MEN1-Related Neuroendocrine Tumors Show c-MET Overexpression, Ghosh et al. (2025), *Journal of the Endocrine Society*, 9 (10), https://doi.org/10.1210/jendso/bvaf147

❖ Background:

A total of 30% to 80% of patients with multiple endocrine neoplasia type 1 (MEN1) develop duodenopancreatic neuroendocrine tumours (dpNETs) in their lifetime. Malignant dpNETs are a major cause of MEN1-related deaths. Multiple studies have shown that approximately 50% to 70% of patients with MEN1 die of causes directly related to MEN1, particularly dpNETs. Distant metastasis is seen in approximately 15% to 25% patients with MEN1.

While c-MET inhibitors in combination with anti-vascular endothelial growth factor therapy have been shown to result in longer progression-free survival in patients with sporadic NETs, data regarding their efficacy in patients with MEN1-related NETs are lacking.

❖ Aim:

The authors sought to characterize c-MET expression in MEN1-related NETs and evaluate its association with clinicopathologic characteristics.

❖ Methods:

Forty-three tumours from 22 genetically confirmed patients with MEN1-related metastatic NETs were identified. Of these, 15 of 22 (68%) patients had distant metastases while the remaining 7 of 22 had locoregional metastases. c-MET expression was assessed in these tumours via immunohistochemistry. A total of 19 of 43 (44%) were primary tumours (duodenum, pancreas, stomach) while the remaining were metastases. c-MET expression was scored as strongly positive in 3 of 43 (H-score >50), weakly positive in 6 of 43 (H-score: 10-50), and negative in 34 of 43 (H-score <10) tumours.

❖ Results:

Twenty-two patients (10 women, 45%) with genetically confirmed MEN1 and metastatic NET with available tumour specimens were identified. In total, 43 tumours from 22 patients underwent immunohistochemical staining for c-MET expression. All 3 tumours with strong positive c-MET expression were from patients with a distinctly aggressive clinical course. The 6 tumours with weakly positive c-MET expression were from patients with stable disease, including 4 with distant metastases. Of the 13 patients with all tumours negative for c-MET expression, all but 1 had stable disease. Age at initial NET diagnosis; tumour site, type or grade; number of sites of distant metastases; total number of surgeries for NETs; or the stability of overall tumour burden did not predict c-MET expression.

❖ Conclusions:

c-MET expression was increased in MEN1-related NETs in 8 of 15 (53%) patients with distant metastases. Of note, findings from the recently reported pivotal phase 3 CABINET trial (NCT03375320) evaluating cabozantinib, which targets c-MET in addition to growth arrest-specific protein 6 receptor and vascular endothelial growth factor receptor, demonstrated improvements in median progression-free survival for patients with advanced PNETs and advanced extrapancreatic NETs.

The authors propose the findings suggest a role for c-MET inhibition in personalizing therapy for patients with MEN1-related NETs. They propose that future research to explore the therapeutic potential of c-MET inhibitors and development of biomarkers to identify patients who may benefit from c-MET inhibition can broaden the treatment landscape in NETs caused by menin loss.

❖ Reflections for practice:

As a genetic counsellor working in the specialist setting of endocrine genetics and seeing families affected by MEN1 regularly, this article was a helpful reminder of the major causes of mortality for individuals with MEN1. As I mainly see child and adult patients for presymptomatic testing I think it's important to keep this in mind, particular as this is a condition that results in reduced life expectancy. It is good to know that research is under way to identify therapeutic targets for MEN1 patients with advanced dpNETs and to further understand the mechanisms of MEN1 molecular pathology. Figure 3 in the paper is particular helpful in illustrating this.

Testing Meningiomas with Methylation Arrays: Insights and Recommendations from a Large Single-Centre Study, Ruiz, Fernanda, et al. (2025), *Neuropathology and Applied Neurobiology*, 51 (3), https://doi.org/10.1111/nan.70018

- Histological diagnosis and WHO grading of meningiomas follow well-established CNS WHO criteria that define 15 histological subtypes and three grades (CNS WHO Grades 1–3). While mitotic figures are the most reproducible grading feature, other histological parameters are subjective and less reliable.
- Molecular profiling, including methylation and chromosomal copy number analysis, has refined prognostication and improved prediction of early recurrence risk in meningiomas.
- The integrated model score combines histological grade, methylation class, and chromosome copy number losses. Scores range from 0–9, corresponding to low (0–2), intermediate (3–5), and high (6–9) risk groups, and are suitable for inclusion in molecular diagnostic workflows.
- Since meningiomas are among the most common adult brain tumours, testing all cases with methylation arrays is not economically feasible, making selective testing essential.
- This study analysed a cohort of meningioma patients using an integrated method combining WHO histological grading, methylation classification, and copy number profiling to determine which subgroups benefit most from molecular testing.

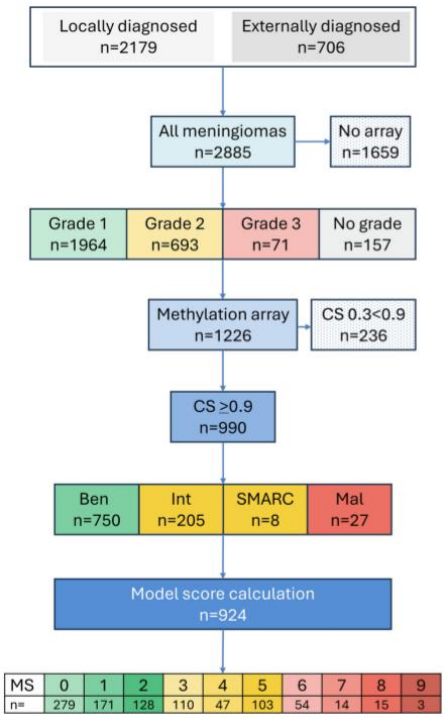

Figure 1. *Diagnostic workflow of the study. Meningioma cases with a calibrated classifier score ≥ 0.9 were included for methylation class definition and integrated model scoring.*

- Methylation array analysis was performed on 1226 samples from the cohort, and arrays with a calibrated classifier score of 0.9 or higher (n=990) were used to establish methylation classes
- Approximately 90% of the Grade 1 meningiomas were assigned a benign methylation class and low-risk model scores. About 10% of the Grade 1 meningiomas were assigned intermediate methylation class and model scores, and one case was SMARCE1-altered.
- Around 2/3rd of the Grade 2 meningiomas were benign, over 1/3rd intermediate, 3% malignant and 1.6% SMARCE-1 altered. The model scores were spread out similarly, ranging from 1 to 8, covering all three risk groups.
- Similar proportions of Grade 3 meningiomas were assigned benign, intermediate, and malignant methylation scores, with model scores between 4 and 9.
- From this study, it was concluded that grade 2 meningiomas benefit the most from methylation profiling because of the wide variability in risk group allocation. It was recommended that grade 2 and grade 3 meningiomas are prioritised for additional methylation analysis under economic constraints.
- If further prioritisation is required, tumours with mitotic counts above 12 per 10 high-power fields can be confidently assigned to intermediate and high-risk groups and do not require additional profiling. Tumours that are ungraded or have chromosome 1p or 22q loss would also benefit from methylation analysis as these features correlate to higher recurrence risk.

Evaluation of whole-body MRI for cancer early detection in Li-Fraumeni syndrome, Sodde et al. (2025), *Cancer Genetics,* doi:10.1136/jmg-2025-110704

Introduction

- The current UK guidelines for LFS surveillance was introduced in 2021 and recommend that LFS patients have access to an annual clinical review, brain MRI and whole-body MRI
- This study evaluates annual WB-MRI and brain MRIs in adults at a single centre

Methods

- Retrospective study looking at adults who accessed annual WB-MRIs between 2012 and 2024 and brain MRIs between 2017 and 2024

Results

- 75 individuals included in the study (72 had a constitutional *TP53* pathogenic variant and three had somatic mosaicism)
- Individuals had an average of 4.3 scans with an average interval of 15.4 months
    - 65.5% of WB-MRIs were reported as normal
    - 34% (112/325) showed abnormalities on the WB-MRI
        - 23/112 showed lesions of concern. 9 cancers were found identified; 7 were primary and 2 were metastatic cancers.
        - 8 interval cancers were diagnosed in 7 individuals following a reported normal WB-MRI scan
        - 89/112 showed benign incidental findings
    - 27.4% (89/325) WB-MRIs in 72/75 individuals identified 65 different benign looking lesions, which resulted in 53 additional investigations In 46 individuals with no cancers identified.

Conclusion

These findings show the urgent need to develop novel means of early detection that either completes imaging as a surveillance tool, or enable imaging to form part of the diagnostic pathway where an abnormal early detection marker is seen in this high-risk population.

Patients' and healthcare professionals' experiences with implementing the Rosa chatbot in mainstream genetic testing for hereditary breast and ovarian cancer, Siglen et al. (2025), *Journal of Genetic Counselling*, 34, https://doi.org/10.1002/jgc4.70119

Introduction

- The Rosa chatbot was developed in Norway and evaluated between the years of 2018 and 2022. It contains information about;
  - Genetic testing with a focus on BRCA genes
  - Surveillance programs
  - Family communication
- By using this chatbot, patients are able to personalise the information flow and read information again as they wish.
- It uses machine learning and natural language processing to understand patient questions and retrieve predefined answers
- The chatbot can be accessed through a mobile app, where they can interact via the chat function, explore additional resources or watch educational videos
- Chatbots have the potential to reduce the time burden and complexity associated with genetic cancer risk assessments

The aim of this study was to explore how newly diagnosed patients with breast or ovarian cancer and healthcare professionals experience the use of Rosa chatbot in mainstream genetic testing and the potential barriers.

Methods

- 335 newly diagnosed breast and/or ovarian cancer patients in Western Norway were invited to use Rosa chatbot for genetic test information alongside mainstream genetic testing
- The chatbot was introduced by the clinician during the consultation when discussing genetic testing, as an additional resource to written and oral information
- Qualitative interview study was conducted with the patients and HCPs
  - 6 patients interviewed with breast cancer and one with ovarian cancer
  - 10 HCPs were interviewed
- Patients interview guide focussed on;
  - Experience with genetic testing alongside receiving cancer diagnosis
  - Using the Rosa chatbot during MGT
  - How was the information and communication with the hospital perceived
  - Experiences of digitalization and how it has influenced relationship with health services
- HCP interview guide focussed on;
  - How was the Rosa app introduced to patients
  - What potential did they see in the communication tool
  - The impact digital tools such as Rosa may have on health services
  - Thoughts on implementing Rosa in clinical care

Results

- 7 thematic groups were created based on the patient interviews and 8 based on the HCP interviews
- The thematic groups were grouped and developed into concepts

1. Trusted supplement to genetic testing

Both patients and HCPs considered the chatbot as a trusted supplement to genetic testing. Common words used were user-friendly, available, safe, professional and trustworthy. Patients

saw the chatbot as objective and trustworthy. HCPs also viewed it as useful and trustworthy for providing consistent and accessible genetic information.

2. Tool for balancing facts, fears and hopes

All the patients said the amount of information at the stage of diagnostic testing is overwhelming. Several patients mentioned that the chatbot meant they could choose what to read and when and avoid topics they did not want to read about just yet. HCPs valued the chatbot as a trusted resources they could confidently recommend for reliable information. They also highlighted the importance of a chatbot being a supplement, not a replacement.

3. Valued support for decision-making

The chatbot was described as a useful tool for clarification. All of the patients expressed they would like to speak with a human if a mutation was detected. Many patients said they would have used the chatbot more if a mutation was detected.

4. Impersonal tool – fear of missing out on human interaction

While Rosa provides valuable information, many patients feel it lacks depth, empathy and personalised support that human interaction offers. One patient feared the risk of misunderstanding. Some mentioned the feeling of responsibility of reading and learning in your own time. Patients also feel uncertain if the information is truly transferable to their unique situation. HCPs mentioned a potential risk of patients not contacting HCPs with questions leading to uninformed patients or misunderstandings. The importance of face-to-face contact was mentioned to pick up on subtle signals patients express.

Conclusion

- Rosa chatbot was regarded as a valuable and trustworthy tool by both cancer patients and healthcare professionals during mainstream genetic testing
- Patients can choose what they read and when. They can also avoid topics that they are not ready to read about.
- Rosa chatbot was considered a valued support for decision-making, providing accurate and timely information
- However, patients also want human validation of the information and interaction
- The findings identify an emotional barrier described by both patients and HCPs which need to be addressed to ensure the successful implementation of the increasing number of digital tools in modern healthcare.

Monthly Journal Round-Up brought to you by:

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