Understanding the crucial role of genetic testing and counseling in Fabry disease

Prepared with the assistance of Staci Kallish, DO, University of Pennsylvania.

How and when to use genetic testing in the diagnosis of Fabry disease

- Genetic testing is the standard for diagnosis and management of Fabry disease[1-4]

- Genetic testing to identify a pathogenic *GLA* variant is required to diagnose Fabry disease in females[1-3]
- Testing for alpha-Gal A enzyme activity in females is inconclusive because they may have alpha-Gal A levels within the normal range[1-3]

- Although enzyme activity is diagnostic in males, genetic testing to identify the pathogenic variant[2-4]:
  - Provides a definitive diagnosis
  - May help in disease management

When to consider genetic testing for Fabry disease

- Patients may present with symptoms in multiple organ systems or in as few as a single organ[1]

Frequent signs and symptoms of Fabry disease[1-3]

	Neuropathic pain; tingling or burning pain in the extremities; heat and cold intolerance; dyshidrosis (hypohidrosis and hyperhidrosis)[1,3]		Impaired heart rate variability; arrhythmias; ECG abnormalities (shortened PR interval); left ventricular hypertrophy; angina; dyspnea[1]
	Microalbuminuria, proteinuria; decreased kidney function[1]		Angiokeratomas (dark red spots, typically between the navel and knees)[1]
	Nausea, vomiting; diarrhea; postprandial bloating and pain; early satiety; difficulty gaining weight[1]		Patients with Fabry disease may have relatives with unexplained kidney failure, stroke, or heart disease[2,3]

These are not all the possible symptoms of Fabry disease.

Considerations before genetic testing

- Identify and partner with a genetics professional, such as a geneticist or genetic counselor, who is easily accessible to you and your patient. They can assist both you and your patient along the journey
  - More information about identifying genetics professionals can be found on the reverse side
- Consider using genetic testing services from a testing kit provider, which simplifies logistics
- Set expectations for your patients before testing can occur. Your genetics partner can help

Potential results of genetic testing

Result	Likely next steps
Positive test: detection of pathogenic *GLA* variant	Baseline assessment of the patient for clinical manifestations of Fabry disease; management of the disease[4]
Negative test: no pathogenic *GLA* variant	Consider other potential causes of the observed signs and symptoms[3]
Indeterminate test: variant of unknown significance (VUS)—may or may not be a cause of Fabry disease	Consultation with a clinical genetics professional is recommended[4]

Alpha-Gal A, alpha-galactosidase A; ECG, electrocardiogram; *GLA*, galactosidase alpha gene.

Choosing and ordering a genetic test

A variety of tests are available from commercial and academic providers

- **Broad tests (multigene panels)** are designed to search for a number of variants associated with multiple genes or diseases,[5] for example:
  - Progressive renal diseases[6]
  - Cardiomyopathy and arrhythmia[7]

- **Broad tests** can identify a range of variants but may:
  - Uncover a disease or disease-causing variant that was unexpected or not the cause of the patient's symptoms[5,8]
  - Identify one or more VUSs, which may require additional interpretation or testing[8,9]
  - Incur additional costs for patients[9]

- **Narrow (single-gene) tests** are designed to identify variants in a specific gene,[5] such as *GLA*

- The choice of test may depend on information available about the specific patient
- Interpretation will be provided by the test provider with the results

Practical issues

- Requirements for tissue samples (eg, blood, saliva, buccal swab) and shipping methods vary among test providers
- Information will be available from the test providers on their requirements

Considerations after genetic testing

- Additional testing may be required
- Treatment is available when indicated
- Expert help is available to provide coordination of care

Medical genetics specialists	Genetic counselors
• Patients with Fabry disease require multispecialty evaluation, monitoring, and care[4] • Consultation with a specialized center is recommended[4] • Medical geneticists are available in many areas and can be found at clinics.acmg.net	• Patients with Fabry disease will likely have many questions about the implications for family members and other issues[3] • Testing of other family members may be considered after consultation with a genetic counselor, which is a standard of care in Fabry disease[3] • Genetic counselors can be found at findageneticcounselor.nsgc.org or www.abgc.net/about-genetic-counseling/find-a-certified-counselor.aspx

References: 1. Germain DP. Fabry disease. *Orphanet J Rare Dis.* 2010;5:30. **2.** Gal A, Hughes D, Winchester B. Toward a consensus in the laboratory diagnostics of Fabry disease – recommendations of a European expert group. *J Inherit Metab Dis.* 2011;34(2):509-514. **3.** Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2013;22(5):555-564. **4.** Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab.* 2018;123(4):416-427. **5.** Medline Plus. Genetic testing. Accessed December 16, 2021. https://medlineplus.gov/download/genetics/understanding/testing.pdf **6.** Invitae. Invitae progressive renal disease panel. Accessed December 16, 2021. https://www.invitae.com/en/physician/tests/75000/?cat=CAT000262 **7.** Invitae. Invitae arrhythmia and cardiomyopathy comprehensive panel. Accessed December 16, 2021. https://www.invitae.com/en/physician/tests/02101/?cat=CAT000001 **8.** Winder TL, Tan CA, Klemm S, et al. Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. *Neurol Genet.* 2020;6(2):e412. **9.** Adams VA, Barnett R, Kaylor J, See T. Insights and considerations for large panel genetic tests. Accessed December 16, 2021. https://informeddna.com/insights-and-considerations-for-large-panel-genetic-tests

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