



A European Cancer Image Platform Linked to Biological and Health Data for Next-Generation Artificial Intelligence and Precision Medicine in Oncology

Deliverable D3.3: Data repository and model for non-imaging data

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1. Version log

Issue Date	Version	Involved	Comments
15/12/2021	1	Lauren Fromont, Aina Jene, Martijn Starmans, Andrea Gutierrez, Anders Nordell	This version contains the whole structure, the main body of the text, with some comments left to be addressed
17/12/2021	final	Isabell Tributsch, Karim Lekadir	Revised and corrected final version.

2. Executive Summary

The present deliverable contains two main objectives:

1. Elaborate a standard data model for non-imaging data (stored at the EGA);
2. Link both repositories for imaging (XNAT) and non-imaging data (EGA).

We have addressed objective (1) by carefully selecting the ICGC ARGO data model for non-imaging data. We detail why this model was selected, as well as the steps that are undertaken to facilitate data harmonisation by the clinical partners. Objective (2) was achieved by an analysis of metadata schemas for each repository, a review of the technical aspects necessary for the linkage to happen, and a description of the implementation of such linkage during the submission of the data to EuCanImage.



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Acronyms

Name	Abbreviation
Accelerate Research in Genomic Oncology	ARGO
Collective Minds Radiology	CMRAD
Data Access Committee	DAC
European Genome-phenome Archive	EGA
European Institute for Biomedical Imaging Research	EIBIR
Extensible Markup Language	XML
International Cancer Genome Consortium	ICGC
JavaScript Object Notation	JSON
Standard Operating Procedure	SOP



1 Introduction

The EuCanImage project gathers data from eight use cases, each consisting of imaging and non-imaging data. The imaging data will be stored on the Euro-BioImaging XNAT hosted by Health-RI, while the non-imaging data will be stored at the European Genome-phenome Archive (EGA). This deliverable covers two objectives:

3. Elaborate a standard data model for non-imaging data;
4. Link both repositories for imaging and non-imaging data.

Objective (1) will allow clinicians to harmonise their data, which will enable more powerful data analyses from the researchers' side. Objective (2) is instrumental to bring together imaging data and their corresponding non-imaging variables.

2 Data model for non-imaging data

2.1 Presentation of the ICGC ARGO dictionary

The [ICGC ARGO dictionary](#) was selected as a basis for the EuCanImage data model. It is a cancer-focused data model that describes the attributes and permissible values for all of the fields within the model. It is used to analyse data in the ICGC platform, which contains specimens from 100,000 cancer patients with high quality clinical data. In addition, several funded projects are using the model, including EuCanCan, an H2020 project in cancer research in Canada and Europe.

A working group including the EGA partners, clinical partners, as well as the ICGC model curator reviewed all data types/variables individually based on the eight clinical use cases that are part of the EuCanImage project. The objective was to assess the extent to which the parameters can be mapped onto the ARGO dictionary, identify the potential gaps based on feedback from the clinical partners and clinical data, and extend the ARGO schema accordingly to obtain a comprehensive data model taking into account heterogeneity between sites. From this qualitative analysis, we derived descriptive statistics reflecting the proportion of variables that are already represented in the ARGO dictionary (see Figure 1 below; a complete report is available [here](#)).

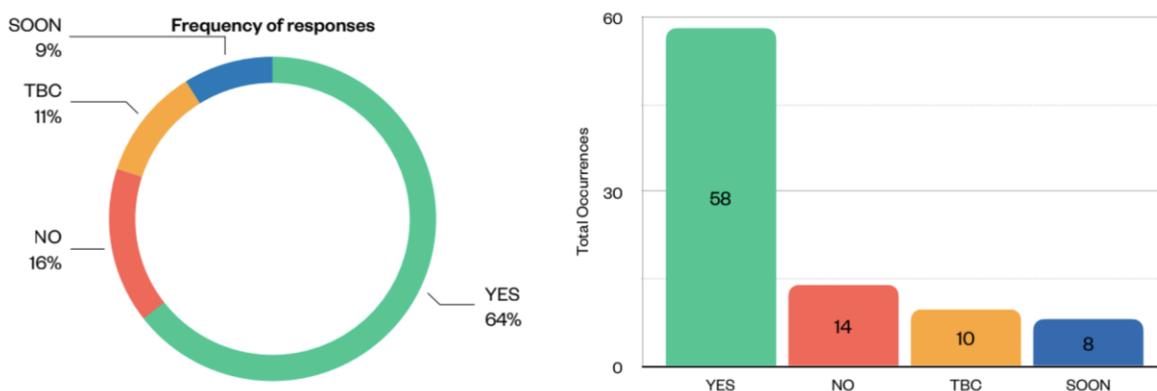


Figure 1: Current level of variable mapping into the ARGO model based on the clinical use cases. TBC: To be confirmed



After reviewing, together with the dictionary curator, all data types/variables individually based on the eight clinical use cases, we observe that the dictionary already has implemented 64% (ranging across use cases from 44% to 80%) of the parameters. An additional 9% are being implemented early 2022. Importantly, a thorough review with the clinical partners showed that the most important variables were already covered. Based on this, we are reasonably confident that our final data model will be comprehensive, easy-to-use and scalable. Furthermore, the data model is intuitive and well-understood by clinical partners, which will facilitate the encoding of the data. This aspect is also important for the AI partners, as it will enable the harmonisation of information and facilitate model learning across datasets and institutions.

2.2 Mapping of the non-imaging variables

In order to efficiently harmonise the non-imaging data, we are currently mapping the non-imaging variables with the data dictionary. The EGA is holding monthly meetings along with key clinical partners and ARGO curator, in order to review all parameters one by one and translate them to ICGC ARGO terms. The [conversion table](#) is in progress, and the working group is aiming to have it ready by Spring 2022, in order to be placed at the disposal of all clinical partners. They will have time to review and comment on it, before the official presentation planned on month 24 in Barcelona.

3 Linking between repositories

Linkage refers to the ability to connect the respective metadata of different repositories. Note that we use the term “metadata” in the narrow sense: i.e., data that describes the data at hand. The objective of this task is to link the metadata between imaging repositories (XNAT) and non-imaging (EGA) repositories. This will allow researchers who browse the EuCanImage catalogue to identify which datasets, e.g. imaging and non-imaging data, belong to the same study or individual.

3.1 Metadata schemas

In order to better understand the connection points between repositories, we will present their metadata schemas.



3.1.1 The EGA

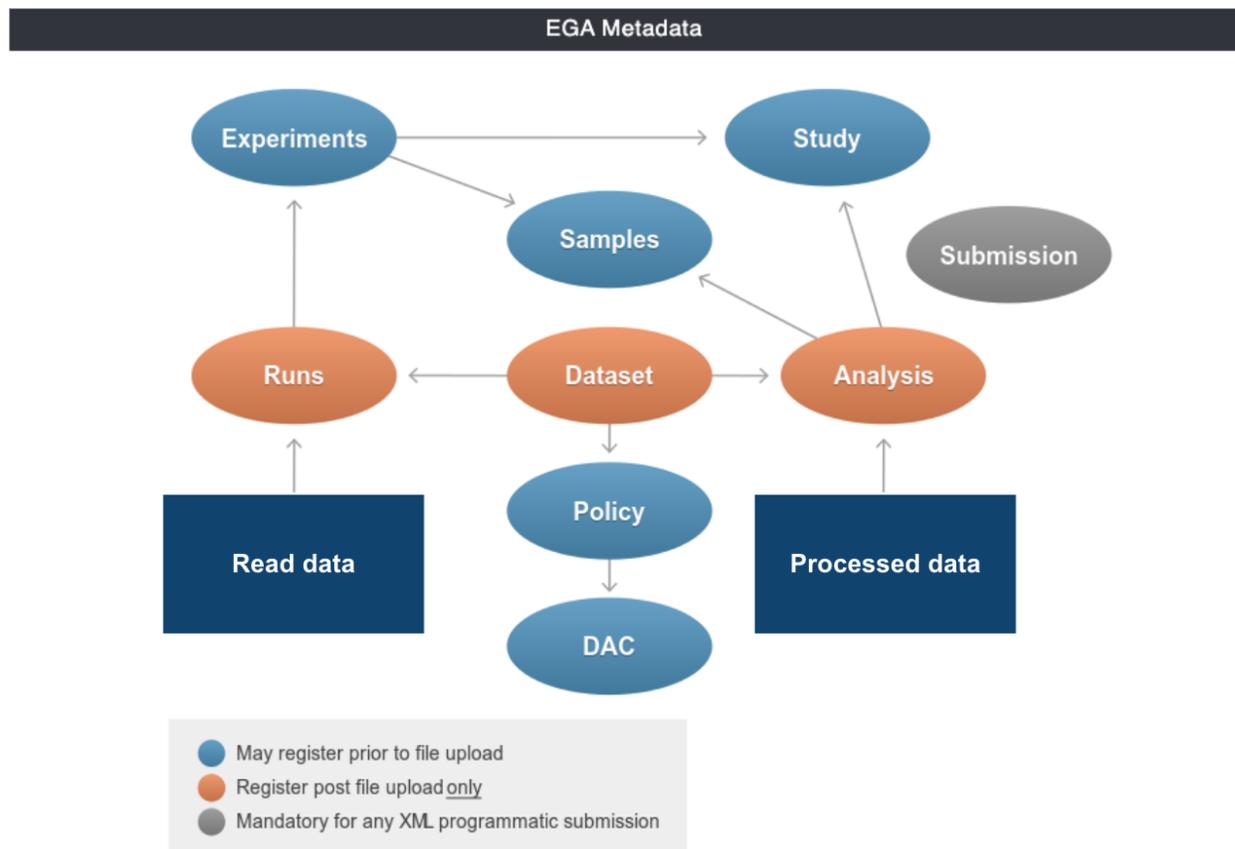


Figure 2: Current EGA metadata schema.

The EGA model can vary depending on the type of submission (sequencing data, array data, phenotypic data). Figure 2 presents an overview of a generic EGA submission.

- Study: information about a project
- Sample: information about the sequenced sample
- Experiment: information about the sequencing experiment (i.e. whole genome sequencing and the technology used)
- Run: link between samples and read data files
- Analysis: link between samples and processed data files
- Policy: information about data use conditions
- DAC: information about the data owners for data requests
- Dataset: contains information of groups of files
- Submission: general object that contains all the objects mentioned above

The two main objects are study and dataset, both being searchable on the EGA webpage (i.e. <https://ega-archive.org/studies/EGAS00001005512>).



The study object refers to the research project itself, being the broader level. Each study could link to one or many datasets that would contain the data information (files, samples, and experiment information). Each dataset links to a policy and data access committee (DAC) object, containing the data use conditions and the relevant contact details of the DAC members for future data access requests.

Another interesting object for this deliverable is the sample object. At the EGA, a sample object contains both information about the *subject*, (i.e. biological sex, age, subject ID), and about the *sample* extracted from the subject (i.e. organism part, phenotype, case/control).

3.1.2 XNAT

An overview of the XNAT data model is depicted in Figure 3. For brevity, we will only describe the high-level components of the XNAT metadata schema here. For detailed information, we refer the reader to <https://wiki.xnat.org/documentation/how-to-use-xnat/understanding-the-xnat-data-model>.

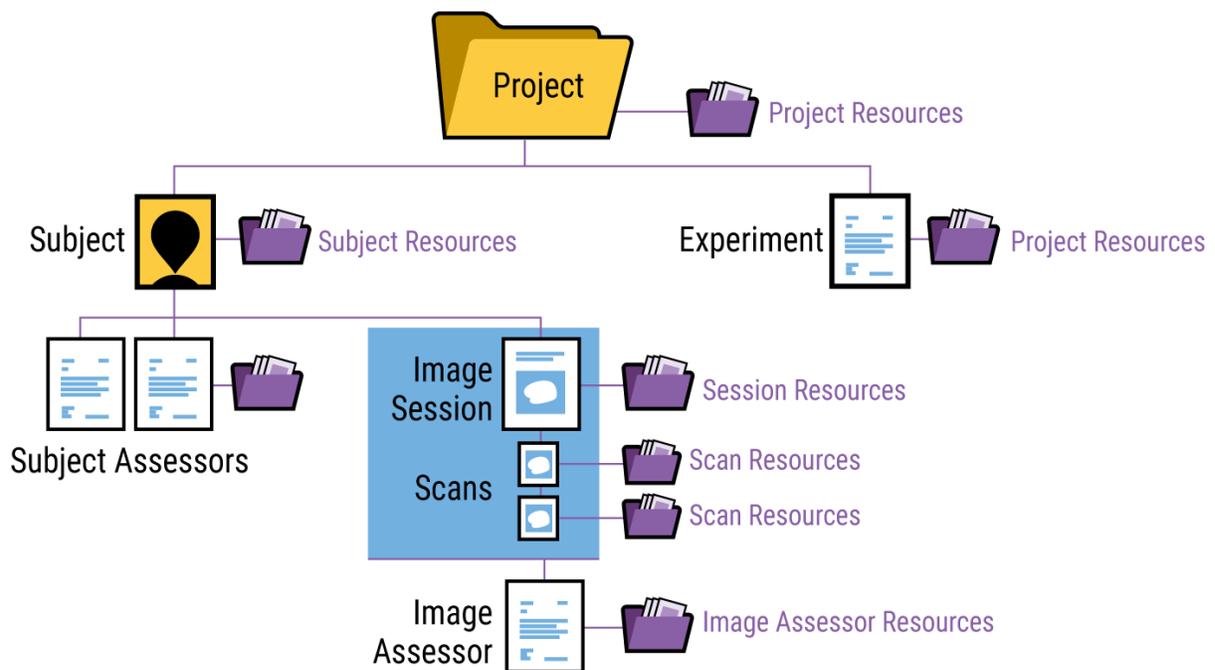


Figure 3: Current XNAT metadata schema. Adopted from <https://wiki.xnat.org/documentation/how-to-use-xnat/understanding-the-xnat-data-model>.

In XNAT, a project is used to define a collection of data, usually a single (multi-site) study. Permissions for users are managed by the owner of a project, which can give users access to a project with different roles (Owner, Member, & Collaborator) or parts of a project.

A subject in XNAT corresponds with an actual subject of a study. Subjects can be registered with other projects and thus be shared between projects. Subjects cannot exist outside of a project.

An experiment corresponds to an event by which data is required. For imaging data, this is usually a scan session, e.g. a CT or MRI session. Non-imaging experiments can also be



defined. Experiments can both be defined on a project level, or on a subject level, depending on the type of experiment. Similar to subjects, experiments can be shared between projects and cannot exist outside a project.

A scan corresponds to a single scanning sequence, e.g. a T1-weighted MRI scan. Typically, an imaging session will consist of multiple scans.

Non-imaging data can in principle be added on any level of the XNAT metadata schema, with entry points defined on all levels within the REST API.

3.1.3 EuCanImage catalogue (MOLGENIS)

The aim of the EuCanImage catalogue is to provide the relevant information about available medical images to researchers so they can easily find imaging data. The catalogue offers a search interface and the imaging data can be found via an url link to the corresponding data repository or via contact information (in case the data needs to be requested).

The metadata model of the imaging catalogue follows relevant standards proposed by the Minimum Information About BIobank data Sharing (MIABIS-2.0) at biobank and collection level. Figure 4 shows an overview of the EuCanImage catalogue metadata model which is divided into three different levels: biobank, collection and imaging data level.

The EuCanImage catalogue is built using the MOLGENIS platform and the user-search-interface, Molgenis-app-biobank-explorer (interface developed for the BBMRI-ERIC directory), has been adapted to include imaging metadata. The EuCanImage catalogue is hosted by the European Institute for Biomedical Imaging Research/EIBIR (www.eibir.org).

The EuCanImage catalogue has the versatility to adapt to new relevant metadata and non-imaging data can also be added at collection level. Note that the imaging catalogue does not provide information at the subject level.

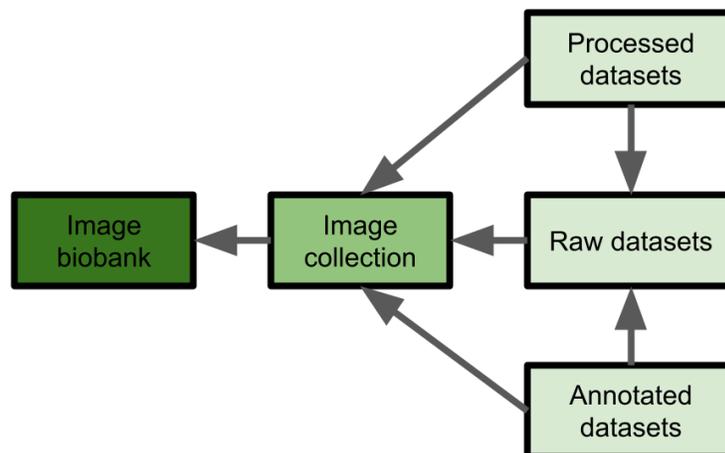


Figure 4: Overview of the current imaging metadata schema.



3.2 Technical considerations: what to link and how

Now that we know the metadata schemas from all parties in this deliverable, we can proceed to explain the technical aspects of how the linkage is going to work.

Table 1 shows the two levels of connection that we have identified for EuCanImage, between EGA, XNAT, CMRAD and the EuCanImage Catalogue.

Table 1: Linking points between repositories

EuCanImage (data)	EuCanImage Catalogue (MOLGENIS)	Local clinical partner	CMRAD	XNAT	EGA
Use Case	Collection	Use Case	Use Case	Project	Study
Subject ID	N/A	local subject ID > Subject ID + Hashkey	hashkey > Subject ID	Subject > Subject Label	Sample > Subject ID

On a higher level, the linkage between Use Case - Collection - Project - Study would encompass the overall information of the project. To this effect, a functional link between repositories will be created.

On a more detailed level, we can include the linkage between subjects. This more specific level will facilitate the data flow between repositories for individuals: a user will be able to connect specific clinical information from a given subject X at the EGA, with the corresponding CT scans from the same individual in XNAT.

EuCanImage subject IDs (Subject ID) are pre-generated and given to clinical partners. The clinical partner assigns a local subject ID to a EuCanImage Subject ID and calculates the hashkey. The local partner shares the subject ID and hash key relationship with all other partners. At the central level the Subject ID is used to link the different repositories together. For pseudonymization of images a fully automatic process is used to replace the local subject ID with the hashkey. The hashkey is then related to the Subject ID at a central level.

3.2.1 Linking from the EGA

1. Study metadata object

At the EGA, the linkage at the use-case level will be added on the study metadata object. The EGA stores all metadata information in JSON objects. JSON is a "self-described" and easy to understand text format for storing and transporting data. Below we can see the JSON schema for a study.

```
{
  "STUDY": {
    "DESCRIPTOR": {
      "STUDY_TITLE": [],
      "STUDY_DESCRIPTION": [],
```



```
"STUDY_TYPE": : [],  
"RELATED_STUDIES": {  
  "RELATED_STUDY": {  
    "RELATED_LINK": {  
      "DB": [],  
      "ID": [],  
      "URL": []  
    }  
  }  
}
```

In the JSON above, we can see the structure of the study tree; the linkage information will be stored under "RELATED_STUDY". In each "RELATED_STUDY" node we will store information about the repository name, unique ID, and unique URL.

```
"RELATED_STUDY": {  
  "RELATED_LINK": {  
    "DB": [XNAT],  
    "ID": [Project_ID],  
    "URL": [XNAT_Project_URL]  
  }  
}
```

The EGA will store the information related to the linkage in a database. For each study, the EGA will show the ID to the other repository on its webpage (with linking information), which will redirect the user to the right endpoint with one click (examples are shown in the [Annex](#)).

2. Sample metadata object

On the subject level, we will use the sample metadata object. Below we can see an example of the JSON schema.

```
{  
  "SAMPLE": {  
    "TITLE": "",  
    "SAMPLE_NAME": {  
      "TAXON_ID": "9606",  
      "SCIENTIFIC_NAME": "Homo sapiens",  
      "COMMON_NAME": "human"  
    }  
  }  
}
```



```
    },  
    "DESCRIPTION": [],  
    "SAMPLE_ATTRIBUTES": [  
      {  
        "TAG": "subject_id",  
        "VALUE": []  
      },  
      {  
        "TAG": "case_or_control",  
        "VALUE": []  
      },  
      {  
        "TAG": "sex",  
        "VALUE": []  
      },  
      {  
        "TAG": "phenotype",  
        "VALUE": []  
      }  
    ]  
  }  
}
```

As previously mentioned, we will take the subject ID under "SAMPLE_ATTRIBUTES" field for this linkage at the EGA. When registering the sample objects at the EGA, the submitter will have to make sure that they use the right EuCanImage ID. For example:

```
"SAMPLE_ATTRIBUTES": [  
  {  
    "TAG": "subject_id",  
    "VALUE": [EuCanImage_ID1]  
  }  
]
```



3.2.2 Linking from XNAT

3. Project metadata object

In XNAT, the Project ID will be used for the linking. This is an example of the metadata structure for a XNAT project (XML):

https://xnat.bmia.nl/app/action/XDATAActionRouter/xdataaction/xml_file/search_element/xnat%3AprojectData/search_field/xnat%3AprojectData.ID/search_value/worc/popup/false.

For EuCanImage projects in XNAT the ID will follow the pattern below.

```
<xnat:Project
  ID="[EuCanImage_UseCase_ID_Hospital]"
</xnat:Project>
```

The related study information will be added in a "fields" variable. The XNAT XML format of the fields variable does not allow the dictionary-based structure of the JSON as used in EGA. However, similar naming will be used as in the EGA structure for linking:

```
<xnat:Project
  <xnat:fields>
    <xnat:field name="related_study_DB"> [EGA] </xnat:field>
    <xnat:field name="related_study_ID"> [EGASTudyID] </xnat:field>
    <xnat:field name="related_study_URL"> [EGASTudyURL] </xnat:field>
  </xnat:fields>
</xnat:Project>
```

4. Subject metadata object

For the subject object, below we can find a schematic XML with the main information.

```
<xnat:Subject
  sharing
  resources
  investigator
  demographics
  metadata
  addID
```



```
fields
experiment
</xnat:Subject>
```

When registering the subject objects at XNAT, the submitter will have to make sure that they use the right EuCanImage ID. For example:

```
<xnat:Subject
  label="[EuCanImage_ID1]"
</xnat:Subject>
```

3.2.3 Linking from the EuCanImage Catalogue

Collection object

Concerning the EuCanImage catalogue, information linking at collection level is proposed in figure 5. Fields for the repository name, unique study/project ID from repositories (XNAT and EGA) and unique URL for imaging and non-imaging data can be displayed in the search interface. These fields can also be extracted via API in the MOLGENIS platform.



Image collection	ID* <i>Unique collection ID according to MIABIS-2.0-0.1 standard</i>
	Name* <i>Image collection name according to MIABIS-2.0-03 standard</i>
	Acronym <i>Image collection acronym according to MIABIS-2.0-02 standard</i>
	Description* <i>Description of the image collection according to MIABIS-2.0-08 standard</i>
	Parent collection <i>Parent image collection (if applicable)</i>
	Body parts of interest* <i>Body parts of interest in this collection (can be multiple)</i>
	Image modality* <i>General image modalities available in the collection (e.g. MRI, PET, CT, etc...)</i>
	Number of subjects* <i>For whose images populate the collection</i>
	Number of centers* <i>That provided the images that populate the collection</i>
	Country*
	Biobank* <i>To which the collection belongs</i>
	Image access fee <i>Denotes whether access to images may be obtained against payment</i>
	Image access description <i>Short description of access rules</i>
	Image repository name <i>Name of repository with imaging data of this collection (e.g. XNAT)</i>
	Image data repository ID <i>Unique ID from image repository related to this collection</i>
	Image access url <i>Website to the access of imaging data</i>
	Non-image repository name <i>Name of repository with non-imaging data related to this collection (e.g. EGA)</i>
	Non-image data repository ID <i>Unique ID from non-image repository related to this collection</i>
	Non-image access url <i>Website to the access of non-imaging data</i>
	Contact* <i>Reference to a contact person</i>
Role <i>Official role of the person in charge of the collection, e.g. PI or Director</i>	

Figure 5: Proposed fields linking imaging and non-imaging data at collection level in the EuCanImage catalogue. Proposed imaging data fields are in blue and proposed non-imaging data fields are in green. Fields with '*' are mandatory.



4 Conclusion: future steps and sustainability

4.1 Data model

Data Harmonisation

Now that the data model has been selected, we will facilitate the harmonisation of the data by providing a [conversion table](#) to all data providers. This table is in progress, and the working group is aiming to have it ready by Spring 2022, in order to be placed at the disposal of all clinical partners. They will have time to review and comment on it, before the official presentation planned on month 24 in Barcelona. Table 2 describes the current and future steps regarding the data model.

Table 2: Overview of the steps regarding the data model for non-imaging data

Step	Date	Description	Status in December 2021
1	30/09/2021	A data model is selected and included in the data management plan v1	100%
2	31/12/2021	A review of the final clinical parameters is done and gathered in a conversion table in order to facilitate the mapping	100%
3	31/03/2021	The mapping between the parameters and data model values is completed and available in the conversion table	60%
4	31/06/2021	The conversion table has been reviewed by clinical partners and interested parties	0%
5	30/09/2021	The data model and final version of the conversion table is presented to the consortium	0%

White paper on data models

The EuCanImage project is an active member of the AI4HI, which is a collaborative project representing CHAIMELEON¹, EuCanImage, INCISIVE², PRIMAGE³, and ProCancer_I⁴. As such, the CRG is participating in the redaction of a white paper under the coordination of Dr Emanuele Neri, to present the EuCanImage data model. The manuscript is planned for submission to a specialised scientific journal referenced in PubMed during the first quarter of 2022.

¹ <https://chameleon.eu>

² <https://incisive-project.eu>

³ <https://www.primageproject.eu>

⁴ <https://www.procancer-i.eu>



4.2 Linkage

The present deliverable shows how two linking points (on the use case and subject levels) have been identified across repositories, and describes how the linkage should be achieved on a technical level. While the linkage on the *subject* level will be done manually by entering a unique EuCanImage ID in the data themselves, the linkage on the *use-case* level will be implemented during the submission.

Protocol for a sustainable implementation

The following SOPs (Table 3) describe the steps that a submitter should follow. We distinguish between two scenarios, depending on whether a submitter wishes to submit non-imaging data (to the EGA) before the imaging data (to XNAT), or *vice versa*. Note that it is particularly important to ensure that the unique ID generated by the EGA and XNAT are communicated to *both* repositories, in order to ensure a sustainable linkage for EuCanImage data.

Table 3: Overview of the submission SOP to ensure linkage between repositories

Step	SOP 1: Submission of <i>non-imaging</i> first	SOP 2: Submission of <i>imaging</i> data first
1	The submitter registers the use-case to CMRAD and obtain the EuCanImage ID	
2	The submitter submits non-imaging data at the EGA ⁵ and adds the EuCanImage ID	The submitter submits imaging data at XNAT and adds the EuCanImage ID
3	The submitter receives a unique ID corresponding to the EGA study	The submitter receives a unique identifier corresponding to the XNAT project
4	The submitter submits imaging data at XNAT and adds the EGA unique ID + the EuCanImage ID	The submitter submits non-imaging data at the EGA and adds the XNAT unique ID + the EuCanImage ID
5	The submitter receives a unique ID corresponding to the XNAT project	The submitter receives a unique ID corresponding to the EGA study
6	The submitter communicates the XNAT ID to the EGA ⁶	The submitter communicates the EGA ID to XNAT

Each repository will have to periodically run a link checker service (i.e. <https://validator.w3.org/checklink>) to validate that the linked resource is still accessible and valid. Ideally, when running the validation step, a report will be created and sent via email with the results. This way, the repositories can make sure that the linkage information is

⁵ <https://ega-archive.org/submission/quickguide>

⁶ <https://ega-archive.org/contact-us>



correct, and in case that the link is broken, it can be updated – or removed – from the webpage.

We will use EuCanImage Use Case 7, which contains both clinical and imaging data, as a working example of the linkage. The clinical information will be stored at EGA, and the imaging data to XNAT and EuCanImage catalogue, hosted by the European Institute for Biomedical Imaging Research (EIBIR). Then, we will use the IDs in each repository for the first cross reference example.

Toward a semi-automatic implementation

While the SOP described above is perfectly functional for the deliverable submission (December 2021), both repositories are planning a semi-automatic way to link between repositories, using the metadata API.

In this implementation, instead of having the submitters contacting the repositories to communicate the unique ID (steps 4 and 6 in Table 3), the repositories would *extract* the relevant information by querying the API. Table 4 summarises the future implementation.

Table 4: Overview of the submission SOP including semi-automatic linkage

Step	SOP 1: Submission of <i>non-imaging</i> first	SOP 2: Submission of <i>imaging</i> data first
1	The submitter registers the use-case to CMRAD and obtain the EuCanImage ID	
2	The submitter submits non-imaging data at the EGA ⁷ and adds the EuCanImage ID	The submitter submits imaging data at XNAT and adds the EuCanImage ID
3	The submitter receives a unique ID corresponding to the EGA study	The submitter receives a unique identifier corresponding to the XNAT project
4	The submitter submits imaging data at XNAT and adds the EGA unique ID + the EuCanImage ID	The submitter submits non-imaging data at the EGA and adds the XNAT unique ID + the EuCanImage ID
5	Both repositories query the metadata API to extract the ID from the other repository	

Note that this implementation also includes the validation step as previously described.

⁷ <https://ega-archive.org/submission/quickguide>



5 ANNEX: Webpage display proposals

EGA Linkage

This is a proposal on how the linkage would work on the EGA webpage. In addition to the study title, accession (EGAS), description, related datasets, and related publications, we suggest adding a "Related repositories" table, showing the linkage detailed in this deliverable. This table will include the logo of the repository (column 1) and their project ID (column2). Users could move between repositories by clicking the Project ID under the Link column.

Study

Integrated RNA-seq analysis of tumor thrombus

Study ID	Alternative Stable ID	Type
EGAS00001005512		Other

Study Description

We prospectively enrolled 83 patients with a renal mass and TT scheduled to undergo surgical resection. To accurately integrate genomic and transcriptomic findings and enable histological co-registration, simultaneous isolation of DNA and RNA was performed from individual samples characterized histologically through immediately flanking sections

Study Datasets 1 dataset.

Click on a Dataset ID in the table below to learn more, and to find out who to contact about access to these data

Dataset ID ^	Description v	Technology v	Samples v
EGAD00001008010	the dataset contains Exome and RNA fastq files of Renal Cell Carcinoma patients, which belongs to "Integrated genomic analysis of tumor thrombus"/		600

Who archives the data?



Related repositories.

Repository	Link
 EUCAN IMAGE	Use Case 1
 XNAT	XNAT - Imaging data Use Case 1

Publications

Determinants of renal cell carcinoma invasion and metastatic competence.

Kim K, Zhou Q, Christie A, Stevens C, Ma Y, Onabolu O, Chintalapati S, Mckenzie T, Tcheuyap VT, Woolford L, Zhang H, Singla N, Parida PK, Marquez-Palencia M, Pedrosa I, Margulis V, Sagalowsky A, Xie Z, Wang T, Durinck S, Modrusan Z, Seshagiri S, Kapur P, Brugarolas J, Malladi S.
Nat Commun 12:2021 5760

Citations

0



EuCanImage catalogue Linkage

Below is an example of how the EuCanImage use cases can be displayed at the collection level of the EuCanImage catalogue. Links to imaging and non-imaging repositories will be displayed in the summary of the collection.

Collection

Use case 07 – EuCanImage

Add to selection

Description: Test for EuCanImage use case 07 integration in the imaging catalogue. Breast cancer case with pre/post breast MRI images and non-imaging data.

Collection id: ECI_UC07_STANDARD001
Size: 353 subjects
Collection type: Disease specific
Body part: Breast
Imaging modality: MRI
Dataset type: raw datasets
Access type: By request
Diagnosis: Malignant neoplasm of breast [↗](#)
Imaging data: https://xnat.bmia.nl/data/projects/ECI_UC07
Non-imaging data: <https://ega-archive.org/studies/EGAS000000xxxx>
Year: 2005 – 2020

Contact Information

Head/PI: No Information

Contact: No information

[✉ Email](#)

Biobank

Use case 07 – EuCanImage
unknown
Spain

[📄 View Use case 07 – EuCanImage](#)

[✉ Email](#)

Biobank id: ECI_UC07

Networks

Name: eucanimage

[📄 View eucanimage network](#)

Raw Datasets

Image type	Body part	# subjects	# timepoints
anatomical MRI	Breast	353	2