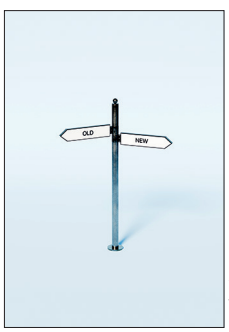
Experience evolves into evidence in the new MEN1 guidelines



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Nearly a quarter of a century has passed since the publication of the first clinical practice guideline on multiple endocrine neoplasia type 1 (MEN1) in 2001, which followed the identification of the *MEN1* gene.[1,2] Together with a 2012 update, those guidelines accompanied the implementation of *MEN1* genetic screening programmes worldwide.[3] Thus began the crucial work of identifying genetically not only MEN1-affected patients but also pre-symptomatic *MEN1* variant carriers at an ever-younger age. The data gathered over this period have shown us the nature of MEN1: that it is one of the most challenging hereditary cancer syndromes in medicine. MEN1 has multifaceted disease manifestations and genetic testing is merely the beginning of a near lifelong process of vigilance that combines clinical examination, hormonal studies, and imaging in patients and carriers of *MEN1* variants. The publication of new guidelines on MEN1 marks an important evolution in how the disease is managed, including 55 specific recommendations covering genetic testing, screening, and management.[4] Owing to the heterogeneity of disease features, the bulk of the recommendations are derived from a Delphi consensus process based on expert opinions. Unlike previous iterations, however, these guidelines now include new evidence-based recommendations generated by a process of three systematic reviews and a meta-analysis.[5]

To generate the new evidence base, the expert group selected three clinically relevant questions to explore, one for each of the three prime tumour sites: the parathyroid glands, anterior pituitary, and endocrine pancreas. For the parathyroids, the question examined was whether subtotal parathyroidectomy was superior to a more conservative less than subtotal parathyroidectomy surgical approach. The resultant finding was logical in that a more complete surgical approach provided lower hyperparathyroidism recurrence, but at the cost of a higher rate of hypoparathyroidism. As neither parathyroid hormone excess nor deficiency are trivial conditions, expertise in parathyroid surgery is a crucial variable to optimise clinical outcomes in MEN1. This finding in MEN1 is strongly supported by independent evidence, most recently from the Get it Right First Time study on parathyroid surgery at National Health Service (NHS) England, where high surgeon case volume significantly increased surgical success and lowered hypoparathyroidism.[6] Given the virtually complete lifetime penetrance of primary hyperparathyroidism in MEN1, clinical MEN1 groups should forge permanent partnerships with high volume parathyroid surgical units.

The second question examined whether active surveillance was a viable option for the management of smaller (ie, sized ≤2 cm) non-functioning pancreatic neuroendocrine tumours in MEN1. As progression and metastasis of pancreatic neuroendocrine tumours is a key contributor to disease mortality in MEN1, there can be concerns about the safety of watchful waiting in smaller, clinically silent tumours, such as non-functioning pancreatic neuroendocrine tumours. The heterogeneity in study design and reported outcomes precluded feasibility of a meta-analysis for this question. However, the systematic review suggested no difference in metastatic disease and mortality outcomes between active surveillance and surgical resection in stable non-functioning pancreatic neuroendocrine tumours (≤2cm). The new guidelines interpret this finding cautiously. In each patient with non-functioning pancreatic neuroendocrine tumours, an individualised approach is recommended to establish the growth characteristics over a period of 2 years. After this time period, stable or slow-growing lesions (<1 mm/year) could be imaged slightly less frequently than before. This management refinement probably will not offer much in the way of resource and time savings, but the pragmatism is warranted given the consequences of missing a growing tumour. Adding to the need for caution is the fact that the comparisons between active surveillance and intervention were informed by a small database of events; undoubtedly this question will need to be monitored and validated in the future.

The group finally assessed the long-debated issue of whether prolactinomas in MEN1 differ from non-MEN1 tumours in terms of responses to dopamine agonists. Historical series of MEN1-related pituitary adenomas have shown that although prolactinomas are the most frequent clinical subtype in both patients with MEN1 and the general population, MEN1-related

prolactinomas seemed to be larger and more resistant to dopamine agonists.[7] However, the new systematic review shows that MEN1-related prolactinomas respond well to dopamine agonists and do not differ appreciably from non-MEN1 controls. The previously observed difference in pituitary adenoma clinical characteristics between patients with and without MEN1 is probably largely due to modern screening measures in carriers of *MEN1* variants, resulting in decreased pituitary adenoma size at diagnosis, albeit accompanied by many clinically innocuous incidentalomas.[8] These factors have encouraged the new guidelines to suggest that carriers of *MEN1* variants begin pituitary screening later than before, with hormonal testing at age 10 years and MRI starting at age 15 years. This change is pragmatic: although germline *MEN1* variants can occur in young patients with large, dopamine agonist-resistant prolactinomas, they are extremely rare and are not typical of MEN1-related pituitary adenomas.[9]

Guidelines aim to deliver clinically relevant recommendations that are appropriate for the so-called typical patient. MEN1 is a very complex disease with challenging presentations and aggressive features. Despite much granular detail in the guidelines, data on aspects of MEN1 are often insufficient to provide clarity. For example, an increased risk of breast cancer in women with MEN1 is known, but as screening methods are heterogeneous in different countries, the new guidelines do not alter screening recommendations. In a wider sense, little is known about how variants in *MEN1* and other common cancer-risk genes interact, and it should be assessed whether other cancer risk alleles (eg, *CHEK2*, *PALB2*, etc) can alter the penetrance or behaviours of tumours in MEN1.

MEN1 can act as a signpost for the management of emerging genetic multiple endocrine syndromes, such as MEN4 and MEN5. There are some important caveats to consider when applying guidelines with extensive recommendations to clinical practice. A multiplicity of tests and interventions are needed to monitor disease onset and activity effectively across various organs. Taken together, the accumulation of clinical, biochemical, and radiological testing is burdensome, particularly as much is borne by pre-symptomatic carriers who are not yet patients per se.[10] Substantial economic and health resource utilisation considerations aside, the application of these MEN1 guidelines in clinical practice needs to be tailored to the clinical benefit of each patient, family member, or pre-symptomatic carrier. One of the goals of evolving guidelines should be the optimisation of surveillance activities and interventions to identify and eliminate those that are unnecessary, have a low yield, or are accompanied by adverse effects. The best way to do this is to use an evidence-based approach as done in this latest revision. Guidelines are, by definition, backward looking, being based on summarising what has been shown to have worked, or to have not worked, in the past. To improve future iterations of guidelines, new ideas need to be assessed. To streamline disease surveillance, there might be potential for identifying circulating tumoral biomarkers or using radiomic analyses to interrogate suspicious lesions. Continued fundamental work is needed to identify whether additional molecular factors can determine when and in whom neuroendocrine tumours or pituitary adenomas are more likely to occur. As patient cohorts with MEN1 continue to expand, this growing population will provide a platform to assess personalised therapeutic approaches in challenging pathologies, such as neuroendocrine tumours. By incorporating an ever-increasing number of evidence-driven findings, best practice recommendations in MEN1 can continue to evolve towards an optimal balance of surveillance and treatment to improve long-term patient outcomes.

AFD declares stock in Grafton Therapeutics.

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