Follow-up recommendations for completely resected Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs): Consensus Guidelines from the Commonwealth Neuroendocrine Tumour Collaboration (CommNETS) in conjunction with the North American Neuroendocrine Tumour Society (NANETS)

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BACKGROUND
- There is no consensus regarding the optimal frequency or modality of follow-up after resection of GEP-NETs.
- Follow-up may consist of clinical history, laboratory tests and/or imaging.
- Current follow-up guidelines for resected GEP-NETs are based on limited evidence and our large, international practice survey showed poor compliance with NET expert guidelines.
- A need for clear and practical guidelines was identified.

OBJECTIVE
- To develop consensus guidelines for follow-up of resected GEP-NETs.

METHODS
- A RAND/UCLA appropriateness process was employed given the lack of randomized controlled trials.
- A multi-disciplinary practice survey was used to understand current follow-up patterns (Table 1).
- Results from two large retrospective reviews (Ontario, Canada and Tampa, Florida) examining outcome following curative surgery were obtained.

Table 1. Summary of follow-up strategies from review

<table>
<thead>
<tr>
<th>Primary NET</th>
<th>Follow-up after resection</th>
<th>Imaging</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>6–12 months regularly 3, 4</td>
<td>Sono, enhanced axial (Sono)</td>
<td>Biomarkers</td>
</tr>
<tr>
<td>NETS</td>
<td>Not specified</td>
<td></td>
<td></td>
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<tr>
<td>Midgut and Hindgut NET</td>
<td>6–12 months regularly 4</td>
<td>CT, MRI (if lesion is 2 cm or larger)</td>
<td></td>
</tr>
<tr>
<td>Upper GI endocrine</td>
<td>Not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal NET</td>
<td>Not specified</td>
<td></td>
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</table>

Pancreatic NET
- Clinical review with cross-sectional imaging (triple phase CT of the abdomen) every year for 2 years after surgery, and every 2 years for 10 years.
- The decision for ongoing surveillance past 10 years should be discussed with patients, appreciating the lower risk of recurrence compared to midgut NET.
- The role of magnetic resonance imaging (MRI) or ultrasonography to detect recurrence is not fully proven but these may be used as an alternative if it is desirable to avoid CT imaging. There is consensus that thoracic imaging is unnecessary.
- For patients with NET the routine use of biomarkers (including Chromogranin A) for recurrence surveillance is not recommended.

Rectal NET
- A fully resected Grade 1, T1, lymph node negative rectal NET does not require any follow up for recurrence.
- If the margins are positive but no further resection was deemed necessary with hemicolectomy with negative lymph nodes, surveillance due to rarity of recurrence.

Appendical NET
- A fully resected G1 appendiceal NET <1cm does not require active surveillance.
- Not specified

Clinical review
- Follow-up should be performed every 1–2 years for at least 10 years.
- The decision for ongoing surveillance past 10 years should be discussed with the patient.
- Consider CT scanning (triple phase CT of the abdomen and pelvic yearly for 3 years, then every 2–3 years for 10 years in total. Thoracic imaging is not recommended.
- Due to concerns from panel regarding radiation exposure.
- The role of MRI or ultrasound to detect recurrence is not fully known but these may be used as an alternative if it is desirable to avoid CT imaging.
- There are no blood or urine biomarkers (including chromogranin A) that are recommended for routine follow up. This is contrary to popular practice, however it was noted that there is no data supporting the value of measuring somatostatin, chromogranin A or any other biomarker.
- Less frequent surveillance than stated above should be strongly considered for a midgut Grade 1, T1 or T2 lymph node negative NET.
- Increasing grade or stage (T2–T3, N1–N2) midgut NETs require minimal or no follow-up.
- The following risk factors may warrant increased follow-up:
  - Higher Ki67 index or positive lymph nodes.
- If the margin for resection is clear, no further follow-up would definitively warrant increased follow-up.

CONCLUSIONS
- These consensus guidelines differ significantly from current practice.
- The expert consensus was informed by previously unavailable large datasets.
- To our knowledge, this is the first NET guidelines using RAND appropriateness methodology, due to the lack of published data.
- Compliance, cost-effectiveness and patient acceptability will be evaluated in future studies.

REFERENCES
2. Chan DLT et al., follow-up and recurrence in resected gastroenteropancreatic neuroendocrine tumours (GEP-NETs). A population-based study. ENETS 2017, poster A35P.