

# Manual for the Pituitary Tumour Module

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**Outcome** = a dataset at a certain timepoint during the follow-up of the patient, could also be referred to as 'return'.

## 1.0 Time-points to create an outcome (return)

In order to structure the data collection, we have selected **standardized timepoints to create outcomes (returns)** during the follow-up of a patient. It is important to always create an outcome **at the time of diagnosis**, in other words, before the start of any treatment. In this outcome, the answers to the questions within the ‘Basic disease module’ tab ‘Has the patient been on medical therapy?’, ‘Has the patient undergone pituitary tumour related surgery?’, and ‘Has the patient received radiotherapy as part of the pituitary tumour treatment’, should be answered with ‘No’.

### 1.1 General follow-up (‘wait-and-scan’ policy)

This scheme forms the basis of the for every patient. In case a patient gets treated, please check under 1.3 ‘Tumour treatment during follow-up’ for the adjusted schemes.

- Create an outcome at the time of diagnosis (before the start of any treatment)
- Create a new outcome 2, 4, 5, 10, 15, 20 etc. years after diagnosis (Figure 1), unless there is progression\* (Figure 2a and 2b) or a treatment (other than endocrine replacement) is initiated (Figure 4a, 4b, 5).



Figure 1 - General follow-up in case of general follow-up without progression

\*In case of progression that is not followed by treatment, create an extra outcome at the time of progression (Figure 2a and 2b).



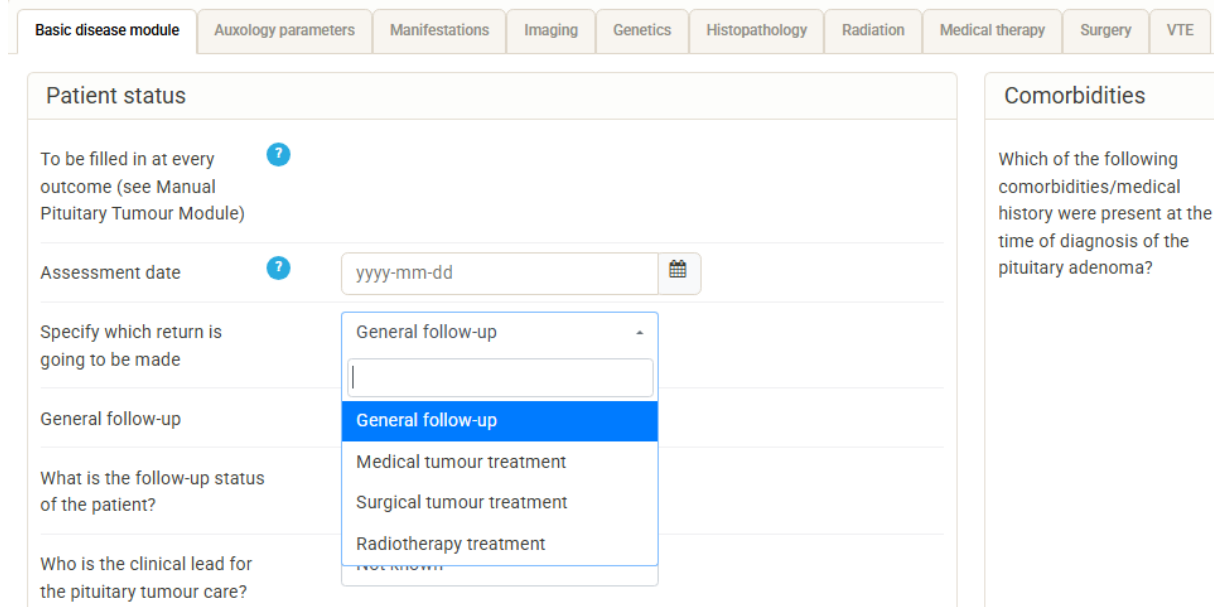
Figure 2a – Example of general follow-up in case of progression not followed by treatment (3 years after diagnosis)



Figure 2b - Example of general follow-up in case of progression not followed by treatment (6/7/8/9 years after diagnosis)

## 1.2 Specify the created outcome

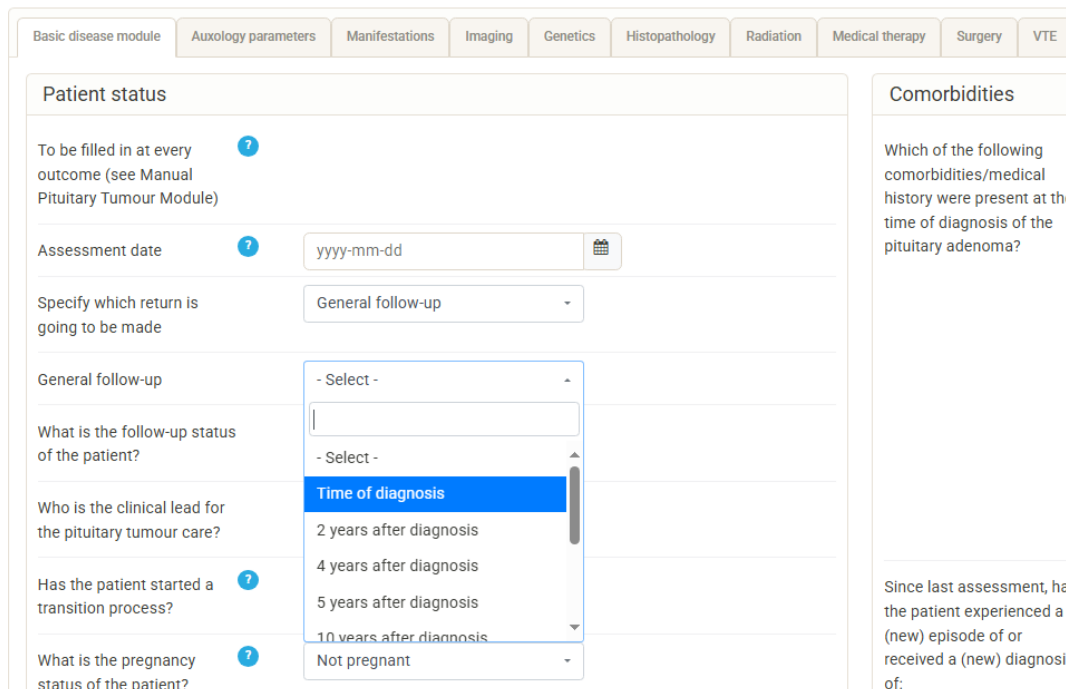
For each outcome (return), specify the moment during the disease process. For the return of the General follow-up, please select 'General follow-up' from the drop-down menu after the questions 'Specify which return is going to be made'.



The screenshot shows the 'Patient status' section of a software interface. It includes a navigation bar with tabs: Basic disease module, Auxology parameters, Manifestations, Imaging, Genetics, Histopathology, Radiation, Medical therapy, Surgery, and VTE. The 'Patient status' section contains several fields: 'Assessment date' (calendar icon), 'Specify which return is going to be made' (dropdown menu), 'General follow-up' (text input), 'What is the follow-up status of the patient?' (dropdown menu), and 'Who is the clinical lead for the pituitary tumour care?' (text input). The dropdown menu for 'Specify which return is going to be made' is open, showing 'General follow-up' as the selected option. Other options include 'Medical tumour treatment', 'Surgical tumour treatment', and 'Radiotherapy treatment'. A 'Comorbidities' section is visible on the right, with a question: 'Which of the following comorbidities/medical history were present at the time of diagnosis of the pituitary adenoma?'.

**Figure 3a – Specify the timepoint of the outcome (return)**

Then, select the specific return, for example 'Time of diagnosis', or '2 years after diagnosis', from the drop-down menu after the question 'General follow-up'.



The screenshot shows the 'Patient status' section of the software interface. The 'Specify which return is going to be made' dropdown menu is now set to 'General follow-up'. The 'General follow-up' dropdown menu is open, showing options: '- Select -', 'Time of diagnosis' (selected), '2 years after diagnosis', '4 years after diagnosis', '5 years after diagnosis', '10 years after diagnosis', and 'Not pregnant'. The 'Comorbidities' section on the right now has a question: 'Since last assessment, has the patient experienced a (new) episode of or received a (new) diagnosis of:'. The navigation bar remains the same.

**Figure 3b – Specify the timepoint of the return (return)**

### 1.3 Tumour treatment during follow-up

! Beware: **medical tumour treatment** is defined as medical treatment directed towards **growth/volume reduction** (e.g. such as with dopamine agonists, somatostatin analogues, or temozolamide) or **biochemical control** (such as metyrapone, dopamine agonists, somatostatin analogues).

**Endocrine replacement therapies in case of hypopituitarism is NOT** considered medical tumour treatment (such as hydrocortisone or levothyroxine).

#### 1.3.1 Medical/surgical/radiotherapy tumour treatment

- Create an outcome at the time of diagnosis (before the start of any treatment), see also paragraph 1.1 General follow-up.
- Create a new outcome right before the start of (medical/surgical/radiotherapy) treatment.
- If **treatment is started within 6 months after diagnosis**, you can combine these two outcomes, by selecting 'Medical/Surgical/Radiotherapy treatment' and 'Time of diagnosis = pre-medical/surgical/radiotherapy intervention' (see 1.2)
- Create a new outcome 6 months (3-9) after (initiating) medical/surgical/radiotherapy treatment.
- Subsequently, fall back into the outcomes of the general follow-up (see paragraph 1.2), unless there is progression or a new treatment
- If a new treatment is initiated, create a new outcome right before the treatment and 6 months after treatment.

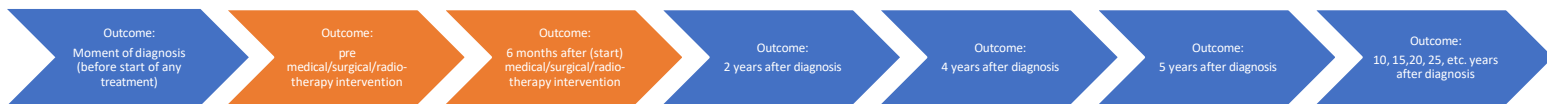


Figure 4a – Example of medical/surgical/radiotherapy treatment started within 2 years after diagnosis

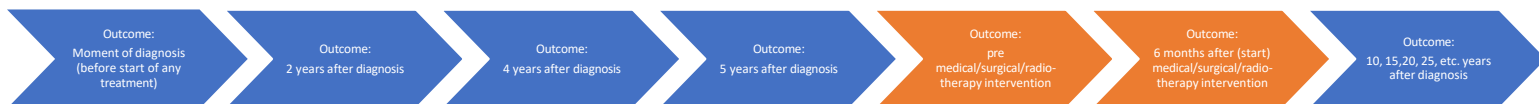


Figure 4b - Example of medical/surgical/radiotherapy treatment started 6/7/8/9 years after diagnosis

#### 1.3.2 Multiple treatment modalities

In case a patient is treated with multiple modalities during their follow-up period, please make sure that you have created an outcome for the moment of diagnoses, 2, 4, 5, 10, 15 years etc. after diagnosis and add treatment specific outcomes (See Figure 5).

At the moment two modalities of treatment are given at the exact same time, these outcomes can be combined.

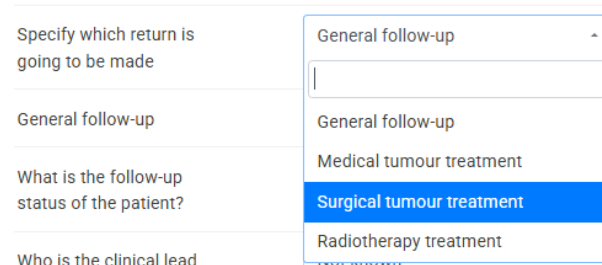


Figure 5 - Example of surgical therapy within 2 years after diagnosis followed by radiotherapy 3/4 years after diagnosis

### 1.3.3 Treatment within six months after diagnosis

In case the first treatment (medical/surgical or radiotherapy) has taken place within the first six months after diagnosis, there is an option to combine the first two outcomes. This is done to prevent a double work-load since these returns will most likely be the same.

1. Indicate the treatment from the drop-down menu after the question 'Specify which return is going to be made', for example 'surgical tumour treatment'.



Specify which return is going to be made

General follow-up

What is the follow-up status of the patient?

Who is the clinical lead

General follow-up

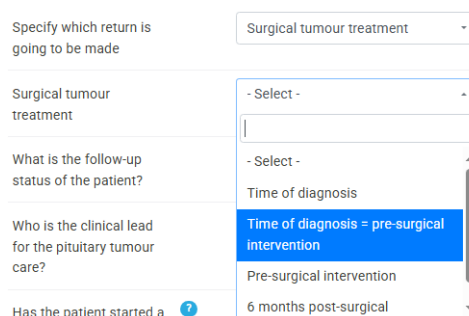
Medical tumour treatment

**Surgical tumour treatment**

Radiotherapy treatment

**Figure 6a** - Combine the Time of diagnosis with a pre-treatment (medical/surgical/radiotherapy treatment) if the treatment is given within six months after diagnosis

2. Select 'Time of diagnosis = pre-surgical intervention' from the drop-down menu after the question 'Surgical tumour treatment'.



Specify which return is going to be made

Surgical tumour treatment

Surgical tumour treatment

What is the follow-up status of the patient?

Who is the clinical lead for the pituitary tumour care?

Has the patient started a

Surgical tumour treatment

- Select -

- Select -

Time of diagnosis

**Time of diagnosis = pre-surgical intervention**

Pre-surgical intervention

6 months post-surgical

**Figure 6b** - Combine the Time of diagnosis with a pre-treatment (medical/surgical/radiotherapy treatment) if the treatment is given within six months after diagnosis

In case the status of the patient differs between the moment of diagnosis and the moment before a treatment, please create two separate outcomes (returns).

## 2.0 Overview of tabs to be filled in per outcome

**Table 1 - Overview of tabs to be filled in per outcome**

	Basic disease module	Auxology parameters	Endocrine manifestations	Secreted hormones	Visual impairment	Imaging	Genetics	Histopathology	Radiation	Medical therapy	Surgical outcomes	VTE
<b>Return</b>												
General follow-up: time of diagnosis	X	X	X	X	X	X	X					**
General follow-up: x years after diagnosis	X	X	X	X	X	X	X			*		**
General follow-up: progression not followed by treatment	X	X	X	X	X	X	X			*		**
Medical tumour treatment: pre-medical intervention	X	X	X	X	X	X	X			*		**
Medical tumour treatment: 6 months after initiating medical intervention	X	X	X	X	X	X	X			X		**
Surgical tumour treatment: pre-surgical intervention	X	X	X	X	X	X	X			*		**
Surgical tumour treatment: 6 months post-surgical intervention	X	X	X	X	X	X	X	X		*	X	**
Radiotherapy treatment: pre-radiotherapy intervention	X	X	X	X	X	X	X			*		**
Radiotherapy treatment: 6 months post radiotherapy	X	X	X	X	X	X	X		X	*		**

\* = only if medical treatment is continued, update assessment date and outcomes. Beware to include the stop date in case the medication has been stopped.

\*\* = only if VTE occurred

### 3.0 Instructions for Pituitary Tumour Module Tabs

#### 3.1 Tab: Basic disease module

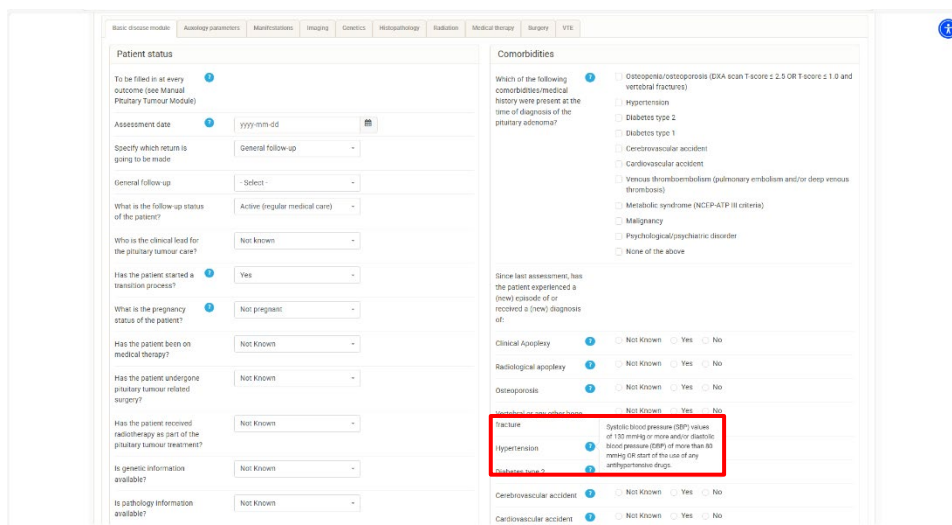
- The return of 'Time of diagnosis' should be filled in before any treatment has been given. The variables 'Has the patient been on medical therapy?', 'Has the patient undergone pituitary tumour related surgery?', and 'Has the patient received radiotherapy as part of the pituitary tumour treatment', should ideally be answered with 'No'.

Has the patient been on medical therapy?	No
Has the patient undergone pituitary tumour related surgery?	No
Has the patient received radiotherapy as part of the pituitary tumour treatment?	No

**Figure 7** – Variables that should be answered with 'No' at the Time of Diagnosis

#### Comorbidities

- Please select all the comorbidities that are present at time of diagnosis. This is needed to excluded patients that are not at risk anymore for one of the events listed below.
- You can find the definitions of the comorbidities and events by hovering over the question marks.



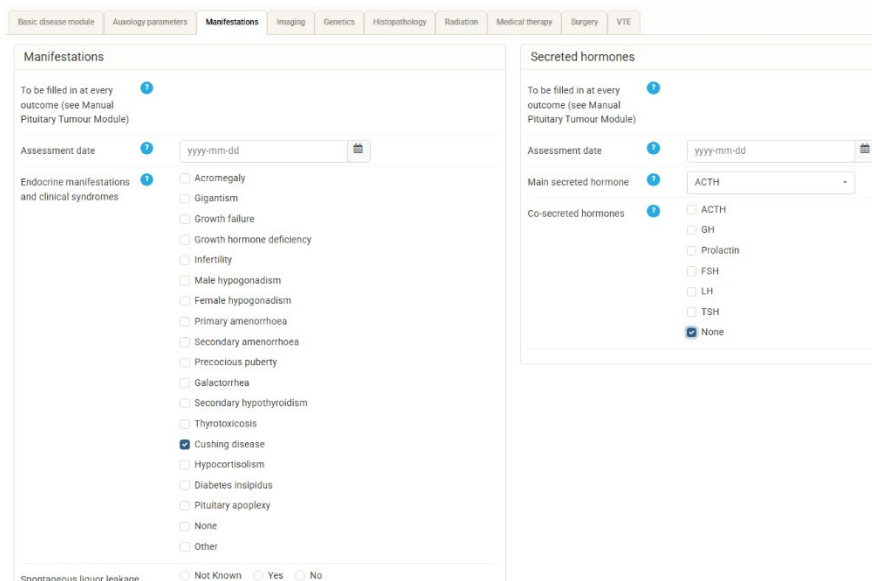
**Figure 8** – Definitions of the comorbidities and events can be found by hovering over the question mark

#### Events

- Please indicate at every outcome whether any of the the listed events has taken place
- Hoover over the question marks to see the definitions
- If selected 'Yes', please indicate the date of the event if known or the date of diagnosis of the event and specific the event.

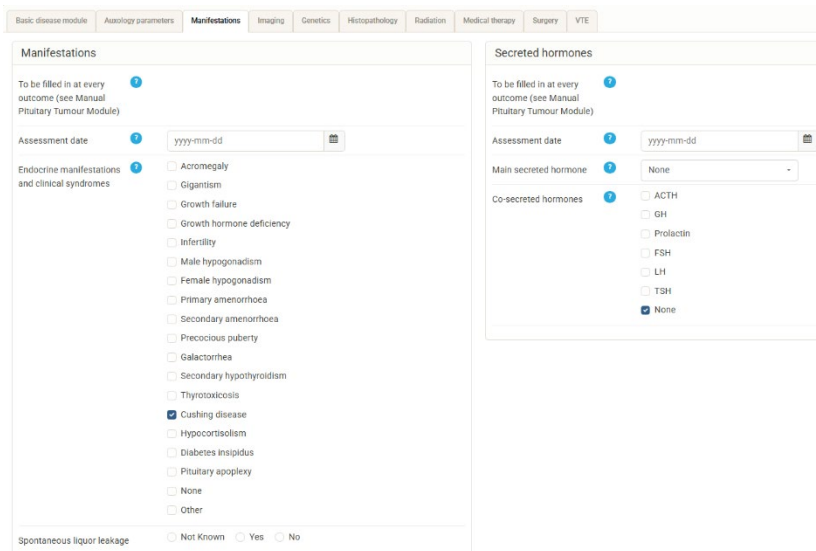
### 3.2 Tab: Manifestations and secreted hormones

- To be filled in for every outcome to monitor hormone excess and pituitary function loss over time for all patients independent of their treatments.
- Manifestations, together with the variable 'Specific Diagnosis' from the Core Registry are, used for the risk factor 'Phenotype' in the PANOMEN 3 Grade score.
- Secreted hormones (meaning biochemically elevated hormonal levels) is used for the risk factor 'Secretory status' in the PANOMEN 3 Grade score.
- In case of remission of hormone secreting adenoma (e.g. Cushing) 'Cushing disease' in the 'Endocrine manifestations' tab stays selected, whilst 'Main secreted hormone' needs to be changed to 'None'. In case of a recurrence 'ACTH' needs to be re-selected (Figure 9a and 9b).



The screenshot shows two side-by-side panels. The left panel, titled 'Manifestations', has a sub-section 'Endocrine manifestations and clinical syndromes' with a list of conditions. 'Cushing disease' is checked. The right panel, titled 'Secreted hormones', has a 'Main secreted hormone' dropdown set to 'ACTH' and a 'Co-secreted hormones' section where 'None' is checked.

**Figure 9a** – Biochemically active M. Cushing with hypercortisolism



The screenshot shows two side-by-side panels. The left panel, titled 'Manifestations', has a sub-section 'Endocrine manifestations and clinical syndromes' with a list of conditions. 'Cushing disease' is checked. The right panel, titled 'Secreted hormones', has a 'Main secreted hormone' dropdown set to 'None' and a 'Co-secreted hormones' section where 'None' is checked.

**Figure 9b** - M. Cushing in biochemical remission (without hypercortisolism, this could potentially be due to the use of medication such as metyrapone or after a successful complete resection during transsphenoidal surgery)

In case of Nelson's syndrome after adrenalectomy (growth of residual tumor, increased

ACTH secretion and hyperpigmentation), please select 'Other' and type 'Nelson's syndrome' in the free text field.

- The variable 'Secreted hormones' is **not be used for hormonal expression in pathology samples**

Examples:

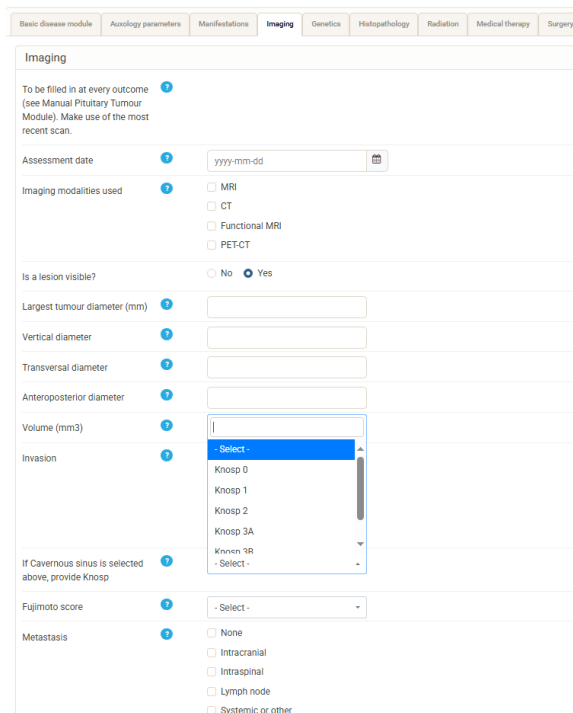
1. FSH and/or LH positivity by immunohistochemistry without biochemical elevated FSH levels in non-functioning pituitary adenoma. FSH/LH positivity by immunohistochemistry can be indicated at the tab 'Histopathology', not at the tab Manifestations – Secreted hormones
  2. ACTH expression by immunohistochemistry without elevated cortisol levels in a patient with a silent corticotroph adenoma. The ACTH positivity by immunohistochemistry can be indicated at the tab 'Histopathology', not at the tab Manifestations – Secreted hormones)
- Moderate elevated prolactin levels assigned to the pituitary stalk effect in an adenoma subtype other than a prolactinoma should not be indicated here, since it is not a secreted hormone by the adenoma tissue itself.
  - In case of additional pituitary axis loss as a result of surgery, the additional pituitary axis loss must be selected in the 'Endocrine manifestations', as well as in the Surgery tab under 'Complications'.  
In case of resolved pituitary axis loss as a result of surgery, the pituitary axis loss must be deselected in the 'Endocrine manifestations' and 'Pituitary Function' under Positives Outcomes in the Surgery tab must be indicated as 'Normalized' or 'improved'.
  - In case of additional pituitary axis loss during follow-up, the additional pituitary axis loss must be selected in the 'Endocrine manifestations'. In case of resolved pituitary axis loss during follow-up, the pituitary axis loss must be deselected in the 'Endocrine manifestations'.
  - Visual impairment  
In case visual impairments have not been objectively assessed, please:
    - Microadenoma: In case there is no compression on the optic system (optic nerve/optic chiasm/optic tract), please fill in the assessment date of the outcome (Basic disease module) and select 'No' for 'Visual field defect', 'Visual acuity', and 'Diplopia'
    - Macroadenomas:
      - In case there is no compression on the optic system, please fill in the assessment date of the outcome (Basic disease module) and select 'No' for 'Visual field defect', 'Visual acuity', and 'Diplopia'
      - In case there is compression on the optic system, please fill in the assessment date of the outcome (Basic disease module) and select 'Not known' for 'Visual field defect', 'Visual acuity', and 'Diplopia'.

### 3.3 Tab: Imaging – Tumour behaviour assessed by post-treatment imaging

- Please fill in as much information as possible
- In case a lesion is visible, at least fill in the Largest tumor diameter, but ideally also the other three dimensions
- It is only possible to select the exact Knosp score if ‘cavernous sinus’ is selected by ‘Invasion’
- Select ‘Cavernous sinus’ at the variable ‘Invasion’ even if the Knosp score is 1. After selecting Cavernous sinus, you can select the correct Knosp score (0, 1, 2, 3A, 3B, 4 or at least 3) (Figure 10).

! As the risk factor Invasion in the PANOMEN 3 Grade Score will give a score of 1 to Knosp 3 and 4, it is highly important to know the exact Knosp Score, rather than just ‘cavernous sinus invasion’. Please check your institution’s/database/registry definition of cavernous sinus invasion to know if they refer to Knosp 3 or 4 when using that term if you don’t have access to the images yourself. An extra option of ‘at least Knosp 3’ will be added to the module.

See Figure 11 and 12 for an explanation on the Knosp score and the Fujimoto score, respectively.

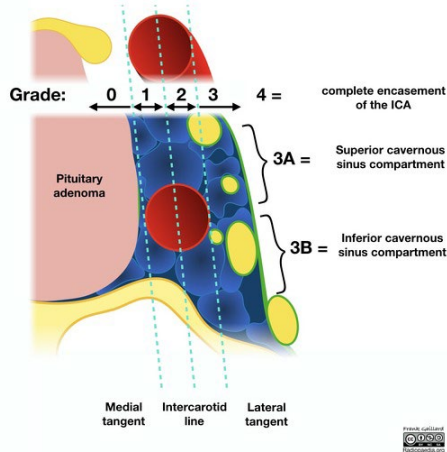


The screenshot shows the 'Imaging' tab of a clinical registry form. The form contains the following fields and options:

- Assessment date:** A date input field with a calendar icon.
- Imaging modalities used:** Four checkboxes: MRI, CT, Functional MRI, and PET-CT.
- Is a lesion visible?:** Radio buttons for 'No' and 'Yes' (selected).
- Largest tumour diameter (mm):** A text input field.
- Vertical diameter:** A text input field.
- Transversal diameter:** A text input field.
- Anteroposterior diameter:** A text input field.
- Volume (mm<sup>3</sup>):** A text input field.
- Invasion:** A dropdown menu with options: '- Select -', Knosp 0, Knosp 1, Knosp 2, Knosp 3A, Knosp 3B, and Knosp 4.
- If Cavernous sinus is selected above, provide Knosp:** A dropdown menu with options: '- Select -' and Knosp 3B.
- Fujimoto score:** A dropdown menu with the option: '- Select -'.
- Metastasis:** Five checkboxes: None, Intracranial, Intraspinal, Lymph node, and Systemic or other.

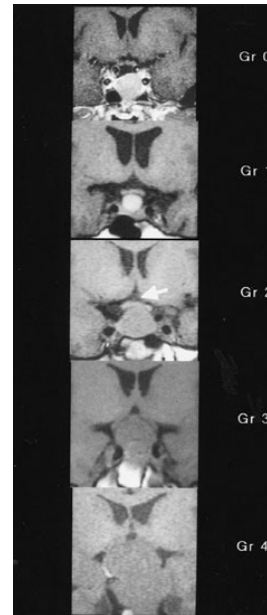
**Figure 10** – After selection ‘Cavernous sinus’, the Knosp classification will appear and you can select the correct Knosp score.

### Knosp classification



**Figure 11** – Overview Knosp score - Knosp classification of cavernous sinus invasion by pituitary macroadenomas | Radiology Reference Article | Radiopaedia.org

Ref: Gaillard F, Sharma R, Khana F, et al. Knosp classification of cavernous sinus invasion by pituitary macroadenomas. Reference article, Radiopaedia.org (Accessed on 28 May 2025)  
<https://doi.org/10.53347/rID-71525>



**Figure 12** – Overview of Fujimoto score - Grade 1 (Gr 1) tumor has contact with optic chiasm without the deformity of upper surface of optic chiasm. Grade 2 (Gr 2) tumor compressed optic chiasm and produced the deformity of the upper surface and visible suprachiasmatic cistern (arrow head). Grade 3 (Gr 3) tumor compressed optic chiasm with invisible suprachiasmatic cistern. Grade 4 (Gr 4) tumor compressed optic chiasm with cerebral deformity. [Figure 1](#) | [Eye](#)

Ref: Fujimoto, N., Saeki, N., Miyauchi, O. *et al.* Criteria for early detection of temporal hemianopia in asymptomatic pituitary tumor. *Eye* **16**, 731–738 (2002).  
<https://doi.org/10.1038/sj.eye.6700165>

- The items ‘progression’, ‘increase of maximal tumour diameter’ and ‘increase of tumour volume’ needs to be compared to the last MRI before treatment when filling in a 6 months post-intervention outcome and compared to the first post-intervention MRI if applicable or the MRI at diagnosis when filling in the general follow-up outcomes.

Tumour behaviour assessed by post-treatment imaging

Assessment Date ?

Age at Assessment Date

Is there a tumour progression?

Has the maximal tumour diameter assessed by post-treatment imaging increased?

Has the tumour volume assessed by post-treatment imaging increased?

Tumour remnant visible on MRI?

Which of the following standard therapies has been used in this patient? ?

Medical therapy  
 Surgical therapy  
 Radiation therapy

**Figure 13** – Fields about progression at the section of tumour behaviour assess by post-treatment imaging

! Make sure that the variables at 'Tumour behaviour assessed by post-treatment imaging' **match the assessment dates and answers** given by 'Imaging'. In other words, indicating that there is no tumour remnant visible on MRI whilst specifying tumour diameters should not be possible. In case there is no tumour remnant visible on MRI, select 'No' for the questions 'Is a lesion visible?'.

#### 3.4 Tab: Genetics

- Fill in whenever possible, but **specifically in patients <30 years of age**.
- Use the Assessment date of 'Basic disease module' in case the analysis has not been performed until that moment in time.
- In case a patient has been tested for genetic disruption, but the results came back negative, you indicate the genes that were tested for in free text after 'other'.

#### 3.5 Tab: Histopathology

- Any remarks on the histopathology results can be given in the free text of 'Histopathology – Other immunohistochemistry parameters'.

#### 3.6 Tab: Radiation

- 'Endocrine response' and 'tumour response' following radiation therapy have to be compared to hormone levels (in case of functional adenomas) and imaging right before the initiation of radiation treatment

#### 3.7 Tab: Medical therapy

- 'Endocrine response' and 'tumour response' following radiation therapy have to be compared to hormone levels (in case of functional adenomas) and imaging right before start of medical treatment
- Please indicate the stop date of the medical therapy if applicable

#### 3.8 Tab: Surgical outcomes

- Endocrine response following surgery has to be compared to hormone levels right before surgery
- Complications: please register all complications that have happened between the surgery and 3-6 months postoperatively. You can select 'transient' or indicate that a complication has been transient in case a complications has happened but is not present anymore at 3-6 months after surgery.

#### 3.9 Tab: VTE

- Fill in only IF VTE occurred