treatments are available to prevent irreversible cell damage in those diagnosed with Fabry disease, but to organize a personalized treatment plan, genetic testing is needed to identify the causative *GLA* variant. Genetic counselors are able to provide patients with information about the genetic testing process and reduce anxiety. Subsidized at-home testing kits can improve the accessibility of genetic testing for those at risk for Fabry disease, but may impact the patient's experience due to the lack of pretest genetic counseling. In order to address this gap in services, this mixed-methods research study invited patients with Fabry disease to share their genetic testing experience to determine what knowledge is desired before undergoing genetic testing for Fabry disease. This information will then be used to create an educational video for patients to view prior to undergoing remote genetic testing. 111 participants completed a survey in which 71% reported not speaking to a genetic counselor before testing and nearly one-third were not given any resources, such as handouts or information packets, from their provider. Eleven patients who completed the survey were interviewed to expand on ideas presented in the survey. Qualitative results from the interviews demonstrate that participants would have appreciated information regarding how genetic testing results would impact insurance, prevention of symptoms, and the disease burden of Fabry disease prior to testing.

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Improvement of Fabry disease-related gastrointestinal symptoms in significant proportions of classic male patients treated with agalsidase beta: A Fabry Registry analysis

Robert J. Hopkin[a], Meng Yang[b], Elvira Ponce[b], Ulla Feldt-Rasmussen[c], Dominique P. Germain[d], Ana Jovanovic[e], Ana M. Martins[f], Kathy Nicholls[g], Alberto Ortiz[h], Carmen Varas[i], Frank Weidemann[j], William R. Wilcox[k], *[a]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States, [b]Sanofi Genzyme, Cambridge, MA, United States, [c]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [d]University of Versailles, Paris-Saclay University, Montigny, France, [e]Salford Royal NHS Foundation Trust, Salford, United Kingdom, [f]Federal University of São Paulo, São Paulo, Brazil, [g]Royal Melbourne Hospital, University of Melbourne, Parkville, Australia, [h]IIS-Fundación Jiménez Díaz/UAM, Madrid, Spain, [i]Hospital San Pablo de Coquimbo, Coquimbo, Chile, [j]Klinikum Vest, Knappschaftskrankenhaus, Recklinghausen, Germany, [k]Emory University School of Medicine, Atlanta, GA, United States*

Fabry disease is a lysosomal disorder with progressive disease burden, including gastrointestinal (GI) complaints, and other major complications. We analyzed Fabry Registry data to assess whether agalsidase beta is associated with improvement in GI symptoms in male patients. Included males started on agalsidase beta (1 mg/kg every other week) aged ≥18 years. We compared self-reports of abdominal pain and diarrhea (responses present/not present since last clinical assessment) at ≥0.5-year ($FU_{\geq 0.5Y}$) and ≥ 2.5-year follow-up ($FU_{\geq 2.5Y}$) in patients with classic or later-onset genotypes (http://dbfgp.org/dbFgp/fabry/) with treatment-baseline. Ages and durations are shown as medians. Ages at Fabry symptom onset, diagnosis, and first infusion were approximately 10, 32, 36 years (classic) and 36, 45, 47 years (later-onset), respectively. Classic patients reported GI symptoms more frequently at baseline than those with later-onset genotypes (abdominal pain: 56% vs. 13%; diarrhea: 57% vs. 23%). Compared with baseline, significantly fewer classic males reported abdominal pain after 4.7-year $FU_{\geq 0.5Y}$ (56% vs. 41% of 171, $P < .001$) and 6.4-year $FU_{\geq 2.5Y}$ (55% vs. 42% of 136, $P < .01$). Moreover, significantly fewer classic males reported diarrhea after 5.5-year $FU_{\geq 0.5Y}$ (57% vs. 47% of 169, $P < .05$); the percentage decrease after 6.2-year $FU_{\geq 2.5Y}$ was similar (58% vs. 49% of 138, $P = .07$). Among males with later-onset genotypes, there were suggestive reductions in abdominal pain (compared with baseline) after 4.2-year $FU_{\geq 0.5Y}$ (13% vs. 4% of 48, $P = .10$) and 5.3-year $FU_{\geq 2.5Y}$ (13% vs. 3% of 30, $P = .08$) and in diarrhea after 4.4-year $FU_{\geq 0.5Y}$ (23% vs. 13% of 47, $P = .13$) and 5.3-year $FU_{\geq 2.5Y}$ (27% vs. 17% of 30, $P = .32$). In conclusion, sustained agalsidase beta treatment was associated with improvement in abdominal pain and diarrhea in significant proportions of classic Fabry males. GI symptoms were less prevalent at baseline among the fewer males with later-onset genotypes and changes over time suggested reductions with treatment. Funding Fabry Registry (NCT00196742), abstract: Sanofi Genzyme.

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Chart review of the management of late-onset Pompe patients diagnosed through newborn screening

Sinead Horgan, Joel Charrow, Susheela Jayaraman, Rachel Hickey, Lauren Hitchins, *Ann & Robert H. Lurie Children's Hospital, Chicago, IL, United States*

In 2014, Illinois initiated a pilot screening program for five lysosomal disorders, including Pompe disease. Statewide screening began in June of 2015. Since the initiation of this screening, the Division of Genetics, Birth Defects and Metabolism at Ann & Robert H. Lurie Children's Hospital of Chicago has evaluated many infants with abnormal screens for Pompe disease 17 of whom are predicted to have late-onset Pompe disease (LOPD) based on their gene variants and clinical data. Currently, the Pompe Disease Newborn Screening Group has released guidelines for the management of asymptomatic LOPD individuals. However, there are few reports in the literature that validate this schedule of assessments. While the early detection of symptoms is crucial for prompting the initiation of ERT therapy, and subsequently an individual's prognosis, the lack literature outlining real-world follow up of these patients makes it difficult to assess the impact of frequent assessment on the clinical burden for the family. We will present our data on the follow-up of the LOPD patients diagnosed through newborn screening, including CK levels, urine Hex4, enzyme levels, follow up frequencies with specialists, and the individual GAA mutations identified. These data may inform changes to the schedule of assessments for individuals with LOPD identified through NBS.

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Inflammation and its alleviation in a fly model for neuronopathic Gaucher disease

Mia Horowitz[a], Sumit Paul[a], Orly Dorot[a], Gali Maor[a], Johannes Aerts[b], Or Cabasso[a], *[a]Tel Aviv University, Ramat Aviv, Israel, [b]Leiden University, Leiden, Netherlands*

Gaucher disease (GD), characterized by decreased activity of lysosomal acid-beta-glucocerebrosidase (GCase), is due to mutations in the *GBA1* gene. As a result, there is accumulation of

glucosylceramide, mainly in monocyte derived cells and of glucosylsphingosine. Aiming at studying the molecular mechanisms and cellular abnormalities associated with neuronopathic GD we used a *Drosophila melanogaster* model. The fruit fly has two *GBA1* orthologs, of which we studied *GBA1b. GBA1b* encodes the major *GBA1* mRNA species in the heads with significant expression in bodies. There is a *GBA1b* line containing a transposable Minos element insertion (*GBA1b*^{m}). This insertion leads to translation of a GCase-like protein with a 133 C-terminal amino-acids deletion, one of which stabilizes the substrate in the active-site pocket. We established flies homozygous for the Minos insertion in the *GBA1b* gene (*GBA1b*$^{m/m}$) and tested the consequences of expression of truncated GCase in the fly. Our results indicated that *GBA1b*-encoded protein is a *bona fide* GCase. Mutant *GBA1b*-encoded GCase (*GBA1b*^{m}) had low activity and, therefore, homozygous *GBA1b*$^{m/m}$ mutant flies accumulated substrates in their heads, bodies, macrophage-like cells and in their liver-like organ. These flies presented ER Associated Degradation (ERAD) of mutant GCase and activation of the Unfolded Protein Response (UPR) as well as inflammation and neuroinflammation. The biomarker chitotriosidase was significantly elevated in the mutant flies and their locomotor function as well as their life span were markedly reduced. We tested whether the GCase specific chaperone ambroxol can alleviate any of the GD-related signs in the mutant flies. Our results showed that this specific GCase pharmacological chaperone significantly reduced UPR, inflammation, and neuroinflammation and increased life span of the flies. Our results highlight the resemblance between the fly *GBA1b*$^{m/m}$ model and neuronopathic GD and underlies its importance in future studies of the disease as well as possible therapeutic modalities.

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DNA methylation study of GLA gene and its association with autophagy and clinical severity of heterozygous Fabry disease females

Mohammad A. Hossain, Chen Wu, Hiroko Yanagisawa, Takashi Miyajima, Ryo Saito, Yoshikatsu Eto, *Advanced Clinical Research Centre, Kawasaki, Kanagawa, Japan*

Fabry disease is an X-linked lysosomal disease caused by a deficiency of α-gal A. The clinical variability of the phenotypes in females is poorly understood. The degree of aberrant methylation of non-mutated alleles is thought to have an effect on X-chromosome inactivation (XCI). In this report, we quantified the methylation of non-mutated alleles of the *GLA* gene in heterozygous Fabry females and observed its clinical and biochemical effects. We summarized 36 heterozygous females with a clinical severity score based on the FAbry STabilization indEX (FASTEX). We quantified α-gal A activity, Gb3, and lyso-Gb3 accumulation and the methylation of normal alleles of *GLA* gene. We examined the mRNA expression level of the mutant allele and observed autophagic flux by LC3 turnover assay and p62 accumulation. The clinical severity score (FASTEX) of 36 patients was ranged 1–20. Quantification of methylation of the normal allele was directly correlated to FASTEX score, Gb3 and lyso-Gb3 accumulation for 75% cases. The correlation between the mRNA the expression level of mutant alleles and disease severity was also confirmed. Impaired autophagic flux and p62 accumulation were observed in severely affected cases. In our study, we found a clear correlation between methylation of normal alleles of heterozygous females and their clinical severity. Therefore, methylation study of *GLA* gene can be useful for clinical and biochemical predictions of Fabry disease in females and helpful for initiation of ERT at the pre-symptomatic stage.

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Adherence to international and local guidelines in Irish Morquio syndrome type A patients

Caoimhe Howard, Eithne Losty, Ellen Crushell, Ahmad Monavari, Joanne Hughes, *Children's Health Ireland at Temple Street, Dublin, Ireland*

In 2018, Ireland approved reimbursement for treatment with elosulfase alfa for patients with mucopolysaccharidosis IVA (MPS IVA - Morquio syndrome type A). Prior to this some patients had received elosulfase alfa in clinical trials and subsequent compassionate use. Treatment agreements (TAs) were introduced following approval. An audit was conducted to compare the management of our cohort against the TA and the recent international recommendations for the management of Morquio A with an aim to improve quality of care. There are 4 patients (3 female) receiving elosulfase alfa, with age at diagnosis ranging from 4 months to 11 years. Compared to the international recommendations, there was good compliance with clinic attendances including general examination. Pubertal status and ENT examination was not routinely documented. Data was not available on compliance with recommendations prior to treatment in the 2 patients enrolled in clinical trials at another centre. All patients had MRI spine performed at diagnosis. One had MRI brain. Subsequent MRI spine has been performed every two to three years, less than the annual recommendation, however our patients have all had corrective surgery and require general anaesthesia for MRI which the recommendations note carries substantial risk in this cohort. There is excellent adherence to recommendations for cardiac, respiratory and ophthalmology assessment. Lack of routine ENT follow up was identified in 2 patients. Since the introduction of TAs in 2018 all patients have pain and QOL assessments monitored at regular intervals. No patient has yet fulfilled the stop criteria of the TA, and all are compliant with regular assessments to monitor response to treatment. In conclusion, we have identified some areas for improvement in our monitoring of these patients. We plan to introduce a standardised checklist at routine clinic visits to ensure optimal patient care.

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Longitudinal assessment and immune response to recombinant GAA in CRISPR-Cas9 generated Pompe disease knock-in mice

Jeffrey Y. Huang[a], Shih-Hsin Kan[a], Emilie K. Sandfeld[a], Yunghang Chan[b], Anthony D. Rangel[a], Evelyn Torres[a], Nancy D. Dalton[b], Jon Neumann[c], Raymond Y. Wang[a], [a]*Children's Hospital of Orange County, Orange, CA, United States,* [b]*University of California San Diego, La Jolla, CA, United States,* [c]*University of California Irvine, Irvine, CA, United States*

The goal of this study is to generate and characterize knock-in mouse models bearing mutations orthologous to human infantile-onset Pompe disease (PD). While a murine model of PD exists, it