Evaluating the benefit of Gene Expression Profiling (GEP) in early breast cancer

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Project manual + FAQ

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1. General project information

This manual has been composed as a guide and reference for filling out the specific registration form for the project **Gene Expression Profiling (GEP)** for a specific target group of patients with early **breast cancer**.

Starting from 01/01/2023, recognised breast clinics have entered into a convention with the National Institute for Health and Disability Insurance (RIZIV/INAMI) for the **reimbursement of GEP tests** for patients with early breast cancer. A GEP test determines the genetic profile of a tumour, hereby predicting the susceptibility to adjuvant chemotherapy. In this way unnecessary administration of chemotherapy can be avoided. The GEP test convention and reimbursement is coupled to a **compulsory registration GEP-specific variables** via the Belgian Cancer Registry (BCR). More information and all relevant documents can be found on the BCR website (Dutch/French), including a link to the RIZIV/INAMI website, from which the written convention can be consulted.

All **questions** may be directed to the RIZIV/INAMI or BCR, depending on the subject:

- Content of the convention and reimbursement
  → contact RIZIV/INAMI: SEC_DIR_MED@riziv-inami.fgov.be
- Variables to be registered, registration procedures or registration deadlines
  → contact BCR: GEPbreast@kankerregister.org or 02/250 10 10

1.1 Patient inclusion criteria

The 'GEP Breast' **patient target population** and associated registration criteria are defined in Article 4 of the RIZIV/INAMI convention:

- patients with a first diagnosis of early breast cancer, tumour size up to 5 cm, maximum 3 positive lymph nodes (pN0 or pN1), HER2-, ER+ and/or PR, menopausal or at least 45 years old, clinical high risk based on a generally accepted algorithm as used, for example, in the MINDACT study (http://www.mymammaprint.com/) or the Magee score (https://path.upmc.edu/onlineTools/MageeEquations.html)
- patients with a Belgian health insurance

For the purposes of this agreement, a relapse 10 years after completion of a previous breast cancer treatment is considered a first/new diagnosis.

Patients for whom a GEP test is performed are selected by the MOC of the accredited breast clinic based on the criteria of the intended target population. In exceptional cases, the MOC may also judge that a patient outside the intended target group is still eligible. GEP tests requested for patients outside the intended target group, but after a positive advice from the MOC, will also be reimbursed provided that this group is limited to 5% of the population tested. Since each centre has only a limited number of GEP tests that will be reimbursed, this may imply that performing this test for a patient outside the target group may result in no reimbursement for a test for another patient inside the target group.

The following points are mentioned in Article 5 and 6 of the convention and are also of importance concerning registration and reimbursement:

- **All patients** for whom the MOC/COM recommends a GEP test, **should be registered** via the BCR.
- A GEP test can only be reimbursed **once per patient** during the whole duration of the convention, meaning from 1/07/2019 onwards
- A GEP test can only be reimbursed if the test used is officially recognised by the RIZIV/INAMI on the day of GEP request (see website RIZIV/INAMI for updates).
- A GEP test can only be reimbursed after a **positive advice of the MOC/COM** (multidisciplinary oncological consult).
- The date of the MOC at which it was decided to request a GEP test is considered the date of prescription, which in turn determines in which year the test may be billed. Thus, an MOC meeting that took place on December 15 of year x with execution of the test in January of year x+1 will still be billed in year x for determining the total number of GEP tests, since the date of the MOC counts as the date of prescription.
- The Belgian Cancer Registry reports to the RIZIV/INAMI the **number of complete registrations** per recognised breast clinic for the past year, on the basis of which the RIZIV/INAMI will **reimburse** the breast clinics.

The **start date of the convention** is **1/01/2023**. All patients for which the **date of the MOC/COM discussion**, where it was **decided to recommend a GEP test**, falls on or after 1/01/2023 are included in the target population and should be registered.

The **reimbursement criteria** for the **patients with a GEP test** are indicated in the table below.

Patient scenario *(inclusion criteria that are not specified can be considered as met)*	**Reimbursement?**	**Registration?**	**Remarks**
Male patients	Yes	Yes	
MOC/COM decision: propose 'no request GEP' to the patient, but a GEP test was performed	No	No	Only after a positive MOC/COM advice to request a GEP, will the GEP test be reimbursed. Only these patients must be registered
MOC/COM decision: propose 'request GEP' to the patient, but no GEP test was performed	NA	Yes	When a GEP test is proposed by the MOC/COM but the patient refuses the GEP test, the patient still has to be registered.
Patient with a 2nd GEP test performed for a 2nd tumour within the inclusion criteria in the convention period	No	No	Only 1 GEP test within the inclusion criteria is reimbursed within the convention (date MOC/COM from 1/07/2019) per patient.
Patient who is not menopausal or is younger than 45 years	(Yes)	(Yes)	Strictly, the convention is only applicable for patients who are menopausal or at least 45 years old. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed.
Relapse of a previously diagnosed breast tumour (ipsilateral)	(Yes)	(Yes)	For the purposes of this agreement, a relapse 10 years after completion of a previous breast cancer treatment is considered a first/new diagnosis. Strictly, the convention is only applicable to firstly diagnosed, new breast

Patient scenario *(inclusion criteria that are not specified can be considered as met)*	**Reimbur-sement?**	**Registra-tion?**	**Remarks**
			tumours. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed.
A 2nd diagnosed breast tumour, on the other side than the 1st tumour (no GEP for the 1st tumour within convention period) (metachronous)	Yes	Yes	The convention is applicable to all firstly diagnosed, new breast tumours. A contralateral breast tumour with a different laterality is considered as a new tumour.
Bilateral tumour, synchronous (both within inclusion criteria)	Yes, 1 GEP	Yes, 1 GEP	1 registration for the most pejorative tumour***** (only this GEP test will be reimbursed).
Bilateral tumour, synchronous (only 1 within inclusion criteria)	Yes, 1 GEP	Yes, 1 GEP	1 registration for the included tumour (only a GEP test on this tumour will be reimbursed).
Multifocal tumour	Yes, 1 GEP	Yes, 1 GEP	1 registration for the most pejorative lesion***** within the inclusion criteria (only this GEP test will be reimbursed).
Breast skin tumour, lymphoma or sarcoma	No	No	
pTis	(Yes)	(Yes)	Strictly, the convention is only applicable to invasive breast cancers, not in situ. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed.
pT1, pT2	Yes	Yes	Tumour ≤5 cm in greatest dimension; pT1mi and pT1a are also included here.
pT3, pT4	(Yes)	(Yes)	Tumour >5 cm and/or locally advanced. Strictly, the convention only applies to early breast cancer. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed
pN0, pN1	Yes	Yes	≤3 positive axillary lymph nodes. Not clinically detected internal mammary nodes are not taken into account.
pN2, pN3	(Yes)	(Yes)	When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed.
c/pM1	(Yes)	(Yes)	Strictly, the convention only applies to early breast cancer. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed.
HER2+	(Yes)	(Yes)	Strictly, the convention only applies to HER- early breast cancer. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour falls outside the specified criteria, the GEP test will be reimbursed. HER2 status is defined by the pathologist/oncologist using the current Belgian guidelines (e.g. IHC 0 or 1+ = HER2-). If only IHC was performed: use IHC result. If FISH/SISH/CISH was performed: use ISH result.
ER- and PR-	(Yes)	(Yes)	Strictly, the convention only applies to ER+ and/or PR+ early breast cancer. When the MOC/COM decides that a GEP test is appropriate, even when the primary tumour

Patient scenario *(inclusion criteria that are not specified can be considered as met)*	**Reimbursement?**	**Registration?**	**Remarks**
			falls outside the specified criteria, the GEP test will be reimbursed. ER and PR status are defined by the pathologist/ oncologist using the current Belgian guidelines. (e.g. Allred score ≥ 3 with a proportion score ≥ 2 (= ≥1% positive nuclei) = ER+ or PR+).
A biopsy was performed but no primary surgery	Yes	Yes	A GEP test can also be performed on the biopsy sample
Prior to surgery the patient received neoadjuvant systemic therapy	Yes	Yes	If a patient already received neoadjuvant systemic treatment, they are part of the target population.
Patient has no official Belgian residence	Yes, only if Belg. Health insurance	Yes, only if Belg. Health insurance	Only if the patient has a Belgian health insurance, the patient can get a GEP test reimbursement
Patient has no national number for social security (INSZ/NISS)	Yes, only if Belgianhealth insurance	Yes, only if Belgian health insurance	Only if the patient has a Belgian health insurance, the patient can get a GEP test reimbursement
Patient has no Belgian health insurance	No	No	Only if the patient has a Belgian health insurance, the patient can get a GEP test reimbursement

* For **multifocal or simultaneous, bilateral tumours**, 1 GEP test can be reimbursed and 1 GEP registration should be performed. The selection of the focus/tumour which would we considered for GEP and which should be registered in the GEP registration, is the one with the **most pejorative pathologic prognostic factors**. This decision is made by the treating physicians.

1.2 Two registration delivery modes: Web Based Cancer Registration application or batch file

The registrations can be delivered to the BCR in two ways:

1. Via the online **WBCR** application
2. Via structured **batch** deliveries (in a predefined format)

1.2.1 Web Based Cancer Registration

The online **WBCR** application of the BCR can be accessed via the BCR website. More information about the login procedure and general operation of this application can be found in the **WBCR manual** for the 'GEP Breast' project (see https://kankerregister.org/GEPBreast).
Registration via WBCR is the **preferred mode of registration for the GEP Breast dataset** because the data are immediately validated, which reduces the number of errors and incomplete registrations.

The WBCR module for the **GEP Breast** project-specific registration can be found as one of the next modules in the online platform (projects listed alphabetically).

Notes:

- **Access** to WBCR is granted via the **(Main) Access Administrator of your hospital**.
- The login procedure is via the eHealth platform. You will need your electronic identity card and PIN code. Alternatively, you could use the 'itsme app'.
- It is possible to save and modify incomplete registrations at any time, before sending them to the BCR. After sending, the registrations can no longer be modified. The registrations can be delivered to the BCR one by one or altogether. The data you have access to, can be downloaded into a CSV file.
- Quality control checks have been added to the online registration form, e.g. to ensure that the dates are filled out chronologically. Possible errors need to be resolved before the registration can be validated and delivered to the BCR.
- Please keep in mind to save a registration within the hour. After staying on the same WBCR page for more than 1 hour, you will be logged off automatically and unsaved data will be lost.
- Registrations older than 3 years are automatically removed from the WBCR database. This is something to keep in mind when downloading your data.

1.2.2 Batch file

A second option is to deliver the registrations in a predefined 'batch file'. The required variables should be registered in one batch file in a predefined order and format.

For the project-specific 'GEP Breast' dataset, all necessary specifications can be found in the "GEP Breast Batch file template", which is accessible via our website (https://kankerregister.org/GEPBreast). The template has three Excel sheets:

- Requested format: All specifications concerning the structure of the batch file and format of the variables is listed. The second column specifies which variable should be put in which column in the batch file.
- Batch file example: This example shows the requested format of the batch file. It is filled out for three test patients to illustrate how the file should be set up.
- Checklist!: Please consult the 8-step checklist to verify whether your batch file was set up according to the requested format.

It is important to use the correct order, format and answer options to ensure that BCR can uniformly process the data and add it correctly to the main database. Note that it is possible that the BCR will send back registrations to complete missing variables, correct mistakes or verify unlikely information.

The data transfer will be performed via BCR's 'secure file transfer protocol (sFTP)' server (https://sftp.kankerregister.be/). A sFTP login and password can be obtained at the BCR by the person responsible for the registrations before each registration deadline.

1.3 Registration delivery

The start date of the convention is 1/01/2023 without a specified end date. All patients for whom the MOC/COM recommends a GEP test should be registered if the MOC/COM date, where the possibility to request a GEP was discussed, falls within this time frame.

Article 6 of the RIZIV/INAMI convention specifies the **yearly deadline** to deliver the registrations:

> *The reimbursement is only possible if the GEP test was registered with the BCR no later than the last day of the 2nd month of the year following the year in which the test was performed.*

Concretely this means that the dataset should be delivered by **the last day of February of the year following the year in which the MOC/COM took place** (i.e. the MOC/COM where the possibility to request a GEP was discussed).

The following table indicates the exact deadlines for the yearly delivery to the BCR of the dataset:

MOC/COM year	Date of MOC/COM (where a GEP test was recommended)	Registration delivery deadline
2023	1/01/2023 – 31/12/2023	29/02/2024
2024	1/01/2024 – 31/12/2024	28/02/2025
…	…	…

2. The GEP Breast registration form

The following types of variables are used in the project:

- Date: 8 digits: 2 for the day, 2 for the month, 4 for the year (dd/mm/yyyy)
- Decimal (DEC): decimal number; can contain up to 1 or 3 decimals.
  A point '.' should be used as decimal separator in WBCR!
- Multi-select (MS): multiple options can be chosen out of a limited selection list.
  This variable is indicated by the following symbol in the registration form: ❒
- Number (NUM): integer number
- Single-select (SS): only 1 option can be chosen out of a limited selection list (e.g. Yes/No).
  This variable is indicated by the following symbol in the registration form: ❍
- Text: free text field, limited to 255 characters

All variables are 'necessary' variables (mandatory to be filled out) unless stated otherwise (e.g. denoted by 'if possible' or 'if applicable'). **It is strongly encouraged to fill out the free text fields in English as much as possible.**
Additional relevant information may be added to the registration in the **general comments field** (see section 2.5 'General comments field').

2.1 Administrative patient data

For each new registration, the administrative patient data needs to be provided.
In WBCR, when the national number for social security (INSZ/NISS) is filled out, the rest of the mandatory administrative patient data will be automatically completed.

In batch deliveries, the health insurance institution and number are not requested.
In WBCR, please note that there is the option 'Unknown' for the health insurance institution and that the health insurance number is only mandatory if the patient does not have an INSZ/NISS.
Important remark: Only patients with a Belgian health insurance are eligible for reimbursement!

2.2 For all patients for whom a GEP test is proposed by the MOC/COM

Name variable	Type	Answer options
Was surgery performed?	SS	Yes *
		No surgery was performed prior to request of GEP
* Date surgery:	Date	dd/mm/yyyy
Date MOC/COM:	Date	dd/mm/yyyy
Woman in menopause?	SS	Yes
		No
		Unknown
		Not applicable (male patient)
Indication:	SS	Patient **belongs** to the target group of the convention (all of the following: early primary breast cancer, pN0 or pN1, maximum 5 cm in greatest dimension, HER2-, ER+ and/or PR+, menopausal or at least 45 years old, without prior neoadjuvant systemic therapy, clinical high risk based on the MINDACT criteria or Magee score)
		Patient **does not belong** to the target group, but MOC/COM decides that a GEP-test is justified**
** Deviation from the target population	MS (+ Text)	Not primary cancer
		Not first diagnosis
		Not pN0 or pN1
		HER2+
		Tumour > 5cm
		Not menopausal/ not 45 years old
		Doubtful clinical low risk; motivation: …
		Other, explain: …
What would be the MOC treatment decision without knowledge of the GEP?	SS	Strong recommendation to administer adjuvant chemotherapy
		Weak recommendation to administer adjuvant chemotherapy
		Strong recommendation not to administer any chemotherapy
		Weak recommendation not to administer any chemotherapy

Firstly, both the following dates should be filled out:

- The **date of the surgery** on which the tumour for a possible GEP analysis was removed. This only has to be filled out if a surgery was performed prior to request of GEP
- The **date of the MOC/COM** (multidisciplinary oncological consult) on which the decision was made to request GEP

Next, it should be specified if the **woman was in menopause** or not. It is possible to use “unknown” as an answer option, but please note that an extra effort should be made to obtain all relevant information about the patient. In case of a male patient, the answer “Not applicable (male patient)” should be used.

The variable “**Indication**” questions whether the patient belongs to the target population. If the patient does not belong to the target population, the type of deviation must be specified. This can be more than 1 deviation. If the deviation is “doubtful clinical low risk” or “other”, more information must be provided.

In addition, also the **MOC treatment decision without knowledge of the GEP** should be indicated, to get an understanding of the impact of a GEP test result on the decision making on adjuvant chemotherapy. It should be indicated whether the current recommendation to (not) administer adjuvant chemotherapy was weak or strong (before knowing the GEP result).

Note: Only if the MOC proposed to request a GEP, it will be reimbursed by the RIZIV/INAMI.

2.3 At consultation after MOC/COM (before request of GEP)

Name variable	Type	Answer options
Was a GEP test ordered after positive advice from MOC/COM?	SS	No *
		Yes
* Reason for not requesting GEP:	SS (+Text)	Patient wants chemotherapy anyhow, despite advice of MOC/COM to request GEP and await results
		Patient does not want chemotherapy, despite advice of MOC/COM to request GEP and await results
		Other. Please specify: …

The decision to request a GEP after positive advice from the MOC/COM should be indicated.

If the final decision was 'no GEP', the **reason for not requesting GEP** should be specified:

- The patient wants chemotherapy anyhow, despite the advice of the MOC to request GEP and await the results.
- The patient does not want chemotherapy, despite the advice of the MOC to request GEP and await the results.
- Another reason than the abovementioned should be specified in a free text field (please in English as much as possible).

Note: A GEP test is only reimbursed when it was proposed by the MOC. If the patient requests one against the advice of the MOC, the GEP test will not be reimbursed by the RIZIV/INAMI

In case no GEP was requested, the registration ends here!

2.4 Only if GEP was requested: GEP result (final situation) and adjuvant chemotherapy initiated

This section should only be filled out in case a GEP test was requested.

Name variable	Type	Answer options
Which GEP test?	SS (+Text)	Mammaprint by Agendia *
		Mammaprint on NGS, by UZ Leuven *
		Oncotype DX by Genomic Health *
		Other. Name of the test: … *
* Please specify the test result (value):	DEC (3)	Mammaprint: … (min-max = -1 - +1 or -99)
	NUM	Oncoype DX: … (min-max = 0 - 100 or -99)
	DEC (3)	Other: … (min-max = -1 - 1000 or -99)
Interpretation of GEP result (as stated on the report):	SS	High risk
		Borderline risk
		Low risk
		Technical failure

Final treatment: Was adjuvant chemotherapy initiated (at least 1 cycle received)?	SS	No **
		Yes ○
** Main reason (for not initiating chemotherapy):	SS (+Text)	GEP low risk
		Patient does not want chemotherapy, despite advise of MOC/COM for chemotherapy
		Other. Motivation: …
○ Main reason (for initiating chemotherapy):	SS (+Text)	GEP high risk
		Patient does want chemotherapy, despite advise of MOC/COM for chemotherapy
		Other. Motivation: …

There are multiple **types of GEP test** available. Only those that have been approved by the RIZIV/INAMI are eligible for reimbursement. The list of approved tests can be consulted on their website:

- French: https://www.riziv.fgov.be/fr/professionnels/etablissements-services/laboratoires/Pages/remboursement-gep-cancer-sein-stade-precoce.aspx
- Dutch: https://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/laboratoria/Paginas/terugbetaling-gep-vroegstadium-borstkanker.aspx

The provided list of predefined GEP tests might expand during the period of the convention. In January 2023, four tests were eligible for reimbursement:

- Mammaprint on microarray by Agendia
- Mammaprint on NGS by UZ Leuven
- Oncotype DX by Genomic Health
- Other. If more types of GEP tests would be approved by the RIZIV/INAMI in the future, they can be indicated in the registration form by selecting the last option 'Other' and defining the **name of the other test**.

For every test, the obtained **test result** (value) should be specified**.** Limits for these values are the following:

- Mammaprint (Index): Minimum: -1 / Maximum: +1
  - Low risk: 0.001 – 1.000
  - High risk: -1.000 – 0.000
- Oncotype DX: Minimum: 0 / Maximum: 100
  - Low risk: 0 – 25
  - High risk: 26 – 100
- Other test: Minimum: -1 / Maximum: 1000

Remark: For a negative Mammaprint test value, the result must be registered without any spaces. This means -0.2 and not – 0.2.

For all tests -99 can be indicated when the test result value is unknown only in case of a technical failure (and the test could not be repeated). If for another reason the test result is unknown, this should be clearly motivated in the General comments field!

Also, the **interpretation of the GEP test result (as stated on the report)** should be registered:

- High (genomic) risk
- Low (genomic) risk
- Borderline risk

- It is possible that a technical failure occurs during the process. If this problem can be overcome, the final test result should always be specified. Only in the rare case the GEP test has led to no result at all, the option 'technical failure' should be selected.

Concerning the **final treatment**, it should be specified if **adjuvant chemotherapy was initiated**, meaning that effectively at least 1 cycle of chemotherapy was received by the patient.

If the final treatment was 'no adjuvant chemotherapy', the **main reason** should be specified:
- GEP low risk
- Patient decision
- Other → a motivation should be specified in a free text field

If the final treatment was 'yes adjuvant chemotherapy', the **main reason** should be specified:
- GEP high risk
- Patient decision
- Other → a motivation should be specified in a free text field

2.5 General comments field

A general 'comments' field is provided, both in the WBCR application and in the batch file (for both the MOC/COM and the GEP-specific dataset). All relevant, additional information may be added to the registration in this field.

This 'comments' field can be found here:
- WBCR: at the bottom of the online registration form
- Batch file: at the end of the registration

Please fill out this field in English as much as possible.

3. Frequently asked questions (FAQ)

3.1 Registration in general

3.1.1 How can registrations be delivered to BCR?

Two modes of registration are possible for data delivery within this project, either delivery via the online WBCR application or through batch file (**see section 1.2** for all specifications).

- It is recommended to send in patient registrations through **WBCR** (https://kankerregister.org/WBCR) as several checks have been built into it to reduce the frequency of registration errors. Please consult the WBCR manual for more information on the access and use of WBCR.
- If registrations are delivered to BCR in **batch**, we request using the specific order of variables and the predefined names, as provided in the Excel template. This will allow us to uniformly process the data and lowers the risk of errors. The data transfer itself will occur through BCR's 'secure file transfer protocol (sFTP)' server (https://sftp.kankerregister.be/). A sFTP login and password can be obtained at the BCR before each registration deadline.

For the GEP Breast dataset, both the WBCR manual and the Excel batch file template can be consulted and downloaded from the BCR website: https://kankerregister.org/GEPBreast.

3.1.2 When should the registrations be delivered to BCR?

According to the convention, the deadline to submit registrations for the project 'GEP Breast' is the last day of February following the year in which the MOC/COM has considered GEP testing for the patient (**see section 1.3** for all specifications).

3.1.3 How should a patient without an INSZ/NISS number be registered?

Only in very rare cases, a patient will not have an INSZ/NISS number. In this case, please make sure to include all other requested administrative patient data, so that the patient can unambiguously be identified. If the patient is not domiciled in Belgium, please indicate the other country and the foreign zip code.

For delivery via WBCR, it will also be required to fill out the health insurance number or another unique identification number.

3.1.4 Is it possible to have multiple registrations for one patient?

No, since only patients for whom the MOC/COM considers a GEP test must be registered, only 1 registration is possible. For **multifocal or simultaneous, bilateral tumours**, 1 GEP test can be reimbursed and only 1 GEP registration should be performed. The selection of the focus/tumour which would we considered for GEP and which should be registered in the GEP registration, is the one with the **most pejorative pathologic prognostic factors**. This decision is made by the treating physicians.

3.1.5 How can I make corrections to send registrations?

Once a registration has been sent to the BCR, it is impossible to modify the registered information in the BCR database. The BCR should be contacted to make the necessary corrections in the database. **For WBCR users, please note that these corrections will not be visible when performing a WBCR download.**

The medium of communication depends on the amount of erroneous data/ mode of initial data delivery;

1. Via TELEPHONE
   In case it concerns only a few errors; communicate with your BCR contact person via telephone.
2. Via sFTP
   In case it concerns a large number of corrections; communicate via our secured online sFTP server. Contact your BCR contact person for a sFTP login name and password so you can access the server. For registrations sent via WBCR, also include the WBCR reference number.
3. Via E-MAIL
   In case the registered case was sent via WBCR; communicate by sending an e-mail to the project e-mail address. **IMPORTANT NOTE:** Only mention the WBCR reference number of the registered case. **Personal data such as name, social security number (INSZ/NISS) cannot be shared via e-mail because of privacy reasons!**

In all cases, please clearly state for each registration which variable needs to be corrected, which incorrect information was first registered and to what this should be corrected.

Only in exceptional circumstances it will be asked to resubmit the complete registration, mentioning in the general comments field: “corrected version”.

3.1.6 Will I receive feedback on the patient registrations that were sent to BCR?

After each registration deadline, feedback will be sent about the completeness of the registrations. If data are missing, you can be asked to complete this information.

3.2 Inclusion criteria

3.2.1 What are the patient inclusion criteria?

These criteria are listed and specified in **section 1.1** ‘Patient inclusion criteria’. Only patients from the target group with a Belgian health insurance are eligible for GEP reimbursement. Patients for whom the COM/MOC decided a GEP test is recommended, need to be registered and will be reimbursed. If a patient is not part of the target population but the MOC/COM decides a GEP test is necessary, this patient also must be registered and the GEP test will be reimbursed.

Only one GEP test per patient can be reimbursed for the duration of the convention (from 01/07/2019 onwards).

3.2.2 Should an in situ tumour be registered (DCIS/LCIS)?

In situ tumours (behaviour \2) do not fall under the strict convention and should **ONLY** be registered **when the MOC/COM recommends a GEP test**. This includes Ductal Carcinoma In Situ (“DCIS”) and Lobular Carcinoma In Situ (“LCIS’’).

3.2.3 Which hormonal receptor statuses are accepted within the convention?

Patients with a HER2- invasive breast cancer which is ER+ and/or PR+ fall into the target population and must be registered. HER2+ tumours do not fall within the inclusion criteria but must be registered **when the MOC/COM recommends a GEP test.**

3.2.4 What to do with Luminal A and Luminal B breast cancers?

Luminal A breast cancers are either ER+ PR+, ER+ PR- or ER- PR+ and are always HER2-. Hence, they belong to the target population and must be registered, even if no GEP was performed.

Luminal B breast cancers are either ER+ PR+, ER+ PR- or ER- PR+ but can be either HER2+ or HER2-. When HER2-, they are part of the target population and they must be registered when a GEP test is recommended by the MOC/COM. When HER2+, they are **NOT** part of the target population. In this case, they only need to be registered when the MOC/COM recommends a GEP test.

3.2.5 Do triple negative breast cancers need to be registered?

Only when the MOC/COM recommends a GEP test, these patients have the be registered.

3.2.6 What to do with patients that received neoadjuvant therapy awaiting their surgery due to COVID-19?

These patients can be registered as usual but with details concerning the therapy in the general comments field.

3.2.7 Should patients not domiciled in Belgium or without a Belgian health insurance be registered?

The convention clearly states that only patients with a Belgian health insurance are eligible for reimbursement of GEP tests. The country of residence or the availability of a national number for social security (INSZ/NISS) does not matter.

Patients without a Belgian health insurance may be registered but this is not mandatory. In this case, enter “no Belgian health insurance” in the General comments field of the GEP registration.

3.2.8 The patient has multiple tumours - which ones are to be registered?

In case of a simultaneous bilateral/multifocal tumour: 1 GEP test can be reimbursed and 1 GEP registration should be performed. The selection of the focus/tumour which would we considered for GEP and which should be registered in the GEP registration, is the one with the most pejorative pathologic prognostic factors. This decision is made by the treating physicians (see section 1.1. for more information).

3.2.9 What if the patient was treated (in part) in a hospital that is no recognised breast clinic?

Only recognised breast clinics can conclude the GEP Breast convention with the RIZIV/INAMI. A patient from the convention target group for which a GEP was performed, but who received surgery and/or the adjuvant chemotherapy in a hospital that has no recognised breast clinic, will only be reimbursed if a MOC/COM in a recognised breast clinic decided to request a GEP and after complete GEP registration by the breast clinic. Patients for whom no MOC/COM for the GEP was done in a recognised breast clinic cannot be reimbursed for a GEP test by the RIZIV/INAMI.

3.3 Registration form variables

3.3.1 Which surgery date to register if multiple surgeries where performed?

When a patient undergoes a lumpectomy, afterwards a mastectomy and both surgeries were followed by a MOC/COM discussion, the following dates should be registered:

- Date of MOC/COM: the last MOC/COM where the possibility of performing a GEP was discussed
- Date of surgery: The date of the surgery at which the resection material was removed for the (possible) GEP test

3.3.2 What to register in case of a bilateral breast tumour, one tumour within and one tumour outside convention?

For such simultaneous bilateral tumours, **the GEP registration should be performed for the tumour within the convention**.

3.3.3 How to register a multifocal tumour?

In case of a multifocal tumour the lesion that falls under the convention (ER and/or PR positive; HER2 negative) with the most pejorative prognosis, thus which is considered for GEP, should be registered. Which tumoural lesion this is, should be decided by the treating physicians. If the lesion with the most pejorative prognosis does not fall under the convention (for example because HER2 positive), but the MOC/COM recommends a GEP test, this patient still must be registered.

Important note: This is different from the rules for the general cancer registration, where the largest diameter should be considered for the TNM (pT) and the worst differentiation grade should be registered. As such, it is possible that the pT registered for the general cancer registration falls into a higher category than the pT for lesion which is considered for GEP (which only includes pT1 and pT2).

3.3.4 What if not enough information is available to fill out the requested variables?

It could be that the required information cannot be found in the available patient files. Please consult the responsible physician/pathologist to be able to fill out all requested variables.

! Please note that we are aware of the fact that some of these data are not easily obtained. Nevertheless, the experts have emphasised the importance of these variables to post-factum determine the rationale and impact of GEP. Therefore, all variables are required to be filled out.

Tip: Ask the physicians and pathologists to standardly include this information in the medical dossier of the patients.

3.3.5 Where can I enter additional information?

Additional relevant information can be entered in the general comments field (see section 2.5), which can be found:

- In WBCR: At the bottom of the online registration form.
- In the batch file: In the last column of the batch file.

Please fill this out in English as much as possible.

3.3.6 In which language should the registrations be performed?

Please fill out all text variables in English as much as possible, as well as the general comments field.