carried that low a threshold for avoiding change in management (Table 2). Even among asymptomatic patients or those with FC I PAH, the likelihood of a change in management was 18% at any given visit. In only one cohort—those patients with improving RV function as measured by echocardiography—were fewer than 10% of encounters associated with a change in management.

We document the types of changes in clinical management in Table 3. Among the 88 visits with a change in clinical management, 66 (75%) were changes in targeted PH medication. Thirty-nine (44%) reported an unplanned added or increased medication, 14 (16%) reported an unplanned discontinuation or decreased medication, and 13 (15%) reported both as changes. Other changes in clinical management included a change in diuretic (1%), scheduling or cancelation of a non-routine test (27%), and unscheduled hospital admission (5%).

We explored other contributors to changes in PAH management. WHO FC was a predictor of change in management. In comparison to patients with fewest symptoms (WHO FC I), Class IV patients were more likely to experience a change in management (odds ratio [OR]: 9.04; 95% confidence interval [CI]: 1.66, 68.12; $p = 0.014$), and Class III (OR: 2.08; 95% CI: 0.99, 4.31; $p = 0.050$) patients but not Class II patients (OR: 1.17; 95% CI: 0.67, 2.08; $p = 0.596$), tended to be more likely to experience a change (Table 4). Years since diagnosis was a nonsignificant predictor for change in clinical PH management (OR: 1.03; 95% CI: 0.99, 1.07; $p = 0.151$).

DISCUSSION

Pediatric PAH is a chronic, progressive illness. Following established guidelines, patients undergo regular assessments including symptom reporting, physical exam, and diagnostic testing. At each visit, clinical decisions are made to either continue or change the current treatment plan based on the diagnostic assessment. The overarching management goals in pediatric PH are to reduce symptoms from PH, minimize side effects of treatment, and improve survival.⁵ In ambulatory follow-up, patients were monitored for symptoms, physical exam findings, and diagnostic testing, with the plan to use this information to reduce or prevent symptoms from either PH or from treatment, and ideally to normalize

TABLE 2 Percentage of visits associated with change in management based on selected clinical status or diagnostic findings

Clinical status or diagnostic finding	Number of visits	Percentage of visits with change in management
Functional class		
I	127	18.1%
II	200	20.5%
III	54	31.5%
IV	6	66.7%
PAH symptoms		
None	220	18.8%
Present	178	26.9%
Dyspnea		
New	21	52.3%
Unchanged	102	27.4%
Improved	25	12.0%
Side effects of targeted medications		
New	25	44.0%
Unchanged	20	20.0%
Improved	6	33.3%
Physical exam		
Unremarkable	395	21.5%
Findings present (edema, work of breathing)	3	100%
Echocardiography performed		
No	64	21.8%
Yes	334	22.1%
RV pressure		
<1/2 systemic	87	18.3%
>1/2 systemic, ≤systemic	208	23.1%
>Systemic	26	38.5%
RV pressure relative to previous echo		
RV Pressure higher	37	45.9%
RV Pressure unchanged	230	17.8%
RV Pressure lower	43	27.9%
RV function		
Normal	236	18.6%
Mildly depressed	45	20.0%
Moderately depressed	29	37.9%
Severely depressed	14	64.3%
RV function relative to previous echo		
RV Function Worse	22	54.5%

(Continues)

TABLE 2 (Continued)

Clinical status or diagnostic finding	Number of visits	Percentage of visits with change in management
RV Function unchanged	280	21.1%
RV Function improved	15	6.7%
6-min walk test		
>10% less than previous (i.e., worse)	25	16.0%
Unchanged ($\pm 10\%$) from previous	161	18.6%
>10% more than previous (i.e., better)	28	17.9%
BNP level		
>20% higher than previous	20	30.0%
Unchanged ($\pm 20\%$) from previous	37	29.7%
>20% lower than previous	18	22.2%

Abbreviations: BNP, B-type natriuretic polypeptide; PAH, pulmonary arterial hypertension; RV, right ventricular.

TABLE 3 Frequency and types of change in clinical PH management ($n = 88$ encounters with change in management)

Type of change(s) in clinical management	N	% ^a
Targeted PH medication		
Add or increase dose, unplanned	39	44.3
Discontinue or decrease dose, unplanned	14	15.9
Both above	13	14.8
Change in diuretic	1	1.1
Scheduling or cancellation of a nonroutine test	24	27.3
Change in exercise prescription	0	0
Unscheduled hospital admission	4	4.5

Abbreviation: PH, pulmonary arterial hypertension.

^aAdds to greater than 100% because a given visit could have more than one type of change.

TABLE 4 Univariate models for change in clinical management ($N = 398$ visits)

Predictor	OR (95% CI)	p Value
Model 1: Functional class		
I	Reference	0.037
II	1.17 (0.67, 2.08)	0.596
III	2.08 (0.99, 4.31)	0.050
IV	9.04 (1.66, 68.12)	0.014
Unknown	1.70 (0.35, 6.38)	0.460
Model 2: Years since diagnosis		
	1.03 (0.99, 1.07)	0.151

Abbreviations: CI, confidence interval; OR, odds ratio.

cardiovascular function. Our clinical practice utilizes diagnostic assessments toward these fundamental goals. Over the course of follow-up, patients undergo many such iterative assessments and decision-making nodes. However, the actual factors associated with decisions to change clinical management are not well known. We analyzed the clinical features associated with change in treatment recommendations or management plan. While symptoms and, less commonly, exam findings, were occasional prompts for changes in clinical management, the largest contributor was diagnostic testing, particularly echocardiography, either by itself or in combination with symptoms and exam findings.

Our findings may have implications for care of pediatric PAH during the pandemic and in an era of virtual health care visits. During the pandemic, clinicians and patients have understandably sought to minimize risks of exposure to protect both the clinical team and the patients through telehealth,¹¹ a particularly compelling consideration for pediatric PAH at a time when many children are yet not fully vaccinated against coronavirus. One goal of our study was to explore whether virtual visits could substitute for more regular, face to face in-clinic assessments. Given the prevalence of test results as drivers of management changes, we continue to believe that such assessments every 6 months remain important. However, we note that symptoms and some physical exam findings (notably, peripheral edema and work of breathing) are collectible data elements during virtual visits and symptoms, in particular, were a frequent contributor to changes in management. We observed that patients with baseline

WHO Class IV functional status were most likely to undergo treatment/management modification. Patients with WHO FC I or II pediatric PAH were far less likely to have management changes. We believe that carefully selected patients with higher functionality at baseline may be suitable for alternating virtual and in-person visits. However, even among patients without symptoms, or in FC I, there was an 18% likelihood of change in management, suggesting that testing and exam play an important, additive role to what virtual visits alone might provide.

Based on these findings we continue to endorse established practice recommendations for every 3-month clinical assessments along with every 6-month echocardiographic evaluations. Established patients in FC I (18.1% change in management) or II (20.5% change in management) may undergo virtual visits via telemedicine alternating with face to face to visits as per physician or patient preference. WHO functional status should be assessed at each visit. New or worsening symptoms warrant additional evaluation. Home 6MWT or remote laboratory evaluation can enhance telehealth visits. Patients in FC III (31.5% change in management) or IV (66.7% change in management) should undergo regular face to face visits and more frequent echocardiographic

evaluation. We propose a clinical care algorithm that reflects this individualized approach for outpatient follow-up of pediatric PAH patients (Figure 2).

At the same time, the pandemic has underscored the urgency of developing appropriate methods for assessing patient symptoms and physiology through remote means.¹¹ Examples might include tools to link home vital signs with electronic health records, reliable determinations of functionality such as 6MWT or accelerometry,¹² personal health devices and apps to record EKGs and other cardiac parameters, and innovative remote monitoring strategies such as implantable hemodynamic sensors¹⁴ for serial assessment of pulmonary artery pressure. There is in particular the additional need to develop and validate these tools in the pediatric population.

We acknowledge several specific limitations of this analysis. First, we selected pediatric PAH patients with multiple outpatient visits, suggesting robust compliance with health care follow-up. We only considered patients with a specific type of PAH (Group 1), and we excluded management changes prompted by interval, unscheduled visits to the clinic or hospital. Thus, while patients were on active treatment, they were sufficiently “stable” to be

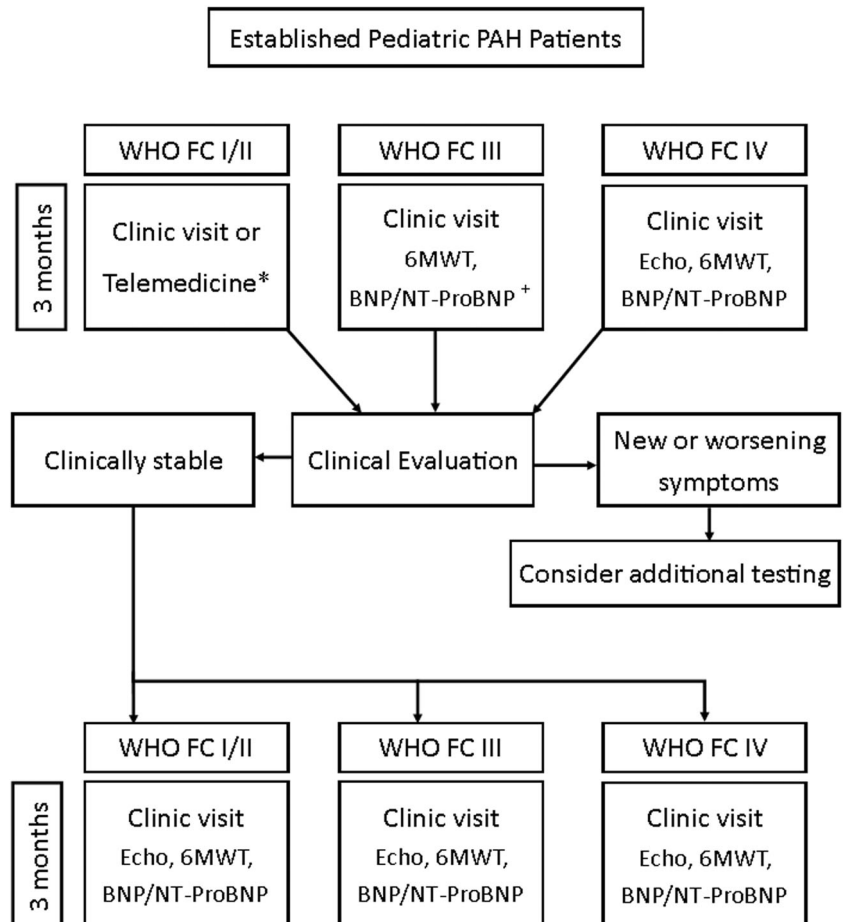


FIGURE 2 Suggested 6-month clinical care algorithm for established WHO Group 1 pediatric PAH patients. 6MWT, 6-min walk test; BNP, B-type natriuretic peptide; NT-ProBNP, N-terminal pro B-type natriuretic peptide; WHO FC, World Health Organization functional class.

appropriate for scheduled routine serial appointments. We focused on complex care conducted at a major academic tertiary center, with care provided by a small number of clinicians with extensive clinical experience. Thus, these findings may not be applicable to patients with acutely unstable symptoms, patients generally non-adherent with routine follow-up, or receiving care in different clinical environments. Finally, this study looked at clinical decision making based on best practices but was not designed to evaluate whether therapeutic decisions affected longer-term outcomes.

Our experience demonstrates the importance of testing in clinical decision making in pediatric patients with PAH. Although symptoms and exam remain essential, the majority of changes in management were due to results of testing alone or combined with other assessments. These results support current recommendations for evaluation and testing in children with PAH. Future research of larger patient cohorts could evaluate optimal intervals for testing, evaluate other WHO groups, identify cohorts of patients that may require less frequent or higher intensity of evaluation and study the association of treatment decisions with clinical outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study, acquisition and analysis of data, drafting and final approval of the manuscript.

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CONFLICTS OF INTEREST

Dr. M. P. Mullen reports Altavant Sciences and Actelion scientific advisory board participation, outside the content of the manuscript. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

This study is approved by the Boston Children's Hospital Institutional Review Board (IRB-P00036852).

ORCID

Mary P. Mullen  <https://orcid.org/0000-0002-0291-9630>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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