**Aim:** To develop a reliable patient-reported outcome (PRO) measure on quality of life (QOL) in lipoprotein lipase deficiency (LPLD) through patient assessment of the existing European Organisation for Research and Treatment of Cancer (EORTC) questionnaires (QLQ-C30 and QLQ-PAN26) and a new questionnaire on disease burden devised by clinicians with experience in treating the condition.

**Introduction:** There is limited data on the impact of LPLD on patients’ QOL.

- LPLD, an ultra-rare (1–2 per 1,000,000) autosomal recessive genetic disorder, is caused by mutations of the gene which encodes lipoprotein lipase (LPL).
- It is characterized by severe chyloptic and chylophia, and severe hyperlipoproteinemia (>2000 mg/dl, or ≥12.6 mmol/l).
- Clinical manifestations of LPLD can be heterogeneous – perhaps due to the large number of different mutations (>200), which have so far been found to cause LPLD.
- At all ages, the most common clinical manifestation is recurrent severe abdominal pain. Other associated symptoms, although not present in all patients are:
  - Eruptive xanthoma
  - Hepatomegaly
  - Lipemia retinalis
  - Dementia, depression and memory loss
- Cardiomyopathic symptoms
- The most severe, sometimes life-threatening complication of LPLD is recurrent episodes of acute pancreatitis, which can lead to pancreatic insufficiency and diabetes.
- Treatment of LPLD has been limited to an ultra-low-fat diet, though this is difficult to sustain and often ineffective. Lipid-lowering drugs show only limited efficacy based on anecdotal evidence.

**Development of a PRO measure in LPLD:**

- Alipogene tiparvovec is the first approved gene therapy in the Western world, developed for the treatment of LPLD.
- Regulators requested development of a reliable measure of QOL in LPLD as part of the risk management plan for alipogene tiparvovec, and for the measure to be included in the GENIALL Registry, a 15-year post-approval safety study on the natural history of LPLD as well as the long-term safety and efficacy of gene therapy (Fig. 1).
- Two existing EORTC questionnaires were considered to have sufficient relevance to LPLD:
  - QLQ-C30: a widely used quality of life measure originally developed to assess the impact of cancer in cancer patients
  - QLQ-PAN26: an add-on module to the QLQ-C30 assessing concerns and symptoms of pancreatic cancer patients
- Both QLQs have been successfully tested among patients with chronic pancreatitis and recurrent acute pancreatitis, and diseases with clinical features overlapping with LPLD.
- A new questionnaire of disease burden has been created by clinicians with experience in treating LPLD to supplement the existing, non-LPLD-specific measures, but has never been systematically assessed by LPLD patients.

**Results:**

- The participants had a mean age of 38 years (range 19–56) and included 6 males and 5 females.
- In the EORTC QLQ-C30 12 of the 30 items (40%) and in the PAN-26 14 of the 26 items (54%) were considered relevant by the majority of the participants.
- Key items were identified aligned closely with the well-known manifestations of LPLD (Figure 2; Table 1).

**Conclusions:**

- This evaluation represents a significant and positive step towards a validated PRO for LPLD.
- Six domains relevant to LPLD among LPLD patients have been identified in the existing EORTC C30 and PAN26 questionnaires.
- The items in the new LPLD-specific disease-oriented questionnaires are relevant, important, and are well understood by patients.
- The revised measure will be psychometrically validated in a broader sample of LPLD patients within the GENIALL Registry.

**Methods:** Quantitative assessment and in-depth interviews

- Participants: 12 genetically confirmed LPLD patients from Canada (N=2), France (N=3), Germany (N=1), Italy (N=1), The Netherlands (N=1), and The United Kingdom (N=1).
- IRB approval was obtained and all participants provided informed consent.
- Procedures:
  - Local language versions were created through standard translation procedures for PROs.
  - Participants individually assessed each item of the three questionnaires for relevance (yes/no), and importance (1=not at all, 4=very much)
  - Patients’ ratings were discussed during an in-depth, face-to-face cognitive debriefing interview
  - Incremental changes were made to the LPLD questionnaire based on participant feedback from the first 7 participants, and the adapted version was tested in another 4 LPLD patients.

**References:**


2. Genetic Risk Reference – a resource of the Wellcome Trust Sanger Institute available via http://www mantra.wtsi.org/qlq-gpa/QLQ-GPA


