

Congenital Cardiovascular Malformations: Questions on Inheritance

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The Baltimore-Washington Infant Study, an epidemiologic investigation of congenital heart disease, searches for genetic and environmental risk factors. Among 2,102 infants with heart disease, 17.5% had a noncardiac abnormality of chromosomal or genetic origin, whereas among 2,328 control infants, only 0.7% had a genetic abnormality.

Familial cardiovascular malformations encountered can be grouped into five distinct etiologic mechanisms. Single gene effects may be responsible for the specific histologic and biochemical changes in familial atrial septal defect with conduction disturbance and also in idiopathic ventricular hypertrophy. Left heart lesions showed familial concordance by the presumed morphogenetic mechanism of abnormal embryonic blood flow with phenotypes of varying severity. Pulmonary stenosis appeared with familial heritable disorders, as well as a partially concordant lesion with

tetralogy of Fallot. Ventricular septal defect with transposition of the great arteries (one sibling pair) and with truncus arteriosus (two sibling pairs) indicate forme fruste expression of conotruncal defects. Endocardial cushion defect occurred with and without Down's syndrome in members of three families, suggesting inheritance of a defect affecting cellular migration. Heritable blood coagulopathies occurred in case families and not in control families. The association of hemophilia and transposition, observed also by others, is extremely unlikely by chance and suggests genetic errors of endothelial cell function.

The description of specific families from a population-based study emphasizes biologic questions on the nature of the inheritance of cardiovascular malformations.

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Population-based epidemiologic studies have achieved remarkable success in adult cardiology with the recognition of elevated serum cholesterol, smoking and hypertension as risk factors for coronary heart disease. Assessment of the differential strengths of genetic and environmental determinants of these risks made possible the design of preventive intervention trials.

Pediatric cardiology has not had a comparable sequence

of studies of risk factors for cardiovascular malformations. In fact, not a single descriptive study had defined differences between case and control families at the time when a proposed hypothesis of an etiologic role of gestational hormone therapy captured professional and societal interest (1,2). Our epidemiologic investigation of maternal hormone therapy (3) made obvious the need to delineate confounding factors for which adjustments should be made before a meaningful evaluation of a potentially harmful single agent could be achieved.

The Baltimore-Washington Infant Study was designed as an exploratory case-control study to provide comparative genetic and environmental data on the families of infants with cardiovascular malformations and the families of control infants representing the birth cohort. Searching for evidence of genetic susceptibility to congenital heart disease, this study describes observations on 2,102 case infants and on 2,328 control infants and presents new questions regarding the nature of the inherited risk factors. Questions are raised about the heritable biologic factors that might account for the familial abnormalities.

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Table 1. Genetic Abnormalities in Case and Control Families

	Cases (n = 2,102)		Controls (n = 2,328)	
	No.	%	No.	%
With noncardiac abnormality	563	26.8	84	3.6
Genetic				
Chromosome abnormality	271	12.9	2	0.1
Syndrome/heritable disorder	98	4.6	15	0.6
Potentially genetic/environmental				
Suspect syndrome	20	1.0	0	—
Nonsyndromic	174	8.3	67	2.9
Without noncardiac abnormality	1539	73.2	2244	96.4
	("Isolated")		(Normal)	

Methods

The Baltimore-Washington Infant Study is an ongoing case-control study of cardiovascular malformations in a defined geographic area of 90,000 annual births (Maryland, District of Columbia and Northern Virginia). The study, initiated on January 1, 1981, has been previously described (4,5). Cases are infants <1 year of age in whom the diagnosis of a cardiovascular malformation has been confirmed by echocardiography, cardiac catheterization, surgery or autopsy, excluding only infants of <38 weeks' gestation with patent ductus arteriosus. Cases are ascertained by the pediatric cardiology centers of the region and by searches of pathology records in 53 area hospitals. A review of death certificates validates this case ascertainment. A sample of control infants is chosen by computer algorithm to be representative of the birth cohort.

Cardiac malformations are coded according to the International Society of Cardiology system (6), which provides a specific code for each component cardiac malformation and for specific complexes of lesions. The principal diagnosis is allocated in a hierarchical order in the following sequence:

abnormalities of the cardiac loop, conotruncal and major septation defects, atresia and hypoplasia, stenotic lesions, septal defects and myocardial lesions. Details of the methodology concerning the ascertainment of noncardiac anomalies have been described (7). Sociodemographic, medical and family history and environmental exposure data are obtained from case and control mothers through a questionnaire administered during home visits by trained interviewers. The family inquiry obtains information on first degree relatives (parents and siblings) of the proband and of each parent concerning congenital heart disease, chromosomal and other malformations and heritable noncardiac disorders. Because the study is population based, the findings represent actual frequencies of cardiac and noncardiac anomalies in the probands and families in the birth cohort.

Results

The presence of genetic noncardiac abnormalities among the infants with cardiovascular malformations and among control infants is shown in Table 1. Chromosomal abnormal-

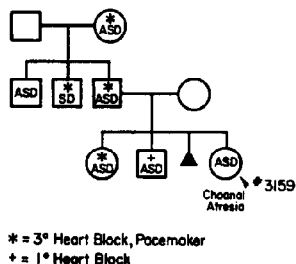
Table 2. Congenital Cardiovascular Malformations (CCVM) in First Degree Relatives

Proband Status	Families With							
	Mother		Father		Full Siblings		Maternal Half Siblings	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Cases								
Isolated CCVM (n = 1388)	14/1388	(1.0)	8/1388	(0.6)	27/677	(4.0)	1/214	(0.5)
With chromosomal abnormality (n = 241)	2/241	(0.8)	1/241	(0.4)	2/141	(1.4)	1/29	(3.4)
With Mendelian abnormality (n = 92)	3/92	(3.3)	0/92	—	3/39	(7.7)	0/13	—
With nonsyndromic abnormality (n = 172)	1/172	(0.6)	2/172	(1.2)	3/86	(3.5)	2/28	(7.1)
Total cases	20/1893	(1.1)	11/1893	(0.6)	35/943	(3.7)*	4/284	(1.4)
Controls	4/2328	(0.2)	8/2328	(0.3)	11/1140	(1.0)	2/343	(0.6)
	p < 0.001		ns		p < 0.001		ns	

*41 total affected siblings: 4 families with 2 affected siblings: proband with isolated congenital cardiovascular malformations; 1 family with 2 affected siblings: proband with Mendelian abnormality; 1 family with 2 affected siblings: proband with nonsyndromic abnormality. Analyzed by method of Fleiss JL, Statistical Methods for Rates and Proportions. 2nd ed. New York: John Wiley & Sons, 1981:19-32.

INHERITANCE OF CARDIAC DEFECT

ATRIAL SEPTAL DEFECT (ASD) WITH CONDUCTION ABNORMALITIES



IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS (IHSS)

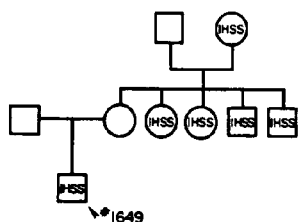


Figure 1. Familial atrial septal defect (ASD) with conduction defects and idiopathic hypertrophic subaortic stenosis (IHSS). Dominant genes in these conditions may, respectively, cause alterations in the atrial septum as a result of autoimmunity or affect the metabolism of ventricular myocardium. SD = septal defect, type unknown.

ities occurred >100 times as often among case as among control subjects. Mendelian disorders and syndromic associations of 44 types occurred in cases compared with only 6 types in controls (7).

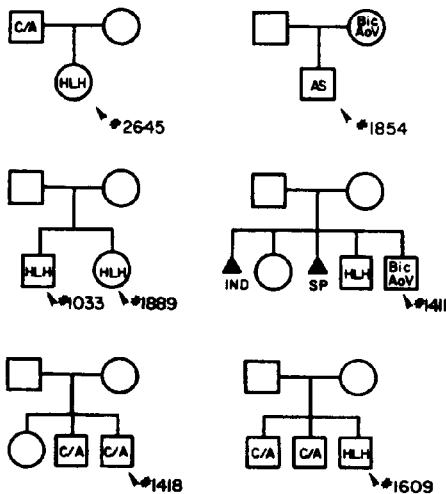
Familial occurrence of cardiovascular malformations (Table 2). Information obtained by interview on congenital cardiovascular malformations in first degree relatives of case and control subjects is available for 1,893 case and 2,328 control families. There is a highly significant case excess of congenital heart disease among mothers and full siblings ($p < 0.001$). Evaluation by the associated noncardiac abnormalities in the probands is impeded by small numbers in the subgroups, but valuable information is obtained by detailed review of selected pedigrees. These are presented according to hypothesized etiologic groups.

Inheritance of cardiac defect as a single gene effect (Fig. 1). Only two families were encountered in which the same malformation was transmitted across three generations. 1) In one family, atrial septal defect associated with congenital heart block occurred in four adults and three children. The

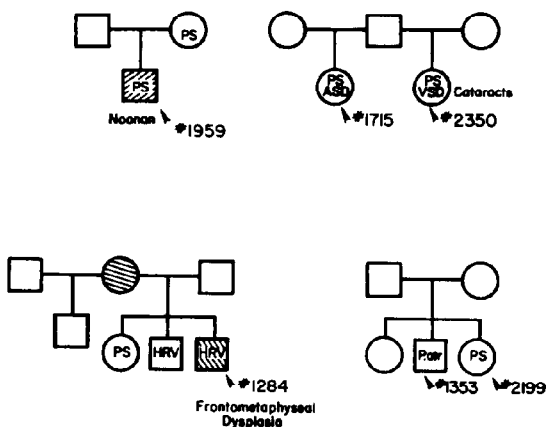
Figure 2. Familial concordance in left-sided obstructive lesions suggests genetic determination of embryonic blood flow alterations, whereas right-sided obstructive lesions may have additional genetic or environmental effects. AS = aortic stenosis; ASD = atrial septal defect; BicAov = bicuspid aortic valve; C/A = coarctation of aorta; HLH = hypoplastic left heart; HRV = hypoplastic right ventricle with severe tricuspid and pulmonary stenosis; IND = induced abortion; P.atr = pulmonary atresia; PS = pulmonary stenosis; SP = spontaneous abortion; VSD = ventricular septal defect. Shading indicates the noted genetic disorder.

FAMILIAL OBSTRUCTIVE LESIONS: WITH VARYING SEVERITY OF PHENOTYPES

LEFT-SIDED LESIONS



RIGHT-SIDED LESIONS



PARTIAL CONCORDANCE OF CONOTRUNCAL DEFECTS (? FORME FRUSTE)

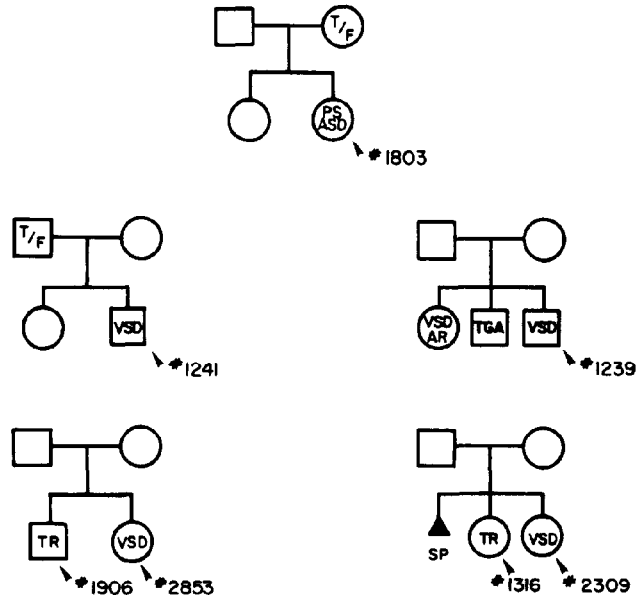


Figure 3. Familial aggregations of lesions indicate susceptibility to conotruncal maldevelopment in probands with pulmonary stenosis (PS) or ventricular septal defect (VSD). AR = aortic valve regurgitation; T/F = tetralogy of Fallot; TGA = transposition of great arteries; TR = tricus arteriosus; other abbreviations as in Figure 2.

disorder affected both male and female members. 2) Idiopathic hypertrophic subaortic stenosis (asymmetric septal hypertrophy) in the mother's family was reported to have also affected more distant relatives, several of whom died suddenly, but the disease was not apparent in the 23 year old mother of the proband infant.

Familial obstructive lesions with varying phenotypic severity (Fig. 2). A different type of familial concordance was noted in families of probands with left-sided obstructive lesions: bicuspid aortic valve, aortic stenosis, coarctation of the aorta and hypoplastic left heart syndrome occurred in six families with no predictable sequence in severity. Among the four families with right heart obstructive lesions, isolated pulmonary stenosis and atresia occurred in only one sibling pair. In each of the other three families, a noncardiac lesion of possible etiologic significance was present in the proband. However, in some family members, the concordant cardiac defect was present without expression of the other disorder.

Familial evidence of conotruncal defects by partial concordance (? forme fruste) (Fig. 3). Familial aggregations of components of conotruncal malformations with pulmonary stenosis or ventricular septal defect in the proband occurred in five families: tetralogy of Fallot was present in two parents of cases, transposition of the great arteries in a sibling and truncus arteriosus in two sibling pairs.

Endocardial cushion defects in euploid and aneuploid family members (Fig. 4). Among six families with endocardial cushion defect in the proband, there were three in which the cardiac defect occurred in euploid as well as aneuploid members. Two mothers, respectively 22 and 26 years of age at the time of the baby's birth, underwent operation for an ostium primum defect in childhood. Each had an infant with a complete endocardial cushion defect with trisomy 21. A complete endocardial cushion defect occurred in half siblings, one with and one without Down's syndrome. Endocardial cushion defect also occurred in a euploid sibling pair. In the fifth family, a proband with surgically treated atrial and membranous ventricular septal defects had a later ascertained sibling with Down's syndrome and a complete cushion defect. In the sixth family, endocardial cushion defect associated with pulmonary stenosis occurred in a proband whose mother had pulmonary stenosis with a secundum atrial septal defect.

Familial noncardiac disorders: heritable blood disorders. Evaluation of familial noncardiac disorders indicates further complexities in the determination of possible genetic susceptibility to abnormal cardiac morphogenesis.

A case-control difference in major familial blood disorders has previously been reported (8). The pedigrees of families with major coagulopathies are shown in Figure 5, together with a remarkable pedigree observed by Dr. James Manning.

Von Willebrand's disease occurred in three case parents:

ENDOCARDIAL CUSHION DEFECTS IN EUPLOID AND ANEUPLOID FAMILY MEMBERS

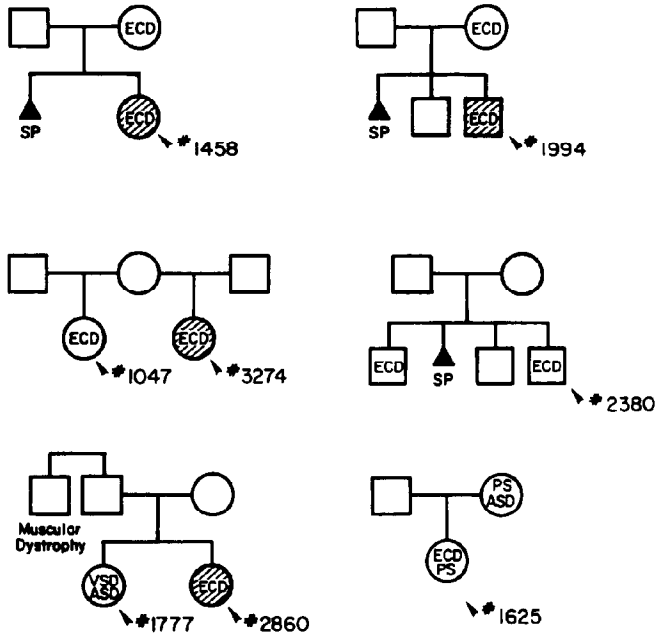


Figure 4. Familial aggregation of endocardial cushion defect (ECD) in members with and without Down's syndrome indicates heritable genetic effect for cardiac malformation. Abbreviations as in Figure 2. Shading indicates Down's syndrome.

the mother of an infant with the Williams syndrome, the father of an infant with ventricular septal defect and the mother of an infant with an atrial septal defect.

Hemophilia was present in the father and uncle of a female carrier infant with transposition of the great arteries and in the brother and two cousins of a baby with atrioventricular canal and trisomy 21. The latter infant had a bleeding tendency, but a factor VIII deficiency was not confirmed. In Dr. Manning's observed family, three brothers had hemophilia, one with an atrial septal defect, and one brother had transposition of the great arteries without diagnosed coagulopathy.

Discussion

Preliminary evaluation of the descriptive epidemiology of cardiovascular malformations raises new etiologic questions as population-based data extend the knowledge derived from clinical studies.

The familial occurrence of atrial septal defect with a conduction abnormality. This malformation was recognized as a syndrome of clinical and genetic importance by Emanuel et al. (9), and further reports of affected families (10,11) led McKusick (12) to describe this entity (McKusick code 10890) as "a specific form of atrial septal defect." The occurrence of a sinus venosus defect with bradyarrhythmia

(13) in a mother and her son and daughter suggested to other investigators a genetically induced tissue alteration.

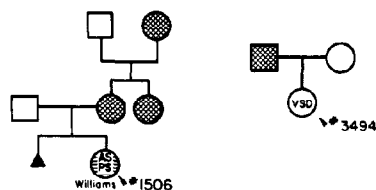
The evolution of a mild conduction abnormality to complete heart block, as seen in our family and in the reports of others, is not unlike that observed in familial congenital heart block (McKusick code 14040). It seems reasonable to hypothesize that atrial septal defect with conduction abnormality is a distinct entity with a different histopathologic origin from that of uncomplicated atrial septal defects. A possible role of autoimmunity and connective tissue disorders must be considered in view of the association of congenital heart block and maternal lupus erythematosus (14-16). Information regarding the cellular pathology of atrial septal defects with associated conduction lesions could help to clarify the etiologic distinctions.

Hypertrophic cardiomyopathy. In contrast to a lack of microscopic descriptions of atrial lesions, extensive histopathologic and metabolic data have been accumulated on ventricular myocardium regarding the origin of idiopathic hypertrophic subaortic stenosis (17), but the mechanism of the inherited risk factors has not yet been defined.

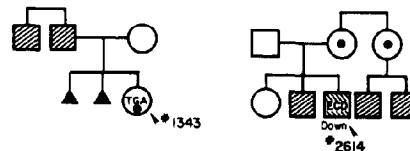
Left heart lesions. The Baltimore-Washington Infant Study data suggest that certain cardiac morphologic phenotypes form seemingly homogeneous groups according to presumed developmental mechanisms, whereas other mechanistic subgroups are etiologically heterogeneous. Left heart

HERITABLE BLOOD DISORDERS

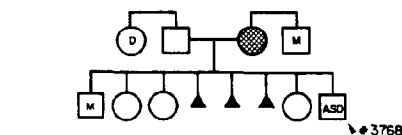
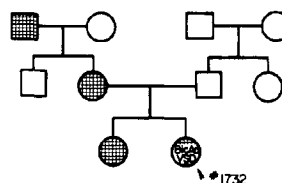
VON WILLEBRAND'S



HEMOPHILIA

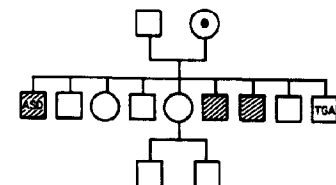


SPHEROCYTOSIS



OTHER INVESTIGATOR

HEMOPHILIA



Courtesy of J.A. Manning, M.D.

lesions that are presumed to be due to altered embryonic blood flow (18) occur in families in various degrees of severity, thus suggesting that genetic factors predispose to left-sided flow alterations, but we have no knowledge of the cause of these flow lesions. Studies of recurrence rates (19) and segregation patterns (20) have suggested a genetic liability consistent with a single gene effect.

Right-sided obstructive lesions and membranous ventricular septal defects. Both of these malformations, also presumed to be due to altered flow, appear to be developmentally heterogeneous as they occur in familial combinations with conotruncal malformations. This partial concordance was described as a "conotruncal susceptibility" by Corone et al. (21) and parallels the spectrum of conotruncal lesions obtained experimentally in Keeshond dogs (22) as "forme fruste" manifestations of conotruncal abnormalities.

Pulmonary stenosis. The association of pulmonary stenosis in the mother of an infant with Noonan's syndrome and pulmonary stenosis could be explained as a genetic lesion if the mother had unrecognized Noonan's syndrome. This would, however, also mean that inapparent syndromes might be present in other cases of simple pulmonary stenosis. Similar considerations apply to the family with frontometaphyseal dysplasia in which both the cardiac and noncardiac lesions occurred together in the proband, but each type of lesion also occurred alone in a first degree

relative, suggesting a probable single etiology. The occurrence of pulmonary stenosis and cataracts in another proband raises the question of rubella syndrome, although a previous sibling also had the same cardiac disorder.

relative, suggesting a probable single etiology. The occurrence of pulmonary stenosis and cataracts in another proband raises the question of rubella syndrome, although a previous sibling also had the same cardiac disorder.

Endocardial cushion defect. The familial association of endocardial cushion defects in euploid and aneuploid individuals was noted in a previous publication (23). Recent morphogenetic studies (24) demonstrated biochemical alterations with increased cellular adhesiveness in patients with Down's syndrome. On the basis of this work, Boughman et al. (23) proposed that specific alleles responsible for these changes may be segregating in some families of patients with Down's syndrome. Recently, Ardinger et al. (25) reported abnormalities in transforming growth factor alpha in euploid and aneuploid cases of endocardial cushion defect, a finding that may lead to answers regarding the nature of the inherited abnormality.

Figure 5. Heritable blood disorders in family members of infants with cardiovascular malformations in case families but none in control families suggests etiologic relation. D = deaf; M = murmur; other abbreviations as in Figures 2 and 3. Shading indicates the noted blood disorder; the solid dot indicates the carrier. We thank Dr. James Manning for his permission to show the pedigree observed by him.

Associated blood disorders. The association of cardiac and blood disorders was previously reported from the Baltimore-Washington Infant Study (8) together with a literature review of hematologic abnormalities in cyanotic and acyanotic patients with congenital heart disease. In addition to the two probands with transposition in this study, two other cases of hemophilia and transposition have been reported (26).

The coincidence of transposition of the great arteries and hemophilia is notable because, by virtue of the rarity of each condition (about 2 : 10,000), this association could be expected to occur by chance in only 1 of 4 million births. Knowledge of several such families raises the hypothesis that genetic errors of endothelial cells may constitute an initiating susceptibility to cardiac maldevelopment with possible variability in expression (27,28). The recent great expansion of knowledge on the role of endothelial cells in coagulation, growth factor synthesis and microvascular development, as described by Jaffe (29), illuminates the likelihood of probable important effects also in embryonic life.

Conclusions. The epidemiologic evaluation of cardiovascular malformations as described in this report of familial aggregations emphasizes the questions of biologic importance: *what are the inherited factors that affect morphogenesis?*

Our description of a population-based case group suggests the need for clarification of the following possibilities: 1) atrial tissue alterations associated with autoimmunity; 2) alterations of myocardial cell metabolism; 3) causes of embryonic blood flow variations; 4) incomplete and variable phenotypic expression of genetic disorders; 5) forme fruste expressions of conotruncal malformations; 6) biochemical alterations affecting endocardial cushion development; and 7) genetic errors of endothelial cell functions affecting coagulation and vascular growth.

Future studies of familial patterns of inheritance should attempt to evaluate cellular, immunologic and mechanistic processes and lead to a biologic recategorization of cardiovascular malformations into etiologically related entities. Coordinated multidisciplinary studies, so successful in adult cardiology, would be promising in the elucidation of etiologic risk factors of cardiovascular maldevelopment.

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Hospital, Harford Memorial Hospital, Holy Cross Hospital of Silver Spring, Howard County General Hospital, Kent & Queen Anne's Hospital, Memorial Hospital at Cumberland, Memorial Hospital at Easton, Montgomery General Hospital, Peninsula General Hospital Medical Center, Physicians Memorial Hospital, Prince George's General Hospital & Medical Center, Sacred Heart Hospital, St. Mary's Hospital, Shady Grove Adventist Hospital, Southern Maryland Hospital Center, Union Hospital of Cecil County, Washington Adventist Hospital, Washington County Hospital Association, all in Maryland; Children's Hospital National Medical Center, District of Columbia General Hospital, Georgetown University Hospital, George Washington University Medical Center, Greater Southeast Community Hospital, Howard University Hospital, Providence Hospital, Sibley Memorial Hospital, Washington Hospital Center, all in Washington, D.C.; Alexandria Hospital, Arlington Hospital, Fairfax Hospital, Fauquier Hospital, Loudoun Memorial Hospital, Potomac Hospital, Prince William Hospital, all in Virginia.

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