# Conducting pituitary care: innovation and standardization in a rare disease

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# 1 General introduction and thesis outline

# INTRODUCTION



Pituitary tumours comprise a heterogeneous disease group with common features but also large differences. If pituitary tumours derive from glandular tissue of the anterior pituitary lobe, they are called adenomas. Adenomas can either cause a pituitary hormone excess, the functioning adenomas, or be clinically "silent", in which case they are classified as non-functioning adenomas. Functioning adenomas cause hormone excess syndromes, in specific: Cushing's Disease, acromegaly, prolactinoma, thyrotropinoma and gonadotropinoma. Additionally, pituitary masses can derive from embryological tissue (craniopharyngiomas and Rathke's Cleft Cysts) or from the posterior pituitary lobe (pituicytoma). Even though incidental pituitary lesions are commonly found in imaging (22.5%) and autopsy studies (14.4%) [1], symptomatic pituitary tumours are considered rare with an incidence of 5.73 new cases per 100,000 per year [2], and a prevalence of 37-116 per 100,000 in population studies [3]. In the majority of cases, highly specialized surgery and multidisciplinary treatment is necessary and requires expert centres that can ensure sufficient experience in the management of these patients.

These different tumour types and diseases vary greatly in symptomatology and clinical presentation, particularly depending on hormone oversecretion syndromes. Common features are clinical symptoms caused by mass effects. These mass effects can result in pituitary hormone deficiencies or visual symptoms due to compression of the optic nerves. Symptomatic pituitary tumours can be treated with surgery, medication, radiotherapy, or multimodal treatment. However, pituitary surgery is the first-line treatment option in the management all of these diseases except for prolactinomas, for which medical treatment is still considered the first treatment option for the majority of cases [3].

This chapter will provide an overview of the anatomy and physiological functions of the pituitary gland, symptomatology and pathophysiology that underly pituitary hormone excess and -deficiencies and mass-effects. Moreover, an outline of the (surgical) management will be presented as well as the different value-based healthcare oriented care pathways. Finally, an explanation of the different coordinating institutions and the development of registries in the organisation of care and outcome registration for these rare diseases will be discussed.

## Pituitary anatomy

The pituitary gland is situated in the bony sella turcica. It consists of an anterior lobe, which is glandular tissue, and a posterior lobe, which consists of neuronal tissue. The pituitary gland in covered by a single meningeal layer of dura mater. Superior to the gland, another meningeal layer of arachnoid separates it from the intra-arachnoidal

cerebral structures and cerebrospinal fluid. It is connected to the hypothalamus by the infundibulum, also called the pituitary stalk, and a portal vein system. Via the portal vein system, stimulatory and inhibitory hormones of the arcuate nucleus of the hypothalamus reach the anterior pituitary lobe to control pituitary hormone secretion. The infundibulum also consists of neural axons from the supraoptic- and periventricular nuclei that lead to the posterior pituitary lobe [4].

The junction of the optic nerves, the optic chiasm, is situated just superior to the sella turcica. The hypothalamus is situated superior to the optic chiasm and just inferior to the third ventricle. Venous sinuses, the cavernous sinuses, are situated bilaterally of the pituitary gland. Within the walls of the cavernous sinuses, parts of the internal carotid arteries and nn. oculomotorius (n. III), trochlearis (n. IV), trigeminus (n. V) and abducens (n. VI) are located [4].

## Function of the pituitary gland

The pituitary gland functions as one of the main conductors of the endocrine system. Under physiological conditions, it critically controls the feedback loops together with the hypothalamus of the peripheral endocrine glands, namely the adrenals, the thyroid gland, the liver, the ovaries in women, and the testes in men. It receives both stimulatory and inhibitory signals from the hypothalamus and in turn secretes hormones that stimulate other endocrine glands that serve a multitude of functions of which only a concise summary is presented in this chapter.

The anterior pituitary lobe secretes 7 hormones upon stimulation of hypothalamic peptide hormones:

- Adrenocorticotropic hormone (ACTH) and α- MSH: ACTH mainly targets the adrenal cortex, which secretes cortisol after binding to the adrenocortical ACTH receptors. Cortisol has its effects in a multitude of tissues and orchestrates the adaptation to stressful situations e.g. by raising blood pressure, glucose concentration, adapts neurocognition, and modulates immune responses.
- Thyroid-stimulating hormone (TSH) stimulates the secretion of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) by the thyroid gland. Thyroid hormones, amongst others, stimulate metabolism and heat production.
- Follicle-stimulation hormone (FSH) and luteinising hormone (LH) stimulate the gonads. In females FSH causes follicular growth, and a monthly peak surge of LH secretion stimulates ovulation. The follicle produces the female sex hormones oestrogen and progesterone which cause the menstrual cycle and secondary female sex characteristics. In males FSH stimulates spermatogenesis in the Sertoli cells, and

LH testicular testosterone production in the Leydig cells. Testosterone causes the secondary male sex characteristics.

- Growth hormone (GH) stimulates mainly the liver to produce insulin-like growth factor 1 (IGF-I). GH and IGF-1 critically control cell growth and programmed cell death (apoptosis), but is best known by the stimulation of linear growth in children and adolescents. Both GH and IGF-1 have strong anabolic properties and stimulate protein, bone, and muscle mass. With regard to insulin sensitivity and lipoprotein synthesis their effects are mainly opposed, in which GH stimulates lipolysis and reduces insulin sensitivity and IGF-1 causes the opposite effects. Increased exposure to GH and IGF-1 accelerates aging whereas GH and IGF-1 deficiency prolongs life span [5].
- Prolactin (PRL) stimulates milk production in the glandular tissue of the breasts in females during lactation. Hyperprolactinemia also inhibits the secretion of gonadotropin-releasing hormone in the hypothalamus and blocks follicular growth and ovulation during lactation [6]. In addition, prolactin has a multitude of effects in the brain and is associated with reproductive behaviour, mood regulation, and neuroprotection [7].

The posterior pituitary lobe secretes 2 hypothalamic hormones:

- (Arginine) vasopressin (AVP, also anti-diuretic hormone (ADH)), the release of which is triggered by increase in plasma osmolality. The result is stimulation of the reabsorption of water in the distal tubules of the kidney, which is a main determinant of the body's fluid and electrolyte balance.
- Oxytocin, which stimulates uterine contraction during partus and milk ejection of the mammary glands during lactation. It also has many psychological effects, like effects on social and nesting behaviour. Moreover, there's evidence it plays a role in the perception of pain.

Under pathological conditions, single or multiple hormone deficiencies may occur or, conversely, excessive, specific hormone secretion can occur, giving rise to typical or less typical clinical syndromes.

## Hormone excess syndromes

### *Cushing's disease*

Cushing's disease is the consequence of excessive ACTH secretion caused by an ACTH-producing adenoma, resulting in systemic cortisol excess, and causing a typical syndrome known as Cushing's syndrome. Symptoms include fatigue, rapid weight gain with fat maldistribution and skeletal muscle wasting with typical central adipositas and, sarcopenia, most typically of the quadriceps femoris, in addition to insulin resistance,

diabetes mellitus, hypertension, depression, and cognitive impairment. Because Cushing's disease is rare and many of the symptoms are non-specific with an insidious course, a long diagnostic delay occurs often. Primary treatment of Cushing's disease is transsphenoidal surgical resection of the adenoma, in which remission can be achieved in approximately 80% of patients. A particular challenge with ACTH secreting adenomas is the fact that they may be so small that they are not detected on regular MRI scans. Some, but not all pituitary centres pre-treat patients prior to surgery with steroid inhibitors to control cortisol excess and post-surgical steroid withdrawal syndrome. However, as surgical failure and recurrence are not uncommon, in these cases adjuvant treatments like re-operation, radiotherapy, medical treatment, and eventually even bilateral adrenalectomy need to be considered. As such, remission can be achieved in nearly all patients. Importantly even when patients are in long-term remission of cortisol excess, residual symptoms may persist in many cases and this is associated with decreased quality of life [8, 9].

### *Acromegaly*

Acromegaly is caused by a GH-producing adenoma, resulting in GH and IGF-I excess. When the epiphyseal plates have not yet closed, this leads to an excess in linear growth, e.g. gigantism. In adulthood, or after closure of the epiphysial plates, it causes acral growth and a typical phenotype characterized by large hands and feet with swollen joints and nose, a prominent jaw and frontal bossing. Moreover, patients often present with diabetes mellitus, arthralgia, obstructive sleep apnoea and excessive sweating. If total resection of the adenoma is considered possible, primary treatment is transsphenoidal surgical resection, with average published remission rates of ~66%. Adenomas are typically larger (macroadenoma) and invasive into the skull base. The adenoma can also be (pre-)treated medically with somatostatin receptor agonists, which can decrease GH-excess and result tumour shrinkage, and with GH-receptor blockers (Pegvisomant). Biochemical control can be achieved with medication alone in ~45% of patients. In persisting cases with poor biochemical control or intolerance to medication, radiotherapy might be considered [10-12].

### *Prolactinoma*

Prolactinomas are prolactin-secreting adenomas. In females, prolactin excess can cause galactorrhoea and hypogonadism, and menstrual cycle disorders, such as oligo- or amenorrhea. In both sexes it can cause decreased libido, sexual dysfunction, and infertility. Primary treatment is medical therapy with dopamine agonists, which results in disease control in 81% and long-term remission without treatment in ~34%. Surgical resection is reserved for patients with intolerance to dopamine agonist, refractory disease or when acute decompression of the optic nerve is necessary. However, recent

publications advocate to consider surgical adenoma resection as a first- or early second-line treatment in selected cases. In persisting cases with poor biochemical control or intolerance to medication, surgical debulking and radiotherapy might be considered [13].

## Mass-effects caused by pituitary tumours

### *Pituitary hormone deficiencies*

When injury of the normal pituitary gland occurs, any pituitary hormone deficiency may occur. This is called hypopituitarism. The diagnosis of panhypopituitarism is reserved for the condition in which the secretion of all anterior pituitary hormones is deficient and this can be with or without diabetes insipidus. Signs and symptoms of pituitary hormone deficiencies depend on the specific deficient hormone(s). Patient with an ACTH-deficiency might complain of severe fatigue and not recovering from intercurrent illnesses, while patients with an gonadotrophin deficiency might complain of decreased sexual function, libido, and infertility. Vasopressin deficiency will lead to diabetes insipidus, which is characterized by polyuria (the excretion of large amounts of diluted urine), polydipsia (unquenchable thirst) to compensate for fluid losses, and potentially dehydration. Cortisol and the thyroid hormones are critical for survival and in case of ACTH and TSH deficiencies, hormonal replacement therapy is mandatory. Other hormones are replaced upon indication, depending on severity of complaints, age, and menopausal status. At present, even when hypopituitarism is optimally treated, quality of life is still reported to be impaired in many patients.

### *Impairments in visual acuity and visual field defects*

When a tumour with suprasellar extension compresses the optic nerves, this may result in visual field defects and decreased visual acuity. Most often, pituitary tumours compress the crossing nerve fibres in the optic chiasm. Compression of these fibres most typically results in bitemporal visual field defects. These deficits may remain unnoticed for a long period, until they are more severe. Typically, patients may not notice cars approaching when participating in traffic and may have to turn their heads further and more often. Some patients with compression appear to have atypical visual field abnormalities, with usually longer diagnostic delay. Decreased visual acuity occurs more often in case of severe compression, or when the pre-chiasmal optic nerve is compressed. Surgical decompression of the optic nerve is a very effective treatment and can rapidly reverse the most severe visual symptoms in most cases. Compression of the nerves that control eye movement rarely occur in pituitary tumours, most notably during an episode of clinical apoplexy in an adenoma, or in case of lateral invasion of the cavernous sinus. Patients with such a cranial nerve palsy may have complaints of double vision.

## Surgical management

For most pituitary tumours, pituitary surgery is the cornerstone of treatment as it can offer long-lasting disease remission. However, the intended effect of surgery might differ between tumour groups and on patient-level. In most functioning adenomas, the intended effect will be to achieve remission. However, a debulking may also be performed in order to decompress surrounding structures or to obtain biochemical control of the hormone excess, with or without concurrent medication or radiotherapy.

In non-functioning tumours, the intended effect of surgery is often decompression of surrounding structures, such as the pituitary gland or optic nerves to preserve or restore pituitary and optic function. When possible, a surgeon will opt for gross total resection without taking unwarranted risks, as this may prevent necessity of reintervention.

### *Endoscopic transsphenoidal pituitary surgery*

For over 40 years, the transsphenoidal approach has been the standard procedure for pituitary surgery in the Netherlands. It has a long history, with the first successful transsphenoidal surgery for acromegaly being performed by Schloffer in 1906. It was popularised by Jules Hardy in the 1970's and the introduction of the surgical microscope. This route through the nasal cavity and sphenoid sinus is minimally invasive as it only requires a incision at the skull base and, in non-extended procedures, does not enter the intra-arachnoidal space. In the last decades major advances have been made in this procedure. In 2001, the first article describing endoscopic transsphenoidal surgery was published and since then this technique has been embraced by an increasing number of centres [14]. This technique allows better visibility of the resection area. Furthermore, technical advances have been made in closure of the skull base preventing postoperative CSF leakage and via extended approaches a larger anatomical range of tumour localisations is accessible for resection.

Transsphenoidal pituitary surgery is a complex procedure necessitating experience and know-how. Complexity may be increased in case of invasive growth, very small tumours that are hard to visualize, more fibrous tumours, reoperations and abnormal nasal and sellar anatomy. Because the number of required transsphenoidal surgeries for symptomatic pituitary adenomas is limited, centralization of care is warranted. Better outcomes and lower complication rates are reported by centres that decreased their number of pituitary surgeons and by surgeons with a higher surgical volume [15, 16]. At the Leiden University Medical Center, this procedure is performed by a combination of 2 specialized pituitary surgeons that make intraoperative decisions together [17].

***Surgical complications***

Following pituitary surgery, a range of complications can occur and patients should be monitored closely. Complications include transient diabetes insipidus vasopressin deficiency), postoperative SIADH (excessive vasopressin secretion), epistaxis, postoperative CSF-leakage, and permanent complications such as anterior and posterior pituitary hormone deficiencies, anosmia and neurological damage. Transient complications occur in approximately half of the operated patients, while lasting endocrine disfunction varies widely between series, ranging from 1.3-30% of patients [15, 18, 19] depending also on the rigorousness of reporting. Mortality after this procedure is rare and mainly occurs when the internal carotid artery is damaged or when there is an emergency not directly related to the pituitary disease, e.g. cardiac ischemia [15].

## Coordination of care

***Multidisciplinary care pathways***

As the diagnosis and treatment of pituitary disease is complex by nature and involves many specialties, including endocrinology, neurosurgery, ophthalmology, neuroradiology and radiotherapy, a multidisciplinary care pathway has been developed at the Leiden University Medical Center. This pathway includes a range of standard, single, and combined personalized consultations, procedures and measurements aiming to optimize treatment outcome and safety, including imaging, laboratory assessments and quality of life measurements. Before surgery a patient visits the combined outpatient clinic with an endocrinologist and a neurosurgeon followed by a consultation with a specialised pituitary nurse. A personalized risk-benefit assessment is made and discussed with the patient before the decision to operate is made by means of shared-decision making. All patients are thereafter discussed in the multi-disciplinary pituitary team meeting. In the perioperative phase, all patients are managed by a pituitary case manager. This case manager provides clear information and instructions both verbally and in writing during this phase, monitors the patient, and is available for (daily) consultations. The procedures and measurements in the care pathway are evaluated periodically and adjusted if necessary [20, 21].

***Value-based health care***

With the continuously rising costs of healthcare over the last decades, it is more important than ever to raise value of healthcare by improving healthcare outcomes and reducing (unnecessary) costs.

This "Value-based healthcare" principle was first described by the economist Porter in 2007. Porter divides outcomes into 3 tiers: health status achieved or retained, process

of recovery and sustainability of health [22, 23]. To be able to adhere to this principle, healthcare providers should first establish measures for outcome. It is of utmost importance to use uniform definitions of these measures to be able to compare outcomes over time and between healthcare providers. In pituitary care, clinician-reported outcomes, such as biochemical control of hormone excess and complication rates have been used traditionally. However, focus is shifting to include patient-reported outcome measures, such as health-related quality of life, measured with generic or disease specific-specific questionnaires. Measuring the effect of different interventions on clinician- as well as patient reported outcome measures, healthcare providers could have a better understanding of what treatment has the best effect on what matters to the patients. Routinely analysing which processes and costs raise healthcare outcomes and adjusting or cutting the ones that do not, will ultimately result in higher value. As Porter advocates, some form of care centralisation is necessary to achieve this, as a sufficient number of patients and procedures is necessary to measure outcomes and as experience will lead to new insight in how value can be increased. With the establishment of a list of features that should be in place in every "Pituitary Tumor Center of Excellence" a first step in centralisation and increase in health-care value is established [24].

***European Reference Network for Rare Endocrine Conditions (Endo-ERN)***

In 2017 the European Commission launched the European Reference Networks. The mission of ERNs is to reduce health care inequalities for all patients with rare or complex conditions across the European Union. This is to be achieved through cross-border expert consultation and guideline conformity, enabling the highest standard of care. The European Reference Network for rare endocrine conditions (Endo-ERN) has defined the landscape of rare endocrine conditions in 8 main thematic groups, of which Hypothalamic and Pituitary disorders is one of the larger ones, when regarded as the number of participating reference centers. For each of the main thematic groups, Reference Centres have been identified that can provide the required expertise based on obtained national and Endo-ERN endorsement after stringent review of their application. Apart from providing specialised care for rare endocrine diseases, these reference centres are expected to establish cross-regional and cross-border collaborations with other care providers to improve care for all patients through facilitating knowledge transfer via, virtual expert consultations, or multi-disciplinary team discussions that would not be possible in non ERN centres. Moreover, Endo-ERN aims to coordinate research efforts and is setting up international patient registries to enable effective research and improvement of care for these rare disease patients. In this effort, they have actively involved patient representatives to incorporate their wishes in coordination of care, education and training, and research efforts [25, 26].

## THESIS OUTLINE

As is evident from this chapter, pituitary disease is not a single disorder, but a complex set of rare diseases which can have overlapping and vary varying symptoms. Presenting outcomes and scientific research in the individual diseases is difficult. Furthermore, the lack generally accepted definitions prohibits outcome comparison between centres and outcome reports in literature. The aims of this thesis are a) to present novel ways to present outcomes of a treatment type – endoscopic transsphenoidal pituitary surgery in this thesis - for multiple diseases, b) to propose standardized definitions for multiple measurements and outcomes, c) to raise awareness of rare presentations of pituitary disease and endocrine complications of common treatments, and d) to make outcome presentation and scientific research more patient-centred. This theses is separated in three parts.

The first part focusses on innovation and standardization in the VBHC Pituitary Care-pathway. **Chapter 2 and 3** present the results of endoscopic transsphenoidal pituitary surgery via Outcome Squares. This novel way of outcome presentation was initially proposed as a easy to interpret report to aid patient counselling for a treatment in a complex the disease. It focusses solely on the two most important outcomes to the patient: achievement of counselled pretreatment aim and the occurrence of long-term complications. However, it may have additional value in outcome presentation for treatments of multiple diseases. In **chapter 4** an overview of the varying measurements and definitions of one of the most common complications of pituitary surgery, diabetes insipidus, is presented. A pathophysiology-based propositions are made for the definition, diagnostics, and therapy of postoperative diabetes insipidus. In **chapter 5** an analysis and comparison is made of two ways to test for postoperative corticotropic insufficiency following pituitary surgery. It analyses the necessity and additional value of the expensive CRH-test. In **chapter 6** an exploratory analysis is performed to analyse if serum-inflammation based scores can have a predictive value in the treatment of pituitary tumours. It analyses a large number of scores and outcomes and can be used as a basis for future research.

The second part focusses on the first data that came available from the European Endocrine Rare Disease Network Endo-ERN. **Chapter 7** describes the effort to establish definitions of different performance measurement and to collect comparable data from the participating centres. **Chapter 8** gives a voice to rare endocrine disease patients and presents their preferences and expectations for scientific research in this field.

The final part focusses on the occurrence, diagnostics and treatment of rare endocrine diseases and rare endocrine complications of common treatments. In **chapter 7** the presentation of visual symptoms in patient with a diagnostic delay of a pituitary tumour is reviewed, in aim to aid ophthalmologist in the recognition of these symptoms. In **chapter 8** a comprehensive review of diagnostics and treatment of hypophysitis is presented. This rare inflammation of the pituitary gland may become less rare with the emergent use of immune checkpoint inhibitors. In **chapter 9** an overview is given of the occurrence of hormone deficiencies in opioid use. The aim is to make health-care professionals more aware of this possible severe side-effect of this widely used group of medications. Finally, in **chapter 12** an example is presented of the complex presentation of pituitary tumours and a plea is made for thorough examination of all available pretreatment diagnostic imaging.

# REFERENCES


1. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101(3):613-9.
2. Miller KD, Ostrom QT, Kruchko C, et al. Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin. 2021;71(5):381-406.
3. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. JAMA. 2017;317(5):516-24.
4. Lechan RM, Toni R. Functional Anatomy of the Hypothalamus and Pituitary. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2022, MDText.com, Inc.; 2000.
5. Ranke MB, Wit JM. Growth hormone - past, present and future. Nat Rev Endocrinol. 2018;14(5):285-300.
6. Freeman ME, Kanyicska B, Lerant A, et al. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000;80(4):1523-631.
7. Cabrera-Reyes EA, Limón-Morales O, Rivero-Segura NA, et al. Prolactin function and putative expression in the brain. Endocrine. 2017;57(2):199-213.
8. Andela CD, Scharloo M, Pereira AM, et al. Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies. Pituitary. 2015;18(5):752-76.
9. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.
10. Katznelson L, Laws ER, Jr., Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51.
11. Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552-61.
12. Colao A, Grasso LFS, Giustina A, et al. Acromegaly. Nature Reviews Disease Primers. 2019;5(1):20.
13. Zamanipoor Najafabadi AH, Zandbergen IM, de Vries F, et al. Surgery as a Viable Alternative First-Line Treatment for Prolactinoma Patients. A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2020;105(3):e32-41.
14. Liu JK, Das K, Weiss MH, et al. The history and evolution of transsphenoidal surgery. J Neurosurg. 2001;95(6):1083-96.
15. Honegger J, Grimm F. The experience with transsphenoidal surgery and its importance to outcomes. Pituitary. 2018;21(5):545-55.
16. Wang YY, Higham C, Kearney T, et al. Acromegaly surgery in Manchester revisited--the impact of reducing surgeon numbers and the 2010 consensus guidelines for disease remission. Clin Endocrinol (Oxf). 2012;76(3):399-406.
17. van Furth WR, de Vries F, Lobatto DJ, et al. Endoscopic Surgery for Pituitary Tumors. Endocrinol Metab Clin North Am. 2020;49(3):487-503.
18. Magro E, Graillon T, Lassave J, et al. Complications Related to the Endoscopic Endonasal Transsphenoidal Approach for Nonfunctioning Pituitary Macroadenomas in 300 Consecutive Patients. World Neurosurg. 2016;89:442-53.
19. Kim JH, Lee JH, Lee JH, et al. Endoscopic Transsphenoidal Surgery Outcomes in 331 Nonfunctioning Pituitary Adenoma Cases After a Single Surgeon Learning Curve. World Neurosurg. 2018;109:e409-e16.
20. Lobatto DJ, Vliet Vlieland TPM, van den Hout WB, et al. Feasibility, safety and outcomes of a stratified fast-track care trajectory in pituitary surgery. Endorine. 2020;In press.

21. Lobatto DJ, Zamanipoor Najafabadi AH, de Vries F, et al. Towards value-based health care in pituitary surgery: application of a comprehensive outcome set in perioperative care. Eur J Endocrinol. 2019.
22. Porter ME. Value-based health care delivery. Ann Surg. 2008;248(4):503-9.
23. Porter ME, Teisberg EO. How physicians can change the future of health care. JAMA. 2007;297(10):1103-11.
24. Casanueva FF, Barkan AL, Buchfelder M, et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. Pituitary. 2017;20(5):489-98.
25. Iotova V, Bertherat J, Mastorakos G, et al. ENDO-ERN ON RARE ENDOCRINE CONDITIONS: Endo-ERN in its fifth year: a pinch of care, science, curiosity and new horizons. Endocr Connect. 2022;11(3).
26. Endo-ERN. About Endo-ERN 2022 [cited 2022 08-02-2022]. Available from: https://endo-ern.eu/about/about-endo-ern/.