

POLICY RECOMMENDATIONS

on Neuroendocrine Tumours (NETs)



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Foreword

While the European Union has shown its commitment to supporting the fight on rare diseases, numerous challenges in the management of rare cancers such as Neuroendocrine tumours (NETs) remain. Low awareness, rise in incidence, difficult early diagnosis, inequalities in access to care and treatment across Europe and the need for support to research and innovation are all aspects on which further efforts are needed to improve the current situation.

As Members of the European Parliament, we strive to create policies that aim to improve the management of care for patients a reality. Only through appropriate implementation of legislation such as EU Directive 2011/24/EU on the application of patients' rights in cross-border healthcare can we improve the management of conditions like Neuroendocrine Tumours. The successful setting up of European Reference Networks (ERN) is one of the examples through which this can be achieved.

These policy recommendations outline the challenges of NETs and their impact on patient lives. They are intended to provide guidance to protect and improve human health through better management of these conditions and contribute to EU and Member States' policy-making in the field while underlining the need for mobilization of all the Neuroendocrine community. With thanks to the Experts from EU Member States contributing to this paper, the recommendations are based upon experience of living with and managing care for NETs.

We are pleased to support them and remain committed to strive for better management of NETs in the European Union.

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Glossary

CANCON – Initiative launched by the European Commission and supported by Member States that aims to raise cancer survival and reduce cancer mortality by creating a European Guide on Quality Improvement in Comprehensive Cancer Control.¹

Council of the European Union – The Council of the EU represents the Member States' governments. Also known informally as the EU Council, it is where national ministers from each EU country meet to adopt laws and coordinate policies.²

European References Networks (ERNs) – EU legislation requires the European Commission to support Member States in the development of European Reference Networks (ERN) to link existing centres of excellence in rare diseases and/or recognise existing networks of centres. Their objective will be to encourage better access of patients to highly specialised and high quality and safe care, European co-operation on highly specialised healthcare, pooling knowledge, improving diagnosis and care in medical domains where expertise is rare, helping Member States with insufficient number of patients to provide highly specialised care, maximising the speed and scale of diffusion of innovations in medical science and health technologies and being focal points for medical training and research, information dissemination and evaluation.³

Horizon 2020 – Horizon 2020 is the biggest EU Research and Innovation programme ever with nearly €80 billion of funding available over 7 years (2014 to 2020) – in addition to the private investment that this money will attract.⁴

Innovative Medicines Initiative (IMI) – The Innovative Medicines Initiative (IMI) is a partnership between the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations). It is the world's biggest public-private partnership (PPP) in the life sciences and works to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. It does this by facilitating collaboration between the key players involved in healthcare research, including universities, the pharmaceutical and other industries, small and medium-sized enterprises (SMEs), patient organisations, and medicines regulators.⁵

Joint Actions – Joint Actions are initiatives that have a clear EU added value and are co-financed either by competent authorities that are responsible for health in the Member States or in the third countries participating in the European Commission Health Programme, or by public sector bodies and non-governmental bodies mandated by those competent authorities.⁶

Orphanet – Orphanet is the reference portal for information on rare diseases and orphan drugs, for all audiences. Orphanet's aim is to help improve the diagnosis, care and treatment of patients with rare diseases.

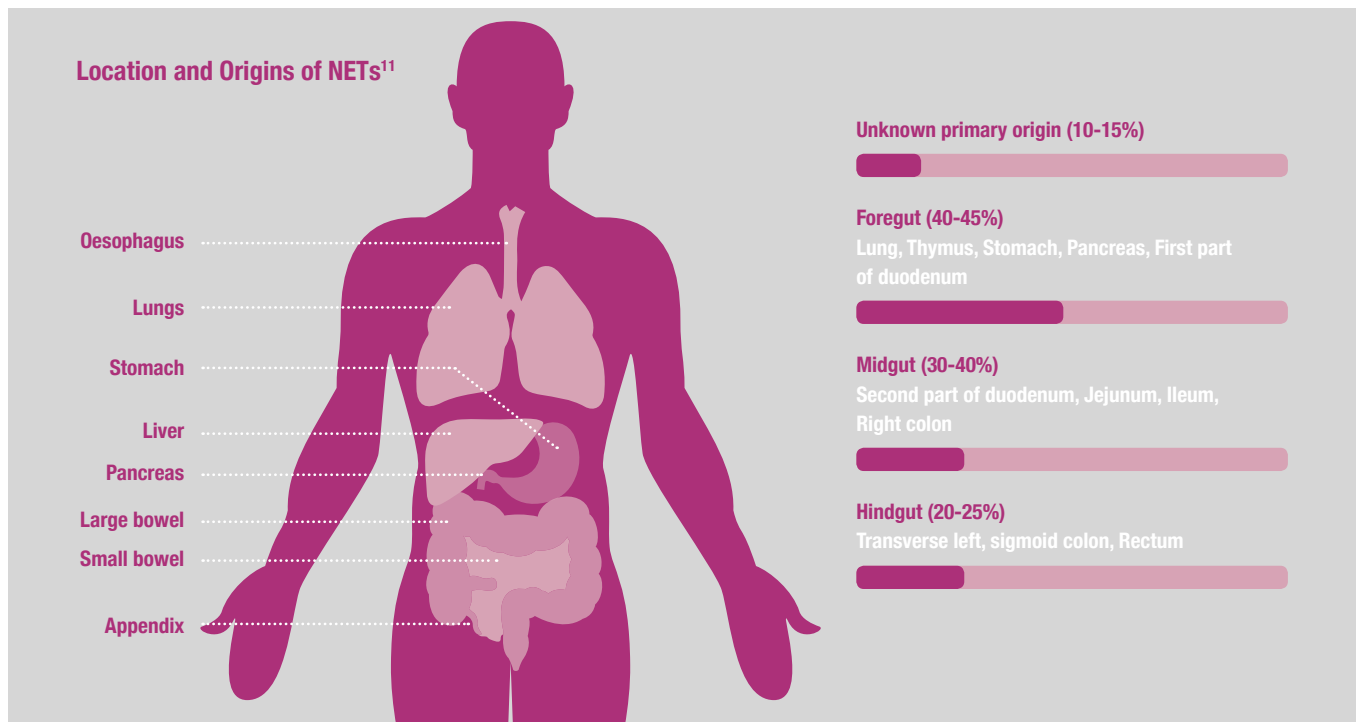
Orphan Medicinal Products Regulation (OMP) – The EU Regulation 141/2000 on Orphan Medicinal Products is a legislation that was introduced by the EU to stimulate the research and development of orphan drugs by providing incentives for the development of orphan and other medicinal products for rare disorders.⁷

Patients' Rights in Cross-Border Healthcare Directive (CBHD) – The EU Directive 2011/24/EU on the application of patients' rights in cross-border healthcare creates a legal framework for the patient's right to seek healthcare in another Member State and to benefit from cross-border healthcare services.⁸

RareCareNet – RareCareNet aims at building an information network to provide comprehensive information on rare cancers to the community at large (oncologists, general practitioners, researchers, health authorities, patients and their families).⁹

II. What are NETs?

Neuroendocrine Tumours (NETs) are a family of cancers that cause tumours in the neuroendocrine system. The neuroendocrine system consists of nerve and gland cells. It produces hormones and releases them into the bloodstream. NETs are generated by cells that release the hormones. The majority of NETs are found in the intestine, pancreas and the lungs.¹⁰



Tumours have behaviours ranging from relatively benign to highly malignant¹² and can be fatal especially if left untreated. In addition to the types of NETs highlighted above, multiple endocrine neoplasia, pheochromocytomas, paragangliomas and medullary thyroid cancers each represent unique medical challenges. NETs are not limited to the gut and lungs but also involve other organs (adrenal glands, thyroid, autonomous nervous system, etc). European expert networks focused on these tumors have emerged during the last decade such as ENSAT and ERCUSYN. The networks perform clinical research, establish registries and have allowed significant improvement in our knowledge for the treatment of patients. In these various multidisciplinary relevant networks for NETs, the endocrinologist plays a leading and coordinating role. The perspective of integrating the current endocrine-related networks in a common approach could support even better co-ordination.

NETs and their symptoms severely impair quality of life. Diagnosis is often difficult as symptoms resemble those of other more common diseases. For this reason, and because NETs are relatively rare¹³, patients are commonly misdiagnosed and diagnosed fortuitously. The time taken to diagnose impacts the treatment options for the patient. Researchers are rapidly developing new screening and imaging technologies which could prove crucial in improving diagnosis.

NETs can be treated through:

- Surgical therapy (cure, debulking treatment/ prevention of complications).
- Symptomatic therapy (control of hormonal symptoms related to carcinoid syndrome).
- Antiproliferative/ anti-tumour therapy (control tumour growth).¹⁴

Being given a diagnosis of having a potentially lethal cancer, such as NETs, has life changing effects for the patient and also for their families. Progress of the diseases can be slow, but it can also be lightning fast.

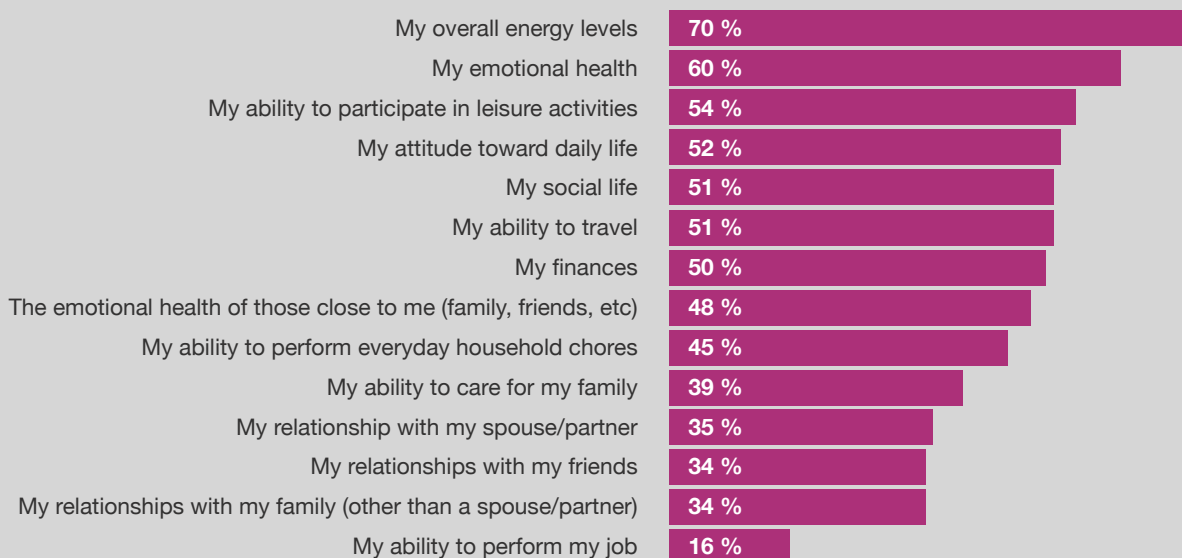
Factbox

- Five out of every hundred thousand people are diagnosed with NETs each year¹⁵
- NETs are difficult to diagnose. For example, diagnosis of tumours in the stomach, intestine and pancreas (GEP-NET) can be delayed up to 10 years¹⁶
- Because NETs are slow-growing tumours, patients may survive for many months after diagnosis.¹⁷
- 60-80% of patients are diagnosed at an advanced stage, often because of similarity of symptoms to other conditions. Therefore, although NET incidence is relatively low, prevalence is quite high¹⁸
- Important research into the heritability of NETs is ongoing and may have important conclusions in terms of diagnosis potential
- Some NETs are inherited disease driven by genes that spread the disease in families of affected members. Therefore screening for genetic causes and early recognition of the disease in gene carriers is an important aspect.
- Within the family of NETs, some conditions are especially rare such as rare pancreatic tumours
- Some NETs also oversecrete hormones in the circulation that are responsible for significant morbidity and mortality

The Zebra, and NET Cancer Day

The NET Cancer Day is organised by the International Neuroendocrine Cancer Alliance¹⁹ on 10 November each year to raise awareness about this condition

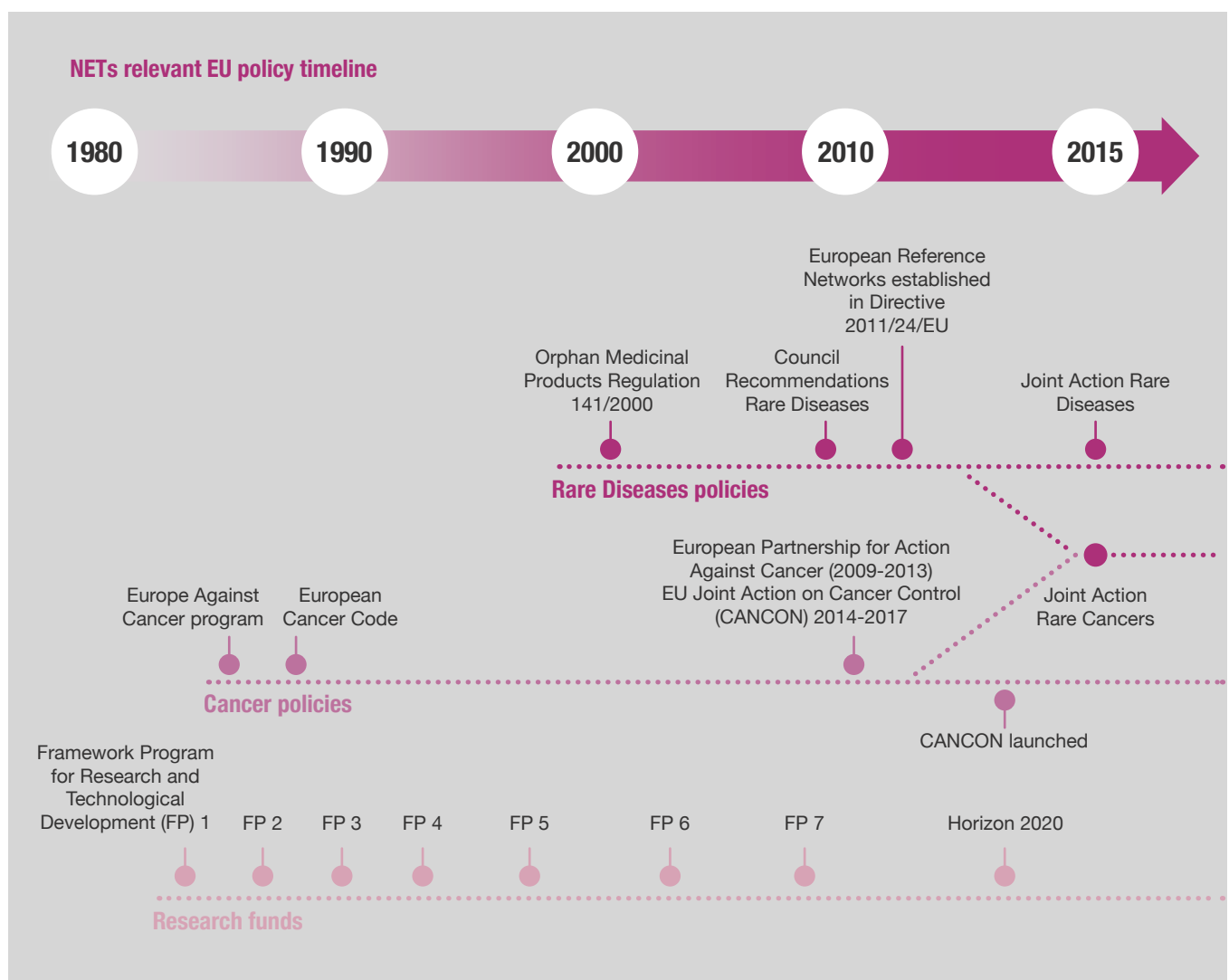
The colours of the Zebra are used to represent NETs to highlight the challenge of diagnosis – when one hears hooves, consider that it may be the rarer zebra and not necessarily the more common horse!

Negative impact of NETs on different aspects of life²⁰

III. Adapted EU Policies for NETs?

The European Union has in the last thirty years launched a number of policies and legislations to try and improve public health provisions. Examples of successful developments include the Patients' Rights in Cross Border Healthcare Directive²¹, the Orphan Medicinal Products Regulation²² and the development of an effective single system of approval of medicines for the European Union. The aim of these legislations, is to speed up patients' access to the treatment, care and expertise they need and to seek to provide a more equitable access for EU citizens to such medicines and specialist medical expertise.

The European Union has also shown the added value it can bring to the coordination and support of national efforts on cancer and rare diseases through the adoption of recommendations in these fields and follow-up establishment of national specific plans for these conditions. NETs find themselves at the confluent of these policies by being recognized as a family of rare cancers²³. Rare cancers policy should clearly be a focus for the NETs community.



These policies have led to the development of different care pathways in Member States in Europe and the development of best practices in the management of NETs.

EXAMPLE OF FRANCE AND THE RENATEN²⁴

Since 2009 following a call of the French health authorities and National Institute for Cancer several networks for rare diseases have been set up in France. The RENATEN Network is dedicated to patients with any kind of NET. This network was developed by members of a French medical scientific society, the Groupe de recherche des Tumeurs Endocrines (GTE), a multidisciplinary group.

The RENATEN network involves 16 centers spread throughout the French territory under the supervision of a coordinating center. Each center corresponds to a multidisciplinary team based in a university hospital (CHU). These teams have developed:

1. Patient care at the regional level with multidisciplinary expert staff. For example, the case of 3745 patients with NETs were examined by the RENATEN network during 2013;
2. Patient care at the national level with one monthly web-staff during which physicians of each center discuss very specific and rare cases;
3. Organization of a national oncogenetic network in France to provide free genetic analysis searching for alterations of genes leading to NETs in affected patients;
4. Registry of NETs in France;
5. Good practice recommendations and expert consensus for care;
6. Teaching to non expert physicians with at least one meeting per year in each region of France and one national congress;
7. Clinical research. More than 40 clinical trials have been conducted and more than 23 scientific papers have been published in peer-reviewed journals since 2009;
8. Information for patients, their families and interactions with patient's association. The close interaction between RENATEN and patients is illustrated by several RENATEN research grants funded by patient's association.
9. The RENATEN Network was evaluated in 2014 by the French health authorities and National institute for cancer and reappointed for 5 years.

THE SITUATION OF NET PATIENT CARE IN SPAIN²⁵

1. The Spanish National Health System (Sistema Nacional de Salud, SNS) is the collection of public health services. Management of these services has been progressively transferred to the 17 autonomous communities of Spain. The activity of these services is harmonized by the Interterritorial Council of the National Health System (Consejo Interterritorial del Servicio Nacional de Salud de España, CISNS) in order to give cohesion to the system and to guarantee the rights of citizens throughout Spain.
2. As a consequence of the decentralization, the mobility of patients between communities has been severely impaired in Spain, mainly due to budget constrictions and limitations to budget mobility between communities. Except for very few specific interventions that are organized at a national level (i.e. organ transplantation), even within a given autonomous community, diagnosis and treatment of rare diseases such as NETs are not centralized in recognized specialized centres, but are rather managed wherever they happen to occur. Thus, mobility of a NET patient to a NET specialist is dependent upon the will and knowledge of Doctor and patient.
3. Despite all of these barriers there are certain centers that are able to develop high standards of care for patients with NETs and treat a significant number of NETs patients. However, the health system organisation does not permit the development of centers managing the care of higher

volumes of patients with rare diseases. This is the reason why no single centre in Spain has ever applied to the ENETS Centre of Excellence Network, despite the active involvement in the field of many Spanish NET specialists, as one of the requirements for this includes to manage at least 80 new patients with NET per year.

4. In this context, a Spanish network for NETs - GETNE (Spanish Task Force for Neuroendocrine Tumors) was developed in 2004. GETNE is a scientific society composed by specialists from multiple disciplines that involves 57 academic and community sites representing all regions of Spain. The main initiatives of GETNE in the field are:
 - RGETNE: this is the National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors coordinated by GETNE, that currently has about 2500 patients registered. This Registry provides valuable insights that may contribute to understand regional disparities in the incidence, patterns of care and survival.
 - NET Discovery: more recently, GETNE has also launched a NET sample collection network (including blood, saliva and tumor samples) linked to the Spanish NET Registry (RGETNE) to promote translational research.
 - Clinical Trials: GETNE is also actively involved in the development of new drugs or treatment strategies, and has a large experience in conducting and coordinating national and international investigator-initiated clinical trials
 - Continued Medical Education: GETNE organizes a yearly international NET Symposium, and several national educational events for non-expert physicians and young specialists in the field. GETNE elaborates clinical guidelines for NET diagnosis and treatment.

ENETS – TACKLING NETS WITH EUROPEAN SPIRIT

The European Neuroendocrine Tumor Society founded in 2004 is the leading international multidisciplinary organization for the care of neuroendocrine tumor patients. It has over 1300 members with a specific interest in tumours including oncologists, surgeons (gastrointestinal, liver, pancreas, endocrine and thoracic), endocrinologists, gastroenterologists, pathologists, nuclear medicine physicians, radiologists, nurses, basic scientists and patient advocates. ENETS has recognized the need to enhance patient care as well as improve the understanding of NETs in the wider medical community. Thus ENETS in addition to its Annual Conferences attended by more than 1500 participants and Summer Schools for young investigators also publishes guidelines for NET management, guidelines for standards of care regarding investigations and therapies, as well as promoting collaborative research and encouraging investigators in their clinical and research development. ENETS has integrated specialist NET nurses within its organization and Advisory Board. The standard of patient care and survival has been enhanced by the development of ENETS Centers of Excellence. There are currently 34 ENETS Centers of Excellence which have each been independently audited and fulfill the following criteria

- EU Centers that meet the standards of care for neuroendocrine cancer as defined by ENETS and the independent audit experts
- Guarantee the patients best quality care
- Provide the patients with choice
- Build a EU network of expertise on neuroendocrine cancer to foster growth, collaboration and generate evidence from patient outcomes and research/clinical trials
- Adherence to standards of care and protocols of management thus enabling more efficient use and cost of therapies and enhancement of patient support and care

The activities undertaken by ENETS demonstrates a clear added value to European co-operation between medical experts, which fits closely with the spirit of European Reference Networks. The Audit specifications and process may be a helpful example of a working “European Reference Network” which could be appropriately adapted for the planned substantive ERN.

IV. Key issues in the management of NETs

1. Knowledge & Diagnosis

NETs are a challenge to diagnose. Depending on where the NET's origin is, symptoms will vary. If symptomatic, misdiagnosis with more well-known conditions such as Irritable Bowel Syndrome (IBS) is also common given that symptoms are similar and many physicians have not been informed about NETs. For example, NETs in your digestive system may cause pain or discomfort in the abdomen that comes and goes²⁶. Some NETs may overproduce a hormone-like substance such as serotonin which will manifest through symptoms called the carcinoid syndrome. There are a variety of syndromes related to NET tumours. However, in most cases symptoms are often non-existent, mild or nonspecific making the diagnosis of NETs a challenge, leading to late diagnosis. In the case of tumours in the stomach, intestine and pancreas (GEP-NET) diagnosis can be delayed by up to 10 years²⁷ and 44%-73% of GEP-NET patients in Europe are diagnosed with metastatic disease²⁸. This is especially concerning given that NETs are incurable once they advance to unresectable metastatic disease.²⁹

It is clear that greater knowledge of medical professionals is needed to diagnose NETs more effectively. Initiatives have taken place at regional and national level led by medical experts on NETs. This is work that is mostly undertaken informally and by persons with a passion for sharing their knowledge with the aim of improving diagnosis and care for NETs patients. It is clear though that resources and support from national governments are needed given that education of primary and secondary care professionals is the objective. This translates into a very large target audience that NETs specialists need help to reach.

The experience of patients in accessing effective diagnosis, and living undiagnosed or misdiagnosed, must be a central focus. Patients report difficulties getting access to the most innovative diagnostic technologies, which is disturbing as it can delay access to appropriate care and appears to be a false economy. The provision of resources by national governments and demonstration of support towards an European Reference Network (ERN) on NETs would be crucial to its success.

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Why is detection of NETs difficult?

- Awareness – physicians are often unfamiliar with NETs
- Size – some NET cancers can be less than a centimeter in size
- Location – NETs can occur in a number of places
- Symptoms – can vary enormously depending on NET
- Testing – given differences in NETs, specialized tests are necessary

What are the symptoms of NETs?

- Flushing, acute diarrhea, palpitations, wheezing
- Low sugars, sweaty, faint
- Recurrent stomach ulcers
- Production of hormones

Methods to diagnose NETs

- CT, MRI, ultrasound, molecular imaging, blood test, urine test and endoscopy, octreotide and MIBG scans, gallium PET

The importance of diagnosis

- NETs often have an associated long-term clinical burden, with the stage of discovery highly impacting the 5 year survival rates (from 93% survival rate in well differentiated localised disease, to 14% in well differentiated disease with distant metastases)³¹