# Evaluation of the Gastrointestinal Manifestation of Fabry Disease

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## BACKGROUND AND SIGNIFICANCE

Fabry disease is an x-linked lysosomal storage disease defined by a deficiency of alpha-galactoside, leading to the accumulation of a cell membrane derived glycolipid, globotriaosylceramide, and its metabolites within the cytoplasm and lysosomes of many types of cells, including endothelial cells, cardiomyocytes, renal glomerular cells, and neurons (Clarke, 2007). Gastrointestinal manifestations such as abdominal pain, diarrhea and nausea are prominent and, although typically non life-threatening, can frequently cause significant morbidity and burden in a patient's life. Recent studies have found that up to 50% (range of 16-70%) of patients with Fabry disease, including both males and females, experience gastrointestinal symptoms (Hoffman et al., 2007). The symptoms are typically one of the first presenting signs of Fabry disease, after acroparesthesia, with the mean onset in males at age 5 years and females several years later at 9.5 years. Although females present later, the severity of the symptoms equalizes as the patient ages (Hoffmann, Schwarz, Mehta, & Keshav, 2007).

The gastrointestinal symptoms can vary in intensity and can occur anywhere along the GI tract including the stomach, small and large bowel. They tend to progress in incidence over time. The most common complaint is abdominal pain with up to one third of adults endorsing this ailment and many children reporting it as their initial GI symptom (Hoffmann et al., 2007; Mehta et al., 2004). It is typically described as a cramping mid-abdominal pain worsened with meals and increased stress. Alterations in bowel habits is the next most common GI presentation, with many patients complaining of urgent, explosive, post-prandial diarrhea frequently necessitating significant lifestyle changes. Others, mostly female, experience constipation (Hoffman, 2007). Less common, but significant gastric symptoms are also reported including nausea, vomiting and early satiety. Patients describe decreased appetite, inability to tolerate many foods and feelings of bloating consistent with gastric dysmotility.

Although the presence of gastrointestinal symptoms in Fabry's disease was first described more than 50 years ago by Van Wayjen in 1958, little remains known about the specific pathophysiology of the symptoms(Van Waygen, 1958). Few case reports have examined the histology and dysmotility affecting those with gastrointestinal symptoms with no large scale studies ever conducted. The symptoms are speculated to be caused by a combination of vasculopathy and neuropathy due to glycolipid accumulation causing ischemia leading to cellular

necrosis and also alterations in cell function resulting in a pro-inflammatory state. The effects on neurons and the nearby blood vessels, both mechanical and functional, are thought to cause dysmotility thus producing many of the gastrointestinal symptoms (Aerts et al., 2008). These pathophysiological mechanisms have been more extensively studied in other systems such as cardiac, renal and dermal, however little is confirmed in the actual gastrointestinal cell (Askari et al., 2007; Liguori et al., 2010; Simon, Frey, Gruler, & Bültmann, 1990)

Several case reports have been published examining the evaluation of patients with gastrointestinal complaints in Fabry disease. Superficial biopsies taken from the small bowel and rectum, showed normal villous architecture and normal surface epithelium under light microscopy with enlarged and vacuolated neurons and with globotriaosylceramide deposition in the neurons and nerve (Flynn et al., 1972; Friedman et al., 1984; Jack et al., 1991; O'Brien et al., 1982). The blood vessels and muscle cells of the muscularis mucosa were noted to have deposits with luxol fast blue positive material. Electron microscopy noted electron dense intralysosomal striped "zebra-like" bodies in smooth muscle and ganglion cells (Sheth et al., 1981). To our best knowledge, all the prior studies have completed analysis with only superficial biopsies, with no more than 2 patients per case series, and all have been published more than a decade ago. Furthermore, there has been no in depth quantification of gastrointestinal cellular injury or comparison to control specimens.

Additionally, there has been only one published report of the underlying functional dysmotility analysis in these patients. In 1987, Argoff et al found that 5 out of 7 patients with gastric symptoms had delay in gastric emptying scan and responded well to metoclopramide, suggesting a similar neuropathy to that seen in diabetic gastropathy (Argoff et al., 1998). Although many of the presenting gastrointestinal symptoms seem to involve dysfunction of the whole gastrointestinal tract, additional motility testing examining the small and large bowel has not been completed in these patients.

As the underlying pathology remains unclear, there is no Fabry-specified protocol for evaluation of patients with gastrointestinal symptoms. Bloodwork is frequently completed for initial evaluation of symptoms including CBC and electrolytes, which are typically normal. Additional workup including imaging such as a KUB may be performed, which is also commonly without abnormalities. In some patients with persistence of concerning symptoms, it may be clinically necessary to complete further evaluation via colonoscopy to evaluate for underlying mucosal disease.

The treatment for the GI symptoms in Fabry disease was historically symptomatic, utilizing promotility drugs, neuromodulators and antibiotics. The management has progressed recently with the initiation of enzyme replacement therapy over the past decade with many patients starting the replacement at younger ages. Although enzyme replacement therapy has shown promising results with some decrease in symptom severity, GI complaints remain a significant cause of morbidity for some patients on ERT (Banikazemi et al., 2005; Barbey et al., 2007; Zarate & Hopkin, 2008). More in depth understanding of gastrointestinal symptoms pathophysiology in Fabry disease is acutely needed in order to develop more specific evaluation of the symptoms and advance the treatment of these patients. By gaining additional insight into

the characterization of symptoms and the relationship to dysmotility, we anticipate improved and more focused adjunct therapies for the patients.

## SPECIFIC AIMS

### Primary Aim – Dysmotility

The primary goal of the study is to gain further comprehension of the pathophysiology underlying dysfunction of the gastrointestinal tract and to correlate the abnormal findings with symptoms in an attempt to further classify the disease manifestation. This investigation will be achieved by examining the gastric, small bowel and colon emptying time. Additionally, neurologic and myopathic changes will be analyzed through evaluation of contractility, pH and temperature of the bowel as measured by the SmartPill study. These results will be correlated with the patient's subjective gastrointestinal symptoms in an attempt to elucidate a causational relationship between functional abnormalities with presentation.

The aim in this phase of the study is to gain additional understanding of the disease manifestation via motility abnormalities in order to improve symptom targeted therapy. They hypothesis is that patients with fabry disease will have abnormal motility which will correlate with the patients symptoms and quality of life as noted on the questionnaires.

### Secondary Aim - Histology

A secondary goal will be examine all aspects of histological injury including neuronal such as myelin depletion and nerve swelling, vascular such as intima thickening and cellular hypertrophy, and GL-3 deposition. This will be completed by obtaining deep specimen biopsies of the mucosa and submucosa for analysis of the histopathology of the gastrointestinal tract in symptomatic patients with Fabry disease who are treatment naive or with only <6 months of treatment.

The specimens will be obtained by a clinically warranted sigmoidoscopy and will include an additional deeper endoscopic mucosal resection. Tissue analysis will include evaluation of abnormalities of cellular structure and morphology with correlation with gastrointestinal complaints for each patient and comparison against age matched non-Fabry patient tissue. The hypothesis is that patients will have abnormal findings on histology, which will correlate with the subjects symptoms and findings of on the questionnaires.

### Secondary Aim – Protocol

There is no uniform protocol for assessment and evaluation of gastrointestinal complaints in patients with Fabry disease. The aim is to create a protocol for Fabry disease caretakers to follow based on the histologic and dysmotility findings.

## SUBJECT SELECTION

### Equitable Selection of Subjects

This study is open to all individuals, male and female, between 18 and 70 years of age who meet all of the inclusion and exclusion criteria, and have been diagnosed with Fabry disease. Women who are pregnant or nursing will not be allowed to enter the study due to unknown risk factors. Subjects who are not able to provide informed consent form themselves will not be enrolled.

**Inclusion/Exclusion Criteria**

*Inclusion Criteria:*

1. Adults ages 18- 70 years who have diagnosed Fabry disease either by enzyme testing in males or by enzyme and/or genetically confirmed mutation in females.
2. Adults with Fabry disease having any gastrointestinal complaints within the past year.
3. Endoscopic Mucosal Resection ONLY – Symptomatic subjects necessitating a sigmoidoscopy who are enzyme replacement therapy naive OR less than 6 months of treatment.

*Exclusions Criteria:*

1. Fabry disease with other concomitant gastrointestinal diagnosis (Example: Inflammatory Bowel Disease, Celiac Disease)
2. Pregnancy
3. Endoscopic mucosal resection exclusions:
    a. Any contraindication to conscious sedation,
    b. Contraindication to endoscopy,
    c. Untreated or unmanageable coaguloapathy,
    d. Thrombocytopenia (<50).
    e. Patient on ERT for more than 6 months.

4. Exclusions for SmartPill:
    a. Previous history of bezoars.
    b. Prior GI surgery except for cholecystectomy, appendectomy, or Nissen fundoplication.
    c. Any abdominal surgery within the past 3 months
    d. History of diverticulitis, diverticular stricture, and other intestinal strictures
    e. Tobacco use within eight hours prior to capsule ingestion and during the initial 8-hour recording on Day 0 or the Ingestion visit.
    f. Alcohol use within eight hours prior to capsule ingestion and throughout the entire monitoring period (5 days).
    g. BMI > 38
    h. Allergies to components of the SmartBar
    i. Use of medical devices such as pacemakers, infusion pumps, or insulin pumps.
    j. Uncontrolled diabetes with a hemoglobin A1C greater than 10.

    Prohibited Medications for SmartPill

    1. No medications which may alter gastric pH around the time of the study, which includes:
        a. Proton Pump Inhibitors for 1 week (examples: omeprazole, lansoprazole and esomeprazole, pantoprazole, rabeprazole)
        b. Histamine$_2$ Blockers for 3 days [(examples: cimetidine (Tagamet HB), famotidine (Pepcid), and ranitidine hydrochloride (Zantac), nizatidine (Axid)]

c. Antacids for 1 day (examples: Maalox, Mylanta, Amphogel, Tums, Rolaids)

2. No medications that affect gastrointestinal motility for 3 full days before the start of the study and during the 5 ensuing days of study including but not limited to those drugs listed below:

    a. Prokinetic agents, such as metoclopramide (Reglan), tegaserod (Zelnorm), domperidone (Motilium), erythromycin, zithromycin, cisapride
    b. Anti-emetics agents, such as phenergan, compazine
    c. Narcotic analgesic agents, such as methadone, fentanyl, percocet
    d. Anticholinergic agents for IBS – Bentyl, Levsin
    e. Medications for constipation, including enemas, cathartics, polyethylene glycol solutions (including Miralax), and lactulose (e.g., enulose). Patients with constipation may take medications to help stimulate a bowel movement with either milk of magnesia, 2.4 to 4.8 grams (30-60 ml), or magnesium citrate, 11 to 25 grams daily in 1 or more doses, up to 48 hours prior to SmartPill ingestion.
    f. 5HT3 antagonists, such as Lotronex (alosetron hydrochloride) and Zofran (ondansetron hydrochloride).
    g. Anti-diarrheal agents, such as Kaopectate (attapulgite, donnagel, rheaban), Pepto-Bismol (bismuth subsalicylate), Imodium (loperamide), and lomotil (atropine diphenoxylate).
    h. Opiate agents used to treat diarrhea.

Permitted Medications for SmartPill

1. NSAIDs (examples: Aspirin, Advil, Motrin) may be used
2. Acetaminophen may be used.
3. Prescription medications for maintenance of stabilized conditions (e.g., hyperlipidemia, chronic anxiety, birth control, etc) with drugs such as anti-hyperlipidemics (e.g., HCG Co-A reductase inhibitors, Lipitor); antidepressants (e.g., Prozac, etc) are permitted if the condition and the dose are stable for six months prior to enrolment in the study.

**Recruitment Procedures**

Patients will be recruited via the Massachusetts General Hospital lysosomal storage disease clinic. The study will be presented to all patients with Fabry disease who have had gastrointestinal symptoms within the past year. Additionally, we will contact physicians who care for Fabry patients via email and conferences to inform them of the study. If patients indicate they are interested in the study to their provider, the patient may be contacted if the provider refers the patient to the study staff. Flyers with the research coordinator's contact information will also be given to interested patients and providers at conferences. At conferences, if interested, patients will be given the opportunity to sign a form that would allow them to be contacted by the study staff to learn more about the study. Subjects identified through RPDR will

receive a recruitment letter signed by the PI and the patient's provider (Please refer to the Protocol Summary for additional information). We expect to enroll all patients over a two-year period.

1. SmartPill study and questionnaires regarding gastrointestinal symptoms, quality of life and psychiatric comorbidities (Please see "study procedures" for additional information) will be administered to approximately 50 patients.
2. Histology section – Recruit up to 15 treatment naive patients or patients with less than 6 months of therapy who have lower GI symptoms including abdominal pain and/or bowel movement alterations for which a sigmoidoscopy would be clinically warranted. An endoscopic evaluation with mucosal resection will be performed.

## SUBJECT ENROLLMENT

The study will be presented to patients at their regularly scheduled Fabry clinic follow up visit if they report any gastrointestinal symptoms currently or within the past year. If the patient is interested in participation, the consent form will be reviewed by the genetics physician or nurse at the visit and the risks and the benefits of the study will be presented. All questions will be answered. The patient can choose to sign the consent form on the day of the clinic visit, but it is not a requirement. They will be given the opportunity to take the consent form home and decide at a later time if they would like to participate. If the patient does not contact the study staff about the study in a week, the patient will be contacted by the research coordinator. If interested, the research coordinator will schedule the visit with the gastroenterologist. If they choose to sign the consent form on the day of the clinic visit, they will be given the option to complete the screening visit on that day or scheduling the screening visit for a later date within the following 2 weeks.

Patients who have contacted the study staff about the study will be pre-screened by the research coordinator to ensure they meet the criteria. If eligible, they will be provided with an electronic copy of the consent form to review. The email will be sent in accordance with Partners Information Security guidelines. The study staff will provide the patient a couple days to review the consent form before contacting them again to answer any questions they may have about the study. If the patient would like to participate in the study, the research coordinator will schedule a visit with the gastroenterologist.

## STUDY PROCEDURES

The study will involve a total of three study visits, with a possibility of a fourth visit. The patient will have the option of signing the consent at their routine Fabry follow up visit or prior to the screening visit. If the patient agrees to participation and signs the consent form, he will be enrolled in the study.

### Screening Visit (Visit 1)

This visit will last approximately 45 minutes. A history and physical will be completed, with particular focus on the gastrointestinal symptoms including gastrointestinal medications and

interventions. Patient will then complete various questionnaires and forms relating to their gastrointestinal symptoms, quality of life and psychiatric issues.

Validated Questionnaires and other data collection – The patient will complete questionnaires including:

1. IBS-QOL (Irritable Bowel Syndrome-Quality of Life)
2. GSRS-IBS (Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome)
3. IBS – work productivity/activity impairment
4. Bristol stool chart
5. BDI (Beck Depression Inventory)
6. HAM-A (Hamilton anxiety rating scale )
7. SSI – Symptom Severity Scale
8. GCSI (Gastroparesis Cardinal Symptom Checklist)
9. PAGI-SYM (Patient Assessment of Gastrointestinal Disorders)
10. The Mayo Clinic bowel disease questionnaire

**Preparation for Study Visit 2**
Prior to the SmartPill study, the subject must remain NPO starting at 10:00pm the night prior to the study initiation. Alcohol is prohibited 8 hours prior to the SmartPill study and throughout the monitoring period. Additionally, tobacco use if prohibited 8 hours prior to initiation and 8 hours after swallowing the capsule. A urine pregnancy test will be completed on any woman of child bearing age as pregnant woman are excluded from the study.

**SmartPill Capsule Ingestion Visit (Visit 2)**
This study visit should take about 2 hours to complete.

At this visit, the test procedure will be explained to the subject. They will then ingest the SmartBar, a standardized meal used to accurately measure gastric emptying time, within 10 minutes. Following ingestion, the subject will swallow the SmartPill capsule with 70cc of water. They will then receive the SmartPill receiver to carry for the duration of the study, lasting 5-7 days.

During the initial 8 hours after capsule ingestion the subject you will not be allowed to sleep because sleep may affect motility.

The subject will remain NPO for 8 hours after ingestion of the capsule. They will drink a bottle of Ensure 8 hours after ingestion. An hour after drinking the Ensure, the subject can return to their normal eating habits. Instructions will be given to the patient about completion of the daily diary in which they will document periods of ingestion, sleeping patterns and bowel movements in addition to marking it on the receiver. They will also be instructed to wait 5 minutes after each bowel movement to ensure recording of possible passage of the SmartPill.

Prior to leaving, the subject will schedule a follow up visit (visit #3) to return the receiver and the diary and discuss any questions about the study. If the patient has travelled a far distance to participate, they will be given instructions on mailing the receiver and diary back to the office.

After the visit, the subject will keep the receiver at no more than 5 feet from their body at all times during the 5-7 day period. They will be instructed to refrain from any strenuous activities during the study period. The prohibited medications will be reviewed. Additionally, they will again be asked to refrain from alcohol use for the duration of the study.

If the subject is unable to make two visits, they will be given the option to condense the first and second visit into one visit. The visit would last about 2 hours long. Prior to scheduling the condensed visit, the subject will receive an electronic copy of the consent form, in accordance with Partners Information Security guidelines, and will be notified of all medications that need to be stopped for the SmartPill. Any questions will be answered and all information about the SmartPill test will be provided.

The first hour of the condensed visit will consist of the screening visit (visit 1). The subject will be consented by the physician prior to starting the medical history and physical, if not already previously consented during their genetics clinic visit. The subject will be given the opportunity to ask any questions they may have. The subject will also answer the questionnaires during this first hour. If eligible, the second hour of this condensed visit will consist of the SmartPill test (visit 2).

**Follow Up Visit (Visit 3)**
This study visit should take about 30-45 minutes to complete and will take place 5 to 7 days after Visit 2.

At this visit, the patient will return the SmartPill receiver and the study diary. We will discuss any questions or concerns they had about the study. If available, we will review the results of the SmartPill test. If it is unclear that the capsule has passed, based on the subject's history or on the study results, we may prescribe erythromycin as a promotility medication or obtain a KUB for verification.

If the patient cannot return the receiver in person, they will be provided with information on mailing the receiver back. Once the results have been reviewed, the patient will be contacted to provide the results of the SmartPill and confirmation of capsule exit.

If the patient is appropriate for the endoscopic mucosal resection, this will be scheduled within the following 3 weeks.

**Sigmoidoscopy and Endoscopic Mucosal Resection (Visit 4)**
This study visit should take about 3.5 hours to complete.

This study visit consists of a sigmoidoscopy with biopsies and an endoscopic mucosal resection. When additional workup of gastrointestinal symptoms is warranted for altered bowel habits and/or abdominal pain, a subset of 15 treatment naive patients or with less than 6 months of treatment will be recruited from those who completed the SmartPill study for a sigmoidoscopy with biopsy collection and additional endoscopic mucosal resection.

The patient will fast the night prior and receive 2 enemas the morning of the procedure. The patient will present for completion of a clinically needed sigmoidoscopy with routine rectal and sigmoid biopsy collection. In addition, an endoscopic mucosal resection will be completed in the rectum. Biopsies will be sent to pathology for the following analysis.

1. Light microscopy with hematoxylin and eosin, periodic acid schiff, toluidine blue and acetylcholine staining.
2. Electron microscopy
3. Immunohistochemistry staining with anti-Gb3 monoclonal antibody.

All specimens will be examined for cellular morphology, other significant noted injury or structural abnormalities and location of deposition. The biopsies will be specifically analyzed for vascular and neuropathic changes. The specimens will be assessed for presence or absence of neuronal swelling, myelination, vascular sclerosis, intimal fibrosis and hypertrophy of the smooth muscles of the arterioles. The neurological and vascular cells will be assessed for deposition and quantification will be determined based on a degree of deposition scale used previously for renal biopsy analysis in Fabry disease (0 No deposit, +deposit present in a few cells, ++ deposits present in some cells, +++ deposits present in many cells) (Valbuena et al., 2008). Finally, results of analysis of all specimens will be compared to healthy aged-matched controls obtained from banked specimens in the pathology department. Once the analysis is completed, results will be correlated with the patient's gastrointestinal symptom presentation.

**Patients Travelling from Out of State**

Prior to scheduling the visit, the patient will be provided with an electronic copy of the consent form in accordance with Partners Information Security guidelines. They will be advised to read it over. The study staff will then contact the patient after a couple days and answer any questions the patient may have about the study and can be put in contact with the physician. The patient will be notified of all medications that needs to be stopped for the SmartPill and if eligible, for the sigmoidoscopy. All information for the sigmoidoscopy will be sent to the patient and the subject can be put in contact with a physician to answer any additional questions. If the patient agrees, the condensed visit will be scheduled.

The scheduled visit will be a condensed visit consisting of visit 1 and visit 2. The patient will be provided with information regarding mailing the receiver back to the study staff.

If the patient is eligible for the EMR, the visit will be condensed into 2 days. On the first day, the scheduled visit will include the screening visit (visit 1) and the sigmoidoscopy and EMR (visit 4). The patient will be consented by the physician prior to conducting the medical history and physical and completing the questionnaires. After, the patient will be prepped for the sigmoidoscopy and EMR. On the second day, the SmartPill visit will be conducted. This option will also be available for patients who are in state but cannot travel to the hospital multiple times.

**ADDITIONAL STUDY INFORMATION**

**Description of SmartPill**

The SmartPill GI Monitoring System includes an ingestible capsule, a receiver, a receiver docking station and display software. The capsule houses sensors for pH, temperature, and pressure, and has the ability to transmit the sensed data at 434 MHz to a receiver worn by the subject. The portable receiver worn by the subject receives and stores data; the MotiliGI software provides calculations and graphical displays to the physician. After activation and ingestion, the capsule signals are transmitted from within the GI tract and are captured by a receiving antenna incorporated into the receiver, which also provides an interface for data transmission to a PC as well as connections for battery charging. The capsule functions for at least 5 days after activation and has a pH range of 0.5 to 9 with an accuracy of ±0.5 pH units. The pressure sensor has a pressure range of 0 to 350 mm Hg with an accuracy of 5 mmHg. The temperature sensor has a range of 25° to 49°C, with an accuracy of ±0.8°C.

**SmartPill Study Procedure**

Patients taking gastric acid suppressants will be instructed to stop proton pump inhibitors 1 week prior to the colonic transit study and histamine type 2 receptor antagonists 3 days prior to the colonic transit study. Patients with constipation will stop treatments for constipation at least 72 hours prior to the study and for the 5 days of the study. This includes enemas, cathartics, PEG solutions (including Miralax, enulose). Patients with constipation may take medications to help stimulate a bowel movement with either milk of magnesia, 2.4 to 4.8 grams (30-60 ml), or magnesium citrate, 11 to 25 grams daily in 1 or more doses, up to 48 hours prior to SmartPill ingestion.

All study subjects will report for the ingestion visit after an overnight fast (beginning at midnight). Date of the start of the last menstrual period for female subjects will be recorded.

The SmartPill capsule will be activated and calibrated. All study subjects will ingest a SmartBar (a nutritional bar) consisting of approximately 254 calories with 120 cc of water, followed by the SmartPill Capsule with 50 ml of water. The subject may drink an additional 50 ml of water if difficulty swallowing capsule for a total of 100 ml with capsule ingestion. Ingestion of the meal, SmartPill Capsule, and water should be completed within 10 minutes.

Intraluminal GI tract pH, pressure, temperature will be measured continuously with the SmartPill capsule. Once the capsule is ingested the patient is free to leave to the facility. At 8 hours after capsule ingestion, with the subject in a sitting position, one can of regular Ensure (Vanilla, lactose-free, 8 fluid ounces [237 ml]; 250 calories) will be ingested.

All study subjects will maintain a diary and will record times of bowel movements, meals, gastrointestinal symptoms (pain/discomfort, nausea, vomiting), and supine/sleeping times. Subjects will be instructed, if they wish, to recover and return the SmartPill capsule along with the diary and receiver at the end of the study. If they are unable to return to the office due to distance, they will be given material to send the items via FedEx.

**Endoscopic Mucosal Resection Procedure**

EMR uses a standard cap device which fits over the end of the endoscope. EMR is used frequently in current practice at the MGH for upper and lower GI tract lesions.

## BIOSTATISTICAL ANALYSIS

Descriptive statistics based on a series of 50 patients for histologic and dysmotility findings. Univariate and multivariate regression analysis of relationship between motility parameters, histologic disease state and GI symptoms in Fabry patients.

**Power**

Based on prior studies examining gastric emptying time (GET), there was found to be a 70% correlation between abnormal gastric emptying time and symptomatic patients. Additionally, in order to have significant power for regression analysis, 25 patients with positive symptom association with gastric emptying time would be needed. Therefore, based on the 70% correlation of symptoms to GET, 35 patients need to have abnormal GET. Based on the results from Argoff et al, 5 out of 7 (70%) of Fabry patients with symptoms of gastroparesis including nausea and early satiety, had delayed gastric emptying time. Thus, extrapolating to this study, 50 Fabry patients will need to be examined for dysmotility, in order to obtain the 35 patients with delayed gastric emptying time for analysis and correlation.
Additionally, larger cohort size enables use of multivariate correlation with increased usage of symptom and demographic variables. However, study size remains restricted due to likely limited patient availability.

## RISKS AND DISCOMFORTS

**The SmartPill Capsule:**

Risks of the ingestion and passage of the capsule through the GI tract are minimal. Currently, several other diagnostic capsules, the Given PillCam and the Heidelberg pH capsule, are FDA released medical devices. The SmartPill is similar in size and shape to the Given capsule and, therefore, poses similar risk. In the 435 healthy and 443 non-healthy individuals who have ingested the Heidelberg pH Capsule, there were no complications in the healthy subjects and one complication in the non-healthy subject. This complication involved a patient with pyloric stenosis, and the capsule was retrieved through endoscopy

An estimated 170,000 capsule endoscopies have been performed since Given Imaging introduced the first ingestible endoscopy capsule for human use in 2000. Today, capsule endoscopy is considered a generally well tolerated and safe procedure. The primary hazard of the procedure is capsule retention. Retention incidence, as determined by a review of published studies of capsule endoscopy in adults, is estimated as 0.75% in patients without known stenosis and 21% in patients with known stenosis. Stenosis and strictures can be complications in inflammatory bowel disease (IBD).

Adverse events and functional technical issues with the SmartPill device may occur during the conduct of the study. The capsule may fail to empty from the stomach and fail to be expelled from the GI tract. Subjects ingesting the capsule or the meal may have nausea, vomiting, aspiration of the capsule or meal, abdominal pain, diarrhea or constipation. In previous studies with adult subjects (n=326), a total of 28 adverse events were reported: 19 were not device related, 7 were probably not device related, 1 was possibly related (sub-sternal pain) and one was definitely related. The one definitely related adverse device effect occurred when the capsule

failed to empty the stomach after 9 days due to entrapment in a bulk forming agent ingested by the subject. The capsule subsequently emptied the stomach after treatment with Erythromycin and passed naturally within 24 hours.

In this study, the exit of the capsule from the GI tract will be confirmed for each subject by examination of the data from the SmartPill study. If the capsule has not passed 5 days after ingestion and confirmation of exit cannot be determined by the SmartPill data, a qualified gastroenterologist will clinically evaluate the study subject and intervene if necessary. Interventions could include use of a laxative to promote capsule transit through the GI tract, endoscopy to retrieve the capsule if within reach of an upper endoscope or colonoscope, or surgical consultation if the capsule appears to be lodged within the small intestine.

Clinical adverse events such as difficulty in device ingestion, vomiting, gastric sensations, and gastric distress shall be assessed during the ingestion day visit. The capsule may fail to empty from the stomach after 8 to 24 hours. The capsule may also fail to pass from the GI tract after 7 days. Subjects ingesting the capsule or the meal may have nausea, vomiting, aspiration of capsule or meal, abdominal pain, diarrhea or constipation.

**Risks of the Washout Period**
Prior to the SmartPill initiation, patients will discontinue many of their gastrointestinal medications. During this washout period, the patient's bowel symptoms may get worse.

**Risks of Endoscopic Mucosal Resection**
Patients enrolled in the study will have one additional low risk procedure (EMR) at the time of their sigmoidoscopy. Patients who warrant a sigmoidoscopy will be asked to participate. Sedation should improve the discomfort of the EMR, but has a risk of complications (primarily low BP, slowed heart rate or respirations) of approximately 1/100. EMR is a common procedure in gastroenterology with a low risk for rectal lesions. In this procedure, one additional small piece of rectal tissue will be obtained for diagnosis.

The risk of one small EMR in the rectum has not been studied in large groups of patients. The risks of EMR in patients with large polyps in the rectum or with large superficial rectal neoplasms vary in the literature. Many smaller studies report no perforations or hemorrhages as a result of EMR. In one large study of EMR for colorectal neoplasia and polyps in 1000 patients, the rate of perforation was 0.2% and bleeding was 2%.**Error! Bookmark not defined.** Large Japanese series with colorectal tumors have reported a perforation rate 0.35% (3/863) and a bleeding risk of 1.16% (10/863) with colonic EMR.**Error! Bookmark not defined.** The risk of one small EMR in the rectum has not been studied in large groups of patients, but presumably has a lower risk than that seen with large resections or piecemeal removal of colonic tumors. There is no psychosocial risk associated with the intervention (EMR). Infants, children age 17 or less, and pregnant or nursing women will not be participating in the trial.

After the procedure, the analysis involves only the pathologic specimens. There is no long-term follow-up of patients for the purposes of this protocol. All enrolled patients will have the same procedure. The intervention in this trial is a one-time event. If a patient does not tolerate sigmoidoscopy or sedation, the procedure may be aborted at the discretion of the endoscopist and

anesthesiologist, in which case the EMR would not be performed. The patients will all receive best standard of care treatment at all times during the study. A patient will be removed from participation in the trial at any time if they request withdrawal.

**Risks of Sedation**
Sedation helps with comfort but carries a risk of reactions, such as low blood pressure or slowed heart rate or breathing. Vitals will be monitored throughout the procedure. Bruising at the IV site is a possibility.

**Unknown Risks**
There may be other risks of SmartPill Tests or EMR that are currently unknown.

**Other Risks**
Filling out the questionnaires could cause the subject distress. It is voluntary and if the patient is upset, the questionnaires can be terminated.

## POTENTIAL BENEFITS

There is no direct benefit to healthy subjects for participation in this study. Results from the study will help to further understand the disease and possibly lead to better diagnosis and treatment of gastrointestinal symptoms in patients with Fabry disease in the future.

## MONITORING AND QAULITY ASSURANCE

The PI and protocol investigators will monitor the study in accordance with the IRB-approved protocol. The investigators will be responsible for completing source documents. An investigator or study coordinator fully trained in human clinical trials will be responsible for verifying source documents, maintaining the electronic enrollment log and database and making sure informed consent is up to date. Adverse events will be reported immediately. Outcomes will be analyzed in an ongoing manner.

Data will be maintained electronically on REDCap, a Partners approved data repository, by the research coordinator copying the subject forms.

Coded information from this study will be shared with the sponsor, Genzyme Corporation. The data that is shared will be coded results with no identifiable information. The principle investigator will retain the key to the code at Partners.

## REFERENCES


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