1. Introduction

1.1. Prevalence & incidence

The Marfan syndrome (MIM 154700) is a rare disease with a prevalence of up to 1–3 per 10,000 individuals [1–4]. It is a multisystem disease of the connective tissue, which affects multiple organ systems, such as the heart and blood vessels, eyes, bones, and lungs resulting in complications. In 50–80% of the individuals, the Marfan syndrome is inherited through an autosomal dominant genetic pattern. However, in about 20–50% of all individuals are de novo mutations meaning where no family history is present [1].

Advances of healthcare have doubled the life-expectancy of patients from 30 to 60 years over the past three decades [5]. This development can be attributed to a better knowledge of the disease and the advancement in diagnostic techniques, for example noninvasive imaging technology and molecular genetic diagnostics. Furthermore, early diagnosis, prophylactic treatment, and intervention allow prolonging or halting early disease progression. Despite all these advancements, a substantial part of Marfan patients is still diagnosed at a very late stage. This is attributable to a lack of awareness of the disease and the large variety of clinical manifestations, which complicates diagnosis [4,6]. However, a potential delay in diagnosis leads to later and less effective preventive treatment, worse outcomes, and higher costs.

1.2. Research objective

With this review, we aim to provide a condense overview over the Marfan syndrome, its care pathways, and its corresponding economic impact on patients and society. First, we provide an overview of the pathogenesis, manifestation, and pathways of care. Then, we present the two coexisting modes of diagnosis, i.e. diagnostics based on phenotypes versus diagnostics based on genetic testing that strongly determine life-time costs and quality of life of Marfan patients. Following that, we approximate the economic costs of the disease. We discuss the impact of different diagnosis and treatment approaches and we conclude by pointing at lessons learned from this review.

2. Marfan syndrome

2.1. Pathogenesis

Marfan syndrome is a genetic disorder that is caused by mutations in the FBN1 gene on chromosome 15 [6,7]. The FBN1 gene codes for production of a 350 kD glycoprotein in the extracellular matrix called fibrillin-1 [1,8,9]. This protein connects with other fibrillin-1 proteins and other molecules to form microfibrils that are vital for the strength and flexibility of connective tissues. Furthermore, microfibrils stabilize latent transforming growth factor β (TGFβ) inactive. Due to these features, a failure in the interaction between fibrillin-1 and LTBP5 result in an excess release of TGFβ, which in return results in overgrowth, less elasticity, and increased instability of the tissues. In some variants of the Marfan syndrome, called Loeys–Dietz syndromes, phenotypes result directly from mutations in the TGF β-receptor 1 (TGFBR1) on chromosome 9 and from mutations in the TGF β-receptor 2 (TGFBR2) on chromosome 3 [10,11].
It is important to note that mutations in the \textit{FBN1} gene are not unique to the Marfan syndrome [12]. \textit{FBN1} mutations can cause disorders, which are similar to Marfan, such as the MASS phenotype (MIM 604308) [13] or isolated ectopia lentis (MIM 129600) [14,15]. Vice versa, not all patients that fulfill the criteria for a positive diagnosis with Marfan demonstrate fibrillin-1 mutations [16,17]. According to a recent systematic review, the share of patients with causative \textit{FBN1} mutation failing to fulfill diagnostic criteria of Marfan syndrome was 7% according to the former Ghent-1 nosology [18] and 15% according to the Ghent-2 nosology [4]. Similarly, the same review identified that 15% and 13% patients with final diagnosis of Marfan syndrome according to Ghent-1 and Ghent-2, respectively, did not have a causative \textit{FBN1} mutation [4]. Moreover, mutations in \textit{TGFBR1} and \textit{TGFBR2} have been described in patients with Loeys–Dietz syndrome, and non-syndromic familial thoracic ascending aortic aneurysm (MIM 608967)[1,11].

2.2. Manifestations, disease stages, and treatment

Manifestations of the Marfan syndrome in the skeletal, ocular, and cardiovascular system are among the most prominent and well-known ones [1,2]. The skeletal manifestation may be the most striking and visible one. Classically, Marfan patients are considered to be tall and slender, but some may be small or obese [19]. Ocular characteristics are a long and narrow face, crowded teeth, and an abnormal curvature of the spine, known as scoliosis or kyphosis. Roughly, 60% of all Marfan patients present scoliosis [20]. Accordingly, back pain is three times more frequent among Marfan patients than in the healthy population. At the same time, Marfan patients are found to incur lower bone mineral density especially in the hip and spine, although no increased rate in fracture could be found if compared to the general population [21,22]. In line with that, some individuals show a protruding or sunken chest (pectus carinatum or excavatum) [23]. Furthermore, the dura, a membrane surrounding the brain and spinal cord, can be abnormally enlarged (dural ectasia) causing pain in the back, abdomen, legs, or head [24–27].

Manifestations in the ocular system are both, highly prevalent and clinically relevant. In about 60%, patients have also been found to exhibit ectopia lentis, a dislocation of the ocular lens [28,29]. Other ocular defects, such as retinal detachment, early cataracts and glaucoma also rank among potential ophthalmic complications of Marfan syndrome [5,30,31].

The most relevant manifestation of the Marfan syndrome is the cardiovascular system including the aorta, the aortic and the mitral valve, and the myocardium [1], where aneurysm of the aortic root, regurgitation of the aortic and the mitral valve, and myocardial dysfunction give rise to aortic dissection, aortic rupture, aortic and mitral valve regurgitation, heart failure, ventricular arrhythmia, and sudden cardiac death [32]. Aortic root dilatation and dissection are the most common cause of morbidity and mortality among Marfan patients [33]. In up to 90% of all patients, mitral valve prolapse is diagnosed [34–40]. In line with that, about 85% of patients exhibit aneurysmal disease of the aorta [34,36,41].

Besides direct clinical manifestations, the Marfan syndrome is also associated with chronic fatigue and pain, psychological despair and lifestyle changes. This negatively impacts the quality of life and restricts the autonomy of Marfan patients [4,42].

Patients with the Marfan syndrome require life-long medical monitoring, support, and treatment. The type of treatment depends on the stage of disease progression. In an early stage, pharmaceutical treatment prevails (Figure 1). Beta-adrenergic blocker (BAB) therapy retards aortic dilatation and is crucial to delay elective surgery especially in young patients with Marfan syndrome. It aims to lower aortic shear pressure and reduce changes in pressure over time. Angiotensin-conversing enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and calcium channel blockers may be reasonable alternatives of medication when beta-adrenergic blocking therapy is not possible [1,43,44]. ARB targets TGBβ, and their use has been found to cure mitral valve disease in Marfan mouse models [45,46], although their use was not found superior to BAB in a randomized controlled study comparing BAB versus ARB [47].

Besides medical therapy, patients require constant monitoring of the progress of their disease. Cardiac manifestations worsen with age but progression remains still difficult to predict. Monitoring includes frequent specialist visits and annual or bi-annual echocardiograms. In line with that, frequent skeletal and ocular inspections are necessary to detect potential deteriorations. Furthermore, patients are advised to abstain from intense and stressful sports to avoid rising blood pressure and excessive cardiac stress [48].

When aortic root dilatation progresses, a prophylactic elective surgery of the aorta is needed. Surgical repair is recommended once the aorta reaches a diameter of 50 mm [49]. In adults, surgery is usually performed if growth exceeds a rate of 5 mm per year or if a significant aortic regurgitation emerges
However, there is less evidence on the optimal timing in children [51].

Elective surgery is either performed as conduit operation with a replacement of the aortic root including the aortic valve by a mechanical prosthetic valve, or as a valve-sparing aortic root reconstruction operation in which the native aortic valve is preserved [52–54]. In contrast to a conduit operation that includes a mechanical valve, the aortic root reconstruction techniques avoid lifetime anticoagulation with warfarin including its risk of thromboembolism and bleeding [55–57]. Aortic valve sparing operations can either be carried out as remodeling technique according to Yacoub [58] or as a reimplantation procedure, according to David [52], where long-term results show superior aortic valve durability and longer freedom from the need for reoperation for the David operation [59,60].

If patients fail to undergo a prophylactic surgery, for example because they have missed their regular check-up, or because the Marfan syndrome has not been diagnosed, the patient’s risk emergency surgery which comes with a significantly higher mortality than a prophylactic surgery [61–63]. In addition, cardiac deterioration occurs at a much faster speed compared to patients who underwent prophylactic surgery.

In addition to aortic surgery, surgeries on the mitral heart valve, the skeletal system including the sternum and the vertebral column, the ocular lenses, or for pneumothorax may become necessary with disease progression and, in some individuals, transplantation of the heart or kidneys may become necessary [20,64–66].

2.3. Diagnosis

The diagnosis of Marfan syndrome is based on various items as defined in the 2010 revised Ghent nosology (Ghent-2; Table 1) which replaces its predecessor from 1996 (Ghent-1) and the Berlin nosology from 1988 [4,67]. Traditionally, the diagnosis of Marfan syndrome required the evaluation of up to 30 clinical features including ocular examinations, echocardiography assessment of family history, an X-ray of the lung, MRI or XCT of the dura and fibrillin-1 mutation testing. All nosologies are understood as an international consensus on rules of how Marfan syndrome should be diagnosed. Such nosology including its broad consensus is essential, because there is no single objective way or external ‘gold standard’ to definitively prove or exclude Marfan syndrome [4]. Accordingly, several critiques prevail [2] and these are unlikely to get fully reconciled in the near future [68].

The authors of the Ghent-2 nosology listed the important changes of Ghent-2 as compared to the revised Ghent-1 nosology. These changes included giving more diagnostic weight to aortic root aneurysm or dissection and ectopia lentis. Moreover, they attributed a more prominent role to molecular genetic testing. In addition, they removed numerous clinical criteria including dilatation of the main pulmonary artery, dilatation or dissection of the descending thoracic or abdominal aorta, increased axial length of globe and abnormally flat cornea, hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis, joint hypermobility, spondylolysisis, highly arched palate, and recurrent or incisional hernia, calcification of the mitral annulus, and apical blebs of the lung.

Moreover, they mitigated the diagnostic relevance of dural ectasia, and they added or modifying clinical criteria such as myopia >–3 diopters, hindfoot valgus, and thoracolumbar kyphosis. Finally, the Ghent-2 nosology listed new alternative diagnoses of Marfan syndrome such as Loey–Dietz syndrome [71]. In summary, the Ghent-2 nosology made it easier to diagnose Marfan syndrome, where a family history, an echocardiogram of the aortic root, the demonstration of ectopia lentis, and assessment of ectopia lentis usually suffice to diagnose Marfan syndrome. In addition, a systematic review of the literature illustrated a similar diagnostic performance of Ghent-1 and Ghent-2 nosologies [4].

3. Economic considerations on Marfan syndrome

Studies reporting economic data on Marfan disease are very scarce. Within our review, we could identify in total three studies that provide insights in the cost of Marfan disease (see Table 1) [43,69,70]. All of the studies originate from Germany and analyze very different aspects in the treatment of Marfan. The study by Manow et al. [69] provides insights in the internal cost structures of an ambulatory care center in Germany. The study by Achelrod et al. [70] uses a genetic matching approach to determine direct (non)medical and indirect costs attributable to Marfan syndrome from healthcare payer and societal perspective. The most recent study by von Kodolitsch et al. [43] evaluates the marginal costs of identifying an additional – otherwise undetected – Marfan patient in a population of persons referred for confirmation or exclusion of Marfan syndrome.

3.1. Cost structures of an ambulatory care center

Manow et al. [69] provide insights in the cost of treatment in a German ambulatory care center. Based on internal service charges, the authors show that the reimbursement of sickness funds does not match their actual costs. This difference sustained even after a considerable increase in reimbursement rates in 2008. The authors calculated that the total facility costs for treatment of 184 Marfan patient in a hospital’s ambulatory care center accrues to EUR 71 607 per year, while the provider received EUR 55 550 as reimbursement. Even after introduction of the new more generous reimbursement scheme, only 84% of the actual costs, i.e. EUR 59 830, were covered.

Besides presenting costs from ambulatory care center perspective, Manow et al. [69] indicate – but not specify – high costs arising through informal caregiving, loss of productivity, and traveling. Across all 184 analyzed patients, 36% traveled for more than 50 km to access treatment at the specialized ambulatory care center [69].

3.2. Economic impact for patients and society and resource utilization

Achselrod et al. [70] show that total costs from sickness fund perspective (cost elements shown in Table 1) amount to EUR 4 416 compared to EUR 1 920 per patient and year in the control group of non-Marfan patients. Largest cost block are direct
medical costs amounting to EUR 4,024. Main elements of direct medical costs are inpatient treatment costs (EUR 1,337) and care provided by nonphysicians (EUR 1,315), e.g. physiotherapy. The difference between Marfan and control group is defined as excess costs caused by Marfan syndrome of EUR 2,496. Main difference of costs from societal perspective and from sickness fund perspective are the additional consideration of indirect costs, i.e. cost of absence from work and the cost of premature death, and the consideration of informal family care. Total costs for a Marfan patient from societal perspective are estimated to accrue to EUR 21,865 per patient and year, while the yearly costs in the control group is EUR 6,137. Indirect costs are estimated to be EUR 10,329, while informal family care, an element of direct nonmedical costs, is calculated to be EUR 7,200 per Marfan patient and year. The excess costs caused by Marfan syndrome from societal perspective amounts to EUR 15,726. If patient level costs are aggregated on national level, the economic impact ranges from EUR 24.0 to EUR 61.4 million from the sickness fund perspective, and from EUR 151.3 to EUR 386.9 million from the societal perspective across one year.

3.3. Cost-effectiveness of DNA sequencing

Von Kodolitsch et al. [43] analyze the cost-effectiveness of high-cost FBN1 gene sequencing based on a sample of 300 persons referred for confirmation or exclusion of Marfan syndrome. The nonfinancial data originates from a study of Sheikhzadeh et al. [17] that shows that 24 out of the 171 truly affected persons could only be detected using gene sequencing. As it is impossible to restrict genetic testing to the 24 individuals a priori, all of the 300 suspected individuals will have to be genetically tested in order to correctly diagnose the 24 patients. Considering that the genetic test accrues to EUR 4,603 per suspected individual, the marginal costs of detecting one of the 24 otherwise nonidentifiable patients amounts to EUR 57,538.

A correct and timely diagnosis of Marfan increases the chances that thoracic aortic aneurysms can be treated in an elective inpatient stay which amounts to EUR 18,622 [70]. A delay in diagnosis bears a high risk of emergency surgery. Emergency interventions are extremely heterogeneous in price and typically require expensive and lengthy follow-up treatments [43] which may easily cause total costs of more

| Table 1. Overview of studies reporting economic data on Marfan disease. |
|-------------------|-------------------|-------------------|
| Objective and cost Perspective | Provide detailed cost and revenue information from provider perspective across one year | Estimate economic impact of Marfan syndrome from third-party payer and societal perspective by age categories | Evaluate value of information of high-cost DNA sequencing from third-party payer perspective |
| Country | Germany | Germany | Germany |
| Time | 2008 | 2008 | 2014 |
| Cost Categories | Direct medical costs based on hospital internal service charges | Direct medical costs | Direct medical costs |
| | Direct medical costs based on German outpatient fee schedule | • Outpatient | • DNA sequencing according to the German |
| | | • Inpatient | • outpatient fee schedule |
| | | • Pharmaceuticals | • Pharmaceutical treatment costs |
| | | • Nonphysician care | • Elective and emergency surgery of the aorta based on German inpatient reimbursement |
| | | • Devices and appliances | |
| | | • Rehabilitation | |
| | | • Direct nonmedical costs | |
| | | • Administration | |
| | | • Sick leave compensation | |
| | | • Other nonmedical services | |
| | | • Informal family care | |
| | | Indirect costs | |
| | | • Lost production due to absence, disability, and premature death | |
| Sample size | 184 persons with Marfan diagnosis | 892 individuals with Marfan syndrome and 892 control subjects | 300 persons referred for confirmation or exclusion of Marfan syndrome |
than EUR 100,000. Therefore, the authors consider the price of EUR 57,538 as cost-effective.

### 3.4. Exemplary cost patterns

Although we cannot directly synthesize cost patterns by treatment out of the existing literature, we believe that we are able to derive two exemplary cost curves from the three studies [43,69,70] that are linked to two exemplary treatment patterns (see Figure 2). As the curves are idealized, they represent the best- and worst-case scenarios. Individual cost curves may substantially deviate because Marfan specific treatment is often highly individualized. The solid line shows the cost curves of a patient that is diagnosed in his early years by expensive FBN1 gene sequencing, leading to a low cost but adequate pharmacological treatment with mostly out of patent drug therapies. Continuous monitoring and regular check-ups lead to early detection of a growing aorta and rather inexpensive preventive surgery of the aorta or of the mitral valve that usually becomes necessary in the 30s [60]. The dashed line shows a patient that is not or even worse wrongly diagnosed in the early years. Here, rather low costs accrue in the early ages but the negligence of adequate treatment leads to high costs of eventual emergency surgery of aortic aneurysms in the patients’ 30s–40s with high follow-up costs.

### 4. Discussion

Present research indicates a link between the treatment pattern, the disease progression, and the economic costs of the disease. It shows that an early detection of the disease and preventive interventions achieve a dual aim. From a patient perspective, it slows the disease progression, it lowers lifestyle restrictions, psychological stress, and it improves the health-related quality of life. In addition, early detection reduces the amount of emergency surgery or intervention and inpatient stays which improves the patient’s quality of life. From an economic perspective, early detection and preventive measures contain costs by reducing the number of inpatient stays as well as the length of stay.

However, early diagnosis and prevention requires a high certainty on the initial diagnosis. As diagnosis is challenging, potential patients should be assessed by multidisciplinary healthcare teams [72]. As neither the phenotypic nor the genetic diagnosis is perfectly unequivocal, it is recommended to blend both techniques to receive a more comprehensive picture [2,4,16,73,74]. The assessment by a multidisciplinary team requires several visits to specialists and several diagnostic procedures, such as an echocardiogram, a CT scan, and an MRI. In addition, genetic testing comes, despite all progress, at very high costs. However, the higher diagnosis costs may be set off by lower treatment costs due to earlier interventions and low-cost preventive measures instead of high costly emergency surgeries of the aorta [43].

Various deficiencies still impede patients from enjoying a close-to-normal life [5]. First and foremost, there is an insufficient awareness of the disease implying that the syndrome is often diagnosed at a late stage or not at all [4,23]. If so, patients risk severe manifestations, such as emergency surgeries of the aorta, which severely lower their life expectancy and increase the financial burden of the disease. This may not be achieved by simply increasing medical supply, such as the density of physicians as research has shown that the time to diagnosis is immune to the regional healthcare structures [75]. This indicates that potential solutions to undertreatment is to be sought in raising awareness among physicians and patients alike and in promoting new diagnostic means in the medical profession [43]. Following from that, health providers and patients alike are in need of clear medical guidelines on how to treat the syndrome. For the time being, revisions of the Ghent nosology foster the identification of joint standards on diagnostic prerequisites [4], but there is no harmonized treatment path for Marfan patients. Besides a joint understanding that a diameter of the aorta of 50 mm or more requires a surgical intervention in adult patients [1,76], there are no joint treatment recommendations. Therefore, standardized treatment guidelines appear desirable. However, treatment cannot follow a ‘one fits for all’ pattern for two crucial reasons: First, in many patients such ‘uni therapy’ can lead to ‘technical treatment failure,’ as we would ignore the patient’s individual physical, or emotional risks that threaten the success of treatment or make it impossible. Second, translation of therapy guideline lead to ‘ethical failure,’ as we would patient’s needs and individual values.

### 5. Future research and limitations

Pathogenesis, diagnosis, and treatment patterns of the disease are well researched considering that Marfan syndrome is a rare disease. However, evidence on economic issues remains scarce. Based on the three studies on economic issues of Marfan syndrome, we believe that there is a link between the treatment pattern, the disease progression, and the economic costs. For a better understanding of this link and to prove a causal relationship, further research is absolutely needed. This research may exploit existing datasets using
machine learning techniques to find better ways to cluster different Marfan treatment patterns.

Although there is a joint understanding that preventive surgery and that an intensified diagnostic procedure may be set off at a later stage [43], cost-effectiveness of those tests is highly sensible on the right preselection of patients. Unrestricted overuse of gene sequencing must be restricted to guarantee access to the patients in need. Also, not every correctly diagnosed patient is prevented from unplanned surgery and not every undiagnosed patient will have to undergo emergency surgery [63]. Here, further research is needed that accounts for uncertainty of the results. Moreover, the lack of cost-effectiveness information in general impedes more expensive diagnostic and nondiagnostic procedures from being reimbursed. Further research in this area is of utmost importance to demonstrate cost-effectiveness of effective diagnostic and nondiagnostic procedure to payers.

At last, we call for more cost studies that incorporate different cost perspectives and include further cost items. Although the claims based study from Achelrod et al. [70] includes a broad spectrum of costs and two perspectives, the authors could not account for cost of premature death. In addition, there is some evidence that costs reported in claims data are underestimating the true efforts taken by the provider [69].

6. Conclusion

Despite great improvements in the treatment of Marfan in the past decades, the disease strongly impacts quality of life. The review of literature shows that quality of life can be substantially improved if the disease is detected early to allow for timely and preventive action. Genetic testing, advancements in medical device technology, and excellence in surgical techniques are contributing to this goal. Researchers, providers, and policy makers are encouraged to explore these options to improve quality of life for Marfan patients while containing costs.

In addition, we point at several persisting limitations in the knowledge of economy and care of Marfan syndrome. First, there is a lack of awareness and a significant share of patients is diagnosed at a late stage, or not at all [75]. Furthermore, several dimensions of the medical treatment of Marfan patients remain vague and unclear. This is partly due to the highly heterogeneous development of the disease in Marfan patients and partly due to a lack of research. However, medical innovations, such as new surgical techniques and new modes of diagnosis, have increased the survival rate of patients significantly. This should be stressed even further.

7. Expert commentary

The biggest leverage for improving survival, physical fitness, and life quality for people with Marfan syndrome is to establish a definitive diagnosis early in life and to provide prophylactic care rather than to fix health catastrophes. It is possible to diagnose rare diseases such as phenylketonuria by simple screening tests right after birth. Unfortunately, there is no such screening test for Marfan syndrome, and it appears unlikely that such test will be available in the near future. Therefore, it remains the major weakness of Marfan healthcare that initial diagnosis still hinges on the personal awareness of individuals to recognize suggestive signs and symptoms. Genetic testing is pivotal to confirm the clinical diagnosis and to dissect Marfan syndrome from similar genetic aortic diseases. Finally, only Marfan centers with comprehensive personal experience, both with affected children and with adults are able to maximize therapeutic success. Such Marfan centers provide healthcare on a high level of expertise in many medical disciplines including heart surgery, vascular surgery, cardiology, orthopedic surgery, ophthalmic surgery, neurology, and psychology. Medical evidence is available to document that such multidisciplinary healthcare centers maximize survival, physical fitness, and quality of life for Marfan patients. In contrast, economic evidence still requires research to document comprehensively that these centers are also capable of minimizing costs of care.

8. Five-year view

In 5 years, there will be three major advances. First, molecular testing will be in much broader use at significantly lower costs. Second, preventive medicine will be on the rise. We will perform prophylactic surgery of the aorta and the heart valves earlier and with still better results than today. We will look at aortic dissection and aortic rupture in Marfan patients as a systematic failure of national healthcare systems. Costs for treating victims of predictable health catastrophes will only be anecdotal. Finally, mechanical heart valves and warfarin will be history of medicine, because reconstructive valve surgery or biological heart valves will be state of the art.

Key issues

- Marfan syndrome is a rare multisystem disease of the connective tissue, that is caused by mutations in the \( FBN1 \) gene and that affects multiple organ systems.
- Medical research provides evidence that a modern treatment pattern doubles the life expectancy and normalizes health-related life quality of patients.
- A modern medical treatment pattern comprises adequate clinical screening for Marfan syndrome in the population, early clinical diagnosis at expert centers, molecular genetics for diagnostic confirmation, counselling for and management of life-style, advanced medication to minimize disease progression, prophylactic aortic and heart valve surgery, and usage of valve-sparing rather than valve replacing surgical techniques.
- Economic research suggests that there may be a link between the treatment pattern, the disease progression and the economic costs of Marfan syndrome. A modern treatment pattern with early diagnosis and preventive measures is likely to contain costs and reduce the number and length of inpatient stays.

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