REGULAR ARTICLE

Genetic Counseling and Testing for Pulmonary Arterial Hypertension in the United States

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INTRODUCTION

Group 1 pulmonary arterial hypertension (PAH) refers to a set of rare proliferative vascular diseases that result in a marked increase in pulmonary arterial pressure and resistance due to narrowing of the pulmonary arterioles.[1] Vasoconstriction, fibrosis, cell proliferation, and thrombosis contribute to these pathological processes.[2] In some cases, PAH may be associated with risk factors such as drug or toxin exposure (eg anorexigens) or other diseases (such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis). When no underlying cause is found, PAH is labeled "idiopathic PAH" (IPAH). There has been increasing recognition that genetic factors play a role in the development of familial and sporadic IPAH.

Heritable PAH (HPAH) is a subgroup of PAH that includes cases with more than one affected family member (familial PAH [FPAH]) and/or cases with an established causative genetic variant, regardless of family history (ie, apparently sporadic IPAH found to have predisposing germline variant on genetic testing). The definition of HPAH also applies to genetically mediated pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (PVOD-PCH), which are pathologically distinct forms of PAH with hemodynamic similarities. In addition, some individuals with PAH presumed associated with anorexigen use[3] or congenital heart disease[4] have also been shown to have an underlying genetic cause.

While multiple single-gene causes and candidate genes for HPAH have been discovered (Tables 1 and 2), the *BMPR2* gene remains the most common and well-studied cause of HPAH. At least 10% to 40% of IPAH and 70% to 80% of FPAH have been shown to have an underlying pathogenic variant[10] and a proportion of PVOD-PCH has been shown to be caused by biallelic pathogenic variants in the *EIF2AK4* gene.[11,12] Inclusion of newly discovered PAH genes increases genetic test yield in FPAH to 92% to 95% (B.G., unpublished data, October 2021).

HPAH is predominately inherited in an autosomal-dominant pattern conferring a 50% risk for first-degree relatives to inherit the familial susceptibility variant. Most HPAH genes exhibit incomplete penetrance and variable expressivity, with the exception of *EIF2AK4*-mediated PVOD-PCH, which is completely penetrant and inherited in an autosomal-recessive pattern.

The purpose of this article is to offer a perspective on the current utility of genetic counseling and testing for PAH; to provide a framework for appropriate anticipatory guidance, supportive counseling, and incorporation of genetic test results into patient care; and to identify areas for future genetics research.

GENETIC COUNSELING

Genetic counseling refers to professional guidance and support provided

Key Words—pulmonary arterial hypertension, pulmonary hypertension, genetic counseling, genetic testing, PAH susceptibility variant
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Table 1. Genes With Well-Established Links to PAH

Gene	% of PAH cases[5]	Features of associated syndromic disease	Mode of inheritance	Penetrance of PAH
ACVRL1[a]	< 1%	HHT2 (OMIM: 600376): telangiectasias, recurrent epistaxis, arteriovenous malformations, gastrointestinal bleeding and anemia	AD	Incomplete
BMPR2[a]	75%[b]	N/A	AD	Incomplete. 14% in males; 42% in females
CAV1[a]	< 1%	N/A	AD	Incomplete
EIF2AK4[a]	10%-25% of sporadic PVOD-PCH[8]	N/A	AR	Complete
ENG[a]	< 1%	HHT1 (OMIM: 187300) telangiectasias, recurrent epistaxis, arteriovenous malformations, gastrointestinal bleeding and anemia	AD	Incomplete
GDF2[a]	< 1%	HHT5 (OMIM: 615506): telangiectasias, recurrent epistaxis, arteriovenous malformations, gastrointestinal bleeding and anemia	AD	Incomplete
KCNK3[a]	1%-3%	N/A	AD	Incomplete
SMAD9[a]	< 1%	N/A	AD	Incomplete
TBX4[a]	< 1%	Ischiocoxopodopatellar syndrome with or without PAH (OMIM: 147891): skeletal abnormalities, short stature, airway diverticulosis, congenital heart defects[9]	AD	Incomplete

Abbreviations: AD, autosomal-dominant mode of inheritance; AR, autosomal-recessive mode of inheritance; HHT, hereditary hemorrhagic telangiectasia; OMIM, online Mendelian inheritance in man; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

[a]Childhood and adult onset of PAH reported.[4,6,7]

[b]Heritable PAH: accounts for ~25% of idiopathic cases; rare cause of pulmonary veno-occlusive disease (OMIM: 265450).

Table 2. Genes With a Potential Link to PAH

ATP13A3	*SMAD1*
BMPR1B	*SMAD4*
KCNA5	*SOX17*
KDR	*TET2*

to patients and their relatives who seek to learn about the inherited nature of a disease, the recurrence risk in family members, and the availability of proactive measures such as clinical surveillance and/or genetic testing for an identified familial variant, when applicable. A key aspect of genetic counseling is also the interpretation and incorporation of genetic test results into clinical care. Genetic counseling is provided by trained specialists such as a geneticist or a genetic counselor and is regarded as a valuable and essential medical service by clients and providers.[13-15]

Several professional societies recommend genetic counseling with genetic testing (Table 3) for individuals with HPAH or IPAH, familial or sporadic PVOD-PCH, and for first-degree relatives once a familial susceptibility variant has been identified,[16-21] as well as for individuals with congenital heart disease–associated PAH,[20] anorexiant PAH,[18,21] and hereditary hemorrhagic telangiectasia–related PAH.[21]

Genetic counseling occurs in two steps, pretest and posttest (Table 4; Figure 1). Genetic counseling prior to undergoing genetic testing is essential to guide the patient or at-risk relative in making an informed decision about testing, and provides valuable disease-specific education and resources that are beneficial to the patient and their family members, even if genetic testing is not pursued.

Pretest genetic counseling begins with collection and assessment of the affected individual's medical and family history which can allow for the diagnosis of unrecognized familial disease, assessment of inheritance pattern, and identification of at-risk relatives in the family, as well as influence the choice of tests if a particular gene is suspected to be involved. Education surrounding PAH symptoms, inheritance, and the genetic testing process, including cost and insurance coverage, as well as benefits, limitations, and potential psychosocial risks of genetic testing, are addressed to allow thoughtful decision-making around testing. Ideally, genetic testing starts with an affected individual as explained in Table 4.

Posttest genetic counseling involves communication with the patient regarding the test result, its interpretation, recommendations for the patient if applicable, and recommendations for relatives based on the result and family history. Posttest genetic counseling also involves provision of resources including a family letter to assist in informing at-risk relatives regarding their potential risk for PAH and recommendations for additional evaluation.

Table 3. Professional Society Recommendations for Genetic Counseling, Genetic Testing and Clinical Surveillance

Professional society	Genetic counseling[a]	Genetic testing[a]	Cascade clinical screening in at-risk individuals with susceptibility variant	Cascade clinical screening in FDRs when HPAH family is genotype negative	Cascade clinical screening in FDRs of individuals with IPAH
American College of Chest Physicians, 2004[16]	Recommended for at-risk relatives in case of FPAH; IPAH should be advised of the option	Recommended for at-risk relatives in case of FPAH; IPAH should be advised of the option	Doppler echocardiogram	Doppler echocardiogram	Not addressed
American College of Cardiology Foundation/ American Heart Association, 2009[17]	Recommended for HPAH and FDRs at-risk for *BMPR2* mutation	Recommended for HPAH and cascade testing for BMPR2 mutation	Annual echocardiogram[b]	Not addressed	Not addressed
European Society of Cardiology/ European Respiratory Society, 2015[18]	Recommended for HPAH, IPAH, anorexiant PAH, and PVOD-PCH	Recommended for HPAH, IPAH, anorexiant PAH, HHT-related PAH, and familial or sporadic PVOD-PCH	Resting echocardiogram recommended. Consider repeating annually	Resting echocardiogram recommended. Consider repeating annually	Not addressed
American Heart Association–American Thoracic Society, 2015[19]	Recommended for IPAH and HPAH	Recommended for IPAH, HPAH, and FDR of genotype positive patients	Serial echocardiograms or other non-invasive studies	Screening with symptoms	Not addressed
European Pediatric Pulmonary Vascular Disease Network, 2019[20]	Recommended for HPAH and IPAH	Recommended for IPAH, HPAH, and FDR of genotype positive patients; consider for drug-induced PAH and CHD-related PAH	Echocardiogram every 1-3 years, initiate in childhood	Serial echocardiograms	Evaluation with symptoms
6th World Symposium on Pulmonary Hypertension, 2019[21]	Recommended for HPAH, IPAH, anorexiant PAH and FDR of genotype positive patients	Recommended for HPAH, IPAH, anorexiant PAH, HHT-related PAH and FDR of genotype positive patients	CPET and annual echocardiogram	Not addressed	Not addressed

Abbreviations: CHD, congenital heart disease; CPET, cardiopulmonary exercise test; FDR, first-degree relative; FPAH, familial pulmonary arterial hypertension; HHT, hereditary hemorrhagic telangiectasia; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease.

[a]FPAH, HPAH, IPAH, PAH, PVOD-PCH: refers to the affected individual.

[b]Refers to *BMPR2* variant carriers only.

GENETIC TESTING FOR PAH AND INTERPRETATION OF GENETIC TEST RESULTS

Due to genetic heterogeneity and an inability to distinguish the underlying genetic cause based on personal and family history in most instances, a comprehensive PAH gene panel including all genes with clear association to PAH is generally recommended and is similar in cost to performing single-gene analysis. If involvement of one gene is strongly suspected, single-gene testing with reflex to the panel in case of a negative result may be considered. Whole exome or whole genome sequencing are generally not needed for sporadic adult-onset IPAH as they have similar yield as a panel test but are more expensive. Whole exome or whole genome sequencing may be considered in large HPAH families with a negative result on panel testing, or in pediatric PAH due to the higher likelihood of novel gene discovery in these populations, and the involvement of genes that are not typically associated with PAH.[4]

Unlike many medical tests, the results of genetic testing for most disorders, including PAH, provide a probabilistic result rather than a binary genetic/not genetic outcome. Panel-based testing identifies multiple genetic variants, and these must be carefully interpreted by the testing laboratory to categorize each variant as pathogenic, likely pathogenic, variant of uncertain significance, likely benign, or benign based on the strength of evidence for or against pathogenicity.[22] While there may be ample evidence available to categorize some variants, other variants may lack evidence to classify as disease-causing or benign,

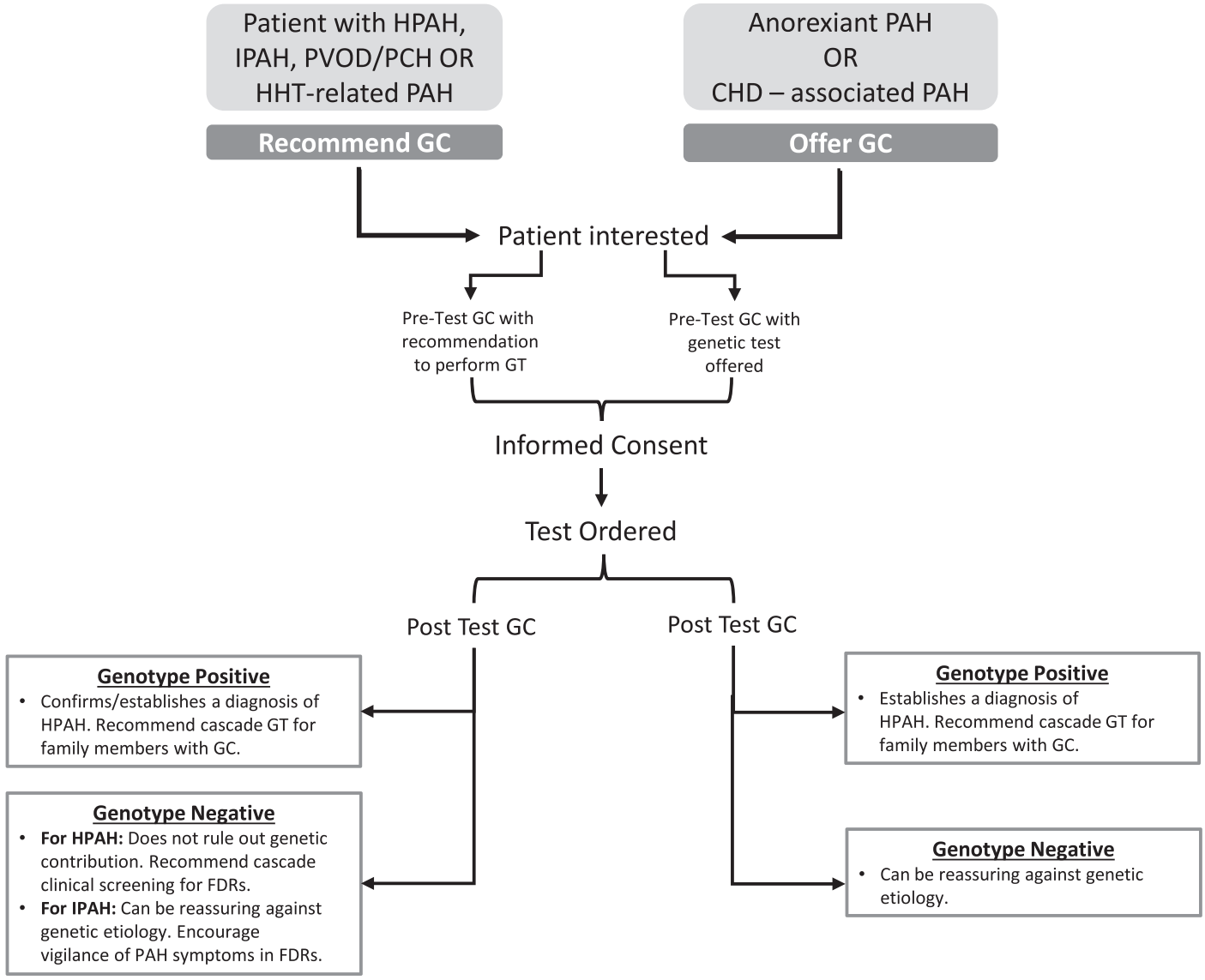

Figure 1: Framework for genetic counseling and testing in pulmonary arterial hypertension. CHD indicates congenital heart disease; GC, genetic counseling; GT, genetic testing; FDR, first-degree relative.

and are placed in the uncertain category. As genetic testing of PAH patients becomes more routine, new evidence is likely to result in reclassification of variants. The results are therefore complex, and best handled by professionals with in-depth genetics knowledge.

Genotype-Positive Result and its Integration Into Medical Care

Identification of a pathogenic or likely pathogenic variant in a PAH-associated gene is considered a positive result. Pinpointing a genetic variant causative of PAH establishes the diagnosis of HPAH in individuals previously diagnosed with IPAH or associated PAH, and confirms genetic etiology in those with FPAH. On occasion, the involvement of a specific gene could have medical management implications for the affected individual. For example, identification of biallelic *EIF2AK4* mutations establishes a diagnosis of PVOD-PCH without a lung biopsy, as well as guides treatment, as vasodilators are contraindicated[8] while early referral for lung transplantation is indicated.[8,19] Identification of *TBX4*-mediated disease in a case of resolved persistent pulmonary hypertension of the newborn (PPHN) would indicate a need for annual surveillance with echocardiogram due to the risk of recurrence.[6] Importantly, knowing the familial susceptibility variant allows for cascade genetic testing (ie, targeted testing for the familial variant in at-risk relatives). Cascade genetic testing even in young children is considered necessary due to the availability of effective medical interventions.

Family members harboring an FPAH-susceptibility variant have an increased risk of developing PAH and other features associated with the identified gene. They can also pass the variant to their offspring. Genetically mediated PAH and PVOD-PCH can manifest as early as infancy,[8,23] and therefore, clinical screening with echocardiograms is initiated in childhood,[20] and repeated every 1 to 3 years or sooner if symptoms develop to facilitate early detection and treatment of PAH.[17,20] In the recently published outcomes from the

Table 4. Framework for Genetic Counseling and Testing in PAH

Pretest Genetic Counseling
Review patient's medical history and collect standard 3-generation pedigree • Attention to disease characteristics within the family such as age at symptom development, age at diagnosis, age at death, consanguinity, and the presence of syndromic features such as those seen in hereditary hemorrhagic telangiectasia and small patella syndrome. • Family history should be updated over time due to its changing nature.
Provide education about disease symptoms, prognosis and genetics
Discuss mode of inheritance • Identification of at-risk relatives.
Recommend genetic testing based on guidelines
Review utility and limitations of testing • Test utility: Identification of known or likely pathogenic variant explains disease and establishes a diagnosis of HPAH in individuals with IPAH, PVOD-PCH, or associated PAH. Additionally, it allows for cascade testing to accurately identify at-risk relatives and for using genetic information in reproductive decision-making. • Limitations: Incomplete detection rate (i.e. not all genes for PAH have been discovered); reduced and sex-influenced penetrance; and variability in clinical presentation, severity, and age at diagnosis (known as variable expressivity).
Explore psychosocial considerations • Impact and feelings surrounding the possibility of a positive or negative result • While cascade testing can assist in identification of at-risk relatives, a cure for PAH does not currently exist. However, clinical screening may lead to identification of disease at an early stage when treatment may slow progression of PAH. • Discuss protection afforded by the Genetic Information Non-discrimination Act for asymptomatic at-risk relatives against discrimination by health insurance and employers, with some caveats. Current lack of protections against discrimination by life insurance, long-term care and disability insurance.
Explore readiness for testing, and support patient's decision
Order appropriate genetic test in the ideal test candidate (ie affected individual) if patient consents: • Testing the affected individual first provides information whether an identifiable susceptibility variant is present or not. In contrast, a negative result in an unaffected relative without knowing the specific familial PAH susceptibility variant would not clarify whether the unaffected relative has not inherited the familial variant, or still harbors a familial variant that is not identifiable due to limitations in current knowledge around PAH genetics.
Provide resources • Include information regarding useful websites (eg Pulmonary Hypertension Association), and relevant clinical trials. • If genetic testing is not pursued, provide a family letter to coordinate cascade clinical screening in HPAH families.
Posttest Genetic Counseling
Review of results and discussion of cascade genetic testing and/or cascade clinical surveillance recommendations based on genetic test results and family history a. Genotype-positive result: • If a PAH susceptibility variant is identified in the affected individual, provide family letter to coordinate cascade genetic testing and/or cascade clinical surveillance. ○ Autosomal-dominant HPAH: cascade testing starts with first-degree relatives and expands to other relatives where applicable. ○ Autosomal-recessive PVOD-PCH: cascade genetic testing is recommended for the affected individual's siblings. • For individuals seeking to learn about prenatal diagnosis or preimplantation genetic testing when the familial susceptibility variant is known, refer to a prenatal genetic counselor. ○ Decisions surrounding prenatal diagnosis or preimplantation genetic testing need consideration of several factors including comfort level with chance (incomplete and gender-influenced penetrance), personal and religious preferences, and financial and emotional burden surrounding the process and procedure.
b. Familial PAH with genotype negative result: • Provide family letter to coordinate cascade clinical surveillance if a PAH susceptibility variant *is not* identified in the affected individual.
c. If a VUS is identified, coordinate segregation studies when indicated. Recontact the patient when a VUS is reclassified. d. Consider DNA banking in case of uninformative genetic test result. DNA banking may be done pretest in some circumstances.

Abbreviations: HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary veno-occlusive disease; VUS, variant of uncertain significance.

DELPHI-2 study,[24] in which 55 adult asymptomatic *BMPR2* mutation carriers received annual multimodal screening for a minimum of 2 years, the overall incidence of PAH was 2.3% per year. Individuals were diagnosed with PAH at an earlier stage than is typical in the absence of proactive clinical screening. Additionally, the 5 patients who were diagnosed with PAH via screening were started on oral combination therapy and at the end of 6 years, they remained in a low mortality-risk category.[24]

If the FPAH-susceptibility variant is known, prenatal diagnosis and preimplan-

tation genetic testing become available family planning options for affected and at-risk asymptomatic males who wish to ensure biological offspring have not inherited predisposition to PAH.[25,26] Pregnancy in affected or unaffected at-risk females is discouraged as it can be life-threatening. It is also unclear if preimplantation genetic testing with gestational surrogacy is safe, as the effect of ovarian stimulation in females with a PAH-susceptibility variant remains unknown.

Guideline authors recommend that adult at-risk individuals in a family receive genetic counseling so they can make an informed decision about undergoing genetic testing and/or serial clinical screening for PAH.[17,19,21] It is also common practice for at-risk relatives choosing not to undergo family-variant testing to have serial clinical screening.

Family members who test negative for the FPAH-susceptibility variant have the general population risk of about 1 in a million to develop PAH, and their children are not at risk for inheriting the familial variant.

Genotype-Negative Result and its Integration Into Medical Care

The absence of a PAH susceptibility variant on a comprehensive PAH panel test in the affected individual is considered a genotype-negative result. In the case of FPAH, a negative genetic test result in the proband is clearly uninformative, does not rule out monogenic etiology, and indicates there are a proportion of genes or genetic mechanisms responsible for FPAH that are as-yet undiscovered. Professional societies recommend clinical surveillance for asymptomatic first-degree relatives with serial echocardiograms even when the affected relative is genotype-negative,[16,17,20] and screening is ideally repeated annually.[18] In the case of sporadic IPAH, a negative genetic test is reassuring, but does not rule out a genetic etiology. Clinical screening for first-degree relatives in this context is not indicated,[25] but the proband is encouraged to inform close relatives regarding the diagnosis and symptoms so they can seek an evaluation if cardiorespiratory symptoms arise.[20]

In most cases, identification of one or more variants of uncertain significance is treated like an uninformative negative result with respect to cascade clinical surveillance, that is, clinical surveillance is recommended for at-risk relatives in FPAH families while surveillance is not recommended for family members of patients with IPAH. In the case of a novel or suspicious variant of uncertain significance identified in a family with HPAH, segregation studies may be performed to understand its role in PAH susceptibility.

Retesting affected individuals with a negative result when new PAH genes are identified should also be considered.

DISCUSSION

Due to the utility of genetic counseling and testing in identifying family members at-risk for PAH, guidelines recommending these services for PAH have been available for over 15 years. Yet, it appears that these recommendations are not often followed by medical providers in the United States, largely owing to a lack of knowledge surrounding PAH genetics, and perceived lack of relevance of genetic counseling and testing in clinical care.[27] Other reasons for not utilizing genetic services highlighted in the same study[27] included high cost or insurance noncoverage for genetic services and a lack of access to genetic counselors.

Additionally, a 2020 survey of patients with IPAH conducted by the United Kingdom Pulmonary Hypertension Association highlighted preference of a majority (74%) of patients with IPAH to undergo genetic testing, and their desire to have cascade genetic testing offered to relatives if the specific genetic cause was pinpointed (80%).[28] Further, PAH is typically advanced by the time it is diagnosed, but with studies starting to document improved outcomes with available therapy even in severe PAH,[24,29,30] it is imperative to implement proactive measures (ie genetic testing with serial evaluation) in individuals at risk for HPAH, to detect disease at an early stage when the impact of therapy can be maximized. Genetic testing has become extremely affordable in the last 5 years. Postnatal targeted testing for a familial variant is in the range of US$200 with many insurance companies covering genetic counseling as well as genetic testing. Therefore, the time has arrived for better utilization of genetics services for patients with PAH. It may be easier to obtain insurance coverage for recommended serial screening in the presence of a PAH susceptibility variant. Genetic counselors specialized in cardiovascular disease or general genetics are ideally suited to coordinate genetics-related care. Providers without local access to a genetic counselor can request services through telegenetics companies.

Future Directions for Precision Genetics in PAH

Despite recent advances in gene discovery for HPAH, there remains a proportion of gene-elusive FPAH cases. Further, in families with a known predisposition, utility of predictive testing is still complicated by incomplete penetrance of disease. Studies to discover the missing genetic contributors to HPAH, as well as to understand contributors to reduced penetrance and variable expressivity are needed. In addition, the most effective clinical screening protocol for individuals at high risk of HPAH addressing at which age evaluations should be initiated, which screening modalities should be utilized, and what the frequency of screening should be in genotype positive versus negative families is yet to be established.

References

1. Thomas CA, Anderson RJ, Condon DF, de Jesus Perez VA. Diagnosis and management of pulmonary hypertension in the modern era: insights from the 6th World Symposium. *Pulm Ther*. 2020;6(1):9-22. doi: https://doi.org/10.1007/s41030-019-00105-5
2. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12 Suppl S):13S-24S. doi: https://doi.org/10.1016/j.jacc.2004.02.029
3. Souza R, Humbert M, Sztrymf B, et al. Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J*. 2008;31(2):343-348 [published correction appears in *Eur Respir J*. 2008;31(4):912]. doi: https://doi.org/10.1183/09031936.00104807.
4. Zhu N, Gonzaga-Jauregui C, Welch CL, et al. Exome sequencing in children with pulmonary arterial hypertension demonstrates differences compared with adults. *Circ Genom Precis Med*. 2018;11(4):e001887. doi: https://doi.org/10.1161/CIRCGEN.117.001887

5. Zhu N, Pauciulo MW, Welch CL, et al. Novel risk genes and mechanisms implicated by exome sequencing of 2572 individuals with pulmonary arterial hypertension. *Genome Med*. 2019;11(1):69. doi: https://doi.org/10.1186/s13073-019-0685-z
6. Welch CL, Chung WK. Genetics and genomics of pediatric pulmonary arterial hypertension. *Genes*. 2020;11(10):1213. doi: https://doi.org/10.3390/genes11101213
7. Navas Tejedor P, Tenorio Castaño J, Palomino Doza J, et al. An homozygous mutation in KCNK3 is associated with an aggressive form of hereditary pulmonary arterial hypertension. *Clin Genet*. 2017;91(3):453-457. doi: https://doi.org/10.1111/cge.12869
8. Montani D, Girerd B, Jaïs X, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. *Lancet Respir Med*. 2017;5(2):125-134. doi: https://doi.org/10.1016/S2213-2600(16)30438-6
9. Austin ED, Elliott CG. TBX4 syndrome: a systemic disease highlighted by pulmonary arterial hypertension in its most severe form. *Eur Respir J*. 2020;55(5):2000585. doi: https://doi.org/10.1183/13993003.00585-2020
10. Zhu N, Swietlik EM, Welch CL, et al. Rare variant analysis of 4241 pulmonary arterial hypertension cases from an international consortium implicates FBLN2, PDGFD, and rare de novo variants in PAH. Genome Med. 2021;13(1):80 [published correction appears in Genome Med. 2021;13(1):106]. doi: https://doi.org/10.1186/s13073-021-00891-1
11. Best DH, Sumner KL, Austin ED, et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. *Chest*. 2014;145(2):231-236. doi: https://doi.org/https://doi.org/10.1378/chest.13-2366
12. Eyries M, Montani D, Girerd B, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nat Genet*. 2014;46(1):65-69. doi: https://doi.org/10.1038/ng.2844
13. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. *J Card Fail*. 2009;15(2):83-97. doi: https://doi.org/10.1016/j.cardfail.2009.01.006
14. Van Engelen K, Baars MJ, Felix JP, Postma AV, Mulder BJ, Smets EM. The value of the clinical geneticist caring for adults with congenital heart disease: diagnostic yield and patients' perspective. *Am J Med Genet*. 2013;161A(7):1628-1637. doi: https://doi.org/10.1002/ajmg.a.35973
15. Davey A, Rostant K, Harrop K, Goldblatt J, O'Leary P. Evaluating genetic counseling: client expectations, psychological adjustment and satisfaction with service. *J Genet Couns*. 2005;14(3):197-206. doi: https://doi.org/10.1007/s10897-005-0519-6
16. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 Suppl):14S-34S. doi: https://doi.org/10.1378/chest.126.1_suppl.14S
17. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53(17):1573-619. doi: https://doi.org/10.1016/j.jacc.2009.01.004
18. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol (Engl Ed)*. 2016;69(2):177. doi: https://doi.org/10.1016/j.rec.2016.01.002
19. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132(21):2037-2099 [published correction appears in *Circulation* 2016;133(4):e368]. doi: https://doi.org/10.1161/CIR.0000000000000329
20. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. 2019;38(9):879-901. doi: https://doi.org/10.1016/j.healun.2019.06.022
21. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801904. doi: https://doi.org/10.1183/13993003.01904-2018
22. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi: https://doi.org/10.1038/gim.2015.30
23. Machado RD, Pauciulo MW, Thomson JR, et al. BMPR2 haploinsufficiency as the inherited molecular mechanism for primary pulmonary hypertension. *Am J Hum Genet*. 2001;68(1):92-102. doi: https://doi.org/10.1086/316947
24. Montani D, Girerd B, Jaïs X, et al. Screening for pulmonary arterial hypertension in adults carrying a *BMPR2* mutation. *Eur Respir J*. 2021;58(1):2004229. doi: https://doi.org/10.1183/13993003.04229-2020
25. Girerd B, Montani D, Jaïs X, et al. Genetic counselling in a national referral centre for pulmonary hypertension. *Eur Respir J*. 2016;47(2):541-552. doi: https://doi.org/10.1183/13993003.00717-2015
26. Frydman N, Steffann J, Girerd B, et al. Pre-implantation genetic diagnosis in pulmonary arterial hypertension due to BMPR2 mutation. *Eur Respir J*. 2012;39(6):1534-1535. doi: https://doi.org/10.1183/09031936.00185011
27. Jacher JE, Martin LJ, Chung WK, Loyd JE, Nichols WC. Pulmonary arterial hypertension: specialists' knowledge, practices, and attitudes of genetic counseling and genetic testing in the USA. *Pulm Circ*. 2017;7(2):372-383. doi: https://doi.org/10.1177/2045893217700156
28. Pulmonary Hypertension Association UK. Genetics and PAH research findings. https://www.phauk.org/app/uploads/2020/03/Genetics-PAH-Research-Results.pdf. Published 2020. Accessed September 30, 2021.
29. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J*. 2014;43(6):1691-1697. doi: https://doi.org/10.1183/09031936.00116313
30. Galiè N, Rubin Lj, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008;371(9630):2093-2100. doi: https://doi.org/10.1016/S0140-6736(08)60919-8