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Toward precision medicine in vascular connective tissue disorders

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Abstract

Tremendous progress has been made in understanding the etiology, pathogenesis, and treatment of inherited vascular connective tissue disorders. While new insights regarding disease etiology and pathogenesis have informed patient counseling and care, there are numerous obstacles that need to be overcome in order to achieve the full promise of precision medicine. In this review, these issues will be discussed in the context of Marfan syndrome and Loeys-Dietz syndrome, with additional emphasis on the pioneering contributions made by Victor McKusick.

KEYWORDS
connective tissue disorders, Loeys-Dietz syndrome, Marfan syndrome

1 | LOOKING BACK: MARFAN SYNDROME

Marfan syndrome (MFS) was first identified in 1896 by a Parisian pediatrician, Antoine-Bernard Marfan, who described a 5-year-old girl with long slender digits and other skeletal abnormalities (Marfan, 1896) (Figure 1). The phenotype was expanded over the next five decades to include other features such as lens dislocation and, in 1943, incorporated the main life-threatening cardiovascular complications—aortic aneurysm and dissection (Baer et al., 1943; Etter & Glover, 1943).

In 1955, cardiologist turned geneticist Victor McKusick systematically described the MFS phenotype and the natural history of disease. He detailed the cardiovascular, ocular, and skeletal manifestations in 50 families, totaling to approximately 105 individuals, and presciently hypothesized that an alteration in a single gene encoding an elastic fiber constituent explained the observed multiorgan involvement (McKusick, 1955). McKusick synthesized his work on MFS, in addition to four other disorders of connective tissue, in the first edition of his seminal monograph Heritable Disorders of Connective Tissue, establishing a broad entity for disease classification and the field of connective tissue genetics (McKusick, 1959). Subsequent editions included additional disorders, totaling to 51 in the fourth edition (McKusick, 1972). He meticulously detailed the clinical presentations of each heritable disorder of connective tissue with exemplative case reports and extensive use of photographs, imaging studies, and histopathology to illustrate diagnostic features.

McKusick generated a nosology and classified these syndromes based on balancing his two primary principles: pleiotropy and genetic heterogeneity. McKusick defined pleiotropy as "many from one"—multiple phenotypic features from one etiological factor, one gene—and genetic heterogeneity as "one from many"—one and the same or almost the same phenotype from several different etiologic factors (McKusick, 1969). For MFS, pleiotropy was exemplified by the multiorgan involvement and genetic heterogeneity was evident after recognizing homocystinuria as a separate syndrome. His philosophy for the organization and naming of diseases was both complex and adherent to the solitary principle of efficient communication of information between disciplines that is grounded by fundamental mechanistic insights garnered through clinical, biochemical, and/or genetic observation. His vision of purposeful precision embraced both "lumping" to accommodate pleiotropy or commonality of mechanism and "splitting" to accommodate genetic heterogeneity. A disease name should, in McKusick's view, avoid oversimplification of a complex phenotype and describe or conjure an image of the defining features of a disease, avoid prejudice as to the nature of the basic defect, and not place a severe strain on the memory.

McKusick's dedication to defining genetic syndromes and disease underpinnings was rooted in the desire to intervene and change the course of disease. His initial MFS case series reported in 1955 was punctuated by reports of early and sudden death secondary to

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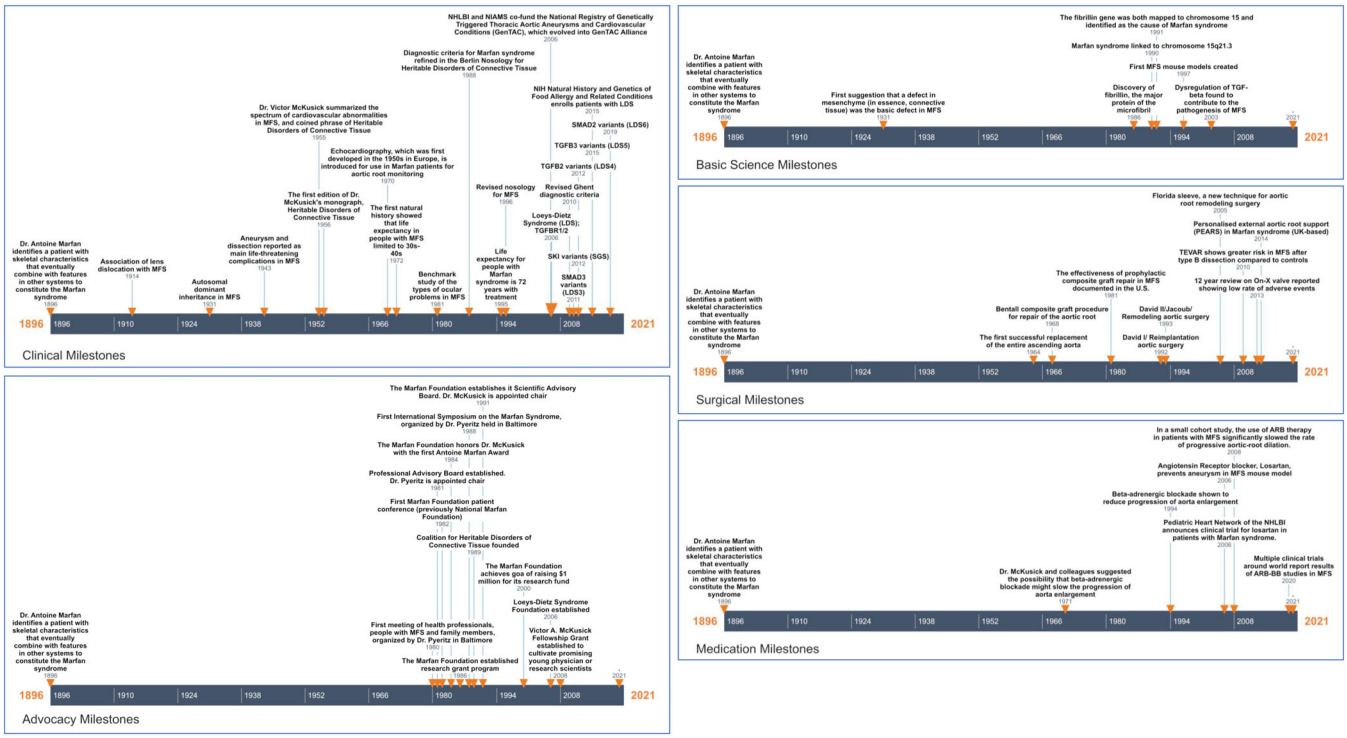

FIGURE 1 Select milestones in the history of Dr. Victor McKusick, Marfan syndrome, Loeys-Dietz syndrome and the Marfan Foundation

cardiovascular complications; mainly dissecting aortic root aneurysms and heart failure. In the early 1970s, prior to the advent of effective surgical approaches, the average age of death for a MFS patient was 32 years (Murdoch et al., 1972). Given this unfavorable prognosis, McKusick proposed the use of blood pressure modulators such as reserpine or beta-blockers. This approach was informed by the favorable response that was observed upon the administration of these drugs to aneurysm-prone turkeys that had received the lysyl oxidase inhibitor B-aminopropionitrile—perhaps the first use of an animal model in this field (Simpson & Boucek, 1983). The first randomized trial of MFS using prophylactic beta-adrenergic blockade suggested slowing of the rate of aortic dilatation in at least some patients, but these studies also documented continued abnormal aortic growth and serious cardiovascular events in the treated population (Shores et al., 1994). It was recognized that medical therapy might only be a temporizing measure and surgical intervention would also be necessary.

Open heart surgery and heart-lung bypass techniques were successfully pioneered in the mid-1950s (Miller et al., 1953). This paved the way for dramatic progress in cardiovascular surgery for MFS and other causes of aortic root aneurysm. The introduction of the Bentall composite graft procedure in 1968 provided a mechanism for safe and effective prophylactic surgery before inevitable aortic catastrophe (Bentall & De Bono, 1968). Prophylactic surgical repair of the aorta was first performed in a MFS patient at Johns Hopkins in 1976. Over the course of 30 years, thresholds for the timing of prophylactic surgery were refined and the preferred surgical approach for prophylactic aortic root repair transitioned to valve-sparing techniques (Cameron et al., 2009; David & Feindel, 1992; Gallotti & Ross, 1980; Gott et al., 1986, 1994). In the mid-1990s, surgical intervention was recommended at an aortic root diameter of ≥5.0 cm, with less tolerance for aortic root growth (diameter ≥ 4.5 cm) in patients with additional risk factors or a family history of aggressive aortic disease; guidelines that still hold true today (Odofin et al., 2021). By 1993, the life expectancy of MFS patients had increased to 72 years (Finkbohner et al., 1995; Silverman et al., 1995).

As surgical techniques were being refined, exploration for the disease-causing gene was underway. Immunohistological studies found that MFS patient samples were deficient in a newly defined connective tissue protein termed fibrillin (Hollister et al., 1990). Biochemical studies reveled that fibrillin was a large extracellular matrix glycoprotein and a structural component of microfibrils (Sakai et al., 1991). Meanwhile, the genetic defect in MFS was mapped to chromosome 15 (Kainulainen et al., 1990) and later narrowed to 15q15-q21.3 (Dietz, Pyeritz, et al., 1991). The fibrillin gene was concurrently mapped to chromosome 15 precisely in the genomic region where the MFS gene had independently been localized (Magenis et al., 1991). In a matter of months, the disease-gene *FBN1*, which encodes for fibrillin-1, was identified and disease variants were found in MFS patients (Dietz, Cutting, et al., 1991; Lee et al., 1991; Maslen et al., 1991). While McKusick described the identification of the *FBN1* gene as the dénouement of this odyssey, he was also hopeful that it was just the beginning of a new era of advances for this condition.

As McKusick predicted, identification of this genetic defect accelerated understanding of the underlying pathophysiology by allowing

generation of model systems, both in vitro and in vivo, to interrogate disease mechanisms. Early investigations showed that *FBN1* mutations causing MFS syndrome came in multiple flavors including those that allow the production of abnormal protein (e.g. missense variants or in-frame indels or splicing events) and those that lead to a premature termination codon and degradation of the mutant transcript through nonsense-mediated mRNA decay (e.g. nonsense variants or frameshifts). The prospect for robust genotype–phenotype correlations that would guide patient prognostication and management simply never materialized, although a few broad rules remain apparent. For example, the so-called dominant-negative missense mutations that allow the production of abnormal protein that can interfere with the secretion, matrix deposition and/or stability of microfibrils, are the most common type of mutation causing MFS and are significantly enriched among patients with either eye lens dislocation or the most severe end of the clinical spectrum with rapid progression of multisystem manifestations of MFS during infancy. The latter group also shows apparent clustering of mutations in a central region of the gene, spanning exons 24–36, that encodes the longest stretch of tandem calcium-binding EGF-like domains in fibrillin-1 (Liu et al., 1996). However, there are exceptions and also many patients with dominant-negative variants in this region with classic, mild or even sub-diagnostic presentations of MFS.

Microfibrils are expressed and serve important functions in both elastic and nonelastic tissues. During embryogenesis, microfibrils composed of fibrillin-1 and/or fibrillin-2 are deposited in the extracellular space and are thought to serve as a structural scaffold for the assembly of elastic fibers. Additional microfibrillar-associated proteins, some of which interact directly with fibrillins, also contribute to elastogenesis in an instructive or structural role. In nonelastic tissues where fibrillin-1 is expressed such as the ciliary zonules, microfibrils also serve essential structural functions (i.e., suspension of the ocular lens). Early pathogenic models for MFS that focused upon loss of structural integrity of the tissues provided a plausible explanation for many clinical manifestations including aortic root aneurysm, pneumothorax, ectopia lentis, or striae distensae, but faired less well at reconciling findings such as craniofacial dysmorphism, bone overgrowth, and low muscle mass and fat stores that are so characteristic of the condition. Each of these findings was more suggestive of altered cellular performance.

Potential insight came upon recognition that fibrillins have homology to latent transforming growth factor-β (TGFβ) binding proteins (LTBPs) that are constituents of the large latent complex of TGFβ, a multipotential cytokine with important morphogenic and homeostatic functions. Subsequent work showed that LTBPs interact directly with fibrillins, serving to sequester latent TGFβ in the extracellular compartment (Dallas et al., 1995, 2000) where it is poised to be released by a variety of activators. In the context of microfibrillar deficiency, as in MFS, examination of affected tissues from patients or mouse models revealed a strong signature for elevated TGFβ activity including activation of signaling intermediates and high output of TGFβ target genes. Attenuation of TGFβ signaling, either directly using specific neutralizing antibodies or indirectly using angiotensin receptor blockers (ARBs, e.g., losartan) in MFS mouse models associated with dramatic improvement in multiple disease manifestations including developmental emphysema (Neptune et al., 2003), myxomatous degeneration of the mitral valve (Ng et al., 2004), skeletal muscle myopathy (Cohn et al., 2007), and aortic root aneurysm (Habashi et al., 2006). Taken together, these data suggested that microfibrils participate in the negative regulation of TGFβ activation and signaling. However, multiple observations challenged this model. First, it was demonstrated that potent pharmacologic or genetic antagonism of TGFβ signaling in late fetal or early postnatal development could impair aortic wall homeostasis in vulnerable mouse strains and accelerate vascular events in mouse models of MFS. Vessel wall deterioration and death occurred within days of conditional provocation and associated with overt inflammation (Li et al., 2014; Wang et al., 2010; Wei et al., 2017). Curiously, aortic protection was again robustly demonstrated if TGFβ antagonism was delayed until a few weeks after birth. Second, it was shown that deficiency of fibrillin-2 associated with impaired activity of bone morphogenetic proteins (BMPs), TGFβ superfamily members that also interact with microfibrils (Arteaga-Solis et al., 2001). These data suggested that while microfibrils might negatively regulate TGFβ signaling by suppressing activation, they can also positively regulate the signaling of TGFβ family members, perhaps by concentrating latent cytokine at sites of intended function.

Despite the complexity of these proposed mechanisms, these discoveries set the framework for trialing new targeted therapies in MFS patients. Preclinical studies consistently demonstrated the efficacy of ARBs in mouse models of both syndromic and nonsyndromic presentations of aortic root aneurysm. Initial studies examined the effect of adding losartan to prior therapy in young children with severe and rapidly progressive MFS. Both found a significant and substantial (∼10-fold) reduction in aortic root growth rate upon the addition of losartan (Brooke et al., 2008; Chiu et al., 2013). In another MFS childhood cohort—with a broader range of patient ages and disease severity—losartan monotherapy slowed aortic root growth rate and suggested that earlier intervention led to better outcomes, an emerging theme (Pees et al., 2013). The prospective randomized COMPARE study reported experience in adults with MFS and found a significant overall decrease in aortic root growth rate in MFS patients receiving losartan; a decline in the rate of growth of the more distal ascending aorta after root replacement was also observed in treated patients (Groenink et al., 2013). The Pediatric Heart Network trial in children and young adults with MFS showed comparable performance (low rate of aortic root growth with a decline in aortic root z-score) with monotherapy with either losartan or high-dose atenolol (Lacro et al., 2014). Other adult studies that included individuals with an ambiguous diagnosis (∼25% with no definable *FBN1* mutation and many with no aortic root enlargement and/or pathologic aortic growth during follow-up) were equivocal (Forteza et al., 2016; Milleron et al., 2015). More recently, the large and well-controlled AIMS trial documented protection in patients with MFS who were randomized to receive irbesartan (Mullen et al., 2019). A long-term follow-up of the COMPARE trial documents a significant and sustained decrease in clinical endpoints such as aortic surgery,

dissection, and death in MFS patients receiving losartan (van Andel et al., 2020). Finally, a recent meta-analysis of seven prospective trials and >1500 patients showed that ARB therapy is associated with slower progression of aortic root or ascending aortic dilation when compared to placebo or when added to beta-blocker therapy (Al-Abcha et al., 2020). Many experts in the field agree that both beta-blockers and ARBs are safe and generally well tolerated in MFS, and that the earlier intervention is initiated, the better the outcome—even in very young children.

2 | LOOKING BACK: LOEYS-DIETZ SYNDROME

As diagnosis and treatment for patients with MFS progressed in the early 2000s, a cohort of patients emerged that were not following the rules (an opportunity for productive splitting, as McKusick would say). Diagnosed initially as "atypical MFS" and found to be *FBN1* mutation negative, these patients often presented with widespread and aggressive vascular disease with frequent aneurysms throughout the arterial tree and at risk for aortic tear and death at younger ages and smaller dimensions, when compared to MFS. While there was phenotypic overlap with MFS including arachnodactyly, pectus deformity, scoliosis, autosomal dominant inheritance, and highly penetrant aortic root aneurysm, a pattern of distinguishing features in many organ systems became apparent, including craniofacial features such as hypertelorism, bifid uvula or cleft palate, and craniosynostosis, a high risk of cervical spine malformation and/or instability, and a strong tendency for clubfoot deformity, childhood-onset osteoporosis with pathologic fractures, eosinophilic and other forms of inflammatory gastrointestinal disease, and atopic manifestations such as food or environmental allergies, asthma, and eczema (Felgentreff et al., 2014; Frischmeyer-Guerrerio et al., 2013; Loeys et al., 2005; MacCarrick et al., 2014; Tan et al., 2013).

Following his principles of nosology, McKusick split this condition from MFS, coining the name Loeys-Dietz syndrome (LDS) in 2005. Subsequent use of sub-classification with numbers accommodated recognition that pathogenic variants in either of the two genes that encode subunits of the TGFβ receptor can cause LDS, with LDS1 or LDS2 caused by mutations in *TGFBR1* or *TGFBR2*, respectively. As might be anticipated, the patients who initially came to clinical attention represented the severe end of a clinical spectrum for LDS. This range widened upon observation of substantial interfamilial and intrafamilial clinical variability and widened further upon recognition that pathogenic variants in additional genes caused conditions with extensive clinical overlap with LDS1 and LDS2 (LDS1/2). Notably, all encode positive effectors of the TGFβ signaling response including the extracellular TGFβ ligands TGFβ2 and TGFβ3 and the intracellular signaling intermediates SMAD2 or SMAD3 (Bertoli-Avella et al., 2015; Lindsay et al., 2012; van de Laar et al., 2011). By current designation based upon chronology of disease gene identification, mutations in *SMAD3*, *TGFB2*, *TGFB3*, or *SMAD2* cause LDS3-6, respectively. There was high incentive to determine the cause of a highly related condition called Shprintzen-Goldberg syndrome (SGS) that includes virtually all craniofacial, skeletal, and cutaneous manifestations of LDS but less common aortic root aneurysm and the added feature of highly penetrant intellectual disability. Demonstration that pathogenic variants in the *SKI* gene that encodes a potent suppressor of the TGFβ transcriptional response cause SGS clearly supported the conclusion that alteration in TGFβ signaling is a common theme in syndromic presentations of aortic root aneurysm (Carmignac et al., 2012; Doyle et al., 2012). Subsequent studies by our group and many others highlighted both the importance and inadequacy of simply considering the disease class (LDS) and gene designation (1–6) in patient counseling and management. While in general terms vascular disease severity tends to follow the rule that LDS1 = LDS2 > LDS3 > LDS4 = LDS5 > LDS6 > SGS, there are many exceptions both between and within affected families.

Early attempts to develop surgical thresholds for LDS1/2 focused on aortic root size, as had worked well for MFS where a threshold of 5.0 cm is generally applied irrespective of age due to the extreme rarity of aortic events in childhood. In our first publications describing LDS, we reported type A aortic dissection and death in a 37-year-old woman, whose aortic root had been documented at 4.0 cm just 3 months earlier. We also reported the death due to aortic dissection of young children with LDS1/2 and relatively mild aortic root enlargement, with the youngest being 6 months old (Loeys et al., 2006). In general, the severity of aortic disease correlated directly with the severity of outward manifestation in the craniofacial system. Many additional examples of aortic dissection at or below 4.0 cm in both adults and children were documented in the literature. At the same time, prophylactic aortic root replacement was proving to be a safe procedure in LDS when performed in experienced centers (Patel et al., 2011). This led to the recommendation for consideration of prophylactic aortic root replacement in older children and adults with LDS1/2 once the maximal dimension was approaching 4.0 cm, with the potential modification of practices based on rate of aortic growth, the emergence of significant aortic valve regurgitation, family history, the natural history of disease in unrelated individuals with the same mutation, or the patient's personal assessment of risks and benefits (Loeys et al., 2005, 2006; MacCarrick et al., 2014). We also suggested consideration of earlier aortic root surgery in young children with the most severe outward presentation of LDS1/2 once the aortic annulus had reached or exceeded ~2.0 cm, allowing placement of a graft of sufficient size to accommodate growth into adulthood. Based on the observation that some people with LDS1/2 did not experience aortic dissection even with an aortic root dimension at 5–6 cm, the American College of Cardiology recommended surgical intervention at a diameter ≥ 4.2–4.5 cm, depending on the modality of imaging (Aftab et al., 2019). Given the often catastrophic outcome of type A dissection and the safety of aortic root repair in this population, the wisdom of averaging patient performances at the extremes to arrive at a general recommendation ("lumping" according to McKusick's dichotomy) remains to be proven.

The discovery of these alterations within the TGFβ pathway has also further delineated disease pathogenesis and started unraveling

basic mechanisms of failed vessel wall homeostasis that culminate in aortic aneurysm and tear. Interestingly, LDS1-6 pathogenic variants are predicted to be loss-of-function and therefore to result in defective TGFβ signaling; however, aortic root tissue from patients and mouse models all show a clear signature of increased TGFβ signaling (Bertoli-Avella et al., 2015; Gallo et al., 2014; Lindsay et al., 2012; Loeys et al., 2005). A proposed model for reconciliation invokes unequal vulnerability of different cellular lineages at the site of aneurysms to the consequence of a heterozygous loss-of-function mutations in a gene encoding a positive effector of TGFβ signaling; the more vulnerable cell type would attempt to compensate through enhanced production of TGFβ ligands, culminating in paracrine overdrive of signaling by less vulnerable adjacent cells (Lindsay & Dietz, 2011). This model has now been fully validated in a mouse model of LDS with AT1r-dependent TGFβ production by second heart field-derived vascular smooth muscle cells (VSMCs) associating with excessive TGFβ signaling by their neighboring cardiac neural crest-derived counterparts (MacFarlane et al., 2019). Informatively, aortic root aneurysm could be fully prevented in a mouse model of LDS1 by targeted disruption of *Smad2* in cardiac neural crest-derived VSMCs. Elucidation of the mechanism by which attenuation of TGFβ signaling in one cell type culminates in a gain of signaling by another will likely inform the spatial distribution of aneurysm predisposition in LDS and the development of targeted therapeutic strategies.

As McKusick predicted, identification of these genetic defects has defined disease mechanisms and revealed novel treatment strategies. Despite this progress, the extensive variability among and within these connective tissue disorders has frustrated precise patient counseling and management. Delineating this variability and embracing individuality will help refine new disease prediction strategies, therapeutics, and surgical guidelines. Continued careful analysis of patients' genotypes and phenotypes both in aggregate and as individuals will help dictate care plans and treatment.

3 | LOOKING FORWARD: BASIC SCIENCE

New technologies are emerging to help further patient-specific research and clinical care. For example, patient-derived induced pluripotent stem cells (iPSCs) offer the opportunity to study patient-specific variants in model systems of aortic diseases while incorporating potentially protective or detrimental genetic backgrounds (Davaapil et al., 2020). These functional in vitro models could also help predict disease severity and individualize care. The challenge will be to fully recapitulate the pathophysiologic complexity of the human system, with integration of variables that include chronicity, cellular heterogeneity, inflammation, humoral factors, biomechanical stress, and relevant morphogenetic, homeostatic, and compensatory events.

While the use of animal models has undeniable obstacles when attempting to translate findings to people, their predictive potential can be optimized when the model has been designed and validated to reproduce critical aspects of the etiology, pathogenesis, and natural history of the human condition. Over the next few years, we expect the emphasis of mouse and human research studies to shift from "What causes MFS?" to "What modifies MFS, even in the face of overt (e.g. highly penetrant and severe) genetic predisposition?" In essence, what environmental and/or genetic factors are capable of averting an apparently unavoidable catastrophic outcome? While much of the interfamilial variation is dictated by the nature of the underlying *FBN1* disease allele via a mechanism that is not completely understood, the clinical heterogeneity seen among family members with the same *FBN1* mutation can be startling. The same can be said for the performance of the same *Fbn1* allele on different inbred mouse backgrounds. We and others have made progress in mapping and functionally characterizing genetic modifiers of MFS in both mice and humans. It is our hope and expectation that drugs or other interventions that leverage nature's successful strategies for disease modification will afford protection to those that were dealt a less good hand of modifiers.

New gene editing technologies, such as CRISPR-cas9, are proving effective at correcting the basic genetic defect underlying genetic disease. While human embryos with a *FBN1* mutation were corrected using CRISPR/cas9 (Zeng et al., 2018), the utility of this approach for therapeutic applications given limited in vivo editing efficiency, a variety of obstacles relating to delivery to diverse cell types, and an improving but unresolved propensity for off-target effects, remains to be demonstrated.

4 | LOOKING FORWARD: CLINICAL HETEROGENEITY

While there has long been recognized genotype–phenotype correlations in vascular connective tissue disorders, perhaps best exemplified by the differential clinical performance in patients with vascular Ehlers-Danlos syndrome who either do or do not express altered type III collagen from their mutant *COL3A1* allele (dominant-negative or haploinsufficient mechanism of disease, respectively) (Frank et al., 2015; Leistritz et al., 2011; Pepin et al., 2000), the patterns are more nuanced and less consistent in MFS and LDS. Given the lack of any common recurrent mutations in these conditions, the rarity of large families, and the lack of standardized clinical practices, the establishment of robust genotype–phenotype correlations is likely frustrated by extreme allelic heterogeneity and ascertainment bias, among other factors. A high degree of locus heterogeneity is an added complication, that allows for broad but imperfect generalizations about the relative severity of disease between genes, but limited prognostic or therapeutic insight from individual genetic variants. At our institution, a review of childhood deaths in the LDS cohort has revealed two particularly aggressive variants: *TGFBR1* p.T200I and *TGFBR2* p.R528H/C. Both children with *TGFBR1* p.T2001 required aortic root replacement less than 2 years of age and died at 8–9 years of age from descending aortic dissections. Patients with the *TGFBR2* p.R528H/C variant ($n = 20$, 35% male and 65% female) required aortic surgery at younger ages compared to all others in the *TGFBR2* cohort ($n = 140$); 7 years versus 22 years, respectively. Heterozygotes

for p.R528H/C comprise approximately 90% of the cohort requiring greater than three surgical interventions in childhood and 80% of childhood deaths. Females with *TGFBR2* variants seem to be predominantly driving the vascular severity signal with a younger average age of aortic root surgery (6 years old compared to 11 years old) and comprising all the p.R528H/C childhood deaths. The transverse aortic arch and the proximal subclavian arteries are prone to rapidly progressive dilatation, pseudoaneurysm, dissection or rupture in childhood in p.R528H/C heterozygotes, prompting consideration of a more extensive aortic surgery at the time of first intervention, including total arch replacement and elephant trunk repair. Ongoing efforts to create large registries of affected patients with vascular connective tissue disorders will undoubtedly facilitate the recognition of clinical patterns and the development of informed and individualized management plans.

5 | LOOKING FORWARD: BIOMARKERS

As noted in McKusick's original collection of case reports on MFS, aortic catastrophe seemed inevitable and unpredictable. While aortic root size and growth rate does inform the risk of type A dissection in both MFS and LDS, there remains a substantial need for better predictors of arterial dissection or rupture both at the root and additionally in the descending thoracic aorta in MFS and many vascular segments in LDS. Currently, the state of biomarker research in aortic disease has focused more on diagnostic applications rather than the risk of impending dissection. Circulating TGFβ, fibrillin-1 fragments, homocysteine, matrix metalloproteinases, collagen processing or degradation byproducts, elastic fiber-related markers, and desmosine have all been studied in patients with aortic disease (thoracic and/or abdominal)) and found to have variable associations, but thus far no strong predictive capacity (Iskandar et al., 2020). It is hoped that a refined understanding of disease pathogenesis and the involvement of the International Registry of Acute Aortic Dissections (IRAD), among other repositories of clinical data and patient samples, will facilitate the development and testing of hypotheses regarding biomarkers that can guide patient care and enhance the accuracy and efficiency of clinical trials.

6 | LOOKING FORWARD: IMAGING

In addition to biomarkers, imaging modalities need refinement. Whereas echocardiogram and CT measurements have historically served as the imaging modalities of choice to determine aortic diameter and timing of surgical intervention, new indices such as the aortic size index and aortic height index, have more recently been proposed as predictors of aortic dissection, but have not yet been rigorously validated in connective tissue populations (Zafar et al., 2018).

The vertebral tortuosity index, the relation between the actual length of the vertebral artery and the "as the crow flies" linear distance between its origin and termination, shows correlation with certain aspects of vascular outcome (Morris et al., 2011). Arterial tortuosity is likely a general (albeit easily standardized and quantified) surrogate of the overall clinical severity that is imposed by the specific underlying disease allele, as opposed to a direct contributor to vascular events. Other imaging techniques such as aortic arch geometry, aortic tortuosity index, carotid tortuosity indices, and the chalice sign have been proposed as either predictors of disease severity or diagnostics markers in LDS (Benson & Brinjikji, 2020; Chu et al., 2018; Mariucci et al., 2020; Morris et al., 2011).

4D-Flow cardiovascular magnetic resonance angiography allows for assessment of volumetric flow quantification, wall shear force, pulse wave velocity, aortic stiffness, and pressure gradients, providing the potential to improve our ability to interpret altered hemodynamics in the context of disease progression and management (Di Giuseppe et al., 2021; Markl et al., 2012). While selected hemodynamic markers have shown correlation with various stages of aortic wall remolding and clinical vulnerability (Campisi et al., 2021), it remains uncertain if some of these markers are disease-drivers or compensatory mechanisms.

7 | LOOKING FORWARD: SURGICAL INTERVENTION

Currently, definitive therapy for aortic root aneurysm remains surgical. Valve-sparing aortic root replacement remains the gold standard prophylactic repair for aortic root aneurysms in MFS and LDS When valve replacement is necessary, newer generation options such as the On-X valve are available. Made from pyrolytic carbon, the On-X valve shows excellent hemodynamics and durability with a significant reduction in anticoagulation-related complications (Yanagawa et al., 2015). Alternate operations that reinforce rather than replace the aortic aneurysm wall have been introduced, specifically, the personalized external aortic root support (PEARS) procedure and the Florida Sleeve (Aalaei-Andabili et al., 2017; Treasure et al., 2014). While not yet fully clinically validated in the management of the full spectrum of presentations of vascular connective tissue disorders, including individuals with large aneurysms that already pose a risk for aortic root dissection or rupture, short-term results are encouraging. Both procedures involve external stabilization of the aortic root using a synthetic mesh and may find early application in centers without extensive experience with valve-sparing root replacement.

In LDS, the presence of aneurysms throughout the arterial tree has led to successful surgical repairs with embolization, coiling, and clipping techniques (Levitt et al., 2012; Liang et al., 2021). The utility of prophylactic descending aortic replacements in the absence of aneurysm or dissection is an open and important question given the lack of reliable predictors of type B dissections in MFS or LDS. Close monitoring of type B dissections, especially in LDS, in the short term is necessary as many patients show rapid expansion necessitating surgical intervention despite optimized medical therapy (Lee et al., 2007).

Open surgical repair for the thoracoabdominal aorta remains the treatment of choice (Ziganshin & Elefteriades, 2014). While in general patients with LDS should have surgery at smaller aortic root

dimensions than in most patients with MFS, refinement of surgical thresholds should continue to be investigated, especially on an individualized basis. Open repair with custom-made fenestrated or branched grafts shows excellent short- and intermediate-term results and may be particularly useful in young LDS patients with diffuse and severe aneurysmal disease (Humphrey et al., 2015).

8 | LOOKING FORWARD: CONSORTIUMS

A powerful tool in our understanding of aortic disease will continue to be multi-institutional consortiums that collect large data sets such as the GenTac Registry, IRAD, PROWGAD (Pregnancy and other Reproductive Outcomes in Women with Genetic-predisposition for Aortic Dissection), TBAD Collaborative (Type B Aortic Dissection), and the Montalcino Consortium. Data collection needs to be expanded, deepened, and combined with more granular precision medicine initiatives, such as the partnership between the National Institutes of Health natural history study (ClinicalTrials.gov Identifier: NCT02504853) and the Kasper Center of Excellence for Pediatric Aortopathies at the Johns Hopkins University. Financial investment into technologies that systematically capture patient data from the electronic patient record, along with genetic, laboratory, imaging, and biochemical studies will expand our capacity to identify and act upon worrisome disease patterns.

9 | LOOKING FORWARD: PATIENT ADVOCACY

Support and advocacy groups will continue to play an instrumental role in promoting advancements in clinical care and research. What started at the house of Dr. Reed Pyeritz in 1980, evolved into the Marfan Foundation, a model of efficiency for all pursuits relevant to the improvement of the length and quality of life for affected individuals. The Marfan Foundation has expanded its scope through partnership with sister organizations that address the needs of people with related disorders including LDS, vascular Ehlers-Danlos Syndrome, and Stickler syndrome. Essential missions include patient and clinician education, fund raising for research, the organization of scientific meetings to share ideas and forge collaborations, lobbying on behalf of constituents, and the facilitation of clinical trials.

McKusick and his contemporary and influential colleague Barton Childs challenged us to move past the question of what "causes" a given condition to the more compelling consideration of "Why is this patient with this condition presenting with this problem at this time?" In essence, the challenge was to extend beyond the traditional guiding principle of evidence-based medicine—"What will work best for the average patient with this condition?"—to the more important question—"What will work best for this genetically—and biochemically—unique person sitting in front of me?" As usual, McKusick's challenges both resonate and linger as the field struggles to catch up.

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