BNMS PET-CT Tracer Commissioning Manifesto

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Produced by

British Nuclear Medicine Society PET-CT Commissioning Manifesto Working Group

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1. Introduction

The decision to produce this manifesto came out of discussions at BNMS council in 2022 where it was felt that the UK was falling behind in access to new (but not particularly novel) PET tracers or indications for their use that were hard or impossible to obtain in the UK but were more available in other comparable nations. It was felt that the UK was falling behind comparatively in this important area of molecular imaging. This was particularly important given the theranostics revolution which is upon us where tracers are used to diagnose disease, check patient suitability for treatment and deliver molecular radiotherapy.

The root causes of difficulty in the UK are regulatory processes and evidential thresholds. We propose solutions to these problems in this manifesto. The BNMS is very willing to work with the appropriate bodies to coproduce enduring solutions which will allow the UK to take full advantage of all that molecular imaging has to offer our patients.

I would like to thank all the contributors to this document who are named in the acknowledgements section. They come from a broad range of disciplines and perspectives. It is this diversity that has made this manifesto a compelling document.

Professor Richard Graham

BNMS President

2. How the efficacy of PET-CT Tracers should be measured

Background

Over 200,000 PET/CT scans that require administration of a radiopharmaceutical (RP) occur in the NHS each year with numbers growing by more than 10% per annum [1]. RPs must be manufactured according to Human Medicines Regulations 2012 [2].

PET RPs can be manufactured from within the NHS or by commercial suppliers. Marketing Authorisation (MA) is required before a medicinal product can be marketed (sold, supplied or exported) in the UK. However, a number of commissioned PET tracers are also produced as specials. Manufacturing sites must hold a manufacturing licence (MIA) or a specials licence (MS) respectively and are subject to MHRA inspection and approval. [3].

Currently, clinical adoption and commissioning of diagnostic radiopharmaceuticals requires either:

1. recommendation by NICE through published guidance or guidelines (only available for medicinal products with MA), or
2. commissioning through NHS specialised services (can include unlicensed medicinal products although those with MA are preferred).

Currently both commissioning routes favour radiopharmaceuticals that have MA and since 2017 there has been a requirement to demonstrate clinical and cost-effectiveness for new specialised services.

RPs are usually administered in minute (less than picomolar) amounts that are adequate for their diagnostic use but have no pharmaceutical effect on the body. Despite this, the level of evidence that may be requested by commissioners can be similar to that required for therapeutics: clinical effectiveness, by demonstrating improvements in outcomes and cost-effectiveness.

When issuing marketing authorisation, the European Medicines Agency (EMA) recognises the differences between diagnostics and therapeutics and has published different assessment criteria for diagnostics. Diagnostic agents are assessed using the following criteria, (i) technical performance, (ii)diagnostic performance, (iii) impact on diagnostic thinking and (iv) impact on patient management/outcome and the EMA recommends that clinical development programmes should be appropriately adapted [4].

Despite this recognition from EMA (and MHRA through recent MA decisions) that diagnostics need to be assessed differently from therapeutics when awarding marketing authorisation, this distinction does not appear to be incorporated into the commissioning process, meaning that further evidence is required post MA for commissioning.

Methods

A group of expert members of the BNMS with experience and knowledge of research and clinical PET radiopharmaceutical use in the UK have provided expert opinion and guidance on the level of evidence that should be required for adoption and commissioning of diagnostic RPs in the UK. The group recognised the need for novel clinical RPs to be safe, effective and cost-effective, preferably with incremental properties compared to current clinical management, whether that be with RPs or other imaging and diagnostics.

The group recognised that:

- RPs are safe, are administered as a very small mass compared to conventional medicinal products, and are not associated with a pharmaceutical effect.
- The metrics applied to therapeutics for evidence of efficacy, e.g. quality-adjusted life years (QALYs), progression-free survival (PFS), overall survival (OS), are not appropriate for RP diagnostics. Diagnostics typically influence management decisions rather than having a direct therapeutic effect. Therefore, the burden of proof for a diagnostic to improve survival outcomes is likely to be much more difficult to obtain and be too high to be reasonably attained with clinical trials.
- The requirements for evidence of efficacy for commissioning of PET tracers is greater than that for other diagnostics that are not centrally funded by specialised services such as US, CT and MRI.
- There is inequity in funding methods of diagnostics; for example, PET is commissioned centrally by NHSE but other diagnostics such as CT and MRI are not. Commissioning of new PET tracers is in competition with the other 146 specialised services that are centrally commissioned, the majority of which are therapeutics and so have direct therapeutic effect which is easier to quantify than for diagnostics. [5]
- The NHSE application process can take 2 years.
- There is no mechanism in the UK to apply for MA as a non-industrial applicant (unlike in the USA or Australia where universities or hospitals can apply for approval e.g. choline/PSMA). A previous application to NHSE for [^{68}Ga]Ga-PSMA use in prostate cancer was rejected, not due to lack of evidence, but because another tracer with MA was available, despite this being designed to image a different biological pathway. In addition, the tracer with MA ([^{18}F]-fluciclovine) has also not been commissioned.
- MA is a costly process that may not lead to additional evidence on safety and efficacy and should not necessarily be required for NHSE commissioning.

Preliminary Recommendations

- Commissioning of current PET radiopharmaceuticals should reflect the most recent RCR/RCP's (Royal College of Radiologists/Royal College of Physicians) Intercollegiate Standing Committee on Nuclear Medicine (ICSCNM) UK guidelines [6].

- There will be an expectation that any RP considered for new commissioning will have undergone appropriate development, including safety assessment, and will have already been used and tested in humans, i.e., first-in-human applications are not appropriate for commissioning.
- There should be flexibility in the level of evidence required depending on the clinical indication and specific RP. Evidence may include an economic evaluation and patient-related factors.
- Clinical IMP trials (a prerequisite for MA) are not necessarily appropriate for evidence generation for new or repurposed diagnostics if there is an alternative standard of truth or surrogate standard of truth available [4]. Clinical studies should suffice, and these could include studies to address technical and biological gaps in translation.
- New or repurposed RPs should be required to show incremental clinical and/or economic benefit compared to standard management, but this should not be restricted to survival outcomes and should not require RCTs (randomised controlled trials), i.e. diagnostic performance rather than survival outcomes.
- Measures of clinical benefit may include observational or interventional studies that measure diagnostic performance (e.g. sensitivity, specificity, accuracy), change in management, facilitation or expedition of management – "the right patient at the right time", "reduced-recall", and "prevention of futile treatment". Additionally, evidence from meta-analyses, systematic analyses and guidelines may be used towards evidence generation.
- Comparative evidence may be included. Comparators could be current standard of care, or other imaging, e.g., CT or other standard nuclear medicine imaging, e.g. [^{111}In]In-Octreotide vs [^{68}Ga]Ga-DOTA-TATE . The population and comparators should reflect the UK population and clinical practice as closely as possible.
- Collection of real-world cohort data, case studies, and published guidelines can be used to create evidence.
- Geographic availability of tracers in the UK may need to be taken into consideration when considering commissioning.

3. Licensing, MHRA market authorisation and specials

The BNMS believes that the commissioning and use of radiotracers in the NHS should be driven by clinical need rather than the portfolio of radiotracers with marketing authorisation (MA). The portfolio of radiotracers with marketing authorisation is determined by industry, who decide whether or not to proceed with the MA process on the basis of the financial return that a successful application would provide. Unfortunately, diagnostic imaging is not as financially attractive as the therapeutic arena, and hence, diagnostic radiotracers with the potential to positively impact patients, developed either in the UK or abroad, are rarely taken forward by industry for MA due to the cost of the phase 1, 2 and 3 clinical trials required and the subsequent MA application fees. The BNMS recognises the need for assessing the safety, quality, and efficacy of radiotracers, and that the requirement of marketing authorisation is one way to ensure those aspects are met. However, the application of such a requirement for the commissioning of radiotracers could hinder the development and translation of potentially valuable radiotracers for NHS patient care and hamper the UK's availability of radiotracers accessible to patients in other countries. **The BNMS believes a process that hampers innovation in this manner is not sustainable.**

In addition, this requirement for MA ahead of commissioning translates into the development of radiotracers being more expensive than other diagnostic methods which don't use a medicinal product and can be assessed by different means. This, in turn, drives the price of the radiotracer to the NHS, which is increased as a mechanism for companies to recoup the costs incurred during the MA application process.

The BNMS believes that the replacement of UK MA as the first criterion for assessing radiotracers in favour of a more flexible approach would result in better value for money for the NHS.

Furthermore, this preference for radiotracers with MA for a specific indication doesn't account for the following two important factors:

1. Different radiotracers for the same indication may have different mechanisms of action in the body and so may provide different information to the clinician. Radiotracers are used to image metabolic pathways, excretory pathways or receptor expression in the body. However, not all radiotracers that enable the visualisation of a given phenomenon are equivalent or provide the same information for the clinician. The preference of commissioning a radiotracer with MA over a radiotracer that best fulfils the clinical need could potentially jeopardise patient outcome. **The BNMS believes that the existence of a radiotracer with UK MA for a specific indication should not block the use or commissioning of another radiotracer without UK MA, if that radiotracer provides different or better information about the clinical status of the patient.**

2. Given the short shelf-life of diagnostic radiotracers and the lack of requirement to have a UK manufacturing site as part of the MA application, a UK MA does not guarantee that the marketing authorisation holder can supply the UK's demand for the radiotracer. Radiotracers with UK MA that cannot be produced in the UK or can only be produced in limited quantity should not be prioritised for commissioning over those without MA which can be produced in the UK at a wide enough range of sites to ensure supply. If the preference of NHS England for UK MA radiotracers to be prioritised for commissioning over others is to remain, then it is essential that a mechanism and a plan to ensure the product is accessible across the UK is in place when UK MA is granted. If that is not possible, consideration should be given to commission alternative radiotracers, even if these do not have UK MA and must be made as Specials. **BNMS recommends that both tracers with and without marketing authorisation should be eligible for commissioning by NHS England Specialised Services and that equitable access to the tracer across the country should be a key consideration and prioritised above MA.**

The UK's current commissioned PET/CT radiotracer portfolio is a mix of products with three different Marketing Authorisation statuses as outlined below. In addition, **table 1** provides examples of radiotracers that are currently produced under each of these categories.

1. Radioactive final radiotracers with marketing authorisation. In this instance, the final product, in the form that will be administered to the patient, is covered by a marketing authorisation. Radiotracers that utilise radionuclides produced on a cyclotron such as ^{18}F most commonly fall into this category. The manufacturers of these products must hold a Manufacturing and Importation Authorisation (MIA) Manufacturer Licence. This restricts their production to commercial facilities, as in the UK only commercial sites hold these types of licences.

2. Radioactive generators and non-radioactive kits both with marketing authorisation are used to manufacture radiotracers. In this instance, the components used to produce the radiotracer have marketing authorisation, but the final radioactive product administered does not. These components are typically a generator that produces the radionuclide for radiolabelling and the non-radioactive kit, which are combined to produce the final radiotracer. The final radiotracer can be manufactured from these components in two different scenarios. The first option is within an NHS hospital radiopharmacy overseen by a pharmacist, working under Section 10 of the UK Medicines Act 1968. The second option is in a facility holding a Manufacturer "Specials" Licence (MS). Such facilities can be either radiopharmacies or PET radiochemistry facilities, and can be run by commercial companies, the NHS or as NHS partnerships with academic institutions.

3. Radioactive final radiotracers that are made from at least one component without a manufacturing authorisation. Outside of a clinical trial, radiotracers that do not have a marketing authorisation, can be produced from starting components that do not have marketing authorisation in facilities that hold a Manufacturer "Specials" Licence (MS). These facilities can be either radiopharmacies or PET radiochemistry facilities and can be run by commercial companies, the NHS or as NHS partnerships with academic institutions.

If NHS England retains the stance that new radiotracers for commissioning should have MA, this would stop radiotracers being made under category (iii) using at least one component without marketing authorisation and made under a Manufacturer "Specials" Licence (MS). This practice is currently happening, in both commercial and NHS facilities, and so is clearly safe and cost-effective.

Applying this additional restriction for new radiotracers would be detrimental to the NHS as it would not drive value for money. It would limit the use of existing infrastructure for the production of new radiotracers, resulting in the underutilisation of the UK's national infrastructure and the waste of investment already made in these facilities.

Additionally, this rule creates greater disadvantages for ^{18}F-labelled tracers and other cyclotron-produced radiotracers than it does for generator-produced PET radiotracers (^{68}Ga-labelled), even though historically the former can be produced at a lower cost per dose than the latter. This is because these radiotracers do not have the option of being produced from a generator and kit, which would enable the manufacture of the final radiotracers for administration in NHS hospitals. It also places the burden of manufacturing new radiotracers onto industry and forces them to produce radiotracers under a Manufacturing and Importation Authorisation (MIA) Manufacturer Licence rather than the Manufacturer "Specials" Licence (MS) which they can also hold. By mandating products are made under a Manufacturing and Importation Authorisation (MIA) Manufacturer Licence, which is more expensive to adhere to than the Manufacturer "Specials" Licence (MS), NHS England is driving up costs of manufacture, without creating any additional benefits for patients in terms of safety or efficacy. Restricting the number of sites that can produce a radiotracer, in this manner will also lead to a reduction in patient access. This is because radiotracers have short half-lives, which means they have to be made on the same day as administration and this restricts the distance over which they can be distributed. This means that a UK network of production sites is needed to provide radiotracers to the point of patient care, with enough capacity in the system to provide backup if there are any production failures or scheduled maintenance of facilities. **The BNMS believes that existing radiotracer production infrastructure should be used to produce new radiotracers commissioned by the NHS and that this will provide both increased patient access and drive value for money.**

In addition, the BNMS would like to highlight that the UK's strict interpretation of GMP requirements for radiopharmaceutical production, comparatively to other nations, is also a factor that restricts the ability of the UK to produce radiopharmaceuticals, even when produced as "Specials". The additional resource required to meet these

standards increases the timeline for radiopharmaceuticals to become accessible across the UK and also drives increases in prices to the NHS.

In conclusion, the BNMS recommends that the fixed rules requiring UK MA for new radiotracers before commissioning should be dropped and instead a more flexible approach should be adopted where priority is instead given to the clinical need for a new radiotracer and ensuring equitable UK-wide access.

Radiotracer Type	Kit (example)	Generator (example)	Radiotracer (example)	Licence Requirement
Radioactive final radiotracers with marketing authorisation	-	-	[^{18}F]FDG (Fludeoxyglucose) Marketing authorisation holder – Ie. Alliance Medical Radiopharmacy Ltd. PL 22443/0001 or Siemens Healthcare Limited PL 45366/0001	Manufacturer Licence - Manufacturing and Importation Authorisation (MIA)
Radioactive generators and non-radioactive kits both with marketing authorisation are used to manufacture radiotracers	SomaKit TOC (DOTA-TOC) – Marketing authorisation holder - Advanced Accelerator Applications - EMEA/H/C/004140	GalliAd, 0.74 - 1.85 GBq, radionuclide generator – Marketing authorisation holder - IRE-ELiT PL 43883/0001	[^{68}Ga]Ga-DOTA-TOC	Manufacturer "Specials" Licence (MS) or Section 10 of the UK Medicines Act 1968
Radioactive final radiotracers that are made from at least one component without a manufacturing authorisation	-	-	[^{18}F]Fluoroethylcholine (No marketing authorisation)	Manufacturer "Specials" Licence (MS) Produced by both commercial and NHS radiochemistry facilities.

Table 1 Examples of radiotracers that are currently produced under each of the three marketing authorisation statuses

4. Proposed process for PET-CT tracer commissioning.

The BNMS believes that the commissioning and use of radiotracers in the NHS should be aligned with current clinical guidelines with particular reference to the most recently published RCR/RCP PET-CT guidance [6].

There should be a drive for equitable access to PET imaging with [^{18}F]FDG and non-[^{18}F]FDG tracers across the UK to ensure patients can access the most appropriate imaging and care without the current geographical barriers. This could be supported by a move from national to local commissioning. The BNMS acknowledges the challenges of aligning commissioned services with Integrated Care Systems (ICSs) and Cancer network boundaries that are not always the same. **The BNMS supports the interim use of mobile scanners and improved utilisation where possible, as well as the development of further fixed sites in reducing the geographical inequalities of patient access.**

Equitable access will require capital investment to support existing PET centres and to grow and develop additional services. The current geographical disparities of gallium-68 generator availability is one example of unequal access to PET imaging and a wide variation in waiting times for these scans. This, in turn, leads to delays in management decisions and impacts on patient care and clinical outcomes. The theragnostic value of PET in selecting patients for targeted molecular radiotherapeutics should also be appreciated[2].

PET currently lies under specialised services but is a routine diagnostic tool in many malignant and benign conditions (e.g., inflammatory/infection, cardiac, neurological disorders, dementia etc); not only in diagnosis, but in gauging response to treatment and detecting early recurrence of many cancers. It is also used for selecting patients for treatment and predicting outcomes. As such, the **BNMS believes PET services should move under Diagnostic Services.**

Supporting the use of contrast-enhanced CT at the time of PET/CT acquisition for certain cancer types, with the appropriate tariffs and infrastructure would also help reduce delays and duplication of imaging services.

The BNMS believes the commissioning process should have inbuilt flexibility to support the developments in radiotracers and therapeutics.

A fixed contract for 10 years does not allow for the integration of new tracers and hinders adaptation to new clinical standards in both oncological and non-oncological conditions such as dementia.

The importance of PET imaging in cancer imaging is established. There is growing evidence of the value of PET imaging in non-cancer conditions such as dementia and parathyroid pathologies. The **BNMS believes commissioning needs to take these non-oncological conditions into account and ensure that providers can offer a full range of PET tracers to reflect clinical needs in both cancer and non-cancer indications.**

The BNMS appreciates that PET imaging can be more costly than conventional cross-sectional imaging. However, the benefit of PET imaging with earlier diagnosis, detecting recurrent disease and assessing response to treatment cannot be ignored and can reduce health costs in the longer term. The impact of PET imaging on patient management has been acknowledged by re-imbursers in the USA with the recognition of the National Oncologic PET Registry (NOPR), set up to explore changes in impact consequent of PET. New indications are re-imbursed if change in management evidence can be shown. **The BNMS would encourage PET commissioners to acknowledge NOPR and other sources of evidence demonstrating the positive impact of PET on patient management.**

In conclusion, the commissioning of NHS PET services in the UK should take both national and local needs into account in order to address the current inequitable patient access. Ongoing development and growth of infrastructure and tracers is required to support the increasing clinical need for PET imaging in both cancer and non-cancer indications.

5. Patient and public involvement

Patient Perspective

The BNMS believes that the commissioning and use of radiotracers in the NHS should be aligned to current clinical guidelines: both RCR/RCP PET-CT and disease-specific: and address the unmet needs of identified patient cohorts:

'To support equitable patient access to and safe delivery of evidence-based theranostic molecular radiotherapy (MRT) across the UK.'

Early, accurate diagnosis is an essential component of modern day and future healthcare.

Research has shown that the earlier the diagnosis and the quicker and more targeted the treatment, the better the outcome for the patient. Even where prognosis is poor, the sooner this can be acknowledged and personal plans made, the better for patients and their families and carers.

Early and accurate diagnosis can identify best treatment options: disease-modifying or curative treatments that can result in lower financial and nonfinancial costs: to patients, their families, the healthcare system, social care, and nation at large.

According to guidelines, recently updated in 2022, PET-CT is a key multimodality molecular imaging technique in the assessment of a wide range of medical conditions: informing clinical practice, in the diagnosis and treatment decision-making, of malignant and non-malignant diseases.

Because nuclear medicine exams can pinpoint molecular activity, they have the potential to identify disease in its earliest stages. They can also show whether a patient is responding to treatment.

Currently, the UK has a limited number of PET scanners (<80, 65 of which are for use in healthcare settings) – less than half the number of those available in other comparable EU countries. Consequently, timely access to PET-CT scans remains challenging for both cancer and non-cancer patients.

Alzheimer's Society Overview on PET-CT in dementia diagnosis

Everyone with dementia should receive a diagnosis specifying the disease that is causing their dementia symptoms early on in their disease progression.

It is not anticipated that PET-CT scanning would be the first biological examination a patient would receive. However, once blood-based biomarkers are approved to detect the diseases that cause dementia, these could be used to screen individuals to highlight those that may require a PET-CT scan to confirm the presence in the brain of disease-related proteins.

Better access to PET-CT scans, with good tracers for disease-related proteins like amyloid, tau and alpha-synuclein would be incredibly helpful in providing early and

accurate diagnoses for patients. It would also avoid the risk of misdiagnosis and the treatment problems this may cause.

Early and accurate diagnosis would also allow eligible patients to access the disease-modifying treatments that are on their way. Once treatments are available, delayed diagnosis in Alzheimer's disease patients could result in harm as access to these new medications relies on patients being in the early stages of disease progression.

Early and accurate diagnosis would also facilitate clinical trials allowing patients to enrol earlier.

Neuroendocrine Cancer UK Overview on PET-CT in Neuroendocrine Neoplasm diagnosis

Neuroendocrine neoplasms (NENs) (Neuroendocrine Cancers) are a diverse group of rare cancers arising in neuroendocrine cells. These cells are present throughout the body, so NENs can occur in the lungs, gastrointestinal tract, female reproductive system, prostate, testicles, thyroid and elsewhere. The WHO identifies 2 key classifications of Neuroendocrine Cancer:

- Neuroendocrine Tumours (NETs): well-differentiated cancers – that vary in aggressiveness and are graded from G1 to G3 on the basis of level of differentiation, and Ki-67 proliferation index or mitotic count.
- NETs, particularly G1-2, often show of somatostatin receptors (SSTRs) on their cell membrane – providing a target for molecular imaging: particularly [^{68}Ga]Ga-DOTA-TATE PET-CT

- Neuroendocrine carcinomas (NECs): poorly-differentiated cancers – Grade 3 with high (aggressive) cellular proliferation rate.
- NECs rarely show overexpression of somatostatin receptors (SSTRs) on their cell membrane; however, they are often metabolically active: making [^{18}F]FDG-PET the preferred PET-CT of choice.

This distinction between NETs and NECs has important diagnostic, therapeutic and prognostic implications: they are biologically and genetically distinct diseases.

N.B. [^{18}F]FDG is the tracer of choice for G3 and some high G2 NETs, which generally have higher glucose metabolism and less SSTR expression than the low-grade NETs.

There is no single test that can confirm a diagnosis of NEN – even histology may be open to misinterpretation. The correct use of the right molecular imaging can aid accurate diagnosis and staging: there is evidence to show that [^{68}Ga]Ga-DOTA-TATE PET-CT outperforms both CT and MRI for detecting both primary and metastatic disease (particularly in G1-2 NETs): as such, it is a recommended diagnostic modality by UK, European and global NEN clinical guidelines. This accuracy (high sensitivity and specificity) can inform clinically appropriate, and cost-effective, treatment decision-making and delivery.

However, there is currently an uneven distribution of NEN diagnostic services across the UK, in particular imaging and scanning facilities. This particularly impacts the availability of PET-CT scanning with Gallium-68 across the country, creating an unnecessary barrier to optimal care. For many patients, access is inhibited by long and difficult journeys – primarily at their own cost (time and financial): provision and accessibility that is dependent upon geography rather than clinical need is inequity – a postcode lottery.

Diagnostic pathway

Alzheimer's Society

The NICE guidelines currently recommend history taking and cognitive assessment in non-specialist settings before referral to Memory Assessment Services (MAS). There further cognitive and neuropsychiatric tests are recommended along with a structural brain scan (CT or MRI).

If the diagnosis is still uncertain and Alzheimer's disease, frontotemporal dementia, or dementia with Lewy bodies are suspected, then it is recommended to carry out an [^{18}F]FDG-PET or perfusion SPECT (if PET is unavailable). If Alzheimer's disease is suspected an examination of CSF for tau or amyloid beta is recommended. Amyloid PET scans are not recommended in the NICE guidelines, due to limited evidence around the accuracy and cost-effectiveness of amyloid imaging despite there now being licensed products available for this in the UK. Instead, a research recommendation was made to focus on the additional value provided by amyloid imaging over and above standard diagnostic assessment. However, with disease modifying treatments on the horizon, it is important to include amyloid-PET within the diagnostic guidelines.

Neuroendocrine Cancer UK

There is no NICE guideline for the diagnosis of Neuroendocrine Neoplasms (NENs), neither is there a specialist service specification. There is no NHS nationally adopted (locally adapted) Neuroendocrine Cancer pathway.

UK & Ireland Neuroendocrine Tumour Society (UKINETs), European Neuroendocrine Tumour Society (ENETs), and European Society of Medical Oncology (ESMO), have each produced comprehensive, expert consensus guidance that informs UK clinical practice.

Initial assessment is based on history taking (including family history- noting NEN-related genetic syndromes e.g., Multiple Endocrine Neoplasia {MEN} disorders) and clinical assessment of symptoms (if present).

Diagnostics including bloods (including Chromogranin A, Gut Hormone Profile, and NEN-related biochemistry), urine (5HiAA or catecholamines), CT and/or MRI, PET-CT ([^{68}Ga]Ga-DOTA-TATE and/or [^{18}F]FDG) +/- site specific imaging/endoscopy. NT-pro-BNP is recommended in those with evidence of Carcinoid Syndrome +/- echocardiogram: to assess risk for or presence of Carcinoid Heart Disease.

Inequity and barriers related to diagnostics

To illustrate inequity in, and barriers to, patient access to PET-CT we have used Alzheimer dementia and neuroendocrine cancer as examples.

Alzheimer's Society

As shown by the NICE guidelines, the diagnosis of the diseases that cause dementia is reliant on accessing the right assessments and tests as well as the right clinical skill. The inequity of access to these means Memory Assessment Services diagnosed between 7% to 82% of patients with Alzheimer's disease. It is unlikely that this disparity is reflective of true diagnoses. Furthermore, it is estimated that only 62% of people living with dementia in England have a diagnosis. Diagnosis rates dropped across all three nations due to the pandemic and are now stagnating.

To avoid inequity in diagnosis, everyone needs access to specific tests that detect biological signs of the diseases that cause dementia, such as PET-CT scanning and CSF examinations. However, the 2021 Memory Assessment Services (MAS) Spotlight Audit showed that 76.9% of MAS were able to access PET scans (44% for CSF examinations). It also found that in only 0.6% of cases, the MAS performed a PET scan as part of a patient's diagnosis (0.1% CSF). There are substantially less PET-CT scanning locations in the UK per head that in other comparable European countries and PET scanners are also largely reserved for oncologic cases, whereas use in Alzheimer's patients is exceedingly uncommon outside of clinical trials. Geographic coverage with cyclotron facilities to produce the tracers for PET-CT scans is sufficient but there are gaps.

Neuroendocrine Cancer UK

Owing to their rarity and diversity, NEN will often not be the first diagnosis suspected. Incidental diagnosis of NENs and cancer more broadly is not uncommon – about 4%.

UK and global surveys show a lack of NEN awareness amongst healthcare professionals – such low suspicion (and inclusion of NEN in the diagnostic differential) inhibits early detection.

The diversity of NENs, in biology and symptomology, can cause significant challenges at the point of diagnosis, including choosing the right diagnostic tests.

NENs are often misdiagnosed, and diagnosis is frequently delayed: the results of a recent survey of more than 300 people with NETs in the UK found a median time of 53.8 months from first symptom to diagnosis. (UK/Europe average is 4 years – longer in US).

Limited access to disease-appropriate diagnostic tools and specialists, especially in certain regions, compounds these delays. [^{68}Ga]Ga-DOTA PET-CT, an advanced and more precise diagnostic tool, has significantly lower usage vs more common diagnostic tools globally and locally (Global: 18%). In a survey of >800 UK patients: initial diagnostic tests included blood tests (75%) and CT scan (67%), with functional

imaging (i.e., PET-CT) infrequently used (<20%). Approximately 40% reported having a biopsy.

It is essential that every person with a NEN diagnosis receives expert confirmation and a tailored treatment plan appropriate for them.

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