Pulmonary Hypertension in the Population with Down Syndrome

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ABSTRACT

Persons with Down syndrome (DS) have an increased reported incidence of pulmonary hypertension (PH). A majority of those with PH have associations with congenital heart disease (CHD) or persistent pulmonary hypertension of the newborn (PPHN); however, there are likely multifactorial contributions that include respiratory comorbidities. PH appears to be most commonly identified early in life, although respiratory challenges may contribute to a later diagnosis or even a recurrence of previously resolved PH in this population. Currently there are few large-scale, prospective, lifetime cohort studies detailing the impact PH has on the population with DS. This review will attempt to summarize the epidemiology and characteristics of PH in this population. This article will additionally review current known and probable risk factors for developing PH, review pathophysiologic mechanisms of disease in the population with DS, and evaluate current screening and management recommendations while suggesting areas for additional or ongoing clinical, translational, and basic science research.

Keywords: Down syndrome; Trisomy 21; Pulmonary hypertension; Pulmonary arterial hypertension; Congenital heart disease

Key Summary Points

Pulmonary hypertension is a common comorbidity in the population with Down syndrome, frequently with multifactorial etiologies including congenital heart disease, developmental lung disease, and other respiratory pathologies.

Screening for pulmonary hypertension in the population with DS remains challenging, but novel biomarkers are currently being investigated.

Understanding the etiology of pulmonary hypertension in the population with Down syndrome can help guide treatment strategies.
INTRODUCTION

Pulmonary hypertension (PH) is frequently identified in individuals with Down syndrome (DS). The high frequency of PH in this population has probable genetic (Table 1), congenital, and environmental contributions [1]. While the lifetime prevalence remains unknown, reports of PH incidence in childhood may be as high as 28% in this population [2]. The etiology of PH in persons with DS varies; however, there is a strong association with congenital heart disease (CHD), which is present in 38–58% of this population [3–6]. Those without CHD also appear to be at higher risk of developing PH when compared to the general population, and there are likely additional respiratory and cardiovascular reasons for this increase [1].

The World Symposium on Pulmonary Hypertension (WSPH) classifies PH into five major groups including pulmonary arterial hypertension (PAH; Group 1); PH due to left-sided heart disease (Group 2); PH due to lung disease or hypoxia (Group 3); chronic thromboembolic PH (CTEPH; Group 4) and PH due to multifactorial, mixed or unclear mechanisms (Group 5) [7]. Many reports of PH in persons with DS attribute the PH to Group 1 PAH; however, there are likely underreported contributions from left heart disease, disorders of the

| Contribution to PH | Gene     | Protein                                      |
|--------------------|----------|----------------------------------------------|
| Hemodynamic stress |          |                                              |
| Congenital heart disease |         |                                              |
| (AVSD)              | CRELD1   | Cysteine-rich with EGF-like domain protein 1 |
| (VSD)               | HEY2     | Hairy/enhancer-of-split related with YRPW motif protein 2 |
|                     | GATA3    | (Transcription factor)                       |
|                     | KCNH2    | Kv11.1                                       |
|                     | ENG      | Endoglin                                     |
|                     | FLNA     | Filamin A                                    |
|                     | GUSB     | Beta-glucuronidase                           |
| Pulmonary hypoplasia|          |                                              |
| Antiangiogenesis    |          |                                              |
|                     | RCAN1    | Regulator of calcineurin-1                   |
|                     | COL18a1  | Endostatin                                   |
|                     | APP      | Amyloid beta protein                         |
| Endothelial dysfunction |        |                                              |
| Proinflammatory     | IFNAR1   | Interferon-alpha/beta receptor 1             |
|                     | IFNAR2   | Interferon-alpha/beta receptor 2             |
|                     | IFNGR2   | Interferon-gamma receptor 2                  |
|                     | IL10RB   | Interleukin-10 receptor subunit beta         |

AVSD atrioventricular septal defect, VSD ventricular septal defect
lung, and complex CHD (Group 5—category that includes segmental pulmonary hypertension, single ventricle disorders, and Scimitar syndrome) [8]. As such, a better understanding of the etiology of PH in the population with DS is necessary to help determine appropriate screening and interventions. This review will serve as a critical evaluation of the current literature, will provide ideas for interim strategies to help manage cardiopulmonary challenges in persons with DS and will offer suggestions for future research. This manuscript is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**EPIDEMIOLOGY**

A recent meta-analysis reported that the average life expectancy for individuals with DS is approximately 30 years less than individuals without DS. In this analysis, cardiovascular disorders accounted for 1.5–24%, cardiac failure 18.8–33%, and CHD accounting for 3–50% of deaths in this population [9]. A large population study using data from the US Centers for Disease Control and Prevention National Center for Health Statistics reported increased odds of death (odds ratio 3.83 with 95% CI 3.60–4.07) from pulmonary vascular disease in persons with DS between 1983 and 1997 [10]. These findings suggest the burden of pulmonary vascular disease is higher in the population with DS.

There are few large cohort studies evaluating the lifetime incidence of PH in individuals with DS from all causes. One moderate-sized \((n = 1242)\), single-institution, retrospective study suggested that childhood incidence of PH is as high as 28%, increasing to 45% in the presence of CHD [2]. The vast majority of studies have evaluated the incidence of PH classified as Group 1, primarily PAH associated with CHD or persistent pulmonary hypertension of the newborn (PPHN; Group 1.7). PPHN has been reported to occur at a rate of 1.2–9.7% in the population with DS (0.1% in the general population), perhaps suggesting an innate abnormality in vasoactive regulation or airway structure associated with the overexpression of human chromosome 21-related genes [2, 11].

The timing of PH onset appears to most commonly occur in the first year of life, particularly with PPHN and in the presence of CHD [2, 12]. In one moderate-sized retrospective study, 70% of children with PH experienced transient disease with resolution following interventions, a small portion (15%) experienced persistent PH, and a similar amount (15%) developed recurrence of PH, frequently as a result of respiratory comorbidities [2]. The average age of recurrence was 1.7 years in this study, suggesting that PH may be most challenging early in life in the population with DS. In another small \((n = 102)\) prospective study, the prevalence of PH in DS was 5.9% at 1 year and 15% at 10 years, although the study appears to have been evaluating older children (mean age 16.4 ± 12 years) without surgically corrected CHD, complicating our understanding of the condition [3].

The need for specialty providers and expensive invasive (cardiac catheterization) or non-invasive (echocardiography) testing to identify PH may have historically hindered a thorough understanding of the incidence of PH in this population. Further, pulmonary hypertension is not always symptomatic, and early recognition of the disease may be limited in more sedentary populations or those who are unable to comply with clinical assessments (e.g., exercise testing or 6-minute walk distance testing), underestimating the population prevalence of PH. There may even be bias against evaluating for the condition in specialty practices without echocardiography (e.g., pulmonology) or failure to recognize the condition in the setting of other CHD (e.g., left heart disease or complex cardiac disease) and thus an underreporting of disease prevalence. Further, in 2018, the Pediatric Task Force of the 6th World Symposium on Pulmonary Hypertension (WSPH; Nice, France, 2018) revised the definition of PH, reducing the diagnostic threshold of mean pulmonary arterial pressure (mPAP) from 25 to 20 mmHg, as studies placed this more than two standard deviations above the population mean [13]. Prior studies have used the higher mPAP...
threshold, likely reducing the reported incidence of PH. Thus, a better understanding of PH disease incidence and prevalence in the population with DS is needed.

CLASSIFICATION, ETIOLOGY, AND RISK FACTORS

Pulmonary hypertension develops when pulmonary arterial pressure increases in order to maintain blood flow in the presence of the increased pulmonary vascular resistance that occurs due to vascular remodeling (Ohm’s law). The etiology of pulmonary hypertension in individuals with Down syndrome is not always straightforward and can often be attributed to multiple underlying challenges to the pulmonary vascular system including increases in hemodynamic stress, abnormalities in lung development, intrinsic endothelial dysfunction, increases in pulmonary vascular resistance, and post-capillary disease (Fig. 1). Large prospective studies evaluating etiologies of PH in the population with DS are lacking; however, a thorough literature review has revealed known and likely risk factors for developing PH (Table 2).

Individuals with Down syndrome very often fit into multiple PH classification categories (Table 3). The most common classification is Group 1, PAH associated with either CHD or PPHN; however, there are frequent contributions from left heart inflow or outflow disease (Group 2), respiratory challenges from chronic or intermittent hypoxia (Group 3), and occasionally complex cardiac disease (Group 5) or metabolic derangements such as hypothyroidism (Group 5). Given the complexity of classifying PH in DS, the WSPH has recommended that in the absence of CHD, individuals with DS who have PH should be categorized as Group 3 disease due to the high frequency of associated respiratory challenges [13].

Fig. 1 Pathophysiology and etiologies of development of pulmonary hypertension in Down syndrome. Early pulmonary arterial remodeling may occur due to an innate interferonopathy, intrinsic endothelial dysfunction or other metabolic conditions. Increases in hemodynamic stress can occur from congenital heart disease (CHD) or patent ductus arteriosus (PDA) causing persistent pulmonary hypertension of the newborn (PPHN) in developmentally immature lungs with high pulmonary vascular resistance. Increased pulmonary vascular resistance can occur from acquired lung disease and capillary or post-capillary disorders.
Increased Hemodynamic Stress

Congenital heart disease is present in 38–58% of individuals with DS, with likely genetic contributions (Table 1) [3–6, 14–16]. Children with DS are more likely to experience PH in the presence of CHD (38–80%) than those with CHD who do not have DS (4–15%).

| Cardiac conditions                                      | % in DS | % in DS with PH [2] | Relative risk for PH (95% CI) [2] |
|---------------------------------------------------------|---------|---------------------|----------------------------------|
| CHD                                                     | 40–75   | 94.2                | 5.3 (3.5–8.2)                    |
| CHD with L-to- R shunt                                  | 35.1    | 59.8                | 2.1 (1.7–2.5)                    |
| AVSD                                                    | 9–49    | 19.9                | 1.6 (1.3–1.9)                    |
| VSD                                                     | 26–35   | 32                  | 1.8 (1.5–2.1)                    |
| ASD                                                     | 2–38    | 46.2                | 1.9 (1.6–2.3)                    |
| PDA                                                     | 3–47    | 59.8                | 1.6 (1.3–1.9)                    |
| CHD without L-to-R shunt                                | 7.2     | 4.6                 | 1.4 (1.3–1.9)                    |

| Pulmonary conditions                                    |         |                     |                                 |
|---------------------------------------------------------|---------|---------------------|----------------------------------|
| Pulmonary hypoplasia *                                   | N/A     | N/A                 | N/A                             |
| OSA                                                     | 45–79   | 77.5                | N/A                             |
| Intermittent or chronic hypoxia *                        | N/A     | 55.5                | N/A                             |
| Recurrent pneumonia *                                    | N/A     | 43.1                | N/A                             |
| Aspiration                                              | 35–39   | 35.5                | N/A                             |
| Asthma                                                  | 32–36   | 20.5                | N/A                             |
| Chronic lung disease/BPD                                 | N/A     | 19.9                | N/A                             |
| Tracheobronchomalacia                                   | 3–33    | 15.9                | N/A                             |
| Tracheal bronchus                                        | 3–5     |                     |                                 |
| Subglottic stenosis                                      | 4–6     | 8.4                 | N/A                             |
| Laryngomalacia                                          | N/A     | 7.8                 | N/A                             |

| Metabolic conditions                                     |         |                     |                                 |
|---------------------------------------------------------|---------|---------------------|----------------------------------|
| Thyroid abnormalities                                    | 27      | 32.1                | N/A                             |

| Gastrointestinal conditions                              |         |                     |                                 |
|---------------------------------------------------------|---------|---------------------|----------------------------------|
| GER                                                     | 9       | 34.4                | N/A                             |

CHD congenital heart disease, AVSD atrioventricular septal defects, VSD ventricular septal defect, ASD atrial septal defect, PDA patent ductus arteriosus, OSA obstructive sleep apnea, BPD bronchopulmonary dysplasia, GER gastroesophageal reflux

N/A not available

L-to- R: systemic to pulmonary

*Case reports/case series
A left-to-right intracardiac shunt, in particular, increases the risk of developing PH in individuals with DS, with a relative risk of 2.1 (95% CI 1.7–2.5; Table 2) [2]. Increases in pulmonary arterial blood flow through an intracardiac shunt can increase pulmonary arterial pressures, create shear stress, and contribute to endothelial dysfunction, vascular remodeling, and altered vasoactive mediator expression [19]. Left uncorrected, ventricular septal defects (VSD) and atrioventricular septal defects (AVSD) frequently progress to Eisenmenger syndrome, an end-stage reversal of the intracardiac shunt [17].

### Pulmonary Hypoplasia

Several small case series have reported evidence of abnormal lung development or pulmonary hypoplasia in individuals with DS [20–22]. These autopsy reports have revealed evidence of increased pulmonary blood flow through dilated or congested pulmonary vasculature, and have revealed evidence of pulmonary arterial remodeling and noted disturbances in microvascular development. The overexpression of the human chromosome 21 (Hsa21)-encoded antiangiogenic genes for endostatin (COL18a1), amyloid beta protein (APP), and regulator of calcineurin-1 (RCAN1) may contribute to impaired pulmonary vascular development [23]. Increased pulmonary blood flow to a pulmonary vascular bed with reduced capacitance may increase the risk of developing PH, as it contributes to hemodynamic stress to the arterial endothelium and exacerbates hypoxia through impairments in diffusion and ventilation-to-perfusion matching.

### Intrinsic Endothelial Dysfunction

The increased prevalence of PPHN and the existence of possible intrapulmonary bronchopulmonary anastomoses (IBA) in the population with DS may suggest an innate abnormality in endothelial function or vasoactive tone in the pulmonary circulation [11, 22]. Reports of elevated endothelin-1 (ET-1; a potent vasoconstrictor) in children with DS who have CHD and reduced endothelial

| WHO classification group | % (n = 346) |
|--------------------------|------------|
| 1 Pulmonary arterial hypertension | 44.8 |
| 1.4.4 CHD-associated PAH | 44.8 |
| 1.7 PPHN | 35.3 |
| 2 PH due to left-sided heart disease | 1.2 |
| 3 PH caused by lung disease or hypoxemia | 17.9 |
| 3.4 Sleep-disordered breathing | 17.9 |
| 3.5 Developmental lung disease | ^ |
| 4 PH due to pulmonary arterial obstructions | 0 |
| 5 PH with unclear or multifactorial mechanisms | 0 |
| 5.3 Thyroid disorders | 0 |
| 5.4 Complex CHD | * |

CHD congenital heart disease, PPHN persistent pulmonary hypertension of the newborn
*Referenced study precedes WSPH updates
^Biopsies not obtained
|                      | AAP standard of care for all patients with Down Syndrome | Any child with chronic respiratory symptoms or conditions | New PH diagnosis or recurrent episode | PH resolved or well controlled | No improvement in PH/worsening |
|----------------------|----------------------------------------------------------|----------------------------------------------------------|--------------------------------------|-------------------------------|--------------------------------|
| Echo                 | First month of life                                      | Consider screening for PH every year                     | With initial evaluation              | Annually until school age for resolved PH (CHD, PPHN, or other cause of PH) | As frequently as PH team suggests |
| Pulmonology consult  | N/A                                                      | Annual pediatric pulmonology evaluation                | With initial evaluation if not previously established | Continue to follow regularly until lung disease ruled out as contributing factor | Continue to follow regularly until lung disease ruled out as contributing factor |
| VFSS                 | In first year of life only if symptoms present           | As soon as respiratory symptoms become apparent       | With initial evaluation              | Annual evaluation by speech–language pathologist and VFSS until age 6 years; consider annual screening thereafter for those with history of diagnosed aspiration | At least annually (more frequent if unexplained worsening) |
| Sleep study          | By age 4 years                                           | Per primary pulmonologist                               | With initial evaluation              | Consider annual sleep clinic evaluation | Annually, repeat after any surgical airway management |
| Chest CT with and without IV contrast | N/A                                                      | Encouraged if signs of lower airway or pulmonary vascular disease | With initial evaluation              | N/A                           | Consider repeating at intervals decided with primary pulmonologist to screen for ongoing evidence of aspiration, other parenchymal lung disease, or pulmonary venous obstruction |
production of nitric oxide (NO; a potent vasodilator) may be secondary to the overexpression and increased activity of four Hsa21-encoded interferon receptors [24–27]. Interferon has negative modulatory effects on NO expression and can lead to upregulation of ET-1 [28]. The therapeutic use of interferon in the non-DS population has led to the development of PAH, a frequent finding in disorders of genetic overexpression of interferon unrelated to DS [29–31].

**Increased Pulmonary Vascular Resistance**

Individuals with DS have a high incidence of respiratory comorbidities including obstructive sleep apnea (OSA), intermittent or sustained hypoxia, recurrent pneumonia, and chronic aspiration (Table 2) [2, 32]. Intermittent or chronic respiratory insults lead to regional or global hypoxic pulmonary vasoconstriction and may contribute to increases in pulmonary vascular resistance. Of particular interest, OSA has been reported in 45–79% of individuals with DS and has been implicated as a cause of PH in this population [33–37].

Congenital airway disorders are frequently reported in this population, particularly in those with chronic cough or recurrent respiratory infections. In children with DS undergoing endoscopic airway evaluations for these symptoms, airway abnormalities were identified in 14–75% of patients (Table 2) [38–40]. Commonly reported findings include tracheobronchomalacia and subglottic stenosis (acquired and congenital). A high incidence of tracheal bronchus (3–5%) and laryngeal cleft (1%) has also been reported in the population with DS, suggesting more obvious etiologies of recurrent pneumonia and aspiration, respectively [38, 40]. Consequential airway compression from cardiovascular abnormalities (e.g., cardiomegaly, vascular abnormalities) may be a complicating factor in those with CHD [39, 40]. Airway disorders can contribute to intermittent hypoxia and impair one’s ability to mobilize lower airway secretions, directly contributing to the increased risk of acquiring lower respiratory tract infections. These insults lead to transient or sustained increases in pulmonary vascular resistance and likely contribute to the higher incidence of PH observed in the population with DS. While direct evidence linking airway disease to the onset of PH is lacking in the population with DS, associations have been described, as the authors have previously
reported new diagnoses of OSA in 21% and recurrent pneumonia in 17% of children with DS prior to identifying a recurrence of their previously resolved PH [2]. Notably, large prospective studies evaluating respiratory comorbidities and risk for developing PH in the population with DS are lacking.

### Post-Capillary Disease

Pulmonary vein stenosis has been reported to occur with increased frequency in the population with DS; however, the exact incidence is unknown [41–44]. Additionally, with the high frequency of CHD, there is likely an increase in disorders of left heart outflow, which can increase pulmonary vascular resistance and can contribute to the onset of PH. Certain forms of AVSD, such as single papillary muscle with deficient mural leaflet, frequently lead to increased left-sided AV valve stenosis or insufficiency causing or exacerbating pulmonary hypertension. Prospective, large-scale studies are necessary to identify the true incidence of left-sided heart disease and its contribution to PH onset (PH Group 2) in the population with DS.

### Screening

There are currently no accepted screening guidelines for pulmonary hypertension in individuals with DS; however, a recent publication by the Pulmonary Hypertension Association has suggested a comprehensive approach (Table 4) [45]. Generally accepted guidelines

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### Table 5 Managing conditions contributing to PH in individuals with DS

| Condition                        | Specialty                  | Evaluations                                  | Possible interventions                                      |
|----------------------------------|----------------------------|----------------------------------------------|------------------------------------------------------------|
| CHD                              | Cardiology                 | Echocardiogram, cardiac catheterization      | Pre-load reduction, surgical correction, targeted vasodilator therapy |
| PPHN                             | Neonatology, cardiology, pulmonology | Echocardiogram                              | Oxygen and ventilation support, targeted vasodilator therapy |
| OSA                              | Pulmonology, sleep provider | Polysomnography, laryngoscopy, bronchoscopy | Surgical intervention, noninvasive ventilation              |
| Pulmonary hypoplasia             | Pulmonology                | CT chest, lung biopsy                        | Limit inflammatory insults, promote growth                 |
| Hypoxia                          | Pulmonology, sleep provider | Polysomnography, CT chest, echocardiogram, cardiac catheterization | Supplemental oxygen, improve pulmonary toilet, ventilatory support, surgical correction |
| Recurrent pneumonia/aspiration   | Pulmonology                | CT chest, bronchoscopy, swallow evaluation   | Improve pulmonary toilet, treat cause of aspiration         |
| Airway disorders (e.g., tracheomalacia) | Pulmonology                | CT chest, bronchoscopy                       | Improve pulmonary toilet, ventilatory support              |
| Thyroid disorders                | Endocrinology              | Serum TSH, free T4                           | Levothyroxine                                              |

CHD congenital heart disease, PPHN persistent pulmonary hypertension of the newborn, OSA obstructive sleep apnea, CT computed tomography, TSH thyroid stimulating hormone
remain limited to the screening of comorbid conditions including CHD (within the first month of life), valvular disease (between 13–21 years), sleep-disordered breathing (by age 4 years), and swallowing disorders (if ever symptomatic) [46]. When diagnosis is uncertain or targeted therapy is being considered, a cardiac catheterization is recommended by the American Heart Association and American Thoracic Society (AHA/ATS) [7]. Understandably, this is not always possible, and clinicians are encouraged to use their best clinical judgment when initiating therapies.

Recent work has identified possible biomarkers of PH specific to the population with DS including evidence of increased circulating inflammatory cells (immunomodulatory myeloid-derived suppressor cells and fibrocytes) [47] and dysregulated angiogenesis favoring antiangiogenesis (high serum levels of endostatin coupled with low levels of angiogenin) [48], although a subsequent study challenged endostatin’s role as a biomarker in favor of the cardiac markers N-terminal prohormone of brain natriuretic peptide and galectin-3 [49]. These small studies were largely specific to the population with PAH (Group 1), and additional, more thorough investigations are needed.

Given the high frequency of disease in the population with DS, new biomarkers of early disease are needed. Echocardiography is an expensive test and identifies late evidence of pulmonary vascular disease (e.g., right ventricular hypertension) while cardiac catheterization is expensive, invasive, and not always feasible. Ongoing work should focus on risk stratification tools, evaluating hemodynamic stress in the vasculature, early or predictive protein signatures, or other biomarkers of early disease.

Management

The multiple underlying causes and risk factors for developing PH in the population with DS requires a multidisciplinary treatment approach. At a minimum, this should include pediatric cardiology, pediatric pulmonology, and relevant surgical subspecialties [45, 50]. Interventions should target the underlying cause of the disease both medically and surgically where appropriate (Table 5). Notably, addressing upper airway obstruction has been reported to improve mPAP on cardiac catheterization [37, 50]. Additionally, given the complexity of the disorder, pre-anesthesia risk stratification specific to the population with DS may help guide safe surgical interventions [51].

In those patients with chronic respiratory symptoms, early referral to a comprehensive aerodigestive team may provide useful diagnostic insight or therapeutic opportunities to address underlying airway or digestive disorders that may contribute to the development of PH. Following American Academy of Pediatrics (AAP) screening recommendations for polysomnography may identify pathology and suggest referral to sleep or pulmonary specialists; however, a low threshold for referral to pulmonary specialists may provide additional benefit [45].

Early surgical correction is often necessary to prevent the development or progression of PH in individuals with DS who have CHD with systemic-to-pulmonary intracardiac shunts, including atrial septal defect (ASD) [52, 53]. Generally, surgical correction of CHD in individuals with DS is recommended by 2 years of age; however, preoperative hemodynamic assessment can aid in risk stratification of patients. In many centers, surgery is performed even earlier. A pulmonary vascular resistance index (PVRi) of < 6 Wood units (WU) m⁻² or ≥ 6 WU m⁻² but with adequate reversibility (vasoreactivity with supplemental oxygen and inhaled NO with a reduction in PVRi < 6 WU m⁻² and pulmonary vascular resistance/systemic vascular resistance [PVR/SVR] < 0.3) response is associated with favorable outcomes [7]. Of note, there have been reports of increases in postoperative PH in children with DS undergoing surgical repair for both ASD (1.7% vs. 0.2%) and VSD (2.2% vs. 0.7%) compared to non-DS controls [54].

For individuals with DS who have intrinsic disease of the pulmonary arteries such as PAH associated with CHD or PPHN, targeted PH pharmacotherapies can be considered. There are very few studies evaluating pharmacotherapies specifically in the population with DS; however,
the studies available and sub-analyses of general PAH population studies have suggested that endothelin receptor antagonists (ERA) can improve quality of life, exercise capacity, and functional classification, and have been generally well tolerated [55–59]. The phosphodiesterase-5 inhibitor sildenafil may not be as efficacious as ERA, as a suboptimal improvement in pulmonary vascular resistance index and mPAP was reported in a DS-specific sub-analysis of the STARTS-1 trial [60]. This study did report that the drug was well tolerated in this population, but did not evaluate for confounding comorbidities or causes of PH in the population with DS involved. Dosing for pediatric [7] and adult [61] targeted therapies can be found elsewhere. Of note, as of the writing of this manuscript, in the United States, the only Food and Drug Administration-approved medication for PAH in children is the ERA bosentan.

**Future Areas of Research**

With updated classifications and a more inclusive definition for pulmonary hypertension, it stands to reason that more people with DS will be diagnosed with PH. Large prospective cohort studies are required to better understand the prevalence and risk factors contributing to the development of PH in individuals with DS. Screening for the condition may be improving, as novel biomarkers have been identified and are currently under investigation [47, 62]. Ongoing PH registries are improving our understanding of how individuals with DS respond to targeted therapies; however, therapeutic studies specific to the population with DS are needed, including those that evaluate the response to treating cardiac and respiratory comorbidities.

Preclinical mouse models of lung disease in the population with DS may prove valuable in studying mechanisms of disease and isolating genetic contributions to the onset of PH [63]. While the mouse orthologues for human chromosome 21 are distributed across three murine chromosomes (Mm10, Mm16, and Mm17), complicating preclinical studies, a trisomic Mm16 (Dp16) mouse, when raised in hypoxic conditions, develops the hypoplastic pulmonary phenotype and has evidence of pulmonary hypertension (data presented in the form of a platform presentation by Bush et al. at the American Thoracic Society International Conference, 2017).

**CONCLUSIONS**

PH in the population with DS appears to be more common than that in the population without DS. There are multifactorial reasons for the higher prevalence of PH in this population including abnormal pulmonary development, increased hemodynamic stress in the pulmonary vasculature, capillary and post-capillary obstructive disorders, and inflammatory and possibly metabolic contributions [64]. Additional large-scale epidemiologic and clinical investigations are needed to understand the impact of this disease on this vulnerable population, and ongoing basic and translational science is required to identify biomarkers of early pulmonary vascular disease, understand genetic and molecular pathways, and evaluate effective targeted therapies.

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