THE MARFAN FOUNDATION

PROFESSIONAL ADVISORY BOARD STATEMENT ON THE ROLE OF GENETIC TESTING IN THE DIAGNOSIS OF MARFAN SYNDROME

For years, geneticists and cardiologists have taken pride in their ability to identify individuals with Marfan syndrome based on clinical assessment alone, and have minimized a role for genetic testing in the diagnosis. Once the gene *FBN1* was found to be the cause of Marfan syndrome, testing was undertaken to determine the role of genetic testing in the diagnosis of Marfan syndrome and if specific clinical features of Marfan syndrome could be correlated with specific *FBN1* mutations. Mutation identification is now incorporated into the diagnostic criteria for Marfan syndrome and if a *FBN1* mutation is not identified, the diagnosis of Marfan syndrome must be questioned. ("The revised Ghent nosology for the Marfan syndrome." *J Med Genet*; 47:476-485 doi:10.1136/jmg.2009.072785)

Several factors brought about this change in the assessment of individuals being evaluated for Marfan syndrome. First, there are the technical advances: sequence analysis of large stretches can be completed in hours to days instead of weeks; mutational databases allow for correlating specific mutations with clinical features; analysis of deletions and duplications is routinely added when a change in sequence is not identified; the cost of the analysis came down significantly; and health insurers almost always cover the costs. Second, there is the recognition that many individuals initially thought to have Marfan syndrome have mutations in other genes. Mutations in the TGFß receptor genes (*TGFBR1* and *TGFBR2*) were identified in a set of individuals who have Marfan-like features, but who also had some distinguishing findings, such as hypertelorism (eyes far apart) and a bifid uvula. Subsequent identification of mutations in *ACTA2, MYH11, MYLK, PRKG1, SMAD3* and *TGFB2* separated out groups of individuals with aortic disease due to mutations in other genes. Importantly, individuals with mutations in these other genes often need to have their aortic disease managed differently than patients with Marfan syndrome. Additionally, some of these other genes confer a risk for problems with other arteries that patients with Marfan syndrome do not have.

The costs for genetic testing are rapidly decreasing. Genetic analysis of the FBN1 gene currently costs about $1,500 and takes about 3 weeks. Most people with Marfan syndrome have changes that alter only one or a few of the building blocks of the gene and these are readily identified. Some, however, have mutations that delete or duplicate large blocks of the gene. These mutations are not detected by the current sequencing strategies and additional testing has to be done, which can add another 2–3 weeks. Once a mutation is identified in one individual in the family, all other family members at risk (parents, siblings, children) can be tested inexpensively, for about $250 each, because each affected family member will have the same alteration or mutation in the gene. Genetic testing of family members at risk can identify those family members who have the mutation from those who do not, which is powerful information for the family. Family members with the mutation can be screened and followed for aortic disease to prevent aortic dissections. Family members without the mutation do not need to be screened for aortic disease. Indeed, the cost for imaging to screen for aortic disease is much greater than the cost of genetic testing. Currently echocardiography costs $2,000 per study and computerized tomographic angiography (CTA) or magnetic resonance angiography (MRA) may cost $5,000 or more.

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What benefit does genetic testing have for the individual? In the face of an apparently clear-cut diagnosis of Marfan syndrome (skeletal findings compatible with the diagnosis and lens subluxation, for example), does testing add anything? In some situations, the answer is a resounding yes. For example, one mutation that substitutes an arginine at position 233 of the fibrillin protein with a cysteine (Arg233Cys) is seen in people with lens subluxation and marked skeletal alterations, but their aorta tends not to enlarge or enlarges extremely slowly over a very long period. Any treatment would appear to have been remarkably successful if we did not know, in advance, the impact of this mutation. Furthermore, these individuals would be subject to multiple rounds of surveillance of their cardiovascular tree for no gain in the absence of genetic testing. Additionally, the differentiation between Marfan syndrome and Loeys-Dietz syndrome may not be apparent on clinical grounds, but it can be readily made with genetic testing. Yet, correctly diagnosing an individual with Marfan syndrome or Loeys-Dietz syndrome makes a difference in the management of the aortic aneurysms and dictates the amount of imaging needed of other arteries. Given these considerations, and the vital role genetic testing plays in the distinction between different Marfan-like conditions, there is little wonder that mutation analysis has become a key element the diagnosis of Marfan syndrome.