Learning a Comorbidity-Driven Taxonomy of Pediatric Pulmonary Hypertension

Mei-Sing Ong, Mary P. Mullen, Eric D. Austin, Peter Szolovits, Marc D. Natter, Alon Geva, Tianxi Cai, Sek Won Kong, Kenneth D. Mandl

Rationale: **Pediatric pulmonary hypertension (PH) is a heterogeneous condition with varying natural history and therapeutic response. Precise classification of PH subtypes is, therefore, crucial for individualizing care. However, gaps remain in our understanding of the spectrum of PH in children.**

Objective: **We seek to study the manifestations of PH in children and to assess the feasibility of applying a network-based approach to discern disease subtypes from comorbidity data recorded in longitudinal data sets.**

Methods and Results: **A retrospective cohort study comprising 6 943 263 children (<18 years of age) enrolled in a commercial health insurance plan in the United States, between January 2010 and May 2013. A total of 1583 (0.02%) children met the criteria for PH. We identified comorbidities significantly associated with PH compared with the general population of children without PH. A Bayesian comorbidity network was constructed to model the interdependencies of these comorbidities, and network-clustering analysis was applied to derive disease subtypes comprising subgraphs of highly connected comorbid conditions. A total of 186 comorbidities were found to be significantly associated with PH. Network analysis of comorbidity patterns captured most of the major PH subtypes with known pathological basis defined by the World Health Organization and Panama classifications. The analysis further identified many subtypes documented in only a few case studies, including rare subtypes associated with several well-described genetic syndromes.**

Conclusions: **Application of network science to model comorbidity patterns recorded in longitudinal data sets can facilitate the discovery of disease subtypes. Our analysis relearned established subtypes, thus validating the approach, and identified rare subtypes that are difficult to discern through clinical observations, providing impetus for deeper investigation of the disease subtypes that will enrich current disease classifications. (*Circ Res*. 2017;121:341-353. DOI: 10.1161/CIRCRESAHA.117.310804.)**

Key Words: cluster analysis ■ comorbidity ■ connective tissue disease ■ hypertension, pulmonary ■ pediatrics

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Classification of diseases has traditionally been shaped by expert consensus. As such, disease taxonomies are subject to the limits of existing knowledge and the biases of experts and may not reflect the underlying disease pathophysiology. In a landmark report Toward Precision Medicine, the Institute of Medicine called for improved approaches to developing disease taxonomies that classify complex diseases based on the molecular and clinical data of individual patients.[1] Here, we developed a comorbidity-driven taxonomy of pediatric pulmonary hypertension (PH) using data derived from administrative claims.

Editorial, see p 317

It is well established that PH is a heterogeneous condition, often with a progressive and potentially fatal course.[2] Effective management of PH relies on early and accurate diagnosis. However, diagnosing PH is challenging, as initial symptoms can be subtle and confounded by other pre-existing comorbidities. Patients with PH are often diagnosed late in the course when the pathological changes are advanced and irreversible.[3–7] For example, 1 in 5 patients with pulmonary arterial hypertension (PAH), a subtype of PH, are diagnosed more than 2 years after symptom onset.[4] Given that the median survival for PAH is 2.8 years without treatment,[8] delay in diagnosis likely worsens prognosis.

Accurate diagnosis of PH subtype is also critical, as available treatments and responses to treatments may differ among PH subtypes. Deaño et al[9] reported a misdiagnosis rate of 33% among patients who were referred for care to tertiary level PH

Original received February 2, 2017; revision received June 7, 2017; accepted June 12, 2017. In May 2017, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 12.28 days.

From the Computational Health Informatics Program (M.-S.O., M.D.N., A.G., S.W.K., K.D.M.), Department of Cardiology (M.P.M.), Division of Critical Care Medicine, Department of Anesthesiology, Perioperative, and Pain Medicine (A.G.), and Department of Anesthesia (A.G.), Harvard School of Medicine, Boston Children's Hospital, MA; Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN (E.D.A.); Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge (P.S.); Department of Pediatrics, Massachusetts General Hospital, Boston (M.D.N.); and Department of Biostatistics, Harvard School of Public Health, Boston, MA. (T.C.).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The online-only Data Supplement is available with this article at http://circres.ahajournals.org/lookup/suppl/doi:10.1161/CIRCRESAHA.117.310804/-/DC1.

Correspondence to Mei-Sing Ong, PhD, Boston Children's Hospital, 300 Longwood Ave, Boston MA 02115. E-mail mei-sing_ong@hms.harvard.edu

© 2017 American Heart Association, Inc.

Novelty and Significance

What Is Known?

- Pulmonary hypertension (PH) is a complex disease with varying disease course and treatment response.
- Formal taxonomies of PH have been developed to guide diagnosis and targeted treatment based on the underlying disease pathophysiology.
- Gaps remain in our knowledge of the diverse forms of PH, especially in children.

What New Information Does This Article Contribute?

- Application of network science to model disease patterns captured in longitudinal data sets provides an unbiased approach to discovering disease subtypes.
- The approach identified rare and novel disease patterns in pediatric PH, providing impetus for deeper investigation that will enrich current disease classifications.

Classification of diseases has traditionally been shaped by expert consensus. As such, disease taxonomies are subject to the limits of existing knowledge and the biases of experts and may not reflect the underlying disease pathophysiology. Here, we establish for the first time the feasibility of applying network science to drive data-driven discovery of disease subtypes in pediatric PH. By modeling the complex interactions of disease symptoms recorded in longitudinal data sets, the approach automatically relearned PH subtypes with known pathological basis and further identified novel and rare disease patterns that are difficult to discern through clinical observations. Knowledge derived from the analysis will facilitate improved diagnosis of PH. Further advances linking disease subtypes to therapeutic response, disease outcomes, and the molecular profiles of individual subtypes will provide impetus for the development of more effective and targeted therapies. Although the current study focuses on pediatric PH, the proposed method has enormous potential for advancing our understanding of other complex diseases.

Nonstandard Abbreviations and Acronyms

GSD	glycogen storage disorder
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PPHN	pulmonary hypertension in newborn
RHC	right heart catheterization
SLOS	Smith–Lemli–Opitz syndrome
WHO	World Health Organization

centers, and half of those who had started receiving medication treatment for PAH were found to either have a different PH subtype or no PH at all. Indeed, misdiagnosis and misuse of therapies exposes patients to the potential side effects of therapies without the supposed benefits; for instance, therapies that are efficacious for PAH (eg, pulmonary vasodilator medications) may actually worsen pulmonary hemodynamics in PH associated with left heart disease, the most common cause of PH.[10,11]

The goal to optimize the treatment of PH based on its pathophysiology has led to the development of a formal taxonomy of PH by the World Health Organization (WHO). The taxonomy (WHO classification of PH) defines 5 distinct PH subtypes: PAH (group 1 PH), PH caused by left heart disease (group 2 PH), PH caused by chronic lung disease and hypoxia (group 3 PH), chronic thromboembolic PH (group 4 PH), and PH because of other multifactorial mechanisms (group 5 PH).[2] More recently, the realization that childhood-onset PH may have unique pathogeneses and association not often observed in adults further prompted the development of a new taxonomy for childhood-onset PH.[12–14] The taxonomy, known as the Panama classification (2011), highlighted a number of features more prominent in pediatric PH, including fetal and developmental origins of vascular disease.[13]

Although these efforts provide a framework for the diagnosis and treatment of PH, gaps remain in our understanding of the disease, especially among children. Because of the rarity of PH in children, comprehensive analysis of its clinical manifestations is challenging. To date, published data on pediatric PH have been limited to several registry-based and small-cohort studies.[3,15–18] Although these studies have greatly advanced our understanding of the disease, they may be subject to referral bias and may not represent the full spectrum of pediatric PH cases.[19,20] Furthermore, because knowledge generated from these studies formed the bedrock of the expert consensus classifications, current taxonomies may not capture the full spectrum of the diverse manifestations of PH.

We, therefore, seek to enrich and extend the current classifications of PH by applying network science methodologies to the largest data set of pediatric PH to date. Our goal is to facilitate improved recognition of clinically relevant patterns of disease manifestation, which can result in meaningful improvements in the timely and accurate diagnosis of PH.

The application of network science has transformed the study of biological systems.[21] Using network theory to model biological systems, nodes in the network represent biological entities (eg, gene, protein, and disease), and links between nodes represent the relationships between entities (eg, transcriptional regulation and correlation in gene expression levels). The emergent properties of a network can provide insights into biological processes that cannot be elucidated by studying individual entities in isolation. For example, gene coexpression network studies have revealed novel genes involved in the pathogenesis of various diseases, whereas protein interaction networks have led to the delineation of new disease pathways. In addition to genomic and proteomic studies, comorbidity networks modeling disease co-occurrence have been shown to capture phenotypic differences between patients with different demographic backgrounds, disease progression, and mortality.[22] Here, we apply for the first time a Bayesian network approach to characterize the comorbidity patterns in pediatric PH.

Methods

This is a retrospective cohort study of an insured population. As shown in Figure 1, we (1) defined the comorbidity profiles of children

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

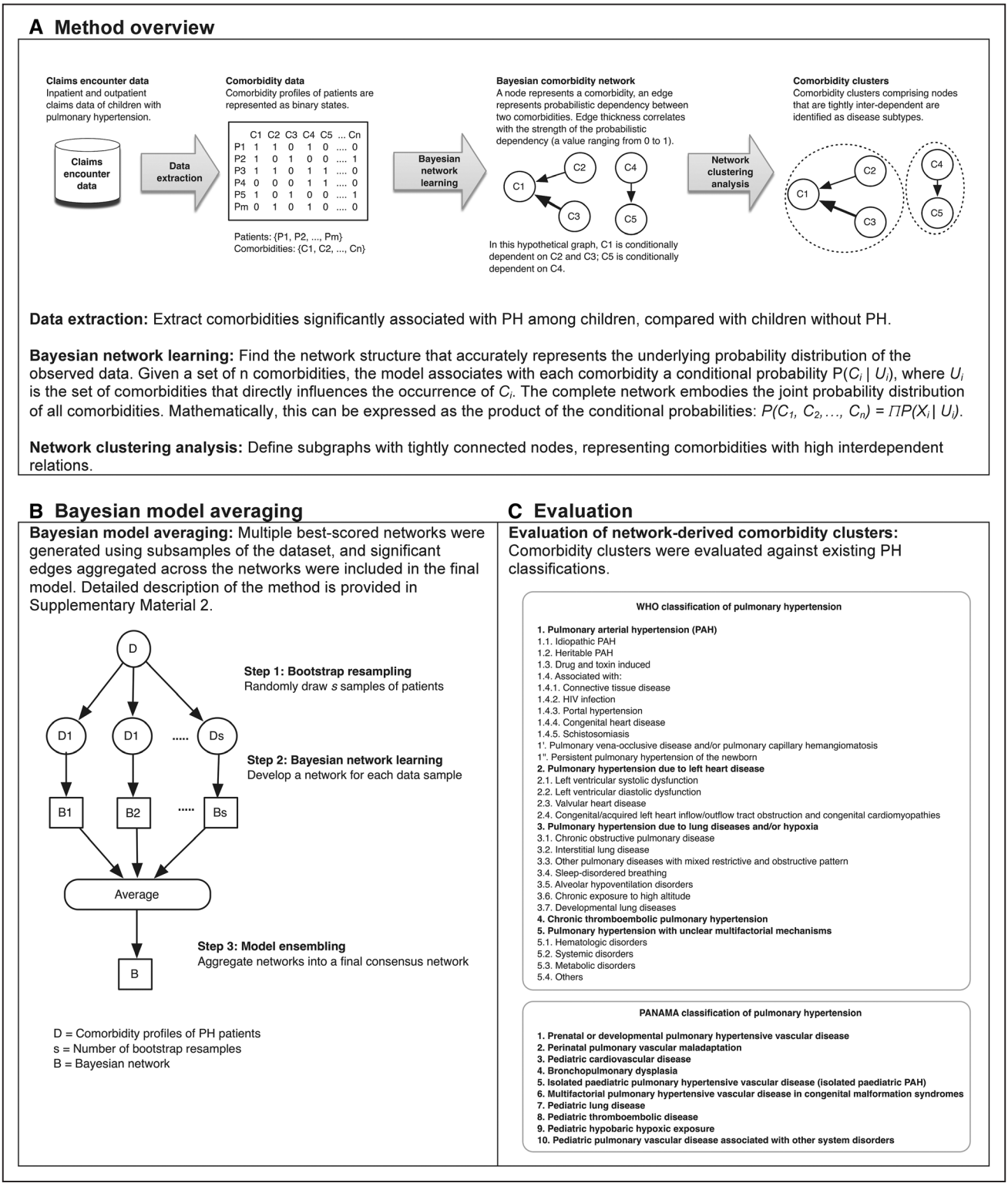

Figure 1. Study methods. PH indicates pulmonary hypertension.

with PH; (2) constructed a Bayesian comorbidity network; and (3) applied network-clustering analysis to define disease subtypes.

Study Population and Data Extraction

To form our study cohort, we examined claims from Aetna, Inc, a major, nationwide employer-provided health insurance plan in the United States, between January 2010 and May 2013. Available information included dates of enrollment in the insurance program, outpatient visit claims, and inpatient visit claims. Demographic data included sex and age. All encounters were coded with *International Classification of Diseases, Ninth Revision* (*ICD-9*), codes. The Boston Children's Hospital Institutional Review Board approved the study and granted a waiver of consent.

Subjects were drawn from 6 943 263 children (<18 years of age) enrolled in the insurer plan. A total of 1583 children met the criteria for PH, defined as having ≥2 healthcare visits associated

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

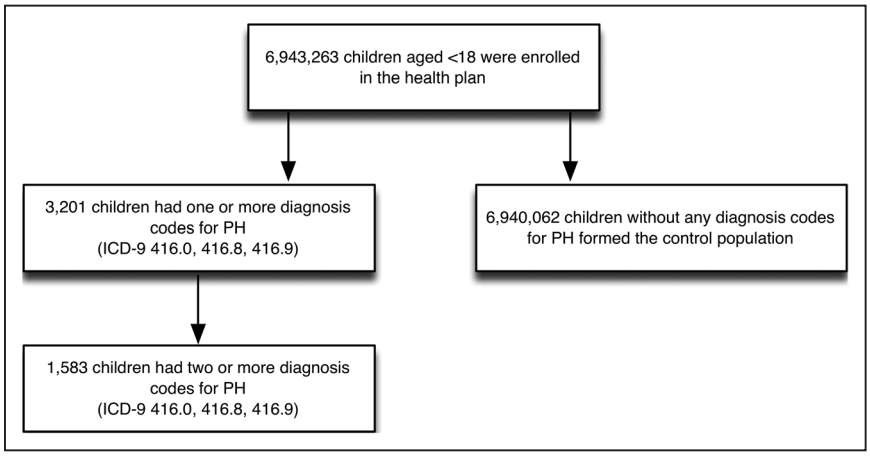

Figure 2. Study participants' selection criteria. ICD-9 indicates International Classification of Diseases, Ninth Revision; and PH, pulmonary hypertension.

with PH (*ICD-9* 416.0, 416.8, and 416.9) during the study period (Figure 2).

We systematically identified all comorbidities significantly associated with PH, compared with the general population of children without PH. We defined the presence of a comorbidity as having ≥2 care encounters related to the condition, identified using *ICD-9* codes. This approach has been previously validated for a wide range of diseases.[23–25] For example, Quan et al[24] showed that patients with hypertension can be reliably identified with high accuracy (specificity: 95% and sensitivity: 73%) when the diagnoses were defined as having ≥2 claims for hypertension within 3 years. We further conducted an additional sensitivity analysis, applying a more stringent algorithm that considered only diagnoses with ≥4 encounter visits. Using χ^2 statistic, we calculated the odds ratio with corresponding 95% confidence intervals and 2-tailed P values to measure the strength of the association between each comorbidity and PH. The α level of 0.05 was used to declare statistical significance. Bonferroni correction was applied to control for 767 comparisons with the adjusted α level being 0.000065.

Bayesian Comorbidity Network

We developed a Bayesian network to model the interdependencies of comorbidities in children with PH. We included in the model all comorbidities found to be significantly associated with PH compared with the general population of children without PH (Online Table B1a). We excluded comorbidities that occurred in fewer than 4 PH patients, because a small number of observations would not suffice to distinguish between true and spurious correlations. Schematically, the model is represented as a directed graph, with nodes representing comorbidities, and edges denoting statistically dependent relations among comorbidities.[26] An edge from node C_i to C_j can be interpreted as the presence of C_i influences the occurrence of C_j. The absence of a link between 2 nodes signifies conditional independence. Detailed description of the methods is provided in Section A1 in the Online Data Supplement.

Network-Clustering Analysis

To define PH subtypes, we partitioned the network into subgraphs comprising highly connected comorbidities using a strict partitioning rule whereby each comorbidity belongs to exactly one cluster. The graph partitioning process involves merging nodes agglomeratively, using a random walk clustering approach.[27] Detailed description of the methods is provided in Section A2 in the Online Data Supplement.

Evaluation

Review by experts evaluated our approach by checking for the identification of established PH subtypes. Accordingly, each comorbidity cluster was assigned a WHO and Panama classification subtype that best describes the cluster. For example, a comorbidity cluster comprising portal hypertension and the associated conditions would be classified as WHO group 1 (PAH associated with portal hypertension), and Panama group 10 (pediatric pulmonary vascular disease associated with other system disorders). Classification was first performed by 1 researcher (M.-S.O.) and then validated by 2 pediatric PH experts (M.H. and E.A.); inter-rater agreement was quantified using Cohen κ statistic, and discrepancies were resolved through consensus. The WHO and Panama classifications comprise 5 and 10 subtypes, respectively; the WHO classification further categorizes some of the 5 major subtypes into 26 minor subtypes (Figure 1C). To ascertain the sensitivity of our analysis, we measured the percentage of subtypes defined in WHO/Panama classifications that were captured by the network. We further conducted a literature review to evaluate network-derived clusters not described in either WHO or Panama classifications to assess whether published evidence supported the co-occurrence of PH with conditions captured by each cluster.

Secondary Analysis

To form the study cohort, we considered children who had ≥2 healthcare visits for PH. However, given that PH can often be miscoded[28] or misdiagnosed,[9,29] we may have inadvertently included patients who did not have PH. Definitive diagnosis of PH requires an elevated mean pulmonary arterial pressure of 25 mm Hg at rest measured by right heart catheterization (RHC). Hence, to address potential coding and diagnostic ambiguities, we performed a secondary analysis that considered only children who underwent RHC, in addition to having ≥2 healthcare visits for PH during the study period. A separate Bayesian comorbidity network was developed for this patient subgroup, and the differences in comorbidities and network-derived clusters were assessed.

Results

A total of 6 943 263 children were enrolled in the insurance plan and 1583 (0.02%) had ≥2 diagnosis codes for PH. The 6 940 062 children without any diagnosis codes for PH formed the control population for this study. A total of 186 comorbidities satisfied our study inclusion criteria (Online Table B1a). When a more stringent algorithm for identifying diagnoses was applied, defined as having ≥4 healthcare visits during the study period, the association between PH and these comorbidities remained statistically significant, with the exception of pyogenic granuloma (Online Table B1b).

The comorbidity burden of children with PH was substantial (Figure 3). The mean and median number of comorbid conditions in individuals with PH were 7 and 8, respectively.

Network Analysis

Figure 4 depicts the Bayesian comorbidity network learned from the data set. The inferred network comprised 365 relations, described in further details in Online Table B2a.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

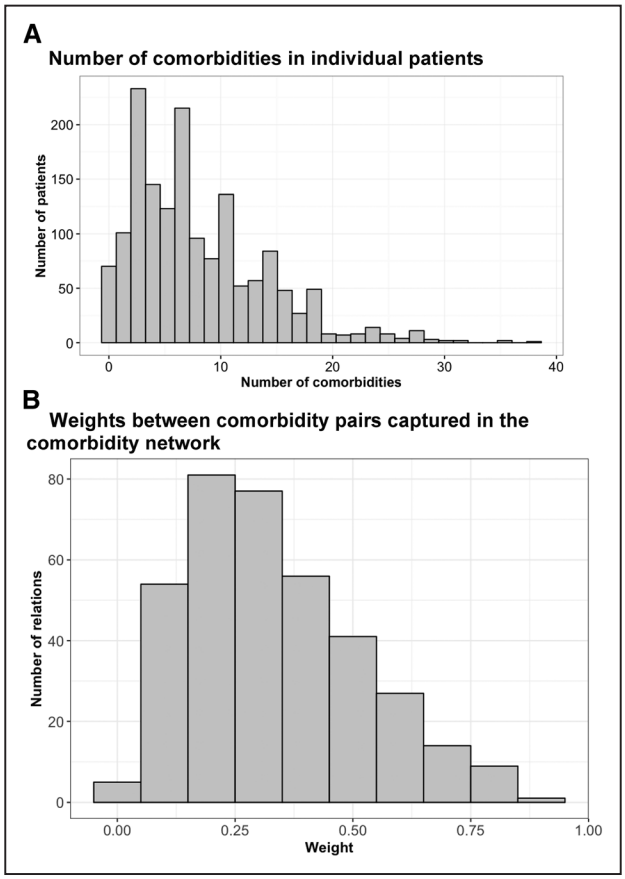

Figure 3. Comorbidity burden in children with pulmonary hypertension.

Detection of Well-Established Subtypes

Cluster analysis of the comorbidity network identified all 5 major subtypes (sensitivity: 100%; κ score: 100%) and 19 of 26 minor subtypes (sensitivity: 73%; κ score: 96%) defined in the WHO classification (Table 1), and 9 of 10 subtypes defined in the Panama classification (sensitivity: 90%; κ score: 90%; Table 2), with a few anticipated exceptions. For example, in the absence of pedigree and genetic data, we were unable to discern the various forms of heritable PAH, with the exception of PH in association with hereditary hemorrhagic telangiectasia, a condition known to associate with PAH and linked to pathogenic variants in *ALK1* and *ENG* genes.[30] The identification of pathogenic drugs and toxins associated with PAH is beyond the scope of this study. We were also unable to detect PH caused by chronic exposure to high altitude: the diagnostic code for the condition is nonspecific (*ICD-9* 993.2: other and unspecified effects of high altitude) and was not assigned to any of the patients in the study data set. The imprecision of *ICD* codes also precluded differentiation between left ventricular systolic and diastolic dysfunctions. Finally, we were unable to discern subtypes associated with HIV infection or schistosomiasis, because none of the PH patients in our US-based, privately-insured claims data set had billing codes for these conditions.

Detection of Rare Subtypes

Our analysis detected known rare associations with PH (Table 3). An example is the co-occurrence of PH with juvenile idiopathic arthritis and hemophagocytic syndrome. The clustering occurrence is not surprising given that PAH has been reported in several patients with systemic-onset juvenile idiopathic arthritis, particularly in association with macrophage activation syndrome.[31,32] It has been hypothesized that PAH may be caused by exposures to interleukin-1 and interleukin-6 inhibitors used for treating systemic-onset juvenile idiopathic arthritis and macrophage activation syndrome[33]; however, the underlying biology of this association remains unknown. In our data set, of 18 patients with both juvenile idiopathic arthritis and hemophagocytic syndrome, 4 patients developed PH, signifying the potential importance of this comorbidity pattern.

The cluster comprising glycogen storage disorder (GSD), hereditary muscular dystrophy, and cardiomyopathy typifies type 2 GSD. Although type 1 GSD has been linked to PH, the relationship between PH and type 2 GSD is less studied. A case report noted the development of PH resulting from respiratory muscular atrophy and alveolar hypoventilation caused by type 2 GSD.[34] Another report documented severe pulmonary veno-occlusive disease in a patient with type 2 GSD.[35]

Another cluster captures the characteristic features of heterotaxy syndrome, including situs inversus, and congenital spleen anomaly. Of the 31 patients in our data set with these conditions, 4 developed PH. Several limited case reports documented the disease pattern in the setting of cardiac defects and pulmonary complications.[36,37]

We further identified several rare genetic disorders among the PH population, including Cri-du-chat, Turner, and Prader–Willi syndromes. Case reports have documented the co-occurrence of PH in children with Cri-du-chat[38,39] and Turner syndrome.[40,41] PH in these patients may be caused by underlying congenital heart disease. In patients with Prader–Willi syndrome, obstructive sleep apnea and other obesity-related comorbidites may have contributed to the development of PH. In our data set, 6 (1.8%) of 329 patients with Prader–Willi syndrome developed PH. However, literature review yielded only 1 case report documenting a sudden death secondary to PH in a child with Prader–Willi syndrome,[42] indicating that the risk of PH in these patients may be under-recognized.

Although some clusters clearly describe syndromes with highly specific and rare comorbidities, other clusters contain unusual combinations of relatively more common conditions, which may represent unrecognized syndromes and generate new hypotheses. For example, the cluster comprising adrenogenital disorder, microcephaly, and adrenal hypofunction may represent Smith–Lemli–Opitz syndrome (SLOS), a rare condition caused by deficiency of 7-dehydrocholesterol reductase. Two potential pathogeneses would support the association between SLOS and PH. First, persistent pulmonary hypertension in newborn in SLOS has been documented in a patient with altered expression of caveolin-1 (*CAV-1*),[43] suggesting that caveolae-dependent signaling may be responsible for the pathogenesis of PH. This hypothesis was further strengthened in a recent study demonstrating an association between mutations in *CAV-1* and PAH through whole-exome sequencing.[44] Second, cardiorespiratory problems can occur in individuals with SLOS, secondary to malformations of the heart or

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

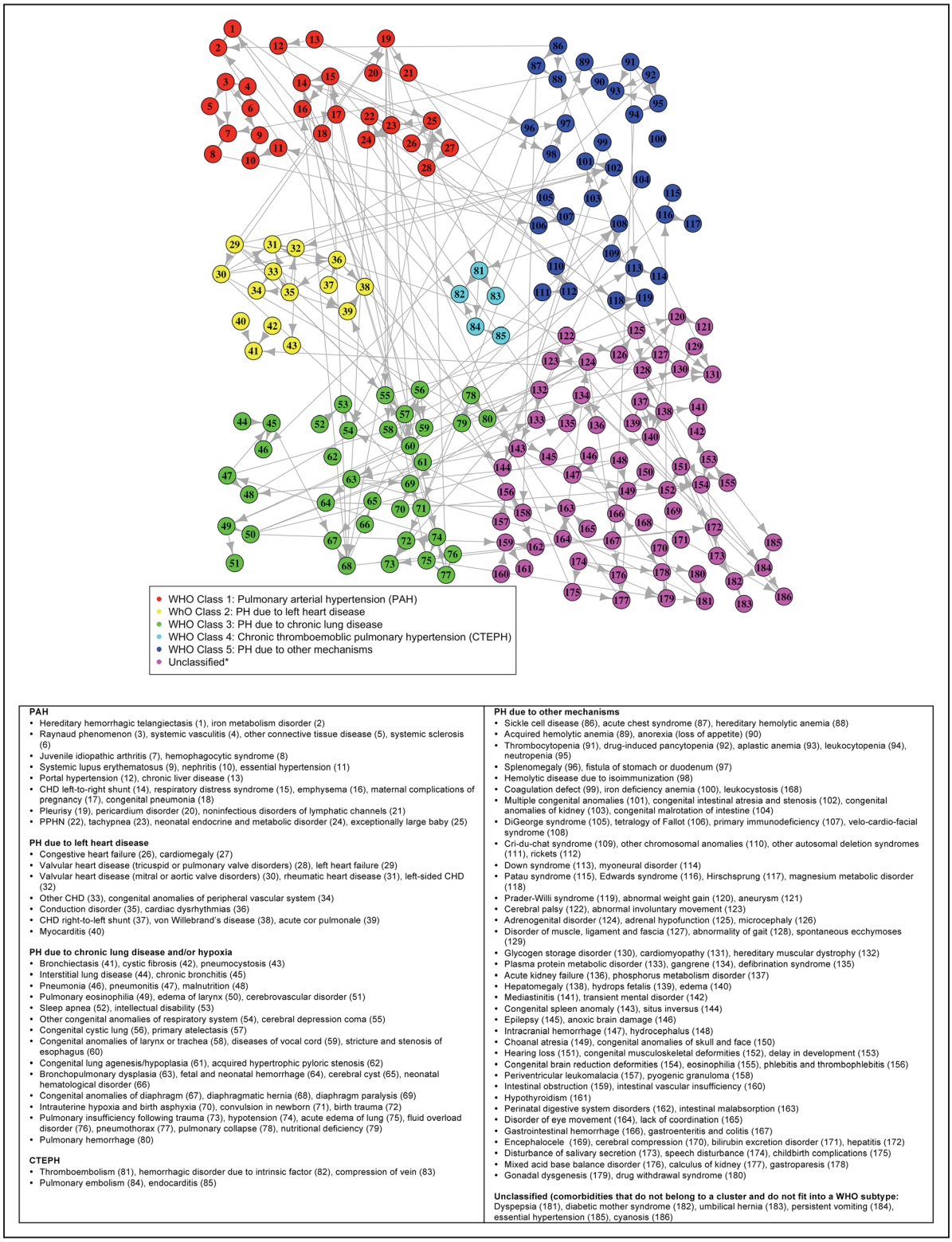

Figure 4. Bayesian comorbidity network of children with pulmonary hypertension.

respiratory tract[45]; these conditions may contribute to the development of PH in patients with SLOS.

We further identified a cluster containing comorbidities suggestive of Ehlers–Danlos syndrome (EDS), a group of genetically determined connective tissue disorders presenting with musculoskeletal dysfunction, encompassing a spectrum of symptoms such as hyperextensible skin, spontaneous ecchymoses, fragile vessels, and hypermobile joints with oftentimes secondary gait abnormalities. Spontaneous vascular or visceral rupture is a feature typifying vascular EDS, a rare subtype of EDS caused by mutations in the *COL3A1* gene that result in increased fragility of connective tissue. In our study population, 2 of 11 children

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Table 1. Mapping of Network-Derived Comorbidity Clusters With PH Subtypes Defined in the WHO Classification

WHO Classification of PH	Network-Derived Comorbidity Clusters
1. PAH	
1.1 Idiopathic PAH	N/A
1.2 Heritable PAH	Hereditary hemorrhagic telangiectasia and iron metabolism disorder
1.3 Drug and toxin induced	N/A (exposures to drugs and toxins were not captured in the data set)
1.4.1 Associated with CTD	Raynaud phenomenon, systemic sclerosis, systemic vasculitis, and other CTD
	Juvenile idiopathic arthritis and hemophagocytic syndrome
	Systemic lupus erythematosus, nephritis, and chronic kidney disease
1.4.2 Associated with HIV infection	N/A (there were no PH patients with HIV in the data set)
1.4.3 Associated with portal hypertension	Portal hypertension and chronic liver disease
1.4.4 Associated with CHD	CHD (left to right shunt), maternal complications of pregnancy, respiratory distress syndrome, emphysema, and congenital pneumonia
1.4.5 Associated with schistosomiasis	N/A (there were no PH patients with schistosomiasis in the data set)
1′ PVOD	Pleurisy, noninfectious disorders of lymphatic channels, and pericardium disorder
1″ PPHN	PPHN, tachypnea of newborn, neonatal endocrine and metabolic disturbance, and exceptionally large baby
	Intrauterine hypoxia and birth asphyxia, birth trauma, and convulsion in newborn
2. PH caused by left heart disease	
2.1 Left ventricular systolic dysfunction	Congestive heart failure and cardiomegaly
2.2 Left ventricular diastolic dysfunction	
2.3 Valvular disease	Valvular heart disease (tricuspid or pulmonary valve disorders), and left heart failure
	Valvular heart disease (mitral or aortic valve disorders), rheumatic heart disease, and left-sided CHD
2.4 Congenital/acquired left heart disorder	Other CHD, and congenital anomalies of peripheral vascular system
	Conduction disorder, and cardiac dysrhythmias
	CHD (right-to-left shunt), Von Willebrand disease, and acute cor pulmonale
	Myocarditis
3. PH caused by lung diseases and hypoxia	
3.1 Chronic obstructive pulmonary disease	Bronchiectasis, pneumocytosis, and cystic fibrosis
3.2 Interstitial lung disease	Interstitial lung disease and chronic bronchitis
3.3 Other mixed restrictive or obstructive pulmonary disease	Pneumonia, pneumonitis, and malnutrition
	Pulmonary eosinophilia, edema of larynx, and cerebrovascular disorder
	Pulmonary insufficiency after trauma, acute edema of lung, hypotension, fluid overload disorder, pneumothorax, pulmonary collapse, and nutritional deficiency
	Pulmonary hemorrhage
3.4 Sleep-disordered breathing	Sleep apnea and intellectual disability
3.5 Alveolar hypoventilation disorders	Congenital anomalies of respiratory system and cerebral depression coma
3.6 Chronic exposure to high altitude	N/A (there are no diagnosis codes for high-altitude PH)
3.7 Developmental lung diseases	Congenital cystic lung and primary atelectasis
	Congenital anomalies of larynx/trachea, diseases of vocal cord, and stricture/stenosis of esophagus
	Congenital lung agenesis/hypoplasia/dysplasia and acquired hypertrophic pyloric stenosis
	Bronchopulmonary dysplasia, fetal and neonatal hemorrhage, cerebral cyst, and neonatal hematologic disorder
	Congenital anomalies of diaphragm, diaphragmatic hernia, and diaphragm paralysis
4. Chronic thromboembolic PH	Thromboembolism, compression of vein, and hemorrhagic disorder because of intrinsic factor
	Pulmonary embolism and endocarditis

(*Continued*)

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Table 1. Continued

WHO Classification of PH	Network-Derived Comorbidity Clusters
5. PH because of unclear multifactorial mechanisms	
5.1. Hematologic disorders	Sickle cell disease, acute chest syndrome, and hereditary hemolytic anemia
	Acquired hemolytic anemia and anorexia (loss of appetite)
	Thrombocytopenia, aplastic anemia, leukocytopenia, neutropenia, and drug-induced pancytopenia
	Coagulation defect and iron deficiency anemia
	Hemolytic disease because of isoimmunization
5.2. Systemic disorders	Essential hypertension
5.3. Metabolic disorders	Glycogen storage disorder, hereditary muscular dystrophy, and cardiomyopathy
	Hypothyroidism
	Plasma protein metabolic disorder, defibrination syndrome, and gangrene
	Mixed acid base balance disorder, calculus of kidney, and gastroparesis
5.1. Others	Acute kidney failure and phosphorus metabolism disorder
	Hepatomegaly, edema, and hydrops fetalis
	Splenomegaly, and fistula of stomach, or duodenum
	Mediastinitis and transient mental disorder

A clinical classification of PH based on similarities in pathophysiologic mechanisms, clinical presentations, and therapeutic approaches. CHD indicates congenital heart disease; CTD, connective tissue disorder; N/A, nonapplicable; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and PPHN, pulmonary hypertension in newborn.

who had codiagnoses of spontaneous ecchymoses, disorder of muscle or ligament, and gait abnormality were diagnosed with PH, raising the hypothesis for an association between vascular EDS and PH. The co-occurrence of EDS and mild PH has been documented in 2 patients[46]; abnormalities in the pulmonary vasculature might also have predisposed these patients to PH.

Table 2. Mapping of Network-Derived Comorbidity Clusters With PH Subtypes Defined in the Panama Classification

Panama Classification of PH	Network-Derived Comorbidity Clusters
1. Prenatal or developmental pulmonary hypertensive vascular disease	Congenital anomalies of diaphragm, diaphragmatic hernia, and diaphragm paralysis
	Congenital lung agenesis/hypoplasia/dysplasia, and acquired hypertrophic pyloric stenosis
	Congenital cystic lung and primary atelectasis
	Congenital anomalies of respiratory system, cerebral depression coma, and childbirth complications
2. Perinatal pulmonary vascular maladaptation	PPHN, tachypnea of newborn, neonatal endocrine and metabolic disturbance, and exceptionally large baby
	Intrauterine hypoxia and birth asphyxia, birth trauma, and convulsion in newborn
3. Pediatric cardiovascular disease	CHD (left to right shunt), maternal complications of pregnancy, respiratory distress syndrome, emphysema, and congenital pneumonia
	Congestive heart failure and cardiomegaly
	Valvular heart disease (tricuspid or pulmonary valve disorders), and left heart failure
	Valvular heart disease (mitral or aortic valve disorders), rheumatic heart disease, and left-sided CHD
	Other CHD and congenital anomalies of peripheral vascular system
	Conduction disorder and cardiac dysrhythmias
	CHD (RL shunt), Von Willebrand disease, and acute cor pulmonale
	Myocarditis
4. Bronchopulmonary dysplasia	Bronchopulmonary dysplasia, fetal and neonatal hemorrhage, cerebral cyst, and neonatal hematologic disorder
5. Isolated pediatric pulmonary hypertensive vascular disease or isolated pediatric PAH	Hereditary hemorrhagic telangiectasia and iron metabolism disorder

(*Continued*)

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Table 2. Continued

Panama Classification of PH	Network-Derived Comorbidity Clusters
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes	Down syndrome and myoneural disorder
	DiGeorge syndrome, velo cardiofacial syndrome, primary immunodeficiency, and Tetralogy of Fallot
	Edwards syndrome, Patau syndrome, Hirschsprung, and magnesium metabolism disorder
	Cri-du-chat syndrome, other chromosomal anomalies, other autosomal deletion syndromes, and rickets
	Turner syndrome (gonadal dysgenesis) and drug withdrawal syndrome
	Congenital anomalies of skull and face and choanal atresia
	Congenital anomalies of larynx/trachea, diseases of vocal cord, and stricture/stenosis of esophagus
	Multiple congenital anomalies, congenital intestinal atresia and stenosis, congenital anomalies of kidney, and congenital malrotation of intestine
	Congenital musculoskeletal deformities, delay in development, and hearing loss
	Adrenogenital disorder, adrenal hypofunction, and microcephaly
	Disorder of muscle ligament and fascia abnormality of gait and spontaneous ecchymoses
	Situs inversus and congenital spleen anomaly
7. Pediatric lung disease	Interstitial lung disease and chronic bronchitis
	Bronchiectasis, pneumocystosis, and cystic fibrosis
	Pneumonia, pneumonitis, and malnutrition
	Pulmonary eosinophilia, edema of larynx, and cerebrovascular disorder
	Sleep apnea and intellectual disability
8. Pediatric thromboembolic disease	Thromboembolism, compression of vein, and hemorrhagic disorder because of intrinsic factor
	Pulmonary embolism and endocarditis
9. Pediatric hypobaric hypoxic exposure	N/A (there are no diagnosis codes for hypobaric hypoxic exposure)
10. Pediatric pulmonary vascular disease associated with other system disorders	Portal hypertension and chronic liver disease
	Raynaud phenomenon, systemic sclerosis, systemic vasculitis, and other CTD
	Juvenile idiopathic arthritis and hemophagocytic syndrome
	Systemic lupus erythematosus, nephritis, and chronic kidney disease
	Sickle cell disease, acute chest syndrome, and hereditary hemolytic anemia
	Acquired hemolytic anemia and anorexia (loss of appetite)
	Thrombocytopenia, aplastic anemia, leukocytopenia, neutropenia, and drug-induced pancytopenia
	Coagulation defect, iron deficiency anemia, and leukocytosis
	Splenomegaly and fistula of stomach or duodenum
	Glycogen storage disorder, hereditary muscular dystrophy, and cardiomyopathy
	Hepatomegaly, edema, hydrops fetalis, and edema
	Pleurisy, noninfectious disorders of lymphatic channels, and pericardium disorder

A clinical classification of PH focusing on the causative factors in pediatric PH. CHD indicates congenital heart disease; CTD, connective tissue disorder; N/A, nonapplicable; PH, pulmonary hypertension; and PPHN, pulmonary hypertension in newborn.

The association of PH with intestinal malabsorption and perinatal digestive system disorders may capture a rare treatable form of PH that is linked to chronic nutritional deficiencies. Severe vitamin deficiencies have been documented in patients with PH, whereby repletion of these vitamins led to the resolution of PH. A recent study showed a high prevalence of vitamin D deficiency in patients with PH and a significant inverse correlation between vitamin D serum levels and disease severity.[47] Furthermore, thiamine deficiency resulting in cardiovascular beriberi has also been reported as a rare reversible cause of PH.[48] PH associated with vitamin C deficiency in the setting of pulmonary complications has been documented in several patients.[49,50] PH in these patients may be a result of reduced synthesis of NO, a potent mediator of vascular muscle relaxation. Vitamin C is also essential for the regulation of hypoxia-inducible family of transcription factors; deficiency in vitamin C can result in the inactivation of hypoxia-inducible factor activity, leading to deleterious pulmonary vasoconstriction and PH.

Discovery of Unknown Subtypes

Several network-derived comorbidity clusters do not fall into any of the categories in the WHO and Panama classifications.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Table 3. Rare Subtypes Identified Through Network Analysis

Network-Derived Comorbidity Clusters	Published Evidence Supporting Subtype Validity
JIA and hemophagocytic syndrome	The co-occurrence of PAH in patients with systemic-onset JIA and macrophage activation syndrome has been documented in several case series.[31,32]
GSD, hereditary muscular dystrophy, and cardiomyopathy	This cluster captures the characteristic features of type II GSD. PH in type II GSD has been reported in several case studies.[34,35]
Situs inversus and congenital spleen anomaly	This cluster captures the characteristic features of heterotaxy syndrome. PH associated with heterotaxy syndrome has been documented in several reports.[36,37]
Cri-du-chat syndrome, other chromosomal anomalies, other autosomal deletion syndromes, and rickets	Case reports have documented the co-occurrence of PH in children with Cri-du-chat, caused by underlying congenital heart disease.[38,39]
Turner syndrome (gonadal dysgenesis) and drug withdrawal syndrome	Severe PH in the setting of cardiovascular abnormalities had been reported in children with Turner syndrome.[40,41]
Prader–Willi syndrome, abnormal weight gain, and aneurysm	A case report documented a sudden death secondary to PH in a child with Prader–Willi syndrome.[42] Obstructive sleep apnea and other obesity-related comorbidities may have contributed to the development of PH.
Adrenogenital disorder, adrenal hypofunction, and microcephaly	This cluster may represent SLOS. The co-occurrence of SLOS and PPHN or PAH has been documented in patients with altered expression of caveolin-1.[43,44]
Disorder of muscle ligament and fascia, abnormality of gait, and spontaneous ecchymoses	This cluster contains symptoms suggestive of EDS. Spontaneous vascular or visceral rupture is a characteristic feature of vascular EDS, a subtype of EDS caused by mutations in the *COL3A1* gene. The co-occurrence of EDS and mild PH has been documented in 2 patients.[46]
Perinatal digestive system disorders and intestinal malabsorption	Severe vitamin deficiencies in the setting of pulmonary complications have been documented in several patients with PH, whereby repletion of these vitamins led to the resolution of PH.[47–50]

EDS indicates Ehlers–Danlos syndrome; GSD, glycogen storage disorder; JIA Juvenile idiopathic arthritis; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and SLOS, Smith–Lemli–Opitz syndrome.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Of note, many of these clusters are linked to neurological defects not commonly thought to be associated with PH, including encephalocele, hydrocephalus, microcephaly, periventricular leukomalacia, and congenital brain reduction deformities (Table 4). It is well established that children with severe neurological impairments are predisposed to respiratory problems that occur as a direct consequence of the underlying disability. For example, oropharyngeal motor problems associated with neurological dysfunctions can lead to recurrent aspiration and pneumonia.[51] Chiari malformation associated with hydrocephalus can cause both maldevelopment of the brain stem respiratory control centers and central sleep apnea.[52] Neurological impairments are also common among children requiring mechanical ventilation at the intensive care unit; PH in these patients may be secondary to mechanical ventilation management. Although we are unable to ascertain the causes of PH observed in our study cohort, our analysis suggests that the association of neurological defects with PH may be under-recognized and deserves further characterization.

Secondary Analysis: RHC Cohort

Of the 1583 patients included in the primary study cohort of children, 308 underwent RHC during the study period. Subject attrition was likely a result of the limited observation period captured in our data set, spanning a period of only 3 years; thus, patients who underwent RHC outside the study observation period would have been missed. Furthermore, published studies have consistently reported that many PH patients do not receive RHC as part of their diagnostic workup, despite being the diagnostic gold standard for PH.[9,29,53]

Of the 186 comorbidities found to be significantly associated with PH in the primary study cohort, 168 were also significantly associated with PH in the RHC cohort, of which 119 were observed in ≥4 patients with PH (Online Table B1c). A larger proportion of patients in the RHC cohort had congenital heart disease, compared with the primary cohort (86.0% [n=1361] versus 67.9% [n=209]; $P<0.0001$). This may reflect a higher utilization of RHC among PH patients treated by cardiologists.[29] There was also a substantial drop in the proportion of patients who had early-life respiratory conditions known to be associated with PH, including pulmonary hypertension in newborn (25.6% [n=406] versus 11.7% [n=36]; $P<0.0001$), congenital cystic lung (11.4% [n=180] versus n=0; $P<0.0001$), and diaphragmatic hernia (3.9% [n=61] versus 0.6% [n=2]; $P=0.0041$).

A separate Bayesian comorbidity network was developed for the RHC cohort. The input of the network comprised 119 comorbidities that were significantly associated with PH and were observed in ≥4 patients in the RHC cohort. The inferred network contained 200 relations, described in further details in Online Table B2b.

Cluster analysis of the comorbidity network identified a subset of the subtypes derived from the primary study cohort. These included all the major subtypes (sensitivity: 100%; κ score: 100%) and 17 of 26 minor subtypes (sensitivity: 65%; κ score: 100%) defined in the WHO classification (Online Table B3a), and 8 of 10 subtypes defined in the Panama classification (sensitivity: 80%; κ score: 100%; Online Table B3b). Subtypes that were not captured included

Table 4. Unclassified Network-Derived Comorbidity Clusters

Encephalocele, cerebral compression, bilirubin excretion disorder, and hepatitis
Epilepsy and anoxic brain damage
Intracranial hemorrhage and hydrocephalus
Congenital brain reduction deformities, eosinophilia, phlebitis, and thrombophlebitis
Periventricular leukomalacia and pyogenic granuloma
Intestinal obstruction and intestinal vascular insufficiency
Perinatal digestive system disorders and intestinal malabsorption
Gastrointestinal hemorrhage, gastroenteritis, and colitis
Disorder of eye movement and lack of co-ordination
Disturbance of salivary secretion, speech disturbance, and childbirth complications
Mixed acid base balance disorder, calculus of kidney, and gastroparesis

PH associated with hereditary hemorrhagic telangiectasia, connective tissue disorders, systemic vasculitis, and GSD—these conditions were significantly associated with PH in the RHC cohort but were observed in fewer than 4 patients and were, therefore, excluded from the network analysis. Rare genetic disorders discerned in the primary analysis, such as Cri-du-chat and Prader–Willi syndromes, were also not captured in the network analysis because of the small number of patients with these conditions.

Discussion

We demonstrated that comorbidity patterns of patients with PH captured in a Bayesian network can be stratified into subtypes that are biologically and clinically informative. Our algorithmic methods automatically relearned most of the major PH subtypes with known pathological basis defined by the WHO classification. Although the similarity of the derived network structure to current taxonomy of PH provides face validity to the approach, it also offers some novel insights.

Specifically, the network approach enriches the current classification of PH. First, it captured several subtypes documented in only a few case studies for which evidence for systematic association remains lacking. This both validates the approach and provides impetus for deeper investigation of the disease subtypes. Clinicians should consider PH when dealing with patients with relevant conditions, whereas studies exploring the molecular and biological connections may reveal important insights. Our analysis also identified rare subtypes with findings consistent with several well-described genetic syndromes. Although we were unable to validate whether these patients indeed had the pathogenic mutations in the absence of genetic data, disease patterns identified through network analysis suggest future research in these areas may accelerate subtype discovery and relevance to PH more broadly. In the same way in which novel genetic associations in PH stimulate new avenues of research, so too may novel phenotypic associations prompt important discoveries related to disease susceptibility, and perhaps resiliency.

To construct the comorbidity network, we applied Bayesian model averaging technique to find a network model that best fits the underlying data. The approach is uniquely suited to accommodate the inherent uncertainties of biological processes and to minimize the effects of noise in the data. In maximizing specificity, however, other subtypes may have been missed. Furthermore, in defining comorbidity clusters, we have applied a strict partitioning rule, whereby each comorbidity belongs exactly to one cluster. Although this approach produces a model that is easier to interpret, the full expression of subtypes may not have been captured. As shown in Figure 4, many comorbidities are linked to comorbidities belonging to another cluster. Of note, a majority of nodes are connected either directly or indirectly to congenital heart disease, the most common comorbidity in our study cohort. Shared features among multiple clusters may also reflect the overlapping phenotypes of PH, an increasingly recognized phenomenon.[14] Future research should explore methods that would facilitate the delineation of subtypes with overlapping manifestations and pathogeneses.

There are several limitations to our study. First, because our study relied on administrative claims, the diagnoses coded for billing purposes may not reflect actual comorbidities in the patients. To improve case identification specificity, we included only diagnoses with ≥2 encounter visits—an algorithm that has been validated in previous studies.[23–25] We further performed a sensitivity analysis with a more stringent case identification algorithm, considering diagnoses with ≥4 encounter visits during the study period; the association between PH and the identified comorbidities remained significant. Although it may not be possible to fully address diagnostic coding inaccuracies in administrative claims, we were able to discern comorbidity relations and derive subtypes that are biologically meaningful, thus lending support to the validity of the study approach. A further strategy we used to reduce uncertainties in our analysis is the exclusion of comorbidities that occurred in fewer than 4 patients and network relations with low probabilistic strengths (Methods A1 in the Online Data Supplement). In doing so, we may not have captured all the comorbidities and subtypes that were present in our study cohort.

A further limitation of our study lies in the difficulty in ascertaining the study cohort—in the absence of RHC results, we were unable to definitively confirm a diagnosis of PH.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Nonetheless, the number of children with PH identified in the primary analysis was within the estimated population prevalence of PH.[17] We have also conducted a secondary analysis of children who underwent RHC and were diagnosed with PH. However, given the limited study period, and the persistent underuse of recommended diagnostic tests in contemporary clinical practice,[53,54] restricting the study population results in the exclusion of several important subtypes. Nonetheless, the ability to reproduce similar subtypes based on the RHC cohort further validates the approach.

Claims data also have limited resolution, and because comorbidities associated with different PH subtypes can often coexist, we were unable to ascertain the PH subtypes of individual patients based on concomitant conditions alone. For example, patients with systemic sclerosis can have both PAH and pulmonary fibrosis; differentiating PAH from PH associated with pulmonary fibrosis can only be achieved through RHC. Finally, although our claims-based data set formed the largest data set on pediatric PH to date, we were unable to capture all PH subtypes seen globally, including those associated with HIV and schistosomiasis.

Although there are limitations to claims data, the availability of a large number of patients makes it possible to study the relationships between rare diseases, which may not have been observable in traditional studies involving chart reviews or surveys. Furthermore, claims data are systematically collected and provide longitudinal information that crosses facilities, geographical locations, and population demographics, thereby enhancing the generalizability of the research and limiting selection biases.

Conclusions

Data-driven discovery of disease phenotypes has enormous potential for advancing our understanding of complex diseases. By modeling the complex interactions of symptoms governing disease subtypes recorded in longitudinal data sets, rare subtypes that are difficult to discern through clinical observations can be identified. Further advances linking disease subtypes to therapeutic response, disease outcomes, and the molecular profiles of individual subtypes will provide impetus for the development of more effective and targeted therapies.

Acknowledgments

We thank the Pediatric Pulmonary Hypertension Network and the National Heart, Lung, and Blood Institute of the National Institutes of Health Pediatric Pulmonary Vascular Disease Outcomes Bioinformatics Clinical Coordinating Center Investigators for their valuable comments. Michelle Heinz (Boston Children's Hospital) is gratefully acknowledged for her assistance in co-ordinating the study.

Sources of Funding

Research reported in this publication was supported by Aetna, Inc, and the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number U01HL121518. M.-S. Ong and A. Geva are supported by the National Institutes of Health (T15LM007092, T32HD040128, and L40HL133929). The funding bodies played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article; and decision to submit the article for publication.

Disclosures

None.

References

1. National Research Council Committee on A Framework for Developing a New Taxonomy of Disease. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. National Academies Press. 2011.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34–D41. doi: 10.1016/j.jacc.2013.10.029.
3. McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, Pepke-Zaba J, Pulido T, Rich S, Rosenkranz S, Suissa S, Humbert M. Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol*. 2013;62:D51–D59. doi: 10.1016/j.jacc.2013.10.023.
4. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. *Chest*. 2014;146:476–495. doi: 10.1378/chest.14-0527.
5. Brown LM, Chen H, Halpern S, Taichman D, McGoon MD, Farber HW, Frost AE, Liou TG, Turner M, Feldkircher K, Miller DP, Elliott CG. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. *Chest*. 2011;140:19–26. doi: 10.1378/chest.10-1166.
6. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, Keogh A. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: the delay study. *Pulm Circ*. 2013;3:89–94. doi: 10.4103/2045-8932.109919.
7. Wilkens H, Grimminger F, Hoeper M, Stähler G, Ehlken B, Plesnila-Frank C, Berger K, Resch A, Ghofrani A. Burden of pulmonary arterial hypertension in Germany. *Respir Med*. 2010;104:902–910. doi: 10.1016/j.rmed.2010.01.002.
8. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349.
9. Deaño RC, Glassner-Kolmin C, Rubenfire M, Frost A, Visovatti S, McLaughlin VV, Gomberg-Maitland M. Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter RePHerral study. *JAMA Intern Med*. 2013;173:887–893. doi: 10.1001/jamainternmed.2013.319.
10. Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, Kiowski W, Kostuk W, Krum H, Levine B, Rizzon P, Soler J, Swedberg K, Anderson S, Demets DL. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. *J Card Fail*. 2005;11:12–20.
11. Haywood GA, Sneddon JF, Bashir Y, Jennison SH, Gray HH, McKenna WJ. Adenosine infusion for the reversal of pulmonary vasoconstriction in biventricular failure. A good test but a poor therapy. *Circulation*. 1992;86:896–902.
12. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. *Eur Respir J*. 2011;37:665–677. doi: 10.1183/09031936.00056110.
13. Ivy DD, Abman SH, Barst RJ, Berger RM, Bonnet D, Fleming TR, Haworth SG, Raj JU, Rosenzweig EB, Schulze Neick I, Steinhorn RH, Beghetti M. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D117–D126. doi: 10.1016/j.jacc.2013.10.028.
14. Cerro MJ, Abman S, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, Haworth SG, Ivy D, Lopes AA, Raj JU, Sandoval J, Stenmark K, Adatia I. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ*. 2011;1:286–298. doi: 10.4103/2045-8932.83456.
15. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing ZC, Bonnet D, Schulze-Neick I, Barst RJ. Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet*. 2012;379:537–546. doi: 10.1016/S0140-6736(11)61621-8.
16. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137:376–387. doi: 10.1378/chest.09-1140.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

17. van Loon RL, Roofthooft MT, Hillege HL, ten Harkel AD, van Osch-Gevers M, Delhaas T, Kapusta L, Strengers JL, Rammeloo L, Clur SA, Mulder BJ, Berger RM. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation*. 2011;124:1755–1764. doi: 10.1161/CIRCULATIONAHA.110.969584.
18. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. *Heart*. 2010;96:1401–1406. doi: 10.1136/hrt.2009.182378.
19. Fraisse A, Jais X, Schleich JM, di Filippo S, Maragnès P, Beghetti M, Gressin V, Voisin M, Dauphin C, Clerson P, Godart F, Bonnet D. Characteristics and prospective 2-year follow-up of children with pulmonary arterial hypertension in France. *Arch Cardiovasc Dis*. 2010;103:66–74. doi: 10.1016/j.acvd.2009.12.001.
20. Miller DP, Gomberg-Maitland M, Humbert M. Survivor bias and risk assessment. *Eur Respir J*. 2012;40:530–532. doi: 10.1183/09031936.00094112.
21. Chan SY, Loscalzo J. The emerging paradigm of network medicine in the study of human disease. *Circ Res*. 2012;111:359–374. doi: 10.1161/CIRCRESAHA.111.258541.
22. Hidalgo CA, Blumm N, Barabási AL, Christakis NA. A dynamic network approach for the study of human phenotypes. *PLoS Comput Biol*. 2009;5:e1000353. doi: 10.1371/journal.pcbi.1000353.
23. Lix L, Yogendran M, Burchill C, Metge C, McKeen N, Moore D, Bond R. *Defining and Validating Chronic Diseases: An Administrative Data Approach*. Winnipeg: Manitoba Centre for Health Policy. 2006.
24. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, Hill MD, Ghali WA, McAlister FA; Hypertension Outcome and Surveillance Team of the Canadian Hypertension Education Programs. Validation of a case definition to define hypertension using administrative data. *Hypertension*. 2009;54:1423–1428. doi: 10.1161/HYPERTENSIONAHA.109.139279.
25. Rector TS, Wickstrom SL, Shah M, Thomas Greeenlee N, Rheault P, Rogowski J, Freedman V, Adams J, Escarce JJ. Specificity and sensitivity of claims-based algorithms for identifying members of Medicare+Choice health plans that have chronic medical conditions. *Health Serv Res*. 2004;39:1839–1857. doi: 10.1111/j.1475-6773.2004.00321.x.
26. Pearl, J. *Causality: Models, Reasoning and Inference*. Cambridge: MIT Press. 2000.
27. Pons P, Latapy M. Computing communities in large networks using random walks. In: *Computer and Information Sciences-ISCIS 2005*. Heidelberg: Springer Berlin; 2005:284–293.
28. Link J, Glazer C, Torres F, Chin K. International Classification of Diseases coding changes lead to profound declines in reported idiopathic pulmonary arterial hypertension mortality and hospitalizations: implications for database studies. *Chest*. 2011;139:497–504. doi: 10.1378/chest.10-0837.
29. Duarte AG, Lin YL, Sharma G. Incidence of right heart catheterization in patients initiated on pulmonary arterial hypertension therapies: a population-based study. *J Heart Lung Transplant*. 2017;36:220–226. doi: 10.1016/j.healun.2016.07.017.
30. Harrison RE, Flanagan JA, Sankelo M, et al. Molecular and functional analysis identifies ALK-1 as the predominant cause of pulmonary hypertension related to hereditary haemorrhagic telangiectasia. *J Med Genet*. 2003;40:865–871.
31. Kimura Y, Weiss JE, Haroldson KL, et al; Childhood Arthritis Rheumatology Research Alliance Carra Net Investigators. Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2013;65:745–752. doi: 10.1002/acr.21889.
32. Li EK, Tam LS. Pulmonary hypertension in systemic lupus erythematosus: clinical association and survival in 18 patients. *J Rheumatol*. 1999;26:1923–1929.
33. Humbert M, Monti G, Brenot F, Sitbon O, Portier A, Grangeot-Keros L, Duroux P, Galanaud P, Simonneau G, Emilie D. Increased interleukin-1 and interleukin-6 serum concentrations in severe primary pulmonary hypertension. *Am J Respir Crit Care Med*. 1995;151:1628–1631. doi: 10.1164/ajrccm.151.5.7735624.
34. Inoue S, Nakamura T, Hasegawa K, Tadaoka S, Samukawa M, Nezuo S, Sawayama T, Higashi Y, Shirabe T. [Pulmonary hypertension due to glycogen storage disease type II (Pompe's disease): a case report]. *J Cardiol*. 1989;19:323–332.
35. Kobayashi H, Shimada Y, Ikegami M, Kawai T, Sakurai K, Urashima T, Ijima M, Fujiwara M, Kaneshiro E, Ohashi T, Eto Y, Ishigaki K, Osawa M, Kyosen SO, Ida H. Prognostic factors for the late onset Pompe disease with enzyme replacement therapy: from our experience of 4 cases including an autopsy case. *Mol Genet Metab*. 2010;100:14–19. doi: 10.1016/j.ymgme.2010.01.015.
36. Brandenburg VM, Krueger S, Haage P, Mertens P, Riehl J. Heterotaxy syndrome with severe pulmonary hypertension in an adult. *South Med J*. 2002;95:536–538.
37. Yousuf T, Kramer J, Jones B, Keshmiri H, Dia M. Pulmonary hypertension in a patient with congenital heart defects and heterotaxy syndrome. *Ochsner J*. 2016;16:309–311.
38. Hills C, Moller JH, Finkelstein M, Lohr J, Schimmenti L. Cri du chat syndrome and congenital heart disease: a review of previously reported cases and presentation of an additional 21 cases from the Pediatric Cardiac Care Consortium. *Pediatrics*. 2006;117:e924–e927. doi: 10.1542/peds.2005-1012.
39. Levy B, Dunn TM, Kern JH, Hirschhorn K, Kardon NB. Delineation of the dup5q phenotype by molecular cytogenetic analysis in a patient with dup5q/del 5p (cri du chat). *Am J Med Genet*. 2002;108:192–197.
40. Bechtold SM, Dalla Pozza R, Becker A, Meidert A, Döhlemann C, Schwarz HP. Partial anomalous pulmonary vein connection: an underestimated cardiovascular defect in Ullrich-Turner syndrome. *Eur J Pediatr*. 2004;163:158–162. doi: 10.1007/s00431-003-1384-7.
41. Tinker A, Uren N, Schofield J. Severe pulmonary hypertension in Ullrich-Noonan syndrome. *Br Heart J*. 1989;62:74–77.
42. Bakker B, Maneatis T, Lippe B. Sudden death in Prader-Willi syndrome: brief review of five additional cases. Concerning the article by U. Eiholzer et al.: deaths in children with Prader-Willi syndrome. A contribution to the debate about the safety of growth hormone treatment in children with PWS (Horm Res 2005;63:33-39). *Horm Res*. 2007;67:203–204. doi: 10.1159/000097928.
43. Katheria AC, Masliah E, Benirschke K, Jones KL, Kim JH. Idiopathic persistent pulmonary hypertension in an infant with Smith-Lemli-Opitz syndrome. *Fetal Pediatr Pathol*. 2010;29:373–379. doi: 10.3109/15513815.2010.512045.
44. Austin ED, Ma L, LeDuc C, Berman Rosenzweig E, Borczuk A, Phillips JA, 3rd, et al. Whole exome sequencing to identify a novel gene (caveolin-1) associated with human pulmonary arterial hypertension. *Circ Cardiovasc Genet*. 2012;5:336–343.
45. Nowaczyk M. Smith-Lemli-Opitz syndrome. *GeneReviews*. 2013.
46. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104:2797–2802.
47. Tashtoush B, Mehta J, Benavides J, Memarpour R, Kachur S, Gleason JB, Hadeh A, Smolley L, Rahaghi F. The prevalence of vitamin D deficiency in pulmonary hypertension patients and its correlation with parameters of pulmonary hypertension severity. *Am J Respir Crit Care Med*. 2016;193:A7358.
48. Goto Y, Awata M, Uematsu M, Yano M, Morozumi T, Kotani J, Watanabe T, Onishi T, Iida O, Sera F, Nanto S, Nagata S. [Shoshin beriberi complicating severe pulmonary hypertension: a case report]. *J Cardiol*. 2007;49:361–365.
49. Duvall MG, Pikman Y, Kantor DB, Ariagno K, Summers L, Sectish TC, Mullen MP. Pulmonary hypertension associated with scurvy and vitamin deficiencies in an autistic child. *Pediatrics*. 2013;132:e1699–e1703. doi: 10.1542/peds.2012-3054.
50. Kupari M, Rapola J. Reversible pulmonary hypertension associated with vitamin C deficiency. *Chest*. 2012;142:225–227. doi: 10.1378/chest.11-1857.
51. Seddon PC, Khan Y. Respiratory problems in children with neurological impairment. *Arch Dis Child*. 2003;88:75–78.
52. Dauvilliers Y, Stal V, Abril B, Coubes P, Bobin S, Touchon J, Escourrou P, Parker F, Bourgin P. Chiari malformation and sleep related breathing disorders. *J Neurol Neurosurg Psychiatry*. 2007;78:1344–1348. doi: 10.1136/jnnp.2006.108779.
53. McLaughlin VV, Langer A, Tan M, Clements PJ, Oudiz RJ, Tapson VF, Channick RN, Rubin LJ; Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative (PAH-QuERI) Investigators. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. *Chest*. 2013;143:324–332. doi: 10.1378/chest.11-3060.
54. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RM; TOPP Investigators. Acute vasodilator response in pediatric pulmonary arterial hypertension: current clinical practice from the TOPP registry. *J Am Coll Cardiol*. 2016;67:1312–1323. doi: 10.1016/j.jacc.2016.01.015.

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

Circulation Research
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learning a Comorbidity-Driven Taxonomy of Pediatric Pulmonary Hypertension

Mei-Sing Ong, Mary P. Mullen, Eric D. Austin, Peter Szolovits, Marc D. Natter, Alon Geva, Tianxi Cai, Sek Won Kong and Kenneth D. Mandl

Circ Res. 2017;121:341-353; originally published online June 13, 2017;
doi: 10.1161/CIRCRESAHA.117.310804
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/121/4/341

Data Supplement (unedited) at:
http://circres.ahajournals.org/content/suppl/2017/06/13/CIRCRESAHA.117.310804.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org//subscriptions/

Downloaded from http://circres.ahajournals.org/ by guest on October 14, 2017

SUPPLEMENTAL MATERIAL

A. Detailed Methods

A1. Bayesian comorbidity network

The construction of a network entails a two-step process: *structure learning* and *parameter estimation*. Structure learning involves determining the network structure that most accurately reflects the observed data [1-3]. In this study, we applied a score-based structure learning algorithm to search for the best-fit model. Specifically, the "tabu search" learning process [2] was used to search through the space of structures, the Bayesian Dirichlet equivalent score (with equivalent sample size of ten) [3] was calculated for each candidate network to measure its goodness of fit, and the network with the highest score was selected. The resulting network was represented as a directed acyclic graph. The next step, parameter estimation, involves finding a set of probability distribution parameters for the learned network that best explains the observed data using Bayes estimation [4]. Given the learned conditional distribution parameters, we estimated the strength of the relations between node pairs by assuming a noisy-OR model, whereby the influence of each parent on a node is independent of other parents. Accordingly, the weight assigned to a directed edge from node *i* to *j* was quantified by calculating the conditional probability of *j* given *i*.

In finding the "best-fit" model, over-fitting can occur when the resultant model describes random error or noise instead of the underlying distribution of the data. To improve the statistical robustness of our analysis, we applied the following strategies. First, instead of building a single model, a model averaging technique [5] was used where multiple best-scored networks were developed using 1,000 subsamples of the dataset generated through bootstrap resampling; the final model was estimated by averaging over the highest scoring networks, such that only network edges (i.e. comorbidity relations) that were statistically significant were selected for inclusion [6], as described Online Box I. The parameters of the selected edges were then estimated using the full dataset in the final network. This technique allows the identification of network features that are robust to perturbations of the observations [5-6]. Second, prior knowledge about the biology of PH informed construction of the set of comorbidities used for developing the network. For example, it is well-established that right and left heart diseases have distinct disease pathophysiology. We therefore grouped diagnosis codes pertaining to left heart disease into a single category, and diagnosis codes pertaining to right heart disease into a separate category. By reducing the number of parameters relative to the number of observations, we restrict the degrees of freedom during learning to obtain a more robust model. A full list of comorbidities is provided in Table B1a. Third, to further reduce the complexity of the model, we considered only comorbidities that were found, in bivariate analyses, to be significantly associated with PH, compared with the general population without PH, and selected those for which the lower 95% confidence interval bound for the odds ratio was greater than five. We also excluded comorbidities that occurred in fewer than four PH patients, since a small number of observations would not suffice to distinguish between true and spurious correlations.

Online Box I. Algorithm for the identification of statistically significant features in the comorbidity network

Step 1: Bootstrap resampling

For $b = 1,2, \dots m$:

(1) Randomly sample a new dataset X_b from the original data X

(2) Learn the structure of the graphical model $G = (V, E_b)$ from X_b

In the current study, the number of iterations m was set to 1,000.

Step 2: Model averaging

For each edge e_i learned through the bootstrap resampling process, estimate the probability that it is present in the true network structure $G_0 = (V, E_0)$ as:

$$\hat{P}(e_i) = \frac{1}{m}\sum_{b=1}^{m} s_b$$

$$s_b = \begin{cases} 1 \; if \; e_i \in E_b \\ 0 \; otherwise \end{cases}$$

The empirical probabilities $\hat{P}(e_i)$ are known as *edge intensities* or *arc strengths*, and can be interpreted as the degree of confidence that e_i is present in the network structure G_0 describing the true dependence structure of the dataset.

Step 3: Selection of significant edges

Significant edges were identified by defining a threshold t, such that only edges with edge intensity greater than t were included in the final model. Thus:

$$e_i \in E_b \; if \; p_{(i)} > \; F^{-1}_{p_{(.)}}(t)$$

where $F^{-1}_{p_{(.)}}(t)$ is the quantile function:

$$F^{-1}_{p_{(.)}}(t) = inf_{x \in \mathbb{R}} \{F_{p_{(.)}}(x) \geq t\}$$

The threshold t was estimated by applying L1 norm to approximate the ideal asymptomatic empirical $F_{p_{(.)}}(t)$:

$$L_1(t; p_{(i)}) = \int \left| F_{p_{(.)}}(x) - \; F_{p_{(.)}}(x; t) \right| dx$$

In the current study, edges with a threshold t greater than 0.50 were considered significant. A more detailed description of the method is provided in [3].

A2. Network clustering analysis

To define PH subtypes, we partitioned the network into subgraphs comprising highly connected comorbidities using a strict partitioning rule whereby each comorbidity belongs to exactly one cluster. The graph partitioning process involves merging nodes agglomeratively. Specifically, a random walk clustering approach was applied to identify the pathways that were closest to each node in the network [7]. The process involves a random walk on a network for *t* number of steps: a walker at node *i* and step *t* randomly selects one of its neighbors to which it hops at step $t + 1$; the probability of walking from node *i* to node *j* is quantified by the weight of the edge divided by the total number of nodes directly linked to *i*. Similarity between two nodes is measured by the L^2 distance between their respective transition probabilities, and cluster analysis involves merging nodes such that the mean of the squared distances between each node and its cluster is minimized. A more detailed description of this approach is provided in Online Box II. The length of *t* must be sufficiently long to gather enough information about the topology of the graph, but short enough to detect clusters. To guide the choice of *t*, we applied a commonly used measure known as “modularity” to quantify the strength of a network division. A positive value of modularity is indicative of the potential presence of community structure [8]. We chose a *t* that maximized modularity; in our analysis, *t* of 3 was found to be optimal. In the cluster analysis, we excluded edges with a weight of less than 0.2, in order to capture the strongest relations.

Online Box II. Network clustering algorithm

A network can be represented as an adjacency matrix A, where A_{ij} is the weight of nodes i and j. The degree of node i can be defined as: $d(i) = \sum_j A_{ij}$.

A random walk process on the network is performed: at each step t, a walker moves from one node to another chosen randomly and uniformly among its neighbors. The transition probability from node i and j can be defined as: $P_{ij} = \frac{A_{ij}}{d(i)}$

The probability of going from i to j through a random walk of length t is P_{ij}^t, and the probability of going from a cluster C to node j in t steps is: $P_{C_j}^t = \frac{1}{|C|}\sum_{i \in C} P_{ij}^t$.

The cluster discovery process involves the following steps:

1. Form an initial partition $P_1 = \{\{v\}, v \in V\}$ of the graph into n clusters, where each cluster contains a single node. Compute distance between all adjacent nodes based on the transition probabilities of the random walk process.

   Let i and j be two nodes. The distance between the nodes is quantified as follows:

   $$r_{ij} = \sqrt{\sum_{k=1}^{n} \frac{(P_{ik}^t - P_{jk}^t)^2}{d(k)}}$$

   The equation can be generalized to describe the distance between two clusters C_1, C_2:

   $$r_{C_1 C_2} = \sqrt{\sum_{k=1}^{n} \frac{(P_{C_1 k}^t - P_{C_2 k}^t)^2}{d(k)}}$$

For each step k:

2. Choose two clusters to merge according to Ward's method, whereby the mean of the squared distances between each node and its cluster is minimized:

   $$\sigma_k = \frac{1}{n} \sum_{C \in P_k} \sum_{i \in C} r_{iC}^2$$

3. Merge the 2 clusters into a new cluster $C_3 = C_1 \cup C_2$ and create the new partition: $P_{k+1} = (P_k \backslash \{C_1, C_2\}) \cup \{C_3\}$.

4. Update the distances between clusters.

5. Stop algorithm after $n - 1$ steps.

B. Supplemental Tables

B1. Comorbidity analysis

This section details comorbidities that are significantly associated with pulmonary hypertension (PH). OR is the odds ratio of having a comorbidity, comparing children with PH against those without PH, calculated using chi-square statistic. Bonferroni correction was applied to correct for multiple hypotheses testing; a p-value of less than 0.000065 was considered statistically significant.

Table B1a. Primary analysis – study cohort comprised children with two or more healthcare encounters for PH during the study period.

Comorbidity	N		OR (95% CI)
	PH (n=1,583)	Control (n=6,941,680)	
CHD LR shunt	918	26,283	363.2 (328.5 - 401.6)
Other CHD	611	16,632	261.7 (236.3 - 289.9)
Pneumonia	440	115,692	22.7 (20.3 - 25.4)
Respiratory distress syndrome	429	15,608	165.0 (147.5 - 184.5)
Pulmonary collapse	418	6,260	397.5 (354.5 - 445.7)
PPHN	406	1,255	1907.6 (1682.4 - 2163.0)
Cardiomegaly	360	3,369	606.2 (536.4 - 685.1)
Bronchopulmonary dysplasia	352	3,784	524.3 (463.7 - 592.7)
Pleurisy	300	6,011	269.8 (237.3 - 306.7)
Cardiac dysrhythmias	300	26,248	61.6 (54.3 - 69.9)
Delay in development	246	35,840	35.5 (30.9 - 40.6)
Neonatal hematological disorder	219	8,258	134.8 (116.7 - 155.7)
Left-sided CHD	206	6,806	152.4 (131.4 - 176.8)
Congestive heart failure	204	1,311	783.2 (669.6 - 916.0)
Primary atelectasis	199	2,224	448.6 (384.5 - 523.5)
Essential hypertension	196	20,560	47.6 (40.9 - 55.3)
Down syndrome	170	5,783	144.3 (122.8 - 169.5)
Valvular heart disease (right-sided)	164	4,754	168.6 (143.1 - 198.7)
Pulmonary insufficiency from trauma	156	2,531	299.7 (252.9 - 355.2)
Hypotension	156	5,239	144.7 (122.4 - 171.1)
Sleep apnea	154	18,262	40.9 (34.6 - 48.3)
Disorder of muscle, ligament, fascia	147	102.938	6.8 (5.7 - 8.1)
Fetal and neonatal hemorrhage	144	3,618	191.9 (161.2 - 228.5)
Neonatal endocrine/metabolic disturbances	142	15,080	45.3 (38.1 - 53.8)
Lack of coordination	141	28,005	24.1 (20.3 - 28.7)
Emphysema	134	3,770	170.2 (142.2 - 203.7)
Valvular heart disease (left-sided)	124	5,273	111.8 (92.9 - 134.6)
Rheumatic heart disease	122	1,869	310.1 (256.4 - 375.0)
Perinatal digestive system disorders	117	2,367	234.0 (193.0 - 283.7)
Thrombocytopenia	114	6,993	77.0 (63.5 - 93.2)
Congenital musculoskeletal deformities	110	39,368	13.1 (10.8 - 15.9)

Congenital anomalies of larynx, trachea, or bronchus	107	3,494	144.0 (118.0 - 175.7)
Pneumothorax	104	3,511	139.0 (113.6 - 170.0)
Epilepsy	99	30,303	15.2 (12.4 - 18.7)
Hearing loss	94	15,763	27.7 (22.5 - 34.2)
Cardiomyopathy	92	2,118	202.2 (163.1 - 250.6)
Pneumonitis	92	1,658	258.3 (208.1 - 320.5)
Conduction disorder	91	4,763	88.8 (71.8 - 110.0)
Thromboembolism	84	2,190	177.6 (142.0 - 222.1)
Acute kidney failure	83	2,722	141.1 (112.7 - 176.5)
Gastroenteritis and colitis	81	59,053	6.3 (5.0 - 7.9)
Congenital anomalies of diaphragm	77	349	1016.9 (790.5 - 1308.2)
Gastrointestinal hemorrhage	76	17,204	20.3 (16.1 - 25.6)
Primary immunodeficiency	75	9,095	37.9 (30.0 - 47.8)
Congenital lung agenesis, hypoplasia, dysplasia	75	430	802.8 (625.0 - 1031.3)
Hypothyroidism	75	27,186	12.6 (10.0 - 16.0)
Acute edema of lung	72	515	642.2 (499.3 - 826.1)
Interstitial lung disease	71	668	487.9 (380.1 - 626.4)
Cyanosis	70	1,535	209.2 (163.8 - 267.2)
Cerebral palsy	70	9,859	32.5 (25.6 - 41.4)
Hydrocephalus	68	4,205	74.1 (58.0 - 94.6)
Other chromosomal anomalies	65	2,862	103.8 (80.8 - 133.4)
Tetralogy of Fallot	64	1,832	159.6 (123.8 - 205.8)
Fluid overload disorder	63	676	425.6 (327.1 - 553.6)
Tachypnea of newborn	63	10,846	26.5 (20.6 - 34.1)
Congenital anomalies of kidney	62	10,200	27.7 (21.5 - 35.7)
Edema	61	7,621	36.5 (28.2 - 47.1)
Intestinal obstruction	61	5,627	49.4 (38.2 - 63.9)
Diaphragmatic hernia	61	1,572	176.9 (136.3 - 229.6)
Chronic liver disease	59	3,985	67.4 (51.9 - 87.6)
Pericardium disorder	58	1,114	237.0 (181.1 - 310.0)
Intestinal malabsorption	57	9,747	26.6 (20.4 - 34.6)
Abnormality of gait	56	20,658	12.3 (9.4 - 16.0)
Drug withdrawal syndrome	50	4,508	50.2 (37.8 - 66.6)
Childbirth complications	46	29,065	7.1 (5.3 - 9.5)
Malnutrition	45	3,220	63.0 (46.8 - 85.0)
Intrauterine hypoxia and birth asphyxia	45	1,999	101.6 (75.3 - 137.1)
Hepatomegaly	44	1,144	173.5 (127.8 - 235.4)
Congenital anomalies of skull and face bones	44	6,672	29.7 (22.0 - 40.1)
Convulsion in newborn	41	992	200.2 (145.8 - 274.8)
Coagulation defect	41	1,771	104.2 (76.1 - 142.6)
Congenital pneumonia	39	930	188.5 (136.3 - 260.7)
Speech disturbance	39	18,000	9.7 (7.1 - 13.4)
Nutritional deficiency	39	4,023	43.6 (31.7 - 59.9)
Intestinal vascular insufficiency	38	552	309.3 (221.8 - 431.3)
Multiple congenital anomalies	37	761	218.3 (156.4 - 304.8)
Pulmonary embolism	36	589	274.2 (195.2 - 385.4)
Chronic kidney disease	35	2,414	65.0 (46.4 - 91.1)
Leukocytosis	32	8,047	17.8 (12.5 - 25.2)

Iron deficiency anemia	31	11,940	11.6 (8.1 - 16.5)
Birth trauma	30	5,609	23.9 (16.6 - 34.3)
Intracranial hemorrhage	30	1,279	104.8 (72.7 - 151.1)
Pulmonary eosinophilia	28	654	191.1 (130.5 - 279.9)
Congenital intestinal atresia and stenosis	28	975	128.2 (87.8 - 187.2)
Neutropenia	28	5,015	24.9 (17.1 - 36.2)
CHD RL shunt	27	349	345.1 (232.6 - 512.1)
Abnormal weight gain	27	22,287	5.4 (3.7 - 7.9)
Abnormal involuntary movement	27	7,666	15.7 (10.7 - 23.0)
Microcephaly	27	1,692	71.2 (48.5 - 104.4)
Sickle cell disease	26	2,279	50.8 (34.4 - 75.1)
Pulmonary hemorrhage	26	169	685.9 (452.5 - 1039.6)
Dyspepsia	25	6,480	17.2 (11.6 - 25.5)
Umbilical hernia	25	7,233	15.4 (10.4 - 22.9)
Hereditary hemolytic anemia	23	3,822	26.8 (17.7 - 40.4)
Diabetic mother syndrome	22	4,218	23.2 (15.2 - 35.3)
Anoxic brain damage	22	740	132.2 (86.3 - 202.6)
Chronic bronchitis	22	5,055	19.3 (12.7 - 29.5)
Maternal complications of pregnancy	22	3,418	28.6 (18.8 - 43.6)
Disorder of lymphatic channels	21	157	594.4 (376.0 - 939.8)
Hemolytic disease due to isoimmunization	20	6,757	13.1 (8.4 - 20.4)
Acute cor pulmonale	20	34	2612.5 (1500.4 - 4548.7)
Other autosomal deletion syndrome	20	681	130.4 (83.4 - 204.0)
Congenital brain reduction deformities	19	1,173	71.9 (45.6 - 113.4)
Left heart failure	19	165	511.1 (317.1 - 823.8)
Cystic fibrosis	19	1,849	45.6 (28.9 - 71.8)
Congenital spleen anomaly	18	246	324.5 (200.6 - 525.1)
Plasma protein metabolic disorder	18	893	89.4 (55.9 - 142.9)
Diaphragm paralysis	18	141	566.2 (345.8 - 927.1)
Exceptionally large baby	18	10,724	7.4 (4.7 - 11.8)
Hydrops fetalis	17	107	704.3 (421.2 - 1177.6)
Edwards syndrome	17	159	473.9 (286.7 - 783.4)
Disorder of eye movement	16	3,612	19.6 (12.0 - 32.1)
Congenital anomalies of peripheral vascular system	16	1,053	67.3 (41.0 - 110.5)
Periventricular leukomalacia	16	409	173.3 (104.9 - 286.3)
Congenital malrotation of intestine	16	399	177.6 (107.5 - 293.5)
Cerebral cyst	16	2,088	33.9 (20.7 - 55.6)
Portal hypertension	15	255	260.4 (154.3 - 439.4)
DiGeorge syndrome	15	425	156.2 (93.1 - 262.1)
Defibrination syndrome	15	246	269.9 (159.9 - 455.7)
Endocarditis	15	153	434.0 (254.8 - 739.3)
Persistent vomiting	15	3,404	19.5 (11.7 - 32.5)
Diseases of vocal cord	14	2,150	28.8 (17.0 - 48.8)
Hepatitis	14	2,031	30.5 (18.0 - 51.7)

Splenomegaly	14	2,535	24.4 (14.4 - 41.4)
Iron metabolism disorder	13	662	86.8 (50.0 - 150.6)
Cerebral compression	13	2,072	27.7 (16.0 - 47.9)
Drug-induced pancytopenia	13	1,414	40.6 (23.5 - 70.3)
Bilirubin excretion disorder	13	1,856	31.0 (17.9 - 53.5)
Compression of vein	12	204	259.9 (144.9 - 466.2)
Mixed acid-base balance disorder	12	165	321.3 (178.5 - 578.6)
Hereditary muscular dystrophy	12	1,153	46.0 (26.0 - 81.4)
Bronchiectasis	12	651	81.4 (45.9 - 144.5)
Transient mental disorder	12	4,024	13.2 (7.5 - 23.3)
Anorexia	12	5,014	10.6 (6.0 - 18.7)
Phosphorus metabolism disorder	11	869	55.9 (30.8 - 101.5)
Intellectual disability	11	1,513	32.1 (17.7 - 58.2)
Calculus of kidney	11	7,329	6.6 (3.7 - 12.0)
Systemic lupus erythematosus	11	1,406	34.5 (19.0 - 62.6)
Leukocytopenia	11	2,294	21.2 (11.7 - 38.4)
Pyogenic granuloma	11	3,975	12.2 (6.7 - 22.1)
Velo-cardio-facial syndrome	10	309	142.8 (75.9 - 268.6)
Other congenital anomalies of respiratory system	10	181	243.8 (128.7 - 461.7)
Aneurysm	10	698	63.2 (33.8 - 118.2)
Fistula of stomach or duodenum	10	187	236.0 (124.7 - 446.7)
Magnesium metabolic disorder	9	1,177	33.7 (17.5 - 65.1)
Spontaneous ecchymoses	9	1,701	23.3 (12.1 - 45.0)
Patau syndrome	9	84	472.5 (237.2 - 941.3)
Acute chest syndrome	8	264	133.6 (66.0 - 270.3)
Rickets	8	460	76.6 (38.0 - 154.5)
Cerebral depression coma	8	391	90.2 (44.7 - 181.9)
Edema of larynx	8	501	70.4 (34.9 - 141.7)
Juvenile idiopathic arthritis	8	5,710	6.2 (3.1 - 12.4)
Situs inversus	8	249	141.6 (69.9 - 286.8)
Aplastic anemia	8	738	47.8 (23.8 - 96.1)
Hirschsprung	8	545	64.7 (32.1 - 130.2)
Acquired hemolytic anemia	7	798	38.6 (18.3 - 81.4)
Hemorrhage disorder due to intrinsic circulating factor	7	104	296.5 (137.7 - 638.3)
Hemophagocytic syndrome	7	126	244.7 (114.1 - 524.6)
Mediastinitis	7	48	642.3 (290.2 - 1421.7)
Gastroparesis	7	1,367	22.6 (10.7 - 47.5)
Choanal atresia	6	249	106.1 (47.1 - 238.7)
Systemic vasculitis	6	1,753	15.1 (6.7 - 33.6)
Prader-Willi syndrome	6	329	80.3 (35.7 - 180.3)
Acquired hypertrophic pyloric stenosis	6	378	69.9 (31.1 - 156.7)
Eosinophilia	6	701	37.7 (16.8 - 84.3)
Systemic sclerosis	6	904	29.2 (13.1 - 65.3)
Raynaud syndrome	5	1,766	12.5 (5.2 - 30.0)
Nephritis	5	1,159	19.0 (7.9 - 45.7)
Encephalocele	5	147	149.6 (61.3 - 365.3)
Myoneural disorder	5	984	22.3 (9.3 - 53.9)
Glycogen storage disorder	5	233	94.4 (38.9 - 229.2)
Adrenogenital disorder	5	910	24.2 (10.0 - 58.3)

Adrenal hypofunction	5	177	124.3 (51.0 - 302.7)
Congenital cystic lung	5	180	122.2 (50.2 - 297.5)
Other connective tissue disorder	5	1,594	13.8 (5.7 - 33.2)
Stricture and stenosis of esophagus	5	420	52.4 (21.7 - 126.6)
Gangrene	4	101	174.1 (64.0 - 473.5)
Gonadal dysgenesis	4	846	20.8 (7.8 - 55.6)
Disturbance of salivary secretion	4	401	43.9 (16.4 - 117.6)
Hereditary hemorrhagic telangiectasis	4	77	228.4 (83.5 - 624.7)
Cerebrovascular disease	4	78	225.4 (82.4 - 616.5)
Pneumocystosis	4	47	374.1 (134.6 - 1039.7)
Von Willebrand’s disease	4	1,211	14.5 (5.4 - 38.8)
Cri-du-chat syndrome	4	87	202.1 (74.1 - 551.3)
Myocarditis	4	216	81.4 (30.2 - 219.1)
Phlebitis and thrombophlebitis	4	159	110.6 (41.0 - 298.7)

Table B1b. Sensitivity analysis - comorbidities were defined as having four or more healthcare visits for the relevant codes. All comorbidities remained significantly associated with PH, with the exception of pyogenic granuloma.

Comorbidity	N		OR (95% CI)
	PH (n=1,583)	Control (n=6,941,680)	
CHD LR shunt	723	13,182	441.9 (399.7 - 488.5)
Other CHD	479	8,423	357.1 (320.1 - 398.4)
Pneumonia	324	28,668	62.1 (54.9 - 70.2)
Respiratory distress syndrome	364	11,786	175.6 (156.0 - 197.7)
Pulmonary collapse	291	2,600	601.1 (526.3 - 686.5)
PPHN	343	896	2142.8 (1869.7 - 2455.7)
Cardiomegaly	207	1,181	884.1 (755.7 - 1034.2)
Bronchopulmonary dysplasia	304	2,880	572.7 (502.7 - 652.3)
Pleurisy	217	2,793	394.7 (340.4 - 457.6)
Cardiac dysrhythmias	193	9,528	101.0 (86.8 - 117.6)
Delay in development	184	23,371	38.9 (33.4 - 45.4)
Neonatal hematological disorder	175	5,523	156.1 (133.1 - 183.0)
Left-sided CHD	155	2,927	257.3 (217.2 - 304.9)
Congestive heart failure	157	795	961.2 (803.8 - 1149.5)
Primary atelectasis	123	1,361	429.6 (354.7 - 520.3)
Essential hypertension	127	9,037	66.9 (55.8 - 80.3)
Down syndrome	160	4,848	160.9 (136.3 - 189.9)
Valvular heart disease (right-sided)	62	1,447	195.5 (150.9 - 253.3)
Pulmonary insufficiency from trauma	100	1,201	389.7 (315.8 - 480.9)
Hypotension	96	1,882	238.1 (192.7 - 294.1)
Sleep apnea	104	904	539.9 (438.0 - 665.5)
Disorder of muscle, ligament, fascia	100	65,912	7.0 (5.7 - 8.6)
Fetal and neonatal hemorrhage	94	1,774	247.0 (199.5 - 305.8)
Neonatal endocrine/metabolic disturbances	91	7,844	53.9 (43.6 - 66.7)
Lack of coordination	92	21,295	20.1 (16.2 - 24.8)
Emphysema	98	2,053	223.1 (181.0 - 274.9)
Valvular heart disease (left-sided)	77	6,377	55.6 (44.2 - 70.0)
Rheumatic heart disease	60	486	562.7 (428.3 - 739.2)
Perinatal digestive system disorders	81	1,338	279.7 (222.3 - 352.0)
Thrombocytopenia	65	3,804	78.1 (60.8 - 100.3)
Congenital musculoskeletal deformities	51	15,619	14.8 (11.2 - 19.5)
Congenital anomalies of larynx, trachea, or bronchus	67	1,598	191.9 (149.6 - 246.3)
Pneumothorax	66	1,941	155.6 (121.1 - 199.8)
Epilepsy	67	19,082	16.0 (12.5 - 20.5)
Hearing loss	28	2,265	55.2 (37.9 - 80.3)
Cardiomyopathy	71	1,128	288.9 (226.1 - 369.2)
Pneumonitis	61	882	315.4 (242.1 - 410.8)
Conduction disorder	56	2,139	119.0 (90.8 - 155.9)
Thromboembolism	63	1,472	195.4 (151.1 - 252.7)

Acute kidney failure	68	1,654	188.3 (147.0 - 241.3)
Gastroenteritis and colitis	26	9,076	12.8 (8.7 - 18.8)
Congenital anomalies of diaphragm	70	220	1459.8 (1110.3 - 1919.2)
Gastrointestinal hemorrhage	43	4,462	43.4 (32.0 - 58.9)
Primary immunodeficiency	61	4,364	63.7 (49.2 - 82.4)
Congenital lung agenesis, hypoplasia, dysplasia	55	253	987.6 (734.6 - 1327.6)
Hypothyroidism	50	13,456	16.8 (12.7 - 22.3)
Acute edema of lung	39	222	789.8 (559.9 - 1114.0)
Interstitial lung disease	45	242	839.2 (608.2 - 1158.2)
Cyanosis	46	428	485.4 (356.6 - 660.6)
Cerebral palsy	42	7,480	25.3 (18.6 - 34.4)
Hydrocephalus	55	2,701	92.5 (70.5 - 121.3)
Other chromosomal anomalies	46	1,546	134.4 (99.8 - 180.9)
Tetralogy of Fallot	56	1,147	221.9 (168.9 - 291.5)
Fluid overload disorder	42	348	543.6 (393.2 - 751.7)
Tachypnea of newborn	39	5,157	34.0 (24.7 - 46.7)
Congenital anomalies of kidney	38	4,572	37.3 (27.0 - 51.6)
Edema	29	2,708	47.8 (33.1 - 69.2)
Intestinal obstruction	32	2,284	62.7 (44.1 - 89.2)
Diaphragmatic hernia	42	416	454.8 (329.8 - 627.0)
Chronic liver disease	42	1,576	120.0 (88.0 - 163.7)
Pericardium disorder	34	444	343.1 (241.3 - 488.1)
Intestinal malabsorption	43	4,178	46.4 (34.2 - 62.9)
Abnormality of gait	36	12,126	13.3 (9.6 - 18.5)
Drug withdrawal syndrome	36	2,468	65.4 (46.9 - 91.3)
Childbirth complications	26	6,084	19.0 (12.9 - 28.1)
Malnutrition	28	1,843	67.8 (46.5 - 98.8)
Intrauterine hypoxia and birth asphyxia	38	1,038	164.5 (118.5 - 228.2)
Hepatomegaly	15	271	245.0 (145.4 - 413.1)
Congenital anomalies of skull and face bones	25	2,236	49.8 (33.5 - 74.1)
Convulsion in newborn	28	620	201.6 (137.6 - 295.3)
Coagulation defect	22	539	181.5 (118.2 - 278.8)
Congenital pneumonia	27	554	217.4 (147.3 - 320.9)
Speech disturbance	27	12,805	9.4 (6.4 - 13.7)
Nutritional deficiency	27	1,405	85.7 (58.4 - 125.8)
Intestinal vascular insufficiency	27	301	400.2 (269.1 - 595.1)
Multiple congenital anomalies	25	341	326.6 (217.0 - 491.8)
Pulmonary embolism	31	459	302.1 (209.2 - 436.0)
Chronic kidney disease	24	1,471	72.6 (48.4 - 109.0)
Leukocytosis	17	1,637	46.0 (28.5 - 74.4)
Iron deficiency anemia	11	2,914	16.7 (9.2 - 30.2)
Birth trauma	19	1,611	52.3 (33.2 - 82.5)
Intracranial hemorrhage	17	575	131.0 (80.7 - 212.8)
Pulmonary eosinophilia	18	171	466.9 (286.5 - 760.7)
Congenital intestinal atresia and stenosis	22	622	157.3 (102.5 - 241.3)
Neutropenia	20	2,682	33.1 (21.3 - 51.5)
CHD RL shunt	19	196	430.2 (268.0 - 690.8)
Abnormal weight gain	6	4,241	6.2 (2.8 - 13.9)

Abnormal involuntary movement	13	2,173	26.4 (15.3 - 45.7)
Microcephaly	13	816	70.4 (40.6 - 122.1)
Sickle cell disease	24	1,769	60.4 (40.2 - 90.6)
Pulmonary hemorrhage	17	121	622.8 (373.9 - 1037.2)
Dyspepsia	6	1,157	22.8 (10.2 - 51.0)
Umbilical hernia	12	1,158	45.8 (25.9 - 81.0)
Hereditary hemolytic anemia	14	1,337	46.3 (27.3 - 78.6)
Diabetic mother syndrome	13	1,744	32.9 (19.1 - 57.0)
Anoxic brain damage	13	449	128.0 (73.6 - 222.7)
Chronic bronchitis	10	1,417	31.1 (16.7 - 58.1)
Maternal complications of pregnancy	19	1,579	53.4 (33.9 - 84.2)
Disorder of lymphatic channels	13	100	574.8 (321.8 - 1026.5)
Hemolytic disease due to isoimmunization	15	2,719	24.4 (14.7 - 40.7)
Acute cor pulmonale	11	20	2428.7 (1161.8 - 5077.1)
Other autosomal deletion syndrome	18	341	234.1 (145.4 - 377.1)
Congenital brain reduction deformities	10	740	59.6 (31.9 - 111.5)
Left heart failure	10	79	558.6 (288.8 - 1080.5)
Cystic fibrosis	13	1,594	36.1 (20.8 - 62.4)
Congenital spleen anomaly	15	123	539.9 (315.1 - 924.9)
Plasma protein metabolic disorder	9	361	109.9 (56.6 - 213.4)
Diaphragm paralysis	14	68	910.9 (511.3 - 1622.5)
Exceptionally large baby	13	2,697	21.3 (12.3 - 36.8)
Hydrops fetalis	14	67	924.5 (518.6 - 1648.0)
Edwards syndrome	14	112	553.0 (316.6 - 966.0)
Disorder of eye movement	4	961	18.3 (6.8 - 48.9)
Congenital anomalies of peripheral vascular system	9	454	87.4 (45.1 - 169.4)
Periventricular leukomalacia	11	266	182.6 (99.7 - 334.4)
Congenital malrotation of intestine	8	206	171.2 (84.3 - 347.4)
Cerebral cyst	5	675	32.6 (13.5 - 78.6)
Portal hypertension	12	166	319.4 (177.4 - 575.0)
DiGeorge syndrome	13	294	195.5 (111.9 - 341.5)
Defibrination syndrome	10	137	322.1 (169.2 - 613.3)
Endocarditis	14	108	573.5 (327.9 - 1003.0)
Persistent vomiting	5	852	25.8 (10.7 - 62.3)
Diseases of vocal cord	2	784	11.2 (2.8 - 44.9)
Hepatitis	8	663	53.2 (26.4 - 107.0)
Splenomegaly	8	649	54.3 (27.0 - 109.3)
Iron metabolism disorder	11	269	180.6 (98.6 - 330.6)
Cerebral compression	11	1,057	45.9 (25.3 - 83.4)
Drug-induced pancytopenia	10	928	47.5 (25.4 - 88.8)
Bilirubin excretion disorder	9	444	89.4 (46.1 - 173.3)
Compression of vein	9	67	592.4 (294.9 - 1190.1)
Mixed acid-base balance disorder	9	51	778.3 (382.5 - 1583.5)
Hereditary muscular dystrophy	8	802	44.0 (21.9 - 88.4)
Bronchiectasis	9	378	105.0 (54.1 - 203.7)
Transient mental disorder	9	1,869	21.2 (11.0 - 40.9)
Anorexia	8	1,106	31.9 (15.9 - 64.0)
Phosphorus metabolism disorder	7	381	80.9 (38.3 - 171.2)

Intellectual disability	8	848	41.6 (20.7 - 83.6)
Calculus of kidney	5	3,272	6.7 (2.8 - 16.2)
Systemic lupus erythematosus	10	928	47.5 (25.4 - 88.8)
Leukocytopenia	4	486	36.2 (13.5 - 96.9)
Pyogenic granuloma*	1	419	10.5 (1.5 - 74.6)
Velo-cardio-facial syndrome	6	183	144.3 (63.9 - 325.9)
Other congenital anomalies of respiratory system	6	76	347.5 (151.1 - 799.0)
Aneurysm	3	216	61.0 (19.5 - 190.9)
Fistula of stomach or duodenum	4	26	676.3 (235.8 - 1940.2)
Magnesium metabolic disorder	2	478	18.4 (4.6 - 73.7)
Spontaneous ecchymoses	2	166	52.9 (13.1 - 213.5)
Patau syndrome	7	54	571.0 (259.4 - 1256.7)
Acute chest syndrome	7	165	186.9 (87.6 - 398.7)
Rickets	5	169	130.1 (53.4 - 317.2)
Cerebral depression coma	7	224	137.6 (64.8 - 292.5)
Edema of larynx	3	133	99.1 (31.5 - 311.5)
Juvenile idiopathic arthritis	6	3,563	7.4 (3.3 - 16.5)
Situs inversus	4	101	174.1 (64.0 - 473.5)
Aplastic anemia	7	448	68.8 (32.6 - 145.4)
Hirschsprung	6	341	77.4 (34.5 - 173.9)
Acquired hemolytic anemia	4	439	40.1 (14.9 - 107.3)
Hemorrhage disorder due to intrinsic circulating factor	4	52	338.2 (122.2 - 936.1)
Hemophagocytic syndrome	6	96	275.1 (120.4 - 628.6)
Mediastinitis	4	29	606.4 (212.9 - 1726.8)
Gastroparesis	3	614	21.5 (6.9 - 66.8)
Choanal atresia	3	139	94.8 (30.2 - 297.9)
Systemic vasculitis	4	1,202	14.6 (5.5 - 39.1)
Prader-Willi syndrome	5	262	83.9 (34.6 - 203.7)
Acquired hypertrophic pyloric stenosis	4	89	197.6 (72.5 - 538.7)
Eosinophilia	4	215	81.8 (30.4 - 220.2)
Systemic sclerosis	5	418	52.6 (21.8 - 127.3)
Raynaud syndrome	3	447	29.5 (9.5 - 91.9)
Nephritis	3	655	20.1 (6.5 - 62.6)
Encephalocele	5	81	271.5 (109.9 - 670.9)
Myoneural disorder	4	582	30.2 (11.3 - 80.9)
Glycogen storage disorder	4	119	147.8 (54.5 - 400.7)
Adrenogenital disorder	2	571	15.4 (3.8 - 61.7)
Adrenal hypofunction	4	72	244.2 (89.1 - 669.3)
Congenital cystic lung	4	104	169.1 (62.2 - 459.6)
Other connective tissue disorder	4	836	21.0 (7.9 - 56.2)
Stricture and stenosis of esophagus	3	167	78.9 (25.2 - 247.5)
Gangrene	1	43	102.0 (14.0 - 741.5)
Gonadal dysgenesis	3	595	22.2 (7.1 - 68.9)
Disturbance of salivary secretion	1	124	35.4 (4.9 - 253.4)
Hereditary hemorrhagic telangiectasis	4	31	567.3 (200.0 - 1608.8)
Cerebrovascular disease	1	28	156.7 (21.3 - 1152.5)
Pneumocystosis	3	37	356.2 (109.7 - 1156.5)
Von Willebrand’s disease	4	508	34.6 (12.9 - 92.7)

Cri-du-chat syndrome	3	62	212.6 (66.7 - 677.9)
Myocarditis	2	118	74.4 (18.4 - 301.3)
Phlebitis and thrombophlebitis	3	61	216.1 (67.7 - 689.3)

(*Comorbidities that were significantly associated with PH in the primary study cohort, but not this analysis)

Table B1c. Secondary analysis – study cohort comprised children who underwent RHC, in addition to having two or more healthcare encounters for PH during the study period.

Comorbidity	N		OR (95% CI)
	PH (n=308)	Control (n=6,941,680)	
CHD LR shunt	208	26,283	547.3 (431.0 - 694.9)
Other CHD	229	16,632	1206.9 (934.2 - 1559.4)
Pneumonia	111	115,692	33.2 (26.3 - 42.0)
Respiratory distress syndrome	44	15,608	74.0 (53.7 - 101.8)
Pulmonary collapse	140	6,260	923.2 (736.7 - 1157.0)
PPHN	36	1,255	731.9 (514.8 - 1040.7)
Cardiomegaly	168	3,369	2471.3 (1969.8 - 3100.6)
Bronchopulmonary dysplasia	52	3,784	372.4 (275.9 - 502.6)
Pleurisy	122	6,011	756.8 (601.5 - 952.3)
Cardiac dysrhythmias	122	26,248	172.8 (137.5 - 217.2)
Delay in development	70	35,840	56.7 (43.4 - 74.0)
Neonatal hematological disorder	27	8,258	80.7 (54.3 - 119.8)
Left-sided CHD	113	6,806	590.5 (467.8 - 745.3)
Congestive heart failure	109	1,311	2899.7 (2281.6 - 3685.3)
Primary atelectasis	32	2,224	361.8 (250.3 - 522.9)
Essential hypertension	54	20,560	71.6 (53.3 - 96.0)
Down syndrome	36	5,783	158.7 (112.0 - 224.9)
Valvular heart disease (right-sided)	63	4,754	375.2 (284.1 - 495.6)
Pulmonary insufficiency from trauma	76	2,531	898.1 (691.2 - 1167.1)
Hypotension	33	5,239	158.9 (110.6 - 228.2)
Sleep apnea	34	18,262	47.0 (32.9 - 67.2)
Disorder of muscle, ligament, fascia	32	102,938	7.7 (5.3 - 11.1)
Fetal and neonatal hemorrhage	16	3,618	105.1 (63.5 - 174.0)
Neonatal endocrine/metabolic disturbances	15	15,080	23.5 (14.0 - 39.5)
Lack of coordination	29	28,005	25.7 (17.5 - 37.6)
Emphysema	13	3,770	81.1 (46.5 - 141.5)
Valvular heart disease (left-sided)	64	5,273	345.0 (261.7 - 455.0)
Rheumatic heart disease	58	1,869	861.4 (645.1 - 1150.4)
Perinatal digestive system disorders	21	2,367	214.5 (137.5 - 334.7)
Thrombocytopenia	37	6,993	135.4 (96.0 - 191.0)
Congenital musculoskeletal deformities	23	39,368	14.1 (9.3 - 21.6)
Congenital anomalies of larynx, trachea, or bronchus	27	3,494	190.8 (128.4 - 283.6)
Pneumothorax	35	3,511	253.3 (177.9 - 360.8)
Epilepsy	27	30,303	21.9 (14.8 - 32.5)
Hearing loss	19	15,763	28.9 (18.2 - 46.0)
Cardiomyopathy	50	2,118	635.0 (467.7 - 862.1)
Pneumonitis	26	1,658	385.9 (257.5 - 578.4)
Conduction disorder	47	4,763	262.3 (192.0 - 358.2)
Thromboembolism	34	2,190	393.2 (274.6 - 562.9)
Acute kidney failure	28	2,722	254.9 (172.5 - 376.6)
Gastroenteritis and colitis	23	59,053	9.4 (6.1 - 14.4)

Congenital anomalies of diaphragm	6	349	395.1 (174.9 - 892.6)
Gastrointestinal hemorrhage	27	17,204	38.7 (26.0 - 57.4)
Primary immunodeficiency	27	9,095	73.2 (49.3 - 108.8)
Congenital lung agenesis, hypoplasia, dysplasia	11	430	597.9 (325.1 - 1099.4)
Hypothyroidism	18	27,186	15.8 (9.8 - 25.4)
Acute edema of lung	41	515	2069.7 (1473.2 - 2907.5)
Interstitial lung disease	22	668	799.3 (514.7 - 1241.3)
Cyanosis	42	1,535	713.9 (513.6 - 992.2)
Cerebral palsy	15	9,859	36.0 (21.4 - 60.5)
Hydrocephalus	9	4,205	49.7 (25.6 - 96.4)
Other chromosomal anomalies	23	2,862	195.7 (127.7 - 299.7)
Tetralogy of Fallot	42	1,832	598.1 (430.6 - 830.8)
Fluid overload disorder	28	676	1026.8 (691.2 - 1525.2)
Tachypnea of newborn	14	10,846	30.4 (17.8 - 52.0)
Congenital anomalies of kidney	14	10,200	32.4 (18.9 - 55.3)
Edema	21	7,621	66.6 (42.7 - 103.7)
Intestinal obstruction	12	5,627	50.0 (28.0 - 89.1)
Diaphragmatic hernia	2	1,572	28.9 (7.2 - 116.0)
Chronic liver disease	18	3,985	108.1 (67.1 - 174.1)
Pericardium disorder	25	1,114	550.4 (364.1 - 831.9)
Intestinal malabsorption	13	9,747	31.3 (18.0 - 54.6)
Abnormality of gait	18	20,658	20.8 (12.9 - 33.5)
Drug withdrawal syndrome	10	4,508	51.6 (27.5 - 97.0)
Childbirth complications*	3	29,065	2.3 (0.8 - 7.3)
Malnutrition	13	3,220	95.0 (54.4 - 165.7)
Intrauterine hypoxia and birth asphyxia	7	1,999	80.7 (38.1 - 171.0)
Hepatomegaly	20	1,144	421.3 (266.8 - 665.3)
Congenital anomalies of skull and face bones	4	6,672	13.7 (5.1 - 36.7)
Convulsion in newborn	3	992	68.8 (22.0 - 214.9)
Coagulation defect	13	1,771	172.7 (98.9 - 301.5)
Congenital pneumonia	2	930	48.8 (12.1 - 196.2)
Speech disturbance	8	18,000	10.3 (5.1 - 20.7)
Nutritional deficiency	21	4,023	126.2 (80.9 - 196.7)
Intestinal vascular insufficiency	9	552	378.5 (194.0 - 738.4)
Multiple congenital anomalies	12	761	369.8 (206.7 - 661.4)
Pulmonary embolism	12	589	477.8 (266.8 - 855.7)
Chronic kidney disease	12	2,414	116.5 (65.3 - 207.8)
Leukocytosis	9	8,047	25.9 (13.4 - 50.4)
Iron deficiency anemia	8	11,940	15.5 (7.7 - 31.2)
Birth trauma*	2	5,609	8.1 (2.0 - 32.5)
Intracranial hemorrhage	3	1,279	53.4 (17.1 - 166.6)
Pulmonary eosinophilia	9	654	319.5 (163.9 - 622.7)
Congenital intestinal atresia and stenosis	6	975	141.4 (62.9 - 318.1)
Neutropenia	7	5,015	32.2 (15.2 - 68.1)
CHD RL shunt	12	349	806.3 (448.5 - 1449.7)
Abnormal weight gain	6	22,287	6.2 (2.7 - 13.8)
Abnormal involuntary movement	7	7,666	21.0 (9.9 - 44.5)
Microcephaly	8	1,692	109.4 (54.1 - 221.1)

Sickle cell disease	4	2,279	40.1 (14.9 - 107.5)
Pulmonary hemorrhage	4	169	540.4 (199.2 - 1466.0)
Dyspepsia	4	6,480	14.1 (5.2 - 37.8)
Umbilical hernia	4	7,233	12.6 (4.7 - 33.8)
Hereditary hemolytic anemia	2	3,822	11.9 (3.0 - 47.7)
Diabetic mother syndrome*	2	4,218	10.7 (2.7 - 43.2); 0.000028
Anoxic brain damage	6	740	186.4 (82.8 - 419.4)
Chronic bronchitis	4	5,055	18.1 (6.7 - 48.4)
Maternal complications of pregnancy	5	3,418	33.5 (13.8 - 81.1)
Disorder of lymphatic channels	13	157	1948.4 (1094.1 - 3469.7)
Hemolytic disease due to isoimmunization*	2	6,757	6.7 (1.7 - 26.9)
Acute cor pulmonale	7	34	4748.0 (2088.5 - 10794.4)
Other autosomal deletion syndrome	11	681	377.5 (205.8 - 692.3)
Congenital brain reduction deformities	9	1,173	178.1 (91.5 - 346.5)
Left heart failure	10	165	1411.7 (738.2 - 2699.7)
Cystic fibrosis	5	1,849	61.9 (25.6 - 150.1)
Congenital spleen anomaly	11	246	1045.1 (565.2 - 1932.3)
Plasma protein metabolic disorder	3	893	76.5 (24.5 - 238.8)
Diaphragm paralysis	10	141	1652.0 (861.3 - 3168.9)
Exceptionally large baby*	2	10,724	4.2 (1.1 - 17.0)
Hydrops fetalis	4	107	853.6 (312.6 - 2330.7)
Edwards syndrome	6	159	867.4 (380.9 - 1975.0)
Disorder of eye movement	4	3,612	25.3 (9.4 - 67.8)
Congenital anomalies of peripheral vascular system	6	1,053	131.0 (58.2 - 294.5)
Periventricular leukomalacia	1	409	55.3 (7.7 - 394.6)
Congenital malrotation of intestine	5	399	287.1 (118.0 - 698.5)
Cerebral cyst*	1	2,088	10.8 (1.5 - 77.1)
Portal hypertension	4	255	358.2 (132.6 - 967.8)
DiGeorge syndrome	9	425	491.6 (251.6 - 960.6)
Defibrination syndrome	2	246	184.4 (45.7 - 744.9)
Endocarditis	9	153	1365.6 (690.6 - 2700.3)
Persistent vomiting	5	3,404	33.6 (13.9 - 81.4)
Diseases of vocal cord	4	2,150	42.5 (15.8 - 114.0)
Hepatitis	6	2,031	67.9 (30.2 - 152.5)
Splenomegaly	4	2,535	36.0 (13.4 - 96.7)
Iron metabolism disorder	4	662	138.0 (51.3 - 371.0)
Cerebral compression	2	2,072	21.9 (5.4 - 88.0)
Drug-induced pancytopenia	2	1,414	32.1 (8.0 - 129.0)
Bilirubin excretion disorder	2	1,856	24.4 (6.1 - 98.2)
Compression of vein	7	204	791.3 (369.4 - 1695.2)
Mixed acid-base balance disorder	6	165	835.8 (367.3 - 1902.2)
Hereditary muscular dystrophy	3	1,153	59.2 (19.0 - 184.9)
Bronchiectasis	2	651	69.7 (17.3 - 280.5)
Transient mental disorder	7	4,024	40.1 (18.9 - 84.9)
Anorexia*	2	5,014	9.0 (2.3 - 36.3); 0.000164
Phosphorus metabolism disorder	3	869	78.6 (25.1 - 245.4)
Intellectual disability*	1	1,513	14.9 (2.1 - 106.5)
Calculus of kidney*	0	7,329	-

Systemic lupus erythematosus	3	1,406	48.6 (15.6 - 151.6)
Leukocytopenia	3	2,294	29.8 (9.5 - 92.8)
Pyogenic granuloma*	2	3,975	11.4 (2.8 - 45.8); 0.000014
Velo-cardio-facial syndrome	5	309	370.7 (152.1 - 903.3)
Other congenital anomalies of respiratory system	0	181	-
Aneurysm	6	698	197.6 (87.8 - 444.8)
Fistula of stomach or duodenum	6	187	737.5 (324.6 - 1675.6)
Magnesium metabolic disorder	3	1,177	58.0 (18.6 - 181.1)
Spontaneous ecchymoses	2	1,701	26.7 (6.6 - 107.2)
Patau syndrome	3	84	812.8 (255.6 - 2585.3)
Acute chest syndrome*	0	264	-
Rickets	1	460	49.2 (6.9 - 350.8)
Cerebral depression coma*	0	391	-
Edema of larynx	3	501	136.3 (43.6 - 426.3)
Juvenile idiopathic arthritis*	1	5,710	4.0 (0.6 - 28.2)
Situs inversus	5	249	460.0 (188.5 - 1122.9)
Aplastic anemia	1	738	30.6 (4.3 - 218.5)
Hirschsprung	2	545	83.2 (20.7 - 335.2)
Acquired hemolytic anemia	1	798	28.3 (4.0 - 202.0)
Hemorrhage disorder due to intrinsic circulating factor	2	104	436.2 (107.2 - 1775.5)
Hemophagocytic syndrome	1	126	179.5 (25.0 - 1288.0)
Mediastinitis	6	48	2873.2 (1220.5 - 6763.7)
Gastroparesis	1	1,367	16.5 (2.3 - 117.9); 0.000137
Choanal atresia	1	249	90.8 (12.7 - 649.2)
Systemic vasculitis*	0	1,753	-
Prader-Willi syndrome*	0	329	-
Acquired hypertrophic pyloric stenosis	0	378	-
Eosinophilia	1	701	32.3 (4.5 - 230.0)
Systemic sclerosis	1	904	25.0 (3.5 - 178.3); 0.000002
Raynaud syndrome	2	1,766	25.7 (6.4 - 103.2)
Nephritis*	1	1,159	19.5 (2.7 - 139.0); 0.000029
Encephalocele	0	147	-
Myoneural disorder	1	984	23.0 (3.2 - 163.8)
Glycogen storage disorder	1	233	97.0 (13.6 - 694.0)
Adrenogenital disorder	1	910	24.8 (3.5 - 177.1)
Adrenal hypofunction	1	177	127.7 (17.8 - 914.8)
Congenital cystic lung*	0	180	-
Other connective tissue disorder*	0	1,594	-
Stricture and stenosis of esophagus*	0	420	-
Gangrene	1	101	223.9 (31.1 - 1609.8)
Gonadal dysgenesis	1	846	26.7 (3.7 - 190.5)
Disturbance of salivary secretion*	0	401	-
Hereditary hemorrhagic telangiectasis	2	77	589.2 (144.1 - 2409.2)
Cerebrovascular disease	1	78	289.9 (40.2 - 2090.5)
Pneumocystosis*	0	47	-

Von Willebrand's disease	3	1,211	56.4 (18.1 - 176.0)
Cri-du-chat syndrome	1	87	259.9 (36.1 - 1871.8)
Myocarditis	2	216	210.0 (52.0 - 849.0)
Phlebitis and thrombophlebitis	2	159	285.3 (70.4 - 1156.1)

(*Comorbidities that were significantly associated with PH in the primary study cohort, but not the RHC cohort)

B2. Network relations (edges) derived through Bayesian network learning

Table B2a. Primary analysis – study cohort comprised children with two or more healthcare encounters for PH during the study period.

Edges	Weight
Other CHD → Tetralogy of Fallot	0.90
Thrombocytopenia → Aplastic anemia	0.84
Other CHD → Congenital anomalies of peripheral vascular system	0.84
Other CHD → Left-sided CHD	0.83
Pleurisy → Disorders of lymphatic channels	0.83
Thrombocytopenia → Drug-induced pancytopenia	0.82
Other CHD → Conduction disorder	0.80
Sickle cell disease → Acute chest syndrome	0.79
PPHN → Birth trauma	0.76
Other chromosomal anomalies → Other autosomal deletion syndrome	0.75
Pulmonary collapse → Fluid overload disorder	0.74
Respiratory distress syndrome → Fetal and neonatal hemorrhage	0.73
Respiratory distress syndrome → Congenital pneumonia	0.72
PPHN → Exceptionally large baby	0.71
Respiratory distress syndrome → Maternal complications of pregnancy	0.70
Pulmonary collapse → Nutritional deficiency	0.69
Pulmonary collapse → Acute edema of lung	0.68
Respiratory distress syndrome → Emphysema	0.68
Pneumonia → Pneumonitis	0.67
Respiratory distress syndrome → Perinatal digestive system disorders	0.67
Other chromosomal anomalies → Cri-du-chat syndrome	0.66
Cardiomegaly → Cardiomyopathy	0.66
Pleurisy → Pericardium disorder	0.65
Other chromosomal anomalies → Primary atelectasis	0.65
Pneumonia → Malnutrition	0.64
Pleurisy → Edema	0.63
PPHN → Primary atelectasis	0.62
Pleurisy → Fluid overload disorder	0.62
Valvular heart disease (right-sided) → Left heart failure	0.61
Thrombocytopenia → Neutropenia	0.61
Other CHD → Down syndrome	0.61
BPD → Fetal and neonatal hemorrhage	0.61
Congenital anomalies of larynx/trachea/bronchus → Stricture and stenosis of esophagus	0.60
Diaphragmatic hernia → Congenital anomalies of diaphragm	0.60
Pleurisy → Pneumothorax	0.60
Cardiac dysrhythmias → Conduction disorder	0.60
Pulmonary collapse → Pulmonary insufficiency following trauma	0.60
Pulmonary collapse → Pneumothorax	0.60
Cardiomegaly → Cyanosis	0.59
Pulmonary collapse → Acute kidney failure	0.59
Raynaud → Systemic sclerosis	0.58
Respiratory distress syndrome → BPD	0.58
PPHN → Convulsion in newborn	0.57
Cardiomyopathy → Glycogen storage disorder	0.57
Perinatal digestive system disorders → Intestinal vascular insufficiency	0.57
Congenital anomalies of larynx/trachea/bronchus → Diseases of vocal cord	0.56
Thromboembolism → Compression of vein	0.56

Sleep apnea → Intellectual disability	0.56
Respiratory distress syndrome → PPHN	0.56
Neutropenia → Leukocytopenia	0.56
PPHN → Tachypnea of newborn	0.55
Pleurisy → Pulmonary insufficiency following trauma	0.55
Respiratory distress syndrome → Neonatal endocrine and metabolic disturbances	0.55
Thromboembolism → Hemorrhagic disorder due to intrinsic circulating factor	0.54
JIA → Hemophagocytic syndrome	0.54
Acute kidney failure → Chronic kidney disorder	0.54
BPD → Congenital lung agenesis/hypoplasia/dysplasia	0.54
Neonatal hematological disorder → Cerebral cyst	0.54
Congestive heart failure → Cardiomyopathy	0.53
Pleurisy → Thromboembolism	0.53
DiGeorge syndrome → Velo-cardio-facial syndrome	0.52
PPHN → Neonatal endocrine and metabolic disturbances	0.52
Epilepsy → Anoxic brain damage	0.52
Neutropenia → Aplastic anemia	0.52
Thrombocytopenia → JIA	0.50
Other CHD → CHD LR shunt	0.50
Raynaud → Other CTD	0.49
Congenital spleen anomaly → Situs inversus	0.49
Sleep apnea → Choanal atresia	0.49
Tetralogy of Fallot → DiGeorge syndrome	0.49
Primary atelectasis → Congenital cystic lung	0.49
Cardiomegaly → Pleurisy	0.49
Cardiomegaly → Pulmonary collapse	0.49
Left-sided CHD → Left heart failure	0.49
Delay in development → Cerebral palsy	0.49
Congestive heart failure → Acute edema of lung	0.48
Valvular heart disease (left-sided) → Myoneural disorder	0.48
Left-sided CHD → Rheumatic heart disease	0.48
Pulmonary collapse → Cardiac dysrhythmias	0.48
Delay in development → Hearing loss	0.48
Chronic kidney disease → Nephritis	0.47
Edema → Hydrops fetalis	0.47
Cardiomyopathy → Hereditary muscular dystrophy	0.47
Pulmonary collapse → Hypotension	0.47
Neonatal hematological disorder → Fetal and neonatal hemorrhage	0.47
Other chromosomal anomalies → Patau syndrome	0.46
Thrombocytopenia → Splenomegaly	0.46
Cardiomegaly → Valvular heart disease (right-sided)	0.46
Lack of coordination → Disorder of eye movement	0.46
Acute kidney failure → Phosphorus metabolism disorder	0.46
Left-sided CHD → Valvular heart disease (left-sided)	0.46
Abnormality of gait → Spontaneous ecchymoses	0.46
BPD → Interstitial lung disease	0.46
Pulmonary collapse → Pneumonia	0.45
Sickle cell disease → Iron metabolism disorder	0.45
Primary atelectasis → Perinatal digestive system disorders	0.45
Lack of coordination → Speech disturbance	0.45
Pleurisy → Pulmonary collapse	0.45

Pneumonitis → Eosinophilia	0.45
Disorder of muscle ligament and fascia → Abnormality of gait	0.44
Primary atelectasis → Intrauterine hypoxia and birth asphyxia	0.44
Neonatal endocrine and metabolic disturbances → Exceptionally large baby	0.44
Down syndrome → Myoneural disorder	0.44
Congestive heart failure → Valvular heart disease (left-sided)	0.43
Other chromosomal anomalies → Edwards syndrome	0.43
Lack of coordination → Abnormality of gait	0.43
Microcephaly → Adrenogenital disorder	0.43
Delay in development → Other chromosomal anomalies	0.43
Valvular heart disease (left-sided) → Rheumatic heart disease	0.42
Drug withdrawal syndrome → Gonadal dysgenesis	0.42
Aneurysm → Prader Willi syndrome	0.42
Congestive heart failure → Pulmonary insufficiency following trauma	0.41
Sickle cell disease → Phlebitis and thrombophlebitis	0.41
Gastrointestinal hemorrhage → Microcephaly	0.41
Speech disturbance → Disturbance of salivary secretion	0.41
Cardiomegaly → Other CHD	0.41
Delay in development → Congenital musculoskeletal deformities	0.41
Defibrination syndrome → Gangrene	0.40
Drug-induced pancytopenia → Neutropenia	0.40
Chronic liver disease → Portal hypertension	0.39
Congenital lung agenesis/hypoplasia/dysplasia → Acquired hypertrophic pyloric stenosis	0.39
Drug-induced pancytopenia → Aplastic anemia	0.39
Perinatal digestive system disorders → Acquired hypertrophic pyloric stenosis	0.39
BPD → Pulmonary collapse	0.39
Congenital anomalies of skull and face bones → Cerebrovascular disease	0.39
Down syndrome → Edwards syndrome	0.39
Delay in development → Congenital anomalies of larynx/trachea/bronchus	0.39
Congestive heart failure → Cardiomegaly	0.38
Pulmonary insufficiency following trauma → Congenital spleen anomaly	0.38
Disorder of muscle, ligament and fascia → Lack of coordination	0.38
Disorder of muscle, ligament and fascia → Chronic bronchitis	0.38
Diaphragmatic hernia → Phlebitis and thrombophlebitis	0.38
Respiratory distress syndrome → CHD LR shunt	0.38
JIA → Other CTD	0.37
Primary atelectasis → Emphysema	0.37
Congenital anomalies of skull and face bones → Choanal atresia	0.37
Down syndrome → Hirschsprung	0.37
Neonatal hematological disorder → BPD	0.37
Neonatal hematological disorder → Respiratory distress syndrome	0.37
PPHN → CHD LR shunt	0.36
Epilepsy → Intracranial hemorrhage	0.36
Cardiomyopathy → Left heart failure	0.36
Edema of larynx → Cerebrovascular disease	0.35
Fluid overload disorder → Transient mental disorder	0.35
Perinatal digestive system disorders → Intestinal malabsorption	0.35
Abnormal involuntary movement → Hereditary hemorrhagic telangiectasis	0.35
Pulmonary embolism → Hemorrhagic disorder due to intrinsic circulating factor	0.35

Iron deficiency anemia → Stricture and stenosis of esophagus	0.34
Hemophagocytic syndrome → Gangrene	0.34
Pneumonitis → Congenital malrotation of intestine	0.34
Cerebral palsy → Abnormal involuntary movement	0.34
Pulmonary collapse → CHD LR shunt	0.34
Hydrocephalus → Intracranial hemorrhage	0.34
Congenital anomalies of diaphragm → Diaphragm paralysis	0.34
Congestive heart failure → Pleurisy	0.33
Raynaud → Systemic vasculitis	0.33
Congenital spleen anomaly → Congenital malrotation of intestine	0.33
Iron metabolism disorder → Hereditary hemorrhagic telangiectasis	0.33
Congenital anomalies of larynx/trachea/bronchus → Edema of larynx	0.33
Thromboembolism → Pulmonary embolism	0.33
Edwards syndrome → Patau syndrome	0.33
Hepatitis → Encephalocele	0.33
Portal hypertension → Splenomegaly	0.32
Pulmonary eosinophilia → Edema of larynx	0.32
Nephritis → SLE	0.32
Velo-cardio-facial syndrome → Von Willebrand's disease	0.32
Pneumonitis → Encephalocele	0.32
Down syndrome → Sleep apnea	0.32
Plasma protein metabolic disorder → Defibrination syndrome	0.31
Epilepsy → Cerebral palsy	0.31
Neonatal endocrine and metabolic disturbances → Tachypnea of newborn	0.31
Patau syndrome → Magnesium metabolic disorder	0.31
Interstitial lung disease → Cystic fibrosis	0.31
Neonatal hematological disorder → PPHN	0.31
Delay in development → Sleep apnea	0.31
Acute chest syndrome → Cerebrovascular disease	0.30
Cyanosis → Congenital spleen anomaly	0.30
Drug-induced pancytopenia → Pneumocystosis	0.30
Periventricular leukomalacia → Acquired hypertrophic pyloric stenosis	0.30
Abnormality of gait → Abnormal involuntary movement	0.30
Emphysema → Pneumothorax	0.30
Cystic fibrosis → Pneumocystosis	0.30
Congenital anomalies of skull and face bones → Gonadal dysgenesis	0.30
Childbirth complications → Disturbance of salivary secretion	0.30
Congenital anomalies of diaphragm → Congenital lung agenesis/hypoplasia/dysplasia	0.30
Congestive heart failure → Cardiac dysrhythmias	0.29
Chronic liver disease → Leukocytosis	0.29
Hereditary hemorrhagic telangiectasis → Hemorrhagic disorder due to intrinsic circulating factor	0.29
Hereditary hemorrhagic telangiectasis → Mediastinitis	0.29
Hereditary muscular dystrophy → Myoneural disorder	0.29
Hereditary muscular dystrophy → Glyocgen storage disorder	0.29
Fetal and neonatal hemorrhage → Hydrocephalus	0.29
Bronchiectasis → Cystic fibrosis	0.29
Abnormal weight gain → Prader Willi syndrome	0.29
Acute cor pulmonale → Von Willebrand's disease	0.29
Left-sided CHD → Valvular heart disease (right sided)	0.29
Patau syndrome → Hirschsprung	0.29
Intrauterine hypoxia and birth asphyxia → Birth trauma	0.29

Splenomegaly → Fistula of stomach or duodenum	0.29
Portal hypertension → Hepatitis	0.28
Raynaud → JIA	0.28
Sickle cell disease → Hereditary hemolytic anemia	0.28
Coagulation defect → Iron deficiency anemia	0.28
Primary atelectasis → Hypotension	0.28
Lack of coordination → Delay in development	0.28
Pneumonitis → Pyogenic granuloma	0.28
Down syndrome → Hearing loss	0.28
Pulmonary embolism → Iron metabolism disorder	0.28
Congestive heart failure → Other CHD	0.27
Epilepsy → Hydrocephalus	0.27
Intellectual disability → Disturbance of salivary secretion	0.27
Congenital anomalies of kidney → Multiple congenital anomalies	0.27
Chronic bronchitis → Splenomegaly	0.27
Intestinal malabsorption → Cri-du-chat syndrome	0.27
Leukocytopenia →gonadal dysgenesis	0.27
Hydrocephalus → Calculus of kidney	0.27
Interstitial lung disease → Chronic bronchitis	0.27
Pulmonary embolism → Acquired hemolytic anemia	0.27
Multiple congenital anomalies → Congenital malrotation of intestine	0.26
Sleep apnea → Congenital anomalies of larynx/trachea/bronchus	0.26
Fluid overload disorder → Acute kidney failure	0.26
Left heart failure → Myocarditis	0.26
Lack of coordination → Gastroenteritis and colitis	0.26
Intestinal obstruction → Intestinal vascular insufficiency	0.26
Adrenogenital disorder → Adrenal hypofunction	0.26
Hydrocephalus → Congenital anomalies of skull and face bones	0.26
Delay in development → Pneumonia	0.26
Raynaud → Systemic lupus erythematosus	0.25
DiGeorge syndrome → Primary immunodeficiency	0.25
Other chromosomal anomalies → Multiple congenital anomalies	0.25
Hemolytic disease due to isoimmunization → Myoneural disorder	0.25
Multiple congenital anomalies → Congenital intestinal atresia and stenosis	0.25
Congenital intestinal atresia and stenosis → Congenital malrotation of intestine	0.25
Eosinophilia → Phlebitis and thrombophlebitis	0.25
DiGeorge syndrome → Diaphragm paralysis	0.24
Plasma protein metabolic disorder → Adrenal hypofunction	0.24
Convulsion in newborn → Intrauterine hypoxia and birth asphyxia	0.24
Chronic liver disease → Coagulation defect	0.24
Edema → Hepatomegaly	0.24
Thromboembolism → Coagulation defect	0.24
Cerebral compression → Encephalocele	0.24
Left-sided CHD → Cardiac dysrhythmias	0.24
Intrauterine hypoxia and birth asphyxia → Phlebitis and thrombophlebitis	0.24
Cri-du-chat syndrome → Rickets	0.24
Intestinal malabsorption → Gastrointestinal hemorrhage	0.24
Acute chest syndrome → Aneurysm	0.23
Iron metabolism disorder → Aneurysm	0.23
Cerebral depression coma → Other congenital anomalies of respiratory system	0.23
Velo-cardio-facial syndrome → Other autosomal deletion syndrome	0.23

Cystic fibrosis → Congenital cystic lung	0.23
Neonatal hematological disorder → CHD LR shunt	0.23
Congenital brain reduction deformities → Eosinophilia	0.22
Leukocytosis → Iron deficiency anemia	0.22
Acute chest syndrome → Hereditary hemolytic anemia	0.22
Acquired hemolytic anemia → Anorexia	0.22
Primary immunodeficiency → Hereditary hemolytic anemia	0.22
Anoxic brain damage → Intrauterine hypoxia and birth asphyxia	0.22
Acute kidney failure → Thromboembolism	0.22
Periventricular leukomalacia → Pyogenic granuloma	0.22
Calculus o kidney → Congenital cystic lung	0.22
Exceptionally large baby → Eosinophilia	0.22
Interstitial lung disorder → Primary immunodeficiency	0.22
Encephalocele → Bilirubin excretion disorder	0.21
Congenital intestinal atresia and stenosis → Intestinal obstruction	0.21
Gastrointestinal hemorrhage → Gastroenteritis and colitis	0.21
Left heart failure → Anorexia	0.21
CHD RL shunt → Von Willebrand's disease	0.21
Hypothyroidism → Down syndrome	0.21
Cri-du-chat syndrome → Velo-cardio-facial syndrome	0.21
Calculus of kidney → Mixed acid base balance disorder	0.21
Convulsion in newborn → Birth trauma	0.20
Disturbance of salivary secretion → Adrenal hypofunction	0.20
Endocarditis → Pulmonary embolism	0.20
Anoxic brain damage → Abnormal involuntary movement	0.20
Conduction disorder → Valvular heart disease (right-sided)	0.20
Mediastinitis → Transient mental disorder	0.20
Birth trauma → Intracranial hemorrhage	0.20
Calculus of kidney → Gastroparesis	0.20
Dyspepsia → Abnormal weight gain	0.19
Chronic kidney disease → Congenital anomalies of kidney	0.19
Defibrination syndrome → Myocarditis	0.19
Congenital pneumonia → Adrenal hypofunction	0.19
Primary immunodeficiency → Disorder of muscle, ligament and fascia	0.19
Systemic vasculitis → Congenital anomalies of peripheral vascular system	0.19
Malnutrition → Hepatomegaly	0.19
Abnormality of gait → Cerebral palsy	0.19
Intestinal vascular insufficiency → Portal hypertension	0.19
Intestinal vascular insufficiency → Intestinal malabsorption	0.19
Choanal atresia → Hirschsprung	0.18
Rickets → Phosphorus metabolism disorder	0.18
Diabetic mother syndrome → Neonatal endocrine and metabolic disorder	0.18
Defibrination syndrome → Systemic lupus erythematosus	0.18
Magnesium metabolism disorder → Periventrciular leukomalacia	0.18
Intestinal vascular insufficiency → Gastrointestinal hemorrhage	0.18
Diaphragmatic hernia → Other connective tissue disorders	0.18
Portal hypertension → Situs inversus	0.17
Chronic liver disease → Intestinal malabsorption	0.17
Systemic vasculitis → Splenomegaly	0.17
Coagulation defect → Transient mental disorder	0.17
Diaphragm paralysis → Transient mental disorder	0.17
Persistent vomiting → Glycogen storage disorder	0.17
Systemic lupus erythematosus → Other connective tissue disorders	0.17

Convulsion in newborn → Congenital anomalies of kidney	0.16
Iron metabolism disorder → Pyogenic granuloma	0.16
Disturbance of salivary secretion → Stricture and stenosis of esophagus	0.16
Endocarditis → Eosinophilia	0.16
Systemic vasculitis → Pneumocystosis	0.16
Cardiomyopathy → Cardiac dysrhythmias	0.16
Pyogenic granuloma → Gastroparesis	0.16
Pulmonary embolism → anoxic brain damage	0.16
Choanal atresia → Exceptionally large baby	0.15
Congenital brain reduction deformities → Multiple congenital anomalies	0.15
Convulsion in newborn → Epilepsy	0.15
Systemic vasculitis → Calculs of kidney	0.15
Cerebrovascular disorder → Hemolytic disease due to isoimmunization	0.15
Cri-du-chat syndrome → Other autosomal deletion syndrome	0.15
Microcephaly → Gastroparesis	0.15
Compression of vein → Calculus of kidney	0.14
Hereditary hemorrhagic telangiectasis → Congenital anomalies of peripheral vascular system	0.14
Acute cor pulmonale → Prader Willi syndrome	0.14
Hirschsprung → Maternal complications of pregnancy	0.14
Congenital anomalies of diaphragm → Pleurisy	0.14
CHD LR shunt → Pulmonary embolism	0.14
Nephritis → Disorder of eye movement	0.13
Cystic fibrosis → Diseases of vocal cord	0.13
Cystic fibrosis → Malnutrition	0.13
Congenital cystic lung → Exceptionally large baby	0.13
Rickets → Diseases of vocal cord	0.12
Encephalocele → Left heart failure	0.12
Disturbance of salivary secretion → Edema of larynx	0.12
Defibrination syndrome → Speech disturbance	0.12
Hereditary muscular dystrophy → Stricture and stenosis of esophagus	0.12
Pneumocystosis → Acute cor pulmonale	0.12
Splenomegaly → CHD RL shunt	0.12
Diaphragmatic hernia → Emphysema	0.11
CHD LR shunt → Sickle cell disease	0.11
Chronic kidney disorder → Essential hypertension	0.10
Encephalocele → Umbilical hernia	0.10
Juvenile idiopathic arthritis → Speech disturbance	0.10
Cerebrovascular disorder → Congenital anomalies of peripheral vascular system	0.10
Magnesium metabolic disorder → Acquired hemolytic anemia	0.10
Transient mental disorder → Diseases of vocal cord	0.10
Diabetic mother syndrome → Cardiomyopathy	0.09
Disturbance of salivary secretion → Nutritional deficiency	0.09
Cerebral depression coma → Childbirth complications	0.09
Juvenile idiopathic arthritis → Interstitial lung disorder	0.09
Systemic vasculitis → Pulmonary hemorrhage	0.09
Pneumocystosis → Pulmonary hemorrhage	0.09
Adrenal hypofunction → Chronic bronchitis	0.09
Exceptionally large baby → Stricture and stenosis of esophagus	0.09
Diabetic mother syndrome → Intrauterine hypoxia and birth asphyxia	0.07
Pneumocystosis → Primary immunodeficiency	0.07
Pneumocystosis → Abnormal weight gain	0.07

Primary atelectasis → Childbirth complications	0.07
Choanal atresia → Hemorrhagic disorder due to intrinsic circulating factor	0.06
Choanal atresia → Pyogenic granuloma	0.06
Phosphorus metabolism disorder → Gastroenteritis and colitis	0.06
Intellectual disability → Prader Willi syndrome	0.06
Other congenital anomalies of respiratory system → Hemorrhagic disorder due to intrinsic circulating factor	0.06
Compression of vein → Other autosomal deletion syndrome	0.05
Aneurysm → Pneumothorax	0.05
Nephritis → Essential hypertension	0.04
Diaphragmatic hernia → Cardiomegaly	0.03

Table B2b. Secondary analysis – study cohort comprised children who underwent RHC, in addition to having two or more healthcare encounters for PH during the study period

Edges	Weight
DiGeorge syndrome → Primary immunodeficiency	1.00
Other CHD → Left-sided CHD	1.00
Cardiomegaly → Pulmonary collapse	0.99
Other chromosomal anomalies → Other autosomal deletion syndrome	0.99
DiGeorge syndrome → Vel-cardio-facial syndrome	0.99
Other CHD → Tetralogy of Fallot	0.97
Epilepsy → Cerebral palsy	0.97
Perinatal digestive system disorder → Intestinal vascular insufficiency	0.96
Tachypnea of newborn → Neonatal endocrine and metabolic disturbance	0.96
Pulmonary collapse → Pleurisy	0.95
Congenital lung agenesis/hypoplasia/dysplasia → Congenital anomalies of diaphragm	0.94
Disorder of muscle, ligament, fascia → Lack of coordination	0.94
PPHN → Neonatal hematological disorder	0.94
Congestive heart failure → Cardiomyopathy	0.92
Valvular heart disease (left-sided) → Left-sided CHD	0.91
Valvular heart disease (left-sided) → Rheumatic heart disease	0.91
Lack of coordination → Delay in development	0.90
Portal hypertension → Splenomegaly	0.90
Left-sided CHD → Conduction disorder	0.90
Dyspepsia → Persistent vomiting	0.89
Congenital spleen anomaly → Situs inversus	0.88
Fetal and neonatal hemorrhage → Neonatal hematological disorder	0.88
Malnutrition → Interstitial lung disease	0.88
Compression of vein → Congenital anomalies of diaphragm	0.88
BPD → Respiratory distress syndrome	0.86
Conduction disorder → Cardiac dysrhythmias	0.86
Chronic kidney disorder → Acute kidney failure	0.85
Cardiomyopathy → Left heart failure	0.85
Edwards syndrome → Congenital lung agenesis/hypoplasia/dysplasia	0.85
Congestive heart failure → Valvular heart disease (left-sided)	0.84
Primary atelectasis → Intrauterine hypoxia and birth asphyxia	0.83
Portal hypertension → Hepatitis	0.83
Sickle cell disease → Iron metabolism disorder	0.83
Pulmonary embolism → CHD (left-to-right shunt)	0.83
Congenital spleen anomaly → Pulmonary hemorrhage	0.82
Perinatal digestive system disorders → Intestinal malabsorption	0.81
Other CHD → CHD (left-to-right shunt)	0.80
Down syndrome → Hypothyroidism	0.80
Respiratory distress syndrome → Primary atelectasis	0.79
Splenomegaly → Fistula of stomach or duodenum	0.79
Multiple congenital anomalies → Congenital anomalies of kidney	0.78
Intestinal vascular insufficiency → Gastrointestinal hemorrhage	0.78
DiGeorge syndrome → Tetralogy of Fallot	0.78
Edwards syndrome → Down syndrome	0.77
Disorder of eye movement → Gastroenteritis and colitis	0.76
Disorder of eye movement → Hepatitis	0.75
Congenital brain reduction deformities → Epilepsy	0.75
Anoxic brain damage → Pulmonary embolism	0.74

Edwards syndrome → Other chromosomal anomalies	0.74
Congestive heart failure → Pulmonary insufficiency following trauma	0.74
Primary atelectasis → Nutritional deficiency	0.73
Diaphragm dialysis → Transient mental disorder	0.72
Velo-cardio-facial syndrome → Other autosomal deletion syndrome	0.72
Hearing loss → Down syndrome	0.72
BPD → CHD (left-to-right shunt)	0.72
Edwards syndrome → Chronic kidney disorders	0.71
Hydrops fetalis → Congenital anomalies of skull and face bones	0.71
Congenital spleen anomaly → Congenital malrotation of intestine	0.71
Pleurisy → Edema	0.71
Congenital anomalies skull and face bones → Neonatal endocrine and metabolic disturbances	0.71
Iron metabolism disorder → ILD	0.70
Pulmonary collapse → Pneumothorax	0.70
Multiple congenital anomalies → Congenital intestinal atresia and stenosis	0.70
Congestive heart failure →Pleurisy	0.69
Chronic liver disease → Hypotension	0.68
Cyanosis → Mixed acid base balance disorder	0.68
Maternal complications of pregnancy → Splenomegaly	0.68
Portal hypertension → Delay in development	0.68
Lack of coordination → Hearing loss	0.67
Disorder of lymphatic channels → Pneumothorax	0.67
Disorder of eye movement → Abnormal weight gain	0.67
Primary atelectasis → Perinatal digestive system disorders	0.67
Hydrops fetalis → Acute cor pulmonale	0.67
Sickle cell disease → Cystic fibrosis	0.67
PPHN → Tachypnea of newborn	0.66
Congenital brain reduction deformities → Hepatitis	0.66
Congenital spleen anomaly → Persistent vomiting	0.66
Neonatal endocrine and metabolic disturbance → Umbilical hernia	0.66
Emphysema → Maternal complications of pregnancy	0.65
Down syndrome → Sleep apnea	0.65
Chronic bronchitis → Congenital malrotation of intestine	0.65
Hepatitis → Microcephaly	0.65
Pulmonary collapse → Pneumonia	0.65
Iron metabolism disorder → Pulmonary embolism	0.64
Aneurysm → Mediastinitis	0.64
Abnormal involuntary movement → Congenital anomalies of peripheral vascular system	0.64
Leukocystosis → Thrombocytopenia	0.64
Portal hypertension → Hypothyroidism	0.64
Dyspepsia → Situs inversus	0.63
Valvular heart disease (right-sided) → Left heart failure	0.63
Pulmonary insufficiency following trauma → Other CHD	0.63
Neonatal endocrine and metabolic disturbances → Hearing loss	0.63
Iron deficiency anemia → Congenital anomalies of peripheral vascular system	0.63
DiGeorge syndrome → Speech disturbance	0.63
Pericardium disorder → Disorders of lymphatic channels	0.63
Sickle cell disease → Other CHD	0.63
Persistent vomiting → Gastrointestinal hemorrhage	0.63
Cerebral palsy → Abnormal involuntary movement	0.62

Chronic liver disease → Intestinal malabsorption	0.62
Umbilical hernia → Down syndrome	0.62
Compression of vein → Hearing loss	0.62
Edema → Hydrops fetalis	0.62
Dyspepsia → Congenital malrotation of intestine	0.61
Chronic kidney disorder → Essential hypertension	0.61
Diseases of vocal cord → Left heart failure	0.61
Neonatal hematological disorder → Drug withdrawal syndrome	0.61
PPHN → Congenital anomalies of skull and face bones	0.61
Persistent vomiting → Gastroenteritis and colitis	0.61
Pulmonary collapse → Congestive heart failure	0.61
Pulmonary insufficiency following trauma → Cyanosis	0.61
Congenital brain reduction deformities → Hydrocephalus	0.61
Disorders of lymphatic channels → Drug withdrawal syndrome	0.61
Mediastinitis → Transient mental disorder	0.61
Other chromosomal anomalies → Disorder of eye movement	0.60
Dyspepsia → Mixed acid base balance disorder	0.60
Chronic liver disease → Anoxic brain damage	0.60
Left-sided CHD → Rheumatic heart disease	0.60
Diseases of vocal cord → Intestinal vascular insufficiency	0.60
Congenital lung agenesis/hypoplasia/dysplasia → Congenital musculoskeletal deformities	0.60
Drug withdrawal syndrome → Thrombocytopenia	0.60
Endocarditis → Diaphragm paralysis	0.60
Congenital spleen anomaly → Umbilical hernia	0.60
BPD → Pneumonitis	0.59
Iron metabolism disorder → Cystic fibrosis	0.59
Abnormality of gait → Abnormal involuntary movement	0.59
Epilepsy → Mediastinitis	0.58
Speech disturbance → Abnormality of gait	0.58
Acute cor pulmonale → Valvular heart disease (right-sided)	0.58
CHD (left-to-right shunt) → Cardiomyopathy	0.58
Sickle cell disease → Sleep apnea	0.58
Iron metabolism disorder → Aneurysm	0.58
Umbilical hernia → Intrauterine hypoxia and birth asphyxia	0.58
Epilepsy → Hydrocephalus	0.58
Cystic fibrosis → Chronic kidney disorder	0.58
Compression of vein → Multiple congenital anomalies	0.57
Cyanosis → Cardiac dysrhythmias	0.57
Maternal complications of pregnancy → Microcephaly	0.57
Congestive heart failure → Acute edema of lung	0.57
Edema → Drug withdrawal syndrome	0.57
Hepatomegaly → CHD (left-to-right shunt)	0.57
Cerebral palsy → Pneumonia	0.57
Hydrops fetalis → Respiratory distress syndrome	0.57
Maternal complications of pregnancy → Drug withdrawal syndrome	0.57
Chronic liver disease → Neutropenia	0.56
Diaphragm paralysis → Abnormality of gait	0.56
Portal hypertension → Disorder of eye movement	0.56
Disorder of eye movement → Speech disturbance	0.56
Edwards syndrome → Acute kidney failure	0.56
Leukocytosis → Neutropenia	0.55
Congenital brain reduction deformities → Multiple congenital anomalies	0.55

Primary immunodeficiency → Disorder of muscle, ligament, fascia	0.55
Maternal complications of pregnancy → Congenital intestinal atresia and stenosis	0.55
Pleurisy → Acute edema of lung	0.55
Pulmonary insufficiency following trauma → Congenital spleen anomaly	0.54
Multiple congenital anomalies → Congenital malrotation of intestine	0.54
DiGeorge syndrome → Congenital anomalies of kidney	0.54
Tachypnea of newborn → Maternal complications of pregnancy	0.54
Neonatal hematological disorder → BPD	0.54
Coagulation defect → Iron deficiency anemia	0.54
Splenomegaly → Thrombocytopenia	0.54
Chronic bronchitis → Disorder of muscle, ligament, fascia	0.53
Congenital lung agenesis/hypoplasia/dysplasia → Congenital intestinal atresia and stenosis	0.53
Acute cor pulmonale → Conduction disorder	0.53
Disorder of lymphatic channels → Gastrointestinal hemorrhage	0.53
Pulmonary collapse → Gastrointestinal hemorrhage	0.53
Thromboembolism → Diseases of vocal cord	0.53
Velo-cardio-facial syndrome → Microcephaly	0.53
DiGeorge syndrome → Intestinal malabsorption	0.53
Tetralogy of Fallot → Left-sided CHD	0.53
Pulmonary collapse → Congenital spleen anomaly	0.53
Congenital brain reduction deformities → Perinatal digestive system disorders	0.53
Sleep apnea → Hypothyroidism	0.53
Tachypnea of newborn → Aneurysm	0.52
Tachypnea of newborn → Emphysema	0.52
Compression of vein → Speech disturbance	0.52
Sickle cell disease → Primary immunodeficiency	0.52
Iron metabolism disorder → Hepatomegaly	0.52
Thromboembolism → Disorders of lymphatic channels	0.52
Pleurisy → Disorders of lymphatic channels	0.52
Anoxic brain damage → Hypothyroidism	0.52
Congenital anomalies of kidney → Chronic kidney disorder	0.52
Epilepsy → Intrauterine hypoxia and birth asphyxia	0.52
Anoxic brain damage → Abnormal involuntary movement	0.52
Leukocytosis → Abnormal weight gain	0.51
Persistent vomiting → Diaphragm paralysis	0.51
Edema → Congenital anomalies of kidney	0.51
Congenital anomalies of kidney → Cyanosis	0.51
Umbilical hernia → Fistula of stomach or duodenum	0.51
Pneumonia → Tetralogy of Fallot	0.51
Acute kidney failure → Thrombocytopenia	0.51
Chronic kidney disorder → Congenital anomalies of peripheral vascular system	0.50
Congenital anomalies of kidney → Congenital lung agenesis/hypoplasia/dysplasia	0.50
Conduction disorder → Thromboembolism	0.50
Congenital anomalies of diaphragm → Hydrops fetalis	0.50
Congenital anomalies of larynx/trachea/bronchus → Hearing loss	0.50
Congenital anomalies of larynx/trachea/bronchus → Pneumonitis	0.50
Acute edema of lung → Primary atelectasis	0.50
Neutropenia → Diseases of vocal cord	0.50

B3. Network-derived clusters in the RHC cohort

Table B3a. Mapping of network-derived comorbidity clusters with PH subtypes defined in the WHO classification.

WHO Classification of PH	Network-derived Comorbidity Clusters
1. Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic PAH	• N/A
1.2 Heritable PAH	• N/A
1.3 Drug and toxin induced	• N/A (exposures to drugs and toxins were not captured in the dataset)
1.4.1 Associated with CTD	• N/A
1.4.2 Associated with HIV infection	N/A (there were no PH patients with HIV in the dataset)
1.4.3 Associated with portal hypertension	• Portal hypertension, hepatitis, microcephaly, disorder of eye movement
1.4.4 Associated with CHD	• CHD (left to right shunt), other CHD, Tetralogy of Fallot, other CHD
1.4.5 Associated with schistosomiasis	N/A (there were no PH patients with schistosomiasis in the dataset)
1' PVOD	• N/A
1'' PPHN	• PPHN, congenital anomalies of skull and face bones
2. PH due to left heart disease	
2.1 Left ventricular systolic dysfunction	• Congestive heart failure, edema, acute edema of lung, pleurisy • Pericardium disorder, disorders of lymphatic channels
2.2 Left ventricular diastolic dysfunction	
2.3 Valvular disease	• Valvular heart disease (tricuspid or pulmonary valve disorders), left heart failure, cardiomyopathy • Valvular heart disease (mitral or aortic valve disorders), rheumatic heart disease, left-sided CHD
2.4 Congenital/acquired left heart disorder	• CHD (RL shunt) • Conduction disorder, cardiac dysrhythmias
3. PH due to lung diseases and/or hypoxia	
3.1 Chronic obstructive pulmonary disease	• Cystic fibrosis, pulmonary embolism, sickle cell disease, iron metabolism disorder* • Chronic bronchitis, congenital malrotation of intestine • Emphysema, tachypnea of newborn, maternal complications of pregnancy, aneurysm
3.2 Interstitial lung disease	• Interstitial lung disease, malnutrition
3.3 Other mixed restrictive or obstructive pulmonary disease	• Pneumonia, pulmonary collapse, pneumothorax, cardiomegaly, gastrointestinal hemorrhage • Diaphragm paralysis, endocarditis • Pulmonary eosinophilia
3.4 Sleep-disordered breathing	• Sleep apnea, Down syndrome, hypothyroidism*
3.5 Alveolar hypoventilation disorders	• Intrauterine hypoxia and birth asphyxia, primary atelectasis, nutritional deficiency
3.6 Chronic exposure to	N/A (there are no diagnosis codes for high altitude PH)

high altitude	
3.7 Developmental lung diseases	• Bronchopulmonary dysplasia, pneumonitis, respiratory distress syndrome • Congenital anomalies of diaphragm, compression of vein • Congenital anomalies of larynx, trachea, bronchus, hearing loss • Congenital lung agenesis/hypoplasia/dysplasia, congenital anomalies of kidney, congenital musculoskeletal deformities, Edwards syndrome
4. Chronic thromboembolic PH (CTEPH)	• Thromboembolism, diseases of vocal cord
5. PH due to unclear multifactorial mechanisms	
5.1. Hematological disorders	• Sickle cell disease, iron metabolism disorder, cystic fibrosis, pulmonary embolism • Neonatal hematological disorder, fetal and neonatal hemorrhage, drug withdrawal syndrome • Thrombocytopenia, acute kidney failure • Coagulation defect, iron deficiency anemia • Leukocytosis, abnormal weight gain
5.2. Systemic disorders	• Essential hypertension
5.3. Metabolic disorders	• Neonatal endocrine and metabolic disturbances, umbilical hernia • Hypothyroidism, sleep apnea, Down syndrome*
5.4. Others	• Chronic liver disease, hypotension, neutropenia, anoxic brain damage • Splenomegaly, fistula of stomach or duodenum • Hepatomegaly • Chronic kidney disease, Congenital anomalies of peripheral vascular system • Mediastinitis, transient mental disorder

(* Overlapping subtypes)

Table B3b. Mapping of network-derived comorbidity clusters with PH subtypes defined in the Panama classification.

Panama Classification of PH	Network-derived Comorbidity Clusters
1. Prenatal or developmental pulmonary hypertensive vascular disease	• Congenital anomalies of diaphragm, compression of vein • Congenital anomalies of larynx, trachea, bronchus, hearing loss • Congenital lung agenesis/hypoplasia/dysplasia, congenital anomalies of kidney, congenital musculoskeletal deformities, Edwards syndrome
2. Perinatal pulmonary vascular maladaptation (PPHN)	• PPHN, congenital anomalies of skull and face bones
3. Pediatric cardiovascular disease	• CHD (left to right shunt), other CHD, Tetralogy of Fallot, other CHD • Congestive heart failure, edema, acute edema of lung, pleurisy • Pericardium disorder, disorders of lymphatic channels • Valvular heart disease (tricuspid or pulmonary valve disorders), left heart failure, cardiomyopathy • Valvular heart disease (mitral or aortic valve disorders), rheumatic heart disease, left-sided CHD • CHD (right to left shunt) • Conduction disorder, cardiac dysrhythmias
4. Bronchopulmonary dysplasia	• Bronchopulmonary dysplasia, pneumonitis, respiratory distress syndrome
5. Isolated pediatric pulmonary hypertensive vascular disease (PPHVD) or Isolated pediatric PAH	• N/A
6. Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes	• Down syndrome, sleep apnea, hypothyroidism • Other chromosomal anomalies, other autosomal deletion syndrome • Multiple congenital anomalies, congenital intestinal atresia and stenosis • Congenital spleen anomaly, pulmonary hemorrhage, situs inversus
7. Pediatric lung disease	• Cystic fibrosis, pulmonary embolism, sickle cell disease, iron metabolism disorder* • Chronic bronchitis, congenital malrotation of intestine • Emphysema, tachypnea of newborn, maternal complications of pregnancy, aneurysm • Interstitial lung disease, malnutrition • Pneumonia, pulmonary collapse, pneumothorax, cardiomegaly, gastrointestinal hemorrhage • Diaphragm paralysis, endocarditis • Pulmonary eosinophilia
8. Pediatric thromboembolic disease	• Thromboembolism, diseases of vocal cord

9. Pediatric hypobaric hypoxic exposure	• N/A (there are no diagnosis codes for hypobaric hypoxic exposure)
10. Pediatric pulmonary vascular disease associated with other system disorders	• Portal hypertension, hepatitis, microcephaly, disorder of eye movement • Sickle cell disease, iron metabolism disorder, cystic fibrosis, pulmonary embolism* • Splenomegaly, fistula of stomach or duodenum • Neonatal hematological disorder, fetal and neonatal hemorrhage, drug withdrawal syndrome • Thrombocytopenia, acute kidney failure • Coagulation defect, iron deficiency anemia • Leukocytosis, abnormal weight gain • Neonatal endocrine and metabolic disturbances, umbilical hernia • Chronic liver disease, hypotension, neutropenia, anoxic brain damage • Hepatomegaly • Chronic kidney disease, Congenital anomalies of peripheral vascular system • Mediastinitis, transient mental disorder

(* Overlapping subtypes)

C. Supplemental References

1. Heckerman D. A Bayesian approach to learning causal networks. UAI'95 Proceedings of the Eleventh conference on Uncertainty in artificial intelligence. 1995:285-295.

2. Friedman N, Nachman I, Pe'er D. Learning Bayesian network structure from massive datasets: the sparse candidate algorithm. Proceeding UAI'99 Proceedings of the Fifteenth conference on Uncertainty in artificial intelligence: 206-215.

3. Cooper GF, Herskovits E. A Bayesian method for the induction of probabilistic networks from data. Machine Learning. 1992;9:309-347.

4. Koller D, Friedman N. Probabilistic graphical models: Principles and Techniques. Massachusetts Institute of Technology. 2009;733-749.

5. Friedman N, Goldszmidt M, Wyner A. Data analysis with Bayesian networks: a bootstrap approach. Proceeding UAI'99 Proceedings of the Fifteenth conference on Uncertainty in artificial intelligence: 196-205.

6. Scutari M, Nagarajan R. Identifying significant edges in graphical models of molecular networks. Artificial intelligence in medicine. 2013:207-217.

7. Pons P, Latapy M. Computing communities in large networks using random walks. Computer and Information Sciences-ISCIS 2005. Springer Berlin Heidelberg. 2005:284-293.

8. Newman ME. Modularity and community structure in networks. Proc Natl Acad Sci U S A. 2006;103(23):8577-82.