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Rare tumors and histologies : clinical management pathway

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Disclosures

- Travel expenses :
  - Pharmamar, Bayer, Pfizer, Ipsen

Definition “rare cancers”

- Classification :
  - primary tumor localization
  - histology
  - (gender)
- **Incidence <6/100.000 persons/year**
- Any threshold for “rarity” is artificial

RARECARENet
Information Network on Rare Cancers

R=rare	Tier	Tumour	Crude incidence rate per 100,000	95% confidence interval	
	1	EPITHELIAL TUMOURS OF OESOPHAGUS	7.81	7.77	7.85
R	2	Squamous cell carcinoma with variants of oesophagus	3.36	3.33	3.39
	3	Squamous carcinoma			
	3	Adenosquamous carcinoma			
	3	Squamous cell carcinoma spindle cell			
	3	Verrucous carcinoma			
	3	Papillary squamous cell carcinoma			
	3	Basaloid squamous cell carcinoma			
	3	Squamous cell carcinoma, adenoid			
R	2	Adenocarcinoma with variants of oesophagus	3.26	3.24	3.29
R	2	Salivary gland type tumours of oesophagus	0.004	0.003	0.005
	3	Mucoepidermoid carcinoma			
	3	Adenoid cystic carcinoma			
R	2	Undifferentiated carcinoma of oesophagus	0.04	0.04	0.05

Definition “rare cancers”

- Belgium : ~ 660 new diagnosis/year
- Incidence in Europe : 541.000 new diagnosis per year = 22%

Rare cancers are not so rare: The rare cancer burden in Europe

Gemma Gatta [a,], Jan Maarten van der Zwan [b], Paolo G. Casali [c], Sabine Siesling [b], Angelo Paolo Dei Tos [d], Ian Kunkler [e], Renée Otter [b], Lisa Licitra [f], Sandra Mallone [g], Andrea Tavilla [g], Annalisa Trama [a], Riccardo Capocaccia [g], The RARECARE working group*

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Gatta G et al., Eur J Cancer 2011;47:2493-2511

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Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study

= Data from 94 registres

- Incidence increases by 0.5% per year
- More frequent at younger age
- Relative survival at 5 years : 48.5% (vs. 63.4% for “common” cancers)
  - on average a worse relative survival of about **15%**
- Relative survival increased by 2.9% between 1999 and 2009

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Gatta G et al., Lancet Oncol. 2017;18:1022-39

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New definition?

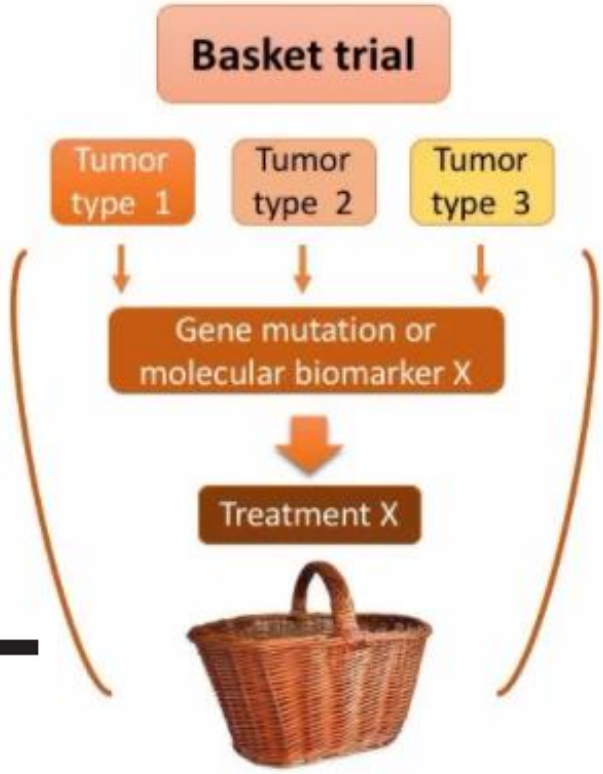
- The advent of massively parallel sequencing with molecular profiling techniques such as
  - whole-genome sequencing (WGS)
  - whole-exome sequencing (WES)
  - targeted gene sequencing (TGS)

  has revolutionized biomarker discovery through the concept of Precision Medicine

→ The more common cancers are now subtyped into rare segments

Tumor-agnostic approach

- Type of therapy that uses drugs
  - based on the tumors' genetic and molecular features
  - without regard to histologic type or localisation



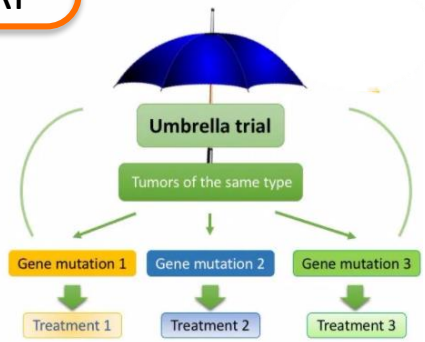
One drug fits all

Cancer drugs are usually approved for specific tumor types—breast, prostate, etc. But tissue-agnostic drugs can treat any tumor as long it has a specific molecular alteration. Here are some of those drugs under development.

DRUG	COMPANY	TARGETED MOLECULAR ALTERATION	STATUS
Pembrolizumab (Keytruda)	Merck	Mismatch repair deficiency	Approved 23 May
Larotrectenib (Loxo-101)	Loxo Oncology	TRK fusions	Phase II
Entrectenib	Ignyta	TRK, ALK, and ROS1 fusions	Phase II
Loxo-195	Loxo Oncology	Loxo-101 resistant TRK fusions	Phase I
Loxo-292*	Loxo Oncology	RET fusions and activating point mutations	Phase I
RXDX-105*	Ignyta	RET alterations	Phase I
TPX-0005	TP Therapeutics	TRK, ALK, and ROS1 fusions	Phase I/II
BLU-667*	Blueprint Medicines	RET alterations	Phase I/II

*Agnostic indication contingent on early trial data

MSI
NTRK
PARP



Difficulties

- Heterogeneous group of diseases, but similar problems:
  - late diagnosis
  - uncertainty of diagnosis
  - lack of expertise and reference centers
  - lack of therapies
  - lack of research opportunities
  - difficulties encountered in clinical trials

Difficulties

Consultative (Expert) Second Opinions in Soft Tissue Pathology

Analysis of Problem-Prone Diagnostic Situations

500 consecutive cases referred for second opinion

Agreement: 68%

Minor discrepancy: 7%

Major discrepancy: 25%

Only 2-3 cases / year for the general pathologist !

Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region

366 patients

Agreement: 54%

Partial agreement (grade or sub-type discrepancy): 27%

Major discrepancy: 19%

Major discrepancy = those that could lead to significant change in clinical management

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Arbiser ZK et al., Am J Clin Pathol. 2001 Oct;116(4):473-6.
Lurkin et al., BMC Cancer 2010 Apr 19, 10:150,

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Expertise and reference centers

BETTER OVERALL AND PROGRESSION FREE SURVIVAL AFTER SURGERY IN EXPERT SITES FOR SARCOMA PATIENTS: A NATIONWIDE STUDY OF FSG-GETO/NETSARC

CONCLUSIONS (1)

- Sarcoma patients operated in a reference center have
  - Worse prognostic factors
  - a significantly higher rate of management according to CPGs,
  - Higher rates of R0 surgery (lower of R2/R.unk)
  - less re-operations
  - better LRFS, RFS and OS in multivariate analysis.
- Management of sarcoma patients in reference centers improves patient outcome.

Should Soft Tissue Sarcomas Be Treated at High-volume Centers?

An Analysis of 4205 Patients

TABLE 7. Significant Independent and Treatment Variables for Patients Undergoing Surgical Resection for Soft Tissue Sarcoma by Multivariate Analysis

Independent and Treatment Variables	*P*	Relative Risk	95% Confidence Interval
High-grade	<0.001	2.521	1.921–3.307
Size >10 cm	0.004	1.443	1.127–1.847
Trunk or retroperitoneal location	<0.001	1.572	1.228–2.014
Low-volume center	0.047	1.292	1.003–1.663

On multivariate analysis, treatment at a HVC was a significant independent predictor of improved survival

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Blay JY, presentation at ESMO 2017
Gutierrez et al., Ann Surg. 2007 Jun;245(6):952-8.

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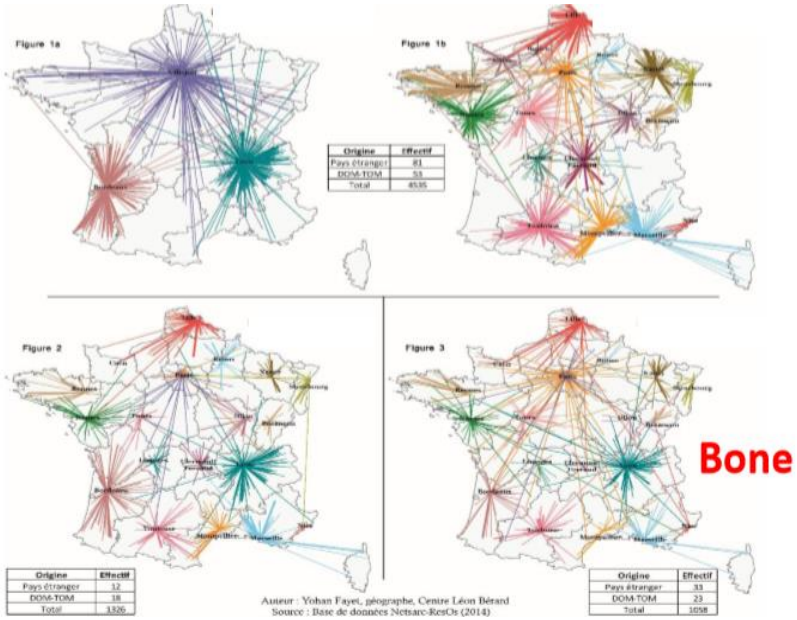
Networks - referral

Soft tissue



Visceral

Bone

NetSARC - France

ENETS Centers of Excellence

European ENETS CoE Neuroendocrine Tumor Society

Assuring Quality since 2009

TUTHYREF

TUMEURS THYROÏDIENNES REFRACTAIRES.

COMETE Cancers de la surrénale

Réseau Expert National

COMETE-Cancers de la surrénale

(Corticosurrénalomes-Phéo/PGLs malins)

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Networks

The first 24 ERNs were launched in 2017, involving more than 900 highly-specialised healthcare units from over 300 hospitals in 26 Member States.

ERN BOND	European Reference Network on bone disorders (Factsheet - Website)
ERN CRANIO	European Reference Network on craniofacial anomalies and ear, nose and throat (ENT) disorders (Factsheet - Website)
Endo-ERN	European Reference Network on endocrine conditions (Factsheet - Website)
ERN EpiCARE	European Reference Network on epilepsies (Factsheet - Website)
ERKNet	European Reference Network on kidney diseases (Factsheet - Website)
ERN-RND	European Reference Network on neurological diseases (Factsheet - Website)
ERNICA	European Reference Network on inherited and congenital anomalies (Factsheet - Website)
ERN LUNG	European Reference Network on respiratory diseases (Factsheet - Website)
ERN Skin	European Reference Network on skin disorders (Factsheet - Website)
ERN EURACAN	European Reference Network on adult cancers (solid tumours) (Factsheet - Website)
ERN EuroBloodNet	European Reference Network on haematological diseases (Factsheet - Website)
ERN eUROGEN	European Reference Network on urogenital diseases and conditions (Factsheet - Website)

ERN EURO-NMD	European Reference Network on neuromuscular diseases (Factsheet - Website)
ERN EYE	European Reference Network on eye diseases (Factsheet - Website)
ERN GENTURIS	European Reference Network on genetic tumour risk syndromes (Factsheet - Website)
ERN GUARD-HEART	European Reference Network on diseases of the heart (Factsheet - Website)
ERN ITHACA	European Reference Network on congenital malformations and rare intellectual disability (Factsheet - Website)
MetabERN	European Reference Network on hereditary metabolic disorders (Factsheet - Website)
ERN PaedCan	European Reference Network on paediatric cancer (haemato-oncology) (Factsheet - Website)
ERN RARE-LIVER	European Reference Network on hepatological diseases (Factsheet - Website)
ERN ReCONNET	European Reference Network on connective tissue and musculoskeletal diseases (Factsheet - Website)
ERN RITA	European Reference Network on immunodeficiency, autoinflammatory and autoimmune diseases (Factsheet - Website)
ERN TRANSPLANT-CHILD	European Reference Network on Transplantation in Children (Factsheet - Website)
VASCERN	European Reference Network on Rare Multisystemic Vascular Diseases (Factsheet - Website)

Euracan Project

Funded by the Health Programme of the European Union

European Reference Networks

EURACAN

European Reference Network

for rare or low prevalence complex diseases

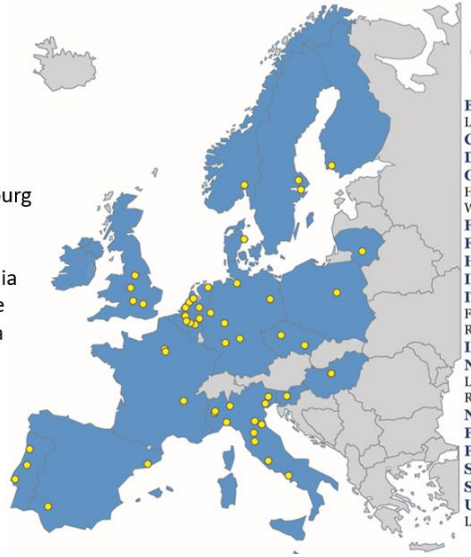
Network Adult Cancers (ERN EURACAN)

SIOPE INCA EORTC EBO OECI ESTRO ESMO esso ecco EURORDIS IBTA Melanoma Patient Network Europe Sarcoma Patients EuroNet

RARE SOLID ADULT CANCERS

DISTRIBUTION OF EURACAN MEMBERS BY COUNTRY

Missing
Spain
Luxemburg
Austria
Croatia
Slovaquia
Lettonie
Bulgaria
Greece
Cyprus



Countries (organizations) participants to EURACAN

BELGIUM (Antwerp, Brussels, Leuven, Liège)
CZECH REPUBLIC (Brno, Prague)
DENMARK (Aarhus)
GERMANY (Berlin, Essen, Mannheim, Hamburg –Eppendorf, Marburg, Würzburg)
FINLAND (Turku)
FRANCE (Lyon, Paris, Villejuif)
HUNGARY (Budapest)
IRELAND (Dublin)
ITALY (Aviano, Bologna, Candiolo, Firenze, Genoa, Meldola, Milan, Naples, Roma, Siena, Torino, Treviso)
LITHUANIA (Kaunas)
NETHERLANDS (Amsterdam, Leiden, Maastricht, Nijmegen, Rotterdam, Gronigen)
NORWAY (Oslo)
POLAND (Warsaw)
PORTUGAL (Coimbra, Lisboa, Porto)
SWEDEN (Karolinska, Uppsala)
SLOVENIA (Ljubljana)
UNITED KINGDOM (Conventry, London, Oxford, Sheffield)

Kick-off meeting Lyon 21-22 april 2017

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EuroBloodNet Project

EuroBloodNet

European Reference Network in Rare Hematological Diseases

Amyloidosis
Atypical lymphoproliferative disorders
Pro-myelocytic leukemia
Acute myeloid leukemia

European Reference Networks

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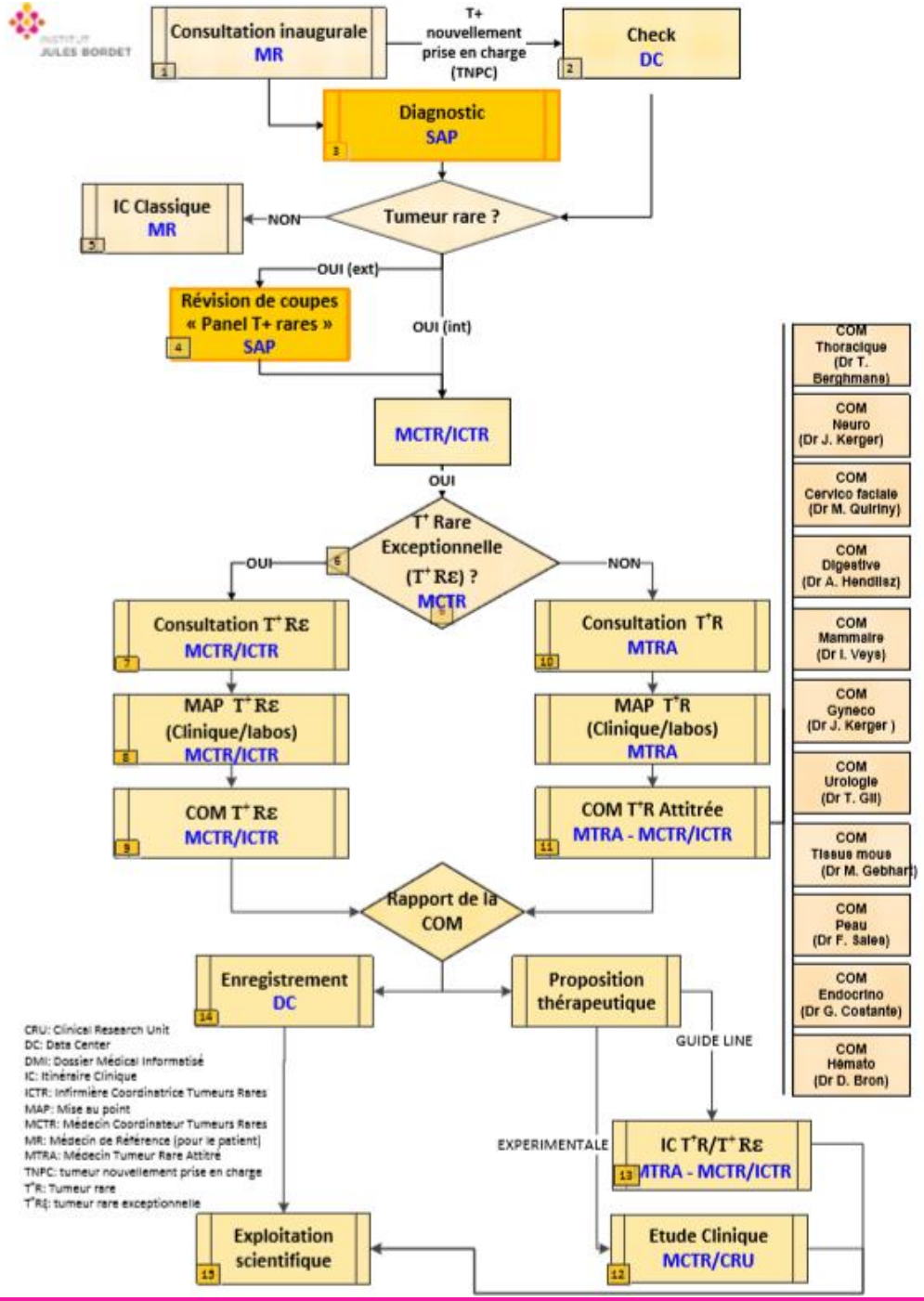
In summary

- Inform the public
- Raise awareness among general practitioners
- Second opinions
- Pathologic review
- Multidisciplinary approach
- Networks !
- **Optimize pathways for those patients !**



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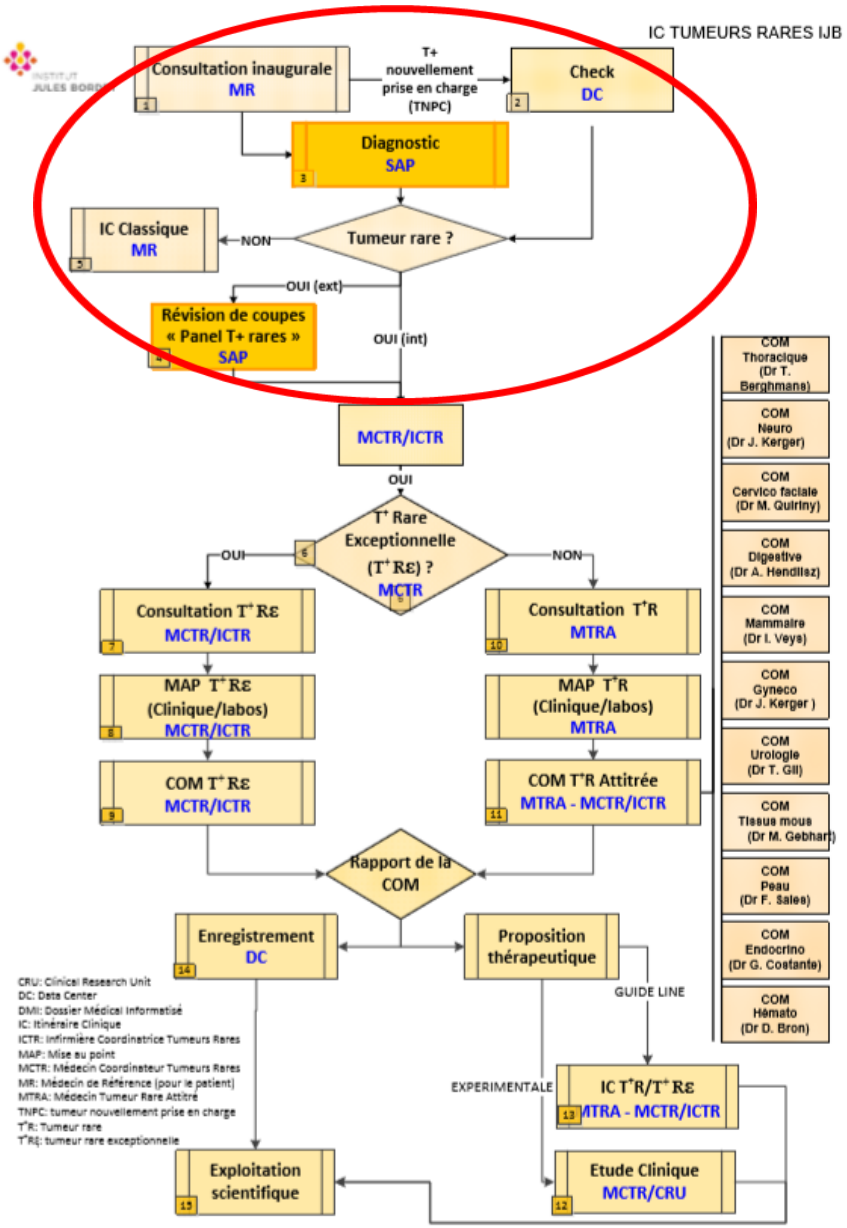
Early detection of rare tumors



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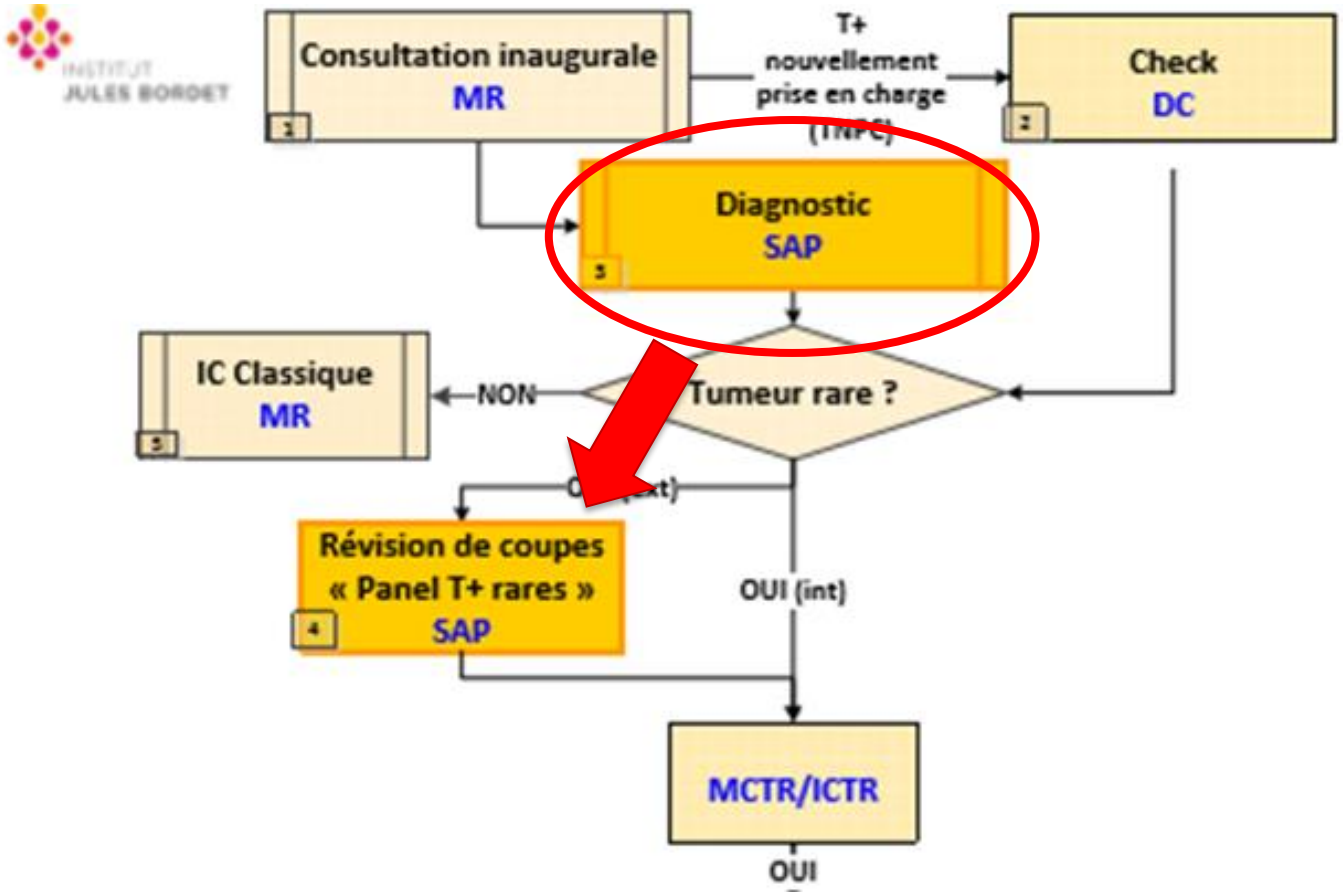
Pathology of rare tumors



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MOLECULAR PROFILING OF TUMORS OF RARE INCIDENCE AND TUMORS OF OUTLIER PATIENTS

MAP-rare

Prospective part

- Characterize the molecular landscape of rare solid tumors

- Find potential “actionable” mutations that could possibly render them eligible for downstream clinical trials
- Discover new predictive or prognostic biomarkers
- Establish a “rare cancer” Biobank

Retrospective part

- Adenoid cystic carcinoma
- Hemangiopericytoma
- Non clear-cell renal cell carcinoma
- Merkel carcinoma
- Ethmoidal carcinoma
- Granulosa cell tumor
- Myoepithelial carcinoma
- Pheochromocytoma / paraganglioma
- Squamous cell carcinoma of the bladder
- Neuroendocrine prostate cancer
- Anal canal cancer
- Thymoma / thymic carcinoma
- Small bowel carcinoma

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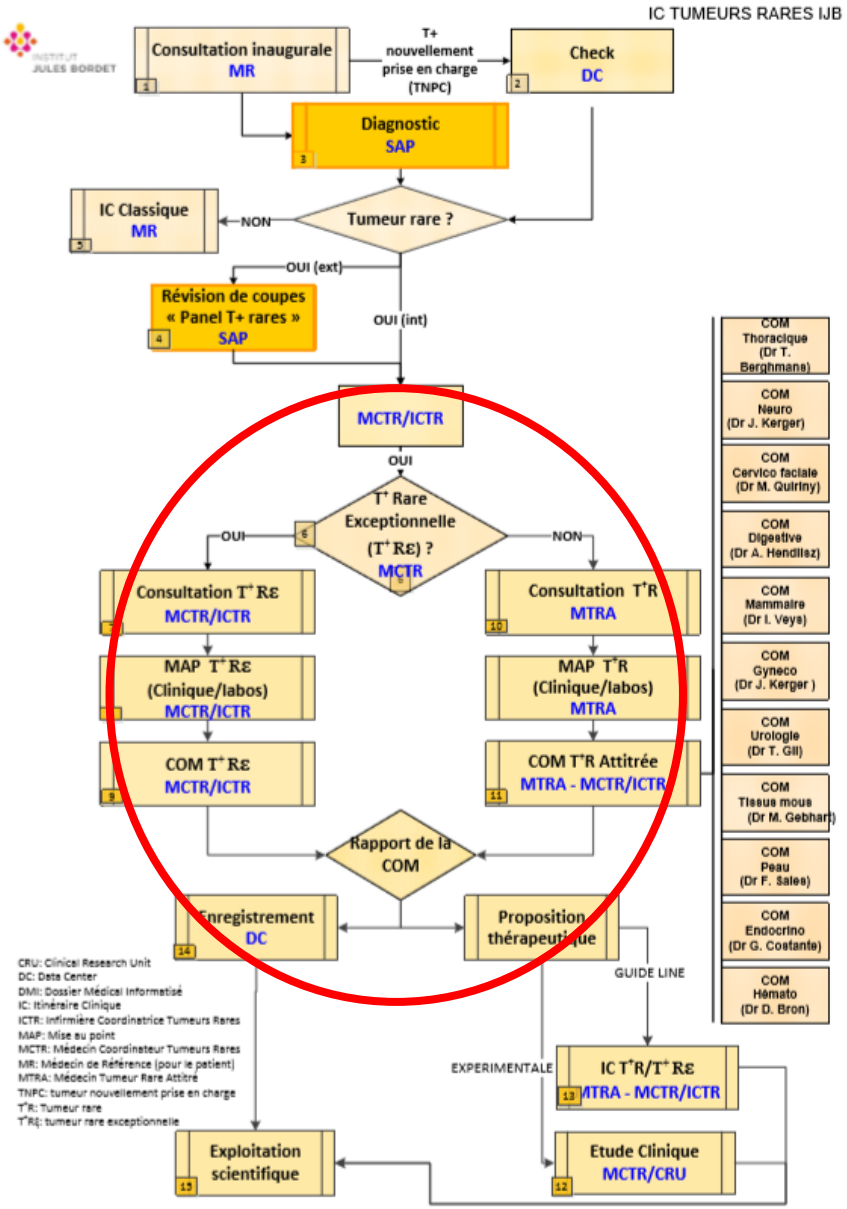
Multidisciplinary boards



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Difficulties

- Heterogeneous group of diseases, but similar problems:
  - late diagnosis
  - uncertainty of diagnosis
  - lack of expertise and reference centers
  - lack of therapies
  - lack of research opportunities
  - difficulties encountered in clinical trials

Difficulties

- Limited number of patients
  - Inability to perform phase 3 studies
  - Impossibility / difficulty of publishing clear guidelines
  - Impossibility / difficulty of reaching an approval for treatments
  - Need to use MNP programs

- Lack of interest from pharmaceutical companies

Solutions

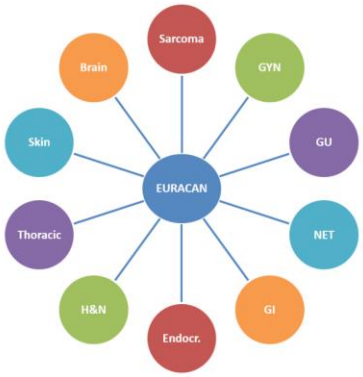
- Centers of excellence for rare cancers or rare cancer groups
  - organizational structure
  - critical mass

  needed to
  - propose appropriate treatment
  - conduct clinical trials
  - develop alternative approaches

- National and international collaborations

National and international collaborations

BSMO



EURACAN

European network for
Rare adult solid Cancer

ONCODISTINCT NETWORK

EORTC

The future of cancer therapy

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National and international collaborations

Task Forces

▪ Breast Cancer task force:	Ahmad Awada	(ahmad.awada@bordet.be)
▪ BSMO trials group:	Michail Ignatiadis	(michail.ignatiadis@bordet.be)
▪ Cancer Survivorship:	Christine Langenaeken	(christine.Langenaeken@klina.be)
▪ Supportive Care	Jean Klasterky	(jean.klastersky@bordet.be)
	Christel Fontaine	(christel.fontaine@uzbrussel.be)
▪ Geriatric Oncology:	Hans Wildiers	(hans.wildiers@uzleuven.be)
▪ Rare cancers:	Christiane Jungels	(christiane.jungels@bordet.be)
▪ Quality task force:	Didier Verhoeven	(didier.verhoeven@klina.be)
▪ Hereditary Cancer Syndromes:	Kevin Punie	(kevin.punie@uzleuven.be)
▪ Melanoma	Annemie Rutten	(annemie.rutten@gza.be)
▪ Sarcoma:	Christine Gennigens	(christine.gennigens@chuliege.be)
▪ Thyroid cancer task force:	Lore Decoster	(lore.decoster@uzbrussel.be)
▪ Uro-oncology (BMUC)	Sylvie Rottey	(Sylvie.rottey@uzgent.be)

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National and international collaborations

Rare cancers:

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▪ Uro-oncology (BMUC)	Sylvie Rottey	(Sylvie.rottey@uzgent.be)

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National and international collaborations

Rare cancers:

Christiane Jungels

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- Aims :
  - Optimize pathways
  - Optimize research
  - Education

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Symposium on rare tumors / rare histologies / tumor agnostic therapies

Program

1. What is the definition of a rare tumor / histology? What should be the route of the patient with a rare tumor / histology?
2. Tumor agnostic approaches: a new entity
3. What are the challenges for the pathologist?
4. What place for molecular biology? What is the role of tumor sequencing?
5. How to improve clinical research and study designs for these clinical entities?
6. What place for nuclear medicine and radio-oncology in the management of rare tumors / histologies ?
7. What place for
    a. Targeted treatments?
    b. Immunotherapy
    c. Antibody drug conjugates?
8. Partnership in the management of rare tumor/histology and tumor agnostic approaches:
    a. Pharma
    b. Health-economic issue
    c. Regulator

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Thank you for your attention