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The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC): Results from Phase I and Scientific Opportunities in Phase II

Barbara L. Kroner, PhD¹, H. Eser Tolunay, PhD², Craig T. Basson, MD PhD³, Reed E. Pyeritz, MD PhD⁴, Kathryn Holmes, MD⁵, Cheryl L. Maslen, PhD⁶, Dianna M. Milewicz, MD PhD⁷, Scott A. LeMaire, MD⁸, Tabitha Hendershot¹, Patrice Desvigne-Nickens, MD², Richard B. Devereux, MD³, Harry C. Dietz, MD, PhD⁵, Howard Song, MD PhD⁶, Danny Ringer¹, Megan Mitchell, MPH², Jonathan W. Weinsaft, MD³, William Ravekes, MD⁵, Victor Menashe, MD⁶, Kim A. Eagle⁹, and for the GenTAC Registry Consortium

¹RTI International (Rockville, MD)

²National Institutes of Health (Bethesda, MD)

³Weill Cornell Medical College (NY, NY)

⁴University of Pennsylvania (Philadelphia, PA)

⁵Johns Hopkins University (Baltimore, MD)

⁶Oregon Health and Sciences University (Portland, OR)

⁷University of Texas Health Sciences Center (Houston, TX)

⁸Baylor College of Medicine (Houston, TX)

⁹University of Michigan (Ann Arbor, MI)

Abstract

Background—Genetically triggered thoracic aortic conditions (GenTAC) represent an important problem for patients and their families. Accordingly, the National Heart, Lung and Blood Institute (NHLBI) established the first phase of its national GenTAC Registry in 2006.

Enrollment and Diagnoses—Between 2007 and 2010, six enrolling centers established the GenTAC I Registry consisting of 2,046 patients [(Marfan syndrome 576 (28.2%); bicuspid aortic valve disease 504 (24.6%), aneurysm or dissection age <50 years 369 (18%), and others.] Biologic samples for DNA analyses (WBC's or saliva) are available in 97% and stored plasma is available in 60% of enrollees.

Results—Initial scientific inquiry using the GenTAC Registry has included validation studies of genetic causes for aortic syndromes, potential usefulness of TGFB blood levels in Marfan subjects, and current surgical approaches to ascending aortic conditions.

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Address for Correspondence: Barbara L Kroner, PhD, RTI International, 6110 Executive Boulevard, Suite 901, Rockville, MD 20852-3907, Phone: (301) 230-4640, Fax: (301) 230-4647, byk@rti.org.

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Future Opportunity—GenTAC II will allow biannual follow-up of GenTAC I enrollees for up to nine years, enrollment of an additional 1,500 subjects, further integration of imaging findings with clinical and genetic data through utilization of an imaging core lab, important validation of phenotype-genotype correlations through a phenotyping core lab, and integration of a scientific advisory committee to help define the full range and depth of the Registry's scientific capabilities. The registry resources are available to the external scientific community through an application process accessible at <https://gentac.rti.org>.

Thoracic aortic aneurysms and related conditions represent an important problem for patients in the United States, and are responsible for thousands of deaths, aortic valve related heart failure, and a large burden of morbidity and costs. Increasingly, studies suggest a strong genetic basis for a number of thoracic aortic disorders. In addition, the complex interplay of genetics and environmental influences in determination of phenotype remains poorly understood. Accordingly, the National Institutes of Health initiated phase I of the GenTAC Registry (GenTAC I) in 2006. Utilizing six clinical centers, GenTAC I steadily enrolled patients with a variety of aortic conditions and began bi-annual follow-up of enrollees. The second phase of the registry (GenTAC II) began in October 2010 and will expand the cohort size and composition, add new contributing clinical centers, extend follow-up, evaluate imaging findings in relation to clinical phenotype and genotype, and further validate genetic underpinnings of thoracic aortic disease. This report summarizes results from GenTAC I and provides a framework for the registry as an ongoing resource available to investigators.

Methods

Registry Design

GenTAC is a longitudinal observational cohort study of affected patients with early-onset conditions or genetic syndromes that result in predisposition for thoracic aortic aneurysms and dissections (TAAD). Understanding the genetic contributions to TAAD through SNP analyses and genome-wide association studies is an objective of the GenTAC Registry. However, the absence of unaffected family members enrolled into the registry prohibits performance of linkage analyses. The registry design, infrastructure, participating organizations, data collection methods and oversight have been previously described (1). Here we provide a summary of the characteristics of the entire patient population enrolled by the end of GenTAC I.

All eligible subjects at the participating clinical centers were approached about enrollment into the registry. Criteria for enrollment were willingness of the subject to provide a biologic specimen (preferably blood), available medical record data to confirm the eligibility diagnosis, subsequent treatment and disease progression, available thoracic imaging data, and availability for biannual follow-up. When blood could not be collected, a saliva sample was obtained as a source of DNA. Excess aortic tissue was frozen from subjects that underwent surgery. All biologic material was sent to a central repository for processing and long term storage. GenTAC II extends the accomplishments of phase I by increasing enrollment, extending follow-up, and examining the associations of imaging results with clinical and genetic information.

To enrich enrollment, phase II added clinical centers at Queen's Medical Center in Honolulu, Hawaii and the National Institute on Aging in Baltimore, Maryland to increase enrollment of minorities and subjects with Ehlers-Danlos syndrome, respectively. GenTAC II also incorporates a Core Imaging Laboratory to provide systematic aortic imaging data and a Core Phenotyping Laboratory to provide validation of eligibility diagnoses. In addition, the Registry will increasingly reach out to non-GenTAC investigators to maximize

the ultimate scientific output of the registry during and after phase II. This will be achieved through creation of an external Scientific Advisory Board, periodic aortic disease scientific summit meetings, refinement of mechanisms for non-GenTAC scientists to propose research studies and/or grants utilizing Registry resources, and dissemination of study findings through publications and presentations. The Registry's website located at <https://gentac.rti.org> provides instructions to researchers for requesting access to GenTAC clinical data and biologic materials as well as a list of ongoing and completed GenTAC research projects. In addition, the website provides information to the lay and patient communities with respect to enrollment eligibility, participating centers, and contact information.

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Results

Patient enrollment began at six clinical centers between November 2007 and March 2008. At the end of GenTAC I which concluded September 29, 2010, 2,046 patients were enrolled with complete clinical data available for analysis and 462 had completed biannual follow-up. Demographic characteristics and frequency of enrollment diagnoses are listed in Table 1. Despite significant representation of clinical centers in geographic locations with large Black and Hispanic populations, only 8.9% of the subjects enrolled were self-identified minority of which 6.6% were of Hispanic origin. Minority race and ethnicity of those refusing to enroll into the registry are similar to those consenting to participation, indicating that the low numbers of minority subjects are representative of the patient populations treated at the enrolling centers. The most common clinical conditions under which patients were enrolled included Marfan syndrome (576 patients, 28.2%), bicuspid aortic valve with aortic enlargement (504 patients, 24.6%) and aneurysm and/or dissection in patients less than 50 years of age (369 patients, 18.0%). Other well represented conditions included familial thoracic aortic disease (165 patients, 8.1%) and Turner syndrome (141 patients, 6.9%). A small number of unaffected family members of interest (n=12) were also enrolled for a special substudy. Selected clinical features in all patients and by the four most common eligibility criteria are listed in Table 2. As expected, positive reports of musculoskeletal, craniofacial, ocular, and cutaneous findings were common in patients with Marfan syndrome, with intermediate frequency in familial aortic disease compared to that in bicuspid aortic valve patients.

The vast majority of subjects in GenTAC I were taking at least one medication to treat their cardiovascular disease (Table 3) at the time of enrollment. The most common types of medication received were beta blockers (54.0%) followed by statins (17.6%), Losartan (16.1%) and ACE-Inhibitors (15.7%). As expected, medications varied somewhat by diagnosis. Surgical intervention was also very common in the GenTAC I population with 1118 patients (54.6%) having a history of a cardiovascular procedure related to their aortic disease at the time of enrollment (Table 4). Not surprising, the most common procedures in all diagnostic categories were aortic root and ascending aorta replacements.

Table 5 presents the number of subjects with specimens collected by diagnosis that are available for future research. More than 97% of enrollees have either white blood cells (buffy coat and PBMCs) or saliva available for DNA analyses, 60% have plasma for biomarker studies, and aortic tissue is available from 96 patients who underwent surgery after enrollment. Subjects with only saliva collected tended to be young children, those enrolled at national patient advocacy meetings or other non-clinical settings, or those with an aversion to needle sticks. Sample collection is still in progress for 35 subjects with missing biologic material. Under phase II of GenTAC, immortalized cell lines will also be established from viable lymphocytes to create a renewable source of DNA.

Although permission to collect a biospecimen (blood or saliva) was one of the inclusion criteria under GenTAC I, a subset of subjects were reluctant to have their samples shared outside the study, particularly the DNA. The GenTAC I consent form provided a tiered set of options regarding use of the biospecimens and it was not uncommon for subjects to refuse permission to create a cell line (11%), allow commercial access to their DNA (12%), allow outside researchers access to any type of sample (7%), or have their samples stored indefinitely (6%).

Over the next five years, phase II of the GenTAC Registry will be enhanced by an addition of 1500 study subjects, collection of longitudinal follow-up data, additional sample collection, creation of an imaging core lab to augment imaging-related research, improved phenotyping, and addition of external scientific partners to leverage the impact of the NHLBI investment in this unique cohort of patients.

Scientific Progress in GenTAC Phase I

The focus of the first phase of GenTAC was to begin to create a unique resource of clinical data, including imaging, and biologic specimens from patients at risk for thoracic aortic aneurysms to enable future research. In the publication describing the study design (1) we identified 27 potential research questions that might be addressed by the registry. Many of the initial research questions require longitudinal follow-up to allow correlation of genotype, phenotype, imaging, and/or therapy with outcomes. Nevertheless, a number of questions have already been addressed or are under active investigation by GenTAC investigators. These are listed in Table 6 and have resulted thus far in five manuscripts published or in press emanating from this work (2,3,4,5,8). Significant findings from these publications are summarized in this section.

One significant step towards disseminating the findings from GenTAC I was the resequencing of candidate genes for TAAD in 560 selected patients not previously tested. These genes included *FBN1*, *TGFBR1*, *TGFBR2*, *COL3A1*, *MYH11*, and *ACTA2*, and analyses of their associations with clinical findings within the GenTAC patient population has stimulated a search for novel mutations associated with TAAD. Using DNA from GenTAC and other cohorts, Kuang et al demonstrated recurrent duplications within chromosome 16p13.1 resulted in a significant 8.8 to 10.1-fold increase in TAAD in adult Caucasians (2). LeMaire and colleagues identified common genetic variants at a 15q21.1 locus encompassing *FBN1* that were significantly associated with sporadic TAAD (3). TAAD is a major complication of Marfan syndrome which is caused by mutations in the *FBN1* gene. Thus this finding suggests that there is a common pathway of TAAD pathogenesis between Marfan syndrome and those with sporadic TAAD disease.

In 2009, Song et al described the characterization of the contemporary surgical treatment of patients with genetically triggered TAAD (4). Not surprising, he found that the most common indications for surgery in the GenTAC cohort were aneurysm, valve dysfunction, and dissection. Future research on the surgical patients in GenTAC will focus on the

syndrome- and gene-specific phenotypes in order to guide decision-making for indicators of optimum treatment outcomes. Matt and colleagues used GenTAC as a means to validate an association of TGFB levels in Marfan patients as related to aortic size (5), extending their preliminary findings from a rodent model of Marfan syndrome and a preliminary study from a human cohort (7). Most recently, GenTAC reported the impact of CT imaging by axial versus double oblique on aortic size in 50 patients (8). Aortic area was systematically overestimated using axial measurements. Oblique yielded improved agreement with a reference of en-face planimetry. These findings support preferential use of oblique planes for clinical imaging evaluation of patients with TAAD, especially when considering eligibility for prophylactic surgical intervention.

Clearly, it is hoped that the GenTAC Registry will ultimately identify and/or validate new genetic underpinnings of aortic disease and phenotypic characteristics that improve patient outcomes, and these aspects of the registry's scientific effort are beginning to bear fruit. Also, imaging information from the imaging core and validated diagnoses from the phenotyping core under GenTAC II will establish uniform measures. The standardized imaging data combined with longitudinal clinical data will offer a unique chance to improve management of thoracic aortic conditions such as understanding mechanisms of aortic valve dysfunction in ascending aortic disease and improving the accuracy of aortic measurement with noninvasive technologies.

Discussion

To physicians who care for patients with genetically determined thoracic aortic conditions, and for lay societies that represent patients and families with these conditions, the decision of NHLBI to fund the GenTAC registry was a welcome event. Thoracic aortic conditions have received far less scientific investment over the past 30 years than more common conditions such as coronary heart disease, heart failure, and stroke. Thanks to impressive progress in genetic analyses, imaging capabilities, and medical therapies, the time is ripe to make forward strides in diagnosis, prevention, better medical therapy, and more effective interventional and/or open surgical therapy for aortic conditions. The major professional societies have published the first US guideline for evaluation and management of thoracic aortic disease (9). In this evolving scientific arena, the decision of NHLBI to fund Phase II of GenTAC is welcome news. By creating a large and high quality clinical and biologic resource, the potential to advance diagnosis and treatment of thoracic aortic disease is before us. The realization of GenTAC's full potential will require careful considerations of how best to target the investment, how to capture the full imagination of aortic disease scientists around the world, and how best to foster creative future grant applications which further leverage the GenTAC resource beyond phase II. For the next 10 years, we should expect the GenTAC registry to play a major role in advancing our understanding and treatment of thoracic aortic conditions.

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Table 1

Characteristics of GenTAC I Patient Population at Enrollment

	Number n=2,046	Percent
Eligibility Diagnosis		
Marfan syndrome	576	28.2
Turner syndrome	141	6.9
Ehler-Danlos syndrome, vascular	56	2.7
Ehlers-Danlos syndrome, other type with TAAD ¹	6	0.3
Loeys-Dietz syndrome	49	2.4
Shprintzen-Goldberg syndrome	9	0.4
Bicuspid aortic valve (BAV) with TAAD	504	24.6
BAV without TAAD with family history of TAAD or BAV	40	2.0
BAV without TAAD with coarctation	48	2.3
Familial TAAD	165	8.1
Other congenital heart disease and TAAD	49	2.4
TAAD without above diagnoses at <50 years of age	369	18.0
Known TAAD mutation ² and none of the above	22	1.1
First degree relative	12	0.6
Gender		
Male	1,225	59.9
Female	821	40.1
Age at Enrollment		
<5 years	49	2.4
5–17 years	363	17.7
18–39 years	577	28.2
40–69 years	964	47.1
>69 years	93	4.5
Hispanic	136	6.6
Race, non-Hispanic		
White	1,710	91.1
Black	89	4.7
Asian	51	2.7
American Indian/Alaskan Native	3	0.2
Native Hawaiian/Pacific Islander	5	0.3
Unknown	52	2.8
History of TAAD	1,803	88.1
History of thoracic aortic dissection	306	15.0
History of TAAD surgery	1,118	54.6

¹TAAD = thoracic aortic aneurysm or dissection

²Mutations = *FBNI*, *TGFBR1*, *TGFBR2*, *ACTA2*, *MYH11*

Table 2
Reported Clinical Features in GenTAC I Subjects by Most Common Diagnostic Criteria (n (%))

Condition	Total (n= 2,046)	Marfan Syndrome (n = 576)	All BAV (n = 592)	Familial TAAD (n = 165)	TAAD diagnosis at < 50 years (n = 369)
Gender:					
Male	1225 (59.9)	299 (51.9)	455 (76.9)	116 (70.3)	275 (74.5)
Female	821 (40.1)	277 (48.1)	137 (23.1)	49 (29.7)	94 (25.4)
Age at enrollment:					
<5 years	49 (2.4)	8 (1.4)	14 (2.4)	3 (1.8)	7 (1.9)
5–17 years	363 (17.7)	129 (22.4)	71 (12.0)	17 (10.3)	49 (13.3)
18–39 years	577 (28.2)	213 (37.0)	118 (20.0)	23 (13.9)	118 (32.0)
40–69 years	964 (47.1)	211 (36.6)	346 (58.4)	99 (60.0)	192 (52.0)
>69 years	93 (4.5)	15 (2.6)	43 (7.3)	23 (13.9)	3 (0.8)
Cardiovascular:					
Aortic coarctation	104 (5.1)	0	59 (10.0)	0	5 (1.4)
Atrial arrhythmia	239 (11.7)	63 (10.9)	96 (16.2)	17 (10.3)	42 (11.4)
Congestive heart failure	244 (11.9)	42 (7.3)	103 (17.4)	20 (12.1)	52 (14.1)
Musculoskeletal:					
Pectus carinatum	250 (12.2)	187 (32.5)	3 (0.5)	10 (6.1)	25 (6.8)
Pectus excavatum	281 (13.7)	194 (33.7)	12 (2.0)	12 (7.3)	29 (7.9)
Recurrent dislocations	89 (4.4)	34 (5.9)	8 (1.4)	6 (3.6)	8 (2.2)
Joint hypermobility	458 (22.4)	284 (49.3)	10 (1.7)	26 (15.8)	55 (14.9)
Wrist sign	392 (19.2)	308 (53.5)	3 (0.5)	13 (7.9)	33 (8.9)
Clinical scoliosis	458 (22.4)	303 (52.6)	21 (3.6)	21 (12.7)	42 (11.4)
Kyphosis/lordosis	151 (7.4)	86 (14.9)	6 (1.0)	8 (4.9)	20 (5.4)
Pes planus	411 (20.1)	279 (48.4)	12 (2.0)	22 (13.3)	49 (13.3)
Thumb sign	415 (20.3)	324 (56.3)	3 (0.5)	15 (9.1)	34 (9.2)
Arachnodactyly	443 (21.7)	352 (61.1)	3 (0.5)	13 (7.9)	30 (8.1)
Craniofacial:					

Condition	Total (n = 2,046)	Marfan Syndrome (n = 576)	All BAV (n = 592)	Familial TAAD (n = 165)	TAAD diagnosis at <50 years (n = 369)
High palate/dental Crowding	605 (29.6)	378 (65.6)	16 (2.7)	27 (16.5)	74 (20.1)
Dolicocephaly	230 (11.3)	190 (33.0)	4 (0.7)	2 (1.2)	22 (6.0)
Malar hypoplasia	254 (12.4)	175 (30.4)	7 (1.2)	5 (3.1)	28 (7.6)
Enophthalmos	129 (6.3)	108 (18.8)	1 (0.2)	1 (0.6)	13 (3.5)
Retrognathia	177 (8.7)	117 (20.3)	3 (0.5)	4 (2.4)	19 (5.2)
Down-slanting palpebral fissures	196 (9.6)	136 (23.6)	4 (0.7)	4 (2.4)	22 (6.0)
Ocular:					
Lens dislocation	265 (13.0)	252 (43.8)	1 (0.2)	0	6 (1.6)
Glaucoma	44 (2.2)	18 (3.1)	13 (2.2)	4 (2.4)	4 (1.1)
Myopia > 4 diopters	199 (9.7)	141 (24.5)	10 (1.7)	8 (4.9)	21 (5.7)
Integument:					
Wide atrophic scars	80 (3.9)	24 (4.2)	5 (0.8)	4 (2.4)	14 (3.8)
Easy bruising	204 (10.0)	41 (7.1)	34 (5.7)	21 (12.8)	36 (9.8)
Striae atrophicae	344 (16.8)	258 (44.8)	11 (1.9)	17 (10.4)	39 (10.6)
Thin translucent skin	120 (5.9)	24 (4.2)	5 (0.8)	5 (3.1)	19 (5.2)

Table 3

Medication Treatment in GenTAC I Subjects [n (%)]

Type of Medication	Total (n= 2,046)	Marfan Syndrome (n = 576)	All BAV (n = 592)	Familial TAAD (n = 165)	TAAD diagnosis at < 50 years (n = 369)
Beta-Blocker	1,104 (54.0)	371 (64.4)	309 (52.2)	107 (64.9)	216 (58.5)
Losartan	329 (16.1)	157 (27.3)	39 (6.6)	24 (14.6)	51 (13.8)
Other ARB	103 (5.0)	22 (3.8)	39 (6.6)	15 (9.1)	19 (5.2)
ACE-Inhibitor	321 (15.7)	51 (8.9)	125 (21.1)	32 (19.4)	72 (19.5)
Statins	361 (17.6)	45 (7.8)	155 (26.2)	45 (27.3)	68 (18.4)
Verapamil or Diltiazem	55 (2.7)	24 (4.2)	11 (1.9)	6 (3.6)	9 (2.4)
Other Ca++ channel blocker	155 (7.6)	33 (5.7)	44 (7.4)	21 (12.7)	47 (12.7)
Other blood pressure lowering drug	175 (8.6)	24 (4.2)	52 (8.8)	21 (12.7)	57 (15.5)

Table 4History of Cardiac and Aortic Procedures in 1,118 GenTAC I Subjects[/]

Surgery	Total (n= 2,152 Surgeries)	Marfan Syndrome (n = 583)	All BAV (n = 849)	Familial TAAD (n = 176)	TAAD diagnosis at <50 years (n = 584)
Patients with one or more cardiovascular operations	1,118 (54.6)	283 (49.1)	404 (68.2)	84 (50.9)	204 (55.3)
Patients with one or more aortic operations	869 (42.5)	249 (43.2)	323 (54.6)	78 (47.3)	155 (42.0)
Aortic valve repair	190 (8.8)	53 (9.1)	71 (8.4)	18 (10.2)	33 (8.6)
Isolated aortic valve replacement	114 (5.3)	15 (2.6)	72 (8.5)	5 (2.8)	16 (4.2)
Aortic root replacement	411 (19.1)	135 (23.2)	170 (20.0)	26 (14.8)	60 (15.6)
Valve-sparing aortic root replacement	156 (7.2)	67 (11.5)	18 (2.1)	21 (11.9)	29 (7.6)
Ascending aortic replacement	510 (23.7)	110 (18.9)	219 (25.8)	54 (30.7)	106 (27.6)
Aortic arch replacement	293 (13.6)	51 (8.7)	142 (16.7)	20 (11.4)	65 (16.9)
Coarctation repair	92 (4.3)	0	58 (6.8)	0	2 (0.5)
Descending thoracic aortic replacement	64 (3.0)	27 (4.6)	5 (0.5)	9 (5.1)	18 (4.7)
Thoracoabdominal aortic replacement	88 (4.1)	54 (9.3)	1 (0.1)	9 (5.1)	18 (4.7)
Mitral valve repair or replacement	91 (4.2)	47 (8.1)	21 (2.5)	3 (1.7)	13 (3.4)
Coronary artery bypass, PTCA grafting	69 (3.2)	14 (2.4)	31 (3.7)	8 (4.5)	11 (2.9)
Pacemaker/ICD implantation	74 (3.4)	10 (1.7)	41 (4.8)	3 (1.7)	13 (3.4)

[/] 248 subjects had 2 procedures, 243 had 3 procedures, 127 had more than 3 procedures for a total of 2,152 surgeries.

Table 5

Biospecimens by Eligibility Diagnosis in GenTAC I Subjects

	No. Subjects	No. with Plasma	No. with WBCs ¹	No. with Saliva	Tissue		
					No. Snap Frozen	No. in RNA Later	No. in Paraffin
Total	2,046	1,244	1,266	745	52	72	72
Diagnosis							
Marfan syndrome	576	363	367	195	15	15	13
Turner syndrome	141	83	88	50	0	0	0
Ehler-Danlos, vascular	56	41	42	14	0	0	0
Ehlers-Danlos, other type with TAAD	6	5	5	1	0	0	0
Loeys-Dietz syndrome	49	19	19	31	0	0	0
Shprintzen-Goldberg syndrome	9	5	5	4	0	0	0
BAV with TAAD	504	310	313	186	16	28	32
BAV without TAAD with family history of TAAD or BAV	40	22	22	17	2	3	3
BAV without TAAD with coarctation	48	22	25	20	0	0	0
Familial TAAD	165	102	103	61	1	6	7
Other congenital heart disease and TAAD	49	33	35	12	1	2	1
Other TAAD not above and < 50 years of age	369	222	225	138	17	18	16
Known TAAD mutation and none of the above	22	7	7	15	0	0	0
First degree relative	12	10	10	1	0	0	0

¹ WBCs = white blood cells including buffy coat and viable lymphocytes

Table 6**Research Questions Initiated Under Phase I of GenTAC**

1	What is the frequency of known genetic mutations (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) among a large group (n=560) of patients with presumed genetic aortic conditions?
2	Can novel mutations be identified that are associated with an increased risk for aortic aneurysms or dissections? (2, 3)
3	What are the currently used surgical strategies in patients with inherited aortic disease? (4)
4	Do TGFB levels in patients with Marfan syndrome related aortic disease correlate with aortic diameter (5)
5	How much heterogeneity exists in how imaging labs at aortic centers report and measure aortic size at various aortic locations?
6	Do patients with Marfan syndrome have a reduced risk of aortic complications with angiotensin receptor blockers and an increased risk with calcium channel blockers?
7	What are the anatomic underpinnings of aortic valve regurgitation in genetically mediated aortic conditions?
8	What is the association of aortic annular dilatation with aortic regurgitation in patients with thoracic aortic aneurysms? (6)
9	What is the impact of imaging methodology on measurements of aortic size and surgical classification in patients with thoracic aortic aneurysms? (8)
10	What are the long term outcomes of Marfan patients undergoing elective versus emergency proximal aortic surgery?