

2016 Canadian Fabry Disease Guidelines

**Canadian Fabry Disease Treatment Guidelines 2016**

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Fabry disease is an X-linked lysosomal storage disease characterized by the development of hypertrophic cardiomyopathy, nephropathy with chronic renal failure and stroke. This condition arises from the deficiency of the lysosomal enzyme alpha-galactosidase A with the resultant accumulation of glycosphingolipids in all cells and tissues. This deposition damages and kills cells resulting in premature death and disability, particularly for affected hemizygotes. Treatment for all patients involves control of cardiovascular risk factors and supportive care for issues related to living with a chronic disease; disease specific treatment with enzyme replacement therapy (ERT) may have benefit for some individuals. Recombinant human alpha-galactosidase A enzyme is available in two forms, agalsidase-alfa (Replagal™eShire Human Genetic Therapies Inc.) and agalsidase-beta (Fabrazyme® Sanofi-Genzyme Corporation). Clinical guidelines for the use of ERT in Canada were first developed in 2005 by an expert committee based upon the medical literature and this process has been repeated annually since 2007.

These Fabry disease treatment guidelines currently form the basis for ERT in Canada, specifically in the multicentre Canadian trial of ERT in Fabry Disease, known as the Canadian Fabry Disease Initiative (CFDI). These guidelines are intended to apply to all patients with Fabry disease in Canada regardless of gender and age.

## **Participants**

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Disclosures for all participants are included below.

## **Process**

Annual literature review has been conducted since the onset of the CFDI to inform the guideline process; for the 2016 guidelines, available literature on Fabry disease published from June 1 2014 to March 31 2016 was determined by an electronic search of Medline and Pubmed using the search terms Fabry and Fabry disease limited to abstracts, English language and research articles in humans. A list of the articles reviewed in 2016 is provided in Appendix 1. Single case reports and review articles were not included in the review unless new information was presented. Standards of evidence were modified from those previously published (Canadian Task Force on the Periodic Health Examination 1979; see Table 2). Consensus was reached by discussion.

## **Support**

Financial support for this guideline review was from the Canadian Fabry Disease Initiative study.

## **Diagnosis of Fabry disease**

The diagnosis of Fabry disease requires the synthesis of clinical, biochemical, molecular and pathologic criteria. Given the challenges with each of these criteria outlined below, it is recommended that a patient have at least 3 of the 4 criteria before making a diagnosis of Fabry disease (van der Tol 2014) although if characteristic pathological findings are present, fewer criteria may be required to point to the correct diagnosis.

### **a. Clinical criteria**

- i. None of the features of classical Fabry disease are diagnostic in their own right. Some features of Fabry disease (for example, nephropathy, hypertrophic cardiomyopathy, stroke) are very nonspecific with a broad differential diagnosis. Other features of Fabry disease (like corneal verticillata, biopsy-proven angiokeratomas) have a more limited differential diagnosis although there are still conditions other than Fabry disease which can cause these more specific findings (for example, amiodarone therapy can cause similar corneal changes). For this reason, clinical findings alone cannot be used to confirm the diagnosis of Fabry disease although more weight can be given in the diagnostic process to those findings (corneal verticillata, biopsy proven angiokeratomas) of higher specificity.

### **b. Biochemical criteria**

- i. Levels of alpha-galactosidase activity measured in whole blood, plasma or leukocytes that are severely decreased or absent (below 5% of the mean) are strongly suggestive of Fabry disease. However, higher levels have been reported in many confirmed cases and are more likely in those patients presenting with a late onset cardiac variant. Women with Fabry disease may also have enzyme activity levels that are not severely decreased (or even normal) despite other clear manifestations of Fabry disease. The presence of reduced levels of enzyme activity in a related male in

the kindred should be sought as strong evidence that Fabry disease is present. However, the absence of low enzyme activity in a male does not rule out this diagnosis in the kindred.

Documentation of reduced levels of alpha-galactosidase activity is the preferred biochemical marker to use in the evaluation of a patient for possible Fabry disease. The absence of reduced levels of enzyme activity in a male in the cohort is strong evidence that Fabry disease is not present.

- ii. Biomarkers in urine and plasma such as globotriaosylceramide (Gb3) and sphingosine-globotriaosylceramide (Lyso-Gb3) are often elevated in patients with Fabry disease although the correlation of these biochemical markers with clinical outcomes remain unclear. Conditions other than Fabry disease can cause elevations in urine Gb3 (Schiffmann 2014). Lyso-Gb3 is a more sensitive marker than Gb3 but still may be normal in confirmed cases, especially in women. The presence of elevated biomarkers then can be used as a feature pointing towards Fabry disease but is not diagnostic but the absence of elevated biomarkers does not rule out a diagnosis of Fabry disease.

### **c. Molecular criteria**

- i. Previously reported mutations - There are databases of mutations which have been found in confirmed cases of Fabry disease. However, it is known that there is a high rate of inaccuracy in these databases with one study suggesting that up to 27% of variants annotated as being disease associated were incorrect (Bell 2011). For this reason, the presence of a DNA change that has been reported to cause Fabry disease cannot be used alone to make the diagnosis but rather must be combined with clinical, biochemical and pathological criteria
- ii. Variants of uncertain significance (VUS) – For DNA changes which have not been previously reported, there are several models which are often used to try and predict pathogenicity but the accuracy of any of these models is limited with most models correctly predicting that a variant is benign or pathogenic in fewer than 80% of the cases (Walters-Sen 2015). Modeling of VUS in cell lines or other systems can be done by some research labs but is not widely available. The presence of a VUS then should not be used as a

diagnostic criterion for Fabry disease consistent with current consensus guidelines (Richards 2015).

**d. Pathologic criteria**

- i. Characteristic changes suggestive of Fabry disease can be found on biopsies of kidney, heart, skin and other tissues. However, in most centers, while a pathologist may be able to identify that storage material is present, they will not be able to characterize the nature of the storage material without doing specific immunohistochemical stains for Gb3, a tool that is not widely available. Also, phenocopies of Fabry disease have been reported where Gb3 storage was documented in tissue (Appelland 2014). Thus, while the finding of characteristic changes in a biopsy is strong evidence for a diagnosis of Fabry disease, it should be combined with at least one other diagnostic feature from the biochemical or molecular categories before confirming the diagnosis). Biopsy of clinically affected tissues can also provide useful prognostic information (such as irreversible changes like the degree of glomerulosclerosis in patients with nephropathy or the degree of fibrosis on a heart biopsy) and it is strongly encouraged that biopsy of clinically involved tissues be obtained as part of the work up for patients with Fabry disease. Skin biopsy, while not useful in providing prognostic information, can sometimes help in the diagnostic process (if read by an experienced pathologist) by documenting the presence of storage material and is easily accessible and only minimally invasive.

A summary of these diagnostic criteria is provided in Table 1 below.

**Table 1. Summary of diagnostic criteria for Fabry disease\***

<b>Criterion</b>	<b>Relevant finding</b>	<b>Points towards diagnosis</b>	<b>Comment</b>
Clinical features	Corneal verticillata or biopsy-proven angiokeratomas	Presence of either or both of these will contribute 1 point	Need to exclude other causes
Alpha-galactosidase activity	Below 5%	1 point	Activity may not be reduced in females but low activity in a male member of the family cohort would contribute towards the diagnosis
Elevated biomarkers	Above reference range for lab; lyso-Gb3 is preferred	1 point	Conditions other than Fabry disease can elevate biomarkers
Molecular change	Mutation defined in literature as disease causing	1 point	High rate of error in annotation of mutations in available databases; the presence of a VUS should not be used to contribute towards the diagnosis
Pathology findings	Presence of typical features of Fabry disease on biopsy of involved tissue	2 points in target organs (kidney, heart) 1 point in other organs (skin)	Should be interpreted by a pathologist with expertise in Fabry disease

Diagnosis of Fabry disease is likely in patients with 3 or more points

\*Adapted from Smid BE et al. Uncertain diagnosis of Fabry disease; Consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. *Int J Cardiol.* 2014;177:400-8.

## **Treatment of Fabry disease with enzyme replacement therapy (ERT)**

ERT should be considered in all patients with documented Fabry disease, of any age and either sex, who meet at least one of the following disease-specific criteria. In all cases, diagnostic accuracy is essential with exclusion of other possible etiologies. The treating physician has the responsibility of ensuring that there is a high likelihood of patient benefit and a low risk of adverse effects of ERT. A diagnosis of Fabry disease in the absence of clinical evidence of organ involvement is NOT an indication for ERT. Some manifestations of Fabry disease are not improved by ERT while others may be improved by ERT. Thus, ERT should be considered when there are manifestations for which ERT is of proven benefit.

### **Renal indications**

Renal disease is a common feature of Fabry disease in males but there are numerous case reports where patients with Fabry disease were found to have an alternate treatable cause for renal dysfunction on renal biopsy (Maixnerova 2013). For this reason, all other causes of reduced GFR and proteinuria (including orthostatic proteinuria) need to be excluded. When reduction of GFR is present, the negative effects on GFR by concurrent medications such as ACE inhibitors, angiotensin receptor blockers, diuretics, non-steroidal anti-inflammatory drugs and other agents should be excluded. A nephrology consultation may need to be obtained. Consideration should be given to a renal biopsy if there is any doubt as to the diagnosis. In addition to ERT, nonspecific measures appropriate for all patients with kidney disease (smoking cessation, control of dyslipidemia and proteinuria, aggressive control of hypertension) are appropriate in patients with Fabry nephropathy. Blockade of the renin-angiotensin system is important in all patients with proteinuria with the goal of reducing 24 hr urine protein excretion below 500 mg/day (Warnock 2015)

### **Renal Disease Evidence level 1 - Grade B**

1 major criterion or 2 minor criteria required

#### **Major criteria:**

- Fabry nephropathy with reduced glomerular filtration rate (GFR)  
For GFR < 60 ml/min/1.73m<sup>2</sup> chronic kidney disease (CKD) stages 3-5: at least 2 consistent estimates or measurements of GFR over a minimum of 2 months.

For GFR 60 - 90 ml/min/1.73m<sup>2</sup>, CKD stage 2: at least 3 consistent estimates or measurements of GFR over at least 4 months with a GFR slope greater than age-related normal.

For GFR >135 ml/min/1.73m<sup>2</sup>: a 15% decrease in GFR or a GFR slope greater than age-related normal as measured by nuclear medicine technique. Estimated GFR is not accurate in this range and thus cannot be used.

Persisting proteinuria of 500 mg/day/1.73m<sup>2</sup> or greater without other cause.

Findings of high risk pathology (glomerular sclerosis, tubulointerstitial atrophy, fibrosis or vascular sclerosis) on renal biopsy are a major criterion in males only (see comments)

### **Comments:**

1. GFR in adults should be estimated (eGFR) by CKD-EPI formula (Levey 2009) and in children by the Counahan-Barrett formula (Counahan 1976). Measured GFR by nuclear medicine technique should be done in adults or children if there is hyperfiltration or inconsistency in renal function. All other methods of estimating GFR such as the MDRD, Cockcroft and Gault formula or old Schwartz formulas or creatinine clearance are less accurate and should not be used (Tondel 2010; Rombach 2010). In particular, these estimates may result in false hyperfiltration readings, especially in children or teenagers. Calculations of GFR in children may be less accurate and, if treatment decisions are to be made using GFR data, clinicians are encouraged to get more accurate measurements of GFR using nuclear techniques.
2. A renal biopsy is not required as a prelude to therapy. However, if the patient has clinical indications for a renal biopsy, renal pathology in men is a major criterion if features known to be of high risk in predicting progressive renal disease (glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis) are present. A pathologist with extensive expertise in the interpretation of renal biopsies in patients with Fabry disease is required in order to ascertain the prognostic significance of pathological changes in the renal biopsy. Some changes (such as glycolipid deposit volume in podocytes and foot process width in Fabry nephropathy) correlate with age (Najafian 2010) while other features (glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis) are more effective in predicting the risk of progressive renal disease. While the presence of lamellar bodies characteristic of Fabry disease can occur in podocytes and in all renal cell types, they are not diagnostic of this condition as they can be observed in sphingolipidosis induced by chloroquine and other drugs. Given these difficulties in interpretation, clinicians are strongly encouraged to involve a pathologist with expertise in Fabry disease in renal biopsy interpretation.



**Minor criteria:**

- Hyperfiltration: There should be at least two (2) consistent measurements of GFR by nuclear medicine techniques at least one month apart when GFR reaches or exceeds 135 ml/min/1.73m<sup>2</sup>. Hyperfiltration by eGFR as calculated by any formula is not accurate and thus not acceptable.
- Isolated proteinuria of 300 mg/day/1.73m<sup>2</sup> or greater than normal for age and gender and persistent for at least one year with exclusion of other causes
- Renal tubular dysfunction. Fanconi syndrome and/or nephrogenic diabetes insipidus confirmed usually with abnormal water deprivation test and resistance to DDAVP.
- Hypertension of at least one year duration
- Renal pathology in women may be taken into account as a minor criterion if the patient has indications for renal biopsy. If a renal biopsy is done, the presence of glomerular sclerosis, tubulointerstitial atrophy and fibrosis or vascular sclerosis should be considered a minor criterion in women.

**Comment:** The development of progressive renal disease in women is much less common than in men (Sirrs 2014). Therefore, the presence of positive renal pathology for Fabry disease in women is not a hallmark for progression of renal disease making interpretation of the significance of renal biopsy changes much less clear in women than in men.

**Cardiac Disease** Evidence level II-2 - Grade B

2 criteria required

**Criteria:**

- LV wall thickness >12 mm in males and >11 mm in females
- LV hypertrophy (LVH) by Estes ECG score must be greater than 5
- LV mass index by 2D echo 20% above normal for age
- Increase of LV mass of at least 5 g/m<sup>2</sup>/year, with three measurements over a minimum of 12 months
- Diastolic filling abnormalities by 2D echocardiogram, Grade 2 or Grade 3 diastolic dysfunction as outlined by ASE and/or the presence of speckle tracking abnormalities
- Abnormal radial and/or longitudinal strain rate

- Increased LA size on 2D echo. In parasternal long axis view (PLAX) >40 mm; Left atrial volume index > 34 ml/m<sup>2</sup>
- Cardiac conduction and rhythm abnormalities: AV block, short PR interval, LBBB, ventricular or atrial tachyarrhythmias, sinus bradycardia (in the absence of drugs with negative chronotropic activity or other causes)
- Moderate to severe mitral or aortic insufficiency
- Late enhancement of left ventricular wall on MRI
- Increase of N-terminal pro-natriuretic brain peptide (NT-proBNP) above the upper limit of normal for age and gender

### **Comments:**

1. Many of the cardiac manifestations may be influenced by the presence of hypertension. In the event of significant hypertension, adequate control of hypertension for a 12 month period should be considered first.
2. Given the development of cardiac fibrosis with late enhancement on cardiac MRI but normal left ventricular (LV) wall thickness (<12 mm) in a significant fraction of Fabry female heterozygotes (Niemann 2011), a lower threshold of LV wall thickness of ≥11 mm is recommended as a criteria for ERT in this group. As women are now recognized to develop left ventricular fibrosis in the absence of LVH, regular cardiac MRI may be preferred to echocardiogram in some women (Niemann 2011).
3. The identification of LV wall abnormalities by cardiac tissue Doppler imaging is an important feature of Fabry cardiomyopathy as this can be corrected by ERT prior to the development of cardiac fibrosis (Koeppel 2012). All other causes of these cardiac features need to be excluded. A cardiology consultation may be required.
4. Consideration should be given to a left ventricular biopsy if there is any doubt as to the diagnosis. Biopsy may help confirm the diagnosis of Fabry disease in patients in whom the diagnosis is not clear (for example, those where mutation analysis reveals a variant of unknown significance) but the finding of changes on a biopsy are not indications for therapy – ie. cardiac findings on pathology alone are not sufficient indication for treatment
5. Atypical chest pain in the absence of LVH may indicate the presence of small vessel disease and patients should undergo specific investigation including cardiac perfusion PET scan (Chimenti 2008).

### **Neurologic Disease** Evidence level III - Grade F

1 major criterion required

- Stroke or TIA documented by a neurologist.
- Sudden onset unilateral hearing loss.
- Acute ischemic optic neuropathy when all other possible causes have been excluded

**Comments:**

1. There is no evidence that ERT prevents stroke in Fabry disease. However, the presence of serious neurological disease (stroke, TIA, acute hearing loss) often with irreversible CNS damage indicates severe Fabry disease so for this reason, severe neurological events are considered an indication for therapy to try and prevent the development of complications outside the central nervous system. The possible beneficial impact of ERT in severe Fabry disease warrants consideration of initiating ERT.

2. Imaging abnormalities (white matter lesions, dolichoectasia, cerebral microbleeds) on their own are not an indication for enzyme replacement as their clinical significance remains unclear.

3. Anti-platelet treatment with ASA and other drugs e.g. clopidogrel, should be the mainstay of treatment unless contraindicated. Aggressive control of cardiovascular risk factors should be implemented in all patients.

4. Drugs that are associated with an increased risk of stroke (such as hormonal forms of contraception) may theoretically increase the risk of stroke in Fabry patients. This possibility should be considered when selecting a method of birth control.

5. Cardioembolic causes of stroke are more likely to be identified with longer duration of recording of cardiac rhythm which should influence decisions as to appropriate investigations in Fabry patients with a new stroke (e.g. holter monitor for 2+ weeks, loop recorder, Reveal device etc.)

**Neuropathic Pain** Evidence level I - Grade E

Pain is **NOT** considered an isolated indication for ERT in most patients.

If pain is the only indication for consideration of ERT, then consideration for a trial of ERT could be given as long as all of the following criteria are met:

- a. Prespecified outcomes as to what would constitute a positive effect of ERT for this symptom are agreed to prior to the trial by the treating physician and the patient. Such outcomes may include tangible benefits such as:

1. Significant reduction in the need for analgesics
2. Significant reduction in time lost from work or school due to pain
3. Significant reduction in the frequency of pain crises etc.

b. Other outcomes may be appropriate treatment targets in some patients and can be determined prior to a trial of therapy on a patient by patient basis. Improvements in validated pain scoring materials can be included as secondary outcomes but should not replace more tangible outcomes

c. Adequate data are to be collected prior to the start of the ERT trial to establish a baseline – for example, a review of use of prescription medication and time lost from work or school

d. Agreement is obtained from the patient and documented in the health record that ERT will be stopped if the prespecified outcomes are not met and no other indications for ERT are present.

**Comments:**

1. Short term controlled clinical trials show conflicting data on the efficacy of ERT for pain (Eng 2001; Schiffman 2001) and effects that have been seen are present within 6-12 months although data are conflicting on this point. There is a paucity of controlled clinical trial data documenting the long term efficacy of ERT on pain in patients with Fabry disease. Analysis of controlled data that do exist do not support a durable effect of ERT on pain in patients with Fabry disease (El Dib 2010;Wyatt 2012; Alegra 2012

2. All other strategies should be considered as treatments of choice for pain in patients with Fabry disease. These should include physical strategies (avoidance of pain triggers such as temperature extremes etc.), supportive care (management of associated anxiety, depression, and sleep disturbance), and pharmacological strategies (anticonvulsants, NSAIDs in patients with normal renal function, analgesics). Referral to a specialist in the management of chronic pain may be needed.

**Gastrointestinal Disease Evidence level II-3 - Grade B.**

- Significant gastrointestinal symptoms unresponsive to other measures for at least six months or associated with poor growth or significant reduction in quality of life.

**Comment:**

There is a high prevalence of positive tests for H. pylori and bacterial overgrowth in Fabry patients when compared with controls populations and these patients are more

symptomatic than those without overgrowth and respond to targeted therapy. (Francieschi 2015). Patients with prominent GI symptoms should be screened for these complications and have a trial of therapy if appropriate before considering enzyme replacement therapy as a treatment for GI symptoms.

### **Contraindications to ERT Evidence level II-I - Grade E**

ERT is not recommended in the presence of the following:

- Pregnancy and lactation. (relative contraindication)
- Severe disease or concomitant medical condition in which death is expected within a year. (absolute contraindication)
- Presence of a severe co-morbid condition such that ERT for Fabry disease is unlikely to significantly improve quality of life. (absolute contraindication)
- Other conditions in which the benefit to risk ratio for ERT use is not favourable. (absolute contraindication)
- Presence of IgE antibody to drug; this may be associated with anaphylaxis. (absolute contraindication)

### **Withdrawal of ERT Evidence level II-2 - Grade E**

Consideration should be given to discontinuation of ERT if there is evidence that the patient is not responding to treatment after a reasonable period of observation, of at least a year.

The treating physician should discuss ERT withdrawal with the patient under the following circumstances:

- Patient request.
- Life expectancy less than one year due to severe comorbid illness or due to severe Fabry disease with end stage heart failure if not a candidate for heart transplantation.
- Permanent severe neurocognitive decline of any cause.
- Severe reduction in quality of life and functional status despite ERT.
- Persistent life threatening or severe infusion associated reactions that do not respond to prophylaxis e.g. anaphylaxis.
- Persisting IgE antibody against agalsidase.
- Lack of response to ERT in standard dose given for a minimum of 1 year when the sole indication for ERT is neuropathic pain.

- Lack of response to ERT in standard dose given for a minimum of 1 year when the sole indication for ERT is the presence of severe gastrointestinal symptoms.
- Poor patient adherence to ERT, where over 50% of ERT infusions in a year have been missed by the patient due to their actions or inactions.
- Ongoing neuropathic pain or significant GI symptoms unresponsive to standard dose ERT given for a minimum of one year in a patient without other indications for ERT.

### **Risk Factors for Cardiovascular and Cerebrovascular Disease**

- Diabetes mellitus
- Hypertension
- Hyperlipidemia
- Smoking
- Positive family history of cardiovascular or cerebrovascular disease
- Sedentary life style
- Microalbuminuria
- Chronic kidney disease

These risk factors should be sought out in all patients with Fabry disease and aggressive treatment provided to reduce these influences recognizing that they will promote atherosclerotic vascular disease that would be superimposed on the vascular damage of Fabry disease. Guidelines for the management of blood pressure, lipids, and glycemic control as well as those for the use of anti-platelet agents at high vascular risk should be followed in all adult patients without contraindications.

### **Potential Benefits of ERT**

Based upon current literature, there is evidence of improvement with ERT in some aspects of Fabry disease as detailed below:

- Stabilization of Fabry nephropathy with stable proteinuria and GFR.
- Stabilization of Fabry cardiomyopathy with stable or declining LVMI, LV wall thickness, normalization of PR interval.
- Improvement in diarrhea, abdominal cramps or pain, nausea, vomiting and heartburn associated with Fabry disease.

Other clinical features of Fabry disease have not yet been shown to respond to ERT:

- Tachy or brady arrhythmias
- Stroke or TIAs
- Proteinuria
- Depression

- Hearing loss

### **Potential Risks of ERT**

- Increased healthcare costs due to costs of drug purchase and drug administration
- Development of infusion reactions to ERT characterized by fever, chills, edema, rash, nausea and dyspnea.
- Development of anti-agalsidase antibodies; IgG antibodies may be associated with infusion reactions as detailed above, with *in vitro* inactivation of agalsidase or with increased levels of urine and plasma Gb3 as well as plasma lysoGb3 (significance currently unknown); IgE antibodies to agalsidase-beta may be associated with anaphylaxis. IgA and IgM antibodies to agalsidase-alfa have also been identified although the significance of these observations is unknown.

### **Choice of ERT and Dose Evidence level II-3 - Grade E**

Although the standard doses of agalsidase alfa (0.2mg/kg) and agalsidase beta (1.0mg/kg) differ, 5 and 8 year follow up data from the CFDI shows that the outcomes of therapy with the two drugs are equivalent (Sirrs 2014; West 2016a). Also, there is no evidence that one agent should be considered as rescue therapy if there is poor clinical response to the other agent (Goker-Alpan 2015; Tsuboi 2014; Lenders 2015). Data concerning altered dose regimens as a means to affect outcomes are limited with mixed results (Hughes 2013; Data on File at Genzyme, Schiffmann 2007, Schiffmann 2015). Data from the CFDI suggests that there may be an increased risk of events for the first 6 months after a drug switch (West 2016b) suggesting that optimal management would be to not switch medications if possible. Given the lack of data to support alternative dose and dosing and possible risks associated with the switch, considerations of changing drug, dose or dosing are best done in the setting of a formal clinical trial.

**Table 2. Levels of evidence and strength of recommendations**

<b>Level of Evidence</b>	<b>Description</b>
I	Evidence obtained from at least one properly randomized trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.
II-3	Evidence obtained from comparisons between times and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
<b>Grade</b>	<b>Description</b>
A	There is good evidence to recommend the clinical preventive action
B	There is fair evidence to recommend the clinical preventive action
C	The existing evidence is conflicting and does not allow a recommendation to be made for or against use of the clinical preventive action: however, other factors may influence decision-making.
D	There is fair evidence to recommend against the clinical preventive action.
E	There is good evidence to recommend against the clinical preventive action.
F	There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making

Table adapted from Canadian Task Force on the Periodic Health Examination. The periodic health examination. CMAJ 1979;121:1193-254.



## **Disclosures**

Dr. Bichet has received consultancy and speaker fees from Sanofi-Genzyme, Shire Inc. and Amicus Therapeutics Inc. These activities and grant support are declared and updated every year for the Department of Medicine, University of Montreal, and Hôpital du Sacré-Coeur, Montreal Quebec.

Dr. Iwanochko has received honoraria, from Sanofi-Genzyme and Shire Inc.

Dr. Khan has received any combination of speaker's fees, travel grants, unrestricted educational grants and research grants from Sanofi-Genzyme, Shire Inc, Actelion, Alexion, Biomarin, Cytonet LLC, Horizon Pharma, Sanofi-Genzyme, and Shire Inc. He also has a technology transfer agreement with the University Health Network for gene therapy for Fabry disease.

Dr. Moore has received research, unrestricted educational, and travel grants for attendance at conferences, as well as honoraria for presentations at conferences from Shire Inc. Dr. Moore is further the PI on the Canadian Fabry Stroke Screening Study funded by an unrestricted educational grant from Shire HGT.

Dr. Oudit has received honoraria and unrestricted research grants from Sanofi-Genzyme, has served as an advisor for Glaxo-Smith-Kline and holds a patent for a proteomic biomarker panel for Fabry disease.

Dr. Sirrs has received honoraria, speaker's fees, or travel grants Sanofi-Genzyme, Shire Inc, Actelion, Pfizer, and Alexion and has participated in research projects funded by Sanofi-Genzyme, Shire Human Genetics Therapies and BioMarin.

Dr. West has received honoraria, consultancy fees and/or research funding from Actelion Pharmaceutical Inc., Alexion, Amicus Therapeutics Inc, Excelsior Biopharma Inc, Sanofi-Genzyme, GlaxoSmithKline, Shire Inc. and Sumitomo Pharma.

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