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# UPDATES IN NEUROENDOCRINE NEOPLASMS : FROM MECHANISMS TO THE CLINIC

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## **ABSTRACT**

Scientific advances constantly improve our understanding of the mechanisms underlying tumorigenesis, allowing us to now analyse cancer in a more precise manner and to identify at an earlier stage the tumours that have an increased risk of aggressive behaviour. Understanding the neuroendocrine neoplasms at a molecular level has permitted us to provide increasingly targeted treatments to our patients, which safety and efficacy have been validated by large randomised trials. Moreover, the first studies to examine the benefits of using targeted therapies after molecular profiling of neuroendocrine neoplasms, have shown encouraging results, allowing us to foresee more and more personalised medical treatments in the future. This literature review aims to summarise recent advances in neuroendocrine neoplasms and to show how the identification of new mechanisms underlying tumorigenesis can be of benefit for the management of patients in clinical practice.

In 2000, Hanahan and Weinberg published a highly-cited paper, 'The Hallmarks of Cancer'<sup>1</sup>, which suggested that the majority of cancers have acquired the same group of functional capacities during their development. They identified six major characteristics responsible for tumour progression, including the escape from apoptosis, the ability to metastasise and the induction of angiogenesis. A decade later, significant progress had been made in our understanding of the mechanisms underlying tumour development, allowing the hallmarks to be updated in 2011<sup>2</sup>, to highlight new characteristics, including the capacity to avoid immune surveillance, the role of inflammation and role of genomic instability. The large number of recent discoveries finally led to a new version of cancer hallmarks being published in 2022, which notably includes the impact of epigenetic modifications and role of the microbiome in tumour development<sup>3</sup>. As well as increasing our understanding of tumour development, the identification of underlying mechanisms has provided new biomarkers for detection and surveillance, and new potential therapeutic targets, notably in the field of oncoendocrinology.

This literature review aims to summarise recent developments in the field of neuroendocrine neoplasms and to show how identification of new genetic and epigenetic mechanisms, developments in histopathology and identification of new proteins underlying tumour development, can have benefits for diagnosis, treatment and prognosis of patients in clinical practice.

## **IDENTIFICATION OF NEW MECHANISMS INVOLVED IN ONCOENDOCRINOLOGY**

### **The place of 'omics'**

'Omics' approaches have become ubiquitous in basic research, however they are now also an integral part of clinical practice and routine patient management. In endocrine and neuroendocrine cancers, the identification of new mechanisms involved in tumorigenesis, new genes linked to cancer predisposition and new target proteins is continuously expanding<sup>4</sup>. However, the growing place of bioinformatics, genomics, epigenomics and proteomics, as well as the study of clinical data and population analysis, is of interest to the clinician only if these make concrete improvements to patient management, result in the identification of new biomarkers, assist in disease prediction or provide new, more precise, and more personalised, therapeutic targets.

### **Advances in genetics**

Cancer is characterised by abnormal and uncontrolled cell proliferation, principally caused by mutations in so called driver genes<sup>5-7</sup>, which affect a group of key cellular functions and confer selective advantages on some cells in an organ or tissue compared to their

neighbours<sup>1</sup>. Since the beginning of the study of molecular biology, one of the principal aims of cancer research has been the identification of these driver genes<sup>7</sup>, which would allow the development of targeted anticancer therapies and the discovery of prognostic biomarkers, as well as provide improvements in therapeutic follow up<sup>2,3</sup>.

#### *Adrenocortical carcinoma and adenoma*

Prior to the arrival of genomics, driver genes were generally discovered due to their presence in familial predisposition syndromes. In the case of adrenocortical carcinoma, the main anomalies which were identified were inactivating mutations of TP53 in Li-Fraumeni syndrome, alteration of the 11p15 region and overexpression of IGF2 in Beckwith-Wiedemann syndrome, and alteration of the beta-catenin signalling pathway and loss of APC expression in familial adenomatous polyposis<sup>8,9</sup>.

There are now several ways to identify new driver genes, including exome sequencing, chromosomal alterations profiling, and integrated genomic characterization. This last method allowed the identification of *ZNRF3* as a new driver gene in adrenocortical carcinomas<sup>8,9</sup>. *ZNRF3* is a tumour suppressor gene that is a negative regulator of the Wnt/ $\beta$ -catenin pathway and has been found to be the gene most frequently altered in adrenocortical carcinomas (20-25% of cases)<sup>9,10</sup>. A group in Clermont-Ferrand (France), has recently shown that combined inactivation of *ZNRF3* and *TP53* by gene knockout (KO) in mice, leads to the formation of aggressive adrenocortical carcinomas with a 36.8% rate of metastasis in 6 month-old KO mice. This result was not reproduced in mice that had a single gene, either *p53* or *ZNRF3*, inactivated<sup>10</sup>.

Apart from the identification of *ZNRF3* deletions being responsible for activation of the Wnt/ $\beta$ -catenin pathway in adrenocortical carcinomas, recent studies have also identified changes in ion channels and intracellular calcium signalling in aldosterone-secreting adenomas, mutations in *PRKACA* resulting in activation of the AMPc/PKA pathway in cortisol-secreting adenomas, and identified the genes *ARMC5* and *KDM1A* as being responsible for germinal predisposition to primary macronodular adrenal hyperplasia<sup>9</sup>.

#### *Pituitary carcinoma*

In a similar way, a number of germinal and somatic mutations have been identified in aggressive pituitary neuroendocrine tumours. The great majority of pituitary tumours are adenomas but in rare cases (<2% of macroadenomas<sup>11</sup>) these tumours can be more aggressive. Aggressive pituitary neuroendocrine tumours are defined by invasion of

neighbouring tissue, rapid growth, resistance to conventional treatments and multiple recurrences. The term pituitary carcinoma is used where there is a metastatic disease<sup>12,13</sup>.

Germinal mutations identified in aggressive pituitary tumours are mostly the same as those seen in predisposition to Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*), being associated with microsatellite instability (DNA mismatch repair)<sup>13</sup>. Four cases of aggressive pituitary tumours have been described in the literature: a corticotroph carcinoma carrying an *MSH2* mutation<sup>14</sup>, an aggressive corticotroph tumour with *MLH1* mutation<sup>15</sup>, an invasive corticotroph tumour and an invasive macroprolactinoma both with *MSH2* mutations<sup>13,16,17</sup>. Somatic analyses has also shown mutations in *TP53*, *ATRX*, *PTEN* in corticotroph tumours and *CDKNA2A/CDKNA2B* mutations in lactotroph and somatotroph tumours<sup>13,18–22</sup>.

In 2020, Casar-Borota *et al*<sup>19</sup> identified somatic mutations in the *ATRX* gene (which is involved in heterochromatin remodelling and telomere maintenance) in a sub-group of aggressive pituitary neuroendocrine tumours, more frequently found in those that were corticotroph tumours. Mutations in *ATRX* were confirmed by immunohistochemistry showing the loss of immunoexpression in 9 tumours (5 pituitary carcinomas (28%) and 4 aggressive pituitary tumours (13%)) out of 48 tumours examined, suggesting the utility of immunohistochemical staining for *ATRX* to identify those patients at high risk of developing aggressive tumours or pituitary carcinomas. In addition, *TP53* mutations were observed in 6 of these tumours<sup>12,13,19</sup>.

### *Pheochromocytoma paraganglioma*

The main epigenetic and transcriptional genetic changes that were found in a study on 128 samples of pheochromocytomas and paragangliomas were listed as nucleotide polymorphisms (Single Nucleotide Polymorphism), DNA methylation, differences in mRNA expression, miRNA sequences and sequences of known driver genes (identified by targeted sequencing). The clinical characteristics associated with particular molecular groups have also been analysed<sup>24</sup>. The samples have been classified according to the mRNA group that they belong to and this integrative genomic characterization of pheochromocytomas and paragangliomas has allowed five principal clusters of tumours with specific genetic, epigenetic or clinical characteristics to be identified. Pheochromocytomas and paragangliomas of cluster 1A are notably the more aggressive tumours, more often metastatic, and often associated with a mutation in *SDHx* genes<sup>24</sup>.

## **Progress in epigenetics**

The development of pituitary tumours is strongly dependent on epigenetic mechanisms such as promoter methylation<sup>25,26</sup>, modification of histone tails and of non-coding RNAs<sup>27</sup>.

The CpG dinucleotides are usually grouped in islands, generally localised in the promoter region of genes, and are normally protected from methylation. When they are methylated, these CpG islands lead to silencing of the gene in question<sup>25</sup>. Studies have shown different somatic mutation and methylation profiles between adenomas, aggressive pituitary neuroendocrine tumours and pituitary carcinomas. Notably, altered methylation appears to be an early event that favours aggressive tumour behaviour and progression towards carcinoma, in a direct or indirect way, by inducing gene mutation<sup>28-30</sup>. Epigenetic analyses have shown a reduction in protein expression by gene silencing of *PARP15*, *LINC00599*, *MIR137HG* and *MIR193a*, when they are hypermethylated, in pituitary tumours and carcinomas. These data confirm previous observations that the expression of these genes is reduced in aggressive pituitary tumours<sup>28,30</sup>.

## **Tumour microenvironment**

### *Pituitary tumour microenvironment*

Apart from non-tumoral cells that are resident or have infiltrated the tumour, the tumour microenvironment consists of blood vessels and lymphatics, as well as extracellular matrix molecules and numerous cytokines and chemokines, which makes it an attractive target both for therapy and for use as a prognostic tool<sup>31</sup>. The immune system, in particular tumour-associated macrophages and lymphocytes in the tumour microenvironment, is the most studied aspect of the pituitary tumour microenvironment<sup>12</sup>.

Significant reciprocal communication exists between pituitary tumour cells and their microenvironment. Pituitary tumour cells secrete cytokines into the tumour microenvironment which stimulate the recruitment and migration of immune cells into the tumour. These immune cells then modify the behaviour of tumoural cells, particularly stimulating their proliferation. Tumour-associated fibroblasts are equally able to secrete cytokines including IL-6 into the tumour microenvironment, which also results in increased invasion by pituitary tumour cells<sup>12,31,32</sup>.

Treatments targeting the pituitary tumour microenvironment need to take into account the different components that it contains (tumour and non-tumour cell, cytokines, chemokines, extracellular matrix and hormones), all of which are interdependent, thus targeting one component will inevitably have an impact on others<sup>12</sup>. Angiogenesis and immune cells have so far been the preferred therapeutic targets, but targeting the pituitary tumour

microenvironment also needs to consider the significant influence of pituitary and hypothalamic hormones produced by either tumour cells or healthy cells. For example, it has been shown that prolactin has a stimulatory role in angiogenesis<sup>33</sup>, and that growth hormone (GH) can stimulate epithelial-mesenchymal transition in several tumour types<sup>34</sup>. Additionally, it has been reported that GHRH receptor antagonists can inhibit the growth and progression of some tumor types, particularly in prostate and thyroid tumours<sup>35-37</sup>.

#### *Pancreatic neuroendocrine tumours microenvironment*

The tumour microenvironment has become a subject of interest in endocrine and neuroendocrine cancers as a whole. Cuny et al published a study examining the effect of stromal fibroblasts on proliferation in human cell lines from pancreatic neuroendocrine tumours. They confirmed a stimulating role of stromal fibroblasts on the growth of human pancreatic NET cell lines and a reciprocal effect of NET cell lines on fibroblasts<sup>38</sup>.

These biochemical, molecular and histological advances are of interest to clinicians only if they can be useful in clinical practice. Therefore, it is important to identify the diagnostic and prognostic improvements that have arisen due to these mechanistic discoveries.

## **NEW DIAGNOSTIC AND PROGNOSTIC TOOLS**

### **Next Generation Sequencing (NGS)**

Thanks to the possibility of sequencing many thousands of DNA sequences at a time, NGS allows routine constitutional or somatic analysis of tumour samples. After extraction of tumour DNA from tissue or cell samples, regions of interest are specifically amplified and sequenced. Thus, identification of specific mutations now allows some patients to benefit from targeted therapies, for example anti-RET or anti-BRAF treatment in the case of thyroid tumours. The identification of specific biomarkers is also absolutely necessary for the regulatory approval of numerous targeted therapies.

Though the condition Multiple Endocrine Neoplasia type 1 (MEN1) is a hereditary syndrome linked to an autosomal dominant mutation in the gene *MEN1*, the frequency of mosaicism is likely under-estimated in patients with suspected MEN1 as it is not the subject of systematic screening. However, though NGS favours the detection of mosaicism, classic methodologies do not dependably distinguish between true mosaicism and sequencing artefacts. Lagarde et al established a targeted digital NGS, including unique molecular identifiers allowing rare molecular events to be detected in somatic DNA. They searched for *MEN1* mosaicism in a cohort of non-resolved cases identified between 2017 and 2019. Three new cases of



mosaicism were identified by targeted digital NGS, favouring the routine use of this technique to reduce the number of false-positives detected<sup>39</sup>.

### **New potential biomarkers**

#### *Pancreatic neuroendocrine tumours and CELF4*

The identification of new biomarkers would be beneficial for both the diagnosis and prognosis of neuroendocrine tumours, particularly digestive tumours, and these would ideally be more specific than chromogranin A, and more sensitive than urinary 5-hydroxyindoleacetic acid (5HIAA). Indeed, new tumour biomarkers are currently being studied. Notably, CELF4 an RNA splicing factor that is dysregulated in pancreatic neuroendocrine tumours, and alterations of which contribute to both tumour development and a more aggressive phenotype via an action on the mTOR signalling pathway. CELF4 is associated with relevant clinical parameters and could have significant predictive potential. Under-expression of CELF4 has notably been associated with an increased frequency of metastases and an increase in abdominal pain symptoms<sup>40</sup>.

#### *Pheochromocytoma, paraganglioma and INSM-1*

Similarly, though assays for plasma or urinary metanephrines are satisfactory in routine clinical practice, a study has examined the potential of proteins of the Granin and INSM-1 family in diagnosis of patients with pheochromocytoma. Of the potential biomarkers studied, INSM-1 had the best diagnostic value in patients with pheochromocytoma and this marker may thus be of interest, in particular in cases where assay of metanephrines leads to a doubtful diagnosis<sup>41</sup>.

### **Functional imaging**

Neuroendocrine tumours are characterised by the expression of specific hormone receptors on the cell membranes of tumour cells, making them ideal targets for radio-labelled peptides. The most commonly-expressed receptors on neuroendocrine tumour cells are somatostatin receptors and the molecular imaging method of choice uses a number of radiolabelled somatostatin analogues (Pentetreotide [Octreoscan], 68Ga-DOTATATE, DOTATOC, DOTANOC), or somatostatin antagonists (68Ga-OPS202) which have given the best imaging quality<sup>42</sup>. Positron emission tomographie (PET) using 18F-DOPA has become the second choice imaging modality in neuroendocrine tumours, with the exception of pheochromocytomas-paragangliomas. Neuroendocrine carcinomas which show low expression of somatostatin receptors (because of dedifferentiation) are best visualised using classical imaging techniques based on glucose metabolism (18F-FDG-PET), a method also

useful in prognosis<sup>42,43</sup>. Lastly, for visualisation of insulinomas, which are often small-sized, GLP-1 receptor imaging has become the ideal choice<sup>42</sup>.

Pheochromocytomas, which are derived from chromaffin cells, can be imaged using 18F-DOPA PET as they over-express type L amino acid transporters (LAT1 and LAT2). An Italian study from 2022 confirmed the over-expression of LAT1, LAT2 and phenylethanolamine N-methyltransferase (PNMT) mRNA in pheochromocytomas compared to normal adrenal tissue, and provided the first experimental evidence of a quantitative correlation between 18F-DOPA signal and the expression level of LAT1<sup>44</sup>.

### **Liquid biopsy**

Liquid biopsies are a diagnostic method becoming increasingly important in cancer diagnosis, particularly for neuroendocrine neoplasms, and are already in routine use in several French centres. Genetic alterations associated with cancer, such as point mutations, copy number variation and chromosomal rearrangements can be detected in samples of circulating cellular DNA. Tumour cells release small fragments of acellular DNA through multiple mechanisms. Through the analysis of this circulating DNA, the aim of liquid biopsy techniques is the early and non-invasive detection of cancers<sup>45-47</sup>.

Liquid biopsies have several potential clinical uses. Aside from their diagnostic benefit, they can be used to monitor the therapeutic response in real-time, and to quantify residual disease<sup>45</sup>. A study that is currently underway in Italy aims to evaluate minimal residual disease using liquid biopsies (the PEGASUS study), as well as the benefit of measuring circulating DNA to monitor the therapeutic response in real time and to evaluate the benefit of retreatment using a targeted therapy ('rechallenge') according to the tumour stage and the evolution of liquid biopsy results (the CHRONOS study)<sup>46</sup>.

### **Metabolomic profile of pheochromocytomas-paragangliomas as a prognostic tool**

In 2021, a German team studied the clinical signs and symptoms linked to catecholamine secretion in patients with pheochromocytomas-paragangliomas (PPGL). The severity of symptoms was found to be correlated with the level of endocrine activity. However, though signs and symptoms were associated with norepinephrine production in patients with metastatic PPGL, and epinephrine in patients carrying non-metastatic PPGL, there was no difference in clinical presentation between the two groups. Thus, clinical signs and symptoms do not appear to be useful in identifying patients who are more or less likely to develop metastases<sup>48</sup>.

Additionally, though a study on a large group of more than 600 patients with PPGL allowed the identification of factors favouring the development of metastases, such as the diagnosis of a tumour in older age, in terms of individual patients it is impossible to predict the development of metastases at the time of PPGL diagnosis<sup>49</sup>.

Finally, histopathology may be useful in predicting the development of metastases in patients carrying PPGL. A study of 143 patients showed that a higher GAPP score (Grading System for Adrenal Pheochromocytoma and Paraganglioma) was associated with more aggressive PPGL while the PASS score (Pheochromocytoma of the Adrenal Gland Scaled Score) was not associated with metastases and also showed a high inter-observer variability<sup>50</sup>.

## **PHEOCHROMOCYTOMAS-PARAGANGLIOMAS: FROM MOLECULAR UNDERSTANDING TO TREATMENT TARGET**

### **Three clusters with specific pathophysiological and phenotypic characteristics**

Pheochromocytomas-paragangliomas are an excellent example of the application of advances in genetics and molecular mechanisms for the diagnostic and therapeutic management of patients. They can be divided into several molecular clusters, defined by the germinal or somatic mutations that underlie their pathophysiology. These clusters have specific clinical, biochemical and imaging characteristics that can be used to direct their treatment and follow up<sup>51</sup>. Indeed, each cluster reflects alterations in several genes that have common signalling pathways. Regardless of the tumour cluster, surgery remains the first-intention treatment of choice, however in the short to medium term, more and more targeted and specific treatments of the different clusters that have been identified can be envisaged.

Cluster 1 tumours present with a more aggressive phenotype, with a greater risk of metastasis, and are more frequently secreting and symptomatic. The severity of these tumours warrants closer monitoring.

Looking in greater detail, pheochromocytomas and paragangliomas arising due to mutation in genes of cluster 1 are associated with a phenomenon of cellular pseudohypoxia. Cluster 1A includes mutations in genes associated with the Krebs cycle, such as *SDHx* genes. Cluster 1B includes mutation in genes linked to the hypoxia pathway, associated with the *VHL* gene. These mutations lead to stabilisation of HIF-2 $\alpha$  and favour angiogenesis, tumour progression, cell migration, invasion and development of metastases. Such mutations result in tumours with a noradrenergic/dopaminergic phenotype and are best evaluated by assays of free plasma normetadrenaline or 3-methoxytyramine. The most sensitive functional

imaging method for screening in cluster 1A tumours is Gallium-68 PET, while 18F-DOPA PET is the most sensitive functional imaging technique for PPGL of the other groups<sup>51</sup>.

Cluster 2 PPGL tumours are associated with mutations in genes including RET, NF1 and MAX. These mutations lead to activation of signalling pathways associated with tyrosine kinases, RAS/RAF and mTOR. As with group 1, these mutations are also associated with increased HIF-2A expression, cell proliferation, cell survival and tumour formation.

Lastly, cluster 3 consists of mutations associated with over-activation of Wnt/ $\beta$ -catenin signalling, leading to (amongst other effects) angiogenesis, proliferation, cell survival, invasion, metastasis and metabolic dysregulation. Cluster 3 PPGL tumours are principally localised in the adrenal, they present most frequently with somatic mutations and have an increased risk of recurrence and metastasis. Overexpression of chromogranin A is also higher than in the other groups.

### **Belzutifan: a new therapeutic option**

The molecular analyses described above allow us to foresee more and more targeted treatments, and the existence of these PPGL clusters is a perfect example of the potential of personalised medicine.

Von Hippel Lindau disease results from inactivation of the *VHL* gene, which causes constitutive activation of the transcription factor, hypoxia-inducible factor-2 $\alpha$  (Hif-2 $\alpha$ ), leading to several hypervascular lesions including renal clear cell carcinoma. An open-label, single-group phase 2 trial was published in 2021, studying the safety and efficacy of belzutifan, a HIF-2 $\alpha$  inhibitor, in patients with renal clear cell carcinoma associated with VHL disease<sup>52</sup>. The principal evaluation criterion was the objective response of the renal carcinoma (complete or partial response). The secondary evaluation criteria were the response to belzutifan in patients with other neoplasms related to VHL disease. After a median follow up of 21.8 months, 49% of patients showed an objective response in terms of their renal carcinoma. Responses were also observed in 30% of patients who had pancreatic lesions or hemangioblastomas in the central nervous system. All those with retinal lesions showed improvement over the course of treatment<sup>52</sup>.

In view of these encouraging results, in particular for non-renal lesions associated with VHL disease, an international phase 2 trial has commenced, which will evaluate the safety and efficacy of belzutifan as monotherapy in patients with an advanced PPGL, a pancreatic neuroendocrine tumour, or any other neoplasm linked to VHL disease.

### **FIRSTMAPPP trial**

Results from the FIRSTMAPPP (First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma) study were presented at the European Society of Medical Oncology (ESMO) conference in 2021<sup>53</sup>. This randomised trial recruited 78 patients with a malignant progressing PPGL, in 15 centres across 4 European countries. Participants were randomised (1:1) to receive sunitinib (37.5 mg/day) or placebo. 35.9 % of patients who received sunitinib reached the principal evaluation criterion of progression-free survival at 12 months. Fourteen patients of the 39 treated with sunitinib showed no tumour progression for at least one year. The median progression-free survival was 8.9 months in the sunitinib group versus 3.6 months in the placebo group. The results of this study suggest that sunitinib should be considered as first-line treatment for malignant PPGL<sup>53</sup>.

### **PERSONALISED MEDECINE IN REAL LIFE**

#### **Molecular profiling for target actionability and clinical benefit**

In 2018, a working group on translational research and precision medicine of the European Society for Medical Oncology (ESMO) proposed a classification system for molecular alterations based on the available evidence to support their validity as clinical targets. A first version of the ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) was produced, defining six levels of clinical evidence for molecular targets according to their involvement in patient management: from level I, targets ready to be used in routine clinical decision making; level II, experimental targets requiring further data; to level X, absence of evidence of actionability. The ESCAT defined criteria that are based on clinical evidence, to rank genomic alterations as markers allowing patients to be selected for targeted therapies<sup>54</sup>.

It is believed that 50-66% of patients with a neuroendocrine tumour have actionable mutations (that can be targeted with existing treatments). *Boilève et al* retrospectively analysed the molecular profile of tumours from 114 patients with thoracic neuroendocrine neoplasms, digestive system tumours, ENT tumours or others. Forty eight percent of analysed lesions showed a genetic alteration that was potentially actionable, amongst which 35% had received a personalised treatment and 78% of these patients had shown a clinical benefit.

#### **Genomic Medicine Plan for France 2025**

Genomics is at the centre of the 21st century medicine. In view of this fact, a national plan – ‘Plan France Médecine 2025’, has been established. This has three principal objectives: to

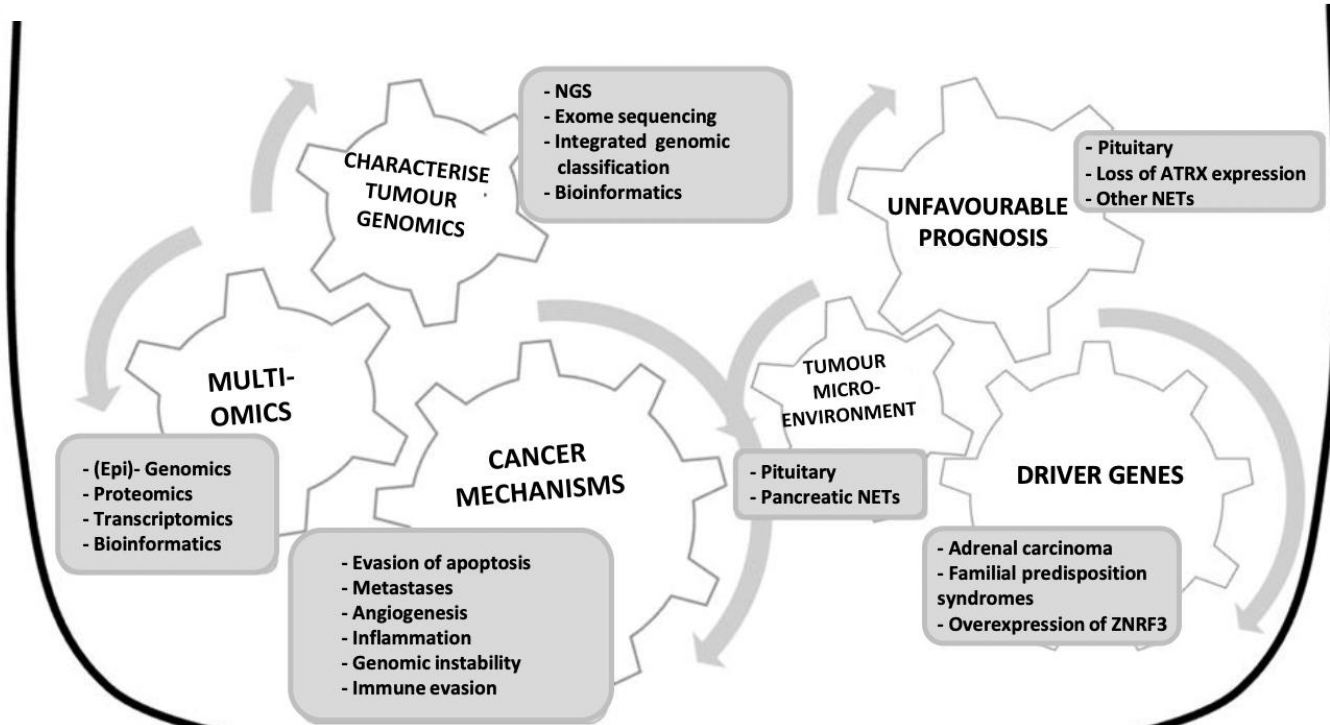
prepare for the integration of genomic medicine into current management of disease; to put in place a pathway so that genomic medicine can be a force for scientific and technological innovation; and to ensure that France is one of the major countries engaged in personalised medicine. This will require scientific, clinical, technological, economic and population aspects to be taken into consideration.

Certainly, thanks to great advances in our scientific knowledge, we are now well-placed to analyse cancer pathologies in a more and more precise manner and to differentiate at an increasingly early stage those tumours with an increased risk of aggressive behaviour. Understanding tumours at the molecular level now allows us to propose increasingly targeted therapies to patients. While large randomised trials will permit the validation of the safety and efficacy of these treatments on a large scale, the first studies analysing the benefit of the specific association of an actionable mutation with a targeted therapy have shown promising results, allowing us to foresee the use of increasingly personalised medicine in the future.

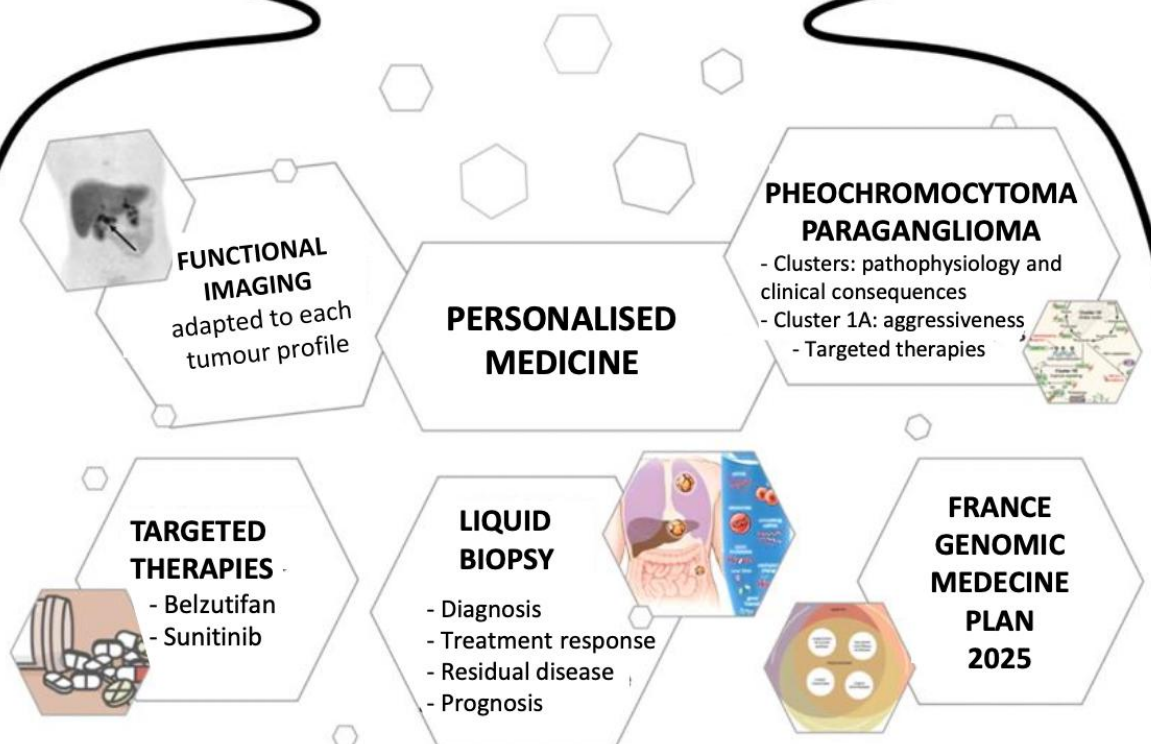
This article had institutional support from Ipsen Pharma, the first author having participated in the Must Endocrinology conference, 2022.

A

## FROM THE IDENTIFICATION OF NOVEL MECHANISMS.....



B



## ...TO PERSPECTIVES FOR CLINICAL BENEFITS

**Figure 1. From mechanisms to the clinic.** A. New epigenetic and molecular mechanisms shown in neuroendocrine neoplasms B. Clinical applications: diagnostic, prognostic and

therapeutic tools. Part B is adapted from figures published in *Refardt et al, JCEM, 2022* ; *Di Nicolantonio et al, Nat Rev Clinical Oncology, 2021* ; *Nolting, Endocrine Reviews, 2022*.



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