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EndoCompass Project: Research Roadmap for Pituitary and Neuroendocrine Tumor Endocrinology

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Significance

The research roadmap for pituitary diseases and neuroendocrine tumor endocrinology project has been an exciting and fruitful collaborative work of many experts highlighting the multitude of challenges associated with the diagnosis and management of these conditions across the lifespan. Systematic, adequately supported by funders' and policymakers' work that focuses on the many identified research priorities is vital for enlightening the mechanisms of disease/tumor biology and ultimately improving patient outcomes. The application of technical and methodological advances, including precision medicine, preclinical models, machine learning and artificial intelligence, are promising, valuable tools for the progress of impactful translational research in modern neuroendocrinology.

Keywords
EndoCompass · Thyroid · Funding · Roadmap

Abstract

Background: Endocrine science remains underrepresented in European Union research programs despite the fundamental role of hormone health in human wellbeing. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding toward endocrinology. The EndoCompass project – a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges. ***Methods:*** Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014–2020). Expert consultation in pituitary and neuroendocrine tumor endocrinology was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups. ***Results:*** Research priorities encompass congenital and acquired disorders, tumor development and progression, and neuroendocrine neoplasms. Key areas include genetic/epigenetic factors, tumor microenvironment, personalized treatment approaches, developing preclinical models, and implementing artificial intelligence. Special emphasis is placed on aggressive tumors, hypothalamic syndromes, and establishing pan-European

biobanks and databases. ***Conclusions:*** This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into pituitary-neuroendocrine disease pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of these disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

Introduction

Pituitary Disease

Pituitary disease can manifest across the whole lifespan, and includes a variety of pathologies, from congenital hypothalamo-pituitary disorders to pituitary tumors and other lesions in this area. The rarity of many of these conditions not only poses challenges for diagnosis and management, but also impacts research efforts to understand their pathogenesis and factors implicated in their prognosis. Comprehensive understanding of the mechanisms of tumor development, regrowth, and aggressive behavior remains deficient, making the discovery of more effective therapeutic agents more difficult.

Congenital hypothalamo-pituitary disorders, with their plethora of phenotypic manifestations, require further elucidation of their underlying pathophysiology, as does the often-daunting hypothalamic syndrome. Finally, the application of technical and methodological advances, including precision medicine, preclinical models, machine learning, and artificial intelligence (AI), constitutes a promising challenge. Their expected contribution to the progress of translational research is a major priority in modern neuroendocrinology.

Neuroendocrine Neoplasms

Neuroendocrine neoplasms (NENs) are malignancies arising from the diffuse endocrine system, which comprises neuroendocrine cells dispersed throughout the bronchopulmonary and gastrointestinal tracts. Incidence and, particularly, prevalence of these neoplasms are steeply rising, making gastroenteropancreatic NENs the second most prevalent malignancy in the gut and the 10th most prevalent malignancy overall [1, 2].

Diagnosis and treatment of NENs are both challenging because of their heterogeneous biological behavior, with more than 60% being metastatic at diagnosis. One major unmet need arises from the paucity of curable/effective therapeutic options. The only treatment that offers cure is surgery, possible in few patients with localized disease, while unresectable NENs are treated with a variety of noncurative options (somatostatin analogs, peptide receptor radioligand therapy, targeted agents, or chemotherapy), which eventually fail due to drug resistance, stressing the need for new therapeutic avenues [3]. Another unmet need is the lack of reliable biomarkers to guide management [4] as patients with the same tumor grade/stage behave heterogeneously in terms of time to tumor progression, tumor recurrence, or treatment response.

Genetics and Epigenetics in Adult Pituitary and Hypothalamic Disease

There is a need to explore genetic and epigenetic factors, including the role of chromatin architecture and regulatory DNA sequences, in pituitary and hypothalamic disorders.

Epidemiology, Societal Impact, and Research State of the Art

Understanding the interplay of genetic and epigenetic factors is essential to improve diagnosis and treatment in patients with pituitary adenomas and arginine vasopressin deficiency (AVP-D). The majority of pituitary adenomas are sporadic, while ~5% are familial or isolated, often presenting at a younger age and having a poorer prognosis [5, 6].

Recurrent somatic variants in *GNAS* and *USP8* exist in around 40% of somatotrophinomas and about 35% of corticotrophinomas, respectively [5]. Aggressive tumors show a relatively high prevalence of *TP53*, *ATRX*, and *SF3B1* variants [7, 8]. Epigenetic modifications in pituitary adenomas are cell lineage-dependent and less explored [9, 10]. Similarly, copy number variations and chromosomal gains and losses in pituitary adenomas are more likely to be histotype-specific [5]. AVP-D is characterized by genomic alterations on genes involved in the vasopressin/aquaporin axis [11, 12].

Future Research Priorities

There is a need for refined diagnostic procedures for the early diagnosis of familial cases and timely prediction of aggressive tumor behavior and prognosis. Technical advances are expected to allow us to elucidate the mutational landscape of pituitary tumors beyond *GNAS* in somatotrophinomas and *USP8* in corticotrophinomas. In the long term, we need to intensify research into the epigenetic mechanisms that underpin the pathophysiology of pituitary adenomas, focusing on lineage-specific patterns of

gene demethylation and chromatin accessibility. We also need to decipher the genetic alterations contributing to hypothalamic disorders. Given the complexity and rarity of cases, interdisciplinary collaboration is essential to effectively address these challenges.

Anticipated Impact of Future Research

Advanced research in pituitary and hypothalamic disorders will have a major impact on understanding their pathophysiology and translation to effective clinical management. Early detection of familial cases of pituitary adenomas, hypothalamic disorders, and aggressive behavior of tumors is essential for timely intervention and improved patient outcome. Unraveling the complex genetic and epigenetic mechanisms underlying these disorders is expected to lead to earlier, more accurate diagnosis and personalized treatment strategies that are effective and have fewer side effects. These advancements will facilitate the precision management of patients with pituitary and hypothalamic disorders.

Tumor Microenvironment in Adult Pituitary Tumorigenesis

An increased understanding is needed of the importance of the environment surrounding a tumor for pituitary tumor pathogenesis and clinical utility.

Epidemiology, Societal Impact, and Research State of the Art

Beyond genetics and epigenetics, the environment within which a tumor exists is defined as the tumor microenvironment. It includes immune and stromal nontumor cells, vascular structures, and noncellular components (extracellular matrix) in a cross-talking continuum.

The tumor microenvironment opened a new area of research to shed light not only on the pathophysiology of neoplasms but also on the identification of those of its components that may provide drug targets [13]. Recently, the tumor microenvironment has been intensely investigated in pituitary tumors, particularly in the subset, which display an aggressive clinical course with rapid progression and resistance to conventional treatments. Some of the potential therapeutic targets among the cellular or noncellular components of the tumor microenvironment have been used in solid tumors as well as in aggressive pituitary tumors. Hence, components of the tumor microenvironment may have a clinical utility, not only as targets for drugs but also as prognostic biomarkers for resistance to treatment, leading to more efficient management [14, 15].

Future Research Priorities

The future research priorities in studying the tumor microenvironment are based on investigation of the following:

1. New tumor microenvironment biomarkers that will identify the more aggressive pituitary tumors in the context of proliferation, and the pituitary tumors resistant to conventional treatment.
2. Genetic, histopathological, and molecular imprints, which enable selection of appropriate drugs for use in each case as a monotherapy or combination therapy, as well as the timing of early management before progression and the most effective sequence of each agent to be used.
3. AI to build an algorithm for individualized treatments, using a combination of omics, epigenetics and tumor microenvironment factors, including the immune component [16, 17].

The methodology to achieve the above goals includes establishment of a biobank (solid and liquid biopsies), as well as common European databases with basal information on patients and characteristics of pituitary tumors, including all the biomarkers studied. Thereafter, randomized, multicenter studies will need to establish the factors influencing aggressiveness and resistance to treatment [18].

Anticipated Impact of Future Research

Immunotherapy and antiangiogenic therapies that target components of the tumor microenvironment have been attempted in a few published cases of aggressive pituitary tumors, with positive outcomes. The rationale for using these therapies is based on the central premise that the tumor microenvironment impacts the pathophysiology of pituitary tumors.

On the other hand, the use of common centralized European pituitary tumor biobanks and databases will help facilitate and accelerate the identification of the tumor microenvironment components that can be used more efficiently as prognostic and predictive biomarkers or as drug targets for pituitary tumor management.

Treatment Options for Adult Pituitary Tumors

(New) treatment options must be investigated for resistant prolactinomas, nonfunctioning pituitary adenomas and Cushing's disease, particularly in settings of recurrence.

Epidemiology, Societal Impact, and Research State of the Art

Prolactinomas

Resistance to dopamine agonist (DA) treatment is uncommon in microprolactinomas and more frequent in macroprolactinomas and invasive tumors. Primary DA resistance occurs in around 20%–30% of the cases treated with bromocriptine and 10% of those treated with cabergoline [19]. Secondary DA resistance is rare and is usually associated with aggressive or malignant tumor behavior [19]. Management approaches in resistant prolactinomas include changing DA, surgery, radiotherapy, temozolomide (in aggressive tumors), or combinations of these. However, these approaches are not always successful [7, 19–21].

Nonfunctioning Pituitary Adenomas

Nonfunctioning pituitary adenomas have a prevalence of between 7/100,000 and 41.3/100,000 and are associated with various morbidities and increased mortality [22, 23]. Surgery combined, or not, with radiotherapy is the main means of treatment, aiming to safely remove the tumor and stop its regrowth. Despite these approaches, regrowth occurs in several patients (the risk of which is currently defined by clinical and pathological parameters). A subset of these tumors demonstrates aggressive behavior [24–26]. Following tumor regrowth, repeat surgery and/or radiotherapy are the first-line approaches, and DAs have been tried for prevention of growth of nonfunctioning pituitary adenomas [24, 27, 28].

Cushing's Disease

Cushing's disease is associated with increased morbidity and mortality [29]. After surgery, the recurrence rate is around 30%. For those cases, radiotherapy and combination drug therapy, targeted for biochemical control (steroidogenesis inhibitors and glucocorticoid-receptor blockers) and tumor control (pasireotide and DAs), are available. The latter have only limited effectiveness and, in some cases, severely impairing side effects.

In cases that are refractory to therapy, aggressively growing corticotrophinomas and adrenocorticotrophin-secreting carcinomas, there have, so far, only been off-label therapy trials with temozolomide, and attempts at individualized therapy with immune checkpoint inhibitors, tyrosine kinase inhibitors and angiogenesis inhibitors, all potentially associated with serious side effects [26].

Following the discovery of the activating mutation in the *USP8* gene and changes in regulators of the cell cycle (cyclin-dependent kinases) in Cushing's Disease, potential molecular targets are now available [30, 31].

Future Research Priorities

Prolactinomas

- Understand the molecular mechanisms involved in resistance to DAs.
- Develop new alternative medical treatments and investigate the efficacy and safety of those proposed to date (e.g., estrogen receptor antagonists, aromatase inhibitors, pasireotide, lapatinib, everolimus, and immune checkpoint inhibitors).

Nonfunctioning Pituitary Adenomas

- Understand the mechanisms implicated in regrowth of nonfunctioning pituitary adenomas after primary treatment.
- Identify molecular prognostic factors associated with regrowth.
- Identify targets for pharmacotherapy that will prevent regrowth or be used as primary medical treatment, particularly for tumors not requiring prompt surgical intervention.

Cushing's Disease

- Identify further molecular mechanisms involved in corticotroph tumors.
- Further investigate existing drugs for molecular targets (i.e., seliciclib) and develop new, tumor-targeted, well-tolerated, and, ideally, oral therapy for recurrent Cushing's disease.

Anticipated Impact of Future Research

In all of the above types of tumors, the outputs of the proposed research will improve management pathways by expanding treatment options and applying personalized medicine. In the long term, they will have a positive impact on the outcomes and prognosis of the patients.

Aggressive Behavior and Targeted Treatment in Adult Pituitary Adenomas

There is a need to identify molecular factors associated with invasive behavior or in predicting aggressive behavior in pituitary adenomas, and to develop targeted therapies.

Epidemiology, Societal Impact, and Research State of the Art

The prevalence of invasive and aggressive pituitary tumors varies widely depending on the definition or criteria used and on the type of patients included. Nevertheless, aggressive pituitary tumors are rare; a recent study concluded that around 0.5% of all clinically

detected pituitary tumors have an aggressive course [25]. On the other hand, invasive pituitary tumors are common (14–40% of surgically treated cases) [32, 33]. Both invasive and aggressive pituitary tumors incur increased morbidity and mortality.

Radiological evidence of tumor extension into the cavernous sinus is not synonymous with invasion per se as this extension can correspond solely to tumor expansion [34, 35]. Moreover, the modified Knosp classification, widely used to define invasiveness, was only intended to predict the probability of intraoperatively observed cavernous sinus invasion and the surgical outcome [34]. Thus, prior to identifying molecular factors associated with invasiveness, clear definitions are needed.

Predicting aggressive behavior remains challenging. A combined clinicopathological classification has proven its value in predicting progression or recurrence following surgery [36] but remains, nevertheless, limited in predicting future aggressive behavior. Recently, a Ki67 index ≥10% has been proposed to predict future malignancy [37], but its value has not yet been proved. Identification of targeted therapies (including combinations), along with establishment of predictors of response to treatment, are needed most, especially following temozolomide failure.

Future Research Priorities

1. It is important to homogenize how "invasiveness" and "expansion" are defined, for both clinical and research purposes.
2. Investigations should determine whether "invasiveness" and/or "expansion" is associated with worse prognosis, independent of the fact that invasiveness/expansion leads to incomplete surgical removal of the tumor.
3. From a biological point of view, investigations are needed to show whether true "invasiveness" has a different molecular and cellular basis compared with simple "expansion." These mechanisms should be dissected to identify a marker that is useable in clinics, as well as new therapeutic targets. We strongly recommend the use of precision technological approaches (e.g., single-cell transcriptomics, as opposed to bulk transcriptomics), followed by validation at the protein level and, ideally, outcomes that are further investigated by mechanistic in vitro and/or in vivo studies. The application of other cutting-edge technologies (such as single-cell multiomics and spatial transcriptomics) is strongly encouraged.
4. Given the rarity of aggressive pituitary tumors and carcinomas, it is of utmost importance to create pan-European Union or, at least, national databases (with clinical, pathology and molecular data), coupled with biobanks that are as comprehensive as possible (tumor tissue, blood). This will enable understanding of tumor biology, identification of therapeutic targets, and identification of predictive/prognostic markers. Including all surgical specimens available in the biobank (initial tumor, recurrences, and metastases) will be crucial in order:
   - to investigate at what point the tumor phenotype has changed and, hence, test whether the identified markers of aggressiveness could serve as predictive makers, prior to clinical evidence of aggressive behavior
   - to study potential predictors of response to different treatments.
5. Similar to the above, a combination of multiomics studies and wet lab approaches should be applied, ideally within consortia with both strong bioinformatics and wet lab expertise.
6. It is important to test the identified predictive markers of future aggressiveness among large cohorts of both aggressive and benign pituitary tumors with a long follow-up (at least 5 years), in order to assess the prevalence and the specificity of the markers. While waiting for additional markers, one marker that is already proposed in the literature and would be simple to test is an initial Ki67 index ≥10% (see above).
7. Given the rarity of patients requiring therapeutic options beyond temozolomide, pan-European Union or, at least, national multicenter studies are needed to assess the efficacy and potential predictors of response to such treatments.

Anticipated Impact of Future Research

From a biological perspective, this research is expected to increase the understanding of the tumorigenesis-related processes linked to invasiveness and aggressiveness. From a clinical perspective, this research is expected to inform future guidelines and to directly benefit patients, leading to personalized approaches, decreased morbidity and mortality, and increased quality of life and survival.

Congenital Hypothalamo-Pituitary Disorders and New Treatment Options in Children

Epidemiology, Societal Impact, and Research State of the Art

Congenital hypopituitarism is characterized by single/multiple pituitary hormone deficiencies, often associated with midline brain/facial/eye and/or forebrain abnormalities,

including septo-optic dysplasia (SOD) and holoprosencephaly. It affects 1/3,000 to 1/4,000 children, with an incidence of SOD in Europe of 1.9–2.5/100,000 births.

Patients with congenital hypopituitarism, particularly SOD, can manifest autism, complex behavioral disorders, sleep dysregulation, and hypothalamic dysfunction including inexorable obesity. The impact on their families and wider society can be considerable, with few patients able to take up full-time employment, and much probably requiring lifelong supervised care. There is an increased risk of mental health problems, including self-harm.

Research suggests that congenital hypopituitarism arises from abnormal hypothalamo-pituitary development. Variants in over 67 genes have been identified, but account for only 10% of patient phenotypes. These genes encode transcription factors, signaling molecules, eukaryotic translation initiation factors and components of splicing machinery. Inheritance can be X-linked, autosomal dominant or recessive with variable penetrance [38, 39].

While SOD represents a spectrum of malformations with unpredictable endocrine and neuroimaging phenotypes, congenital hypopituitarism associated with multiple pituitary hormone deficiencies is more homogeneous [40]. Stalk and posterior pituitary abnormalities increase the risk of early onset deficits.

Future Research Priorities

There needs to be a greater understanding of the phenotypic heterogeneity observed, including growth in the absence of growth hormone (GH), unusual patterns of GH secretion, evolution of hormonal deficiencies, and pubertal development and obesity in SOD. Clinical features, such as impaired olfaction, pain insensitivity, and autonomic dysfunction, need to be studied in more detail. Improved neuroimaging techniques with better visualization of the hypothalamus and pituitary stalk may help predict clinical/metabolic outcomes and aid targeted therapy. Long-acting GH and glucocorticoids may improve quality of life, alongside treatments for hypothalamic obesity.

Research should also focus on mental health, neurocognition, behavior, autism, attention deficit hyperactivity disorder, aggression with self-harm, and sleep disorders. Additionally, given that the majority of cases remain genetically unexplained, we need to improve our understanding of the etiology of congenital hypopituitarism using comprehensive, unbiased modern multiomic techniques, including genomic, epigenomic, transcriptomic, and proteomic approaches, with the inclusion of AI.

Anticipated Impact of Future Research

Better understanding of the underlying pathophysiology and underlying molecular basis will not just improve genetic counseling, but also lead to improved prediction of the clinical trajectory of endocrinopathies and associated hypothalamic dysfunction, with better clinical outcomes.

Acquired Hypothalamo-Pituitary Disorders and New Treatment Options in Children

Epidemiology, Societal Impact, and Research State of the Art

Acquired hypothalamo-pituitary dysfunction can be caused by (supra)sellar tumors or their treatment, traumatic brain injury, infection, autoimmune processes, granulomatous disease, iron overload, or vascular insults. Endocrinopathies and hypothalamic dysfunction can evolve, causing significant morbidity and mortality. The close proximity to the optic chiasm may cause associated visual impairment.

The combination of hypothalamo-pituitary dysfunction, visual impairment, and neuro-behavioral disturbance can severely impact the quality of life of patients and their families, with significant socioeconomic cost, and increases the risk of mortality [41, 42]. Current research focuses heavily on the genetic etiology of these tumors to identify novel therapeutic targets.

Future Research Priorities

Targeted therapies may aid in limiting the role of surgery and radiotherapy (e.g., craniopharyngiomas [43], Cushing's disease) or in overcoming treatment resistance (e.g., prolactinomas and somatotrophinomas). Elucidation of tumorigenic pathways may help in the development of newer, less toxic treatments. Additionally, more intensive treatment may be offered for tumors deemed high risk at a molecular level.

Neuroimaging needs to improve to achieve more accurate diagnoses and to grade hypothalamic tumoral invasion and the degree of disruption of the surrounding hypothalamic neurocircuitry, in order to increase the precision of treatment strategies. New therapies also need to be developed for other, rarer causes of acquired hypothalamo-pituitary dysfunction, such as hypothalamitis and hypophysitis, and sarcoidosis or granulomatous disease.

Anticipated Impact of Future Research

Improved neuroimaging and molecular techniques will improve diagnostic accuracy and risk stratification of acquired hypothalamo-pituitary lesions [44], as well as the development of new treatments for tumors in this region. It will lead to fewer off-target effects, reducing the injury to healthy brain tissue incurred by neurosurgery and radiotherapy. Inclusion of markers of hypothalamo-pituitary dysfunction in clinical trials for novel oncology treatments will clarify the effect of such interventions on long-term quality of life. Overall, this will improve progression-free and event-free survival, reduce toxicity and adverse effects on the hypothalamo-pituitary axis, optimize metabolic and reproductive outcomes and, ultimately, improve the quality of life of survivors and their families.

Hypothalamic Syndrome and New Treatment Options in Children

Epidemiology, Societal Impact, and Research State of the Art

"Hypothalamic syndrome" encompasses a range of clinical features: dysregulated appetite and thirst, inexorable morbid obesity, multiple endocrinopathies (including deficiencies of adrenocorticotrophin and AVP), thermoregulation issues, fatigue, and behavioral, mental health, and sleep difficulties [45–48].

Due to our currently incomplete understanding of the complex neuroendocrine hypothalamic circuitries, many of these problems remain untreatable. This results in morbidity and disability, with a consequent burden on health systems as well as national economies.

Recently, newer molecular techniques have revealed the components of the hypothalamic circuitry, and the importance of hypothalamic hormones in appetite and weight regulation [45]. Correlation of function with neuroimaging markers has been difficult as conventional magnetic resonance imaging (MRI) cannot precisely define the hypothalamic nuclei.

Future Research Priorities

At present, there are no universal biochemical or neuroradiological diagnostic criteria for hypothalamic syndrome. More precise neuroendocrine, genomic and epigenomic markers to pinpoint pathogenic changes need to be identified, to better understand and treat the various domains of hypothalamic dysfunction. Similarly, there is a need to establish the etiology of other congenital hypothalamic syndromes, such as ROHHAD(-NET) (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation, and neuroendocrine tumor [NET]).

Advanced neuroimaging is required to more precisely define hypothalamic damage and determine how this correlates with the phenotypes observed. Prospective intervention studies are needed for the treatment of hypothalamic obesity and fatigue. The high rate of neuropsychological disturbances and autistic spectrum and mental health disorders associated with hypothalamic syndromes also needs to be better understood to develop effective interventions.

Anticipated Impact of Future Research

The development of successful therapies for hypothalamic obesity will reduce long-term complications, such as cardiovascular morbidity and type 2 diabetes. Identifying neuroradiological correlates of hypothalamic dysfunction will allow the development of medical treatments and reduce the risk of complications, by improving the precision of neurosurgery and radiotherapy. Understanding the nature of congenital hypothalamic syndromes such as ROHHAD(NET) will aid early diagnosis, genetic counseling, and development of targeted therapies for this life-limiting condition. Overall, achievement of these research priorities will improve the long-term quality of life and reduce long-term mortality for these patients, as well as decrease the significant socioeconomic burden on health- and social-care systems.

Developing Precision Medicine Approaches for Pituitary Tumors

Epidemiology, Societal Impact, and Research State of the Art

Precision medicine for pituitary tumors involves tailoring diagnosis, treatment, and monitoring strategies to the individual characteristics of each patient and their tumor. This requires identification of biomarkers to guide patient treatment based on individual conditions, as is being pioneered in acromegaly [49].

Evolution of image guidance and visualization technologies in pituitary surgery, including intraoperative MRI suites and biological imaging strategies, will be critical in this regard [50, 51]. Indeed, the endoscopic transsphenoidal approach has improved earlier surgical outcomes [52]. However, the anatomical complexity and heterogeneous biology of pituitary tumors challenge their management, demanding multimodal integration of surgery, radiosurgery, radiation therapy, and medical therapy [53].

Future Research Priorities

The development of precision pituitary medicine will require genomic sequencing of each tumor to identify specific mutations, gene expression patterns and molecular signatures, and to predict their impact on tumor behavior. This could facilitate the establishment of a true clinico-molecular classification and stratification of tumors and the identification of molecular targets in specific tumor subtypes.

Circulating biomarkers (e.g., hormones, cytokines, and metabolite levels) could leverage this approach, jointly providing information on tumor progression, invasion, and therapy response, improving patient monitoring and prediction of prognosis. Advancing this strategy requires the development of algorithms to integrate clinical, molecular, and imaging data, in order to stratify patients into risk groups based on tumor aggressiveness, recurrence potential and treatment responsiveness. In turn, this will allow surveillance protocols and treatment interventions to be tailored according to individual risk profiles.

Additionally, targeted therapies will have to be developed, such as small molecule inhibitors, monoclonal antibodies or peptide receptor ligands, selectively disrupting tumor growth and hormone secretion while minimizing off-target effects. This will only be possible through advanced integrative computational models that are able to predict treatment outcomes, recurrence risk, and long-term prognosis for individual patients, while enabling algorithm refinement by machine learning from patient outcomes and real-world data. Naturally, this necessitates interdisciplinary and international collaborations among researchers, clinicians, patient advocates, and industry partners.

Anticipated Impact of Future Research

Integrating these strategies will accelerate discovery and translation and boost precision medicine approaches for pituitary tumors. This can revolutionize their management and offer personalized diagnostic, therapeutic, and prognostic solutions tailored to the unique characteristics of each patient. Implementation of precision pituitary tumor medicine will impact the future of research, healthcare systems and patient care by providing more accurate diagnosis and prognosis prediction tools, to help tailor treatment.

In addition, molecular profiling can lead to more effective and personalized therapies, improving patient outcomes and quality of life, and helping to overcome treatment resistance by applying molecularly targeted therapies to each tumor. Overall, the future impact of precision medicine on pituitary tumors promises to be transformative, offering patients more personalized and effective treatment options, while advancing our understanding of tumor biology and improving healthcare outcomes.

Developing Preclinical Models for Hypothalamic and Pituitary Pathophysiology

Epidemiology, Societal Impact, and Research State of the Art

Establishing in vitro or in vivo models to study hypothalamus/pituitary function is inherently challenging, due to the complexity of this neuroendocrine axis, which involves intricate interactions between diverse cell types and multiple hormones, regulated through dynamic feedback mechanisms. Accurately modeling these interactions in the laboratory require the precise control of differentiation and functional maintenance of specific cell types.

Pituitary tumor cell models first established in 1968 (rat GH3, mouse AtT-20 and, later, rat MMQ cells) are still some of the few cell lines that are widely used in research, despite the limitation of their rodent origin [54]. Numerous attempts to develop human cell lines have failed to faithfully replicate any specific type of pituitary tumor. To circumvent this, labs commonly employ primary cell cultures derived from human pituitary tumors, a more pathophysiologically relevant model compared with immortalized cell lines, although with a limited lifespan and high variability [55, 56].

Fortunately, recent advances in cell culture techniques and stem cell and organoid research have facilitated the development of human and murine pituitary organoids derived from embryonic stem cells, induced pluripotent stem cells, and fetal or adult stem cells [57]. Indeed, various models are currently available for the normal and affected pituitary, including hypopituitarism, craniopharyngioma and anterior pituitary tumors, especially corticotrophinomas and prolactinomas. These may serve to evaluate drugs, assess tumor growth and restore pituitary function [58]. Similar approaches have been employed for hypothalamic studies [59] and, although no perfect models can recapitulate pituitary/hypothalamus dysfunction, several recent models can be used, depending on the disease [60].

In vitro systems lack the capacity to mimic the complex feedback loops and environmental influences (stress, nutrition, and circadian rhythms), further limiting hypothalamo-pituitary studies. Nevertheless, 3D chips are being developed to emulate hypothalamus-pituitary crosstalk [61].

Future Research Priorities

Future research should prioritize the development of pituitary and hypothalamic organoid models to better replicate the complex cellular interactions and dynamic

feedback mechanisms inherent to these systems. Advances in stem cell technology and bioengineering must be leveraged to create more accurate and functional in vitro models. Additionally, developing 3D culture systems and organ-on-a-chip technologies will be crucial to simulate physiological conditions such as stress, nutrition and circadian rhythms, as well as enabling detailed investigation of disease mechanisms, leading to the discovery of new therapeutic targets and more effective treatments. Efforts should be focused on creating human-derived cell lines to improve translational relevance and facilitate personalized medicine applications for neuroendocrine disorders.

Anticipated Impact of Future Research

Development of more accurate and functional models should revolutionize the understanding of pituitary and hypothalamic pathophysiology. These advancements will improve drug screening processes, reduce the dependence on animal models, and facilitate personalized treatment strategies. Ultimately, this research holds the potential to restore pituitary function in patients with related disorders, significantly improving their quality of life and clinical outcomes.

Machine Learning and AI in Research and Management of Pituitary Diseases

Epidemiology, Societal Impact, and Research State of the Art

Artificial intelligence and machine learning have gained momentum in recent years as integrative techniques for diagnosis and intervention in pituitary diseases. They enable more holistic and multidimensional approaches and facilitate the management of the increasingly large amount of data associated with clinical and basic research [62].

For clinical research, the main areas for application of machine learning are predictive algorithms for tumor aggressiveness and clinical outcomes of surgery and medical treatment [51, 63]. Algorithms may become helpful tools in complex differential diagnoses, but differences in training sets could affect the replicability of results. In basic research, machine learning is usually applied to pathomic and transcriptomic studies.

Future Research Priorities

Two critical issues in studies involving machine learning are appropriate sample size and algorithm/model homogeneity. Many different algorithms have been used in pituitary research to train datasets, including a broad range of subjects. Moreover, predictive algorithms are often designed to replicate clinician-made evaluations (texture, development of pituitary deficiencies), which limits their impact on clinical decisions. Surgical outcomes are usually center-specific. With larger, collaborative datasets, radiomic studies could help unveil other disease-specific characteristics of pituitary neoplasms. Moreover, longitudinal studies with standardized follow-up intervals might help identify patients who require more proactive interventions than those in which "watchful waiting" could be a reasonable approach.

For basic research, pathomic studies could provide insightful results on pituitary neoplasm recurrence and aggressiveness, and patient response rate to standard medical regimens. Algorithm analysis of pathological images, ideally integrated with clinical and transcriptomic data, could help identify reliable predictors guiding treatment and follow-up regimens. Furthermore, identifying neoplasm-specific biomarkers in peripheral blood could help develop reliable "liquid biopsies," allowing less invasive diagnosis and surveillance.

Complex machine learning techniques, such as neural networks, are often burdened by a lack of explain ability, which is a mainstay of transparency in the use of AI algorithms in healthcare. However, machine learning–assisted clinical decisions will become increasingly prevalent in the coming decades. Therefore, the aim should be to combine data from different countries and settings, minimizing training-related biases, such as the underrepresentation of minorities.

Anticipated Impact of Future Research

Patient-centered precision medicine is the future of healthcare, where each person will be characterized by an increasing amount of data. Patients with pituitary disorders face numerous challenges during their lifespan, often with little knowledge at diagnosis of what their path will be. Predictive algorithms could help healthcare professionals identify "high-risk" and "low-risk" patients, probability of remission, and development of complications, so empowering people with pituitary disorders to be part of the decision-making process. Moreover, machine learning techniques could help bridge knowledge gaps in rare pituitary diseases by unveiling new patterns and developing novel therapeutic strategies.

Understanding NENs Biology

Epidemiology, Societal Impact, and Research State of the Art

Neuroendocrine neoplasms are divided into well-differentiated NETs and poorly differentiated neuroendocrine carcinomas (NECs) [64]. Ki67 is the most

important prognostic biomarker of NENs, marking cycling cells, a crucial tool for grading [65]. For diagnostic purposes, alterations in TP53 and RB1 are considered biomarkers of NECs [66]. In contrast, MEN1, DAXX, and/or ATRX mutations are typically associated with NETs in some districts [67]. DNA methylation profiling has recently been proposed as a powerful source of diagnostic and prognostic biomarkers [68]. With the introduction of new therapeutic strategies into the clinic, new biomarkers with predictive value are urgently needed.

Future Research Priorities

Beyond the distinction between NETs and NECs, the entire NENs category should be considered a continuous entity, without the well-demarcated boundaries imposed by classification needs. Thus, one of the most crucial research priorities is to address the large gray areas within each neoplasm subgroup. One example is the G2 category, which includes tumors with totally different proliferation and clinical behavior. The most advanced next-generation techniques should be implemented in this category, including single-cell omics, with epigenomics and transcriptomics [69]. In addition, the use of spatial transcriptomics to investigate the tumor microenvironment is a promising methodology to further explore this heterogeneous tumor context [70].

Historically, improvements in establishing experimental models of NETs have been modest. Cell lines derived from different NETs have been generated, but most cell lines are only partially representative for their NETs of origin. Similar issues relate to the use of NETs animal models. NETs xenograft models are difficult to establish and generally slow-growing [71]. In recent years, promising 3D spheroid and organoid models of mainly high-grade NETs and NECs have been established [72, 73], but there remains an unmet need for preclinical models of low-grade NETs. The majority of NET models does not address tumor heterogeneity or incorporate the complex tumor microenvironment. Future research should address these issues, by 3D techniques and novel technologies such as tumor-on-a chip [74].

Anticipated Impact of Future Research

Developments in molecular and preclinical research in the field of NENs are expected to foster progress in understanding the mechanisms underlying neoplasm formation, and, ultimately, to fundamentally improve their diagnostics, therapeutic methods and patient outcomes. Thus, identification of new biomarkers, accompanied by designing reliable molecular tests, and advances in anatomical and functional imaging techniques, will improve the current methods to diagnose and monitor NENs and to predict their progression.

Likewise, advancements in treatment strategies, including new therapeutic targets in the field of biotherapy, molecular targeted therapies, radioisotope therapies, chemotherapy, and immunotherapy (as well as combinations of these therapies) should provide more effective treatment options, especially for advanced NENs. Additionally, innovative surgical techniques, including minimally invasive methods, will foster improved outcomes.

However, as we embrace the era of precision medicine, personalized, individualized treatment approaches based on genetic tests will become available to optimize therapy selection and sequencing and, thereby, minimize side effects. Most importantly, research and technological advances will focus on the patient, leading not only to better treatment outcomes and enhanced survival rates, but also to an improvement in the quality of life of patients. In summary, research advances should facilitate a better understanding of NEN pathobiology and leverage the development of improved and early diagnostic tools and more effective treatments, ultimately benefiting patients with NENs and healthcare systems alike.

How to Improve Therapy in NENs

Epidemiology, Societal Impact, and Research State of the Art

The existing treatment options in advanced NENs are limited, highlighting the unmet need for novel therapeutic approaches. One of the new options includes immune-based treatments, which have been at the epicenter of cancer therapy in recent years. Immunotherapy has been evaluated in NENs of different origin and differentiation, but with limited efficacy shown only in some high-grade NENs, and particularly as combination therapy [75]. Another option includes cancer vaccines, based either on tumor-associated or on tumor-specific antigens. Carcinoembryonic antigens and chimeric antigen receptors are under development [76]. The molecular profiles of patients have also been exploited with limited success in rare individual cases where mutations have been identified that could provide drug targets [77]. Additionally, identification of the preferred sequence in existing therapies is another major unmet need. Despite initial insights from recent studies, a general approach for application in clinical practice is missing [78].

Future Research Priorities

Future research priorities in NENs treatment are based on personalized medicine, specifically focusing on the investigation of: (1) new biomarkers to identify the disease and appropriate timing of early management before progression, (2) patient-derived organoids for closer to real-life screening of drug efficacy, and (3) pathological and/or molecular imprints to individualize the sequence and combinations of treatments (omics, immunological, epigenetic, and microenvironmental factors).

The methodology should include establishing biobanks (with solid and liquid biopsies) inside a common European network of expert centers, to integrate information on patients and their respective NENs, including disease features and treatment sequence/outcomes. Moreover, this approach will allow randomized, multicenter studies to be undertaken, focusing on molecular profiles pre-/post-surgery and pre-/post-therapies, through the investigation of omics, metabolic alterations, cancer immunology and microenvironment, and mapping the different neoplasms. Integrating the use of novel models such as organoids, 3D tumor cultures and xenografts into this research network will enable testing of novel drugs and potential cancer vaccines. Finally, AI can help pinpoint the right algorithms for combination and sequential therapies for each patient group.

Anticipated Impact of Future Research

Establishing a common European biobank and registry network will help identify novel prognostic and predictive biomarkers, the right timing and sequencing of existing drugs, and novel, efficient, individualized approaches, ultimately improving the prognosis and quality of life of patients with NENs.

Fibrosis in NETs

Epidemiology, Societal Impact, and Research State of the Art

Neuroendocrine tumors retain the ability to secrete hormonally active substances and consequently to elicit hormonal symptoms in patients. The most common hormonal syndrome, encountered in ~20% of patients with NETs, is carcinoid syndrome, which is characterized by secretory diarrhea, flushing and fibrotic complications [79], and reduced quality of life compared with patients who do not have the syndrome [80, 81]. Carcinoid syndrome is predominantly encountered in patients with a metastatic NET originating from the small intestine, followed by those of lung, pancreatic, ovarian, or thymic origin. Although serotonin is considered a critical mediator of carcinoid syndrome, the condition's precise pathophysiology and determinants are incompletely understood [82].

Importantly, fibrotic complications may be observed in patients with NETs, usually, but not exclusively, within the context of carcinoid syndrome. These include mesenteric fibrosis and carcinoid heart disease.

Mesenteric fibrosis is a pathognomonic feature of mesenteric metastases of small intestinal NETs, characterized by radiating fibrotic strands from a central mesenteric mass. Local fibrosis can induce venous ischemia, ileus, obstruction, and perforation of the bowel, and is associated with an impaired overall survival.

Carcinoid heart disease is encountered in 20%–30% of patients with carcinoid syndrome. It is characterized by right-sided heart valve and endocardial fibrosis, potentially leading to tricuspid valve and pulmonary valve regurgitation and stenosis and, ultimately, right-sided heart failure with increased mortality and morbidity.

In both mesenteric fibrosis and carcinoid heart disease, there appears to be a crucial role for serotonin derived from local and/or systemic NETs cells, and activation of its 5-HT2b receptor [83]. Besides serotonin, several other profibrotic factors have been postulated to contribute to the development of NET-associated fibrosis, including prostaglandins, histamine, bradykinin, tachykinins (substance P, neurokinin A, and neuropeptide K), and growth factors (transforming growth factor-β, platelet-derived growth factor, and connective tissue growth factor). Moreover, mitochondrial dysfunction also reportedly contributes to the fibrotic process, but the specific mechanisms of mitochondrial involvement in this setting are unclear.

The use of 5-hydroxyindoleacetic acid, a serotonin metabolite, for patients at risk of diagnosis with carcinoid heart disease, is possible only in individuals with serotonin hypersecretion, within specific diet and laboratory constraints. To this end, there are no specific/sensitive markers to assess the presence, severity, and risk of fibrosis in clinical practice to date.

Future Research Priorities

A better understanding of the pathophysiological mechanisms within the tumor cell and its microenvironment will help delineate the therapeutic targets for NET-associated fibrosis.

Specifically, for carcinoid heart disease, we propose that the priorities should be:

- Establishing a multinational, multidisciplinary working group to study basic, translational, and clinical aspects of carcinoid heart disease by

combining patient databases, imaging records, and biobank samples of blood and tissue.
- Identifying NET-secreted endocrine factors and local cellular and paracrine mediators of carcinoid heart disease in ex vivo and in vitro experimental models.
- Improving clinical risk stratification of carcinoid heart disease by combining patient and tumor characteristics, circulating biomarkers, and imaging features.
- Developing therapeutic strategies for effective identification and prevention of carcinoid heart disease (progression) in high-risk patients with carcinoid syndrome through randomized controlled trials.
- Determining the optimal timing of surgical valve replacement for carcinoid heart disease.

For mesenteric fibrosis, the priorities should be:
- Developing an experimental model that successfully recapitulates the tumor microenvironment.
- Identifying tumor-/patient-specific factors within the tumor microenvironment that determine the development of mesenteric fibrosis.
- Developing a risk assessment tool to identify, which patients with mesenteric fibrosis require preventive surgical resection.
- Discovering novel medical targets to prevent progression of mesenteric fibrosis and testing these in multicenter randomized controlled trials.

Anticipated Impact of Future Research

Given the paucity of current knowledge on the pathophysiology of NET-associated fibrosis, these future research endeavors will increase our understanding of the most relevant molecular and cellular contributors. Together with superior risk stratification for the development or progression of fibrosis, they will lead to the first interventional clinical trials aimed specifically at treating/preventing NET-associated fibrotic complications. This will ensure high-grade evidence needed to change clinical practice and improve patient outcomes.

Conclusions

There is no doubt that hypothalamo-pituitary disease remains enigmatic in many of its aspects, ultimately affecting patients' prognoses and outcomes. The many unmet gaps in research that are described above require attention and action from funders, policymakers, healthcare systems, clinicians, and academics, for the benefit of those living with these conditions in the years to come.

Likewise, despite some recent advances in the field of NENs diagnosis and treatment, there is still limited improvement in the real-life approach to these diseases and the related patient outcomes. International funding should focus on promoting further research to fill the gap that exists today between our knowledge and the heterogeneous and still unsolved biological behavior of these rare cancers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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