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Commentary: Moving beyond phenotypic diagnosis

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French pediatrician Antoine Marfan first described the syndrome that bears his name in 1896, observing the physical traits of a young patient. Over time, it became clear that these characteristics could run in families or could appear de novo. Marfan remained a clinically diagnosed syndrome—a constellation of traits—until 1991, when it was conclusively associated with defects in *FBN1*,¹ the gene encoding extracellular matrix protein fibrillin-1. Five years later, the Ghent nosology for clinical classification² added consideration for molecular testing. The 2010 revised Ghent criteria³ give greater weight to genetic testing but remain primarily based on phenotypic trait assessment.

In 2010, state-of-the-art genetic testing meant examining a patient's DNA for the presence or absence of specific mutations known to cause disease. This was a reasonable strategy when searching for the most common mutations, but many patients with less-common mutations were undoubtedly missed. Now, for a few hundred dollars, we can obtain the complete sequence of every protein-coding gene in the patient's entire genome. Known as whole-exome sequencing, this technology enables detailed analysis of both the gene of interest (*FBN1*) as well as related genes (eg, *FBN2*, *TGFBR1/2*). With information this specific, we may eventually understand the molecular basis for the pleiotropic effects of diseases like Marfan syndrome.

In their case report, Brahmandam and Vallabhajosyula⁴ used whole-exome sequencing to identify a novel and rare fibrillin mutation in 2 adult patients. Mother and son

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CENTRAL MESSAGE

Whole-exome screening is a powerful and cost-effective tool allowing clinicians to readily identify rare genetic mutations with meaningful implications for patients and their families.

displayed distinct aortic pathologies but serendipitously presented at the same time to the same treatment team. Neither patient had clinical features of a connective tissue disorder. Neither patient had Marfan syndrome according to the revised Ghent criteria. Only a few years ago, testing strategies would likely have missed this rare variant in *FBN1* and the familial connection it indicates. Fortunately, both patients received the medical and surgical therapies needed to restore their health. Family screening may result in even greater benefits.

Our tools now far exceed the visual observations that once characterized medical diagnosis. We can literally look inside a patient's DNA and examine the variations that both make that patient unique and that put them at risk. We can do this for approximately the same price as a computed tomography scan. The need for complex aggregate phenotypic labeling has passed. What we need now is a 21st-century system for risk stratification and identification of patients—and their families—who benefit from screening for treatable conditions. We have amazing diagnostic and therapeutic implements at our disposal. Let's use them!

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