Liver involvement in Myotubular and Centronuclear Myopathy:
Review of one year of data collected by the MTM & CNM Patient Registry

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Study Background

What is the Myotubular and Centronuclear Myopathy Patient Registry?

The Registry is a patient-initiated international platform, collecting data from Myotubular Myopathy (MTM) & Centronuclear Myopathy (CNM) patients. Key features include:

- **547** participants from **57** countries
- Questionnaires available in **ten** languages.
- **Collaborations with patients and professional leaders** to expand clinical knowledge and support evolving research.

Why are we studying liver health?

There is growing awareness of liver related dysfunction (naturally occurring & treatment related) in MTM patients:

- Three clinical trials halted due to liver-related serious adverse events **(four liver related deaths in ASPIRO gene therapy trial)**
- Ongoing reported cases of liver health problems within MTM patient community

What is the MTM-CNM Liver Collaborative?

Patient organisations MTM-CNM Family Connection (US) and Myotubular Trust (UK) recognised the **urgent need to better understand liver-related dysfunction** and brought together experts from clinical research, patient advocacy, and pharmaceutical industry to create MTM-CNM Liver Collaborative in August 2021.

Methodology

Two new questionnaires (Liver Health and Diet & Nutrition) were designed by the Liver Collaborative and made available for data collection via the patient registry in April 2023 and July 2024 respectively. The group adopted a **consensus-building approach** driven by **patient leaders,** prioritizing real-world experiences of liver, nutrition and diet health.

- Data collected directly from patients (>18) and carers, through Registry platform to ensure quality and availability to stakeholders.
- Newly added sections promoted by *Registry*, *MTM-CNM Family Connection* and *Myotubular Trust.*
- Registrations verified by **review of genetic reports** where available.
- Aggregate data reported from participants' most recent entries and response rates shown by denominator in figure titles.

Liver Collaborative Questionnaires

Liver Health Questionnaire

- Questionnaire added to assess liver screening prevalence and improve liver health understanding
- We present results from **228 liver health** responses collected (April 2023 – March 2025)

Diet and Nutrition Questionnaire

- Questionnaire created in response to emerging evidence of **relationship between diets and liver health** in XLMTM mouse models (*Dowling Lab – Myology 2024)*
- Questions added to understand **what, when and how** patients eat
- We present early findings from **99** responses collected (August 2024 – March 2025)

Key Findings & Further Research Questions

Diagnosed liver conditions and abnormalities more prevalent in MTM patients than CNM patients

- What is the underlying cause of these liver issues and why do they impact MTM patients?

Those who indicated using invasive ventilation had higher incidences of liver abnormalities.

- Are both ventilatory and liver manifestations indicators of underlying increased severity?
- Is this higher incidence unique to this patient cohort?

Of living patients who indicated liver abnormalities, only half have been diagnosed with a liver condition.

- Are liver diagnoses being underreported?
- Is there a need for increased awareness/surveillance and further research into possible underlying liver disease?

Ultrasound indicated as most common form of liver imaging in respondents with liver diagnosis.

- Is ultrasound the best liver imaging modality for MTM/CNM?
- Do considerations in MTM/CNM (tracheostomies or surgical hardware) hinder use of imaging techniques that may be better for liver imaging?

Lessons Learned

This patient-driven initiative demonstrates the power of collaboration among patient organizations, clinicians, researchers, and industry to address key research questions. Data collected through the Registry has provided clinically relevant evidence directly from the patient perspective.

- *Registry and Liver Collaborative* demonstrated ability to respond to evolving research needs, mobilize stakeholders, and **prioritize patient reported outcomes & real-world data.**
- **High response rates** to questionnaires in short timeframes suggests an engaged **patient cohort.**
- Collaborative effort enhances understanding of comorbidities and may guide future drug development initiatives
- Further investigation can be **aided by the *MTM-CNM Patient Registry*.**

Liver Health Questionnaire Results

228 participants responded to the Liver Health questionnaire

- 204 living participants (120 male and 84 female)
- 24 deceased male patients (22 had MTM, 2 had CNM)*
- Mean age (±SD) of living individuals was 27.3 ± 21.6 years (range 0-87 years)
- Genetic confirmations received from 77% of respondents

Individuals with **MTM are defined as anyone with a mutation in the **MTM1 gene**. Individuals with **CNMs** are defined as anyone with a recognised genetic basis of CNM, which **includes mutations in BIN1, DNM2, RYR1, TTN**. The category **'MTM Female'** is defined as women with a mutation in the MTM1 gene and is a combination of patients, who are manifesting female carriers, and non-manifesting female carriers.*

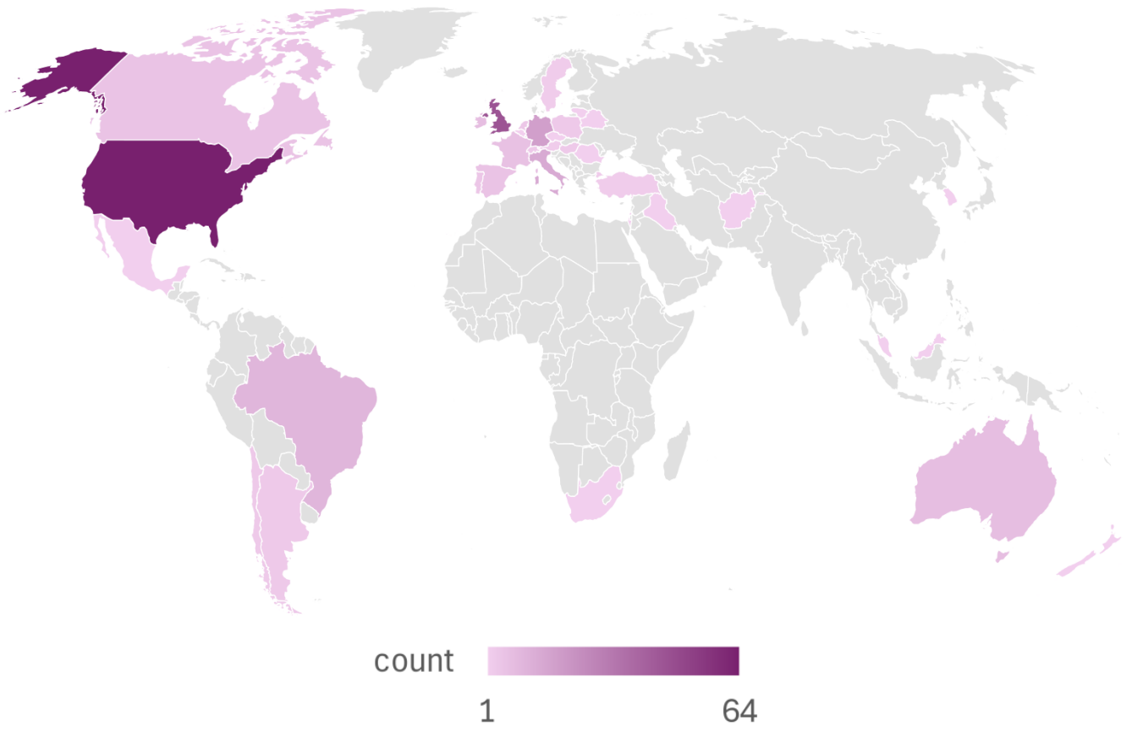

Figure 1: Map of liver health questionnaire respondents' country of residence by number of responses *(n=228)*

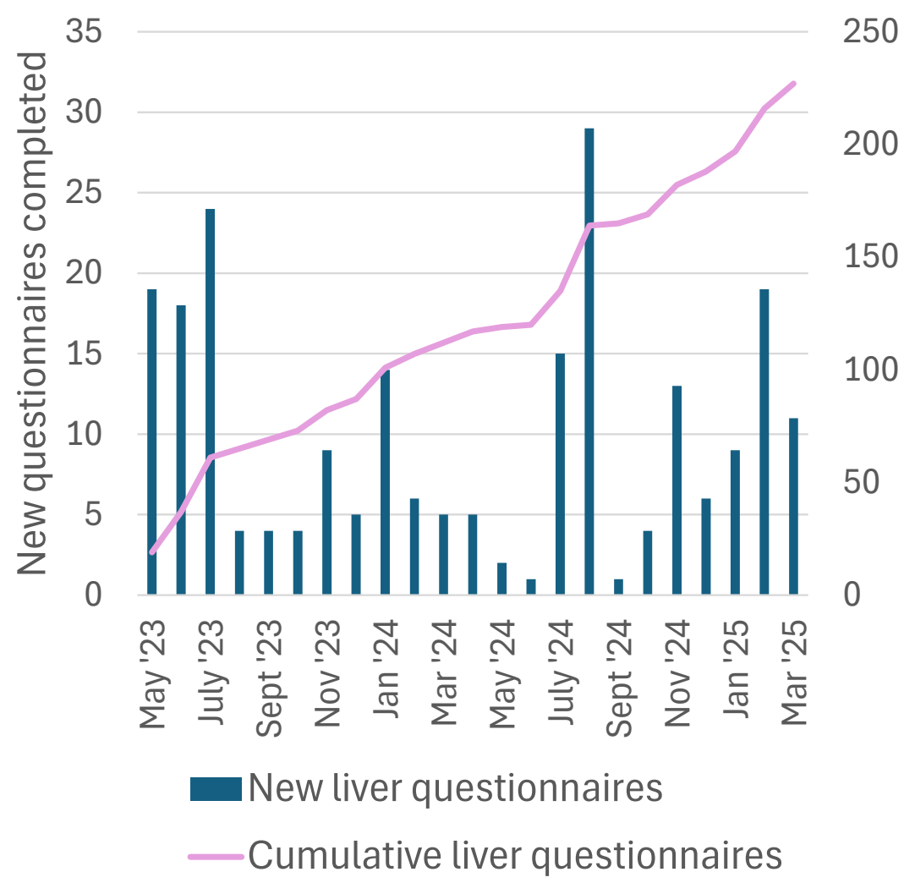

Figure 2: Response rate of liver health questionnaire over time *(n=228)*

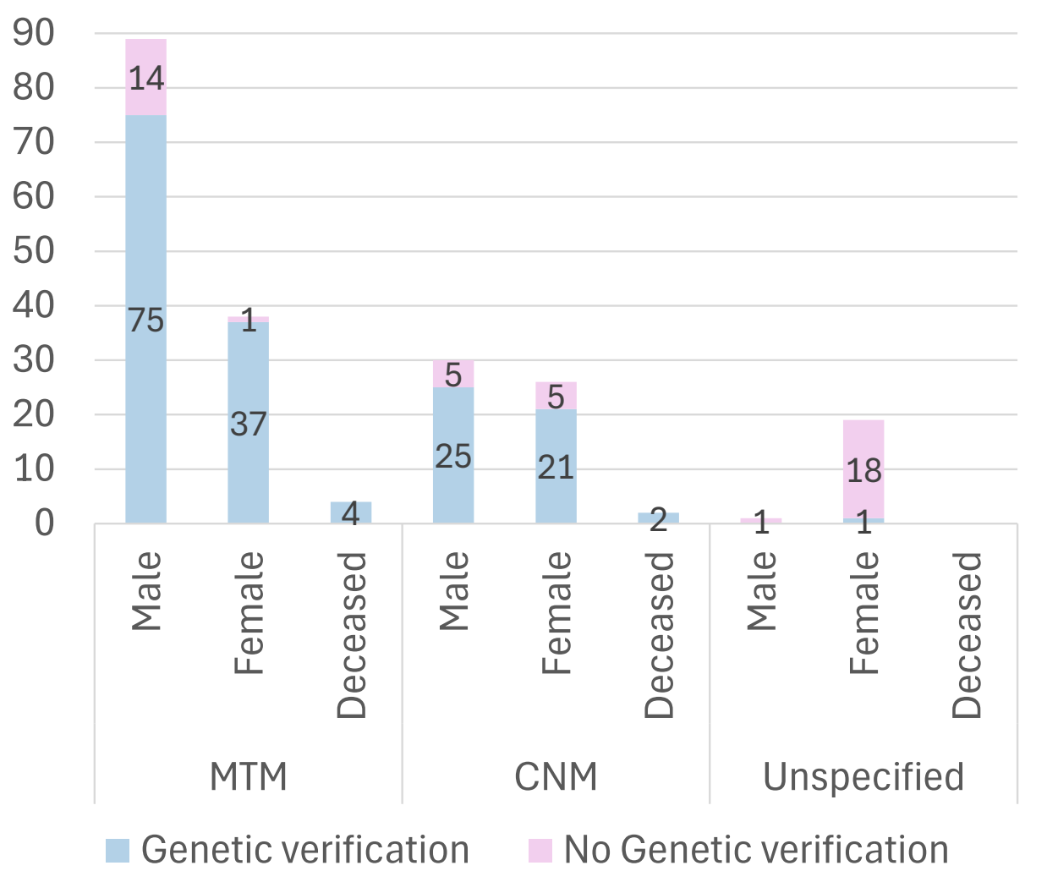

Figure 3: Neuromuscular diagnosis of the liver health questionnaire respondents *(n=228)*

Liver health questionnaire respondents were asked about their **liver symptoms, labs and diagnosis.** Of the **228** liver questionnaire respondents, **33** patients reported a **diagnosis** of one or more **liver conditions (14.5%)**

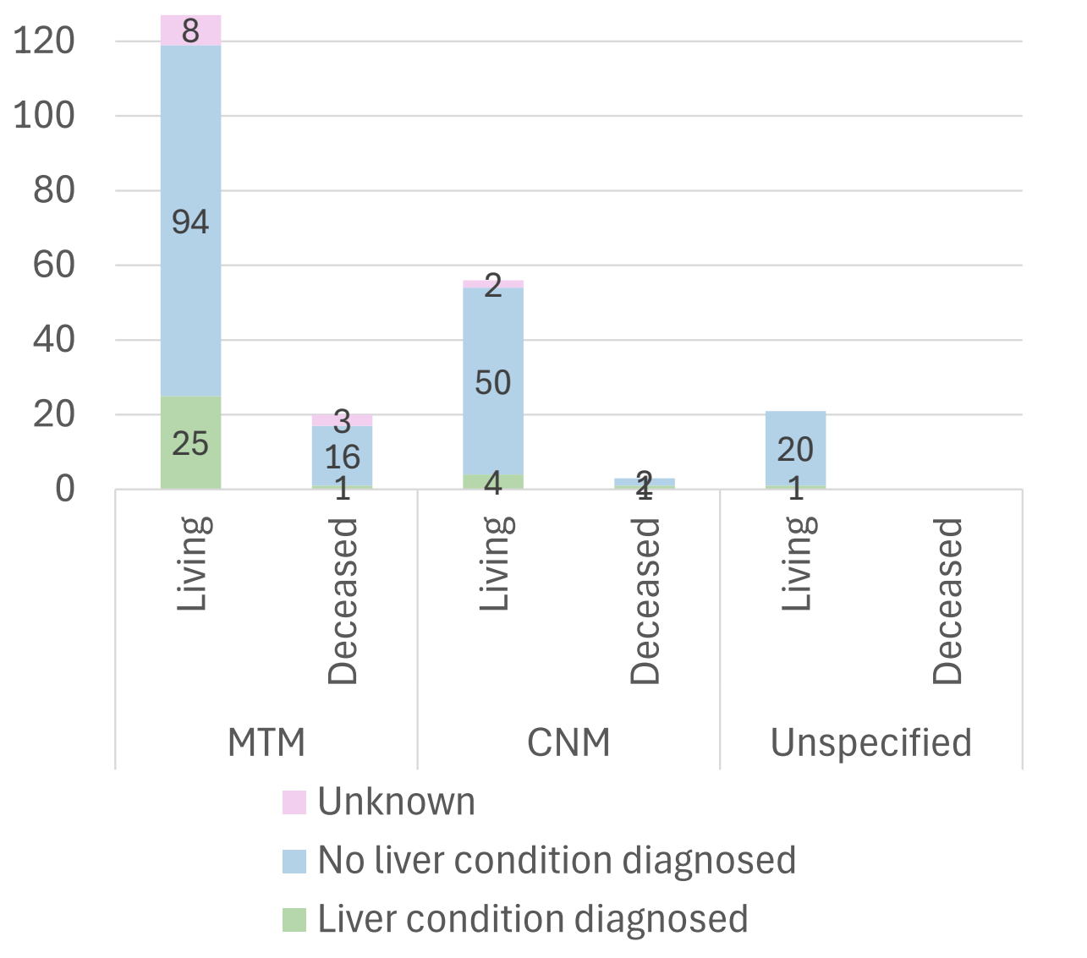

Figure 4: Neuromuscular diagnosis of patients reporting on liver diagnosis status *(n=227)*

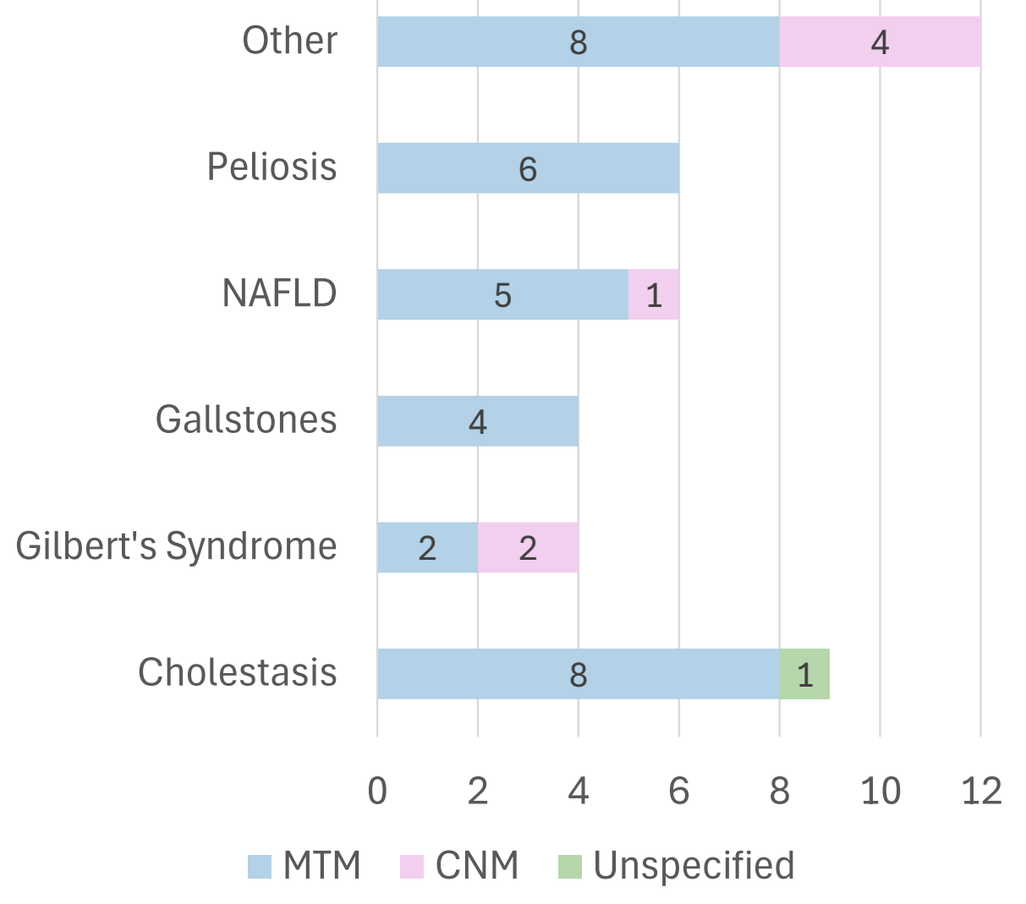

Figure 5: Diagnosed liver conditions of questionnaire respondents *(n=33)*

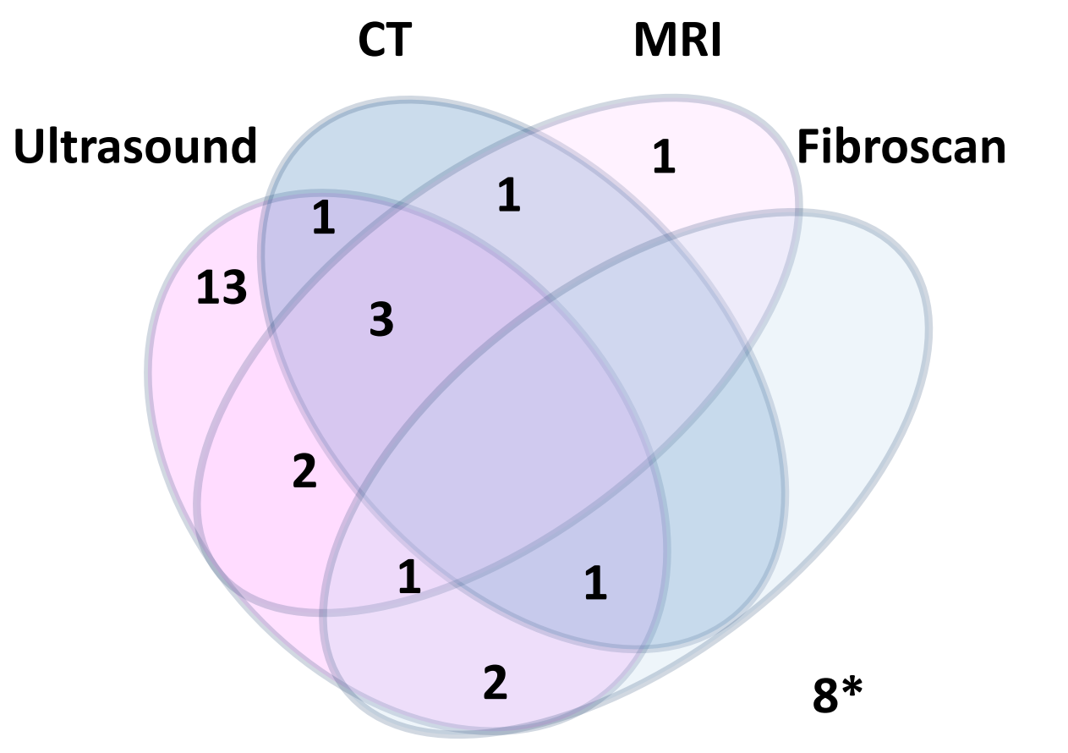

Figure 6: Liver imaging received by patients who reported a diagnosed liver condition *(n=33)* *8 patients reported diagnosis but did not receive liver imaging

Some patients reported abnormal liver lab values including abnormal **serum bile acid, PT, GGT, AST, albumin, bilirubin, ALP and ALT.**

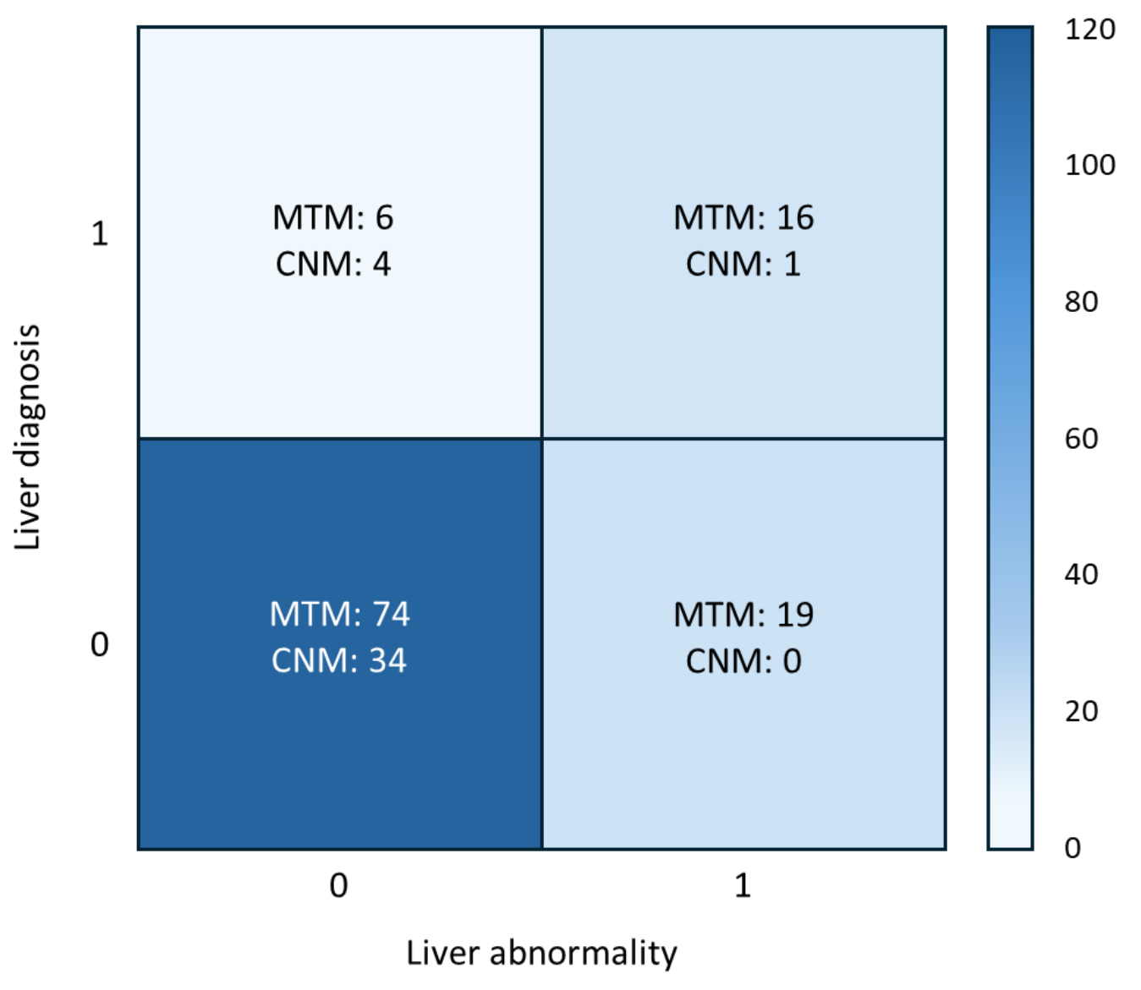

Figure 7: Correlation between abnormal liver lab values and a diagnosed liver condition *for living, genetically confirmed patients (n=159)*

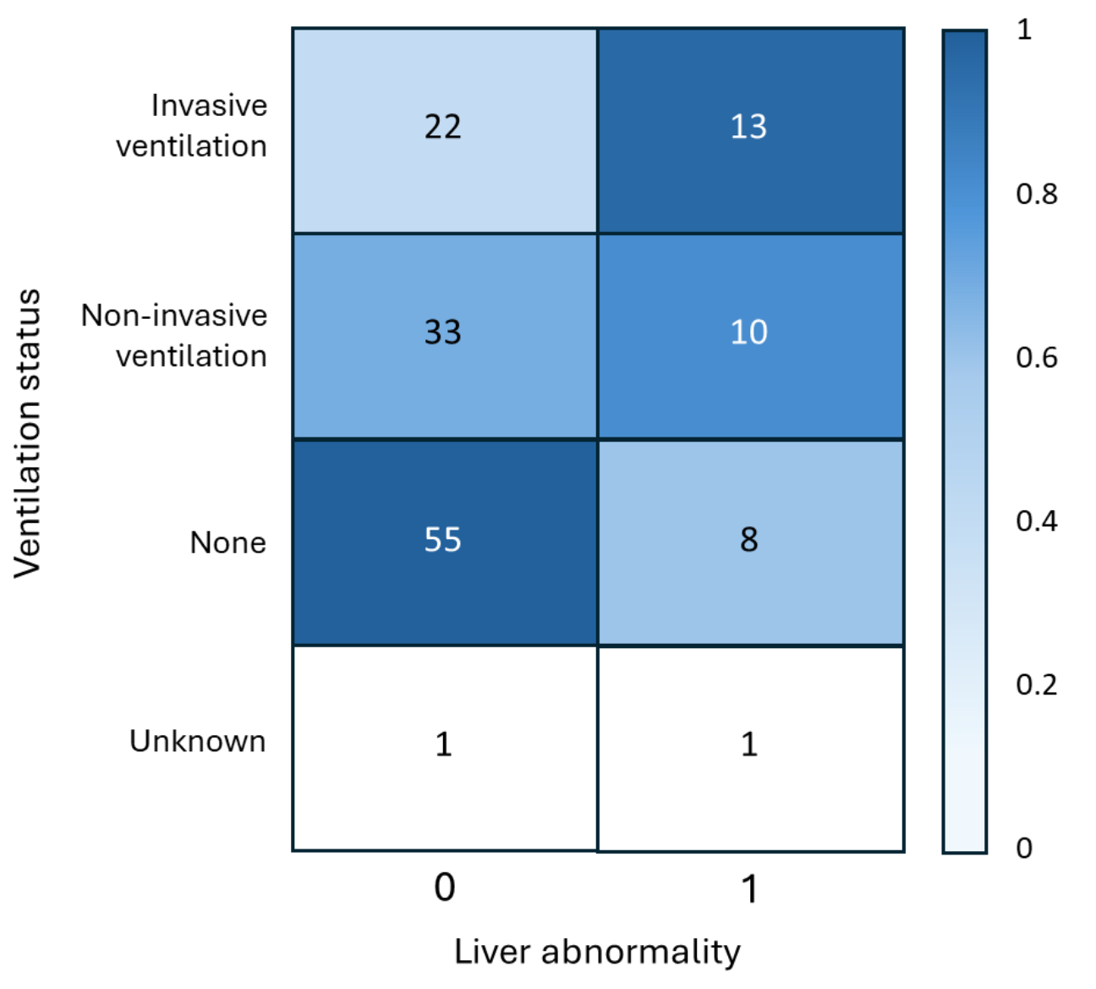

Figure 8: Correlation between abnormal liver lab values and ventilation support required, normalised by column *for living, genetically confirmed patients (n=143)*

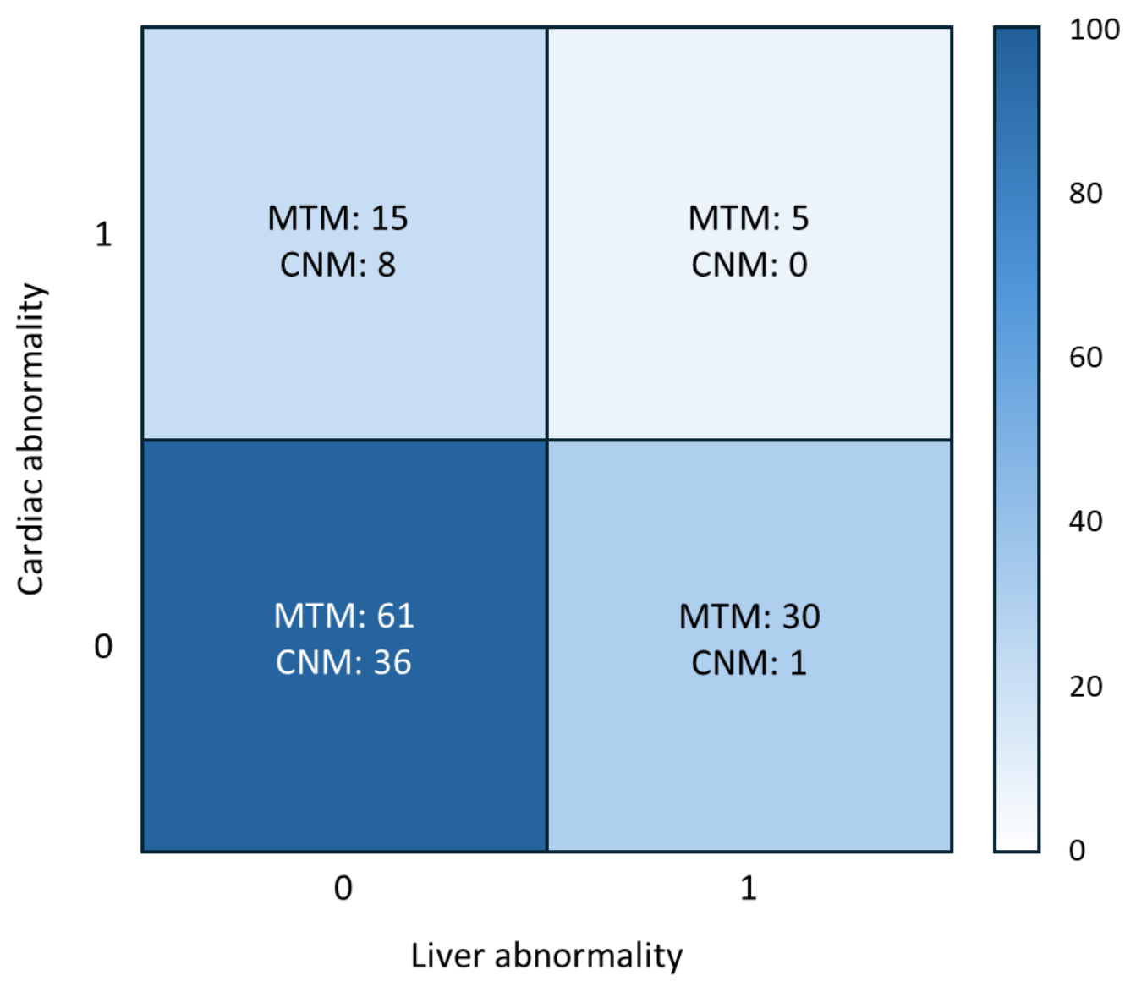

Figure 9: Correlation between abnormal liver lab values and abnormal cardiac values (*abnormal ECG and/or ECHO)* for *living, genetically confirmed patients (n=156)*

Diet and Nutrition Questionnaire Results

99 participants responded to the Diet and Nutrition questionnaire over a seven-month period

- 92 living respondents (53 male and 39 female)
- 7 deceased male patients with XLMTM diagnosis
- Genetic confirmations received from 79.8% of respondents

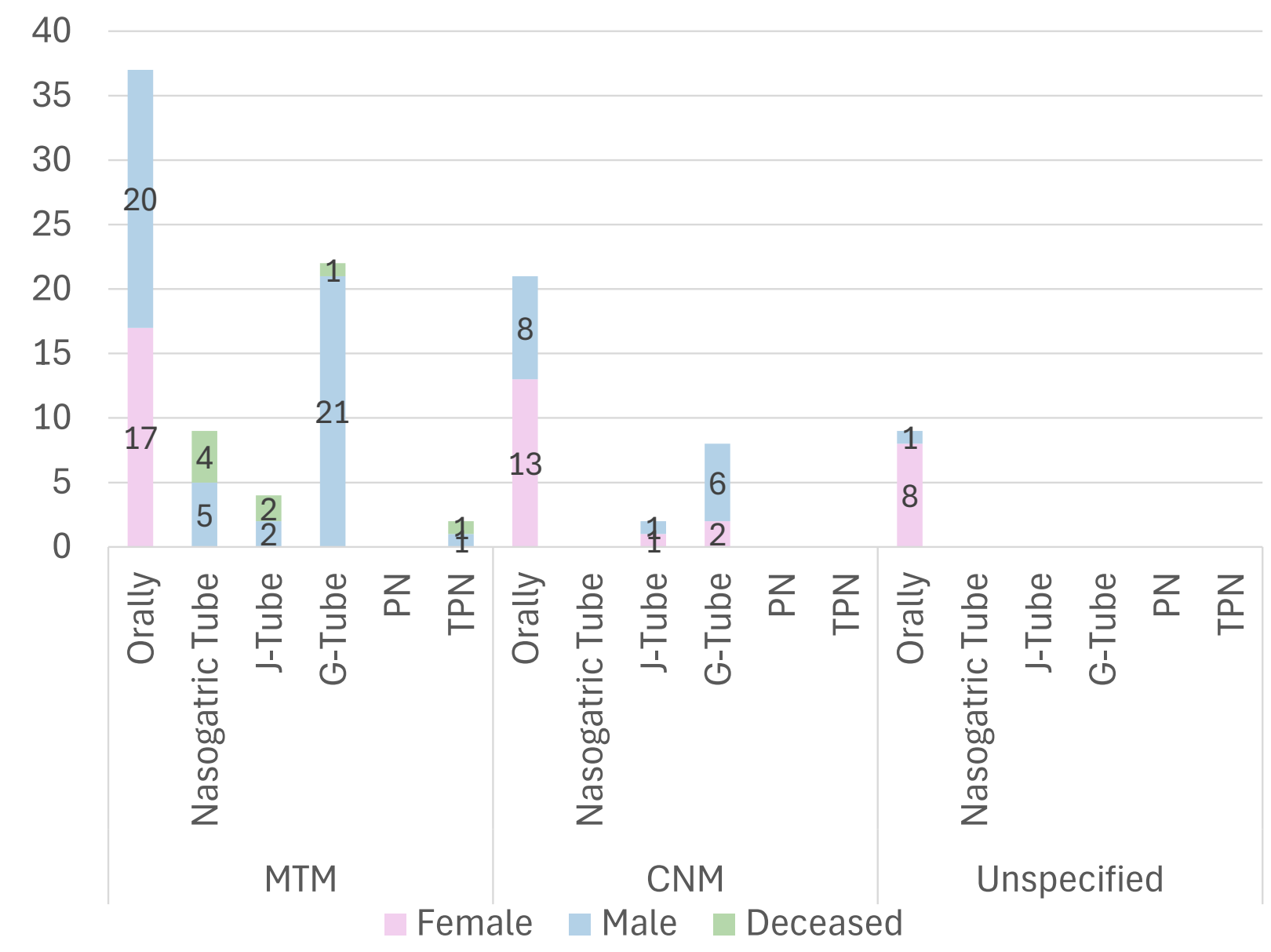

Figure 10: Reported 'current' or 'typical' modes of nutrition for nutrition questionnaire respondents *(n=99)* Patients were asked to select <u>all</u> modes of nutrition

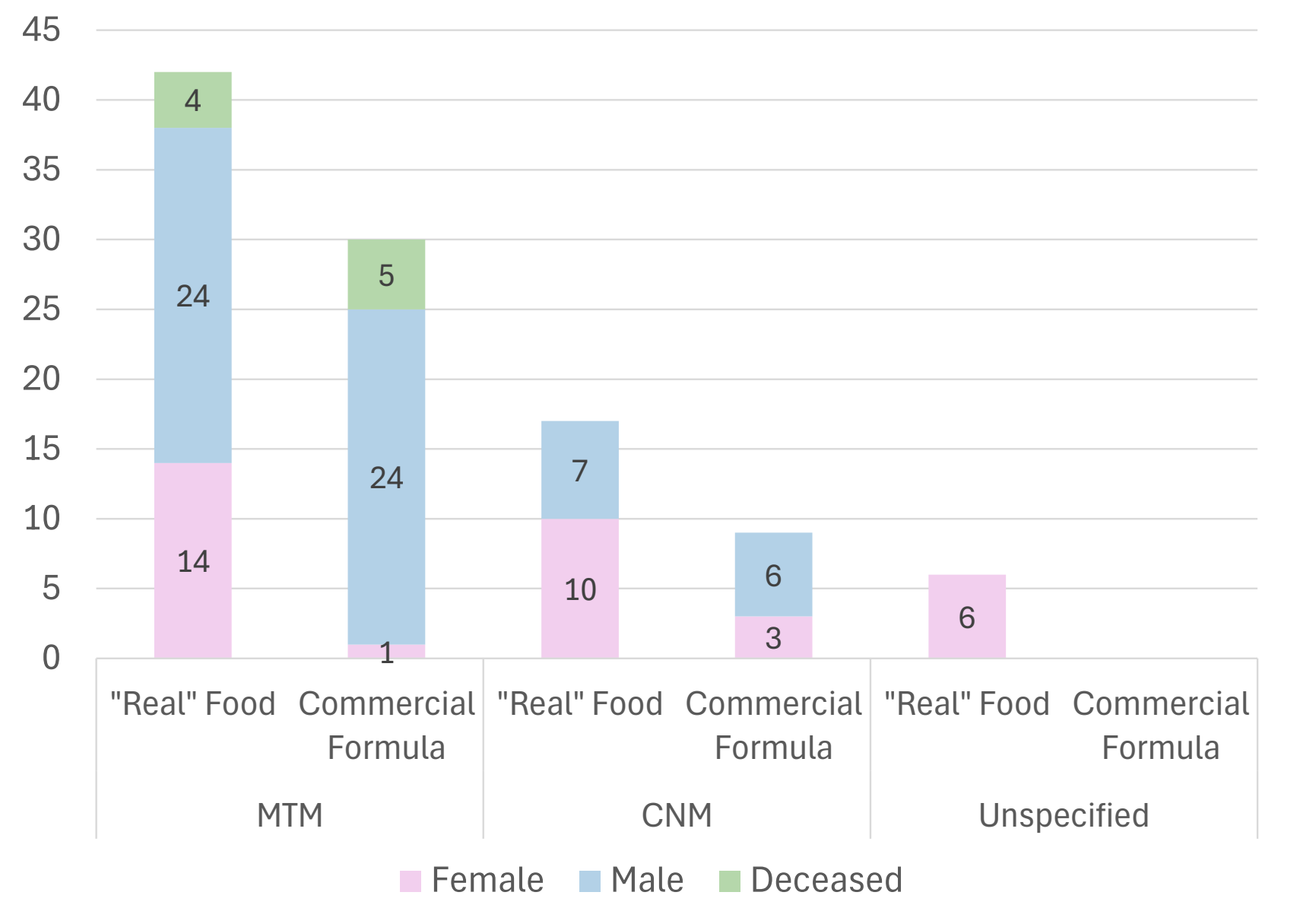

Figure 11: Reported 'current' or 'typical' diet for nutrition questionnaire respondents *(n=85)* Patients were asked to select <u>all</u> modes of nutrition

We are grateful to (i) registry participants for their involvement in entering data, (ii) the Liver Collaborative Working Group for their enthusiasm, commitment and input into developing the questions (iii) patient organisations MTM-CNM Family Connection and the Myotubular Trust UK for their drive, determination and enthusiasm to learn more, enrich the community and support research (iv) MTM-CNM Steering Group for on-going support and direction of the registry

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