The Importance of Early Diagnosis, Testing, and Recognition of Unusual and Heterogeneous Symptoms and Hallmarks of Fabry Disease Across Multiple Clinical Specialties

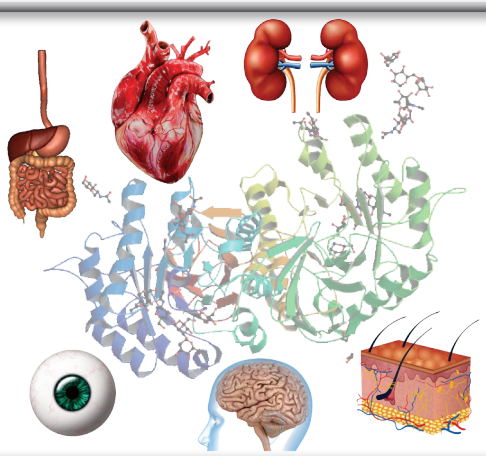
A Year 2020 Diagnostic, Assessment, and Fabry Disease Management Update for the GI, Neurological, Renal, CV, Dermatologic and Clinical Genetics Specialist

iQ&A Fabry Disease Diagnostic Intelligence Zone

A Year 2020 Testing-to-Treatment Best Practice Update

The Importance of Early Diagnosis, Testing, and Recognition of Unusual and Heterogeneous Symptoms of Fabry Disease Across Multiple Clinical Specialties

Focus on Cardiovascular, Renal, Neurological, Gastrointestinal, and Dermatologic Manifestations and Hallmarks of FD



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QUESTION #1: What are the characteristic angiokeratoma skin lesions and dermatologic hallmarks associated with Fabry Disease (FD)? At what age do they present? In what distribution? And with what other conditions might they be confused in the differential diagnosis?

QUESTION # 2: At what point in the natural history of FD do the dermatologic manifestations of FD appear? And to they tend to appear prior or after other collateral manifestations—for example, GI symptoms or acroparesthesias—or are they usually co-existent with other physical and symptomatic manifestations of FD?

QUESTION # 3: What is the pathophysiology of the angiokeratomas and telangiectasias seen in FD, what is the typical distribution of these lesions—in male versus female patients—and with what other conditions might these hallmarks of FD be confused?

QUESTION # 4: How often are the dermatologic manifestations of FD the portal of entry into the diagnosis of this condition, and what is the role of the dermatologist for ensuring the diagnosis of FD is made as early as possible?

QUESTION # 5: What is the natural history of FD dermatologic lesions over time? Do the angiokeratomas and telangiectasias evolve, change distribution, or regress over time? What is the differential diagnosis? What does a biopsy show in FD?

QUESTION # 6: What is the differential diagnosis of the angiokeratomas and telangiectasias that are characteristic of FD? With what other conditions might these lesions be confused?

QUESTION #7: What are the ophthalmologic findings of FD and how are they temporally related to the dermatologic manifestations of FD?

QUESTION #8: When you encounter angiokeratomas that you think are characteristic of FD, what is your next step in the diagnostic process? Do you routinely biopsy the lesions? What are the characteristic findings, and do you do genetic testing?

QUESTION #9: From a dermatologist's perspective, why is it important to make the diagnosis of FD? What therapeutic action steps can be taken if the diagnosis is confirmed? And what role can the dermatologist play in potentially preventing the development of more significant target organ involvement?

QUESTION #10: What percentage of patients with FD actually have dermatologic manifestations?

QUESTION #11: If FD disease is diagnosed by a dermatologist during childhood or adolescence, what is the therapeutic/management/referral roadmap in this patient population? How do you approach the multidisciplinary nature of this condition?

QUESTION #12: What can dermatologists do to raise awareness of FD and ensure the diagnosis is confirmed

John Jefferies, MD, MPH

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QUESTION #13: What is the spectrum of cardiovascular manifestations of FD? What is the age of onset? And how is the presentation variable in men and women? Why is it important that we recognize the cardiovascular clinical phenotypes—arrhythmias, hypertrophic cardiomyopathy, stroke, etc.—of FD?

QUESTION #14: What surveillance strategies, in the context of cardiovascular disease, optimize early detection, assessment, and monitoring of patients with suspected or confirmed FD?

QUESTION #15: How does the underlying pathophysiology of Fabry, as a lysosomal disorder, produce the wide range of cardiovascular manifestations that should alert physicians to suspect FD as an underlying cause for unexplained CV symptoms and findings in men and women?

QUESTION #16: Given the new therapies—including chaperone therapy with migalastat and ERT—available for FD, and the progressive, multi-organ impact of this lysosomal disorder, why do you believe there should be a "call to action" among the CV specialist community that would heighten awareness of this disease?

QUESTION #17: What is the rationale for disciplined surveillance systems for FD patients with either asymptomatic CV or those in whom the diagnosis has been confirmed? And what evidence do we have that treatment of FD with either chaperone therapy or RT can slow progression of either myocardial dysfunction (cardiomyopathy/HF of FD) or frequency of arrhythmias?

QUESTION #18: Are there prospective studies that, in fact, are designed to evaluate the effects of currently approved chaperone- and ERT-based treatments for FD on the progression of CV complications of FD?

QUESTION #19: Although GI and dermatologic manifestations tend to dominate the clinical phenotype of FD in childhood, are there cardiovascular manifestations—i.e. arrhythmias—in this subgroup that might point to the disease? And what triggers for screening do you employ?

QUESTION #20: How do the CV manifestations of FD disease change and/or present during adolescence? And what is the role of cardiac MRI in this age group and how does it help you identify the FD phenotype?

QUESTION #21: What are the CV manifestations of FD disease in the adult population and how does the triad of arrhythmias, early MI, and/or cardiomyopathy set into motion diagnostic tests and surveillance strategies to evaluate the presence of FD as the underlying etiology for these cardiac abnormalities?

QUESTION #22: Because awareness of FD may be low among CV specialists, there is sometimes a preconception that women, who are "carriers" for FD, do not suffer from its CV complications and the diagnosis, therefore, is missed or delayed with adverse consequences? Can you elaborate on this?

QUESTION #23: Can you provide a roadmap for cardiologists that sets out a disciplined approach for detecting, screening, and diagnosing patients they see in their practice who present with specific findings, family history, and/or a characteristic clinical phenotype—hypertrophic cardiomyopathy, in particular—suggestive of underlying Fabry Disease?

QUESTION #24: What guidance can you give your cardiologist colleagues to enhance detection of patients with FD? What collateral co-morbidities should be investigated? And how is your management strategy changed if the diagnosis of FD is confirmed?

Professor Alberto Ortiz, MD

Chief of Nephrology and Hypertension
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QUESTION #25: Can you summarize the pathophysiology and pathobiology of renal impairment, and associated findings—in particular, albuminuria—on renal function testing, in the setting of Fabry Disease, and why it's critical for nephrologists, internists, primary care physicians and related specialists to be aware of the renal manifestations of FD?

QUESTION #26: What is the role of lysosomal and extralysosomal globotriaosylceramide (Gb3) accumulations in the pathology—including, as soluble, circulating mediators—of renal disease in FD? And what are the common pathobiological features in the nephropathy of FD and that found in diabetic kidney disease?

QUESTION #27: What are the key diagnostic parameters—specifically, urinary and related renal biomarkers, including albuminuria and creatine—that should increase awareness of and prompt evaluation and further genetic testing for Fabry disease? And how often is renal disease the first manifestation of FD, how does penetrance differ in males and females?

QUESTION #28: How early in childhood are the renal manifestations present in classic Fabry in males? What is the natural history of renal dysfunction and what specific metrics related to albuminuria/proteinuria should be followed and increase suspicion of FD?

QUESTION #29: Can you construct a diagnostic roadmap—including family history, symptom complexes, and/or biomarker manifestations—for the nephrologist that will optimize detection of FD at the front lines of practice? What are the clinical phenotypes that merit our attention and what other conditions may complicate the differential diagnosis?

QUESTION #30: What is your systematic, step-by-step diagnostic work-up for a young/adolescent male in whom the diagnosis of FD must be considered and/or ruled out? What genetic tests should be performed? Should this be the standard diagnostic work-up of every patient with proteinuria? Are there differences in how these genetic tests should be interpreted in male vs female patients?

QUESTION #31: If initial genetic tests or the clinical picture—proteinuria, family history, no evidence of diabetes—suggest FD, what is the next level of diagnostic genetic tests, i.e. mutational testing, that should be performed? And why is this important and how might it influence your approach to therapy?

QUESTION #32: Is there a relationship between Gb3 levels and renal Fabry Disease and what is the relationship between Gb3 levels in the classic variant of FD?

QUESTION #33: Do all patients with FD have the same propensity to develop Fabry renal disease, and how does the male/female incidence discordance help us make the diagnosis? And what is the role of the severity of the mutation in determining the natural history of kidney disease in FD?

QUESTION #34: Once the diagnosis of Fabry renal disease is suspected or confirmed, what other target organs, in addition to the kidney, should be evaluated to corroborate the diagnosis? What is the natural history of FD and what is its relationship to the severity of the mutation? What is the "pathologic march" of FD and what is the sequence of target organ deterioration in males with classic disease vs. females?

QUESTION #35: Why is it important—the mandate, in fact—to diagnose FD, and what is the current evidence and/or expert consensus about the use of either chaperone therapy with migalastat or ERT to mitigate progression of FD in the kidney and in other target organs?

QUESTION #36: Can you summarize the current guidelines and/or recommendations from Europe and the U.S. for diagnostic evaluation and treatment of FD?

Robert J. Hopkin, MD

Associate Professor of Clinical Pediatrics
Cincinnati Children's Hospital Medical Center
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QUESTION #37: Can you provide a synopsis of the inheritance patterns of Fabry Disease, the penetrance of target organ manifestations and symptomatology in men vs. women, and the diagnostic implications of the heterogeneity of this Fabry?

QUESTION #38: What is the underlying pathobiology of this lysosomal disorder, and how does the presentation differ in men and women?

QUESTION #39: To improve awareness, suspicion, and diagnostic accuracy for Fabry Disease, can you discuss the expected manifestations of FD based on gender and age? And how do the clinical phenotypes and symptoms segregate among different patient subgroups? Can you provide a detailed sequence of symptom evolution that characterizes the natural history of FD?

QUESTION #40: Because many of the symptoms, complaints, and manifestations of FD can overlap with other conditions, in what age groups should the clinician be alert for the patterns you describe in order to improve detection and mutational testing for Fabry?

QUESTION #41: Given the heterogeneity of symptoms—especially GI, pain, acroparesthesias, and neurological—that herald the initial onset of Fabry Disease, as well as overlap of Fabry symptoms with those that characterize other entities, what counsel can you give clinicians to test for FD and/or distinguish Fabry from other conditions that make early diagnosis challenging?

QUESTION #42: Although acroparesthesias in childhood represent a well-documented symptom portal for triggering diagnostic consideration of and/or testing for FD, what other corroborative manifestations and familial, historical features of FD should clinicians inquire about to solidify their suspicion for the diagnosis?

QUESTION #43: What is your systematic line of inquiry and evaluation strategy for diagnosing Fabry Disease, both (a) in patients who present with the classical constellation of symptoms as well as (b) those who present in a more nuanced, non-specific manner, thereby making the diagnosis of FD more elusive and challenging?

QUESTION #44: Once you determine that a male or female patient's symptoms and/or physical manifestations are consistent with a diagnosis of Fabry Disease, what disciplined, systematic approach to you use to genetic, mutational testing?

QUESTION #45: What exactly are the symptomatic, age of onset, and enzymatic activity criteria that discriminate between so-called "classical" vs "non-classical" Fabry Disease? And is there a further delineation of these two groups based on gender? Or variants of the disease linked to specific target organ manifestations?

QUESTION #46: If a clinician wishes to confirm the diagnosis of FD, what is the systematic roadmap to ensure the appropriate biomarkers and genetic information have been obtained with enzymatic activity and/or genetic (sequencing) tests? And why is genetic testing, specifically, valuable for selecting between treatment alternatives, i.e., chaperone therapy vs. ERT?

QUESTION #47: In patients with FD, how do use genetic testing and results of enzyme activity levels of alpha-galactosidase A (a-Gal A) to determine whether oral chaperone therapy with migalastat vs. IV ERT is best suited for an individual patient? What is the importance of evaluating a specific mutation's potential for having significant residual enzyme activity and what levels of such enzyme activity are required to meet the threshold for chaperone therapy?

QUESTION #48: What category of mutation—one that is associated with some degree of production of the alpha-galactosidase A (a-Gal A) enzyme—is amenable to the FDA-approved oral chaperone therapy, migalastat? How should clinicians translate mutational results—deletion vs. mis-sense mutations—to the front lines of Fabry Disease?

QUESTION #49: Can you provide a "real world" example of a patient and associated family members with Fabry Disease that you have treated and that illustrates the clinical decision tree that traces the journey from mutational testing to selection of optimal therapy? How do sort out the pros and cons of each kind of therapy?

QUESTION #50: Given the availability of new agents to treat FD, the severity of target multi-target organ disease, and a growing body of evidence that enzyme-focused treatment—whether chaperone or direct replacement approaches—might mitigate progression of FD, what is the rationale for suspecting and confirming the diagnosis of Fabry Disease? What do the U.S. and European Guidelines recommend as far as timing of intervention for FD?

QUESTION #51: Are there registry or prospective trial data showing that early treatment of FD improves clinical outcomes? How well do the dots connect?

QUESTION #52: What have long-term registries taught us about the effects of treatment on mitigating risk and/or progression of target organ deterioration—in particular, of cardiac disease, need for kidney replacement, and/or stroke—in patients with FD?

QUESTION #53: What specific symptom-related issues, especially late complications of FD, such as stroke, are being assessed in relation to impact of therapy on disease progression?

QUESTION #54: After the diagnosis of FD has been confirmed, and genetic mutational signatures have been generated—and enzyme activity levels measured—at what age can available therapies be started? And how long should patients be treated?

QUESTION #55: How do the presentations of Fabry Disease differ in men and women? And what are the implications for how the disease should be treated in each gender?

QUESTION #56: What is the underlying cause of the "Failure to Diagnose" Syndrome as it relates to "classical" Fabry Disease? And given our improved understanding of clinical phenotypes, inter-gender differences, and natural history of the disease, why are clinicians—including subspecialists—failing to diagnose and test for FD at a time point when treatment interventions can potentially make a difference in patient outcomes and survival?

QUESTION #57: What are the challenges of diagnosing "non-classical" Fabry Disease in the adult population? What is the importance of testing all patients with unexplained, progressive renal disease and hypertrophic cardiomyopathy?

QUESTION #58: To whom should patients with confirmed FD be referred? What is the ideal way to follow these patients? And what is the role of the clinical geneticist? Is a multi-disciplinary approach preferred?

QUESTION #59: Can you discuss the diagnostic and clinical importance of lymphedema as a manifestation of FD? What is the etiology of lymphedema in FD?

Heather A. Lau, MD

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QUESTION #60: What are the initial neurological manifestations of Fabry Disease as they present in childhood and adolescence?

QUESTION #61: How do the neurological symptoms—in particular, acroparesthesias, hyperhidrosis, and their triggers—of classical FD present in male vs female populations, and what other concurrent symptoms should the clinician inquire about to corroborate the diagnosis?

QUESTION #62: What is the neuropathobiology of alpha-galactosidase A deficiency and how does this enzyme deficiency produce these heterogeneous neurological symptoms?

QUESTION #63: What is the pattern of progression of neurological symptoms of Fabry Disease?

QUESTION #64: Can you share with as an example of a patient who was ultimately diagnosed with Fabry Disease on the basis of neurological symptoms—including acroparesthesias—and why the diagnosis was almost missed initially, as it so often is in childhood and adolescents?

QUESTION #65: Why do the heterogeneous neurological manifestations make the diagnosis extremely challenging? Do all patients with FD either present with or eventually develop such neurological symptoms as acroparesthesias?

QUESTION #66: How often is cryptogenic stroke or early onset stroke a marker of Fabry Disease in the young adult population, and what is the etiology of this neurological manifestation? What does registry data teach us about the incidence of stroke in male and female patients with FD, and what are the diagnostic implications for neurologic specialists?

QUESTION #67: Can you discuss some of the less well appreciated manifestations of Fabry Disease—vestibular dysfunction, hearing loss, and autonomic dysfunction—and how their presence can aid in making the diagnosis of Fabry Disease?

QUESTION #68: Why is it important to recognize the neurological manifestations of FD? And what advantages accrue to the patient from early diagnosis? In which target organs affected by FD can we potentially ameliorate disease progression and why is recognition of the neurological symptoms particularly important?

QUESTION #69: What specific, additional testing—enzyme activity levels and/or genetic mutational assessment—is required in patients who present with neurologic symptoms characteristic of Fabry Disease? And to whom should such patients be referred for diagnostic confirmation and treatment?

QUESTION #70: Why is confirmatory, genetic testing mandatory for helping clinicians identify therapeutic agents that are best suited for an individual patient? And to determine whether a mutation is amenable to chaperone therapy?

QUESTION #71: Can you summarize the central importance of the neurological symptoms, findings and complications of FD and how their early recognition can aid in prompt, definitive diagnosis, initiation of treatment, and therefore, mitigate progression of disease in other target organs?

Claire Zar-Kessler, MD

Medical Director, Pediatric Neurogastroenterology Program
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QUESTION #72: Since a heterogeneous range of gastrointestinal symptomatology is associated with Fabry Disease, can you discuss the spectrum of symptoms that are encountered, how often they represent the initial presentation of FD, at what age they manifest, and finally, are there gender-specific patterns in GI symptomatology that can improve diagnostic detection of this lysosomal disorder?

QUESTION #73: What are the specific GI symptoms encountered in patients with FD? And what specific symptom patterns should alert the clinician that FD should be excluded in the differential diagnosis? From a frontline perspective, what can the GI specialist do to tease out the etiology of these non-specific GI symptoms and link them to FD?

QUESTION #74: At what age can FD-consistent GI manifestations first emerge? What is the most frequent misdiagnosis of GI symptoms that, in retrospect, were the first signs of FD in an individual patient? Is linking these non-specific GI manifestations—abdominal pain, diarrhea, IBS-like complaints, and nausea—to the diagnosis of FD more problematic in pediatric patients or in the adult population?

QUESTION #75: What is the differential diagnosis of the non-specific GI symptoms reported by patients with FD, and what entities must be systematically excluded as part of the work-up for the non-specific manifestations of FD? And if the diagnosis is missed based on GI symptoms, what is the most common misdiagnosis to which these symptoms are ascribed? And what is the natural history of the GI symptoms in Fabry Disease, from childhood to adulthood?

QUESTION #76: Can you focus on the earliest age group in which GI symptoms of FD can plausibly be detected? And what corroborative information should the clinician seek from the patient to link abdominal pain, diarrhea and nausea with the lysosomal disorder of Fabry Disease?

QUESTION #77: How does deficiency of the lysosomal enzyme, alpha-galactosidase A lead to GI symptoms? What is the GI-related pathobiology of Fabry Disease? Through what vascular, tissue, and neuropaths mechanisms does GL-3 accumulation cause GI symptoms?

QUESTION #78: Is there evidence that treatment of Fabry Disease—either with migalastat-based chaperone therapy or ERT—is capable of mitigating progression of GI symptoms?

QUESTION #79: Other than ERT and chaperone therapy, what other pharmacologic interventions are effective and safe for treating the GI symptoms of FD?

QUESTION #80: Can you discuss a specific adult patient who came to you with GI symptoms and confirmed Fabry Disease, in whom therapeutic intervention improved their GI manifestations and quality of life? Typically, do you supplement enzyme-focused treatment—chaperone therapy or ERT—of Fabry with other pharmacologic therapy to optimize clinical results?

QUESTION #81: How often are GI symptoms the primary portal for clinically entertaining and confirming the diagnosis of Fabry Disease? How do you balance the proclivity or need to do wider screening for FD based on GI symptoms against the potential improvements in diagnosis that will accrue only from increasing awareness?

QUESTION #82: With respect to screening for FD in the pediatric age group, what features of the family history should be elicited in order to guide the diagnostic evaluation, including enzyme activity levels and genetic testing? Should FD be part of the newborn screen?

QUESTION #83: Based on Registry Data for Fabry Disease, what have we learned about the importance of GI symptoms—including gender-based differences—in the context of improving awareness of FD as a condition for which we should screen and as a gateway toward more precise patient identification and genetic testing for Fabry Disease?

iQ&A **Fabry Disease Diagnostic Intelligence Zone**

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Recognizing Unusual, Early, and Difficult-to-Characterize Symptoms and Manifestations of Fabry Disease: Focus on Cardiovascular, Renal, Neurological, Gastrointestinal, and Dermatologic Manifestations and Clinical Hallmarks

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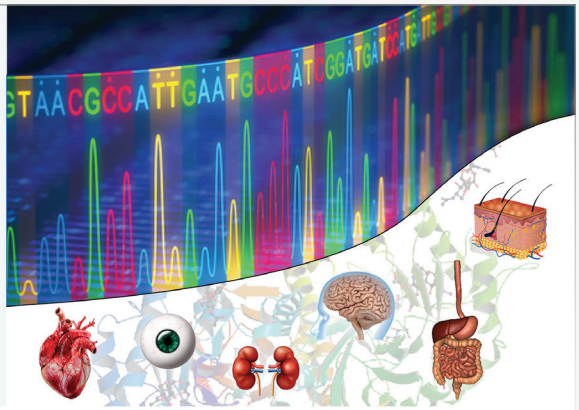

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ACCESS RESOURCES AND TRIALS IN FABRY DISEASE

ABOUT THIS PROGRAM AND FACULTY DISCLOSURES