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Current state and future directions of genomic medicine in aortic dissection: A path to prevention and personalized care

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Supplementary materials

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Abstract

Aortic dissection confers high mortality and morbidity rates despite advances in treatment, impacts quality of life, and contributes immense burden to the healthcare system globally. Efforts to prevent aortic dissection through screening and management of modifiable risk factors and early detection of aneurysms should incorporate genomic information, as it is integral to stratifying risk. However, effective integration of genomic-guided risk assessment into clinical practice will require addressing implementation barriers that currently permeate our healthcare systems. The Aortic Dissection Collaborative was established to define aortic dissection research priorities through patient engagement. Using a collaborative patient-centered feedback model, our Genomic Medicine Working Group identified related research priorities that could be investigated by pragmatic interventional studies aimed at aortic dissection prevention, utilization of genomic information to improve patient outcomes, and access to genomic medicine services. Further research is also needed to identify the genomic, lifestyle, and environmental risk factors that contribute to aortic dissection so these data can be incorporated into future comparative effectiveness studies to prevent aortic dissection.

1. Introduction

The genomic contribution to aortic dissection (AD) is substantial, and although heritable thoracic aortic disease (HTAD) gene discovery has enabled tailored management and earlier identification of high-risk patients, superior methods are needed to stratify AD risk [1]. The AD Collaborative was established to develop a patient-centered research agenda for AD through patient, clinician, researcher, and advocacy engagement [2]. A Genomic Medicine Working Group was specifically assembled to review and outline genomic medicine research priorities after AD Collaborative stakeholders identified this as an important topic. Here we review key genomic contributions that have improved our understanding of thoracic aortic disease and present future research needs, focusing on topics that could be investigated using interventional comparative effectiveness methods. We identified research priorities addressing the following topics: 1) integrating genomic risk assessment into clinical practice to prevent AD, 2) alternative approaches to genomic testing and risk assessment delivery, and 3) impact of genomic medicine on behaviors and decisions of patients, family members, and clinicians. Patient-centered outcomes research is needed to identify optimal strategies to integrate, sustain, and measure the impact of genomic medicine on individuals with increased AD risk and should be supported by engagement with patients, family members, clinicians, researchers, and policy makers.

2. Genomic insights into AD

2.1. Historical perspective

Decades before the first human genome was sequenced, genetic syndromes were diagnosed by phenotypic evaluation. Even after pathogenic variants in *FBN1* were identified as the cause of Marfan syndrome (MFS) in 1991, gene sequencing was not used routinely for

diagnosis until Ghent diagnostic criteria were revised in 2010 (see Supplementary Table 1 for additional references). By this time, next-generation sequencing made it possible to assay multiple genes simultaneously at a relatively low cost, expediting use of diagnostic genetic testing in clinical practice and the rate of novel gene identification for HTAD.

Accelerated gene discovery and the rise in clinical testing generated important phenotypic and mechanistic insights into thoracic aortic disease. First, it unmasked genetic heterogeneity in HTAD, helping to differentiate MFS from Loeys-Dietz syndrome in patients with overlapping clinical features [3] (see Supplementary Table 1 for additional references). It also highlighted the phenotypic variability within these genes, exposing a range of clinical manifestations beyond the aorta. A new category of "nonsyndromic" HTAD emerged when *ACTA2* and *MYH11* were identified as disease-causing HTAD genes (see Supplementary Table 1 for additional references). Patients with variants in these genes came to attention because of the increased burden of aortic disease in their families. This clinical variability was further underscored as patients without syndromic physical features and family history of aortic disease were found to harbor pathogenic variants in genes associated with MFS and Loeys-Dietz syndrome [4,5]. As more genes linked to aortic aneurysm and dissection were identified, genetic testing became a first-line diagnostic tool for HTAD.

Diagnosis and management guidelines support genetic testing to stratify thoracic aortic disease risk, tailor surveillance and surgical management, and identify at-risk relatives [1]. Accurate molecular diagnosis of HTAD is critical, as medical management recommendations are derived from genelevel data. Multigene panels are widely used for diagnosis and include a core set of 11 genes (*FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2, COL3A1, ACTA2, MYH11, MYLK*, *PRKG1*, and *LOX*) with established clinical validity, in addition to genes with emerging evidence, but these panels cannot detect all HTAD cases [6,7]. Exome and genome sequencing provide large-scale analysis beyond targeted gene panels, but practice guidelines caution these tests may not yield higher rates of clinically actionable findings [8].

2.2. Defining "heritable" thoracic aortic disease

Most Mendelian forms of HTAD follow an autosomal dominant inheritance pattern, although X-linked and recessive conditions are recognized. Commercial genetic testing for HTAD is designed to identify genetic variants conferring a "high risk" for aortic disease (eg, penetrance), which translates to a >50% lifetime risk [7]. In 2015, the American College of Medical Genetics and Genomics developed variant classification criteria specifically to differentiate variants associated with high disease risk (pathogenic and likely pathogenic variants) from "variants of uncertain significance" and benign variation (see Supplementary Table 1 for additional references). However, a newly defined class of genetic variants, termed *risk alleles* or *reduced-penetrance variants*, has become increasingly important for risk prediction of complex diseases. These low-to-moderate penetrance variants are more common in the general population than most Mendelian alleles and likely interact with each other in combination with environmental risk factors to increase dissection risk. An increased burden of rare and common single nucleotide variants and copy number variants in established HTAD genes and novel genes, has been observed in sporadic AD cohorts,

some of which are classified as variants of uncertain significance, implicating them as risk modifiers [5,9] (see Supplementary Table 1 for additional references).

Estimation of the genetic contribution to a phenotypic trait, defined as heritability, is variable among AD populations, differentiating Mendelian HTAD from sporadic AD. The heritability of sporadic AD incorporates genetic influence attributed to other risk factors including hypertension and aortic hemodynamics (see Supplementary Table 1 for additional references). This highlights a potential flaw in the way “genetic aortic disease” is presented in clinical practice and in the scientific literature, propagating a misconception that, in the absence of MFS-like features or family history, patients with common clinical risk factors, such as hypertension, have “non-genetic” forms of aortic disease. However, it is likely that one or more genetic factors contribute to AD risk. Although early-onset aortic disease, positive family history, aneurysms/dissections involving other arteries, and syndromic features are useful for identifying the patients most likely to carry a pathogenic variant in an HTAD gene, individuals falling outside these criteria can still benefit from genomic risk assessment. In contrast to a binary “genetic” and “nongenetic” categorization, reframing the conversation in clinical practice to counsel on the extent or relative genomic contribution to AD risk will be essential for effective risk assessment.

2.3. Novel genomic discovery: future directions

Primary prevention of AD before pathologic processes develop is ideal but requires a cost-effective strategies to identify high-risk individuals and effective interventions to prevent AD. Secondary AD prevention by prophylactic ascending aortic aneurysm repair in patients with heritable aortic diseases like MFS, has proven effective in reducing the prevalence of type A AD [10–12]. However, there is no consensus on the most effective metrics to predict type A dissection in most patients with aneurysmal disease and no effective screening strategies for type B dissection [13].

Although pathogenic variants in HTAD genes are established drivers of thoracic aortic disease, we are only beginning to understand the implications of interactions between low-to-moderate penetrance risk variants and environmental factors that contribute to AD risk. Further research is needed to identify and model the dynamic interactions between genetic variants, epigenetic modifiers, and lifestyle and environmental factors likely to drive aortic pathology in up to 80% of patients with sporadic AD who do not have family histories of aortic disease or clinical manifestations of syndromes [14] (see Supplementary Table 1 for additional references). It will be imperative to involve underrepresented populations in this research, as inadequate representation of non-White/European populations used to define clinical manifestations of MFS and other HTAD conditions has contributed to underdiagnosis [15] (see Supplementary Table 1 for additional references). Inequities have also limited the utility of genomic population databases like the Genome Aggregation Database, which are instrumental for genetic variant interpretation. Finally, genomic research findings must be shared publicly in a privacy-preserving fashion to maximize impact of data generated (see Supplementary Table 1 for additional references).

3. Genomic-guided risk stratification for AD

Health risk assessments can incorporate data from the medical and family history, physical examination, imaging and laboratory studies, and genomic testing. Most notably, the value of genomic risk assessment is not limited to clinical genetic testing. Effective risk stratification should maximize identification of patients with increased AD risk, while minimizing risk overestimation, and perform equally for all patients regardless of race, ethnicity, and socioeconomic background. Family health history, lifestyle, socioeconomic factors, patients' perceived risk, and value system should be integrated into health risk assessment in accordance with primary prevention practice guidelines for cardiovascular disease [16].

3.1. Family history to assess risk

Pedigree analysis of family health history is a fundamental component of the clinical genetics evaluation and is particularly relevant for AD risk assessment. Approximately 20% of first-degree relatives of individuals with thoracic aortic disease without defined genetic diagnoses are also affected [17–19]. Because a positive family history is associated with a significantly increased risk of AD (more than sixfold) at earlier ages, and confers a higher probability of future surgical aortic repair in patients who have had AD, family history can be used independently for risk stratification to enable medical management and lifestyle modifications [14,19–21]. Family history is also a primary predictor of hypertension, a known AD risk factor present in up to 75% of patients [22].

To be an effective risk assessment tool, family history must be accurately collected and interpreted by clinicians, and clinical recommendations should be discussed with patients. Common barriers to obtaining family history from the clinician's perspective include time required to obtain history (15–30 minutes), lack of reimbursement for time, and providers' perceived limitations to counsel on heritable findings [23] (see Supplementary Table 1 for additional references). Patient-facing web tools for family history collection have demonstrated superior data quality and completeness compared with traditional in-person collection, and improved the accuracy of risk stratification for other diseases [24]. Incorporating family history into risk prediction models for AD with genome sequencing may confer an even greater incremental value compared with other complex diseases, given the significant thoracic aortic disease burden in families [14,17,19,21].

3.2. The role of cascade testing

Cascade testing is used to identify relatives at increased risk of thoracic aortic disease either through imaging in cases when the genetic cause of disease is not defined or via genetic testing if a pathogenic variant in an HTAD gene was detected in the family. Despite 2010 joint professional society practice guidelines that recommend thoracic aortic imaging of first-degree relatives of individuals with thoracic aortic aneurysm or dissection, there is a dearth of evidence regarding the optimal strategy, effectiveness, and associated outcomes of familial aortic surveillance [1,25]. This evidence gap is reflected by the Centers for Medicare and Medicaid Services' lack of coverage for echocardiography (or computed tomography/magnetic resonance imaging) to screen patients with AD risk factors, including

family history, despite recognizing that screening high-risk patients is good medical practice (see Supplementary Table 1 for additional references). Although a recent study provided evidence to support the cost-effectiveness of aortic surveillance in relatives of patients with bicuspid aortic valve disease in Israel, retrospective analysis of 112 pediatric probands with bicuspid aortic valve and/or thoracic aortic aneurysm in the United States showed that only 38.7% of 150 at-risk siblings pursued aortic imaging, indicating that many at-risk relatives are not being imaged [26,27]. Literature reviews of cascade testing barriers and facilitators in different patient populations point to patient knowledge, income, perceptions and attitudes toward relatives, family communication, accessibility to testing/services, and provider awareness and engagement as influential factors [28] (see Supplementary Table 1 for additional references). Currently, the effectiveness, sustainability, and outcomes of cascade genetic testing and aortic surveillance programs for individuals at high risk for AD are unknown. Our Working Group determined that studies to address this gap in knowledge should be prioritized and should include measures to evaluate the impact of race, ethnicity, and healthcare policy coverage.

3.3. Using clinical criteria to identify candidates for genomic testing

Practice guidelines and expert opinion continue to support use of clinical criteria (eg, “red flags”) to identify optimal genetic testing candidates who represent patients most likely to have a highly penetrant form of thoracic aortic disease [8]. However, this approach relies on providers collecting and interpreting detailed patient phenotype and family history information, which is not routinely performed [29]. Flow charts detailing criteria incorporate age of aortic disease onset, family history of aortic disease or premature sudden death, and physical features of syndromes predisposing to thoracic aortic disease, but they do not uniformly align on age thresholds for testing patients with sporadic AD (younger than 50 years, younger than 55 years, and younger than 60 years) or inclusion of bicuspid aortic valve disease and aneurysms/dissections involving other arteries [6,8,30,31]. In addition, evidence used to develop these criteria were not generated from studies specifically designed to address this research question.

3.4. Alternative approaches to genomic testing

Factors to consider when evaluating genomic testing strategies include the purpose of testing (eg, screening, diagnostic, and research), proposed testing population (eg, general population and high-risk), and test method (eg, sequencing multiple genes, exome, and genome). Emerging evidence suggests HTAD is underdiagnosed, and expanding the testing population beyond patients who meet clinical criteria based on phenotype and family history may be beneficial. In more than 13,000 individuals older than 70 years with no history of cardiovascular disease, Lacaze et al [32] found that 1 in 110 had a pathogenic variant in a cardiomyopathy-, arrhythmia-or aortopathy-associated gene. Notably, of the 11 established HTAD genes, only *FBN1* was assayed, limiting the interpretation for HTAD. In another study, Murdock et al [33] assessed the utility of sequencing 158 highly penetrant cardiovascular disease genes in 709 patients in an ambulatory cardiology clinic. This study offered the following important insights: 1) most patients (81%) pursued genetic testing when offered; 2) 64 patients (9%) were diagnosed with a Mendelian disease and only 2% of the cohort reported family history of cardiovascular disease; 3) the diagnostic yield

was higher (13% hereditary cardiomyopathy and 12% aortopathy) in patients who reported family history of related diseases; and 4) surveyed cardiologists (n = 13) recommended changes to medical management for 84% of patients, including 72% who already had a clinical diagnosis [33]. It is possible that genetic diagnoses were missed because genetic testing is not routinely offered in clinical practice and/or that some patients with HTAD and other Mendelian cardiovascular diseases did not satisfy clinical criteria for testing. Notably, when these patients received diagnoses, most providers recommended changes to clinical care.

3.5. Who should lead the charge in risk assessment?

A shift toward disease prevention and early intervention supported by data that health risk assessments correlate with a reduction of chronic disease risk factors has magnified the need to engage patients, family members, and clinicians in this process (see Supplementary Table 1 for additional references). Historically, genetic counselors and geneticists played central roles in enabling or limiting access to genetic testing, but risk assessment and counseling in the primary care or non-genetics specialty settings has the potential to identify more patients at risk for AD. Primary care providers often follow patients across generations from diverse socioeconomic and racial and ethnic backgrounds, which provides a unique opportunity to discuss risk among family members and coordinate screening and management.

Although interested, primary care providers are hesitant to integrate genomics into their practice due to perceived knowledge gaps, lack of infrastructure, little incentive to coordinate, and concern for patient comprehension [34]. Providers have expressed a need for automated screening tools to signal which patients would benefit from genetic testing and modified management based on family history. A genetic counselor helpline or ”buddy system” was another proposed strategy to facilitate genomic risk assessment [35]. Researchers from the Implementing Genomics in Practice (IGNITE) network conducted an interventional study in the primary care setting to investigate the effectiveness of family health history assessment using a web-based tool (Me-Tree); they found that 46% (n = 1,443) of participants stratified into Mendelian or familial risk categories (high to moderate risk) and 56% were at risk for common multifactorial diseases [23]. Additional research is needed to evaluate the effectiveness of similar web-based/automated tools for genomic risk assessment in federally qualified community health centers and other specialty practices, as cardiologists and cardiothoracic and vascular surgeons play significant roles in the assessment and management of risk in families with aortic disease.

3.6. Opportunity for comprehensive cardiovascular disease risk assessment

Primary prevention of atherosclerotic cardiovascular disease has been established as a top research priority and the Centers for Disease Control and Prevention categorized familial hypercholesterolemia as a Tier 1 genomics application disease for population-based genomic screening (see Supplementary Table 1 for additional references). Genomic-guided risk stratification using polygenic risk scores can predict the risk of atherosclerotic cardiovascular disease better than traditional clinical and lifestyle factors alone [36] (see Supplementary Table 1 for additional references). Interventions targeting lifestyle modification, patient education, primary care engagement, and care coordination positively

correlate with improvements in blood pressure, lipid maintenance, and tobacco abstinence in high-risk populations with coronary artery disease [37]. Similarly, risk stratification coupled with preventative intervention improves health outcomes in individuals with familial hypercholesterolemia [38].

Convergence of common risk factors for thoracic aortic disease, coronary artery disease, and cardiomyopathy (eg, hypertension and hyperlipidemia), highlights an opportunity for comprehensive cardiovascular risk assessment. Although family health history alone is a useful risk-stratification tool for several cardiovascular conditions, in the future, statistical models incorporating genomic, environmental, and lifestyle factors could be used to stratify and discriminate risk of various cardiovascular diseases [39]. The feasibility and effectiveness of comprehensive genomic risk assessment for multiple cardiovascular conditions should be investigated. In the future, qualitative and quantitative methods could be used to assess patient and provider experience, decision-making, risk communication, comprehension, behavior modifications, and multiple cardiovascular-related health outcomes.

3.7. Intersection of technology and genomic medicine

Technological advances in healthcare have led to novel genomic risk assessment strategies. Studies using electronic medical records to systematically stratify risk for various diseases have been successful, and when combined with large-scale genomic analysis, generated novel genotype-phenotype insights. [40] (see Supplementary Table 1 for additional references). Although machine learning models have been developed to predict AD diagnosis in acute settings, in-hospital mortality, and surgical re-intervention, models aimed at stratifying high-risk patients before ADs occur are limited [41,42]. Comprehensive genome-phenome analysis for AD risk stratification has not been investigated but would be beneficial, as the heritability of thoracic aortic disease is comparatively higher than other complex cardiovascular diseases where similar approaches performed well. In the future, risk-stratification tools could be integrated into electronic medical record infrastructures for clinicians and be made accessible to patients.

Scalable solutions are needed to address the supply–demand imbalance of the clinical genetics workforce. Alternative genomic medicine delivery models incorporating artificial intelligence-powered chatbots to engage patients and facilitate risk communication have been well received by patients and family members [43] (see Supplementary Table 1 for additional references). Traditional in-person genetic counseling in a cardiology setting was shown to increase patient empowerment, awareness of surveillance recommendations, and promote risk discussion among relatives, but studies are needed to investigate the effectiveness of alternative risk communication methods using text/short message service, chatbots, or other mobile interventions for AD risk assessment and cascade test facilitation [44].

3.8. Risk assessment and stratification: future directions

Comparative effectiveness studies are needed to investigate AD risk-stratification interventions, such as family health history tools, electronic medical record data mining,

broadening clinical criteria for offering HTAD genetic testing, and, in the future, population-based genomic risk assessment. Precautions should be taken to minimize potential risks related to patient privacy, incidental findings, and data sharing. Our Working Group determined that studies designed to evaluate the optimal timing/age of initial risk assessment, frequency of reassessment, and service delivery models (eg, intervention in primary care setting, direct engagement of patients and relatives), would be beneficial. Further evidence is needed to support the effectiveness of alternative approaches for communicating and discussing AD risk within families. Patient motivations for communicating risk to relatives, modifying behavior/lifestyle, and pursuing aortic surveillance or genetic testing were deemed important outcomes. Future research should focus on including non-White and geographically isolated populations from various socioeconomic backgrounds. Finally, there is a need to evaluate the cost-effectiveness of implementation strategies for cascade testing and risk assessment for AD.

4. Clinical utility and access to genomic medicine services

Evidence-based guidelines support gene-based diagnosis and management for HTAD. Myriad expert reviews and editorials discuss the impact of genomic medicine on surgical decision-making, medical management, clinical outcomes, and lifestyle modifications, but studies evaluating patient and clinician decision-making, behaviors, and health outcomes are lacking. Maximum clinical utility of genomic testing and family health history assessment can only be achieved if index cases are diagnosed and counseled, clinicians and patients agree on and adhere to a management plan, and familial cascade genetic testing is pursued so clinical recommendations extend to at-risk relatives.

In 2015, the American College of Medical Genetics Board of Directors proposed broadening measures of clinical utility for genetic diseases to include prognosis, therapeutic choice, psychological health, and familial impact (see Supplementary Table 1 for additional references). Because highly penetrant heritable aortic diseases are individually rare and some only newly discovered, evidence that gene-based diagnosis reduces the prevalence of AD is limited to MFS [10–12]. Retrospective analyses of intermediate clinical and surgical outcomes have been reported for other HTAD genes, but prospective interventional studies are needed to better understand the adoption and impact of gene-based guidelines (see Supplementary Table 1 for additional references).

4.1. Patient and clinician decision-making and behaviors

HTAD is underdiagnosed and, if untreated, leads to fatal outcomes [25,32,33]. The feasibility and effectiveness of genomic testing and family health history assessment in different patient populations at risk for AD (eg, meet clinical genetic testing criteria *v.* all patients with AD) is not known and should be investigated prospectively. This research could help delineate the value of genomic risk assessment beyond diagnostic testing yield and identify patients with HTAD who would otherwise have been missed. A landscape analysis of 21 systematic reviews of comparative effectiveness research in genomic medicine identified an overabundance of studies focusing on the impact of genetic test results on clinician decisions compared with impact on patient behaviors or lifestyle [45]. The

authors emphasized the importance of analyzing meaningful outcomes beyond traditional clinical measures, such as social, lifestyle, and reproductive factors, to determine the impact of genomic testing and risk assessment. Patient-centered measures of acceptability, service uptake, access to services, and patient activation should be evaluated in addition to feasibility and effectiveness. Use of patient empowerment methods designed to foster self-efficacy—a patient's belief that they can modify behavior to improve health—have been associated with lifestyle modification and reduced cardiovascular risk [46].

Currently, most patients who undergo genetic testing for HTAD have already been diagnosed with an aneurysm or dissection, but test results can still be used to guide arterial surveillance protocols and surgical reintervention [6]. As options for interventional management of AD continue to expand, patients and providers must consider the benefits and risks of various approaches. For this reason, genomic data (molecular test results and family history) should be collected in new device and treatment trials to inform future surgical planning and decision-making. Patients prefer to have an active role in the surgical decision-making process; strategies to facilitate shared decision-making in vascular surgery are currently under investigation [47].

4.2. Access to genomic medicine services

The American Heart Association issued a scientific statement in 2021 on genomic research in marginalized populations that underscored the importance of equitable research design for effective translation to clinical care [48]. Special consideration should be given to community collaboration, transparency, and improving trust between researchers and marginalized populations. Interventional research using "real-world" study design is one way to improve the diversity of study populations, but participation is still inhibited by access-to-healthcare barriers, including patient well-being or health status, lack of understanding the study purpose or health service, language, forgetting to schedule or attend appointments, transportation, and health insurance/cost [49] (see Supplementary Table 1 for additional references). Alternative healthcare delivery strategies, including extension of service hours (eg, weekend or evening screening clinics), direct telephone contact with providers, and telemedicine services have been linked to increased utilization of healthcare services [50,51].

Interdisciplinary and multidisciplinary patient- and family-centered healthcare service models adapted to address cardiovascular disease prevention in families are cost-effective and associated with improved health outcomes [52]. Improved surgical outcomes have been observed in patients with AD treated by a multidisciplinary team, but the impact of multidisciplinary expert care on AD prevention and risk reduction has not been studied [53,54]. Patients who have had genomic risk assessment and counseling are more likely to pursue genetic testing and have a better understanding of their risk of disease, emphasizing the importance of investigating the impact of integrating genomic services into multidisciplinary aortic care teams [50] (see Supplementary Table 1 for additional references).

4.3. Utility and access to genomic information: future directions

Current evidence supports clinical actionability of gene-based diagnosis and management for HTAD [7]. However, traditional randomized controlled trials that assess morbidity and mortality outcomes cannot be used to evaluate the clinical utility of genetic testing for HTAD because withholding testing and beneficial interventions would be unethical. Similarly, from a practical standpoint, prospectively investigating clinical utility in a pragmatic trial would be time-prohibitive given the overall low prevalence of molecularly-confirmed HTAD. However, observational cohort studies and disease registries are well-suited to address these questions. Data on therapeutic efficacy, including changes to clinical recommendations and interventions based on genomic information should be collected longitudinally in aortic disease registries in addition to molecular genetic diagnosis. “Big data” from electronic medical records and patient-reported outcomes could also be used to evaluate health outcomes through statistical modeling.

Prospective studies assessing the clinical utility of genomic testing and risk assessment are lacking in patients with history of AD and those at high risk. Selecting useful intervention strategies and outcomes is critical. In addition to health outcomes and provider-centric outcomes, data are needed to characterize patient awareness regarding the genomic contribution to dissection, commitment to action, and adherence to management recommendations after genomic risk assessment and counseling. Research priorities outlined by this Working Group were consistent with themes reported by a patient-centered collaborative in the United Kingdom and Ireland, which included a need for early screening programs, healthcare provider engagement, and multidisciplinary care with psychological support and longitudinal follow-up [55]. Cost-effectiveness studies were not deemed high priority by patient stakeholders in either collaborative working group but were acknowledged as necessary measures of clinical utility by clinicians. Our Genomics Working Group agreed on the need for pragmatic studies to evaluate effectiveness, acceptability, feasibility, decision-making, and behavior modifications after genomic testing and risk assessment. Evaluating different genomic risk assessment approaches that involve an expanded testing population and alternative service delivery methods and tools, were also deemed important.

5. Conclusions

Our Genomic Medicine Working Group established the following overarching research focuses: 1) AD prevention and 2) utilization of genomic information to improve patient health outcomes. Within these categories, we defined future research topics that could benefit from comparative effectiveness studies. We reviewed various methods of delivering genomic medicine services and measures to evaluate the impact of genomic risk assessment across populations. We identified health disparities, team-based care, and shared decision-making as essential themes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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