PRIMAGE

Medical imaging
Artificial intelligence
Childhood cancer research

D9.1 – Data Management Plan

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1. Introduction

1.1 Biobanks

Biobanks are repositories for the storage and retrieval of biological samples of a large number of subjects[1]. A major goal of biobanks is the organised collection of biological material and associated information to spread access among scientists requiring this information. The first biobank project, established in 1948, collecting blood samples and data, was the Framingham Heart Study (FHS), funded by the National Institute of Health-National Heart, Lung, and Blood Institute (NIH-NHLBI) [2]. A recent review performed by Kang et al. reported that 70 % of the world's biobanks are located in Europe and that the top six countries with biobanks are the UK (n = 15), USA (n = 14), Sweden (n = 12), France (n = 9), The Netherlands (n = 8) and Italy (n = 8) [3].

Distributed Research Infrastructures are gaining political traction in Europe to facilitate scientific research. This development has gained particular momentum in the area of biobanking where cross-national attempts have been made toward harmonizing the biobanking standards across the European Union through the establishment of the organization BBMRI (BioBanking and Biomolecular Resources Research Infrastructure). BBMRI was established in 2013 by the European Commission and represents the widest biobanks network implementing a European 'roadmap' for research infrastructures.

The mission of BBMRI is to link and provide access to local biobanks of different formats, including tissue collections, harmonize standards, establish operational procedures which properly consider ethical, legal, societal aspects, and to secure sustainable funding. Pathology plays a key role in development and administration of tissue banks and is, thus, a major partner for collaboration, expertise and construction of this pan-European research infrastructure. To date, with the notable exeption of the UK Biobank and the German National Cohort, such biobanks do not include data from diagnostic imaging, as computed tomography (CT) and MRI.[4,5]

1.2 Imaging biobanks

In 2014, the European Society of Radiology established an Imaging Biobanks Working Group (WG) of the Research Committee, aimed at defining the concept and scope, exploring the existence and providing guidelines for the implementation of imaging biobanks. The WG defined imaging biobanks as 'organised databases of medical images, *and associated imaging biomarkers* (radiology and beyond), shared among multiple researchers, linked to other biorepositories' and suggested that biobanks (which focus only on

[1] Hewitt R, Watson P (2013) Defining biobank. Biopreserv Biobank 11:309–315

[2] Dawber TR, Kannel WB (1966) The Framingham study, an epidemiologic approach to coronary heart diseas. Circulation 34:553– 555

[3] Kang B, Park J, Cho S, Lee M, Kim N, Min H et al (2013) Current status, challenges, policies, and bioethics of biobanks. Genomics Inform 11:211–217

[4] Petersen SE, Matthews PM, Bamberg F et al (2013) Imaging in population science: cardiovascular magnetic resonance in 100,000 participants of UK Biobank—rationale, challenges and approaches. J Cardiovasc Magn Reson 15:46

[5] Starkbaum J, Gottweis H, Gottweis U et al (2014) Public perceptions of cohort studies and biobanks in Germany. Biopreserv Biobank 12:121–130

the collection of genotype data) should simultaneously come with a system to collect related clinical or phenotype data. [6], [7]
The basis of this assumption was that modern radiology and nuclear medicine can also provide multiple imaging biomarkers of the same patient, using quantitative data derived from all sources of digital imaging, such as CT, MRI, PET, single photon emission CT (SPECT), ultrasound, x-ray, among others. Such imaging biomarkers, which express the phenotype, should therefore be part of the multiple biomarkers included in biobanks.

The imaging biobanks WG performed a survey among members of the European Society of Radiology (the largest radiological society in the world) and among the responders 27 declared to have implemented an imaging biobank, of which 13 are oncologic disease-oriented. The prevalence of oncologic-oriented imaging biobanks in Europe was partially expected considering that many imaging biomarkers developed in diagnostic imaging are clinically used for oncologic purposes.

1.3 Imaging biomarkers (data)

Biomarkers are defined as 'characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathological processes, or pharmaceutical responses to a therapeutic intervention'. In the specific context of diagnostic imaging biomarkers are the expression of biosignal, since they detect and analyze an electromagnetic, photonic or acoustic signal emitted by the patient, in contrast to the biospecimen type which are obtained by removing a sample from a patient (genes and proteins detected from fluids or tissue samples.

In oncologic imaging the value of imaging biomarkers has been tested in multiple cancer types, but few have been recognized as sufficiently robust, reliable and well-characterized to be used as routine tools in clinical cancer research.

Imaging biomarkers and their processing through radiomics are the main data of the PRIMAGE project. Here follows a "use case" to describe the imaging biomarkers that can be collected.

1.3.1 The CT study of a patient with Neuroblastoma

A contrast enhanced CT for staging of neuroblastoma includes a unenhanced phase (no contrast), enhanced arterial, portal and late phases which allows to determine the vascularity of the tumor and also to detect metastases in other organs. The visual assessment is the main method used by radiologists to stage the disease. However, the tumor vascularity (which in practical means vitality and neo-angiogenesis) can be also quantified by measuring with a region of interest the Hounsfield density of the lesion in the various phases of the acquisition. Such measurements compose a biomarker of tumor vascularity.

To date the continuous evolution of software and hardware in medical image analysis has brought to new tools for image analysis, as radiomics [8]. Radiomic is the discipline that deals with the extraction, and analysis of quantitative features from diagnostic images. The basis of radiomic is that such extracted features are the phenotype, the image quantitative expression of pathophysiological processes that can

[6] European Society of Radiology (ESR). ESR Position Paper on Imaging Biobanks. Insights Imaging. 2015 Aug;6(4):403-10. doi: 10.1007/s13244-015-0409-x. Epub 2015 May 22. PubMed PMID: 25999018; PubMed Central PMCID: PMC4519817.

[7] Neri E, Regge D. Imaging biobanks in oncology: European perspective. Future Oncol. 2017 Feb;13(5):433-441. doi: 10.2217/fon-2016-0239. Epub 2016 Oct 28. PubMed PMID: 27788586.

[8] Lambin P, Rios-Velazquez E, Leijenaar R et al (2012) Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 48:441–446

be expressed also by other “omics”, included in the terms genomics, transcriptomics, metabolomics, proteomics etc. Examples of features that can be extracted by a radiomic analysis are the shape/size-based, the histogram-based, and the texture analysis.

Radiomic is therefore a process of extraction of features from diagnostic images, as it is in other omics fields, but at the end of the process, the final product is a quantitative feature/parameter, measurable and mineable. The concept of quantitative feature combines with that of “imaging biomarker”.

In solid tumor patients, such as the Neuroblastoma case discussed in this section, a further quantitative analysis can be performed on the target lesion by extracting radiomics features.

At the end of the quantitative analysis in a single lesion (the main tumor) multiple imaging biomarkers are collected as:

- contrast-density curves
- shape/size
- histogram
- texture analysis

However, these biomarkers can be collected also in other secondary lesions (in liver, lungs, etc) if the patient has metastases.

The composition/cluster of the biomarkers of the tumor in this specific patient will represent a signature (patient’s specific), but such signature alone is not meaningful if not combined with other biomarkers of the patient, as pathological samples, blood samples, genomic profiles, etc. All these data need to be grouped and correlated, and this is the purpose of the biobank that will be developed in PRIMAGE.

Aim of the deliverable

The deliverable is first aimed at defining the pipeline to collect, process, organize, secure the data that will be the core and content of the PRIMAGE biobank and, second, to define the strategy to provide an access to data by the scientific community through a biobanks network.

The deliverable is linked to most of the work packages, but with major impact in WP3 and WP11.

2. DATA MANAGEMENT PLAN

2.1 Data collection: how to retrieve the data

Data/biomarkers collected in the project will be initially derived from PRIMAGE´s clinical partners (HULAFE, CCRI, UKOELN), but it is also expected the contribution of other hospitals which have been invited to collaborate to this R&D project providing data from their NB and DIPG patients..

A relation of the kind of clinical data that will be collected in the data repository is listed in Annex 1. This is the first draft elaborated by the Paediatric Oncology Unit of HULAFE, which still has to be reviewed and agreed by the three clinical partners. The final selection of the clinical variables will be reported in the deliverable D1.1: Users´ requirements and use scenarios.

The images to be processed to identify the imaging biomarkers will be those coming from the clinical data of the patients included in this project after considering the inclusion and exclusion criteria.

The analysis of imaging data will be performed first on a visual basis to perform lesion segmentation, in order to guide the accurate extraction of imaging biomarkers.

The segmentation (or annotation of images) will serve to address dedicated softwares (QUIBIM, Medexprim) to extract meta-data and the different biomarkers. A deep learning algorithm is envisaged to be implemented to foster the segmentation process and the radiomics analysis.

Even if a part of the retrospective analysis will be dedicated to images, a vast amount of information will be retrieved from clinical data, as patient's registry, pathology, molecular biology, associated symptoms, treatment.

All data will be linked in the patient's folder to the stage of the disease, at diagnosis and at follow-up.

Data organization and management

All collected data will be organized in the "extended" central repository of the project, based on QUIBIM Precision platform (project funded under SME Instrument Phase 2, project 778064).

The actual format of the platform is designed to include image and clinical data but it will be enhanced to include information on molecular biology (genetics), clinical data related to neuroblastoma and imaging data through DICOM format.

The PRIMAGE platform will include:

- DICOM metadata (connected to raw data: DICOM files)
- Imaging biomarkers (connected to raw data: DICOM files) (i.e. volume)
- Pathology biomarkers (connected to raw data: digital pathology DICOM files)
- Clinical biomarkers

See Annex 1 for a detailed description of data that will be included in the biobank.

All data will be linked in the same patient folder and grouped in a so called "e-form".

Table. 1 shows and example of e-form, where at a specific time of evaluation (i.e. the primary staging of the patient) all biomarker are collected from salivary, blood and urines samples, imaging, pathology, etc….

Each biomarker is reported with a value except for the Staging systems as the International Neuroblastoma Risk Group Staging System (Annex 2), where the "value" is expressed by a categorical biomarker.

Table 1. Example of E-Form (Electronic Form)

Name	John Doe
Disease (code) (WHO - ICD ver 11)	• 2D11.2 (Neuroblastoma of adrenal gland)
Stage (International Neuroblastoma Risk Group Staging System) (Annex 2)	Categorical biomarker value • L1
Time of evaluation	May 2017
Lab biomarkers • Homovanillic acid (HVA) • Vanillylmandelic acid (VMA) • blood cell counts • liver function values	Value • …….. • …….. • …….. • ……..

• kidney function values • Electrolytes (Na, Mg, ..) • Urinalysis	• …….. • …….. • ……..
Other Lab biomarkers • DNA ploidy • *MYCN* gene amplifications • Chromosome changes • Neurotrophin (nerve growth factor) receptors • Ferritin • Neuron-specific enolase (NSE) • Lactate dehydrogenase (LDH) • Ganglioside GD2	Value • …….. • …….. • …….. • …….. • …….. • …….. • ……..
Imaging biomarkers • CT ROI Tumor (Density) • CT ROI Tumor (Volume) • CT ROI Tumor (Shape: regular, irregular) • CT ROI Tumor (Diameter: maximum, minimum) • CT ROI Tumor (Texture features: a) b) c) d) e) …… • DICOM metadata	Value • …….. • …….. • …….. • …….. • …….. • …….. • …….. • ……..
Pathology biomarkers • Tumor (Grading) • Tumor (Cell type) • ……..	Value • …….. • …….. • ……..

2.2 Securing and sharing data on a Cloud-based database

A cloud-based database will be implemented for the management of the anonymised data generated during the virtual clinical testing sessions from the clinical centres, and other data from subsystems testing.
With respect to security, functional and technical requirements will be defined with respect to data transformation (including de- identification and encryption), infrastructure (e.g., user identity management, audit log) and data access and movement (including authorisation and transmission protection).

The main requirements implemented in the platform are:

- **Modular:** organized in different blocks (DICOM compatibility, image visualization, reports generator, analysis algorithms, database, back-end, front-end user interface) and layers able to work as connected components.
- **Integrated**: the solution should be adapted to current healthcare information systems (i.e. understanding standards like DICOM, XML, HL7 messaging).
- **Scalable:** Elastic architectures should be achieved, allowing for the wake up process of new servers when an increase demand in the analysis exists. In PRIMAGE, both private and public clouds will be implemented.
- **Pipelines**: The platform is pipeline oriented, following step-wise strategy and differentiating image preparation, image analysis, results measurement and extraction steps.

- **Data mining**: The platform allows also for Big Data management and exploitation for scientific purposes.
- **Web-based**: The platform is accessible from any place by simply using a web browser.
- **Vendor-agnostic**: The platform is able to process images from any manufacturer.
- **Marketplace strategy**: The platform allows for plugins oriented architecture, allowing for researchers to adapt their algorithms to the platform.
- **Structured Quantitative Reporting**: The platform provides a quantitative output in structured reports, easy to understand for the end-user.

The cloud architecture implemented consists of a web application (for web platform deployment), the Cloud storage (for DICOM images storage) and Virtual Machines (for image analysis by cloud computing processes). DICOM encryption and dissociation is performed accomplishing data protection directives and Health Insurance Portability and Accountability Act (HIPAA) standards. Microsoft (Microsoft, Redmond – WA, USA) services are the ones originally used for the architecture implementation due to the variety of services provided and the third party services available from its markets. Nevertheless, PRIMAGE will implement cloud services beyond Azure. The database technology is third party and non-SQL (MongoDB). The platform is programmed in NodeJS language and JavaScript was used for the front-end application with Angular as the main library.

Prospective data collection

The retrospective collection of data from SIOPE repositories is aimed at establishing the rules for the prospective collection. Such rules should consider the following.

- Definition of the appropriate prospective image acquisition modalities and protocols. In specific, which modality is appropriate and which standardized acquisition protocol should be used, in order to harmonize the data collected.
- Definition of the meaningful biomarkers that should be routinely extracted from the tumor and from the patient body regions, all compliant to a defined standard (tumor boundaries, number of sections, type of MR sequences and/or CT phases, etc)
- Definition of data to be stored and linked to other biomarkers.
- Definition of the level of anonymization and sharing (full or partial datasets, specific biomarkers, etc)

2.3 Link to other biorepositories

The data collected within the PRIMAGE project will be available for consultation to the scientific community. To allow the accessibility of the data, it will be necessary to organize them according to a standard format, compatible with the format through which the data of the biobanks are organized.

The ideal model to follow is that represented by the biobanks of the BBMRI network and so called “directory” (Fig 1).

The directory represents the starting point for the search for biological material through the network of biobanks that adhere to BBMRI. It is the tool for sharing aggregate information about the biobanks that are willing to cooperate externally.

The data contained in the banks are classified according to the type of material to be searched, the country where the biobank is located, the authority that certified the biobank, the type of collection (Case-Control, Disease specific, Image collection, Population-based, Rare disease collection, etc), the type of data collected (Biological samples, Genealogical records, Imaging data, Medical records, National registries, Physiological/Biochemical measurements, Survey data, etc). The directory also includes a precise map of biobanks connected by the BBMRI network (Fig.2). [9]

Imaging data are included as shown in Fig.3 (a screenshot of the imaging data)

The Directory also includes a collection of rare diseases biobanks (Fig. 4), in which the PRIMAGE databases could be included.

[9] Holub Petr, Swertz Morris, Reihs Robert, van Enckevort David, Müller Heimo, and Litton Jan-Eric. Biopreservation and Biobanking. December 2016, 14(6): 559-562. doi:10.1089/bio.2016.0088.

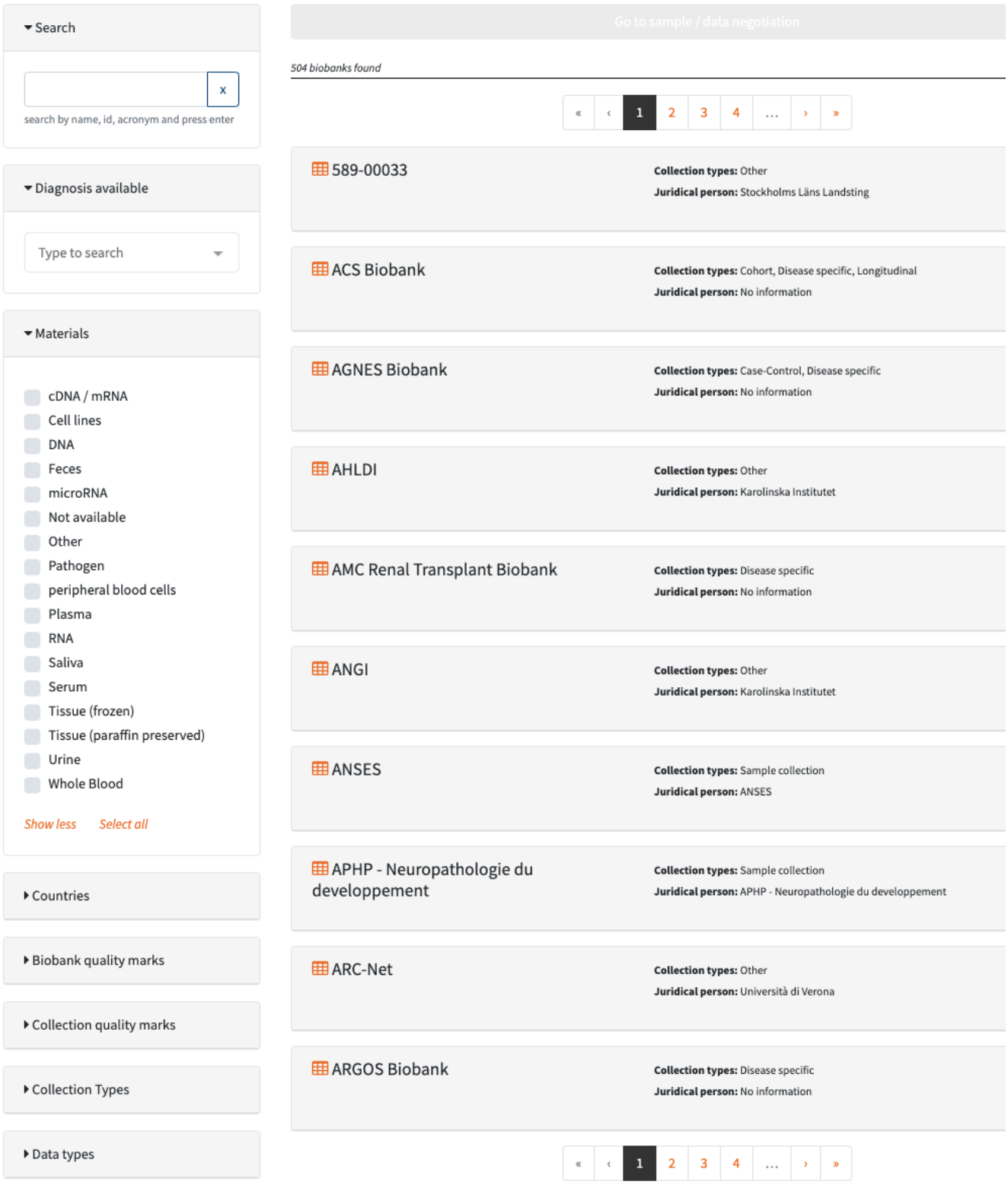

Figure 1. Screenshot of the homepage of the BBMRI directory

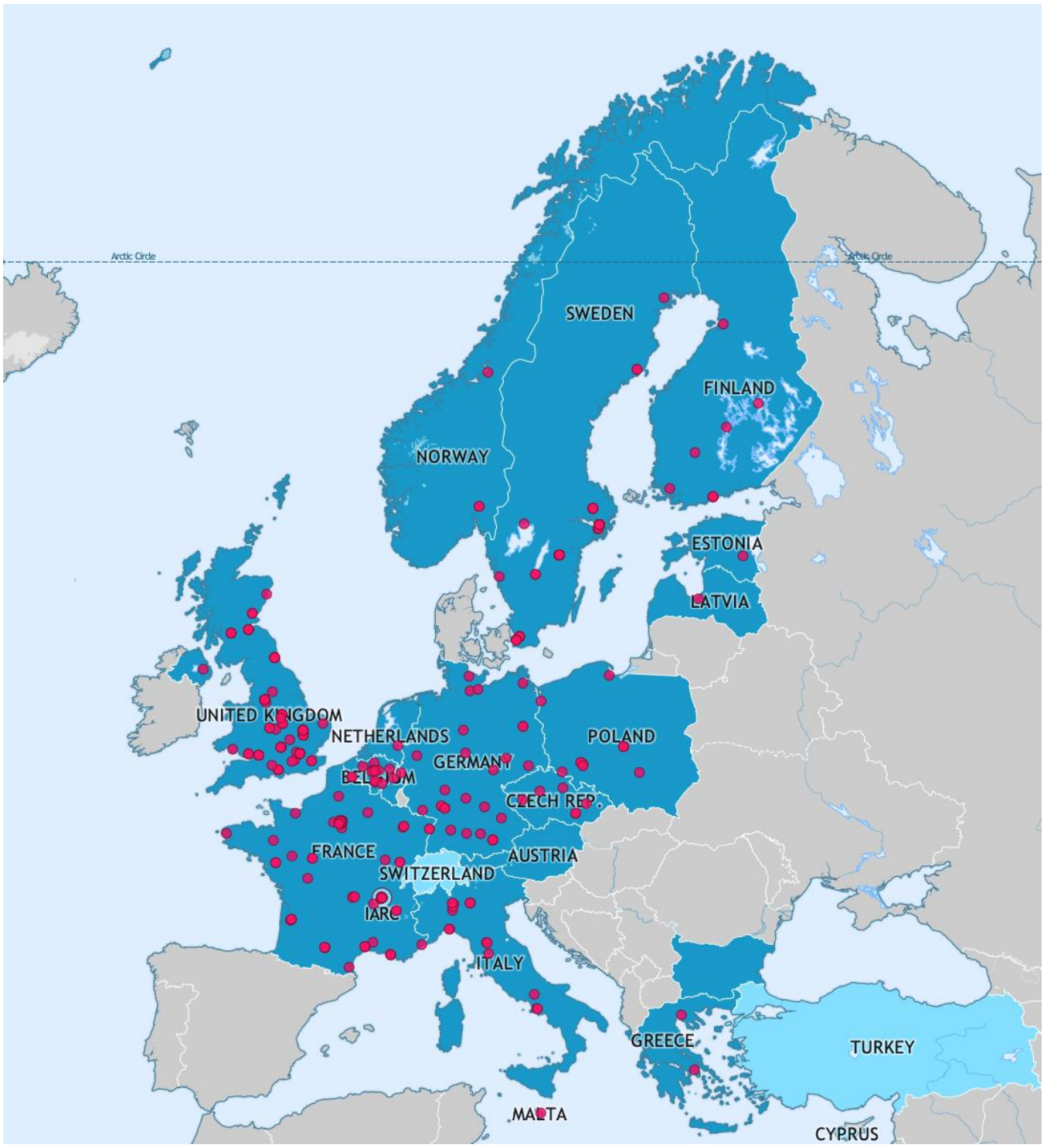

Figure 2. Map of BBMRI biobanks

Autorefraction	DICOM	An acquisition device, process or method that m...
Audio	DICOM	An acquisition device, process or method that r...
Bone Densitometry (ultrasound)	DICOM	An acquisition device, process or method that p...
Biomagnetic imaging	DICOM	An acquisition device, process or method that p...
Bone Densitometry (X-Ray)	DICOM	An acquisition device, process or method that p...
Computed Radiography	DICOM	An acquisition device, process or method that p...
Computed Tomography	DICOM	An acquisition device, process or method that p...
Diaphanography	DICOM	An acquisition device, process or method that p...
Digital Radiography	DICOM	An acquisition device, process or method that p...
Electrocardiography	DICOM	An acquisition device, process or method that p...
Cardiac Electrophysiology	DICOM	An acquisition device, process or method that p...
Endoscopy	DICOM	An acquisition device, process or method that r...
General Microscopy	DICOM	An acquisition device, process or method that p...
Hard Copy	DICOM	A device, process or method that creates images...
Hemodynamic Waveform	DICOM	An acquisition device, process or method that r...
Intra-Oral Radiography	DICOM	An acquisition device, process or method that p...
Intraocular Lens Data	DICOM	
Intravascular Optical Coherence Tomography	DICOM	An acquisition device, process or method that p...
Intravascular Ultrasound	DICOM	An acquisition device, process or method that p...
Keratometry	DICOM	An acquisition device, process or method that p...
Key Object Selection	DICOM	A device, process or method that creates Key Ob...
Lensometry	DICOM	An acquisition device, process or method that p...
Laser surface scan	DICOM	An acquisition device, process or method that p...
Mammography	DICOM	An acquisition device, process or method that p...
Magnetic Resonance	DICOM	An acquisition device, process or method that p...
Nuclear Medicine	DICOM	An acquisition device, process or method that p...
Ophthalmic Axial Measurements	DICOM	An acquisition device, process or method that m...
Optical Coherence Tomography (non-Ophthalmic)	DICOM	An acquisition device, process or method that u...
Ophthalmic Photography	DICOM	An acquisition device, process or method that p...
Ophthalmic Mapping	DICOM	An acquisition device, process or method that m...
Ophthalmic Tomography	DICOM	An acquisition device, process or method that p...
Ophthalmic Visual Field	DICOM	An acquisition device, process or method that m...
Optical Surface Scan	DICOM	An acquisition device, process or method that p...
Positron emission tomography (PET)	DICOM	An acquisition device, process or method that p...

Figure 3. A short list of the type of imaging data in DICOM format included in the Directory

Autorefraction	DICOM	An acquisition device, process or method that m...
Audio	DICOM	An acquisition device, process or method that r...
Bone Densitometry (ultrasound)	DICOM	An acquisition device, process or method that p...
Biomagnetic imaging	DICOM	An acquisition device, process or method that p...
Bone Densitometry (X-Ray)	DICOM	An acquisition device, process or method that p...
Computed Radiography	DICOM	An acquisition device, process or method that p...
Computed Tomography	DICOM	An acquisition device, process or method that p...
Diaphanography	DICOM	An acquisition device, process or method that p...
Digital Radiography	DICOM	An acquisition device, process or method that p...
Electrocardiography	DICOM	An acquisition device, process or method that p...
Cardiac Electrophysiology	DICOM	An acquisition device, process or method that p...
Endoscopy	DICOM	An acquisition device, process or method that r...
General Microscopy	DICOM	An acquisition device, process or method that p...
Hard Copy	DICOM	A device, process or method that creates images...
Hemodynamic Waveform	DICOM	An acquisition device, process or method that r...
Intra-Oral Radiography	DICOM	An acquisition device, process or method that p...
Intraocular Lens Data	DICOM	
Intravascular Optical Coherence Tomography	DICOM	An acquisition device, process or method that p...
Intravascular Ultrasound	DICOM	An acquisition device, process or method that p...
Keratometry	DICOM	An acquisition device, process or method that p...
Key Object Selection	DICOM	A device, process or method that creates Key Ob...
Lensometry	DICOM	An acquisition device, process or method that p...
Laser surface scan	DICOM	An acquisition device, process or method that p...
Mammography	DICOM	An acquisition device, process or method that p...
Magnetic Resonance	DICOM	An acquisition device, process or method that p...
Nuclear Medicine	DICOM	An acquisition device, process or method that p...
Ophthalmic Axial Measurements	DICOM	An acquisition device, process or method that m...
Optical Coherence Tomography (non-Ophthalmic)	DICOM	An acquisition device, process or method that u...
Ophthalmic Photography	DICOM	An acquisition device, process or method that p...
Ophthalmic Mapping	DICOM	An acquisition device, process or method that m...
Ophthalmic Tomography	DICOM	An acquisition device, process or method that p...
Ophthalmic Visual Field	DICOM	An acquisition device, process or method that m...
Optical Surface Scan	DICOM	An acquisition device, process or method that p...
Positron emission tomography (PET)	DICOM	An acquisition device, process or method that p...

Figure 4. Screenshot of the list of rare diseases biobanks

3. CONCLUSION

The ultimate goal of the data management plan is to link the PRIMAGE repository with the existing biobanks network (BBMRI). To reach this goal the data must be in a structured and standard format that allows to link imaging biomarkers with other biomarkers and metadata included in the biobanks.

The link to BBMRI will be strategic to open the PRIMAGE biobanks to the scientific community; PRIMAGE will be visible and searchable through the biobanks network and exploitable by the scientific community for further research purposes.

ANNEX 1: First draft of the Data to include in PRIMAGE Platform

Neuroblastic tumors

Patient data

- Date of birth
- Sex
- Nationality
- Race
- Hospital principal

Diagnosis

- Date (date of biopsy)
- Age at diagnosis que la calcule el programa

Associated symptoms at diagnosis

- LTS (life threatening symptoms)
    - Start date
    - Intraspinal neuroblastoma (yes/no)
    - Pain requiring opiate treatment (yes/no)
    - Vomiting needing nasogastric/IV support (yes/no)
    - Weight loss >10% body weight (yes/no)
    - Respiratory distress without evidence of infection (yes/no)
    - Hypertension (yes/no)
    - IVC compression ± leg oedema (yes/no)
    - Creatinine > 2x ULN1 (yes/no)
    - Urine output < 2mls/kg/day (yes/no)
    - Hydroureter/ hydronephrosis (yes/no)
    - Abnormal liver function > 2x ULN1 (yes/no)
    - Evidence of DIC (yes/no)
    - Platelets < 50 x109/L (yes/no)
    - Bladder/Bowel dysfunction secondary to mass effect (yes/no)
    - Very large tumour volume causing concern of possible tumour rupture and/or the possible rapid development of systemic upset (yes/no)

- Spinal cord syndrome (yes/no)
- OMS (opsoclonus-myoclonus syndrome) (yes/no)
- NF (yes/no)
- Genetic syndrome (yes/no) which

Tests

Lab (hospital/máquina-técnica)

- LDH (done/not done)
    - Upper normal value (at local site) IU/L
    - LDH result IU/L
- NSE (done/not done)
    - Upper normal value (NSE) ng/ml or microg or IU/l (standar europeo)
    - Results (NSE) ng/ml or microg or IU/l
- Ferritin (done/not done)
    - Upper normal value (ferritin) microg or IU/l
    - Results (ferritin) microg or IU/l
- Catecolamines
    - Urinary VMA (done/not done)
        - Upper normal value (VMA) µmol/mmol creat
        - Results (VMA) µmol/mmol creat
    - Urinary HVA (done/not done)
        - Upper normal value (HVA) µmol/mmol creat
        - Results (HVA) µmol/mmol creat
    - Urinary Dopamine
        - Upper normal value (dopamine) nanomol/mmol creat
        - Results (dopamine) nanomol/mmol creat

Imaging

Radiology

- MRI
  Yes/no
  Equipo (teslas y Vendor)
  (thorax, abdomen, pelvis, craneal, facial, axial, others?)
  Date
  Contrast (yes/no//which)
- CT
  Yes/no
  Equipo (rows y Vendor)
  (thorax, abdomen, pelvis, craneal, facial, axial, others?
  Date
  Contrast (yes/no//which)

IDRF (Image defined risk factors)

- Ipsilateral tumour extension within:
    - Neck-chest (yes/no)
    - Chest-abdomen (yes/no)
    - Abdomen-pelvis (yes/no)
- Neck (yes/no)
    - Tumour encasing carotid and/or vertebral artery and/or internal jugular vein (yes/no)
    - Tumour extending to base of skull (yes/no)
    - Tumour compressing the trachea (yes/no)

- Cervico-thoracic junction (yes/no)
  - Tumour encasing brachial plexus roots (yes/no)
  - Tumour encasing subclavian vessels and/or vertebral and/or carotid artery (yes/no)
  - Tumour compressing the trachea (yes/no)
- Thorax
  - Tumour encasing the aorta and/or major branches (yes/no)
  - Tumour compressing the trachea and/or principal bronchi (yes/no)
  - Lower mediastinal tumour, infiltrating the costo-vertebral junction T9 and T12 (yes/no)
- Thoraco-abdominal
  - Tumour encasing the aorta and/or vena cava (yes/no)
- Abdomen/Pelvis
  - Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament (yes/no)
  - Tumour encasing branches of the superior mesenteric artery at the mesenteric root (yes/no)
  - Tumour encasing the origin of the celiac axis and/or of the superior mesenteric artery (yes/no)
  - Tumour invading one or both renal pedicles (yes/no)
  - Tumour encasing the aorta and/or vena cava (yes/no)
  - Tumour encasing the iliac vessels (yes/no)
  - Pelvic tumour crossing the sciatic notch* ( ) yes
- Intraspinal tumour extension whatever the location provided that:
  - More than 1/3 of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal (yes/no)
- Infiltration of adjacent organs/structures
  - Pericardium, diaphragm, kidney, liver, duodenopancreatic block and mesentery (yes/no)
- Conditions to be recorded but not considered IDRFs
  - Multifocal primary tumours (yes/no)
  - Pleural effusion (with or without malignant cells) (yes/no)
  - Ascites (with or without malignant cells) (yes/no)
- Conclusion of the surgeon (a surgical procedure will be performed or not)

- Yes/no (autocalculable)

Nuclear medicine

- MIBG entire body
  Yes/no
  Técnica (SPECT, planar)
  Equipo (vendor)
  Dose (mCu, time)
  Date
  Positive/negative
  Location (primary site/metastasis/ambas)
  Score SIOPEN (description y criteria)
- PET/CT entire body

Yes/no
Equipo (Vendor)
Date
FDG-18F (administred dose)
Positive/negative
Location (primary site/metastasis/ambas)

Pathology tumor

- Date
- Laboratory
- Type of sample (biopsy primary tumor/metastasis)
- Histology type (INPC)
    - neuroblastoma, ganglioneuroblastoma, ganglioneuroma
    - grade of differentiation
- MKI (high/intermediate/low/not valuable/not done)

Molecular studies

- Laboratory
- Status N-MYC
    - Amplified (yes/no)
    - Gain? (yes/no)
    - Method: FISH/PCR/SOUTHERN
- Status genes: NAG, DDX1, ALK (amplified or not)
- Ploidy (diploid, tetraploid)
- Numerical chromosomal alterations (NCA)
- Segmental chromosomal alterations (SCA) (-1p, +1q, +2p, -3p, -4p, +11p, -11q, +17q, others)
- Mutation: ALK
- Metabolomics profile (response)
- Pharmacogenetics (response)

- Expression of TrkA, B o C
    - Low expression of A and C
    - High expression of B
- Mutation ATRX
- TERT traslocation
- Telomerase?
  Overexpression of the gene and increase in enzime activity
- Metabolomics profile (retrospectivo)
- Pharmacogenetics
  polymorphisms on genes (germinal NGS data): VDR, MTHFR, ABCC1, NR1/2, ABCB1, XRCC1, ABCC2

Pathology bone marrow

- Done/Not done
- Not valuable
- Date
- Laboratory
- Aspirate (yes/no, positive/negative)
- Trephine biopsy (yes/no, positive/negative)
- MRD
  - Not done
  - Bone marrow
    - number (TH/DCX/PHOX2B//DCt-TH/Log-TH, DCt-PHOX2B/log-PHOX2B)

Biopsia líquida

MRD Peripheral blood

- number (TH/DCX/PHOX2B//DCt-TH/Log-TH, DCt-PHOX2B/log-PHOX2B)

Autocalculable

Primary tumor site (abdomen → adrenal gland/pelvis/thorax/cervical/unkown/others)

Metastasis (bone, bone marrow, liver, lymph nodes, skin, lung, orbita, CNS, other?)

Staging

- INRGSS (AUTOCALCULABLE)
- INSS (criteria) (autocalculable)

First treatment

- Date of initiation
- Protocol (clinical trial or not)
  - Risk group (very low/low/intermediate/high) (autocalculable?)
  - LINES (group of treatment)

Treatment evaluation

- Very low patients (wait and see): date
- In low or intermediate patients:
  - Pre-surgery
    Date
    - After CO (yes/no and number of cycles)
    - After VP/Carbo (yes/no and number of cycles)
    - After CADO (yes/no and number of cycles)
  - At the end of treatment

Date

- In high risk patients:
  - After induction
  - Date
    - After N7
    - After Rapid COJEC
    - After TVD
  - At the end of treatment
    Date

Primary tumor response RECIST (Response Evaluation Criteria in Solid Tumors) (primary (soft tissue) site)

- Complete response
- Partial response
- Stable disease
- Progression

Metastasis response (SIOPEN MIBG score/RECIST) (bone, bone marrow/soft tissue)

- Complete response
- Partial response
- Stable disease
- Progression

Type of global response (INRC) (autocalculable)

- Complete response
- Partial response
- Minor response
- Stable disease
- Progression

<u>Progression</u>

- Yes/no
- Date
- Number
- Primary tumor/metastasis (which one)/primary tumor and metastasis (which ones)

<u>Current status</u>

- Alive/death
- Cause of death (espacio libre)
- Date of death
- Date of last visit

Inclusion criteria

NB

- Age under 21 years old
- Diagnosis of neuroblastoma by pathological anatomy or liquid biopsy
- In case of newborns with adrenal masses is required positivity of liquid biopsy or by MIBG image in the first three months of life
- Correct staging according to INRGSS
- Complete studies according to SIOPEN (NGS, FISH)

DIPG

- Age under 21 years old
- Diagnosis of DIPG by RM image

Exclusion criteria

- Patients without image studies at diagnosis or which are incomplete or with bad quality
- Chemotherapy received before the diagnosis
- Diagnosis finally not confirmed
- Patients with NF type 1?

Difuse intrinsic pontine glioma (DIPG)

Patient data (in parallel (excel) Name + SIP/CHN)

- Date of birth
- Sex
- Nationality
- Hospital

Diagnosis

- Date (image/biopsy)
- Image/Biopsy
- Age at diagnosis (categories: <3a, 3-10a, >10a) calculado de forma automática por el programa

Associated symptoms

- Pyramidal tract signs: mono-, hemi-, or quadriparesis; hyperreflexia; or positive Babinski sign
- Cerebellar signs: dysmetria, ataxia, dysarthria, or nystagmus.
- Cranial nerve palsy
- Duration (start date)
- KPS (Karnofsky scale)/Lansky scale

Tests

Lab

- CSF (yes/not done—why?)
    - Positive/negative

Radiology

- MRI
  Yes/not done—why?
  Cranial-axial (diffusion, perfusion, spectroscopy, tractography), others?)
  Date
  Contrast (yes/no)
    - Which contrast
- CT
  Yes/not done
  Cranial-axial
  Date
  Contrast (yes/no)
    - Which contrast

Pathology

- Date
- Type of sample (biopsy/surgery/autopsy)
- WHO Grade (low grade I-II/high grade III-IV)

Molecular studies

- Mutation BRAF-V600E? (glioblastoma)
- Mutation K27 in H3.3 (wild-type)
- Mutation H3.3
- Mutation H3.1
  Histones study: sanger sequencing (NGS), whole-exome sequencing (WES), or whole-genome sequencing (WGS), polymerase chain reaction (PCR), or immunohistochemistry (IHQ)
- Mutation HIST1H3B
- Mutation ACVR1
- Mutation TP53
- Amplification or mutation PDGFRA
- Gain in PARP-1
- Mutation PIK3CA
- 1q+, 17p-
- Amplification MET or IGF1R

Treatment

- Date
- Type (no treatment, surgery, RT, cytotoxic, corticoids, bevacizumab, tumor vaccines, target treatment)
- Clinical trial (yes/no)
    - Name

Evaluation (treatment response) RANO criteria

- Date

Image

- MRI (type? /cranial/cranial-axial?
    - Differentiation of pseudo-progression de progression?

Type of response

- Stable disease
- Progression
- Partial response
- Complete response

Progression

- Yes/no
- Date
- Symptoms

Lines of treatment

- Re-irradiation
- Corticoids
- ?

Current status

- Alive/death
- Date of death
- Cause of death (free space)
- Date of last visit

ANNEX 2: STAGING SYSTEM

International Neuroblastoma Risk Group Staging System (INRGSS)

The INRGSS was developed to help determine a child's stage and risk group before treatment has started. It has also helped researchers around the world compare results of studies to help figure out which treatments are the best. Before it was developed, researchers in different countries couldn't easily compare study results because of different staging systems. INRGSS uses imaging tests (usually a CT or MRI scan, and an MIBG scan), as well as exams and biopsies to help define the stage. The stage can then be used to help predict how resectable the tumor is – that is, how much of it can be removed with surgery.

The INRGSS uses image-defined risk factors (IDRFs), which are factors seen on imaging tests that might mean the tumor will be harder to remove. This includes things like the tumor growing into a nearby vital organ or growing around important blood vessels.

The INRGSS has 4 stages:

- L1: A tumor that has not spread from where it started and has not grown into vital structures as defined by the list of IDRFs. It is confined to one area of the body, such as the neck, chest, or abdomen.
- L2: A tumor that has not spread far from where it started (for example, it may have grown from the left side of the abdomen into the left side of the chest), but that has at least one IDRF.
- M: A tumor that has spread (metastasized) to a distant part of the body (except tumors that are stage MS).
- MS: Metastatic disease in children younger than 18 months with cancer spread only to skin, liver, and/or bone marrow. No more than 10% of marrow cells are cancerous, and an MIBG scan does not show spread to the bones and/or the bone marrow.