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Indication Criteria for Genetic Testing
Evaluation of validity and clinical utility

Indication criteria for disease:
Marfan-syndrome (Type 1) [FBN1]

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2. Disease characteristics

2.1 Name of the Disease (Synonyms): *Marfan syndrome type 1 and related phenotypes*

2.2 OMIM# of the Disease: *154700*

2.3 Name of the Analysed Genes or DNA/Chromosome Segments: *FBN1*

2.4 OMIM# of the Gene(s): *134797*

2.5 Mutational Spectrum:
Over 1700 different disease-causing mutations have been described (UMD-FBN1 database, http://www.umd.be; Collod-Beroud et al.,2003) (Collod-Beroud G. personal communication).
All types of mutations have been reported. From a study of 1013 probands with a pathogenic FBN1 mutation, the distribution was as follows: 56% missense mutations; 17% frameshift mutations; 14% nonsense mutations; 11% splice mutations, 2% inframe deletions (Faivre et al., 2007)

2.6 Analytical Methods:
Two different strategies for FBN1 mutation screening procedures are currently applied:

- *Direct sequencing of genomic exonic DNA with flanking intronic sequences.*
- *Or DHPLC or High Resolution Melting (HRM) with confirmation by direct sequencing*

When no mutation is identified, a search for FBN1 genomic rearrangements by MLPA or related techniques could be proposed in clinically convincing cases. Indeed, this search appears to add a few % to FBN1 mutation uptake number. From a study of 101 patients with Marfan syndrome or related phenotypes but absence of FBN1 mutation after direct sequencing, 2 FBN1 genomic deletions (2%) were found using MLPA (Màtyàs et al., 2007). Similarly, Liu et al. (2001) identified 2 FBN1 genomic deletions using RT-PCR out of a series of 60 patients (3.3%), 55 of which met diagnostic criteria for MFS.

SSCP analysis does not appear as a satisfying technique for FBN1 mutation screening since it has been shown that it was less efficient than direct sequencing. Indeed, Loeys et al. (2004) detected 73 sequence variants in 95 patients after screening by SSCP. They identified 13 additional mutations by performing direct sequencing in patients with normal SSCP.

2.7 Analytical Validation
Sequencing of both strands. When a mutation is identified, the validation of the results using a second primer set is recommended, +/- using a second technique (PCR with restriction enzyme digestion, High Resolution Melting or DHPLC) when possible.

2.8 Estimated Frequency of the Disease in Germany
(Incidence at birth ("birth prevalence") or population prevalence):
Population prevalence about 3/10.000 (http://www.orpha.net)

2.9 If applicable, prevalence in the ethnic group of investigated person:
Not applicable

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2.10 Diagnostic Setting:

	Yes.	No.
A. (Differential) diagnostics	☒	☐
B. Predictive Testing	☒	☐
C. Risk assessment in Relatives	☒	☐
D. Prenatal	☒	☐

Comment: *FBN1 mutation screening does not appear to be useful for the positive diagnosis of Marfan syndrome in patients fulfilling international Ghent criteria (De Paepe et al., 1996). However, it appears useful in the following situations, in order to determine if follow-up and preventive treatment for aortic dilatation is indicated (De Backer et al., 2007; Faivre et al., 2008):*
- patients not fulfilling international Ghent criteria, in particular patients with isolated ectopia lentis and patients with suggestive cardiovascular features combined with skeletal findings, or in sporadic cases of young age (Faivre et al., 2009b)
- predictive testing in young children (offspring of an affected parents) or relatives (large clinical heterogeneity) (Faivre et al., 2009a)

The decision on to whether searching FBN1 gene mutation in such cases will vary and depend on specific family and individual circumstances. The indications of genotyping could be extended to all cases/families in which the proven genetic diagnosis could influence the life style (athletes), the initiation of treatment, the rate of clinical controls/monitoring.

FBN1 mutation screening can also be indicated in an affected patient with reproductive issues.
A prenatal test for Marfan Syndrome is rarely requested, but it is expected that the greater availability of mutation testing of the FBN1 gene will increase requests for prenatal diagnosis. Prenatal diagnosis is technically possible by analysis of DNA extracted from foetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation (Loeys et al., 2002). Prenatal diagnosis is possible when the disease-causing mutation has been identified in the family with careful exclusion of maternal DNA contamination when the mother is the affected parent. In a few cases, when a family can be sampled at large and the disease-causing mutation has not been identified, linkage analysis can be performed. Prenatal diagnosis can be then offered only if conclusive linkage has been obtained and an unambiguous disease-associated haplotype has been identified. A careful analysis of intra- and extragenic FBN1 markers is required.
Prenatal diagnosis can be discussed case-by-case with couples requesting it in the framework of a genetic clinic, especially in families with severe cardiac manifestations. Practical use of prenatal diagnosis remains difficult because of the extremely broad variability of clinical expression, even within families, and our inability, at present, to predict the severity of the disease in a given individual. However, it is unlikely that a neonatal MFS occur in newborns of an adult affected parent. Neonatal MFS cases are always caused by de novo FBN1 mutations.
Alternatively, preimplantation genetic diagnosis (PGD) can be offered for families in which the disease-causing mutation has been identified in an affected family member. However, rules laws and regulations vary in the different European Countries, and PGD is illegal in some countries.

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3. Test characteristics

		genotype or disease	
		present	absent
test	pos.	A	B
	neg.	C	D

A: true positives C: false negatives
B: false positives D: true negatives

sensitivity:	A/(A+C)
specificity:	D/(D+B)
pos. predict. value:	A/(A+B)
neg. predict. value:	D/(C+D)

3.1 **Analytical Sensitivity**
(proportion of positive tests if the genotype is present)
practically 100%
The possibility of preferential amplification of one allele if primers are localised on a SNP or because of deletion exists although these events are exceptional. Classical criteria for determining the pathogenicity of an FBN1 mutation are the following:

- *Nonsense mutation*
- *Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level*
- *Out of frame and inframe deletion/insertion*
- *De novo missense mutation (with proven paternity and absence of disease in parents)*
- *Missense mutation previously been shown to segregate in Marfan family*
- *Missense replacing/creating cysteine (42% of missense mutations)*
- *Missense mutation affecting cbEGF consensus sequence (22% of missense mutations)*
- *Missense mutation involving an highly conserved amino acid (6% of missense mutations)*

For other missense mutations, the search for segregation in family should be performed if possible, as well as the absence of the variant in 400 ethnically matched control chromosomes.

3.2 **Analytical Specificity**
(proportion of negative tests if the genotype is not present)
practically 100%

3.3 **Clinical Sensitivity**
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.
A few studies have addressed the question of clinical sensitivity for FBN1 mutation recognition. Results are variable depending on the method used for mutation screening, but also depending on the set of clinical criteria required for molecular diagnosis. Indeed, a high variable expressivity has been reported in FBN1 mutations and the clinical sensibility is higher when patients fulfilled the Ghent criteria. Results of the more recent studies, including a reasonable number of patients, are as follows:
- Identification of FBN1 mutations in 86/93 individuals presenting with classic Marfan syndrome all fulfilling Ghent criteria (93%), using SSCP and direct sequencing in negative cases (Loeys et al., 2004)
- Identification of FBN1 mutations in 74/81 individuals presenting with MFS or Marfan-like phenotypes (91.35%), using DHPLC (Arbustini et al., 2005)

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- Identification of FBN1 mutations in 69/105 individuals with suspected MFS all fulfilling Ghent criteria (76%), using direct sequencing (Tjeldhorn et al., 2006)
- Identification of FBN1 mutations in 90/110 individuals fulfilling Ghent criteria (82%), in 84/315 individuals with incomplete MFS (27%), in 19/38 individuals with EL (50%) and in 0/45 individuals with isolated ascending aortic aneurysm using SSCP or DHPLC. Mutation rate was higher with DHPLC. For example, in individuals with classical MFS, the mutation detection rate was 91% using DHPLC vs 75% using SCCP (Comeglio et al., 2007)
- Identification of FBN1 mutations in 80/85 individuals fulfilling Ghent criteria (88%) and in 36% of patients with other fibrillinopathies type I using DHPLC (Attanasio et al., 2008)
- Identification of FBN1 mutations in 193/266 individuals fulfilling Ghent criteria (72.5%), in 61/105 with incomplete Ghent criteria (58%) and in 3/21 (14.3%) in patients referred as possible MFS but with no major diagnostic criterion in any organ system (Stheneur et al., submitted).

Some explanations can be given accounting for the imperfect clinical sensitivity for FBN1 mutation screening in MFS:
- Genetic heterogeneity: mutations within the TGFBR1 and TGFBR2 genes have been reported in patients with MFS or suspected MFS (Mizuguchi T, et al., 2004). Sakai et al (2006) found 1 patient with a TGFBR1 mutation out of a series of 49 patients (2%) and 2 TGFBR2 mutations (4%); Màtyàs et al (2006) reported 10 TGFBR1 or TGFBR2 mutations in 70 unrelated individuals with MFS-like phenotypes who were previously tested negative for mutations in FBN1; Singh et al (2006a) found 2 TGFBR1 and 5 TGFBR2 mutations in 41 unrelated patients fulfilling or not the diagnostic criteria of Ghent nosology, in whom mutations in the FBN1 coding region were not identified; Stheneur et al. (2008) found 6 mutations in the TGFBR2 gene and 1 in the TGFBR1 gene in 105 MFS patients and 9 mutations in the TGFBR2 gene and 2 mutations in the TGFBR1 gene in 247 patients with incomplete or probable MFS that were negative for a FBN1 gene mutation. Screening for TGFBR1/2 should be indicated in the first step when one of the following clinical or imaging features is encountered: hypertelorism, bifid uvula, cleft palate, craniosynostosis, clinical features of vascular Ehlers-Danlos syndrome, arterial tortuousity and aneurysms.

- Incomplete detection of mutations with the method used: mutations in the 5' upstream regions (Singh et al 2006b) or intronic mutations (Guo et al., 2008).

3.4 **Clinical Specificity**
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.
Probably 100%, but no data available for this measure

3.5 **Positive clinical predictive value**
(life time risk to develop the disease if the test is positive).
nearly 100%
Exceptional cases of incomplete penetrance have been reported (Buoni et al., 2004).
Of notice, a high number of MFS manifestations are age-dependent. A child with a FBN1 mutation can be identified as at-risk but only present MFS features at a later age.
Although all patients with FBN1 pathogenic mutation will present a clinical feature at some time during life, it is possible that some patients will not fulfil international criteria for MFS throughout life.

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3.6 **Negative clinical predictive value**
(Probability not to develop the disease if the test is negative).
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
nearly 100%

Index case in that family had not been tested:
Predictive testing for family member should only be proposed when a pathogenic mutation has been identified in an index case

4. Clinical Utility

4.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 2.10 "A" was marked)

4.1.1 Can a diagnosis be made other than through a genetic test?

No. ☐ (continue with 4.1.4)
Yes, ☒
clinically. ☒
imaging. ☒
endoscopy. ☐
biochemistry. ☐
electrophysiology. ☐
other (please describe) *+ family history (Ghent criteria, De Paepe et al., 1996)*

4.1.2 Describe the burden of alternative diagnostic methods to the patient
Cardiological (including echocardiography), orthopaedic (including X rays), and ophthalmologic investigations can altogether establish a diagnosis (but not always).
MRI to diagnose/exclude dural ectasia is occasionally necessary to establish the diagnosis, in patients not fulfilling the international criteria with the previously cited investigations. Dural ectasia is present in many other connective tissue disorders, such as Ehlers Danlos or Loeys-Dietz syndrome, so this will not on its own, allow establishing a diagnosis.

4.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?
Unknown

4.1.4 Will disease management be influenced by the result of a genetic test?

No. ☐

Yes. ☒
Therapy (please describe) *Indication of drug therapy or replacement of dilated aortic segments (Keane and Pyeritz. 2008) is similar in patients diagnosed with Marfan syndrome with or without identification of the molecular FBN1 defect. Indeed, since the mutation detection rate is not 100% and the availability of FBN1 screening different from country to country, appropriate treatment should be prescribed for all patients with a clinical diagnosis of MFS.*

Since the presence of a mutation in the FBN1 gene is a major criterion of the international nosology, the

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	genetic result may lead to diagnosis of Marfan syndrome that could have consequences in terms of regular cardiologic follow-up, and prescription of drug therapy for preventing or limiting aortic dilatation.
Prognosis (please describe)	*Similarly, the identification of a FBN1 mutation in a MFS patient will not lead to a different prognosis when compared to patients with MFS but in whom a mutation has not been sought or identified. Nevertheless, there is evidence that patients with TGFBR1/2 mutation need more extensive imaging of the aorta, and in some series, have increased risk for dissection at smaller aortic diameters (Loeys et al., 2006). Therefore, identification of either an FBN1 compared to a TGFBR1/2 mutation could influence prognosis, management and therapy.*
Management (please describe)	*The results of genetic tests will influence genetic counselling by permitting predictive testing of children or paucisymptomatic family members and determining accurate recurrence risk. Rare cases of somatic or germline mosaicism have been reported (Tekin et al., 2007; Rantamaki et al., 1999; Collod-Beroud et al., 1999).* *The identification of a FBN1 mutation might also be helpful in patients not fulfilling clinical Ghent criteria and without aortic manifestations in order to reduce the risk of loss to follow-up (Pepe et al., 2007; Faivre et al., 2008). All cases should be integrated in a multidisciplinary clinic. Preventive medical treatment for aortic dilatation are recommended in patients with the clinical diagnosis of MFS and patients with an FBN1 mutation, even in the absence of aortic manifestations (Keane and Pyeritz. 2008; Faivre et al., 2008), but attitudes could vary between countries through Europe. Indeed, some teams propose to install medical therapy only when regular echocardiograms do demonstrate some definite progressive involvement, arguing that some families with ocular and skeletal manifestations only do not demonstrate cardiac involvement (Lonnqvist et al., 1994).*

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