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REVIEW ARTICLE

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Differential drug response in pulmonary arterial hypertension: The potential for precision medicine

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Abstract

Pulmonary arterial hypertension (PAH) is a rare, complex, and deadly cardiopulmonary disease. It is characterized by changes in endothelial cell function and smooth muscle cell proliferation in the pulmonary arteries, causing persistent vasoconstriction, resulting in right heart hypertrophy and failure. There are multiple drug classes specific to PAH treatment, but variation between patients may impact treatment response. A small subset of patients is responsive to pulmonary vasodilators and can be treated with calcium channel blockers, which would be deleterious if prescribed to a typical PAH patient. Little is known about the underlying cause of this important difference in vasoresponsive PAH patients. Sex, race/ethnicity, and pharmacogenomics may also factor into efficacy and safety of PAH-specific drugs. Research has indicated that endothelin receptor antagonists may be more effective in women and there have been some minor differences found in certain races and ethnicities, but these findings are muddled by the impact of socioeconomic factors and a lack of representation of non-White patients in clinical trials. Genetic variants in genes such as *CYP3A5*, *CYP2C9*, *PTGIS*, *PTGIR*, *GNG2*, *CHST3*, and *CHST13* may influence the efficacy and safety of certain PAH-specific drugs. PAH research faces many challenges, but there is potential for new methodologies to glean new insights into PAH development and treatment.

KEYWORDS
diverse populations, pharmacogenomics, pharmacotherapy, pulmonary arterial hypertension

Abbreviations: 6MWD, 6-min walk distance; APAH, associated pulmonary arterial hypertension; APAH-CTD, PAH associated with connective tissue disease; CCBs, calcium channel blockers; cGMP, cyclic guanosine monophosphate; CYP, Cytochrome P450; EDNRA, endothelin receptor type A; ERAs, endothelin receptor antagonists; ETA, endothelin receptor A; ETB, endothelin receptor B; ET-1, endothelin-1; GWAS, genome-wide association studies; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NO, nitric oxide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5 inhibitors, phosphodiesterase type 5 inhibitors; PTGIR, prostaglandin I2 receptor; PTGIS, prostaglandin I2 synthase; PVR, pulmonary vascular resistance; RHC, right heart catheterization; sGC, soluble guanylate cyclase; WHO, World Health Organization.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive cardiopulmonary disease with no cure apart from a lung transplant. Small arteries in the lungs become overly constricted and force the right ventricle of the heart to work harder to overcome the increased resistance, creating heart damage in the form of right ventricle hypertrophy over time that can eventually be fatal. PAH has an estimated prevalence of 47.6–54.7 cases per one million adults,[1] and prognosis worsens with delayed treatment.[2] The normal course of treatment includes one or more PAH-specific pharmacologic treatments. There are four main classes of drugs approved for PAH: endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5 inhibitors), prostacyclin analogs or prostacyclin receptor agonists, and soluble guanylate cyclase (sGC) stimulators. However, there are many subclasses of PAH with different etiologies, survival rates, and possibly responses to treatment. There are currently 13 PAH-specific Food and Drug Administration (FDA)-approved drugs and each drug is often used in combination with another PAH drug of a different class (Table 1). At present, clinicians are unable to predict the most effective treatment for each patient. Individualized PAH treatment could have several benefits such as improved outcomes and reduced disease progression as a result of immediately identifying an effective drug regimen. Here, we briefly summarize the pathophysiology and clinical presentation of PAH and survey the current literature on inter-individual variability in pharmacological response in PAH patients.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION

PAH is hemodynamically defined as having mean pulmonary arterial pressure ≥20 mmHg, relatively normal left atrial pressure (≤15 mmHg pulmonary arterial wedge pressure), and pulmonary vascular resistance (PVR) ≥3 Wood units.[3] It is characterized by progressive thickening of pulmonary arteries, resulting in narrowed blood vessel lumens that require more force to pump blood through (Figure 1). Over time this increased load on the heart causes right ventricle hypertrophy, leading to eventual heart failure and death. The arterial thickening and subsequent vasoconstriction is caused by a combination of endothelial cell dysfunction and

TABLE 1 FDA-approved pharmacotherapy for the treatment of pulmonary arterial hypertension.

Drug class	Drug name	Brand name	PAH classification
Calcium channel blockers (CCBs)	Amlodipine	Katerzia, Norliqva, Norvasc	–
	Dilitiazem	Cardizem, Tiazac	Class I
	Nifedipine	Procardia	Class I
Endothelin receptor antagonists (ERA)	Ambrisentan	Letairis	Class II, III, and IV
	Bosentan	Tracleer	Class II, III, and IV
	Macitentan	Opsumit	Class II, III, and IV
Type IIA-Fc fusion protein[a]	Sotatercept[a]	–	–
Phosphodiesterase type 5 inhibitors (PDE5i)	Sildenafil	Revatio, Viagra	Class II, III, and IV
	Tadalafil	Adcirca, Alyq, Cialis, Tadliq	Class II, III, and IV
Prostacyclin analogs or prostacyclin receptor antagonists	Epoprostenol	Flolan, Veletri	Class III and IV
	Iloprost	Ventavis	–
	Treprostinil	Orenitram, Remodulin, Tyvaso	Class II (iv and oral only), III, and IV (iv only)
Soluble guanylate cyclase (sGC) stimulators	Riociguat	Adempas	Class II, III, and IV
Oral prostacyclin (PGI2) receptor agonist	Selexipag	Uptravi	Class I

Abbreviation: FDA, Food and Drug Administration.

[a]Sotatercept is not currently FDA approved for the treatment of pulmonary arterial hypertension. iv indicates intravenous.

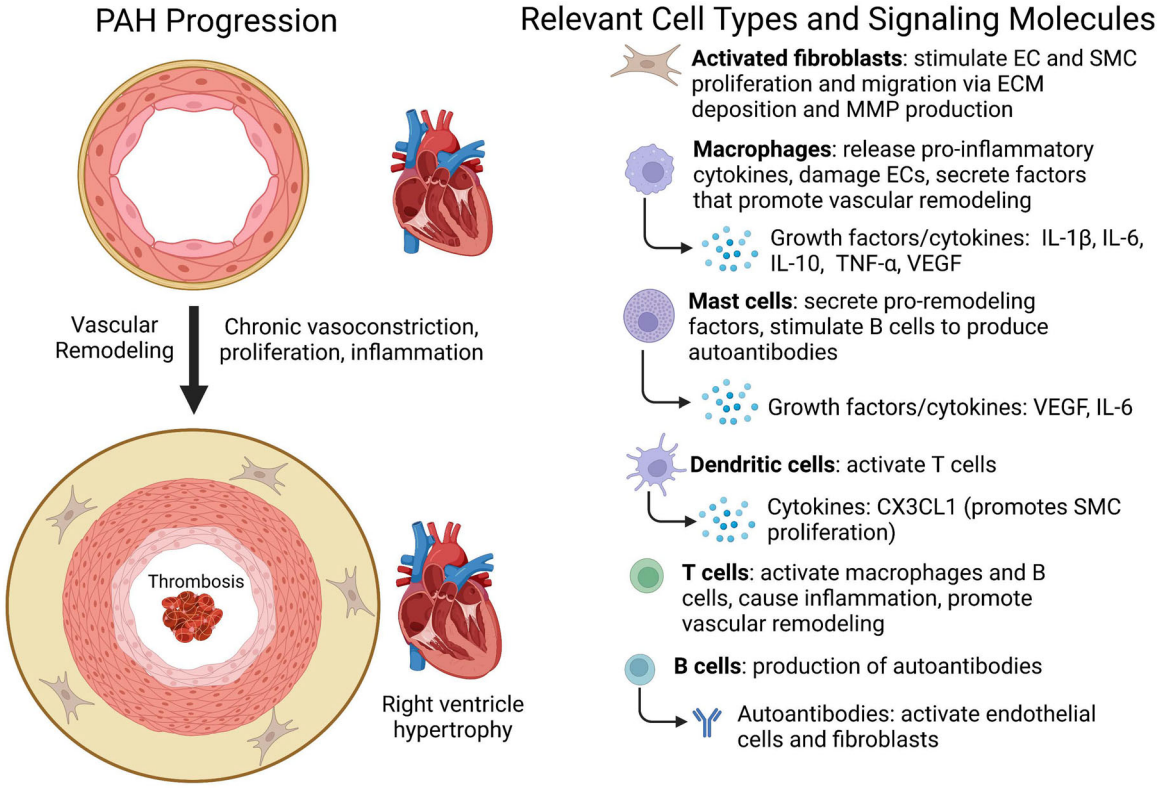

FIGURE 1 Pulmonary artery remodeling and known cellular interactions in PAH. Left: Diagram of PAH progression in pulmonary arteries and right ventricle of the heart. Right: Key cell types and signaling molecules involved in PAH pathology and progression. EC, endothelial cell; SMC, smooth muscle cell; VEGF, vascular endothelial growth factor.

proliferation, smooth muscle cell overproliferation, immune response, and other factors.[4,5] PAH is diagnosed by right heart catheterization (RHC) and can be found in any population, including pediatric patients, but is most commonly diagnosed in women with a female/male ratio of almost 2:1.[4,6] The severity of PAH is assessed by several parameters including World Health Organization (WHO) and New York Heart Association (NYHA) functional classes. Both scales use a four-point index (I–IV) with higher numbers associated with more severe symptoms even at low physical activity.

PAH is broken down into subtypes based on etiology including idiopathic (idiopathic pulmonary arterial hypertension [IPAH]) where there is no known underlying cause, heritable (heritable pulmonary arterial hypertension [HPAH]) where a genetic risk factor such as a *BMPR2* mutation is present, PAH associated with other conditions such as connective tissue disease or schistosomiasis (APAH), and PAH induced by drugs or toxins. IPAH is the most prevalent subtype and is responsible for more than 50% of all PAH cases.[7] However, it is unclear if these clinical subgroups constitute a single heterogeneous disease, but there are some known differences between classifications such as differing survival rates. PAH associated with congenital heart disease (CHD) and HIV (67% and 64%, respectively) has the highest 7-year survival rates of PAH subtypes and portopulmonary hypertension and connective tissue disease have the lowest survival rates (29% and 35%, respectively).[2] In addition, PAH associated with connective tissue disease (APAH-CTD) is less responsive to PAH therapies than patients with IPAH.[8] PAH is a common complication in patients with CHD and is the most preventable form of PAH.[9] Surgical correction in pediatric patients is the most effective form of prevention and treatment, and studies have found a correlation between acute vasoreactivity and improved surgical outcome and survival.[10,11]

HPAH is a common subtype and at least 16 PAH risk genes have been identified.[12,13] *BMPR2* mutations are the most frequent, with more than 70% of HPAH cases identified to have a *BMPR2* mutation.[14] PAH patients with *BMPR2* mutations often develop more severe disease at a younger age and are potentially at increased risk of death.[15] BMPR2 is highly expressed on vascular endothelial cells in healthy lungs and forms a complex with ALK1 or ALK2 receptors. BMP9 (encoded by *GDF2*) and BMP10 ligands activate the complex with coreceptor ENG and protect against apoptosis and excessive proliferation.[12] Loss of BMPR2 causes endothelial

dysfunction, transition to a mesenchymal cell phenotype, and overproliferation of smooth muscle cells.[12] Mutations in *ALK1*, *ENG*, *SMAD* genes (downstream mediators of BMP signaling), and *CAV1* (protein component where BMP receptors are located, may be required for initiation of BMP signaling) can also cause PAH.[12] *SOX17*, *HLA-DPA1/DPB1*, and *IL6* promotor variants have also been associated with PAH disease risk.[16,17] While genetic variation has an established role in PAH development, it may also impact response to treatment as discussed later.

Patients with PAH are often prescribed drug treatment paired with an exercise program and undergo regular, lifelong evaluations to monitor disease progress and treatment efficacy. There are 13 medications currently approved for PAH in the United States and a combination of these is recommended, even at the beginning of treatment.[18] ERAs, prostacyclin analogs/receptor agonists, PDE5 inhibitors, and sGC stimulators are the four main classes of PAH drugs (Figure 2). ERAs act upon the endothelin-1 (ET-1) receptors, ETA and ETB, and repress their activation. When stimulated by ET-1, ETA receptors cause vasoconstriction, smooth muscle cell proliferation, production of reactive oxygen species, and promotion of an inflammatory response, while ETB receptor activation leads to vasodilation.[19] Prostacyclin analogs activate the prostacyclin pathway, which aids PAH patients in vasodilation, improvement of endothelial dysfunction, anti-proliferation, and strengthening of right heart contractions amongst other benefits.[20] The newest FDA-approved drug for PAH, Selexipag, is an oral prostacyclin receptor agonist.[21] PDE5 inhibitors act on the nitric oxide (NO) pathway. In this pathway, NO binds to sGC and leads to the synthesis of cyclic guanosine monophosphate (cGMP), which causes vasodilation and reduction of smooth muscle cell proliferation. PDE5 inactivates cGMP in the lungs, so PDE5 inhibitors repress this inactivation and allow for the positive effects of cGMP to occur in PAH patients. One of the newer PAH drug classes is sGC stimulators, which activate sGC without NO. Riociguat is currently the only PAH drug in this class and was FDA approved in 2013. Calcium channel blockers (CCBs) can also be used to treat PAH, but only in a small subset of patients.

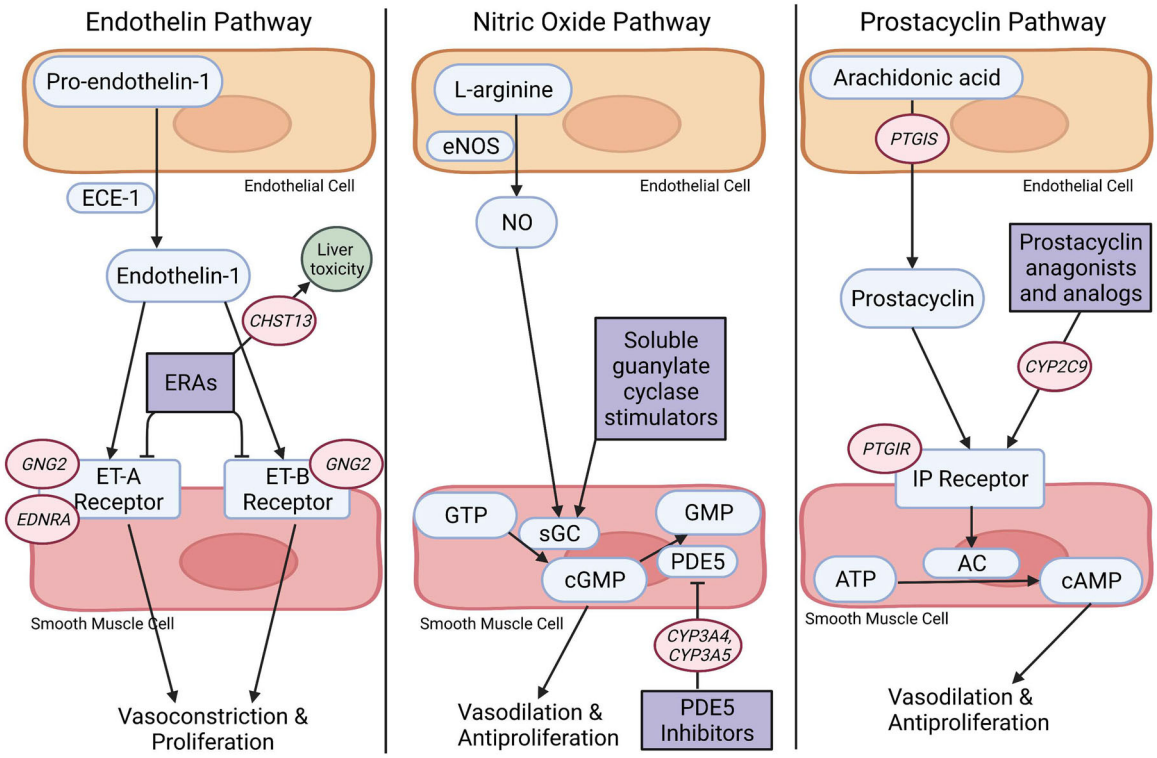

FIGURE 2 Mechanisms of action of PAH drugs (purple boxes) in the three biological pathways they act upon (blue) and related pharmacogenes (red ovals). AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ECE-1, endothelin converting enzyme 1; eNOS, endothelial nitric oxide synthase; ERAs, endothelin receptor antagonists; ET-A receptor, endothelin receptor type A; ET-B receptor, endothelin receptor type B; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IP receptor, prostacyclin receptor; NO, nitric oxide; sGC, soluble guanylyl cyclase; PDE5, phosphodiesterase type 5; PTGIS, prostacyclin synthase.

CCBs inhibit a subset of calcium channels, reducing calcium influx into smooth muscle cells, causing vasodilation.

Although not yet FDA approved as of April 2023, recent studies indicate sotatercept is beneficial in the treatment of PAH. Several studies have shown sotatercept's impact in the treatment of symptomatic PAH (WHO functional Class II and III). In the phase-2 study, PULSAR, sotatercept showed a significant, dose-dependent reduction of PVR at 24 weeks compared to placebo in patients on maximum tolerated PAH therapy.[22] In STELLAR, a phase-3 study, sotatercept demonstrated a significant increase in 6-min walk distance (6MWD, a commonly used test to measure exercise capacity in PAH) at 24 weeks compared to placebo.[23] Sotatercept is a fusion protein that consists of the extracellular domain of human actin receptor type IIA linked to the Fc domain of human IgG.[22] This novel drug binds actins and growth differentiation factors to re-establish balance between PAH growth promoting and signaling pathways.[23]

DIFFERENTIAL DRUG RESPONSE BY VASORESPONSIVENESS

A small portion of PAH patients are considered vasoresponsive, which may dramatically improve clinical outcomes and offer new treatment options. During a diagnostic RHC in PAH, a pulmonary vasodilator challenge is performed to test for vasoreactivity using a short-acting pulmonary vasodilatory agent such as inhaled NO, nebulized epoprostenol, inhaled treprostinil, inhaled iloporst, intravenous adenosine, or intravenous epoprostenol.[24] Pulmonary arterial pressure is measured at rest and after drug exposure and the test is considered positive if there is a decrease of ≥10 mmHg in mean pulmonary artery pressure that reaches an absolute value of ≤40 mmHg without a decrease in cardiac output. Pulmonary vasoreactivity testing is typically reserved for IPAH, HPAH, or drug-induced PAH patients considering high-dose CCB treatment. In all other forms of PAH and PH, results can be misleading.[25] Positive vasoreactivity tests are relatively rare and patients can lose vasoreactivity over time. Acute responders can lose responsiveness to CCBs within a year of treatment while long-term vasoresponders have sustained improvement in hemodynamics from CCB treatment alone after at least 1 year and are in NYHA functional class I or II.[26] One study reported that only 13% of IPAH patients are acute vasoresponders and 7% are long-term responders.[26] Another study that included all subtypes of PAH found that only 2.4% were long-term responders, with the highest frequency of responders occurring in anorexigen-associated PAH (9.4%).[27] Patients with *BMPR2* mutations may be even less likely to be vasoresponsive (3% vs. 13%).[15,28] Long-term responders are not only more likely to have less severe PAH,[26] but can also benefit from treatment with CCBs.[27,29] Long-term responders have significantly better survival than non-responders, with one study in patients with PAH reporting that long-term CCB responders had a survival rate of 97% after 7 years while non-responders revealed a 48% survival rate after 5 years.[26] An accurate vasoresponsive diagnosis is critical, as use of CCBs in nonresponsive patients can cause serious adverse events such as hypotension, decreased systemic oxygen saturation, and worsen right ventricular function.[30–33] It remains unclear why certain patients respond well to CCB therapy while it can be deadly in most PAH patients. Although vasoreactivity testing cannot definitively determine whether patients will experience clinical improvement with CCBs, decoding the mechanism of vasoresponsive PAH could guide new therapeutic approaches in PAH.

Vasoreactivity in PAH may partly be explained by genetic variation. A study observed that 35% of patients with silent *BMPR2* mutations displayed acute vasoreactivity while only 4% of patients with dysfunctional *BMPR2* mutations were responders.[28] While the *BMPR2* gene is strongly implicated in some PAH cases, other genes not as directly connected to PAH have also been implicated. Vascular smooth muscle contraction genes were found to be more enriched in circulating lymphocytes of vasoresponsive patients than non-responsive patients with PAH.[34] No genetic tests to predict acute and long-term vasoreactivity have yet been proposed, but such tests could reduce the need for periodic pulmonary vasodilator challenge tests to confirm continued responsiveness.

SEXUAL DIMORPHISM IN PAH DRUG RESPONSE

It is well-established that PAH occurs more commonly in women, although men have decreased survival rates.[35–37] This may be partially attributable to estrogen levels, but there is conflicting evidence in the role of estrogen in PAH pathology especially between humans and models of PAH known as the "estrogen paradox."[38–40] Researchers have recently observed benefits of increased estrogen levels on PAH outcome and severity.[41–43] In the study by Wu et al.,[43] higher estradiol and estradiol/testosterone levels were associated with risk of PAH diagnosis (odds ratio [OR] of 3.55 in estradiol and 4.30 in estradiol/testosterone), while higher testosterone and progesterone

were associated with a reduced risk (OR of 0.48 in testosterone and 0.09 in progesterone). The same study found that the 5-year survival rate in patients also differed significantly as men with higher estradiol levels had a survival rate of 38.6% while those with lower estradiol levels had a survival rate of 68.2%. Sex-based differences in treatment response to PAH-specific medications have also been observed in several studies (Table 2). ERAs tend to be more effective and have greater benefit in women, with women having significantly greater improvement in 6MWD than men treated with ERAs.[44] Additionally, women on ERAs have significantly reduced risk of clinical events compared to men[44,45] Little research has been performed focusing on sex differences in PDE5 inhibitor treatment, and there are conflicting results between studies. One study found a correlation with better prognosis in women than men on PDE5 inhibitors.[45] Another study focused on tadalafil found that men had better 6MWD outcome and were more likely to achieve minimum difference in outcome.[46] Yet another study in a Spanish registry observed that male sex was a predictor of favorable response to PDE-5i when used as mono- or add-on therapy.[47] Further research is needed on this topic to elucidate interactions between sex and PDE5 inhibitor treatment response. A single study looked at sex and prostacyclin analog treatment such as beraprost and epoprostenol and found no significant difference in survival between sexes.[45] While the correlation between ERA safety in women is stronger than the limited evidence in other PAH drug classes, more research is needed to affirm the findings. While there is very limited evidence presently available for sex-based differences in treatment response, it is intuitive that there may be a distinction between sexes based on known differences in PAH epidemiology, prognosis, and the role of estrogen in PAH.

DIFFERENCES IN DRUG RESPONSE BASED ON RACE, ETHNICITY, AND ANCESTRY

Differences in PAH outcomes have also been suggested based on race and ethnicity. At least two-thirds of PAH patients are white and there is an overrepresentation of black people and an underrepresentation of Hispanics and Asian/Pacific Islanders in PAH based on the general population.[51,52] Multiple analyses have found increased mortality in nonwhite patients, especially black patients, although two analyses of the REVEAL study suggested that mortality is somewhat higher in white patients than black patients or that there is no difference in survival based on race at all.[48,49,53–55] Recent data in large national cohorts also suggests reduced mortality in Hispanic patients and patients with Native American ancestry.[50] Self-reported Hispanic patients ($n = 290$) exhibited significantly reduced mortality versus non-Hispanic white patients ($n = 1970$) after global meta-analysis (hazard ratio [HR]: 0.60 [0.41–0.87], $p = 0.008$). Although not significant, increasing Native American genetic ancestry appeared to account for part of the observed mortality benefit (HR: 0.48 [0.23–1.01], $p = 0.053$) in the two national registries. An inpatient mortality benefit was also observed for Hispanic patients ($n = 1524$) versus non-Hispanic white patients ($n = 8829$; OR: 0.65 [0.50–0.84], $p = 0.001$) and for Native American patients ($n = 185$) versus non-Hispanic whites (OR: 0.38 [0.15–0.93], $p = 0.034$). Importantly, this study did not account for sociocultural factors that may also underly these associations and therefore these apparent differences may not necessarily be driven by genetics. One registry study with 98 Hispanics also found a significant survival benefit for Hispanics, but when adjusted for social factors such as access to healthcare, education level, and income, there was no longer an association between Hispanic ethnicity and survival.[56] Researchers have also found a sex difference in PAH prevalence between racial groups. A higher ratio of women with PAH was found in nonwhite populations than in the white population.[52] The significance of these findings remains debated, but there is potentially some variation between PAH patient racial populations, and this may extend into response to PAH drug treatment.

One study exploring possible differences in response to ERAs based on race found no significant difference but did note that white patients had fewer clinical events and a large increase in 6MWD while black patients had a small reduction in 6MWD with ERA treatment.[44] The authors propose a potential explanation for this observed difference, citing that black people have higher circulating ET-1 levels and a greater increase in ET-1 in response to stress, so ERAs are not able to sufficiently inhibit ERs. No studies on differential treatment response in PDE5 inhibitors based on race and ethnicity have been performed in the context of PAH, but tadalafil was shown to be as effective and well-tolerated in black and Hispanic patients as in white patients with erectile dysfunction.[57,58] Likewise, no studies have yet been performed examining the possible influence of race and ethnicity on prostacyclin analog treatment response.

It is important to remember that any possible drug response differences between races or ethnicities may not represent biological differences, but may be more explained by lack of representation in clinical trials and by systemic racial/ethnic disparities in healthcare systems, including differences in socioeconomic status,

TABLE 2 Studies of differential drug response by sex and race/ethnicity.

Study	Drug/drug class	Patients (*n*)	Female, *n* (%)	Race distribution, *n* (%)	PAH etiology, *n* (%)	NYHA or WHO functional class, *n* (%)	Summary of findings
Gabler[44] (2012)	ERAs	Treated: 773 Untreated: 257	Treated: 615 (80) Untreated: 279 (78)	Treated White: 577 (75) Black: 45 (6) Other: 151 (20) Untreated White: 259 (73) Black: 20 (6) Other: 78 (22)	Treated IPAH: 478 (62) APAH-CTD: 216 (28) APAH-CHD: 54 (7) Other: 23 (3) Untreated IPAH: 229 (64) APAH-CTD: 86 (24) APAH-CHD: 30 (8) Other: 11 (3)	NYHA Treated I–II: 256 (33) III–IV: 516 (67) Untreated I–II: 114 (32) III–IV: 243 (68)	Women treated with ERAs had greater improvement in 6MWD than did men on ERAs. ERAs significantly reduced the risk of clinical events among women
Mathai[46] (2015)	Tadalafil	405	318 (78)	White: 326 (81)	IPAH: 247 (61) APAH-CTD: 95 (24) APAH-CHD: 47 (11) Other: 16 (4)	WHO I: 4 (1) II: 130 (32) III: 264 (65) IV: 7 (2)	Men were significantly more likely to achieve minimum difference in outcome than women on tadalafil
Kozu[45] (2018)	Monotherapy or combination therapy of prostacyclin analogs, ERAs, and PDE5 inhibitors	129	95 (74)	Not reported	IPAH/HPAH: 45 (35) APAH-CTD: 41 (32) APAH-CHD: 31 (24) Other: 12 (10)	WHO III–IV: 52 (40)	ERA and PDE5i use in women correlated with a better prognosis than in men. No sex difference was found in response to prostacyclin analogs
Medrek[48] (2020)	CCB, ERA, PDI, prostacyclin (survival study)	3046	2404 (79)	White: 2202 (72) Black: 393 (13) Hispanic: 263 (9) Asian: 100 (3) Other: 88 (3)	IPAH: 1425 (47) HPAH: 82 (3) APAH-CTD: 810 (27) APAH-CHD: 297 (10) Other: 432 (14)	NYHA I: 24 (3) II: 130 (16) III: 404 (45) IV: 125 (10) Unknown: 147 (26)	Prognosis for patients with severe PAH remains poor despite advancements in PAH therapy
Farber[49] (2015)	N/A	2171	1619 (79)	White: (72) Black: (13) Hispanic: (9) Other: (6)	IPAH: 950 (47) HPAH: 64 (3) APAH-CTD: 236 (24) APAH-CHD: 236 (12) Other: 270 (13)	NYHA I: 162 (8) II: 792 (39) III: 991 (49) IV: 94 (5)	In comparison to other races or ethnicities, white PAH patients have relatively poor 5-year survival rates.

(Continues)

TABLE 2 (Continued)

Study	Drug/drug class	Patients (*n*)	Female, *n* (%)	Race distribution, *n* (%)	PAH etiology, *n* (%)	NYHA or WHO functional class, *n* (%)	Summary of findings
Karnes[50] (2020)	N/A	2515	1973 (78)	White: 1970 (78) Black: 255 (10) Hispanic: 290 (12)	IPAH & HPAH	Not reported	Hispanic PAH patients have improved survival
Gaznabi[51] (2020)	N/A	10,300	Not reported	White: (67) Black: (19) Hispanic: (8) Asian: (2) Native American: (<1) Unknown: (3)	Primary or secondary (APAH)	Not reported	Patients of Asian/Pacific Islander decent had longer hospital stays, higher mortality scores and higher mean readmission scores than other racial groups.

Abbreviations: APAH-CHD, PAH associated with congenital heart disease; APAH-CTD, PAH associated with connective tissue disease; CCB, calcium channel blocker; ERA, endothelin receptor antagonist; HPAH, hereditary PAH; IPAH, idiopathic pulmonary arterial hypertension; NYHA, New York Heart Association; PDI, phosphodiesterase inhibitor; WHO, World Health Organization.

education level, access to care, quality of care, and environmental exposures. Historically, the biological construct of ancestry has been conflated with the sociocultural constructs of race and ethnicity. This has led to erroneous conclusions that genomic associations with disease or drug response are driven by biological rather than social influences.[59,60] The majority of PAH clinical studies recruit at least 78% white patients and have been unable to recruit a diverse patient population with sufficient sample size to establish differential effects by race/ethnicity and accurate PAH subtype prevalence by race/ethnicity.[52] A study by Pakish et al.[55] aimed to investigate the association of race, disease characteristics, and insurance status with clinical PAH outcomes. They found that when adjusting for only age and PAH functional class, black patients had a greater mortality risk than white patients. However, when adjusting for insurance status (Medicare, Medicaid, private, or self-pay), there was no difference in survival rate between the two groups.[55] These observations underscore the importance of characterizing social determinants of health in determining influences on disease and drug response, especially when genetic analyses are being performed. Concurrently, while there is little concrete evidence on any PAH drug response differences between races or ethnicities, any potential racial variation in PAH drug response may also be due to genetic polymorphisms that are more prevalent in one race or another, and several pharmacogenomic differences are explored in the next section.

PHARMACOGENOMICS IN VARIABLE PAH DRUG RESPONSE

Genetic variants like those in the *BMPR2* gene have been associated with PAH development, outcomes, and treatment response.[15,61] Genetic differences outside of those implicated in PAH can also affect individual response to treatment. Variants in genes encoding for enzymes that metabolize PAH drugs can alter enzyme function, leading to variable metabolic processing of the drug and subsequent drug response. Cytochrome P450 (CYP) enzymes are the main class of drug-metabolizing enzymes in humans and large variations in metabolizing ability can be due to genetic factors. In fact, approximately 90% of variation in hepatic CYP3A4 (one of the most abundant enzymes in the liver) activity is under genetic control.[62] Many PAH medications are metabolized by CYPs, and thus a relatively large amount of research has been performed on the impact of CYP genetic variants and response to PAH medications (Table 3).

TABLE 3 Clinical pharmacogenomic studies in pulmonary arterial hypertension.

Study	Gene(s) investigated	Patients (*n*)	Female, *n* (%)	Race or national origin, *n* (%)	PAH etiology, *n* (%)	Method(s) used	Summary of findings
Shon[63] (2011)	*CYP3A5*	21	0 (0)	Korean: 21 (100)	No PAH	Single dose PK study	Disposition of PDE5Is are differently influenced by *CYP3A5*3* genotype
de Denus[64] (2018)	*CYP2C9*, *CYP3A4*, and *CYP3A5*	85	39 (46)	White: 78 (92) Black: 4 (5) Other: 3 (3)	No PAH, heart failure with preserved ejection fraction	Genotyping (PLEX ADME PGx Pane), dose concentrations	*CYP3A4*22* variant associated with high dose-adjusted concentration of sildenafil
Coons[65] (2021)	*CYP2C8*, *CYP2C9*, and *ABCC4*	15	11 (73)	White: 14 (93)	IPAH: 6 (36) APAH-CTD: 6 (43)	Treatment discontinuation, genotyping (TaqMan® allelic discrimination assay), PK analysis	*CYP2C9* decreased function alleles (*2, *3) are significantly associated with lower treatment persistence of oral treprostinil
Wang[66] (2020)	*PTGIS*	230	164 (71)	Chinese: 230 (100)	IPAH: 230 (100)	WGS or WES with splice sites; discovery and replication cohort	3 rare loss-of-function variants in the *PTGIS* gene identified
Calabrò[67] (2012)	*EDN1* and *EDNRA*	98	64 (65)	White: (100)	IPAH: 34 (35) APAH-CTD: 21 (21) APAH-CHD: 43 (44)	Genotyping (ABI PRISM BigDye® Terminator v3.1 Ready Reaction Cycle Sequencing Kit)	Potential link between *EDNRA* genotype and PAH susceptibility and severity
Benza[68] (2015)	*EDN1*, *EDNRA*, *EDNRB*, and 26 genes encoding proteins involved in response to endothelin	715	562 (79)	White: 715 (100)	IPAH/HPAH: 380 (53) Other: 330 (47)	GWAS, genotyping (Illumina Omni Express platform)	rs11157866 associated with clinical improvement in ERA-treated patients
Yorifuji[69] (2018)	231 genes involved in drug metabolism, excretion, and transport	66	51 (77)	Japanese: 66 (100)	IPAH/HPAH: 13 (20) APAH-CTD: 18 (27) APAH-CHD: 4 (6) Other: 31 (47)	Affymetrix Drug Metabolizing Enzymes and Transporters (DMET) Array	Two SNPs in *CHST3* and *CHST13* were significantly associated with bosentan-induced liver injury

Note: *ABCC4*: ATP Binding Cassette Subfamily C Member 4; *PTGIS*: Prostaglandin I2 Synthase; *EDN1*: Endothelin 1; *EDNRA*: Endothelin Receptor Type A; *EDNRB*: Endothelin Receptor Type B.

Abbreviations: APAH-CHD, PAH associated with congenital heart disease; APAH-CTD, PAH associated with connective tissue disease; HPAH, hereditary PAH; IPAH, idiopathic pulmonary arterial hypertension; WES, whole exome sequencing; WGS, whole genome sequencing.

CYP3A5 and CYP3A4 are the main metabolizers of PDE5 inhibitors, and genetic polymorphisms may contribute to variability between individuals, especially for CYP3A5 polymorphisms and vardenafil.[63,70] The CYP3A5*3 allele (rs776746) creates enzymes with reduced activity, and one study showed that individuals with the CYP3A5*3/*3 genotype had higher mean plasma concentrations of sildenafil than individuals with a CYP3A5*1/*3 or CYP3A5*1/*1 genotype.[63] This discrepancy in pharmacokinetic profile between genotypes may lead to variable clinical response. The CYP3A5 allelic distribution may also provide a genetic link to potential racial disparities in PDE5 inhibitor response. CYP3A5*3 allele frequency varies from approximately 50% in African Americans, 70% in Chinese, to 90% in Caucasians.[71,72] The CYP3A5*1 allele is found in up to 15% of Caucasians, 60%–90% of African descent, and 23%–40% of Asians.[73] In addition to CYP3A5, the CYP3A4*22 (rs35599367) variant may also be associated with peak plasma concentrations of sildenafil, but this only reached significance in a white population.[64]

CYP2C9, prostaglandin I2 synthase, and prostaglandin I2 receptor variants have been shown to affect response to prostacyclin analogs. In a study on oral treprostinil treatment, 83% of patients with at least one decreased function (*2, rs1799853) or nonfunctional (*3, rs1057910) CYP2C9 allele discontinued oral treporostinil treatment due to adverse events.[65] Some patients were able to switch to a different route of treprostinil administration, but the study did not report if the adverse events stopped when transferred to an alternative formulation and route of administration. Some of the patients in the study had previously been taking treprostinil in its injectable form before switching to the oral form for the study, but it is unknown if these patients had any prior adverse events from taking the drug. It is, therefore, unclear whether the potential adverse event problem is related to treprostinil itself or just the oral formulation.

In the lungs, prostaglandin I2 synthase (*PTGIS*, CYP8A1) is mainly found in endothelial cells and plays a role in cell viability and apoptosis, which is critical to PAH development.[74,75] It is also downregulated in lung vasculature of patients with severe PAH.[74] Rare *PTGIS* variants were associated with improved response to iloprost, although the clinical effect remains to be researched.[66] However, rare variants in the prostaglandin I2 receptor (*PTGIR*) were found to decrease the binding affinity of iloprost and cause defective cAMP production.[76,77] The R212H variant in particular had adverse effects on receptor activation.[77] The clinical implications of these rare variants have not been explored, but these studies may provide some evidence for avoiding the prescription of prostacyclin analogs in patients with such variants.

Little research has been performed on the potential effect of genetic polymorphisms on ERA response, but researchers have suggested gene candidates for this research including a His323His variant in endothelin receptor type A (*EDNRA*), the major site of action for ERAs.[67] In one study, patients with the rs11157866 variant in the gene *GNG2*, which has a role in apoptosis, proliferation, inflammation, and drug response, showed improved walk distance after 12 months of ERA treatment compared to patients without the variant.[68] Genomic variants can also be associated with increased likelihood of adverse events. A recent study found that two SNPs in *CHST3* and *CHST13* (genes responsible for proteoglycan sulfation) were significantly associated with bosentan-induced liver injury.[69] This highlights the importance of testing for genetic variants to reduce risk of harm to patients and take a step toward individualized medicine. While little is known about pharmacogenomic influences on PAH drug response, current evidence warrants further investigation of these and other potential factors that may allow avoidance of adverse events in some patients. Pharmacogenomic research and implementation in clinical settings could provide the ability to predict clinical response to therapy, allowing for more efficient therapeutic decisions.

FUTURE DIRECTIONS

While the future promise of personalized medicine draws closer, there is potential to apply these techniques to PAH and improve clinical practice in a patient population with great need. There are currently many gaps in knowledge of this devastating disease, its subtypes, and the best way to treat it. Drug response research based on pharmacogenomics for the newest PAH drug class, sGC stimulators, has yet to be explored, but riociguat dose exposure shows moderate interindividual (60%) and low intraindividual (30%) variability in PAH patients.[78] One of the greatest issues facing PAH research is the rarity of the disease. It is difficult for studies to recruit large numbers of patients, especially for different PAH subtypes and with representative racial diversity. Larger, more focused studies on potential factors impacting PAH drug response are needed to elucidate new findings that can be applied in a clinical setting and in future research. Further research is needed especially in the area of vasoresponsiveness, as an understanding of what differentiates acute responders, long-term responders, and non-responders could inform the development of new drugs or drugs to sensitize patients to CCB therapy and

allow them to benefit from CCB therapy. Drug-drug interactions and combinations with non-PAH drugs are also important considerations, especially when the drugs act upon, induce, or inhibit relevant metabolic pathways. Treatment options with reported potential have yet to be explored include repurposing of current drugs, such as HMG-CoA reductase inhibitors (statins) and some tyrosine kinase inhibitors, and gene therapy.[76]

Another challenge for researchers is finding common pathways to target for the treatment of all subtypes of PAH, but recent evidence suggests that the current classification of PAH subtypes may not be optimal. Rather than etiologic subclasses, classification based on biomarkers may be more useful and classification based on endophenotypes should be explored. Other fields have advanced precision medicine through identification of endophenotypes defined by distinct biologic mechanisms that are identifiable with biomarkers. In asthma, various asthma phenotypes that are characterized by specific biomarkers have been identified.[79,80] Biological drugs can be used to treat severe persistent asthma according to Type 2 inflammation biomarker profiles based on the role of Type 2 (Th2) lymphocytes. Increasingly, acute respiratory distress syndrome is being recognized as a collection of heterogeneous syndromes with potentially distinct responses to therapy.[81,82] Research aimed at discovering distinct mechanisms of syndromes within a disease has the potential to identify biomarkers that predict drug response, to refine pathways contributing to disease pathogenesis, and also to streamline clinical trials focused on differential treatment effects through enrichment for specific biological mechanisms. The field of oncology provides many excellent examples of defining endophenotypes and predicting drug response based on molecular mechanisms of individual cancers.[83,84]

A new perspective was recently proposed that suggests PAH can be classified into four distinct immune endophenotypes rather than the many clinical subtypes listed today, as none of those subtypes had a distinct immune signature.[85] These four immune endophenotypes are based on distinct blood cytokine profiles, have different disease severity and survival rates, and could stimulate new mechanistic studies and inform the best patient-specific treatment options.[85] Other literature suggests that endophenotypes based on transcriptomics or proteomics can predict survival[86,87] and it is likely that these differences in profiles and signatures could also be predictive of drug response. More studies utilizing these new systems of classification are needed to determine if molecular endophenotypes would provide more granular, tailored therapy and better predict optimal treatment for individual patients, a major goal of the Redefining Pulmonary Hypertension through Pulmonary Vascular Disease (PVD) Phenomics (PVDOMICS) initiative.[88] PVDOMICS aims to integrate genomics, metabolomics, proteomics, tissue functioning and other clinical traits into the classification of PVD. By performing comprehensive, deep phenotyping across 1000 participants with various types of PH, and 500 participants without or at risk for PH, PVDOMICS is aimed at deconstructing the traditional classification and defining new subclassifications of patients with PH.

The complexity of PAH suggests that agnostic approaches, which do not rely on prior biological knowledge, may be more fruitful in identifying pathogenic mechanisms of PAH. Emerging approaches that have not been sufficiently applied to PAH disease and drug response research include bioinformatics like genome-wide association studies (GWAS), RNA-seq, and single cell sequencing approaches. Such methodologies could uncover new biomarkers and mediators of PAH and lead to the development of new therapies.

CONCLUSION

PAH is a rare but devastating disease whose only cure is a lung transplant and there is still a need for better treatments. While research continues to better understand PAH pathophysiology and develop new treatments, in the meantime we may be able to better utilize the medications we currently have to delay PAH progression and extend the lifespan and healthspan of patients suffering from PAH. Current research has found that ERAs may be more effective in women, but race-based differences have been unclear and difficult to study, as the vast majority of patients in clinical trials have been white. There has been more research on the impact of pharmacogenomics on PAH drug response. The *CYP3A5*3* allele may reduce response to PDE5 inhibitors and *CYP2C9*2* and **3* alleles were associated with more frequent adverse events when treated with oral treprostinil, although more research should investigate if this is the case with other prostacyclin analogs. Rare *PTGIS* variants may improve iloprost response while rare *PTGIR* variants may diminish iloprost response, but more research is needed on the potential clinical effects and if they extend to other prostacyclin analogs. Additionally, patients with the *GNG2* rs11157866 variant have better outcomes when treated with ERAs. Pharmacogenomics can also be used to prevent adverse reactions, as in the case of patients with two SNPs in CHST3 and CHST13 were prone to liver injury from bosentan treatment. Considering factors such as sex and pharmacogenomic variants when prescribing treatment could reduce the time required to find an effective treatment, slowing

disease progression and extending the lives of PAH patients.

AUTHOR CONTRIBUTIONS

Elise Miller and Jason Karnes: conceptualized the idea. **Elise Miller and Chinwuwanuju Sampson**: contributed to literature search. **Elise Miller, Chinwuwanuju Sampson, Ankit Desai, and Jason Karnes**: prepared the manuscript. All authors meet criteria to qualify as authors, have contributed sufficiently to the manuscript, and have reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated.

ETHICS STATEMENT

Our manuscript is a review article of the existing literature on the topic. There is no research or direct use of any animal or human data or tissue, thus no ethical requirements were relevant for this paper. The corresponding author accepts full responsibility for this published work.

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