COHORT INNOVATION DAY

Academic book

October 3, 2018

aviesan
alliance nationale
pour les sciences de la vie et de la santé
ITMO Santé publique

www.cohortinnovationday.com

Credits:
Scientific Direction : Aviesan ITMO Santé publique
Editorial and Scientific conception : Inserm Transfert
Design and layout : Inserm Transfert

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INTRODUCTION

Aviesan (Alliance for Life Sciences and Health) and ARIIS (Alliance for Research and Innovation in Health Industries) have joined forces for the third time to set-up this Cohort Innovation Day (CID - October 3, 2018), with the spirit of fostering and promoting public / private collaborations around existing high potential epidemiological and translational research platforms.

Over the last 10 years France has substantially invested for the funding and set-up of several large high-quality epidemiological cohorts and associated biobanks, with the goal to develop a large national research infrastructure, often in connection with similar European networks. In the recent past, legislative changes have led to better opportunity for researchers to link these cohort databases with the National Health Data System (SNDS, social security database covering all the French population from cradle to grave). Combining the strength of highly precise phenotypic, biologic and genomic data from volunteers enrolled in the cohort with the extensive life course follow-up and health services consumption of individuals provides new and promising avenues for medical and public health research.

In March 2018, following the Villani report "Giving meaning to artificial intelligence: for a national and European strategy", the President of the Republic, Emmanuel Macron, announced a €1.5 billion investment plan to support the development of artificial intelligence in France, and notably in the health sector. Furthermore, he announced the creation of a Health Data Hub, a common national infrastructure where clinical, biological and genomic data generated in the hospitals, data produced in the context of research (including cohorts), as well as data participating in the enrichment of the national health data system (SNDS) will be organized in a coherent data warehouse. In turn, this national Health Data Hub will be used as a resource to accelerate research, taking advantages of massive data, development of algorithms, and artificial intelligence, with the aim to improve health of the population.

In this context, the CID 2018 will make a particular focus on the potential of exploiting large cohorts with new methods and approaches in the area of artificial intelligence, massive data, connected objects and e-health.

In the program of this Cohort Innovation Day, 15 cohorts have been rigorously selected based on a number of criteria, including scientific excellence, competitive positioning, unique differentiating features, extent and quality of the database, associated features (i.e., biobanks using state-of-the-art technology, imaging data, etc…), scientific leadership and track-record of the cohort leadership team. All these cohorts have a strong potential for public-private partnership with industrial partners. Potential collaborations may be of various types, and can encompass all aspects of the value chain:

- from early research (including patho-physiology, generation of new hypotheses, development or validation of biomarkers, disease-models, translational research)
- to clinical development (including implementation of nested trials or ancillary studies, patients segmentation, identification of target population, development and validation of study endpoints, patients-related outcomes, access to well-characterized and annotated biological samples and/or imaging data)
- and « real-life » studies (including pharmaco-epidemiological surveys, social, behavioural and economic studies, QoL studies, benefit/risk assessment, long-term follow-up, etc…).

Cohorts on the program include disease-specific cohorts in several important therapeutic areas, as well as population-based cohorts, both in adults or children.

There are many challenges ahead. By continuing to bring together the academic scientific strengths of our research teams, who are involved in the design and set-up of these cohorts and associated research and biobanks platforms, with the skills, outcome orientation and capabilities of Health Industry partners, we make our efforts for innovation and population health a reality.

Pr. Corinne Alberti
Director, Aviesan Institute for Public Health

BACAP:

Biological and Clinical database on Adenocarcinoma Pancreatic Cancer

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http://www.chu-toulouse.fr/-projet-bacap-

OVERVIEW

AT A GLANCE

> **Oncology**
> **Pancreatic** cancer
> Coordinated by Pr. B. BOURNET and managed by C. CANIVET
> Toulouse University Hospital sponsorship
> Funded by INCa
> **Key words** : Cancer – Pancreas – Biobanking – Tumor Banking - Clinical data

KEY FACTS & FIGURES

> Status : inclusion starts the 15th of May 2014
> **1000 patients** already enrolled
> 250-300 patients enrolled per year
> At least **4 years follow-up**
> National multicenter cohort with **15 open centers** (CHU, CH and private clinics)
> **Biobank**: tumor, blood, serum, plasma, saliva, DNA and RNA from tumors cells

The aim of BACAP is to deliver to the scientific community the rare biological material and clinical data on patients with pancreatic cancer.

Positioning

> To date, **it doesn't exist other similar cohort** in France collecting so widely clinical, biological and tumor data on pancreatic cancer
> The BACAP cohort aims to be opened to scientific community at European and International levels for academic as well as industrial researchers
> BACAP has approached an **European Biobank**
> BACAP is **opened to set up new partnerships with industrials**

LEADERSHIP

BACAP's leadership team is composed of renown clinicians, surgeons and epidemiologists, involved in this disease area since 15 years.

Pr Barbara BOURNET ***Gastroenterologist, MD, PhD, Toulouse University Hospital***

- 15 years experience in the field of pancreatic disease and more specifically in pancreatic cancer. Investigator associate of a gene therapy clinical trial in pancreatic cancer
- Participation or elaboration of many cohorts in pancreatic disease such as Intra Papillary Mucinous Neoplasms in pancreas (IPMN), chronic and acute pancreatitis
- Relevant experience in translational cancer biomarkers for diagnostic or chemosensibilization research projects

Dr. Cindy Canivet, ***PhD in immunology, Project manager of the BACAP cohort***

- Relevant experience in clinical research, project coordination and management, in immunology, neurology, gastro-enterology and oncology
- Relevant experience in project development (research protocol, case report form, inform consent writing), regulatory support, help obtaining funding
- Relevant experience in basic science as immunologist

SCIENTIFIC NETWORK & MANAGEMENT

NETWORK MANAGEMENT

- Coordination committee is composed of:
  - The **coordinator of the BACAP** project: B. Bournet
  - The **project manager**: C.Canivet
  - A representative member of the **Toulouse University Hospital**
- Steering committee is composed of the principal investigator from each of the 15 centers participating to the study

SCIENTIFIC MANAGEMENT

- Each research project is evaluated by the **Scientific Committee**
- The Scientific Committee is composed of **experts in pancreatic cancer** but not only. This committee notably ensures the **scientific project review.**
- Each Scientific committee member has been elected by the BACAP's partners
- The Scientific committee is currently composed of a gastroenterologist, an oncologist, a digestive surgeon, a pathologist, a researcher, an epidemiologist, a Biological Resources Center manager, a Data Treatment Center manager
- The **project request form is available** on BACAP website and the Scientific Committee uses an evaluation grid to assess the scientific quality, the operative and technical feasibility of the project

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Primary objectives
  - > Make available to the scientific community **a clinical biological base** from patients with pancreatic adenocarcinoma
  - > Understand the **development** of pancreatic carcinogenesis
  - > Determine an **early diagnosis** and screening of pancreatic adenocarcinoma with the **identification of biomarkers** (Proteomic signatures, miRNA, genomic DNA, micro particles) and **associated thrombosis risks**
- Secondary objectives
  - > Develop new **in vitro tools** for pancreatic cancer diagnostic
  - > Evaluate **clinical and biological development of cachexia** from patients with pancreatic cancer
  - > Determinate **factors inducing cancer cells spreading** such as inflammation markers
  - > Identify **biomarkers indicating sensibility or resistance to chemotherapy**
  - > Develop **new therapeutic targets**

INNOVATIVE SCIENTIFIC FEATURES

- **Nationally representative** sample of pancreatic cancers
- Will provide an **unbiased view** of routine pancreatic cancer care in a wide variety of settings while collecting standardized data
- The **BACAP research platform** can be used for ancillary studies and innovative projects

GENOMICS

- BACAP has begun to establish **the methylome and the RNAseq** of a part of the collected samples. These data will be associated to the current database by the datacenter of Montpellier.
- The project is funded in partnership with “La ligue contre le Cancer”. This first part aims to **compare the methylome and RNAseq** of patient **according to the stage of the disease at the diagnosis and survival.** This work is under development.

METHODOLOGY QUALITY

- The **BACAP database is approved** by both the participating BRCs and the Data treatment Center
- The database is managed by the Institut Régional du Cancer de Montpellier
- Integrated **consistency checking of data**
- **Procedures for data entry** including those related to biological samples into the BACAP centralized database

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	Patients with pancreatic cancers
Sites:	15 centers participating (CHU, CH and private clinics)
Inclusion criteria:	Patients with adenocarcinoma specifically located in the pancreas regardless the stage considered (resectable, locally advanced or metastatic) and virgin of any chemotherapy treatment for the pancreas
Exclusion criteria:	Patients with previous chemotherapy treatment for the pancreas

INCLUSION

Database:
Demographic, risk factors linked to PDAC, clinic, biologic, therapeutic, imagery data and family history data

Biobank:
Tumor, blood, serum, plasma, saliva, DNA and RNA from tumors cells

FOLLOW-UP : every 3 months or at each medical, clinical or imagery re-assessment of the patient

Database:
Biologic, therapeutic, imagery data, survival data and date of death

DATABASE & BIOBANK CONTENTS

DATABASE

- From patient questionnaire:
  - **Demographic**: Year of birth, gender, school level, job
  - **Risk factors linked to PDAC**: Alcohol and tobacco consumption, MTEV risks, family cancer
  - **Clinic**: Weight evolution, height, WHO performance status, medical co-morbidities, past history of other cancer, date of first symptoms/description, diagnostic data, tumor information
  - **Family history data**
- From medical exam:
  - **Imagery**: TDM, Echo-endoscopy, IRM, PET-SCAN, for each exam details about tumor localization, expansion, ganglia, metastasis are collected (at the diagnosis and follow-up)
  - **Biologic**: Full biologic analysis, CA19.9
  - **Therapeutic**: Medical, surgical, radiotherapeutic, palliative strategies with evaluation of response and tolerance of the treatment
  - **Survival data**
  - **Date of death**

BIOBANK

- **Originality**
  - BACAP is the **first prospective cohort** on pancreatic cancer worldwide
  - This biobank has not only tumor tissues coming from surgical specimens but also **cells and biopsies** from unresectable and/or metastatic **tumor samples** under endoscopic ultrasonography within referral centers for this technique
  - This biobank can be involved both within research and epidemiological projects
- **Scientific objectives**
  - Understand the development of pancreatic carcinogenesis
  - Identify **molecular markers** (biopsies, saliva or circulating blood) for the diagnosis, the prognosis, or the predictive response to chemotherapy
  - Determine an early diagnosis and screening of pancreatic adenocarcinoma with the identification of biomarkers (Proteomic signatures, miRNA, genomic DNA, micro particles) and associated thrombosis risks
- **Samples**
  - Tumor/Pathology: Pre-therapeutic biopsies, tumor banking, pTNM stage, Histology, DNA and RNA from tumor cells
  - Biological samples: Whole blood (6ml), serum (3ml), plasma (3ml) and saliva (1ml)
  - Blood samples are collected at the diagnosis before any treatment. All patients included in BACAP have a blood sample
- **Associated resources**
  - Human resources: A clinician network is involved in this project with gastroenterologists, surgeons, oncologists, pathologists
  - Know-how: Specialized platforms with high quality standards (Biological resources centers, molecular biology) linked to BACAP

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Biological samples are treated in each participating centers and then stored in Toulouse
- **Procedures of processing methods** for sample treatment exist and are implemented in each participating center
- A **virtual biobank** allows to get access to all the sample information linked to each patient
- Each BRC identifies each biological sample according to a number specific from the local biobank process linked to the patient IDs referenced into the database

BIOBANK-ASSOCIATED DATABASE

- A **biobank catalogue** is available on request

SPECIFICATIONS

- Date of the first sampling : 15th May 2014
- Sampling at the inclusion phase only
- Biobank is under the responsibility of the Toulouse University Hospital (Pr Barbara Bournet)
- The biobank is organized around **biological research centers** using **Standard Operating Procedures** and labeled by INCa
- A protocol for the biological sample collection exists
- Biological samples are available

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological sample	Status *	Origin of the sample	Quantity of the sample/ concentration available	Number of aliquot	Number of patients who have been sampled (expected/ ongoing	Preservation or storage conditions	Samples from relatives available
At Baseline (date of the first sampling): 15thMay 2014							
Tissues biopsies	NA	Pancreatic tissue or metastasis		[1-4]	980 (26/04/2018)	Paraffin or liquid nitrogen	no
Plasma	A	Blood	500µl	[4-6]	ALL expected	-80°C	no
Serum	A	Blood	500µl	[4-6]	ALL expected	-80°C	no
Total whole Blood	A	Blood	1ml	[4-6]	ALL expected	-80°C	no
saliva	A	Saliva	1ml	1	ALL expected	-80°C	no
DNA	A	Pancreas	[40-2000ng]	1-2	786 (26/04/2018)	-80°C	no
RNA	A	Pancreas	[40-2000ng]	1-2	806 (26/04/2018)	-80°C	no

*Status of the biological sample: (A=Affected, NA= Non-affected)

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **Charter** specifying biobank access is being drafted
- Biological samples, including **biological derivatives** (i.e. DNA, RNA), are accessible to public as well as to private/industrial teams
- To access biological samples, the industrial research team needs to fill out a **specific research project form**, available on request. The process is described on the web site of the BACAP cohort.
- Biological sample transfer might be considered under **specific conditions** after agreement of the scientific committee of the cohort
- Biological samples **might be shareable with a foreign private company** after agreement of the scientific committee of the cohort

BIOLOGICAL SAMPLE ANALYSES

- The protocol specifies collected samples analysis to be performed by the team of the BACAP cohort
- The collected samples are used for the **validation of disease diagnosis**
- A biobank-associated analysis **platform exists for DNA and RNA analysis**
- **Biological sample analysis-derived data are accessible** to public and private/industrial teams

COST

- An **estimation of the cost of each sample** contained in the biological collection is available on request and on the BACAP website: http://www.chu-toulouse.fr/-projet-bacap-

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Identification of **new biomarkers to predict pancreatic cancer**
- Determine an **early diagnosis and screening of pancreatic adenocarcinoma** with the identification of biomarkers (Proteomic signatures, miRNA, genomic DNA, micro particles) and associated thrombosis risks
- To carry out pharmaco-genomic studies to **characterize patient profile resistant to treatment**
- Determinate **factors inducing cancer cells spreading** such as inflammation markers

CLINICAL DEVELOPMENT

- Validation of **prognosis value of biomarkers in various sub-population defined by cancer evolution**
- Evaluate **clinical and biological development of cachexia** from patients with pancreatic cancer
- Develop **new therapeutic targets**
- **Epidemiological studies** (risk factors…)

OUTCOMES RESEARCH

- **Pharmaco-epidemiological studies**, drug safety, “real-world” use
- Studies of **effectiveness**, practice patterns, **adverse drug events**

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CANTO:

Chronic toxicities after anticancer treatments in patients with early breast cancer

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OVERVIEW

AT A GLANCE

> **Breast cancer**, treatment and chronic toxicities
> Early breast cancer patients
> Coordinated by Pr. Fabrice ANDRE
> **UNICANCER** sponsorship
> Funded by **ANR** (Ligue & private funds)

KEY FACTS & FIGURES

> Status: **inclusions started in February 2012**
> **12 000 patients expected**
> 11 630 included patients by April 2018
> **10 years follow-up**
> **Multicentric cohort** with 26 clinical sites
> **Biobank:** blood, serum, plasma, DNA and microbiota
> Linkage with **SNDS** expected

Quality of life is worse in cancer survivors and there is a poor evaluation of health-related issues in this population.
The aim of CANTO is to **build a Breast Cancer Survivorship Research Program** to **improve clinical care and providers as well as patients education** with a particular **focus on the adverse effects of treatments.**

Positioning

> **Unique international clinical study** dedicated to survivorship with data collected from a such large sample size, at diagnostic, before and after the first breast cancer treatment and during 10 years thereafter
> CANTO is involved in large consortia: **RHU Lumière and Labex GENMED**
> CANTO has already established partnerships with:
  > **Private companies** (Pharma and other private actor types)
  > **National and international academic partners** (Ligue, Dana Farber CI / Harvard Medical School, Memorial Sloan Kettering (NYC), UCLA, Yale)

LEADERSHIP

CANTO's leadership team, led by Pr. F. ANDRE, brings together renown epidemiologists, clinicians and translational research scientists, who have been committed to the field of the breast cancer during six years.

Pr. Fabrice ANDRE
Clinician/Oncology in breast cancer, Research Director, Inserm U981, Institut Gustave Roussy, Villejuif

- Pr. Fabrice André is a past recipient of Young Investigator and Career Development awards from the American Society of Clinical Oncology (ASCO) and is currently Professor in the Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France
- His research work, in the field of **biomarkers and personalized therapies,** focuses **on biomarker discovery, development of targeted agents and implementation of personalized medicine**. His team includes 50 people working on basic sciences, bioinformatics, biotechnologies and clinical research. He is also leading phase I-III trials testing targeted agents in the field of breast cancer and large national trials testing implementation of high throughput technologies in the health care system.
- Pr. André is **chairman of the biomarker group at UNICANCER** (French cooperative group) and was a member of several scientific committees for international meetings, including SABCS, AAACR, ECCO, ESMO, and IMPAKT
- Pr. André has been a member of the *Annals of Oncology* Editorial Board (2010-2013), Associate Editor since 2014 and in September 2017 became Editor-in-Chief
- Pr. André has published **more than 200 peer reviewed papers**, including papers in the *New England Journal of Medicine*, *Lancet*, *Nature Medicine*, *Science, Lancet Oncology and Journal of Clinical Oncology*, either as main or co-author

SCIENTIFIC NETWORK & MANAGEMENT

CANTO is a consortium between five entities: UNICANCER, the French federation of cancer centers; Gustave Roussy Cancer Center, the leading cancer center in Europe; Centre Leon Bérard, a leading cancer center in the field of bioinformatics and translational research; Centre Baclesse, which hosts a leading research unit in the field of survivorship; Centre F Leclerq, which hosts the database

The cohort is organized in working groups (lead experts as mentioned below)

- **Neuropsy** (Dauchy Sarah and Joly Florence)
- **Medico-eco, social sciences** (Dumas Agnès)
- **Treat compliance** (Pistilli Barbara)
- **Radiation Therapy** (Rivera Sofia)
- **Systemic effect of treatment** (Cottu Paul)
- **Fatigue, Physical activity** (Vaz-Duarte-Luis Ines Maria)
- **Biology** (Boyault Sandrine)
- **Valorization** (Pelletier-Bressac Isabelle)
- **Call for projects** (André Fabrice)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- The primary objective of the CANTO cohort study is to **identify predictive factors of chronic toxicities in patients** treated for a non metastatic early breast cancer
- Secondary objectives:
  - > **Describe and quantify chronic toxicities** observed throughout the follow-up phase in 12 000 patients stage I to III
  - > **Describe chronic toxicities, their incidence**, their future and their correlation with biological characteristics
  - > **Describe psychological, social and economical impacts** of these chronic toxicities at individual and populational levels

INNOVATIVE SCIENTIFIC FEATURES

- **Nationally representative samples** of Breast Cancer patients
- **Will provide an unbiased view of breast cancer care** in a wide variety of settings while collecting standardized data
- **CANTO cohort serves for ancillary studies, innovative projects**. Broad use of data by external research groups will be encouraged.

METHODOLOGY QUALITY

- **A web-based data collection system** was developed for CANTO using a secured software, ENNOV CLINICAL, Clinsight
- Confidentiality, security and the integrity of data are covered by the **Data Center of Dijon (CGFL)**
- Serum and plasma are stored in the Institut Gustave Roussy CRB and total blood are stored in the Centre Léon Bérard biobank CRB (Certification Afnor NFS 96-900)
- **SOPs** used to collect data and samples to ensure a homogeneity between the different centers

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	12 000 patients with a localized breast cancer, stage I to III
Sites:	26 clinical sites (20 French Comprehensive Cancer Centers (FCCC), 2 AP-HP centers, 2 CH and 2 private centers)
Inclusion criteria:	Invasive breast cancer, cT0-3 and CN0-3 tumors, no evidence of metastase at inclusion, no on-going treatment (as well as surgery)
Exclusion criteria:	Metastatic or locally recurrent breast cancer, history of other cancers within 5 years before start of study, treatment already received for the ongoing breast cancer, blood transfusion given within 6 months before inclusion

INCLUSION AND DURING THE FISRT 5 YEARS: Once a year

Database:
Clinical, biological treatment, environmental and social data integrated through clinicians/CRAs and self-reporting

Biobank:
Blood, serum and plasma sampling

FOLLOW-UP FROM 5 TO 10 YEARS: Once a year

Database:
Combination of follow-up visits or telephonic contacts

DATABASE & BIOBANK CONTENTS

DATABASE

- eCRF variables collected:
  - **Patient characteristics** / medical history / family history
  - **Tumor characteristics**, previous treatments
  - **Clinical and biological** examinations
  - **Treatments** for the breast cancer (surgery, chemotherapy, hormonotherapy, targeted therapy)
  - **Evaluations for chronic toxicity research**: gynecologic, rheumatologic, neurologic, cardiologic, pulmonary, gastrointestinal, skin, general troubles, infectious problems…
  - **Quality of life - Psychological and social - economic data** directly collected via ePRO since march 2017
- **Patient questionnaires**: patient reported data (HADS, LOT, BDI SF, QLQC30, BR23, FA 13, SF12, GPAQ16, social situation)
- **Imagery data** will be soon collected for the radiotherapy component (investigation of chronic toxicities due to radiotherapy)
- **Expected linkage** of the database with others databases such **as SNDS**

BIOBANK

- **Originality**
  - A large scale biobank with samples collected from **> 12 000 expected patients**: serum, plasma, total blood microbiota
- **Scientific objective**
  - Biobank aims to **carry out future studies for identifying genetics and proteomics markers** of chronic toxicities such as:
    - Genome Wide Associations Study
    - Post-therapeutic mutagenesis
    - Metabolomic, proteomic and microbiota
- **Samples**
  - Nature(s) of the samples:
    - Blood samples collected at baseline (for 12 000 patients) and at 3 years post-treatment (for the first 10 000 patients)
    - Plasma and serum collected at baseline (for 12 000 patients), at 1 year and 3 years post-treatment (for the first 10 000 patients); quality already checked in 100 random samples
    - DNAs extraction: A Genome Wide Associations Study planned this year on 5 000 samples (Illumina GSA)
    - Microbiota: sampling before and after chemotherapy (150 patients)
    - Ongoing collection of tumor samples

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Biological sample centralization:
  - > Plasma and serum samples are centralized in the Institut Gustave Roussy CRB (Villejuif)
  - > Total blood samples are centralized in the Centre Léon Bérard CRB (Lyon)
  - > Microbiota samples are centralized in the Institut Gustave Roussy CIC BT 507 (Pr. L. Zitvogel, Villejuif)
- **Safe transport of the biological samples** from each center to CRBs ensured by:
  - > IGR for plasma, serum and microbiota samples
  - > Datacenter of Dijon for total blood samples
- Biological sample **identification system : barcodes**

SPECIFICATIONS

- **Protocol for the biological sample** collection exists
- **A minimum dataset** for each CANTO biological sample **is available in the Data Center of Dijon (CGFL)**
- **Label of quality:** Institut Gustave Roussy CRB and Centre Léon Bérard CRB **quality standard** (Standard Operating Procedure)

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological samples	Origin of the sample	Quantity of the sample	Number of patients who have been sampled (ongoing/ expected)	Preservation or storage conditions
At Baseline				
Plasma	Blood	10 mL	11 108 / 12 000	- 70/ - 80°C
Serum	Blood	10 mL	11 108 / 12 000	- 70/ - 80°C
Total blood	Blood	2x6 mL	11 108 / 12 000	- 70/ - 80°C
During the follow-up				
Plasma after 1, 3 and 5 years post-treatment	Blood	10 mL	9 516 (6 724 1 year, 2 635 3 years, 157 5 years) /10 000	- 70/ - 80°C
Serum after 1, 3 and 5 years post-treatment	Blood	10 mL	9 513 (6 724 1 year, 2 632 3 years, 157 5 years) /10 000	- 70/ - 80°C
Total blood after 3 years post-treatment	Blood	2x6 mL	2 209/ 3 000	- 70/ - 80°C
Microbiota Feces (before and after chemotherapy)	Feces	10 g	before : 77 pts, after: 41 pts / 150	- 70/ - 80°C
Microbiota Plasma (before and after chemotherapy)	Blood	40 mL	before : 90 pts, after: 75 pts / 150	- 70/ - 80°C
Microbiota Serum (before and after chemotherapy)	Blood	5mL	before : 80 pts, after: 67 pts / 150	- 70/ - 80°C

BIOLOGICAL SAMPLE ACCESS MODALITIES

- **A document specifying CANTO biobank access is available** and sent by Unicancer **on request**. Each project and request access is discussed during **Executive Committees for approval.**
- **Biological samples, including biological derivatives (i.e. DNA), are accessible** to public as well as private/industrial teams
- **Specific biological sample access will be granted on the acceptation of the research project proposa**l submitted to Steering Committee
- **Biological sample transfer** is allowed pending that the research project proposal has been submitted to Steering Committee and accepted
- **Biological samples are shareable with a private company**

BIOLOGICAL SAMPLE ANALYSES

- Collected samples will be **used for the identification of biological markers** related with long term toxicities
- **Proteomic analysis** performed from the collected samples are not yet drawn, in progress
- **Micobiota analysis** are performed by the L. Zitvogel team (CIC BT 507)
- **Biological sample analysis-derived data are not yet accessible** to public teams and private/industrial teams

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Identification of predictive biomarkers of toxicities (genotype, microbiota, …)
- Identification of molecular surrogates of long term toxicities (mutagenesis, clonal haematopoiesis …)
- Development of new prognostic tools

CLINICAL DEVELOPMENT

- Development of interventional trials to improve quality of life in cancer survivors
- Regulatory : use CANTO as a regulatory tool for further phase IIIb trials
- Pharmaco-epidemiological studies: “real-world” use, practices patterns, acceptance…
- Psychological and socioeconomic impact of chronic toxicities
- Use CANTO data as historical cohorts for projects aiming to develop new anticancer drugs with decreased toxicities

OUTCOMES RESEARCH

- Pharmaco-epidemiological studies: Identification/validation of chronic toxicities and predictive markers of chronic toxicities, “real-world” use, compliance, practice patterns
- Pharmaco-economic studies: cost/benefit, health economic outcomes related to breast cancer treatment and impact on employment
- Cancer and evolution of cognitive functioning
- Analysis of health care trajectories

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  - I. Léger et al., 2018, MASCC, Cognitive impairment in breast cancer patients before surgery?
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  - I. Vaz Luis et al., 2018, ESMO, Breast Cancer (BC) related fatigue: a longitudinal investigation of its prevalence, domains and correlates.
  - A. Di Meglio et al., 2018, ESMO, Physical Activity (PA) and patterns of Quality of Life (QOL) after adjuvant chemotherapy (CT) for breast cancer (BC).

Dr. Bénédicte STENGEL
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at Inserm

CKD REIN
Préserver la santé rénale

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https://ckdrein.inserm.fr

OVERVIEW

AT A GLANCE

> Nephrology
> **Chronic Kidney Disease (CKD)**
> CKD patients
> **Coordinated by Dr. Bénédicte Stengel**
> Paris Sud University coordination
> Inserm Sponsorship
> Funded by ANR, PHRC & Private funds

KEY FACTS & FIGURES

> Status: inclusions started in July 2013 and ended in Q1 2016
> **3 033 included patients**
> **5 years follow-up**
> **Multicentric cohort** with 40 clinical sites
> **Blood, serum, plasma, DNA and urine** biobanking
> **Administrative database linkage** expected with **SNDS**

CKD-REIN cohort will serve to improve our **understanding of the determinants associated with CKD progression and adverse outcomes** and to **identify best clinical practices** in collaboration with the international CKD Outcome and Practice Pattern Study (CKDopps).
CKD-REIN will foster CKD epidemiology and outcomes research and provide evidence to improve health and quality of life of CKD patients and the performances of the healthcare system in this field.
A total of 40 clinical sites participate in the cohort. Stratified selection of clinical sites yields a sample that represents the diversity of settings, e.g., geographic region or public vs for-profit and non-for-profit private clinics.

Positioning

> The CKD-REIN cohort contributes to the international study called **CKDopps** (CKD Outcomes and Practice Patterns Study)
> The CKD-REIN study is the first large (N=3 033) cohort based on a national sample of adult CKD patients receiving nephrologist-led care
> **Public-private partnerships with 8 pharmaceutical companies. Five of which are on going.**

LEADERSHIP

CKD-REIN's leadership team, led by Dr. B. Stengel, brings together renown epidemiologists, nephrologists, health economists, and scientists who have been committed to the field of CKD and renal care for more than 20 years.

Dr. Bénédicte Stengel, ***Epidemiology/CKD, Research Director, Inserm U1018 CESP, Center for Research in Epidemiology and Population Health, Villejuif, Paris***

- **20 years experience** in the field of **CKD epidemiology**, principal investigator of several epidemiological studies on determinants and complications of CKD
- **Study coordinator of NephroTest** (A cohort study of over 2,000 adult patients included from 2000 to 2012 with chronic kidney disease stages 1 to 5)
- **Membership of international consortia**: CKD Prognosis, CKDopps, International Network of Chronic Kidney Disease Cohorts (iNETCKD)
- **Design of the "Renal Epidemiology and Information Network" registry protocol** for renal replacement therapy managed by the Biomedicine Agency
- Member of several international scientific committees
- Collaborations with numerous researchers in France and abroad
- **More than 120 peer-reviewed publications**

Pr. Ziad Massy, ***Nephrology/Head of Nephrology Division, Ambroise Paré Hospital, Paris-Ile-de-France-Ouest University (UVSQ)***

- **Relevant experience in clinical research** specifically focused on **etiology and slowing of CKD progression**, cardio-vascular complications in CKD, description of uremic toxin impact on CKD, CKD biomarkers and therapeutic trials
- **More than 300 peer-reviewed publications**

SCIENTIFIC NETWORK & MANAGEMENT

SCIENTIFIC NETWORK

CKD-REIN is linked with **the international cohort CKDopps** (coordination by Arbor Research, US); the French "branch" of the CKDopps cohort is coordinated by Pr C. Combe (CHU Bordeaux) and B. Stengel.

SCIENTIFIC MANAGEMENT

- **Pr. Christian Combe, Nephrology/Head of Nephrology Division, CHU Bordeaux**: relevant expertise in etiology and slowing of CKD progression, hemodialysis, nutrition and psychology
- **Pr. Denis Fouque, Nephrology/Head of Nephrology Division, C. Bernard Lyon University**: relevant experience in slowing of CKD progression, mineral and bone disease in CKD, nutrition, hemodialysis and peritoneal dialysis
- **Pr. Serge Briançon, Epidemiology/Patient-Reported Outcomes, Head of Public Health Division, CHU Nancy** : relevant experience in epidemiology and Patient-Reported outcome studies in chronic diseases
- **Pr. Luc Frimat, Nephrology/Head of Nephrology Division, CHU Nancy**: relevant experience in descriptive and analytical epidemiology of CKD, impact of CKD on patient quality of life, patient satisfaction, hemodialysis and peritoneal dialysis
- **YE. Herpe, Operational manager of the Picardie Biobank, CHU Amiens**: relevant expertise in both "systematic" biobanking and "project-driven" biobanking
- **Dr Joost Schanstra, Inserm U1048, I2MC, Toulouse**: relevant expertise, at international level, in renal fibrosis and in urinary proteomics
- **JF Deleuze, Head of CEA-CNG, Evry**: relevant expertise of the CEA-CNG in whole genome association studies (GWAS), pan-genomic expression profiling, epigenetic studies and whole genome sequencing
- **B. Robinson, CKDopps coordinator, Arbor Research, Ann Arbor, Michigan USA** : relevant expertise in nephrology, biostatistical analyses, clinical practice, collection and management of large data sets, economics, and public policy to inform health care practitioners and policy makers. B. Robinson scientific work has contributed to improve CKD patient care and revisions of public policy in the US and internationally
- **P. Morel, Head of Etablissement Français du Sang Bourgogne Franche-Comté, Besançon**: relevant expertise in collection of blood, plasma and platelet donations, in processing, screening and distribution of labile blood products (LBPs) to health-care establishments
- **Christian Jacquelinet, Scientific director, Agence de la Biomedecine**
- **Christophe Pascal, Economist, Lyon 3 University**

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- **The primary objective** of the CKD-REIN cohort study is to develop a research platform to address key questions regarding various patient-level factors and biomarkers associated with CKD outcomes and to assess clinical practices and healthcare system-level determinants of CKD outcomes
- **Secondary objectives** such as
  - > Assess the associations of a set of **psychosocial, environmental, biological, and genetic factors** and their interactions with several renal and non-renal outcomes
  - > Assess the value of new **biomarkers to predict CKD progression and outcomes**
  - > Evaluate the associations of a set of determinants regarding **CKD management, healthcare organization and clinic services** offered to CKD patients with end-points such as **survival, ESRD (End-Stage Renal Disease) incidence, hospital admissions, patient-reported outcomes** and achievement of clinical practice guidelines at both national and international (CKDopps) levels
  - > Identify and quantify net costs of different treatment strategies and combine these with patient outcomes to provide estimation of incremental **cost-effectiveness ratios at both national and international levels**

INNOVATIVE SCIENTIFIC FEATURES

- **Nationally representative** sample of nephrology clinics and CKD patients
- Will provide **an unbiased view of routine CKD** care in a wide variety of settings while collecting standardized data
- The CKD-REIN research platform can serve for ancillary studies, in that prospect, **innovative projects** and broad use of data by external research groups will be encouraged

GENOMICS

- **GWAS data** associated with detailed phenotypes and treatments offer opportunity for **pharmacogenomic studies**

METHODOLOGY QUALITY

- A web-based data collection system was developed for CKD-REIN using the same **secured web portal and patient identification module** as the REIN registry
- Confidentiality, security and the integrity of data are covered by the Biomedicine Agency
- **Standardized protocol for biological sampling and shipping** set up by the EFS (Etablissement Français du Sang)
- Serum, plasma, urine and DNA are stored at ultra-low temperature at the **Picardie Biobank**, **an ISO 9001 and NFS 96900 certified biological resources center**

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	3 033 patients CKD stage 3-4 receiving nephrologist-led care 1 672 stage 3 and 1 361 stage 4 patients
Sites:	**40 nephrology clinics**. Clinical center selection followed a stratification (e.g., based on survey data) to yield a sample that represents the diversity of outpatient nephrology clinics across the country
Inclusion criteria:	**eGFR between 15 and 60 ml/min/1.73m2 for at least 1 month** and no prior chronic dialysis or transplantation – Proven CKD diagnosis
Exclusion criteria:	<18 years old, prior chronic dialysis or transplantation, pregnancy, institutionalized, unable to give inform consent, decline participation

INCLUSION

Database:
Clinical, biological, treatment, environmental and social data collected from patients and providers by CRAs and self-administered questionnaires
Biobank:
Plasma, serum and urine sampling

FOLLOW-UP : Once a year

Database:
Combination of systematic follow-up visit with using a variety of different national administrative databases and sources to ascertain death and other health-related information
Biobank:
Sampling follow-up will be at 2nd and 5th years

DATABASE & BIOBANK CONTENTS

DATABASE

- **Patient-Level Variables**
  - **Medical Questionnaire (MQ), Interval Summary (IS) & Termination Form (TF)**
    - ***Patient characteristics***: Demographics, cause of CKD…(MQ)
    - ***Medication categories***: All meds recorded including RAS antagonists, statins, phosphate binders, ESAs therapy… (MQ/IS)
    - ***Clinical measures***: Blood pressure, weight, height, MMSE…(MQ/IS)
    - ***Biochemical measures***: 25 routine blood and urine values including serum creatinine, hemoglobin, urinary protein, …(MQ/IS)
    - ***Nutrition***: Prescribed restrictions of protein, potassium, sodium and phosphorus (MQ/IS)
    - ***RRT planning***: Vascular access referral, placement & procedures, services used (education programs, social worker, dietician), timing of decision about RRT modality, transplant wait-listing (MQ/IS)
    - ***Dialysis data***: eGFR at dialysis initiation, clinical measures & dialysis modality and dose (IS)
    - ***Clinical outcomes***: Hospitalizations (IS), death (TF), study departure (TF)
- **Patient Questionnaire (PQ)**
  - **Patient-reported data:** QoL (KDQoL…), burden of kidney disease, functional status, self-reported depression (CESD), satisfaction with care, involvement in decision-making, using validated instruments when possible
- **Provider-Level Variables from Clinician Survey (CS)**
  - **Medical Director Survey**: Clinic protocols for achieving practice guidelines (e.g., vascular access, kidney transplantation)
  - **Physician practices not covered by protocol**: Preferences for levels to initiate therapy and target for blood pressure, hemoglobin, phosphate, proteinuria - Treatment preferences
  - **Surveys of other health care providers**: Nutrition, social work, vascular access, ESRD education programs; staffing levels; integration of care (multidisciplinary care clinic); palliative care services
- **Expected linkage** of the database with others databases such as **SNDS, RNIPP...**

BIOBANK

- **Originality**
  - **A large scale biobank with 2 700 patients sampled, nationwide**: Serum, plasma, DNA and urines, with storage of 1/3 of the samples in liquid nitrogen for long term conservation and 2/3 at -80°C
  - CKD REIN is member of an **international cohort network**, Global Network-CKD including 14 cohorts, 12 with a biobank. The coordination of this network is performed by the International Society of Nephrology.
- **Scientific objective**
  - Future studies of uremic toxins, progression, inflammation and oxidative stress biomarkers, genetics and proteomics, and cardiovascular risk markers and factors are planned to be carried out using the biobank
  - Current research project using the biobank : blood and urine proteomics by J. Schanstra (supported by ANR)
- **Samples**
  - Plasma, Serum and Urine. DNA is extracted from blood samples.
  - Number of samples per patient at the inclusion and during the follow-up :
    - Plasma: 19 aliquots (500 µL)
    - Buffy coat: 2 aliquots (500 µL) only at baseline
    - Serum: 8 aliquots (500 µL)
    - Urine: 8 aliquots (5 mL)
  - **2 700 patients** sampled at baseline, **1 300 at** the 2 year follow-up and **1 600 expected** at the 5 year follow-up
  - **140 000 blood** (plasma, serum, buffy coat) and **urine samples collected; 56 000 expected** at the 5 year folluw-up
- **Associated ressources**
  - The CKD REIN cohort owns the know-how, the required **equipment and the human resources** to exploit the biological samples through **GWAS and Proteomic analysis**, in collaboration with the CEA-CNG platform (JF. Deleuze) and the Inserm Laboratory at Toulouse (J. Schanstra), respectively; Both of them are partners of the CKD REIN project.

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- **Picardie Biobank centralizes the CKD REIN biological samples** and is responsible of all the biobank quality procedures
- Biological sample collection, treatment, short-time **storage and shipping to Picardie Biobank** is organized and **performed by ESF** in most sites for procedure harmonization
- Picardie Biobank ensures the long-term conservation in liquid nitrogen for 1/3 of all the CKD REIN biological samples, **2/3 being stored at -80°C**
- Each biological sample is identified with a 2D and 1D barcode (same). Theses IDs are different from the patient ID and only the Biomedecine Agency (CKD REIN partner) has the correspondence between both.

SPECIFICATIONS

- Male and Female patients, > 18 years, CKD stage 3 and 4, no prior chronic dialysis or transplantation
- Date of the first sampling: 07/01/2013
- **Sampling frequency**: At baseline, and at 2nd, and 5th year follow up
- Responsible: **Picardie Biobank (Y.E. Herpe)**
- Protocol for the biological sample collection exists but confidential
- **A minimum dataset** for each CKD REIN biological sample **is available on databiotec server** managed at the Picardie Biobank whereas the main database is managed and hosted at the Biomedecine Agency
- **Label of quality**: CKD REIN biobank received a bio-collection authorization from the French Ministry of Research, CODECOH n° AC-2012-1624 based on the **Picardie Biobank quality standard**
- Biobank procedures were developed by the CKD REIN coordination team in order to **apply standardized methods for sample collection, treatment and conservation** (Standard Operating Procedure)
- CKD REIN biological samples are **available**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Origin	Quantity / concentration available	No. of aliquots	No. of subjects who have been/will be sampled (collected/ expected)	Storage conditions
At Baseline (date of the first sampling): 7th January 2013					
Plasma	Blood	500 µg	14	**2725**	-80°C
Plasma	Blood	500 µg	5	**2725**	Liquid nitrogen
Serum	Blood	500 µg	6	**2725**	-80°C
Serum	Blood	500 µg	2	**2725**	Liquid nitrogen
Buffy coat	Blood	500 µg	2	**2725**	-80°C
Urines	Urines	5 mL	5	**2725**	-80°C
Urines	Urines	5 mL	3	**2725**	Liquid nitrogen
During the follow-up : 2nd and 5th year follow up					
Plasma	Blood	500 µg	14	**1300** / 1600	-80°C
Plasma	Blood	500 µg	5	**1300** / 1600	Liquid nitrogen
Serum	Blood	500 µg	6	**1300** / 1600	-80°C
Serum	Blood	500 µg	2	**1300** / 1600	Liquid nitrogen
Urines	Urines	5 mL	5	**1300** / 1600	-80°C
Urines	Urines	5 mL	3	**1300** / 1600	Liquid nitrogen

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **document** specifying **the CKD REIN resources access has been drawn**
- Biological samples **are accessible** to public as well as to industrial research teams
- Specific biological samples **access** will be granted on the **acceptation of the research project proposal submitted to the Steering Committee**
- To access biological samples, **the industrial company needs to become a CKD REIN partner and then to submit its specific research project through a proposal to the Steering and Scientific Committees for review**
- Biological sample **transfer is not allowed**
- Biological samples **are not shareable with a foreign company**

BIOLOGICAL SAMPLE ANALYSES

- The CKD REIN protocol stipulates GWAS and proteomic analysis as studies conducted upon CKD REIN biobank
- The collected samples are planned to be used for:
  - > the **identification of new biomarkers** to predict CKD progression and metabolic complications
  - > the **validation of the CKD disease** diagnosis

COST

- Access to biospecimens is under condition: private companies need to sign a partnership with already defined modalities to access to biobank and associated data
- **A financial estimation** of the CKD REIN biological samples is still in reflection

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- **Identification of new biomarkers** to predict CKD progression and metabolic complications
- **Pharmaco-genomic studies** to characterize **patient profile resistance to treatment**

CLINICAL DEVELOPMENT

- **Validation of prognosis value of biomarkers** in various sub-populations defined by age, gender and diabetes status
- **Optimization of clinical studies** (variations in the prevalence and distribution of patient clinical and biological characteristics…)
- **Epidemiological studies** (prevalence and incidence of CKD-related outcomes and co-morbidities) to support market access

OUTCOMES RESEARCH

- **Pharmaco-epidemiological studies**: drug safety, "real-world" use, effectiveness, practice patterns, compliance, risk/benefit, adverse drug events of anti-hypertensive, lipid-lowering and antidiabetic drugs and of CKD-specific drugs (EPO ...)
- **Pharmaco-economic studies**: cost/benefit, health economic outcomes related to end-stage renal disease treatment : dialysis, transplantation, conservative management
- **Quality of life** and **patient satisfaction** studies

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COBLAnCE:

A COhort to study BLAdder CancEr

ITMO Santé publique

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OVERVIEW

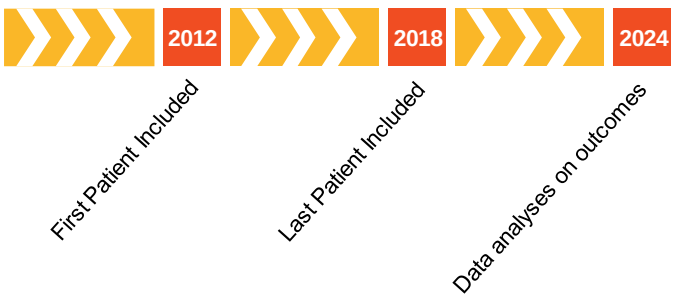
AT A GLANCE

> Oncology
> **Bladder cancer**
> Coordinated by Pr. **S. Benhamou**
> **INSERM** Sponsorship
> Funded by the Investissements d'Avenir
> Key words: bladder cancer, environment, genetics, health economy, quality of life, pathology, prognosis, molecular biology, biobanking

KEY FACTS & FIGURES

> Status: inclusions start the 22th of October 2012; **today 1 805 patients enrolled**
> **2 000** enrolled patients **expected** or end of inclusions planned by the end of June 2018
> Annual follow-up for **6 years**
> National **multicentric** cohort (14 public or private for profit hospitals)
> **Biobank**: tumor (frozen and formalin-fixed paraffin-embedded), blood, urine and nail collections
> Linkage to the SNDS is ongoing

The aim of COBLAnCE is to **investigate various factors influencing bladder cancer outcomes** (local and distant recurrences, survival) and to develop diagnosis and prognosis markers.



Positioning

> COBLAnCE is one of the few cohorts of bladder cancer patients with samples well **clinically and biologically characterized**
> The **size of the cohort and the quality** of annotations will support highly competitive projects focusing on gene-environment interactions, molecular classification, biomarker discovery, therapeutic innovation and healthcare resource
> Participation of COBLAnCE in projects submitted in response to both the **INCa** and **RHU calls** (application 2018)
> **A public/private partnership** has been designed and set up with one pharmaceutical company. It is under discussion with others.

LEADERSHIP

COBLAnCE's leadership is set up with a tandem of the renown epidemiologist, S Benhamou and clinician, T Lebret, who are committed in the field for more than 10 years.

Simone Benhamou, ***Epidemiologist, PhD***

- Leads a research group in INSERM U946
- Heads several epidemiological programs to investigate the impact of genetic markers and environmental factors on molecular characteristics and prognosis of cancer
- Is involved in international consortia on genetic susceptibility to bladder, lung, and head and neck cancers since 1995
- Member of the Scientific Council of the Swiss Cancer league for Research in epidemiology
- Reviewer for numerous journals (CCC, Cancer Res, CEBP, Carcinogenesis, Int J Cancer, JNCI, Oncogene, Int J Epidemiol, BJC, etc.)
- Current collaborations: International Agency for Research on Cancer, Geneva Cancer Registry, Gustave-Roussy, etc.)
- Articles: 225, H-index: 62

Thierry Lebret, ***Urologist, MD, PhD, Professor of Urology***

- Chairs the urology department in Foch Hospital
- Well known for his work on orthotopic bladder replacement
- One of the leaders of a French consortium on bladder tumor research with F Radvanyi
- Active Member of the European Association of Urology and belongs to the Guidelines Panel on bladder cancer
- General secretary of the French Urology (AFU) in 2011
- Collaborations with the Conway Institute, Dublin
- Articles: 298, H-index: 32

SCIENTIFIC NETWORK & MANAGEMENT

SCIENTIFIC NETWORK

- COBLAnCE is partner of **ICBC,** an international consortium upon bladder cancers, for sharing scientific reflections
- COBLAnCE has set up a **collaboration with Spanish scientists** who are establishing a cohort of 2000 bladder cancer patients using the same study design and questionnaires. This collaboration will enable analyses of combined data for specific subgroups of patients with appropriate statistical power

SCIENTIFIC MANAGEMENT

- **Yves Allory, Uropathologist, MD, PhD,** Professor of Pathology: Leads a research group in Institut Curie, and develops research projects dedicated to diagnostic and prognostic biomarkers in genito-urinary cancers. Co-founder of the LNCC French bladder cancer consortium and the new French Bladder Cancer cohort for which he is the coordinating pathologist. Member of the scientific board of ESUR.
- **Julia Bonastre, Senior health Economist, PhD**: 20 years of experience in economic evaluation, health care resource use and applied econometrics. Head of the team Etudes et Recherche en Economie de la Santé (ERES) at Gustave Roussy since 2002. She is in charge of many cost-effectiveness studies alongside clinical trials.
- **François Radvanyi, Molecular biologist, PhD**: Head of the Molecular Oncology team at the Institut Curie. Responsible for the French bladder cancer consortium. In collaboration with MDs and analysts, he uses bioinformatics methods followed by functional validation to identify genes and pathways involved in tumor progression. His work extends from basic to translational research.

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Primary objectives:
  - > **Investigate various factors** influencing bladder cancer outcomes (local and distant recurrences, survival)
  - > **Develop diagnosis and prognosis** markers
  - > This study will provide clinicians with necessary information to decide on appropriate treatments for bladder cancer patients and **improve quality of care**
- Secondary objectives:
  - > **Investigate interactions between host** (genetic variants) and **environmental** (tobacco, occupations,...) factors on bladder cancer outcomes
  - > **Describe treatment patterns** and assess **quality of life** and **direct and indirect costs** attributable to bladder cancer from the payer perspective with a long-term follow-up

INNOVATIVE SCIENTIFIC FEATURES

- **Nationally representative** sample of patients with bladder cancer
- Provide an **unbiased view of routine bladder cancer care** in a wide variety of settings while collecting standardized data
- The COBLAnCE cohort can serve for ancillary studies and innovative projects

GENOMICS

- RNA sequencing, target sequencing of cancer genes and RPPA data will constitute a large omic database**. Associated with detailed phenotypes and clinical data, this database will offer opportunity for pharmaco-genomic and -proteomic studies.**

METHODOLOGY QUALITY

- All data are entered, validated, and stored using the MACRO software (data entry performed by each center via internet) in 3 independent databases at Gustave Roussy
- **High quality standard** for molecular extractions (DNAs, RNAs and proteins)

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	2 000 bladder cancer patients or end of inclusions planned by the end of June 2018
Sites:	14 participating centers
Inclusion criteria:	Patients newly diagnosed with bladder cancer All histological types, stages and grades are included. No selection on age or gender
Exclusion criteria:	Patients with bladder cancer diagnosed for more than one year

INCLUSION

Database:
Epidemiology, disease management, pathology, resource use and quality of life (face to face interviews, medical files)

Biobank:
Tumor, blood, urine and nail collections

FOLLOW-UP

Database:
Disease management and resource use (M3, M6, M12 and once a year until M72; medical files), pathology (at each recurrence; medical files), quality of life (M6, M12 and once a year until M72; M3 after recurrence or progression; self-administered)

Biobank:
Tumor collection at each recurrence; urine collection 1 year after inclusion

DATABASE & BIOBANK CONTENTS

DATABASE

- **Epidemiology**
  - **Sociodemographic characteristics**: age, gender, place of birth, educational level, marital status, household income, working situation, history of residences and of occupations
  - **Lifestyle**: history of tobacco consumption, dietary habits and physical activity
  - **Medical history and medication use**: weight, height, urinary tract infection, hematuria, kidney stones, skin or respiratory allergies, anti-hypercholesteremic and anti-inflammatory drugs, hormonal treatment, personal and family history of cancer
- **Disease management**
  - **Disease presentation**: presence of symptoms (hematuria, pollakuria, dysuria, urgency, hydronephrosis), alteration of health status
  - **Procedures before diagnostic resection**: urinary cytology, urine culture, abdominal ultrasound, urinary tract fibroscopies, imaging (scanner, MRI)
  - **Diagnosis through transurethral resection of the bladder**: Hervix or Narrow-Band-Imaging fluorescence, number and location of resected tumors, size and aspect of the largest tumor
  - **Treatment**: for NMIBC intravesical instillations and cystectomy; for MIBC: chemotherapy, radiotherapy, for both NMIBC and MIBC: lymphadenectomy, urethrectomy, nephro-urethrectomy, urinary diversion, blood transfusion, any hospitalization and complications
  - **Outcomes**: locoregional and distant recurrences (dates, sites, pathology, treatments, etc.) and death (date and place)
- **Pathology**
  - Histological type and subtype, prognostic factors, pathological review for all cases at initial diagnosis and in case of recurrence
- **Resource use**
  - **All hospitalizations**: dates, type of facility, service, type of care and diagnosis-related group
  - **Outpatient and community care**: cystoscopies, imaging (CT, MRI, ultrasound, etc.), urine cytology, urine culture and tumor biomarkers
  - **Sick leaves**
- **Quality of life**
  - **Generic measures** (EuroQol EQ-5D-3L & EORTC QLQ-C30)
  - **Specific measures** (EORTC-BLS24 & EORTC-BLM30)

BIOBANK

- **Originality**
  - Very **large sample collection**: tumor, blood, urine and nail collection at inclusion; tumor collection at each recurrence; urine collection 1 year after inclusion
- **Scientific objectives**
  - Identification of mechanisms involved in bladder cancer development
  - Identification of predictive and prognostic markers of disease evolution and treatment response
- **Samples**
  - **At inclusion**
    - Blood samples for DNA and RNA extractions, PBL isolation; Urine samples for DNA, RNA and protein extractions
    - Frozen tumor sample for DNA, RNA and protein extractions; Formalin-fixed paraffin-embedded tumor for IHC and FISH studies, DNA and RNA extractions
  - **During follow-up**
    - Urine samples one year after inclusion
    - Frozen tumor sample and formalin-fixed paraffin-embedded tumor at each recurrence
- **Associated resources**
  - Human resources and know-how: more than 40 specialists in a multidisciplinary setting (clinics, epidemiology, health economy, pathology, molecular biology, genetics) and 4 Biological Resources Centers for sample processing, quality control, and storage

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- The Biobank **spreads over 4 Biological Resource Centers (BRCs)** according to the 4 types of biological sample collected. Each BRC sends an update of the hosted samples for centralization.
- Each biological sample is identified by a patient-specific bar code

SPECIFICATIONS

- Date of the first sampling: **October 23, 2012**
- Sampling frequency: **At one year** after diagnosis for urine sampling and at **each recurrence** for tumor collection
- Responsible for the biobank: **4 BCRs** according to the type of sample collected (blood, urine, tumors and nail)
- Protocol for the biological sample collection available
- A **minimum data associated** to each sample may be **available on request**
- **Label of quality**
  - > Each BRC evaluates the yield of the molecular extractions (quality and quantity of DNA, RNA and proteins)
  - > **The 4 BRCs are certified NFS96-900**
  - > The certification **ISO9001:2015** has been obtained in March 2017 for the COBLAnCE biological collection and associated data
- Biological samples will be available when the inclusion is completed

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Status *	Origin	Quantity / concentration available	No. of aliquot	Expected percentage of sampled patients	Storage conditions	Characteristic
At Baseline (date of the first sampling): the 23th October 2012							
Lymphocytes	A	Blood (ACD)		1	99%	-196°C	(b) (c)
Plasma	A	Blood (EDTA)	2 ml	4	99%	-80°C	(b) (c)
DNA	A	Blood (EDTA)	≈144µg	2	99%	-80°C	(b) (c)
RNA	A	Blood (Paxgene)	≈7.7µg	1	99%	-80°C	(b) (c)
DNA	A	Stabilized Urine	≈6.7µg	1	91%	-80°C	(a) (b)
RNA	A	Stabilized Urine	≈0,8µg	1	96%	-80°C	(a) (b)
Proteins	A	Frozen Urine	in progress	4		-80°C	(a) (b) (c)
Urine aliquot for ELISA	A	Frozen urine		1	85%	-80°C	(a) (b) (c)
DNA	IT	Frozen Tumour	≈46 µg	5	60%	-80°C	(b) (c (d)
RNA	IT	Frozen Tumour	≈28 µg	7	50%	-80°C	(b) (c (d)
Proteins	IT	Frozen Tumour	≈1087 µg	5	42%	-80°C	(b) (c (d)
Paraffin Embedded tissue block	IT	Formalin fixed Tumour	1 block		90%	20°C	(e)
Pathology Slides	IT	Formalin fixed Tumour	1 to 10		99%	20°C	(e)
nails	A				68%	20°C	
During the follow-up: every 1year after inclusion for urine sample (since 11/06/2013) and at each recurrence and/or progression of the disease for tumor samples (since 06/12/2013)							
DNA	A	Stabilized Urine	≈3.3µg	1	70% with still bladder	-80°C	(a), (b)
RNA	A	Stabilized Urine	≈0.8µg	1	65% with still bladder	-80°C	(a) (b)
Proteins	A	Frozen Urine	in progress	4		-80°C	(a) (b) (c)
Urine aliquot for ELISA	A	Frozen urine		1	80% with still bladder	-80°C	
DNA	IT	Frozen Tumor	In progress		88%	-80°C	(b) (c) (d)
RNA	IT	Frozen Tumor	In progress		50%	-80°C	(b) (c) (d)
Proteins	IT	Frozen Tumor	In progress		59%	-80°C	(b) (c) (d)
Paraffin Embedded tissue block	IT	Formalin fixed Tumour	1 block		80% with recurrence and/or progression	20°C	
Pathology Slides	IT	Formalin fixed Tumour	1 to 10		80% with recurrence and/or progression	20°C	

*** Status of the biological sample: A=Affected, IT=indication of grade of tumor + value**
(a) Composition of the urine; (b) Quality controls; (c) Delay between the sampling and the freezing; (d) % of tumorous cells; (e) Time of tissue fixation

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **charter**, specifying the access modalities of the COBLAnCE resources, **is being finalized**
- Biological samples **will be accessible** to public and/or private/industrial teams **through a specific research project proposal** to address to the Steering and Scientific Committees for review, **according to the project submission procedure** described in the Charter. This procedure includes feasibility, financial, and scientific evaluations.
- A **restriction access** will be applied for samples with small quantities of molecular extracts
- Biological samples can be transferred to public, private teams or foreign companies according to modalities defined in a contract between INSERM and the teams
- Biological sample analysis-derived data will be accessible to public and private/industrial teams after evaluation of scientific project which will involve them

BIOLOGICAL SAMPLE ANALYSES

- The COBLAnCE cohort envisages exploiting the biological samples to:
  - > **Investigate genetic and/or epigenetic** background on bladder cancer outcomes (from blood)
  - > **Investigate DNA mutations** for molecular characterization of bladder cancer (from tumors)
  - > **Identify prognostic markers** of bladder cancer (from sequential urine and tumor sampling)

COST

- A financial estimation of the biobank constitution is being established
- A price list regarding the cost of each biological sample will be established later

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- **Identification of genetic/epigenetic factors** on bladder cancer outcomes (recurrences, progression, survival)
- **Interactions** between **host** (genetic variants) and **environmental** factors (flue- or air-cured tobacco) on outcomes
- **Molecular characterization** of bladder cancer in relation with environmental/behavioral factors (tumor types according to carcinogen exposures)
- **Importance of continuing smoking** after bladder cancer diagnosis on outcomes

CLINICAL DEVELOPMENT

- **Identification of diagnostic and prognostic biomarkers** of disease evolution (local and distant recurrences, survival) and treatment responses based on comprehensive biological and clinical data
- **Identification of homogeneous subtypes of bladder cancer** integrating transcriptome (coding and non-coding DNA, genomic alterations and epigenetic modifications) for **tailored treatments**

OUTCOMES RESEARCH

- **Pharmaco-economic studies: direct and indirect costs** attributable to bladder cancer, **cost-effectiveness** of many recent and costly interventions
- **Quality of life studies**: Impact of disease, treatment and long-term surveillance on various dimensions of quality of life (functional dimension and anxiety)

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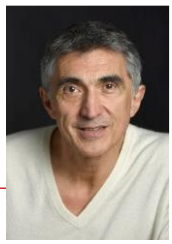
colibri



Pr Bernard AGUILANIU
Associated Professor of Pulmonology, Grenoble Alpes University

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OVERVIEW

AT A GLANCE

> **Real-life observatory** for two groups of pulmonary diseases :
  > ***Obstructive Lung Diseases (OLD):*** COPD/Emphysema at this time; Bronchiectasis and Asthma in perspective
  > ***Interstitial Lung Diseases (ILD)*** for all etiologies
> **All patients** without exclusion criteria
> Two Scientific Committees for OLD and ILD
> Sponsor: Association for Consolidation of Knowledge and Practices in Pneumology (ACKPP)
> Funded by private grants for both OLD and ILD
> **Digital technology for the daily management** of chronic respiratory disease, in order to prepare clinicians to concretely approach the 4P medicine

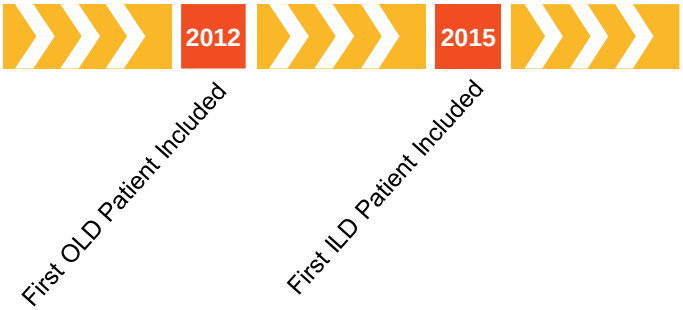
KEY FACTS & FIGURES

> Patients pool : **unlimited** at this time, large diversity of patient profiles
> Number of patients included by June 2018
  > ***OLD** (COPD/Emphysema) : **4 600 patients***
  > ***ILD : 1 800 patients***
> **Follow-up period is unlimited** and depending on the funding
  > OLD : 6 years follow-up
  > ILD : 3 years follow-up
> **Multicentric French observatory** (hospital and private practices)
> **Biobank :** web application available for biobanking ancillary projects, which allows to make links between local biobanks and the Colibri database
> Linkage to SNDS and CepiDC expected

The overall aims of the Colibri program are:

> To support step by step the use of digital technology for the daily management of chronic respiratory disease in order to prepare clinicians to concretely approach the 4P medicine
> To improve the validity of observational research taking into account the diversity of patient profiles and also the diversity of clinical practice

Real-life observatories are complementary to academic cohorts.



Positioning

> Participation in the AIR project : “Sentinel’’ circulating tumor cells and early diagnosis of lung cancer in patients with Chronic Obstructive Pulmonary Disease (COPD)
> Colibri is opened to set up public-private partnerships for ancillary studies

LEADERSHIP

Bernard Aguilaniu

Associated Professor of Pulmonology, University Grenoble Alpes. France

- Adjunct Professor Dep. Physical Education McGill University – Montreal
- **Coordination of 2 hospital programs :**
  - > Clinic of COPD
  - > Center of competency for rare pulmonary diseases
- **Expertise :** COPD - Interstitial lung disease (ILD) - Exercise Physiopathology - Rehabilitation – Dyspnea
- **Committee membership**
  - > Expert in several national boards of pharmaceutical industry for COPD-ILD
  - > Member of the French Society of pneumology (SPLF) and specially in working group on COPD and Exercise & Rehabilitation
- **Current collaborations**
  - > Respiratory Epidemiology and Clinical Research Unit Montreal Chest Institute McGill University Health Centre, Montreal, QC
  - > National Reference Center for rare pulmonary disease. Department of respiratory diseases - Louis Pradel Hospital UMR 754 - Claude Bernard Lyon 1 University
- **Publications**
  - > Around 70 peer-reviews on topics of interests : COPD-ILD - Diagnosis process - Exercise Tests - Rehabilitation - Chronic dyspnea

Charles-Hugo Marquette

Professor of Pulmonology, University of Nice Sophia Antipolis, Nice, France

- **Head of pulmonology, thoracic oncology and critical care department** University of Nice Hospital
- **Expertise :** lung oncology, ILD
- **Member of Inserm U10181/UMR CNRS 7284**. Institute for Research on Cancer and Ageing – University Nice Sophia Antipolis, France
- President of the French College of Professors in Pulmonology (2008-2012)
- **Publications**
  - > 149 publications referenced on PUBMED, including 2 N Engl J Med and 2 JAMA

SCIENTIFIC NETWORK & MANAGEMENT

Colibri's scientific management is decentralized

- Each team or doctor participating to the project can write a research protocol, request an extraction, analyze the results and write an article
- All research protocols are validated beforehand by a Scientific Committee, with experts on OLDs and ILDs
- The decentralized research teams work closely with the project manager and the statistical team of Colibri

Colibri-OLD Scientific Committee

- Pr. J. Bourbeau (Montréal)
- Pr. N. Roche (Paris)
- Pr. PR. Burgel (Paris)
- Pr. B. Maitre (Créteil)
- Pr. J. Gonzalez (Paris)
- Dr. E. Kelkel (Chambéry)
- Pr. B. Aguilaniu (Grenoble)

Colibri-ILD Scientific Committee

- Dr. R. Borie (Paris)
- Pr. G. Ferretti (Grenoble)
- Dr. S. Lenoy (Nice)
- Dr. F. Lintz (Toulouse)
- Pr. S. Marchand-Adam (Tours)
- Dr. G. Prévot (Toulouse)
- Dr. S. Quétant (Grenoble)
- Pr. F. Thivollet (Lyon)
- Pr. B. Aguilaniu (Grenoble)

Statistical modelling

- Pr . A. Antoniadis (Captown)
- Pr. Zhi Li (Montréal)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- ***Colibri-ILD:*** **To analyze the fibrosing ILD's progression** from the day when diagnosis is proposed by the multidisciplinary board
- ***Colibri-OLD*** : **To highlight real-life subgroups of OLD patients** (description of phenotypes of interest), then validate them according to **several outcomes/endpoints**
- ***Developing specific Ensemble Learning Process*** (ELP) for the **prediction of complex multifactorial clinical endpoints** (ex : decline, excessive sedentarity, etc.) for both the projects (ILD & OLD)

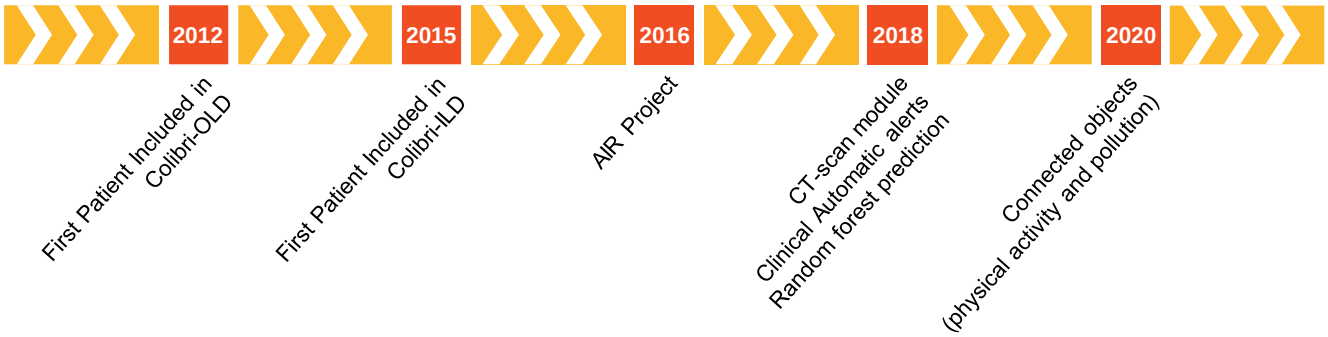
INNOVATIVE SCIENTIFIC FEATURES

- Colibri has been built as a **consultation tool** to help physicians to follow their patients. The observatory gives therefore real-life data, which are complementary to academic cohorts, with strengths and weakness:
  - > The main strength is to take in account all patients seen in clinical practice, leading to a great number of cases with profiles which are not present in selected academic cohorts
  - > The challenge is to get complete and reliable data. To overcome this weakness, Colibri platform is designed to provide scalable and agile services to the user hoping to improve user engagement.
- Many useful tools are available for the physician, for example:
  - > **Sharing the patient record between physicians** (ex: in case of hospitalization / to seek an advice, for rehabilitation programs…) to get a medical file as inclusive as possible
  - > **Pulmonary rehabilitation program** (standardization of kinesiologist evaluation)
  - > **Automatic alerts** to determine the patient profile and to suggest adapted treatments
  - > **CT-scan module** (possibility to upload DICOM and full-web viewing)

METHODOLOGY QUALITY

- **Accredited Hosting Provider** in Health Personal Data
- Colibri includes cross-checking procedures to improve completeness and reliability of data, comparing declarative information and results of exams. In case of unusual data, the physician is informed.
- Moreover, statistical methodologies allow to perform imputation of missing data if few criteria are not complete

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives:	No limitation of participants
Sites:	360 pulmonologists from all professional backgrounds (University or General Hospitals, Private practice) are registered in the Colibri observatory, and 238 pulmonologists use the observatory
Inclusion criteria:	Any patient with a OLD or ILD, without exclusion criteria

INCLUSION

There is no mandatory data. Only useful examinations for patient follow-up are entered.

Database:
Lifestyle, exposure, treatments, comorbidities, exacerbations, symptoms, pulmonary function, disability and quality of life, CT-Scan, biology, cardiac examinations, other examinations, diagnosis, prescription

FOLLOW-UP

For each follow-up visit, a new file is created, which contains the same fields as the original file, but is organized so that the updates are easily inserted.

The date of the next visit is not enforced because data are collected in conditions of a real-life monitoring arrangement.

DATABASE & BIOBANK CONTENTS

DATABASE

- The data are collected following the usual order of a consultation:
  - > Lifestyle, Exposure, Addictions
  - > Pharmacological Treatments : link with VIDAL database to identify all prescribed treatments
  - > Non-pharmacological treatments: Oxygen, Ventilation
  - > Comorbidities: cardiac, metabolic, etc.
  - > Exacerbations, Symptoms (MRC Score), Clinical examination
  - > Imaging : CT-Scan (DICOM uploaded)
  - > Pulmonary Function Test, Blood-gas
  - > Quality of life questionnaires (CAT, DIRECT, HADS)
  - > Exercise testing
  - > Standard Biology (OLD) and Specific Biology (ILD)
  - > Cardiac examinations / Other examinations
  - > Diagnosis
  - > Drug prescription

BIOBANK

- **Originality**
  - > A biobank application has been developed for the AIR project by P. Hofman (1081 INSERM Research Unit Nice) allowing any center to interface their clinical records on Colibri with their own biobanking system
  - > Biobanking system is decentralized and depends on each participating center

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> N. Roche and al. **Determinants of treatment choices in COPD: what is the weight of clinical presentation?** (submitted).

> PR. Burgel and al. **Random Forest prediction of excessive sedentarity in COPD** (in preparation).

> N. Roche and al. **Is there a clinical rationale behind physician's treatment choices in COPD?** (in preparation).

> B. Aguilaniu and al. **Prevalence and spectrum of ILD's in French real-life practice** (in preparation).

Posters :

> Colibri-OLD : 12 scientific posters since 2014

> Colibri-ILD : 4 scientific posters since 2016

Constances:

CONSulTANts des CES-Centres d'examens de santé

ITMO Santé publique

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Paris Descartes University

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OVERVIEW

AT A GLANCE

> **Epidemiology and Public Health**
> **General** population
> Population-based cohort
> Coordinated by **Marie Zins & Marcel Goldberg**
> **INSERM, UVSQ and Paris Descartes University** Sponsorships
> Funded by ANR (PIA), in-kind from CNAM and by industrial partners

KEY FACTS & FIGURES

> Status: **almost 190 000 participants already** enrolled and follow-up ongoing
> **200 000 expected subjects** aged 18 to 69 years
> **400 000 subjects in a control cohort**
> Follow-up period : annual questionnaire and medical examination every 4 years
> **Multicentric** cohort
> **Blood and urine biobanking** for 85 000 subjects (20 aliquots per subject)
> **Administrative database linkage** (SNDS, Cnav) for participants and control cohort

Constances is a multi-purpose population-based cohort of 200 000 subjects, representative of the French population aged from 18 to 69 years at inception.
Constances is designed and managed **to ensure a longitudinal follow-up over the longest possible period**.
The project covers a wide range of **personal, behavioral and environmental risk factors and health problems**, notably **chronic diseases and women's health**, as well as disorders related to **ageing, quality of life, sleep disorders, limitations and handicaps**.

Positioning

> Constances **works closely with a large network of French and international researchers**
> Constances is involved **in several European cohort consortia**: BBMRI-LPC, IDEAR, LIFEPATH, OMEGA-NET
> Constances coordinators are also responsible of the **GAZEL cohort** (20 000 people since 30 years), more than 80 projects carried out thanks to this platform and about 300 publications
> **A specific Public/Multiprivate Partnership** has been designed and set up. Several pharmaceutical companies are already Constances partners. The partnership development is **on going with other companies.**

LEADERSHIP

Zins Marie, *Epidemiologist, Inserm, Paris*

- **Director of the Population-based Epidemiologic Cohorts Unit (UMS 011)**
- **Co-leader of the GAZEL** Cohort
- **Expertise**
  - Grant application reviews for INCa, Swiss National Science Foundation, ANR, IReSP
- **Scientific evaluation & Committee Membership**
  - Member of the **MetaboHub National Infrastructure Advisory Board** (PIA)
  - Member of the **Public Health Multi-Bodied Subject-based Institutes (ITMO) Expert Committee**
  - Former Member of the **National German Cohort Scientific Advisory Board** (2014-2016)
  - Former member of **National Biomonitoring Programme (2010-2014) Advisory Board**
  - Former member of the **Defense' Health Observatory** Scientific Committee
- **Current Collaborations**
  - BBMRI-LPC Consortium (FP7), LIFEPATH Consortium (H2020), IDEAR consortium, OMEGA-NET COST Action, National Institute for Health Surveillance
- **Publications**
  - **More than 170 peer-reviewed publications** (h-index: 31)

Marcel Goldberg, *Epidemiologist, Inserm, Paris*

- **Emeritus Professor of Epidemiology**
- **Co-leader of the GAZEL** cohort since 1989
- **Expertise**
  - Former Coordinator of the Information Systems Working Group of the High Council of Public Health
  - Former president of the French Speaking Epidemiological Association
  - Former Director of the Inserm Unit 88
- **Scientific evaluation & Committee Membership**
  - Former president of the Public Health Inserm Scientific Committee (CSS8)
  - Former Member of the European Scientific Committee on Occupational Exposures Limits
  - Former member of the Swiss National Scientific Cohorts Committee
- **Current Collaborations**
  - BBMRI-LPC Consortium (FP7), LIFEPATH Consortium (H2020), IDEAR consortium, OMEGA-NET COST Action
- **Publications**
  - **More than 360 peer-reviewed publications** (h-index: 51)

SCIENTIFIC NETWORK & MANAGEMENT

- **Constances participates to European population-based cohort consortiums**
  - IDEAR (Integrated Datasets across Europe for Ageing Research) consortium
  - BBMRI-LPC consortium associating European "mega cohorts" in UK, Germany, Netherlands, Finland, Sweden….
  - P3G : Public Population Project in Genomics
  - LIFEPATH Consortium (H2020)
  - OMEGA-NET Consortium (COST Action)
- **Constances is collaborating with other population based cohorts in France**
  - COSET Cohort (National Institute for health Surveillance), ELFE birth cohort
- **Constances participates to French multidisciplinary consortiums**
  - RHU Innovation in Atherothrombosis Science (iVASC)
  - SIRIC CARPEM - Cancer Research for Personalized Medicine
  - SIRIC ILIAD-Imaging and longitudinal investigations to ameliorate decision making in multiple myeloma and breast cancer
- **Constances User Clubs bring together researchers in various scientific fields:**
  - Aging
  - Respiratory Health
  - Occupational Health
  - Women's Health

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Constances is a large population-based general-purpose **observational prospective cohort** managed as a National Research Infrastructure that contributes to the **development of epidemiologic research** and provides public health information
- Constances is an **" epidemiologic laboratory "** opened to specific **nested ancillary research studies** from academic and private, French and international research community
- Constances provides new information on the **impact of major determinants of health in the French population**, providing a sound base for targeted prevention

METHODOLOGY QUALITY

- Representativeness of the cohort ensured thanks to the **randomly selected control-cohort** (n=400 000)
- **Prospective follow-up of this control-cohort** for health and social characteristics in administrative databases
- Deep experience in database **management with high security**
- **Statistical Quality Label** (CNIS: National Committee for Statistical Information)
- High-level of bioclinical databases with SOP implementation and **intra- and inter- "Health Screening Centers" standardization**; Permanent **quality control program performed** by independent provider

INNOVATIVE SCIENTIFIC FEATURES

- **Random sample of the French adult population** (18-69 at inception)
- Identification of **prevalent and incident diseases** among the participants and ascertainment of diagnosis (notably cardiovascular events, cancers and neurodegenerative diseases)
- **Comprehensive detailed data** on health care, prescription drugs and medical devices
- **Linkage with national administrative databases** (SNDS, Cnav)

PROJECT DESCRIPTION : ARTIFICIAL INTELLIGENCE TOOLS

LINKAGE TO HEALTH DATABASES

- **With SNDS**
  - > Constances is linked to SNDS and data are available for all participants and a cohort of non-participants (twice as large as Constances) **since 2009**
  - > The main difficulties came from the volume, the complexity and the validity of SNDS database. We set up a team specifically devoted to the management of SNDS data and developed a series of tools for facilitating its use.
- **With other health database(s)**
  - > Constances is also linked to the "Caisse nationale d'Assurance vieillesse" database which provides exhaustive data on employment and job trajectories, including periods of non-employment such as unemployment
- Benefits for the cohort
  - > **Quickly available data, completeness, absence of lost to follow-up, more precise and reliable data** than those obtained by self-report for the consumption of care and hospitalizations, data available over several years before subjects enter the cohort

E-HEALTH AND PARTNERSHIPS

- Up to now, the **use of big data techniques is performed within the Constances team**, including a collaboration with an **Ecole Polytechnique team** with the aim of training Polytechnique students to work on Constances data
- Thanks to the diversity of data on health, physiological and biological parameters, lifestyle and environment collected from the participants and by linkage with administrative bases, **Constances offers unique opportunities to develop AI approaches**
- Constances is fully open to partnerships with other academic and industrial teams in that field

PROJECT DESCRIPTION : ARTIFICIAL INTELLIGENCE TOOLS

CONNECTED OBJECTS AND ALGORITHMS

- The connected objects are not yet a subject considered by the cohort mainly due to the collected data validity issue through connected objects:
  - > Constances is particularly attentive to the quality of the data and has set up an important program of quality control
  - > More validation studies are needed before including data from connected objects in Constances
- **Specific algorithms** for large quantity of data analysis within the view **to carry out AI projects** are a subject considered by Constances
  - > Up to now, **big data techniques** have been used in Constances for studying care trajectories and for appraisal of efficiency of different types of drugs
  - > Constances also uses **REDSIAM algorithms** for identifying case of specific diseases; thanks to its multiple sources of data, Constances is used to validate these algorithms
  - > Constances **intends to develop AI** in the very near future

GENOMICS

- Constances is the support of the **population-based part of the France Médecine Génomique program**; 3 000-5 000 DNA samples will be collected and whole genome sequenced
- Constances is currently **implementing a biobank for about 85 000 Constances participants**. The biobank will be open for **academic and industrial genomics projects**.

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	200 000 participants The population is that of the people in France whose health insurance is administered by the CNAM (more than 85% of the French population).
Sites:	21 Health Screening Centers (HSC) HSC located across the country and equipped to collect biomedical data
Inclusion criteria:	All subjects aged from 18 to 69 years

INCLUSION

Database:

Questionnaires: Health & lifestyle, job history, women's health, working conditions and occupational exposures

Health Examination in HSC: Anthropometry, vision, hearing, spirometry, electrocardiogram, blood pressure, basic biology; physical and cognitive functional assessment for 45 years old subjects and over

Administrative national databases (SNDS, CNAV): health care use, hospital discharge records, mortality; employment, income

Biobank:

Serum, plasma and urine collected during health examination

FOLLOW-UP

Database:

Annual self questionnaire**:** Health status, life events, smoking, alcohol,

Health Examination in HSC: every 4 years

Regular linkage with national administrative databases

DATABASE & BIOBANK CONTENTS

DATABASE

- **Health examinations and questionnaires:**
  - **Social and demographic characteristics**: Employment status, education level, marital status…
  - **Health data**: Incident and prevalent diseases, self-reported health and quality of life scales, personal and family history (cancer, cardiovascular, psychiatric), cause of death
  - **Health problems specific to women**: Treatment for menopause, osteoporosis and osteoporotic fractures, infertility and delayed childbearing, sexual transmitted diseases and issues related to sex life …
  - **Behaviors**: Smoking and alcohol consumption, dietary habits and physical activity, marijuana use and sexual orientation
  - **Occupational factors**: Job history, lifelong and current occupational exposure to chemical, physical and biological agents, postural, mechanical and organizational constraints and stress at work
- **Collection specificities**:
  - **Functional physical and cognitive capacity** assessments **every 4 years** for people aged 45 years and older
- **Linkage to administrative databases**:
  - For each subject, personal health and social data from the national health and socioeconomic **databases (SNDS, Cnav) are linked to data collected from Constances** questionnaires and health examinations. This **linkage is fully operational.**
- **Other types of specific data**:
  - **Outcome adjudication platform**: Collection of data or documents (examination or hospitalization reports, etc.) used to validate the health events and to collect detailed information essential for research
  - **Environmental data**: Geocoding of residential addresses, linkage to environmental databases
  - **Imaging data** can be collected under specific scientific projects which can be performed on part of the subject sample

BIOBANK

- **Originality**
  - A very large biobank **(85 000 subjects)**
  - A **population-based biobank**
  - A biobank **involved in the French BIOBANQUES and in the European BBMRI infrastructures**
- **Scientific objective**
  - Biobank aims to carry out future studies on:
    - **Distribution of biological parameters** in France
    - Identification of **early predictive biomarkers of diseases**
    - Various **“omics” studies**
- **Samples**
  - Blood, Serum, Urines
  - **20 aliquots per subject**
  - Total number of aliquots: **1.7 millions**
- **Associated resources**
  - The biobank is managed by Integrated BioBank of Luxembourg (IBBL) (https://www.ibbl.lu/)

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Biological samples **are centralized** in IBBL facilities in Luxembourg
- Biological samples are **identified by 2-D bar codes**

SPECIFICATIONS

- Expected date of the first sampling : **2019**
- Sampling frequency: at the **inclusion** and might be possible **every 4 years**
- Responsible for the Biobank: the **Constances team**
- Protocol for the biological sample collection available upon request but depending on the purpose
- **A large set** of data prospectively collected and stored in the Constances database (personal characteristics of the subject, health, risk factors…) are **associated for each sample**
- **Quality assurance program and Standard Operating Procedures** defined with IBBL
- Biological samples are not **available** by now but **expected to be from 2020**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biospecimens	Origin	Quantity / concentration available	No. of aliquot	No. of subjects expected to be sampled	Storage conditions
First sample collection in 2019					
Serum	Blood	500 µg	4	85 000	Liquid nitrogen
Plasma lithium heparinize	Blood	500 µg	4	85 000	Liquid nitrogen
Plasma EDTA K2	Blood	500 µg	4	85 000	Liquid nitrogen
Total Blood		500 µg	4	85 000	Liquid nitrogen
Urine	Urine	2 ml	4	85 000	Liquid nitrogen

BIOBANK SAMPLE ACCESS MODALITIES

- A **Charter** document **specifying biobank access** modalities **is available** on Constances website
- To access to Constances biological collection, **the industrial research company needs to become a Constances partner by signing a partnership** whose access modalities have already defined
- Biological samples **access will be granted on the acceptation of the research project proposal submitted** to the cohort team and reviewed by the **International Scientific Committee**. The Research application form is available on the Constances website.

BIOLOGICAL SAMPLE ANALYSES

- Several research groups have planned **to exploit the futur biospecimen through the following research projects** approved by the Constances governance:
  - Adiposity and inflammation in relation to cognitive and motor function
  - Air pollution and rhinitis
  - Asthma COPD overlap syndrome
  - Blood inflammatory patterns and asthma
  - Body composition and respiratory diseases
  - Early screening of cirrhosis complications
  - Depression and cardiovascular diseases
  - Dyspnea in respiratory diseases
  - Frailty in the elderly
  - Risk and protective factors for Parkinson's disease
  - Role of vascular risk factors in ageing phenotypes

COST

- Financial estimation for biological samples is not yet available but is currently being finalized

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- **Neuropsychological testing as young as 45**, allowing for predicting future neurodegenerative diseases during follow-up
- Establishment of normative scores for standard cognitive scores
- Study of the role of **vascular risk factors in ageing phenotypes**
- Study of the **role of obesity** on **respiratory chronic diseases**
- Definition of a **validated measure of frailty among ageing** subjects

CLINICAL DEVELOPMENT

- Use of **biochemical markers Nonalcoholic steatohepatitis (NASH)** for **mass screening**
- **Estimation of disease and risk factors prevalence** for numerous conditions
- Screening for **cervical cancer and contraception** among diabetic and obese women
- Impact of **anticholinergic drugs on cognitive functioning**

OUTCOMES RESEARCH

- Studies on **incidence, prevalence, risk factors and Surveillance of chronic respiratory diseases, diabetes, cancer….**
- Ageing and evolution of **cognitive functioning**
- Description of the use of drugs in real life, **observance and practice patterns** for several chronic diseases (diabetes, asthma…)
- **Estimation of the economic burden** of several chronic diseases (diabetes, asthma…) including medical costs and impact on employment
- Analysis of **health care trajectories**
- Impact of chronic diseases on **Quality of Life**

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https://www.elfe-france.fr/

OVERVIEW

AT A GLANCE

> Health, Environment, & Social sciences
> **Multidisciplinary cohort**: Perinatal health, growth, development, accidents and injuries, respiratory diseases & allergies, digestive health infections, mental health, healthcare consumption
> **Children**
> Scientific Coordinator : **Marie-Aline Charles**
> Coordinated by the National Institute for Health and Medical Research (**INSERM**) and National Institute for Demographic Studies (**INED**) in close collaboration with the French National Blood Service (**EFS**)
> Major Grants: ANR, IRESP

KEY FACTS & FIGURES

> **Follow-up ongoing**
> **18 329 childrens already included**
> Follow-up from birth to adulthood
> 320 participating maternity units in France in 2011 to Elfe study
> **Biobank**: cord blood, maternal urine, breast milk, maternal hair, infant stools, child urine, hair and stools
> **Administrative linkage** to death certificates, Hospital information system, Health Insurance Data Base

Elfe takes a multidisciplinary approach and aims to assess **the impact of environmental exposures, socioeconomic** and **familial factors** on children's development, health, and behavior.

Positioning

> Elfe collaborates with the Epipage 2 (premature babies) cohort in the framework of the **RECONAI platform**, funded by the ANR (PIA 1)
> Elfe is involved in the **H2020 project Lifecycle** (10 European cohorts)
> **Partnership with other international cohorts:**
  > Environment and children international birth cohort group (Japan, China, Germany), Eucconet, Millennium Cohort Study
> Elfe has already set up partnerships with **one private actor**
> Elfe is opened to set up **new partnerships with industrials**

LEADERSHIP

Marie-Aline Charles, epidemiologist at Inserm, is the director of the "Elfe" INED-INSERM-EFS joint unit. She is assisted by a deputy director, Bertrand Geay, Professor of Education at the University of Picardy.

Marie-Aline Charles, MD, PhD

- **Epidemiologist** and research director at Inserm
- **Team leader** of "Early origin of the child's health and development", Centre of Research in Epidemiology and Statistics Sorbonne Paris Cité
- Expertise: growth, obesity, metabolism, nutrition
- **Committee membership**: founding member and president of the French DOHAD Society, past member of the scientific committee of the French diabetes society and Aviesan research in Public Health group
- **Current collaborations**: environment and children international birth cohort group (Japan, China, Germany), network of European birth cohorts
- Awards:
  - Prix Ajinomoto pour la Recherche en Nutrition 2004
  - Prix de recherche Benjamin Delessert en 2011
  - Prix Guy Demarles Enfance et bien manger 2016
- More than 280 peer-reviewed publications

Bertrand Geay, Pr

- **Sociologist** and Professor at the University of Picardy
- Director of the CNRS-Picardie University mixed research center on public action and politics (CURAPP)
- Expertise: education & socialization
- **Committee membership**: early childhood national observatory
- **Current collaborations**: National institute for education of young handicaped people (INS-HEA), German national educational panel (NEPS)

SCIENTIFIC NETWORK & MANAGEMENT

- Funded European projects:
  - **FP7 ENRIECO** (Environmental Health Risks in European Birth Cohorts) coordinated by Prof. M. Kogevinas and Dr. M. Vassilaki from the Department of Social Medicine, Medical School, University of Crete, Greece
  - **H2020 LIFECYCLE** (Early-life stressors and LifeCycle health), coordinated by Pr Vincent Jaddoe, Erasmus university Medical Center Rotterdam
- Elfe also has direct links with several **major foreign cohorts**, notably :
  - The **Millennium Cohort Study** in the United Kingdom coordinated by Emla Fitzsimons, Professor of Economics, Institute of Education, London
  - **National Educational Panel Study** (NEPS) in Germany coordinated by Hans-Günther Roßbach, Director of Leibniz Institute for Educational Trajectories
- The study's scientific aspects are monitored by a scientific council made up of independent experts from France and abroad:

Health (Perinatal period accidents and injuries, Asthma, respiratory diseases and allergies, Healthcare consumption, Infectious disease):

- Frédéric Villebrun
- Juliane Léger
- Serge Hercberg
- Fred Pacaud
- Emmanuelle Rial-Sbbag

Health environment (Exposure to environmental polluants, physical exposure):

- Fanny Rancière

Social sciences (Demography & family, Socialization & education, Economic status & insecurity):

- Alain Chenu
- Michel Fayol
- Cécile Lefèvre
- Gille Pison
- Jérôme Deauvieau
- Heather Joshi
- Anne-Marie Nybo-Andersen

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Observing children born within the same year over a period of two decades will offer a unique opportunity to **identify the factors that help or hinder their development**
- Analyzing how these children find their place in **society**. Their health, their schooling, what they eat and where they live, as well as their **family and social life**, will be scrutinized by **one hundred and fifty researchers involved** in the study.
- Thanks to crossing the data collected, it will be possible to answer many **questions that parents and scientists ask** about early development, and thus **promote children's physical health and psychological well-being**

INNOVATIVE SCIENTIFIC FEATURES

- First **longitudinal study** of this nature in France
- Involve **150 researchers** from more than 80 research teams
- Nationally representative
- Elfe team had launched a **pilot survey** in 2007 in 62 maternity units to check the study's feasibility and validate the methodology before scaling it up to cover the whole of the country

METHODOLOGY QUALITY

- Every **stage** of the project and each separate **procedure** is **monitored** by the **National Council for Statistical Information** (CNIS)
- Data collected in **standardized interviews** conducted by trained interviewers
- Self-completed questionnaires firstly tested in a pilot study
- Every data file received are rendered anonymous for inclusion in Elfe's secure database

PROJECT DESCRIPTION : ARTIFICIAL INTELLIGENCE TOOLS

LINKAGE TO HEALTH DATABASE

- **With SNDS (linkage in 2018)**:
  - > For **mother health care consumption during pregnancy**
  - > For **child health care consumption** from birth to 5 years ongoing

CONNECTED OBJECTS AND ALGORITHMS

- **Academic research projects using connected objects are carrying out in the Elfe cohort**:
  - > 3 to 7 days physical activity monitoring performed by **accelerometry** in a subgroup of 400 children at 3,5 years old
  - > **Specific program developed** to characterize the level of physical activity and sleep time for young children

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	18 000 children
Sites:	**320 participating** maternity units / 51% of participation to Elfe study among the solicited mothers)
Inclusion criteria:	Children whose parents consented to their inclusion all selected purely on the basis of their date and place of birth
Exclusion criteria:	Stillbirth, birth <33 weeks of gestation and plans to move out of metropolitan France in the following 3 years

INCLUSION

Database:
Face-to-face interview with the new mother (at the maternity unit) & medical file data collection

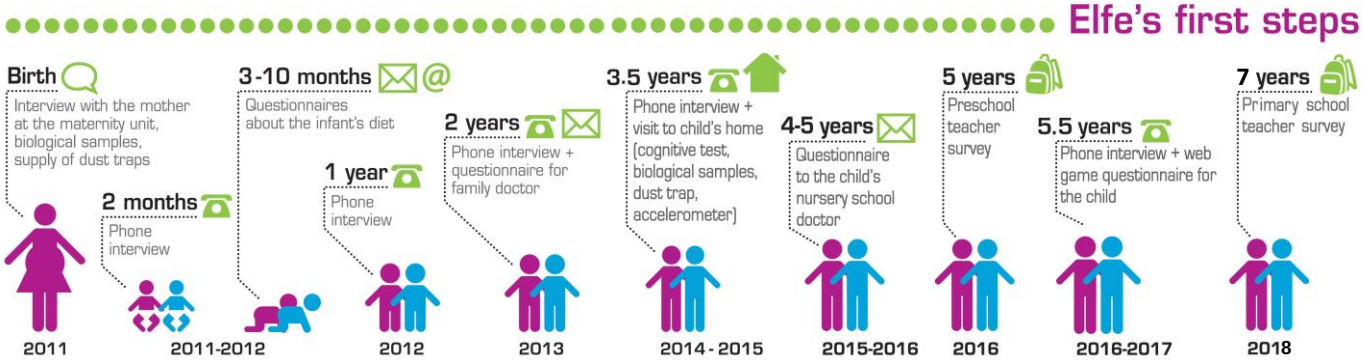
Biobank: (sub-group of 154 maternity units):
Maternal blood, various maternal material (urine, hair, breast milk)
Child : cord blood, cord fragment, meconium, & faeces

FOLLOW-UP
Database:
2 months, 1 year, 2 years, and 3,5 and 5,5 years: Phone interview
3-10 months: Postal or Internet questionnaires on child's diet
2 years: Questionnaire filled out by the family doctor
3,5 years: child cognitive testing,
4-5 years: exam by school doctor (subgroup)
4 and 6 years: teacher surveys

Biobank: *at 3 years*:
Collection of child's urine and stools

DATABASE & BIOBANK CONTENTS

DATABASE



- Retrospective data on exposures during pregnancy and then a prospective follow-up of the child:
  - > **Exposures**: medication, air pollution, occupation, tobacco, alcohol, social position, nutrition, pregnancy **complications**, health service, **contaminants**
  - > **Outcomes: birth defects, infections, immunity, asthma/allergies, pubertal development, growth/obesity, neurodevelopment, behaviors, self-esteem, quality of life**
  - > **Data available in medical files at the time of delivery**: characteristics of the newborn child (weight, size, gestational age, birth defects, circumstances of delivery)
  - > **Data gathered by questionnaires** submitted to the mother at birth, at home by an investigator and self questionnaires
  - > **Impedancemetry and spirometry**: in testing for a 9,5 year old clinical exam
  - > **Medical examinations**, hearing and neuro-psycho-motor testing at various ages
  - > Environmental measurements at home
  - > **Register-based follow-up**: death certificates, hospital information system, health insurance database

BIOBANK

- **Originality**
  - > **A large scale biobank with more than 2 500 mothers and 2 500 children sampled at enrollment associated** to a longitudinal child biobanking
- **Scientific objective**
  - > Biobank aims to carry out future studies to detect the possible presence of **infectious agents, pollutants, biomarquers** or help scientists to understand the interactions between the environment and the genome
- **Samples**
  - > Mother & child sampling at birth. Additional child sampling at 3 years follow-up
  - > A large variety of biospecimens with numerous aliquots per participants
- **Associated resources**
  - > The Elfe cohort is organized by thematic group

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- The Elfe biobank is centralized in 3 certified Biological Resources Centers at Annemasse, Bois-Guillaume and Dijon. Biological samples treatment and storage are also organized and performed by **EFS (Etablissement Français du Sang)** in sites for procedure harmonization.
- Biological samples are **stored at -80°** in certified Biological Resources Centers.
- Each biological sample is identified with unique and common label with sample tracking sheets. Theses IDs are different from the patient ID in the database. A secondary ID has been generated for the correspondence between both.

SPECIFICATIONS

- Mothers and her babies who consent to participate to Elfe study and consent to participate to the biobank part of the study performed in **154** of 349 Elfe maternity units
- Date of the first sampling: 07/06/2011
- **Sampling frequency**: At baseline, and 3 years follow up. **Planned at 9 years (currently test in the pilot cohort)**
- **Responsible for the biobank: EFS**
- Protocol for the biological sample collection exists
- **The biological collection is managed** by a multisite online dedicated software hosted by the Elfe research unit
- **Label of quality**: Elfe biobank received a bio-collection authorization from the French Ministry of Research, CODECOH n° AC-2011-1367 based on the **EFS quality standard**
- 3 participating certified BRCs for hosting biobank
- Biobank procedures were developed by the Elfe biobank coordination team in order to **apply standardized methods for sample collection, treatment and conservation** (Standard Operating Procedures)
- Elfe biological samples **are available**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biospecimens	Origin	Quantity / concentration available	No. of aliquots	No. of subjects available	Storage conditions
At Baseline in 2011					
Hair	Mothers	-	-	1477	Envelop
Breast milk	Mothers	1 mL	5	1616	Cryotube
Serum	Mothers	2 mL	3	588	Cryotube
Serum	Mothers	0.5 mL	9	1735	Frozen stick
DNA	Mothers		Extraction in progress		
Plasma	Mothers	0,5 mL	4	2740	Frozen stick
Whole blood	Mothers	0,5 mL	2	2800	Frozen stick
Urine	Mothers	19,5 mL	-	2019	
Meconium	Childs	40 mL	-	1380	Coprology pot
Stools	Childs	40 mL	-	1209	Coprology pot
Tissues	Umbilical cord	2 mL	2	981	Cryotube
Cord DNA	Cord blood		Extraction in progress		
Red blood cells	Cord blood	1 mL	6	1686	Cryotube
Plasma	Cord blood	0,5 mL	6	2481	Frozen stick
Whole blood	Cord blood	6 mL	-	286	Paxgene
Whole blood	Cord blood	0,5 mL	2	2748	Frozen stick
Serum	Cord blood	0,5 mL	10	2803	Frozen stick
During the follow-up at 3 years (in 2014)					
Urine	Childs	1 ml	20	2100	Cryotube
Stools	Childs			830	Cryotube

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **document** specifying **biobank access is available**
- To date, biological samples **are accessible** to public research teams
- Specific biological samples **access** is granted on the **research project proposal basis** selected through a call for proposal
- To access biological samples, the industrial research team needs to fill out a **specific research project proposal**, available on request

BIOLOGICAL SAMPLE ANALYSES

- Research team proposing a project needs to identify the laboratory able to perform sample analysis and to find the specific funding for biological measurements
- The results generated from sample analysis through a specific research project will be made available to the whole research community from the Elfe database

COST

- Costs related to sample release and transport to the lab will be borne by requesting research team, and if applicable, also for the cost to process aliquoting samples
- Access right to Elfe data is also mandatory in order to contribute to cohort management and sustainability. The pricing principles are currently under development.

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Study consequences of premature birth or the incidence of infections contracted by a mother during her pregnancy on the future health of her child
- Study interactions between genetics and the environment in asthma or obesity for instance
- Look at the impact of diets and weight change prior to pregnancy on the risk of delayed growth in utero

CLINICAL DEVELOPMENT

- Study on long term consequences for the child of pregnancy complications, maternal frequent diseases, drug use during pregnancy
- Studies on drugs and recourse to care for frequent child diseases or handicap

OUTCOMES RESEARCH

- Study impact of exposure to various pollutants such as lead, pesticides and phthalates (found in many plastic consumer products, as well as cosmetics)
- Investigate the possible link between the early introduction of certain foods and the risk of food allergies
- Investigate family, economic and sociocultural factors that determine children's long-term educational outcomes
- Risks posed by occupational exposure to cosmetics or working in a healthcare setting during pregnancy

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Epipage 2
Étude épidémiologique sur les petits âges gestationnels

Pr Pierre-Yves Ancel, MD, PhD
Epidemiologist and EPOPé research team leader, Inserm

Pierre-yves.ancel@inserm.fr

http://epipage2.inserm.fr/index.php/fr/

OVERVIEW

AT A GLANCE

> **Preterm birth management**, perinatal care
> **Development, child health status, respiratory diseases**, mental health, nutrition, sleep, healthcare consumption
> Very preterm children born **between 22 and 34 weeks' gestation**
> Coordinator: Pierre-Yves Ancel
> Sponsored by the National Institute of Health and Medical Research (**Inserm**)
> Funded by TGIR-IRESP, EQUIPEX – ANR and private funds

KEY FACTS & FIGURES

> **Inclusion closed**; **follow-up ongoing**
> **7 804 infants included at birth in 2011**; **5 173 included in the follow-up**
> **Followed from birth to 12 years of age**
> All maternity and neonatal units **in 25 French areas in 2011**
> **Biobank:** cord blood and maternal blood (RNA and DNA extracted), child's stools saliva and urine samples
> Administrative linkage to Health Insurance database (SNDS) planned

Epipage 2 is the **only national prospective population-based cohort on preterm births** in France.
It aims to **better understand the long-term outcome of preterm children** and **evaluate their specific needs** in term of **care and education.**

Positioning

> Epipage 2 cohort works closely **with the Elfe** (Growing up in France) cohort launched at the same time all together (more than 18 000 nationally representative children born after 24 weeks' gestation, planned to be followed-up from birth to adulthood)
> Epipage 2 is also **part of the European project RECAP preterm** (Research on children and adults born preterm in Europe).
> Epipage 2 is also **associated with the EPICE European project** (European Commission - Horizon 2020 project)
> Partnerships are set up with pharmaceutical laboratories including food industry

LEADERSHIP

Epipage 2's leadership team, led by Pr Pierre-Yves Ancel, brings together renown epidemiologists, gynecologists, paediatricians, and scientists who have been committed to the field of preterm birth management.

Pierre-Yves Ancel, MD, PhD

- **Epidemiologist**, University professor – **hospital practitioner** at Paris-Descartes University
- Team leader of the **Obstetrical, Perinatal, and Pediatric Epidemiology Team** (EPOPé), **Center for Epidemiology and Statistics** Sorbonne Paris Cité (U1153)
- **Coordinator of the Center for Clinical Investigation** P1419, Cochin – Port-Royal Hospital
- Collaborations with numerous researchers in France and abroad

SCIENTIFIC NETWORK & MANAGEMENT

- **Research on children and adults born preterm in Europe (RECAP preterm, 2017-2021)**
  - > Funded by the Horizon 2020 research and innovation program of the European Union
  - > Jennifer Zeitlin, research director at EPOPé Team, is part of the coordination team of the project
  - > Pierre-Yves Ancel and Jennifer Zeitlin are the leaders of one of the work package (hypothesis-driven very preterm child health research)
  - > **Overall aim:** to improve the health, development and quality of life of children and adults born very preterm or very low birth weight by developing a sustainable, geographically diverse and multidisciplinary platform of national and European cohorts of VPT/VLBW, that will optimize the use of population data for research and innovation in healthcare and health, social and education policy

- **Epipage 2 has direct links with several major foreign cohorts**
  - > **EPICE-SHIPS** (2011- ongoing) – Population-based cohort in 19 European regions, co-coordinated by Dr. J Zeitlin, EPOPé Team, Inserm (FP7, 2010; H2020 program 2015)
    - > *Together they offer the opportunity to study the diversity of practices for the management of preterm children in Europe.*
  - > **EPICure** in England
  - > Cohorts in Canada and New-Zealand

- **Epipage 2 Scientific committee**
  - > **Epidemiologists** : Pierre-Yves Ancel, Catherine Arnaud, Jeanne Fresson, Monique Kaminski
  - > **Gynecologists** : François Goffinet, Bruno Langer
  - > **Paediatricians:** Olivier Claris, Stéphane Marret, Jean-Christophe Roze, Véronique Pierrat

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- The Epipage 2 cohort aims to
  - > **Study short- and long-term outcomes** in very and moderately preterm babies and their families
  - > **Assess changes in medical practices** and **organization of care,** and **assess their impact on child health and development**
  - > Identify **early predictors of health** and **developmental problems**
- The Epipage 2 study also allows **to investigate very specific research areas** by setting up, within the cohort, **ancillary projects** (7) or **interventional studie**s (3)

INNOVATIVE SCIENTIFIC FEATURES

- **Co-PI of the RECONAI Platform** (Research on French birth cohorts), based on two constituent cohorts (**Elfe and Epipage 2**)
  This platform was set up
  - > **to mutualize tools** and **processes for data collection, storage access**
  - > **to promote associated projects** to test specific questions and mechanisms, using **muti-disciplinary approaches** on subsamples
- All preterm births included (including all infants live born, still born and terminations of pregnancy).
- 93% of the infants born alive have been included in the follow-up

METHODOLOGY QUALITY

- Health outcomes have been collected from medical records at birth in the maternity and neonatal units, paediatricians at 2 years follow-up, a comprehensive psychological and medical examination at 5 and a half years follow-up or from the parents (1, 2 and 5 years follow-up), via web/paper questionnaires
- Cognitive and visuo-motor assessments performed at 5 and a half years follow-up during a specific examination performed by a paediatrician and a neuropsychologist

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives: 7 804 babies included at birth; 5 170 included in the follow-up

Sites: All maternity units (540) and neonatal units (280) in the 25 participating French regions (21 of the 22 metropolitan regions and 4 overseas regions)

Inclusion criteria: Stillborn, termination of pregnancy and birth between 22 and 34 completed weeks of gestation
Only children whose parents were ≥ 18 years and agreed to participate

Exclusion criteria: Parents who declined to participate or anonymous childbirth

INCLUSION

Database:
Medical records completed by questions to obstetrical and neonatal teams
Face-to-face interview with the mothers (during their child's hospitalization in the neonatology department)
Self-administered questionnaire to the parents

Biobank:
Mother: blood collected at delivery (sub-group of 13 maternity units)
Child: cord blood (sub-group of 13 maternity units), stools (sub-group of 18 neonatal units)

FOLLOW-UP

Database:
At 1 year: Parental self-administered questionnaire
At 2 years: Parental self-administered questionnaire and doctor questionnaire
At 3 ½ years: Parental self-administered questionnaire (in a subgroup)
At 5 ½ years: Study-specific child's examination made by a physician and a neuro-psychologist (110 sites disseminated in the 25 participating regions), parental self-administered questionnaire

Biobank:
At 3 ½ years: Child's stools (in a sub-group, ancillary project)
At 5 ½ years: Child's saliva (in 14 regions), child's urines (in 7 regions, ancillary project)

DATABASE & BIOBANK CONTENTS

DATABASE

Data collected through parental self-administered questionnaires, medical and neuro-psychologist examination specifically implemented for the study

- **At Birth :**
  - *From Mother:*
    - Data on her pregnancy and delivery (complications, treatments), collected from medical records
    - Her environment and experience of this birth (face-to-face interview)
    - Physical and emotional health status before her child's discharge from the hospital (self-administered questionnaire)
  - *From Child:*
    - Child's health at birth and during his (her) hospitalization (complications, treatments, nutrition, medical management…) collected from medical records
    - Organization of care specific for preterm babies: by the collection, from the maternity units and neonatology departments
    - Information describing the medical practices used to care for mothers and babies and through the collection of information from the perinatal health networks of each region
- **During the 1 and 2 years follow-up**
  - *From Mother:*
    - Her physical and emotional health
  - *From Child:*
    - Medical management since discharge (new hospitalizations, consultations, vaccinations, treatments …), growth, health status, language, behavior and overall development, sleep, childcare arrangements). These date were completed at 2 years by the information collected from the physician (disease, psychomotor development).
- **At 5 and a half years follow-up**
  - *From Mother:*
    - Her physical and emotional health
  - *From Child:*
    - Global health since the age of 2 (new hospitalizations, consultations, vaccinations, treatments …), growth, health status, language, behavior and overall development, sleep, childcare arrangements), neuro-motor assessment (MABC-2 test), neuropsychologist assessment (NEPSY-2 and WPPSI IV tests)
- **Cerebral imaging (MRI):** A sub-group of 581 infants born between 26 and 31 completed weeks' gestation was included in the EPIRMEX ancillary project with MRI performed at term to investigate cerebral lesion
- **Linkage with the Health Insurance Database** (SNDS) planned

BIOBANK

- **Originality**
  - **A large scale biobank** with **several types of biological samples** (blood, stools, saliva)
    - **Blood** collected from mothers and preterm infants at birth
    - **DNA and RNA biobanks** (extracted from blood samples)
    - Saliva samples collected at 5 and a half years follow-up in preterm children and in a control group of term-children (initially included in the Elfe cohort)
- **Scientific objective**
  - To **further identify biomarkers** related **to preterm birth** that could be **associated with several outcome** (infections, age-related disease, metabolism…) from DNA and RNA samples extracted from blood or saliva collected at 5 and half years follow-up
  - **Ancillary studies** on the biobank:
    - **EPIFLORE-METAKID** (2011-2014): to study the relation between the development of intestinal flor and the risk of subsequent complications in very premature children
    - **EPIPRETERM** (2018-ungoing): to identify genetic/epigenetic biomarkers in the cord blood of the preterm infant in order to anticipate the risk of age-related diseases.
    - **EPIVAREC** (2018-ungoing): identify a SNP polymorphism (rs11671975), possibly involved in eating disorders
- **Samples**
  - Mother's samples : maternal blood collected at birth (n=129)
  - Child's samples: Cord blood (n=129), stools (n= 659) at birth at 3 ½ years (n=212), saliva samples (n=1335), urine samples (n=162) at 5 years
  - Samples from a term control group initially included in the Elfe cohort : saliva sample (n=254), urine sample (n=92)
- **Associated resources**
  - The Epipage 2 cohort owns the know-how, the required **equipment and the human resources** to exploit the biological samples through:
    - **Extraction the genetic material (RNA and DNA),** in collaboration with the CEPH – Jean Dausset Foundation (Centre d'Etude du Polymorphisme Humain)
    - **Identifying genetic/epigenetic biomarkers** in collaboration with the Pasteur Institute of Lille (EPIPRETERM project).
    - **Analysis of the intestinal microbiota is performed by pyrosequencing** in collaboration with INRA, Jouy-en Josas (National Institute of Agronomic Research)

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Blood and saliva sample (including DNA and RNA extracts) treatment and storage are organized and performed in collaboration with the **CEPH - Jean Dausset Foundation** which is responsible for the **biobank quality procedures**
- CEPH-Fondation Jean Dausset also ensured the **safe transport** of the Epipage 2 biological samples from each center, **procedure harmonization and their long-term conservation (-80°C)**
- Stools samples are collected and stored at -80°C into the **"Pédiatrie" bio-collection at Nantes University Hospital**
- Urines samples are stored at the **Biological Resource Centre of Nantes University Hospital**
- Each biological sample is identified by **bar codes or by an anonymous identification code**

SPECIFICATIONS

- Very preterm children born **between 22 and 34 weeks' gestation**
- **Sampling frequency**: at baseline, and at **3 ½ and 5 ½** years follow-up
- **All samples can be linked to all the other data** collected by questionnaires or after medical and psychological examinations
- **Label of quality:**
  - > Epipage 2 blood biobank received a bio-collection authorization from the French Ministry of Research (DC-2012-1649)
  - > The Biological Resource Center of Nantes University Hospital **applies standardized methods for sample collection, treatment and conservation** Epipage 2 biological samples
- Epipage 2 biological samples are available **through response to periodical calls** for proposals

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological sample	Origin	Quantity available	Number of aliquot	Number of patients	Storage conditions
At Baseline : 2011 (Child Birth)					
DNA	Mother / Child	93 µg (average)	3	129	Cryotube; -80°C
RNA	Mother / Child	29 µg (average)	3	129	Cryotube; -80°C
Stools	Child		6 +2 in case of NEC	727	Cryotube; -80°C
During the follow-up : 2014 (3 ½ years old Follow-up)					
Stools	Child		1	212	Tube RNAlater
During the follow-up : 2016 (5 ½ years old Follow-up)					
Saliva	Child	1 ml	2 tubes/ child	1335	Cryotube; -80°C
Urines	Child		1	162	-80°C

BIOLOGICAL SAMPLE ACCESS MODALITIES

- To date, biological samples are **accessible to Epipage public research teams only**
- Epipage 2 biobank **could be made available** to public and private research teams **in the future**

BIOLOGICAL SAMPLE ANALYSES

- A research team proposing a **project needs to identify the laboratory able to perform sample analyses** and **should secure specific funds** for biological measurements
- The results generated from sample analysis through a specific research project will be made available to the whole research community from the Epipage 2 database

COST

- Cost related to sample release and sample transport will be borne by the requesting team

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Pathophysiology studies for the understanding of disease etiology
  - > Microbiota
  - > Cerebral imaging
  - > Epigenetic
- Identification of biomarkers of diseases based on the correlation of biological (microbiota, DNA, RNA) and clinical data

CLINICAL DEVELOPMENT

- Development and validation of predictive models of diseases and developmental issues
- Epidemiological studies on medical practices and drugs to evaluate and improve current perinatal care
- Implementation of clinical trials based on the population of children included in the cohort

OUTCOMES RESEARCH

- Long-term consequences of very preterm births
  - > Growth
  - > Health
  - > Motor, sensory and cognitive outcomes
  - > School performance
  - > Quality of life
- Impact of medical practices as well as organization of child health care and development
- Evaluation of perinatal and early childhood needs
- Family impact of a preterm birth

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Project ESME:

Epidemio-Strategy & Medical Economics in metastatic breast cancer, ovarian cancer and advanced & metastatic lung cancer

ESMÉ
unicancer

Dr Mathieu Robain
M.D, Ph.D, Head of real world data at Unicancer

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OVERVIEW

AT A GLANCE

> **Monitoring cancer therapeutic management and the patient care**
> Three platforms:
>> **Metastatic breast cancer** (MBC)
>> **Ovarian cancer** (OC)
>> **Advanced and metastatic lung cancer** (AMLC)
> **Coordinated by R&D Unicancer Group for all contributing sites**
> Global funding by private partners

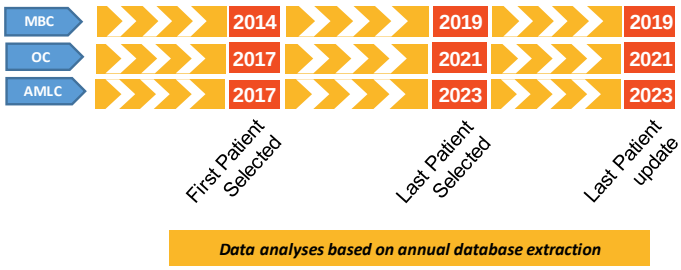
KEY FACTS & FIGURES

> Status: **retrospective data collection**
> **Metastatic breast cancer**: +21 000 cases selected and completed / **26 000 cases expected**
> **Ovarian cancer**: +6 000 cases selected and completed / **14 000 cases expected**
> **Advanced and metastatic lung cancer**: +11 000 cases selected and completed / **26 000 cases expected**
> French **multicentric** retrospective cohort populated using existing data
> No Biobank
> Linkage to SNDS: submission to be planned

ESME cohorts aim to describe the **evolution of patient care and the therapeutic strategies in routine practice.**

Project brief summary:

> Population of **existing data from patient medical files** without clinician's intervention in the data collection
> All consecutive patients treated for a MBC, an OC or an AMLC in the contributing centers
> Provide **data on relevant outcomes** such as survival (OS) or alternative endpoints (PFS, ..)
> **Scientific analysis projects** are performed based **on annual database locks** through the period of time



Positioning

> To our knowledge, ESME is a unique program which centralizes a such amount of data on metastatic breast, ovarian and lung cancers
> Partnership with 7 private companies through multi-year partnerships

LEADERSHIP

Mathieu ROBAIN, MD, PhD, *Epidemiology and Public Health*

- 4 years at INSERM U292 on HIV national cohorts developing epidemiological research projects
- Manager of a Clinical Research Organization for Biometrics services dedicated to managing clinical data from clinical and epidemiological studies in various pathologies for 10 years
- Medical Director in a global service company supporting the development of clinical trials and epidemiological studies providing methodological expertise to medical experts, institutions and pharmaceutical firms, particularly in Oncology
- Director of the Medical Data Unit at R&D Unicancer in 2014 developing the ESME Program dedicated to the Real World Data in Oncology

SCIENTIFIC NETWORK & MANAGEMENT

- Committees overseeing the program:
  - Scientific Committee
  - Deontology Committee
  - International Advisory Board

- ESME gathers a network of clinicians and epidemiologists

- The ESME Scientific Committee is organized around three work packages including well-known experts:
  - Metastatic breast cancer Group
  - Ovarian cancer Group
  - Advanced and metastatic lung cancer Group

Scientific Committee's President is Dr David PEROL, Centre Léon BERARD, Lyon.

- The role of this Scientific Committee mainly consists to define the scientific missions and valorization of research projects

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- To enable the description and understanding of the **impacts of innovation on the evolution** of metastatic breast, ovarian and lung cancer's **medical care**, over a period of time **framing the arrival of innovative drugs**
- To provide data to support **the Health Economic Models** and requirements from **Health Technology Assessment** (HTA) bodies

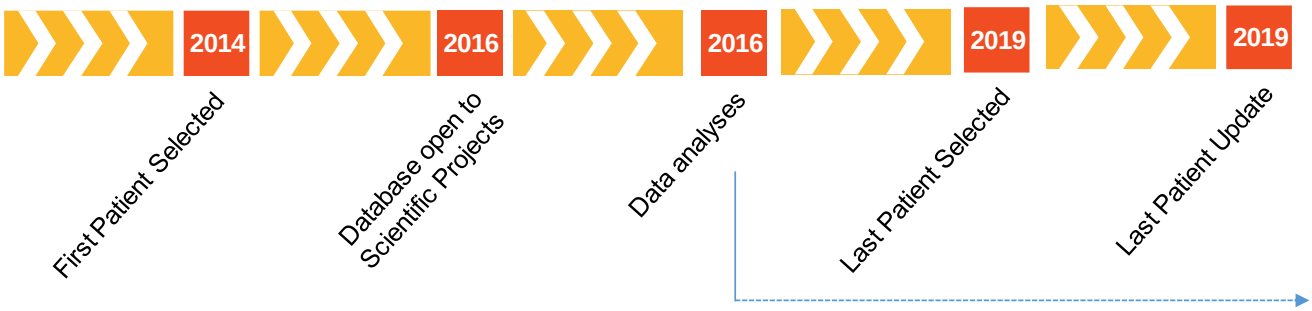
INNOVATIVE SCIENTIFIC FEATURES

- Real-life data provide additional information to clinical trial data and contribute to the improvement of scientific knowledge
- **National multicentric** database
- **Unique electronic tool for data collection** with dynamic edit checks
- Database available for scientific projects submitted by participating center's researchers; projects being validated by Scientific and Ethical Committees
- **Development of research projects on artificial intelligence**

METHODOLOGY QUALITY

- In each participating center, data collection is available on the basis of the variables defined by the plateform to be collected from patients
- **Compliance with recommendations** for best practices applicable to the fields
- Data control, validation and coding of centralized data
- **Supervision of expert groups** for the planning, execution and follow-up of the project
- **Random on-site quality review process** on all screened cases
- **Annual (internal and external) audit program** : data management, project management, on-site operations, project providers

DESIGN, METHODOLOGY & TIMELINE: METASTATIC BREAST CANCER PLATEFORM



Recruitment objectives:	26 000
Sites:	All French Comprehensive Cancer Centers (20 FCCC)
Inclusion criteria:	- Initial therapeutic management -completely or partially- (by radiotherapy, chemotherapy, targeted therapy or endocrine therapy) for metastatic breast cancer - From 2008 - Adult population
Exclusion criteria:	Other metastatic cancer

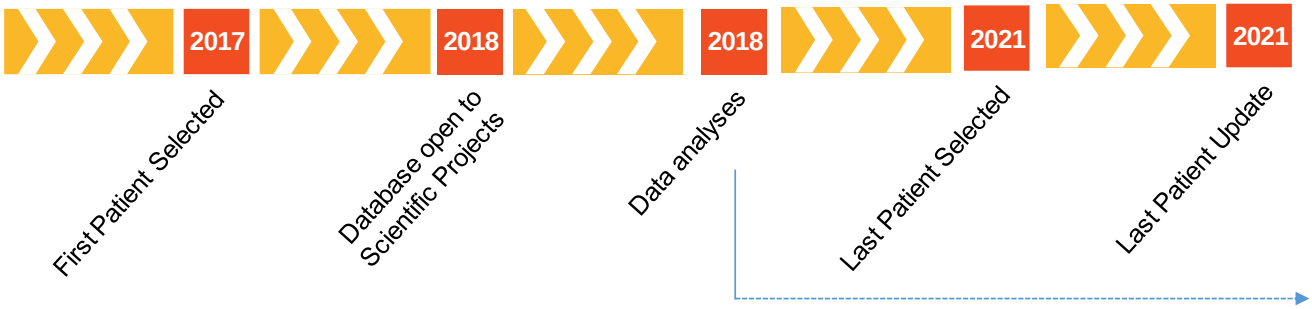
INCLUSION

Database:
Standardized and scalable collection of data on patient characteristics (socio-demographic, comorbidities), characteristics of the tumor, integrating molecular biology, management characteristics (type of treatment, number of lines, reason for termination...), care consumption (hospitalizations, medications, acts,...) and patient follow-up throughout the metastatic breast cancer medical care

FOLLOW-UP: based on routine practice

Database:
Patient's follow-up data update on an annual basis

DESIGN, METHODOLOGY & TIMELINE: OVARIAN CANCER PLATEFORM



Recruitment objectives:	14 000
Sites:	All French Comprehensive Cancer Centers (20 FCCC)
Inclusion criteria:	-Therapeutic management of ovarian cancer (by surgery, chemotherapy, targeted therapy, immunotherapy, endocrine therapy or radiotherapy) - From 2011 - Adult population
Exclusion criteria:	Other metastatic cancer

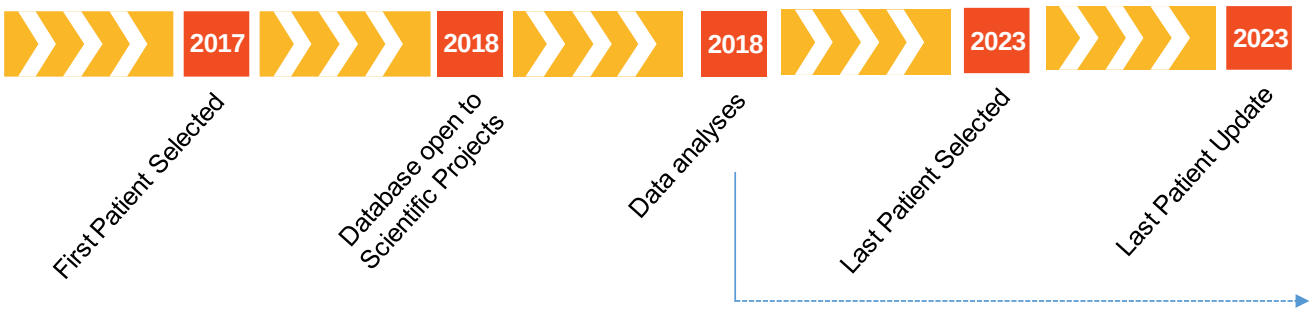
INCLUSION

Database:
Standardized and scalable collection of data on patient characteristics (socio-demographic, comorbidities), characteristics of the tumor, integrating mutation screening, management characteristics (surgery, type of treatment, number of lines, reason for termination...), care consumption (hospitalizations, medications, acts,...) and patient follow-up throughout the ovarian cancer medical care

FOLLOW-UP: based on routine practice

Database:
Patient's follow-up data update on an annual basis

DESIGN, METHODOLOGY & TIMELINE: ADVANCED AND METASTATIC LUNG CANCER PLATEFORM



Recruitment objectives:	26 000
Sites:	36 clinical centers (50% FCCC centers, 50% university and general hospitals)
Inclusion criteria:	-Therapeutic management of lung cancer (by chemotherapy, targeted therapy, immunotherapy or radiotherapy) or diagnosis of metastatic lung cancer - From 2015 - Adult population
Exclusion criteria:	Other metastatic cancer

INCLUSION

Database:
Standardized and scalable collection of data on patient characteristics (socio-demographic, comorbidities), characteristics of the tumor, integrating mutation screening, management characteristics (type of treatment, number of lines, reason for termination...), care consumption (hospitalizations, medications, acts,...) and patient follow-up throughout the lung cancer medical care

FOLLOW-UP: based on routine practice

Database: Annual patient's follow-up data update

DATABASE CONTENTS

- Hospitalization Database (20+ variables)
  - Hospitalizations: dates, diagnoses, GHS code
  - Medical procedures (inc. Radiotherapy): dates and code

- Treatment Database (10+ variables)
  - Pharmacy record: dates, cytotoxic drugs, therapeutic protocol and other concomitant drugs

- Patient Database (200+ variables)
  - Collection based on patient medical records
  - Patient data:
    - Demographics
    - Cancer management
    - Clinical events (progression, relapse)
    - Pathological report
    - Metastatic disease
    - Anti-cancer treatment (chemotherapy, endocrine therapy, immunotherapy, targeted therapy), and other therapeutic care (radiotherapy, surgery) or supportive care

Data administration using an Oracle Solution and hosted by a « Certified Personal health data hosting » provider

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Pathophysiology studies for the understanding of disease history (etiology)
- Development and validation of novel measurement scales and disease models

CLINICAL DEVELOPMENT

- Validation of biomarkers to define clinical stages and improve therapeutic guidance
- Optimization of clinical studies (timing, measures and scales, sub population characterization, design…)
- Epidemiological studies to support market access

OUTCOMES RESEARCH

- Pharmaco-epidemiological studies: drug safety, "real-world" use, effectiveness, practices patterns, acceptance, risk/benefit, risk management
- Pharmaco-economic studies cost/benefit; Health economic outcomes
- Comparative studies to assess product efficiency

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« Données de vraie vie en oncologie. Méthodologie de constitution d'une plateforme de données exhaustive multisource : l'exemple de la base ESME » - Guesmia T (*Unicancer Paris*) and al.

ESME Advanced and metastatic lung cancer

22e CPLF 2018 - Poster:

> "**Programme Epidémio-Stratégie Médico-Economique: une base nationale de données de vie réelle pour mieux comprendre la prise en charge du Cancer Broncho-Pulmonaire en France**" Robain M (*Unicancer Paris)* and al.

ESME Metastatic Breast Cancer

ASCO Posters:

> "**Assessment of multiple endocrine therapies for metastatic breast cancer in a multicenter national observational study**" - Le Saux O (*Centre Léon Berard, Lyon)* and al.

> "**Evolution of overall survival according to year of diagnosis (2008-2014) and subtypes, among 16703 metastatic breast cancer (MBC) patients included in the real-life "ESME" cohort**" - Delaloge S (*Institut Gustave Roussy Villejuif*) and al.

ESMO Posters:

> "**Use of Everolimus in advanced hormone receptor positive metastatic breast cancer in a multicenter national observational study**" - Cottu P (*Institut Curie Paris*) and al.

> "**FICHE-YOUNG: FIrst-line treatment CHoicE in hormone receptor positive (HR+)/ HER2- negative metastatic breast cancer patients (MBC) ≤45 years old. A large observational multicenter cohort survival analysis**" - Pistilli B (*Institut Gustave Roussy Villejuif*) and al.

> "**Survival of patients with aromatase inhibitors sensitive HR+/HER2 - metastatic breast cancer treated with a first-line endocrine therapy or chemotherapy in a multicenter national observational study**" - Jacquet E (*Centre Léon Berard, Lyon)* and al.

SABCS Posters:

> "**Overall survival (OS) of women with HER2 positive (HER2+) metastatic breast cancer (MBC) by adjuvant trastuzumab (aT) treatment in the large scale French ESME UNICANCER program**" – Saghatchian M (*Institut Gustave Roussy Villejuif*) and al.

> "**Impact of loco-regional treatment (LRT) on overall-survival (OS) in patients with de novo metastatic breast cancer (MBC): results of the French ESME multicenter national observational program**" - Pons-Tostivint E (*Institut C. Regaud Toulouse*) and al.

> "**Impact of age at diagnostic of metastatic breast cancer on overall survival in the real-life "ESME" cohort**" - Frank S (*Institut Curie Paris*) and al.

> "**Oral etoposide (VP-16) in heavily pre-treated metastatic breast cancer: a multicenter national observational study**" - Lerebours F (*Institut Curie Paris*) and al.

> "**Real-life activity of eribulin among metastatic breast cancer patients in the multicenter national observational ESME program**" - Jacot W (*Institut du Cancer de Montpellier*) and al.

E3N – E4N:

Etude épidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale
Etude épidémiologique des enfants de femmes de l'Education Nationale

ITMO Santé publique

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http://www.e4n.fr/

OVERVIEW

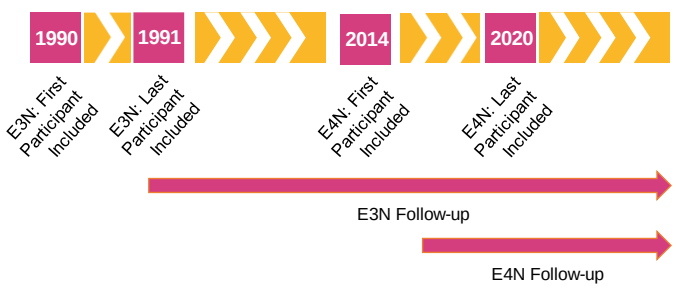
AT A GLANCE

> Factors influencing **the development and evolution of cancer** and **other chronic diseases**
> **Epidemiological** approaches combining **exposome and constitutional factors**
> **E3N Scientific coordinator**: MC Boutron-Ruault
> **E3N Partners**: Inserm (sponsor), Gustave Roussy, MGEN, Ligue contre le Cancer
> **E4N Scientific coordinator**: Gianluca Severi
> **E4N Partners**: Inserm (sponsor), Paris Sud University, Gustave Roussy
> E4N funded by **PIA/ANR**; E3N funded through **international and national research**

KEY FACTS & FIGURES

> Status:
  > E3N: ongoing follow-up since 1991
  > E4N: recruitment started in 2014, **20 000 participants already included** by June 2018 while 90 000 are expected
> **Biobank**: saliva blood and DNA for E3N included, collection of tumor tissue actually on going; saliva for all recruited participants for E4N
> **Administrative database linkage**: MGEN and CepiDC databases (E3N); SNDS expected (for both E3N and E4N)

The **E3N** is a **prospective** cohort of 98 995 **French women** initiated in 1990 to investigate the **risk factors associated with cancer** and **other major non-communicable diseases in women**.
E4N is a **prospective** cohort study based on E3N that will ultimately **include the spouses (G1)** (specifically, the fathers of E3N women's children), **children (G2), and grandchildren (G3)** of the E3N women.
E3N-E4N is a "family cohort" built on **3 generations**. It will expand the E3N cohort study by investigating **health and diseases in men as well**, and by creating a suitable framework to investigate **familial aggregations of diseases** through common **exposures and/or genetics**.



Positioning

> E3N is the French component of the European **EPIC Cohort** (500 000 subjects)
> E3N-E4N will be **one of the largest and internationally recognized multi-generation cohort**
> Participation of E3N in the **LifePath project** (social inequalities and biological pathways to health and diseases, funded by H2020) and in numerous consortia and collaborative projects with French and international academics
> **Several companies** are already **E4N partners** and E3N-E4N are opened to set up new collaborations with industrial or academic partners

LEADERSHIP

E3N-E4N's leadership team, led by Gianluca Severi, brings together epidemiologists and clinicians, who have been committed in the field of etiology of major chronic diseases for more than 20 years.

Principal Investigators

Gianluca Severi, PhD
DR Inserm, Cancer epidemiology and methodology
- Previous co-PI of the Melbourne cohort (MCCS)
- Steering Committee of the EPIC cohort
- Scientific Committee of La Ligue Contre le Cancer – Grand Ouest, partner of the Lifepath consortium
- More than 291 publications, H-index 57 (Web of Science)

Marie-Christine Boutron-Ruault, MD
Nutritional epidemiology, diseases of the digestive tract
- Steering Committee of the EPIC cohort
- Vice-President of the Inserm Commission CSS6
- Vice-President of the ANSES Expert Committee in Human Nutrition
- E3N-CVD program with Fédération Française de Cardiologie
- More than 670 publications, H-index 72 (Web of Science)

Guy Fagherazzi, PhD
Senior scientist, diabetes epidemiology, e-health
- Coordinator of the diabetes program in E3N-E4N
- Collaborations with industry (e.g. Nokia-Withings) to implement and evaluate the use of connected objects in epidemiological cohorts
- More than 180 peer-reviewed publications, H-Index 51

Working groups

- **Cancer**: G Severi, MC Boutron-Ruault M Kvaskoff, C Besson, P Arveux, A Fournier
- **Pharmaco-epidemiology**: A Fournier
- **Diabetes**: G Fagherazzi, F Bonnet
- **Parkinson disease**: A Elbaz, M Canonico
- **Cardiovascular disease**: MC Boutron-Ruault , C Mounier-Vehier
- **Nutrition**: MC Boutron-Ruault
- **Environmental exposures and chronic diseases**: F. Mancini
- **Endometriosis:** M Kvaskoff
- **Asthma/respiratory diseases**: R. Varraso
- **Depression**: E. Corruble
- **Rheumatoid Arthritis:** R. Seror

SCIENTIFIC NETWORK & MANAGEMENT

- **E3N is the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC)**
  - **EPIC** was initiated in 1992 to investigate the relationships between diet and cancer and other chronic diseases
    - The EPIC study is hosted by the International Agency for Research on Cancer (IARC, Lyon, France) and jointly coordinated by Pr Elio Riboli (Imperial College, London), Dr Marc Gunter and Dr Paul Brennan (IARC Lyon). EPIC has received substantial financial **support from the Europe Against Cancer Program** of the **European Commission.**
    - In 1993, a portion of the E3N cohort (women who answered the dietary questionnaire; n = 74 529) was included in the EPIC study
    - EPIC is a cohort of 521 000 participants recruited across **10 European countries and followed for almost 15 years**
    - MC Boutron-Ruault and G Severi are members of the EPIC Steering Committee as representatives of E3N (EPIC-France)
    - The **E3N-E4N's team is actively involved in different working groups** such as Breast cancer, Colorectal cancer group, Nutrition, InterAct-Diabetes, Lymphoma, Thyroid cancer …
    - EPIC is **member of the NCI Cohort Consortium**
- **Participation to other international consortia**:
  - **LifePath** (social inequalities and health, funded by H2020)
  - **Premenopausal Breast Cancer** Collaboration
  - **ESCAPE** and **ELAPSE** (air pollution); **EPITHYR** (thyroid cancer)
  - Various consortia for the study of molecular markers related to cancer and other diseases

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Main objective: establishing the largest French family cohort and one of the largest in the world to study the **familial aggregation of health condition and health determinants** including transmitted **genetic factors**, **markers of exposure** (i.e. transmissible epigenetic modifications) **and behaviors**
- Secondary objectives: establishing a cohort **with innovative digital tools** for data collection and follow-up of the participants
- Domains of research:
  - > **Genomics, epigenomics and other omics** as markers of exposures, behaviors and health status
  - > **Pharmacoepidemiology**
  - > **E-Health and e-Epidemiology**: evaluation of the impact of the use of **connected objects** on health and randomized intervention studies nested in E4N

INNOVATIVE SCIENTIFIC FEATURES

- E4N: development of an **innovative and flexible web platform** conceived as **a "Data Hub"** to collect and manage data from various sources
- E4N: integration of **new technologies** and the use of **connected devices** to collect high-quality data
- E3N-E4N **technical platform** set up for ancillary studies (access to existing data and samples, data acquisition, validation and coding of pathologies, validation of new tools (questionnaires, e-tools))
- **Multi-generational** cohort

SCIENTIFIC OBJECTIVES

- **Whole genome sequencing** (on DNA samples from tumors, adjacent normal tissue as well as blood and saliva samples)
- **Methylation profile studies on breast cancer in the E3N cohort** (≈ 600 breast cancer cases/600 controls; as part of collaborative projects within EPIC)
  - > To identify and study mutational signatures and methylation changes linked to cancer
  - > To try and link such marks to their causes (e.g. exposures to environmental changes)

METHODOLOGY QUALITY

- State of art management tools: structured data management, cleaning and storage, validation of health events are ensured by the "Health across generations" group, part of the CESP (Centre de Recherche en Épidémiologie et Santé des Populations, Inserm U1018)
- Certification ISO9001: process under way (for data acquisition/data management and statistical analysis process)
- E3N: validation of self-reported diseases through medical records and, for certain diseases, through the MGEN database
- EFS and CRB are certified structures for storing and processing biological samples
- Epiconcept as service provider for the management of the IT infrastructure of the E3N-E4N databases

PROJECT DESCRIPTION: ARTIFICIAL INTELLIGENCE TOOLS

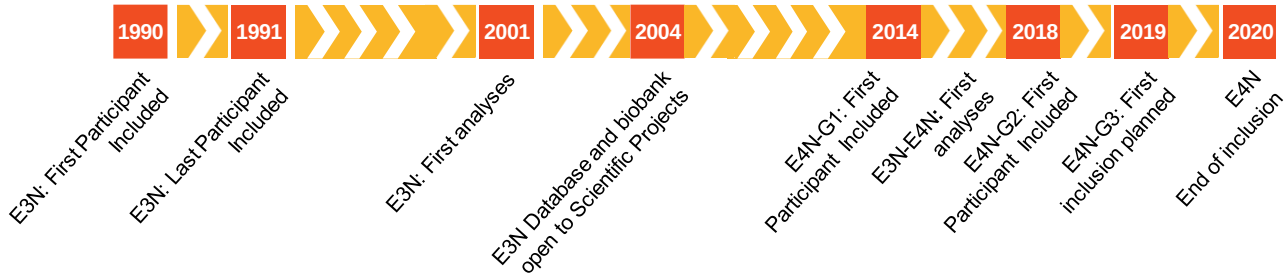
LINKAGE TO HEALTH DATABASE

- The E3N cohort is linked to the **MGEN reimbursement database since 2004** (ie. 14 years of data) and to CepiDC (mortality data)
- The reflection has been initiated for **a linkage to SNDS** with the executive committee and the sponsor (INSERM)
- There are several **key benefits to a linkage**:
  - To **identify or validate use of specific drugs** by the cohort participants
  - To **identify or validate health-related events**
  - To work on **trajectories of care**
  - To develop **large sized pharmacoepidemiology studies** with precise information on both drug use and cofactors

CONNECTED OBJECTS, ALGORITHMS AND ARTIFICIAL INTELLIGENCE

- E3N/E4N is currently involved in two public-private partnerships
  - **Nokia/Withings**
    - Objectives of the partnership: working on the use of **connected devices for e-epidemiology and identify innovative digital biomarkers of health**
    - Research axis: identifying **markers of sleep and physical activity** associated with obesity, type 2 diabetes or breast cancer survival
  - **Epiconcept**
    - Objectives of the partnership: working on the use of **social media data for medical research** and **classify patients' emotions** from textual data using **AI approaches** (Natural Language Processing, Deep Learning) / develop a chatbot (AI-based computer program which acts as a conversational agent to simulate inclusion and follow-up in a worldwide virtual e-cohort study).
    - Research axis: Identifying **patterns of diabetes-related distress** from Twitter data

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives:	E3N	ca 90 000 women included
	E4N-G1	18 000 men, objective of 25 000
	E4N-G2	Objective of 50 000 children (ongoing)
	E4N-G3	Objective of 20 000 great children (will start in 2019)
Inclusion criteria:	E3N	Women born between 1925 and 1950 and insured by the MGEN
	E4N-G1	Men who had at least one child with a E3N woman;
	E4N-G2	Children of a E3N woman
	E4N-G3	Grand children of a E3N woman
Exclusion criteria:	None specified	

INCLUSION E3N
Database:
Socio-economic status, health status, gynecological past, tobacco, physical activity, body silhouette over the life course, personal and familial medical history, medication…

INCLUSION E4N
Database:
Socio-economic status, tobacco, alcohol, physical activity, anthropometry, hormones and reproductive health, health status, strass and depression, personal and familial medical history, medication…
Biobank:
Saliva (18 000 samples already collected and 70 000 expected before 2020)

FOLLOW UP E3N
Database:
Socio-economic and health status, diet, tobacco, alcohol, physical activity, anthropometry, hormones and reproductive health, healthcare consumption, stress and depression
Biobank:
Blood (25 000 in 1996-1999), saliva (47 000 in 2009-2010), tumour tissues in some case
FOLLOW UP E4N
Database:
Socio-economic and health status, diet, tobacco, alcohol, physical activity, anthropometry, hormones and reproductive health, healthcare consumption, stress and depression…
Biobank (expected before 2024):
Samples of blood, urine, feces, hair, and nails from a deeply-phenotyped sample of 20 000 E4N participants

DATABASE & BIOBANK CONTENTS

DATABASE

E3N Database

- Type of collected data **by self questionnaire**:
  - Administrative (vital status)
  - Health status and outcomes, treatments, causes of death, lifestyle, diet, reproductive history, anthropometry
  - Clinical (anatomo-pathology report and other medical documents including diagnostic)
  - Biological data (biomarkers, …)
  - Environmental data (air and food pollutants databases)
- **Linkage of the database** with others databases:
  - E3N: operational (RNIPP, CéPiDC, the MGEN reimbursement database since 2004) and in progress (SNDS)
- **Mammographies** are collected (9 000 women, repeated over time)

E4N-G1 Database

- Type of collected data **by self questionnaire:**
  - Administrative (vital status)
  - Health status and outcomes, treatments, causes of death, lifestyle, diet, anthropometry
  - Clinical (anatomo-pathology report and other medical documents including diagnostic)
  - Biological data (biomarkers, …)
  - Environmental data (air and food pollutants databases)
- **Linkage of the database** with others databases:
  - E4N: operational (RNIPP, CEPIDC) and in progress (SNDS)

E4N-G2 and G3 databases

- The **recruitment has been launched in May 2018** exclusively **through the web-portal** (main difference with respect to E3N and E4N-G1)

BIOBANK

- **Characteristics**
  - **2018**: 25 000 blood samples (E3N), 65 000 saliva samples (E3N-E4N)
  - **2020**: 135 000 saliva samples expected (after collection of samples from E4N-G2 and G3)
  - **2024**: (pending financing) collection of blood, urine, feces, hair, and nails from a deeply-phenotyped sample of 20 000 E4N participants that will be used to identify biomarkers **2017-onwards**: tumor tissue collection (e.g. initial focus on breast cancer; it will be extended to other cancer types)
- **Originality**
  - **Large size of biological samples** (e.g. 67 000 saliva samples collected/130 000 expected)
  - **Multi-generation collection** (e.g. DNA samples belonging to three generations of at least 20 000 families)
  - **The possibility to collect samples at different times** for the same individuals
  - The E3N biobank **linked to the European EPIC cohort study**: a mirror E3N biobank is located at IARC, Lyon
- **Scientific objective**
  - **To identify biomarkers of risk** of chronic disease: numerous studies have been conducted using serum / plasma samples constitutional DNA samples, tumor DNA samples (to identify genetic and epigenetic markers of the carcinogenic processes)
  - **To identifiy biomarkers of exposure / physiology**: using serum / plasma samples and DNA samples for assessing modifications of DNA methylation due to externals factors)
  - **To study the microbiome and identify dysbiosis** linked to “exposures” and disease

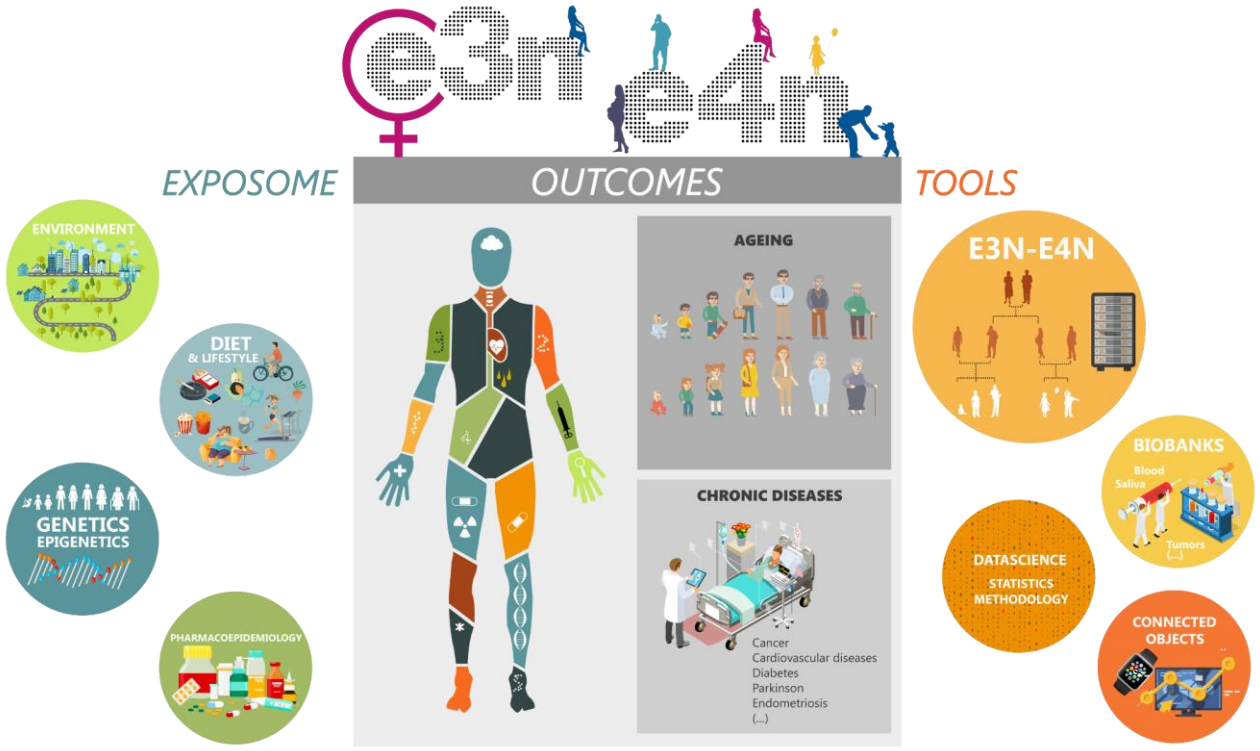
TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- **The E3N blood samples** are centralized **in EFS Annemasse**
- The **E3N-E4N DNA samples** are centralized in the **CRB Bicêtre**
- The **E3N-E4N saliva samples** are currently centralized at **Gustave Roussy** but will be transferred in another facility before the end of 2018
- The E3N blood biobank is the **mirror-biobank of the French-EPIC biobank**, centralized at **IARC-Lyon**
- The biological sample identification system is based on **bar codes**

BIOBANK-ASSOCIATED DATABASE

- An anonymized database associated with the biobank includes:
  - > Basic information on the participant
  - > Conditions of the sample collection
  - > Storage, traceability
- The biobank database is linked to E3N and E4N database



BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological sample	Status *	Origin of the sample	Quantity of the sample/ concentration available	Number of aliquot	Number of participants who have been sampled (expected/ ongoing	Preservation or storage conditions	Characteristic of the samples**
At Baseline							
Saliva (E4N) 2014-	no selection on A/NA criteria	saliva	2ml (+ 2ml solution)	1	18 000 (98 000 expected)	-20°C	saliva collection kit (Oragen 500)
During the follow-up							
Blood (E3N) 1996-1998	idem	blood retrieval	14 straws, 0.5ml/ straw	plasma : 6 Serum: 4 Buffy coat: 2 Erythrocytes: 2	25 000	in liquid nitrogen	plastic straws : serum, plasma, buffy coat and red blood cells
Saliva (E3N) 2009-2010	idem	saliva	2ml (+ 2ml solution)	1	47 000	-20°C	saliva collection kit (Oragen 500)
DNA (E3N-E4N)	case-control	blood or saliva		1 or 2	approx 4 000	-80°C	
Tissues biopsies 2017-	A (first: breast cancer on samples from Gustave Roussy Institute)	breast (lung, prostate, lymphoma expected)				frozen / parafin embedded	tumour tissue

A: Affected; NA: Non Affected

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **charter specifying biobank** (and associated data) **access is available** since 2014 for E3N and in 2018 for E4N
- **Biological samples**, including DNA, **may be accessed** by external researchers (**academic or private actors**) for research use under the conditions set in the charter
- Specific biological samples access will be granted **on the acceptation of the research project proposal submitted** to the relevant steering committee (E3N / E4N)
- To access biological samples, the applying academic or private team needs to:
  - > Follow the specific process defined in the charter
  - > Sign a research agreement
- **Biological samples cannot be transferred** to or accessed **by a foreign private company**

BIOLOGICAL SAMPLE ANALYSES

- **Analyses** based on the E3N-E4N biological samples are **performed in external laboratories** that vary according to the type of analysis and the type of biological sample and biomarker
- The biological sample analysis-derived data may be accessible to public and to private/industrial teams upon evaluation of project proposals

COST

- **Access to biological samples is associated with a cost** that includes sample identification, retrieval, preparation and shipment
- Costs depend on the project and are **provided upon request**

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- **Elaboration of scores to predict disease risk** (e.g. coronary heart disease or cancer risk) or disease evolution. Through E3N, it may be possible for high-quality proposals to request access to EPIC data and biobank.
- **Pathophysiology studies** to understand the etiology and evolution of chronic diseases
- **Development and validation of novel measurement scales** and disease models

CLINICAL DEVELOPMENT

- **Validation of biomarkers** for early-detection of major chronic diseases
- Validation of biomarkers of exposure to environmental pollutants
- Validation of biomarkers of healthy / unhealthy behaviors
- **Identification and validation of digital biomarkers**, or **AI-based algorithms**
- **Real-life studies** on **connected medical devices** or **smartphone apps**
- **Interventional studies TWICs** (Trials Within Cohorts): for example to attempt to modify unhealthy behaviors and disease risk

OUTCOMES RESEARCH

- **Pharmaco-epidemiological studies** : identification of protective and/or deleterious effects of large scale treatments on other conditions such as cancer
- **Pharmaco-economic studies** on screening procedures and prevention strategies
- **Quality of life studies**: for example on cancer survivors or on people with other chronic diseases such as diabetes
- To conduct studies on **multi-morbidities or co-morbidities**
- Studies on **Patients-Reported Outcomes**

BIBLIOGRAPHY

- More than 800 publications in total, including
  - **E3N Cohort profile***: Clavel-Chapelon F. Int J Epidemiol. 2015. Cohort Profile: The French E3N Cohort Study.*
  - Publication related to the collaboration with Nokia/Withings: *Fagherazzi G et al. JMIR 2017. An International Study on the Determinants of Poor Sleep Amongst 15,000 Users of Connected Devices.*
- Major recent publications based on E3N/E4N cohort data in top international journals
  - Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjønneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajès V, et al. **General and abdominal adiposity and risk of death in Europe**. *N Engl J Med*. 2008 Nov 13;359(20):2105-20.
  - Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, Ricceri F, d'Errico A, Barros H, Bochud M, Chadeau-Hyam M, Clavel-Chapelon F, et al; LIFEPATH consortium. **Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women**. *Lancet.* 2017 Mar 25;389(10075):1229-1237.
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  - Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Chen C, Goodman G, Field JK, Liloglou T, Xinarianos G, Cassidy A, McLaughlin J, Liu G, Narod S, Krokan HE, Skorpen F, Elvestad MB, Hveem K, Vatten L, Linseisen J, Clavel-Chapelon F, et al. **A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25**. *Nature*. 2008 Apr 3;452(7187):633-7.
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  - Kvaskoff, M.; Bijon, A.; Mesrine, S.; Vilier, A.; Baglietto, L.; Fournier, A.; Clavel-Chapelon, F.; Dossus, L.; Boutron-Ruault, M.-C. **Association between melanocytic nevi and risk of breast diseases: The French E3N prospective cohort**. *PLoS Med*. 2014, 11, e1001660, doi:10.1371/journal.pmed.1001660.
  - Fournier, A.; Mesrine, S.; Gelot, A.; Fagherazzi, G.; Baglietto, L.; Clavel-Chapelon, F.; Boutron-Ruault, M.-C.; Chabbert-Buffet, N. **Use of Bisphosphonates and Risk of Breast Cancer in a French Cohort of Postmenopausal Women**. *J. Clin. Oncol*. 2017, 35, 3230–3239, doi:10.1200/JCO.2016.71.4337.
  - Touvier M, Kesse E, Clavel-Chapelon F, Boutron-Ruault MC. **Dual Association of beta-carotene with risk of tobacco-related cancers in a cohort of French women**. *J Natl Cancer Inst*. 2005;97(18):1338-44.
- Congress co-organization (with AVIESAN and AFCROs):
  - International Workshop on E-tools for epidemiology, Paris, May 2013.
  - International Conference on e-Health Research (EHR2016), Paris, October 2016. (http://ehr2016.com/).

FREGAT:

FRench EsoGAstric Tumor database

aviesan
ITMO Santé publique

FREGAT
Base de Données Nationale
Des Cancers Oeso-Gastriques

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OVERVIEW

AT A GLANCE

> **Oncology**
> **Oesophago-gastric** Cancers
> Coordinated by Pr Guillaume PIESSEN
> Lille University Hospital Sponsorship
> Funded by INCa and private funds

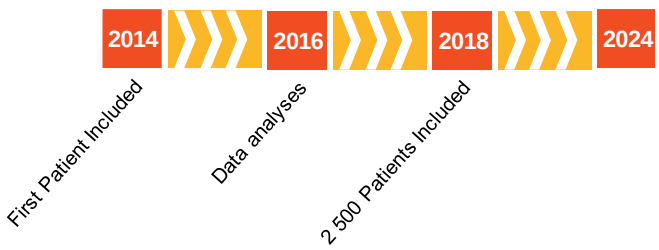
KEY FACTS & FIGURES

> Status: inclusion **started in 2014** (June 17th) and still **in progress**
> **2 500 patients enrolled** by June 2018
> 500 patients expected by year
> At least **3 years follow-up**
> **National Multicentric** cohort
> **Biobank**: tumor and serum

The challenges of FREGAT are to investigate causes of treatment resistance observed in oeso-gastric tumors.

FREGAT is a prospective clinico-biological database **dedicated to oesophago-gastric cancers** that unites the vast majority of clinical teams and University hospital centers which struggle against these cancers and **care for the majority of cases nationally**, based on many existing networks that ensure its implementation, and its quality.

A **personalized approach to oesophago-gastric cancers** is emerging and requires a rapid and multi-disciplinary development. The care of oesophago-gastric cancers is complex and resistance to loco-regional and systemic treatments is frequent, meaning new clinical and epidemiological studies, relying on **biological and tumoral collections**, must be put in place in a **large scale.**



Positioning

> To date, there is **no similar project worldwide** collecting so widely clinical, biological and tumor data
> FREGAT Database aims to be **opened to scientific community at European and International levels** for academic as well as industrial researchers
> A **specific Public/Multi private Partnership** has been designed and set up. Several pharmaceutical companies are already FREGAT partners. The partnership development is on going with other companies.

LEADERSHIP

Guillaume PIESSEN

MD, PhD, Professor of Surgery, Head of the Surgical and Clinical Research department, CHU Lille

- **Main investigator** or involved in several phases I to III clinical trials, basic and translational research programs
- **Expert in the field of medical and surgical approaches in oesophageal and gastric cancers**. Invited to conferences in French and European scientific societies (FFCD, AFC, ESSO)
- **Reviewer** for Journal of Visceral Surgery, European Journal of Surgical Oncology, European Surgical Research, Journal of Surgical Oncology, Expert Opinion On Pharmacotherapy, Diseases of the Esophagus, BMC Gastroenterology
- **Network**
  - Member of the ESSO (European Society of Surgical Oncology)
  - Member of the working group FREGAT (French Oeso Gastric Tumors working group)
  - Member of the French Federation of Surgical Research (FRENCH)
  - Member of the French Federation of Digestive Oncology (FFCD – PRODIGE)
  - Member of the French Society of Digestive Surgery (SFCD) – Participation in producing national recommendations in surgery with the Health ministry (HAS) and the National Cancer Institute (INCa) in 2008, 2009 and 2012
  - Member of the French Association of Surgery (AFC)
- **Current collaborations**
  - EORTC and PRODIGE oncological groups
  - Many Europeans investigators and scientific societies
  - Different industrial sponsorships
- **Publications**
  - 109 peer-reviewed publications
  - H Index Web of Science: 21

Antoine ADENIS

MD, PhD, Professor of Medical Oncology, **ICM Montpellier**

- **Expert in multidisciplinary gastrointestinal oncology**
- Principal investigator or co Investigator in several phase I to III clinical trials
- **Network**
  - Public Health expertise at the ANSM
  - Member of Consensus Groups, on behalf the “Haute Autorité de Santé” (HAS), in charge of producing national recommendations on colon, and rectal cancer, and liver metastases treatment
- **Editorial board and reviewing**
  - Reviewer for Br J Cancer, Eur J Cancer, Ann Oncol, JAMA Oncol
  - Reviewer for clinical trial grants dealing with GI oncology
- **Current collaborations**
  - EORTC, PRODIGE and UNIcancer GI oncology groups
  - EORTC and French Sarcoma Groups
  - Different industrial sponsorships
- **Publications**
  - 242 peer-reviewed publications
  - H Index Web of Science : 41

SCIENTIFIC NETWORK & MANAGEMENT

- FREGAT is also collaborating with **Johannes Schumacher** from the Institute of Human Genetics (University of Bonn) in a genome-wide association study in European gastric cancer population through FREGAT biobank

- **Ancillary studies** are in progress :
  - **EASTMAN:** Establishment of functional molecular signatures of adenocarcinoma
  - **PROMOREC:** Analysis of the molecular profile of oesogastric adenocarcinoma recurrence
  - **RECOMICs:** Identification of therapeutic targets for recurrence of gastric poorly cohesive carcinoma
  - **DAMCHIR:** Impact of depression and anxiety on morbidity and postoperative mortality after surgery for gastroesophageal cancer and their regulation by emotional competence
  - **CEMA:** Effect of perceived medical empathy and emotional competency of patients on their adjustment to gastroesophageal cancers
  - **EMOVOL:** Impact of emotional regulation patient-doctor on the medical evolution of the patient
  - **CARDIA:** Search for biomolecular markers of sensitivity to perioperative chemotherapy of adenocarcinoma of the gastroesophageal junction and the stomach

- Through its **Scientific Committee**, FREGAT implicates experts in:
  - **OGC:** Well-recognized experts in the field of oesophago-gastric cancers
  - **Epidemiology:** Pr A **Duhamel / D Duflot**, Pr G **Launois**
  - **Tumor Biobanking:** Pr MC **Copin**
  - **Biostatistic:** Pr A **Duhamel**, Pr A **Kramar**
  - **Human and social sciences:** Pr V **Christophe**
  - **Quality of life:** Dr A **Anota**
  - **Ethical and legal issues:** M **Caillier**

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- The main scientific questions that can be addressed are:
  - > Identification of **new prognostic and predictive** factors
  - > Validation of **promising predictive markers** of anti-tumoral therapy
  - > Understanding of underlying **mechanisms and new drugs development**
  - > **Impact evaluation** of current treatment strategies
  - > Identification of **epidemiological and socioeconomic determinants** which barrier access to health care system and medical treatments starting
  - > Better understand **therapeutic strategy efficiency** and their impact on the patient survival and quality of life

INNOVATIVE SCIENTIFIC FEATURES

- **First and the largest** dedicated OG clinico-biological data
- Human and social science data
- National network
- Built to be **extended to European partners**
- Based on a network that has already produced high level scientific papers

METHODOLOGY QUALITY

- All data will be transmitted from the interface to the database in a **secure channel** through a protocol such as SSL. The clinical database will be stored in the Methodology Unit - Biostatistics and Data Management (CHU Lille)
- **Data monitoring and monitoring of the quality** of preserved tissues will be performed every six months
- **Site audit** will be performed every year for quality
- **Data monitoring** and quality of preserved tissues
- All FREGAT's procedures are **in compliance with national and international guidelines**

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	5 000 newly diagnosed OGC patients
Sites:	38 centers with 52 clinical teams
Inclusion criteria:	Patient with oesophageal carcinoma, of oesogastric junction or gastric newly diagnosed by biopsy, irrespective of histological type, tumoral stage, first physician seen or the therapeutic strategy Patient (men or women) ≥ 18 years old Treatment-Naïve Patients Patient healthcare insurance
Exclusion criteria:	Patient under 18 year old Patient under administrative supervision Not French speaking patients Patient refusal or without sign consent

INCLUSION

Database:
Prospective collection of clinical, epidemiological, behavioral and social data, histological diagnostic

Biobank:
Blood and tumor

FOLLOW-UP

Database: *(nature of the data collected depends on the treatment regimen)*
Clinical data, therapeutic strategies, severe toxicity (grade 3-4), behavioral, social and quality of life data
Biobank: *(at the end of neoadjuvant treatment (if it occurs), at surgical or endoscopic treatment with curative intent (if it occurs), at the end of adjuvant treatment (if it occurs), at recurrence (if it occurs))*
Blood and tumor

DATABASE & BIOBANK CONTENTS

DATABASE

- **Demographic** : Date of birth, Place of birth, Gender, Current residence / Description, Distance to the physician, Distance to the healthcare centre, Transport, Environmental factors, previous history of cancer
- **Risk factors linked to OGC**: Alcohol and tobacco consumption, reflux, obesity, dietary habits
- **Clinic**: Weight, height, Medical co-morbities, Past history of other cancers, Date of first symptom/ description, Date of first consultation, Type of clinician consulted, Symptoms, Current medications for other diseases, Nutritional parameters
- **Biologic**: Collections of variables related to inflammation, nutrition
- **Therapeutic**: Medical, Surgical, Radiotherapeutic, Palliative strategies with evaluation of response and tolerance
- **Psycho-socio-economic variables**: Family circle, Isolation, Education, Job at inclusion, Coping and other psychological factors evaluated with a specific questionnaire
- **Quality of life**: EORTC QLQ-C30 general questionnaire and EORTC QLQ-OG25 specific module
- **Date and cause of death, date of last follow-up**

BIOBANK

- **Originality**
  - > Very large sample, **tumor and blood collection** before and at time of treatment and at time of recurrence, **QOL and Human Sciences data**, all tumor stages and treatment types included
  - > The FREGAT biobank is a member of the French Tumor bank network set up by the INCa
- **Scientific objective**
  - > Predictive and prognostic markers of treatments, personalized therapeutic approach, identification of mechanisms involved in tumor and host resistance to treatments
  - > FREGAT biobank is implicated in a genome-wide association study in European gastric cancer population through its collaboration with the Institute of Human Genetics (University of Bonn)
- **Samples**
  - > Tumor samples and Blood samples
  - > **9** samples for tumor per patient; **29** ml for blood per patient
  - > **1721** patients consent to have tumor samples stocked by FREGAT
  - > **1354** patients consent to have a blood sampling
- **Associated resources**
  - > **Human resources**: more than 50 specialists in clinical, tumoral, biological, QOL and human sciences domains
  - > **Know-how**: specialized platforms (NGS, molecular biology …) and competences (clinical, tumoral, biological, QOL …) over the country linked to FREGAT

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- The blood biobank **spreads over 6 certified BRCs**. The tumor biobank spreads over all FREGAT clinical sites through the INCa tumor-bank certified network
- Each BRC and tumor-bank sends an update of the hosted samples for centralization. They mainly use **DIAMIC software** which is integrated in the laboratories' information system **to ensure sample traceability.**
- Each biological sample is identified by a **patient-specific code**. The clinical database hosts each **patient-specific code** for traceability.

SPECIFICATIONS

- Date of the **first sampling: June 17, 2014** for both tumor and blood samples
- Sampling frequency **according to patient treatment**
- **Biobanking** is performed from patients consenting to be sampled and **followed in the 6 of 38 selected centers** with a certified Biological Resources Center for blood samples and in all 38 centers for other patients
- Biobank coordinators
  - > Tumor bank : MC Copin / F Renaud
  - > Blood sample bank: P Gelé
- Protocol for the biological sample collection available
- A **minimum dataset is associated** to each sample: patient-specific sample code, sample number, sampling date, FREGAT identification number, and storage condition
- **Label of quality:** Beside quality control procedures developed by each site for tumor banking and harmonized at the national level by INCa, FREGAT collaborates with **certified NFS96-900 Biological Resources Center** to collect blood samples. FREGAT also develops procedure to standardize sample collection to **ensure treatment homogeneity between each center.**
- Biological samples are available under specific modalities

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Bio specimens	Origin	Quantity / concentration available	No. of aliquots	No. of subjects who have been sampled (on 30th May 2018)	Storage conditions
At Baseline					
Plasma EDTA	Blood	500 µL	10	648	-80°C
Buffy coat	Blood	1 mL	1	648	-80°C
Plasma heparin	Blood	500 µL	8	648	-80°C
Serum	Blood	500 µL	9	648	-80°C
Frozen tumor	Tumor	-	~5	474	-80°C
Paraffin embedded	Formalin fixed Tumor	1 block	~4	430	Paraffin embedded
During the follow-up: at end of neoadjuvant treatment (if it occurs), at surgical or endoscopic treatment with curative intent (if it occurs), at the end of adjuvant treatment (if it occurs), at recurrence (if it occurs)					
Plasma EDTA	Blood	500 µL	10	1 153	-80°C
Buffy coat	Blood	1 mL	1	1 153	-80°C
Plasma heparin	Blood	500 µL	8	1 153	-80°C
Serum	Blood	500 µL	10	1 153	-80°C
Frozen tumor	Tumor	-	~4	206	-80°C
Paraffin embedded	Formalin fixed Tumor	1 block	~5	192	Paraffin embedded

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A **Charter**, specifying the biobank access, **is being drafted for private companies**
- Biological samples **will be accessible** to public and/or private/industrial teams
- To access to the biological resources, a research project shall be submitted to the FREGAT Scientific Committee which assesses the project. Procedures for accessing biological samples will be described in the Charter. They include feasibility, financial, and scientific evaluations.
- Biological samples can be transferred to public or private teams according to modalities defined in a contract. All transfers must be previously approved by the Scientific Committee.

BIOLOGICAL SAMPLE ANALYSES

- To date, a part of tumor samples are used for diagnosis validation in the routine patient care
- The FREGAT cohort envisages to exploit the biological samples to:
  - > **Investigate genetic** and/or **epigenetic** background on gastric cancer outcome (from blood)
  - > **Investigate DNA mutations** for molecular characterization of gastric cancer (from tumors)
  - > Identify **prognostic markers** of gastric cancer
- To date, there is no biological sample analysis-derived data. When available, access to these data will be approved by the Scientific Committee.

COST

- Access to biospecimens: private companies **need to sign a partnership** with defined modalities **to access to biobank and associated data**
- Cost of each sample type is **already established** but confidential

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Identify and validate underlying **molecular mechanisms** responsible for **tumor response** and/or long tem survival in order to discover and develop **new targeted therapies**
- Evaluating **tumor molecular characteristics variations** before and after neoadjuvant chemo(radiation) in OGC
- Identification of **predictive factors** for response to neoadjuvant treatment through **correlation of molecular data** (pretherapeutic biopsies) and **clinical data** with histopathological response in patients undergoing surgical resection for an OGC after neoadjuvant treatment

CLINICAL DEVELOPMENT

- Identify **key factors** and **key molecular determinants** linked to tumoral response/resistance to treatment, which will allow to design dedicated trials for sub-groups of patients and provide a **personalized therapeutic approach**
- Better understand OGC evolution by analyzing **epidemiological variations** across time periods and region
- **Validation of promising molecular markers** recently identified

OUTCOMES RESEARCH

- Better characterize environmental and **behavioral risks**
- Analyze **socio-geographic OGC disparities** and reduce health and social inequalities in French OGC patients
- Evaluate the **impact** of the various **therapeutic strategies** used in OGC patients and eventually in different at risk subgroups (older patients, histological subtypes, tumoral stage)
- Provide data to health authorities regarding **OGC surgical and medical practice** in France for further socio-economic health decision making
- Improve access to care and to treatment in this high risk population
- Increase knowledge of **HRQL in OGC** subgroups of patients (old patients, high comorbidity patients)

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MEMENTO:

deterMinants and Evolution of AlzheiMer's disEase aNd relaTed disOrders

ITMO Santé publique

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OVERVIEW

AT A GLANCE

> Neurology, Aging & Neurodegenerative diseases
> Patients with either isolated **cognitive complaints** or **mild cognitive impairments**
> Coordinated by **Geneviève Chêne** and **Carole Dufouil**
> **Bordeaux University Hospital** Sponsorship
> Funded by Fondation Plan Alzheimer, French clinical research projects funding program (PHRC) and industrial partnerships
> **Key words**: Alzheimer's disease, biomarkers, natural history, early diagnosis, longitudinal, imaging

KEY FACTS & FIGURES

> Status: **enrollment ended in 2014**
> **Multicenter cohort** with 28 memory clinics in France
> **2 323 non demented participants** enrolled
> At least **5 years follow-up**
> **Centralized biobank** at Pasteur Institute (Lille) comprising serum, plasma, DNA, RNA, & CSF samples
> Process for linkage with SNDS database initiated

The objective of MEMENTO is to better **understand the natural history of Alzheimer's disease** and related disorders (AD) by characterizing, through the **analysis of risk factors** and **multiple biomarkers alone or in combination,** the **determinants of transitions** from early signs and symptoms of AD (cognitive complaints, mild cognitive impairment) to clinical dementia.

Positioning

> MEMENTO is a large **observational study** enrolling patients at an early stage before dementia and with a **highly comprehensive and standardized workup** (clinical, biological, imaging, socio-economics)
> **A unique platform for research** : no similar cohort at an international level
> Collaboration with **the Framingham cohort** and within **the IMI Roadmap**
> **Partnerships with pharmaceutical companies**

LEADERSHIP

Geneviève Chêne, *Biostatistics and Public Health Professor, ISPED, Bordeaux*

- Director, ISPED/Bordeaux school of public health, university of Bordeaux
- Teaches clinical epidemiology at the Bordeaux school of Public health, including e-learning since 2001
- Director, Department of public health, CHU Bordeaux
- Head of EUCLID, a F-CRIN services platform for clinical trials
- Coordination of large scale studies, including EU-funded collaborations
- Major Collaborations with MRC, UCL, Bristol & Boston University, Harvard SPH
- More than 360 publications, H-Index=61

Carole Dufouil, *Neuroepidemiology, Director of research Inserm, ISPED, Bordeaux*

- Co-PI of the 3C-Dijon study (large population based study on dementia)
- PI of the neuroimaging ancillary study of the MAPT trial (national multi-domain prevention trial of cognitive decline)
- Coordinator of an international collaboration on optimizing methods in longitudinal analyses of dementia database (Melodem)
- Collaborations with the Framingham study (Boston university), the Institute of Public Health (Cambridge, UK) and the department of epidemiology (UC, San Francisco
- External reviewer for NIH, MRC, UCSF, Boston University, ERC
- More than 165 publications, H-index=50

SCIENTIFIC NETWORK & MANAGEMENT

SCIENTIFIC NETWORK

- **Current collaborations**
  - > **IMI Roadmap**: pooled cohort studies on validation of prognosis models for AD
  - > **Framingham cohort**: determinants of dementia and associated disorders with a special focus on vascular risk factors, temporal trends in dementia, cross validation of neuroimagingand blood biomarkers between Memento and Framingham
  - > **MELODEM** (Methods in longitudinal dementia research)
- **Future collaborations**
  - > **Mayo Clinic Study of Aging**, Rochester, Minnesota, USA: To replicate in a different setting (population based study) and different country findings from MEMENTO
  - > **Center Brain Health**, New-York, USA: To set up ancillary studies to test the added value of novel biomarkers
  - > **Institute for Stroke and Dementia Research** (ISD), Munich, Germany: To validate new neuroimaging biomarkers (freewater)
  - > **Imperial College**, London, UK: Metabolomics pathways for brain changes

SCIENTIFIC MANAGEMENT

- Through its external Scientific Committee, MEMENTO involves experts in:
  - > **Basic science**: Mony de Leon (New York University School of Medicine and Scientist, US)
  - > **Social sciences**: Lisa Berkman (Harvard, US)
  - > **Neurology**: Ronald Petersen (Rochester, US)
  - > **Biostatistics**: David Clayton (MRC, UK)
  - > **Neuroimaging and biomarkers of AD**: Philip Scheltens (Vrije Universiteit Amsterdam, Netherlands)

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- **Main objective**
  - > **Identification and validation of biomarkers or combination of biomarkers** that best predict the occurrence of dementia
- **Secondary objectives**
  - > Provide an extensive **characterization of the natural history** of well phenotyped patients with potential early signs of Alzheimer's disease
  - > Investigate the **impact of vascular burden on cognitive health**
  - > Document the **socio-economic burden** of Alzheimer's disease and related disorders for patients, caregivers and society
  - > Provide for a **national integrated research platform** with standardized clinical, biological and imaging assessments

INNOVATIVE SCIENTIFIC FEATURES

- The **largest naturalistic cohort on brain health**, with a rigorous prospective design
- **Extensive follow-up** (at least 5 years)
- **Standardized procedures**, multiple biomarkers (imaging, blood CSF) assessed with **standardized acquisitions and analyses**

GENOMICS

- GWAS analysis is planned very soon: the MEMENTO cohort has secured the funding through an European consortium
- GWAS data will be available soon

METHODOLOGY QUALITY

- **Harmonization** and **Standardization** of assessments
- E-CRF and robust **data-monitoring**
- Certification of **imaging centers**, centralized imaging analysis through Neurospin **CATI** (Saclay)
- **Centralized biobank and neuroimaging** (CATI, Neurospin)

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	2 323 consecutive individuals recruited
Sites:	28 Memory Research Centers in France
Inclusion criteria:	Adults; either a recently evaluated (< 6 months) cognitive performance worse than one standard deviation to the mean in one or more domains or an isolated cognitive complaint (patient aged ≥ 60 years); Non-demented; Clinical Dementia Rating Scale (CDR) ≤0.5
Exclusion criteria:	Guardianship; Meeting brain MRI exclusion criteria or refusing MRI; Illiteracy

INCLUSION
Database:
Clinical data: Cognitive testing, cognitive complaints, psychopathology, social & human sciences, vascular risk factors and history
Imaging collection: Brain MRI (including DTI and rs-fMRI), 18F-FDG PET, Amyloid PET
Biobank:
Cerebrospinal fluid (CSF) and blood samplings

FOLLOW-UP : at least yearly

Database:
Clinical data : At least every year
Cognitive testing, cognitive complaints, psychopathology, social & human sciences; vascular damages
Imaging collection : Every 2 years
- Brain MRI (including DTI and rs-fMRI), 18F-FDG PET, Amyloid PET
- CSF and blood samplings

DATABASE & BIOBANK CONTENTS

DATABASE

- **Clinical data**
  - The database is comprehensive, with a **clinical assessment of patients every 12 months**, for at least **5 years**
    - **Clinical** assessment, **memory** tests, **neurological** and **psychiatric** assessment, **socioeconomic** data (burden of disease), **quality of life, social sciences** (social and family environment, caregiver's assessment) etc…
    - **Linkage** of the database with other databases as **SNDS** is planned
- **Imaging collection**
  - Imaging is performed **at inclusion and every 24 months**
  - **Cerebral MRI**
    - 3D-T12D, T2 FLAIR, 2D-T2* (GRE) + phase, 2D-T2 TSE/FSE 1 echo, Resting state (BOLD EPI), diffusion (DTI – DWI EPI)
    - Visual assessment recorded in e-CRF
    - Quality assessment of each sequence with automated test procedures and report
    - Automated analyses: brain tissues and hippocampus volumes, global and ROI-based cortical thickness, gyrification index, fold opening
  - **FDG PET**
    - Harmonization using phantoms
    - Optimization of reconstruction parameters
    - Automatic quantitative analysis

BIOBANK

- **Originality**
  - Collection according to **standardized procedures (SOPs) for the treatment, storage and transfer of the sampled biospecimens**
  - A duplication of all the biospecimens has been organized through the constitution of a **mirror biobank** hosted at the ICM (Institut du Cerveau et de la Moelle Epinière, Paris) **to ensure the biological samples safety**
  - Repeated measures are performed to ensure the biospecimens **quality**
- **Scientific objective**
  - **Developing novel blood-based biomarkers** for Alzheimer's disease
- **Samples**
  - **Blood** (mandatory and includes serum, plasma, DNA, RNA) and **CSF** (optional)
- **Biobank key facts**
  - Sampling **at baseline, 2 and 4 years follow-up**
    - **Baseline samples** obtained **for 2 283 participants**
    - 2- and 4-years follow-up samples ongoing
  - For blood sampling at each wave: **28 aliquots stored**

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- **Centralized storage** in a **principal and a mirror biobanks**
  - > Principal storage at the Genomic Analysis Lab, (LAG, Pasteur Institute, Lille)
  - > Mirror storage at ICM (Brain & Spine Institute, Paris)
- LAG is responsible for organizing transport from local biobanks to centralized biobank as part of its assignments in contract
- Biological samples are identified using a **bar code system**

SPECIFICATIONS

- The first sampling has been performed in **July 2011**
- Sampling frequency: **every 2 years**
- **Responsible** for the biobank: **Bordeaux University Hospital**
- The **database associated to each sample** includes information on:
  - > Collection, transport & storage conditions
  - > Date of birth
  - > Gender of participant
- Biobank is being constituted according to standardized protocol for sampling, **Standard Operating Procedure** for ensuring the homogenization in terms of treatment and storage quality and **high standards with quality checking procedures**
- **Biological samples are** available for collaborations through a research project application, according to the modalities specified in the MEMENTO data **access charter**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological specimens	Origin	Quantity available	No. of aliquot	No. of subjects who have been sampled (expected/sampled)	Storage conditions
At Baseline: start in July 2011					
Serum	Blood	0.25 mL	12	2 323/2 283	-80°C
Plasma EDTA	Blood	0.25 mL	8	2 323/2 283	-80°C
Total blood heparin	Blood	1 mL	2	2 323/2 283	-80°C
Plasma heparin	Blood	500 µg	4	2 323/2 283	-80°C
Blood EDTA without plasma	Blood	0.25 mL	1	2 323/2 283	-80°C
Blood heparin without plasma	Blood	3 mL	1	2 323/2 283	-80°C
Tempus	Blood	3 mL	2	2 323/2 283	-80°C
CSF	CSF	O.25 µL	16	400 sampled (sampling on going)	-80°C
During the follow-up sampling frequency: every 2 years					
Same collection as baseline					

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A charter **specifying biobank access modalities is available since 2013** and describes the MEMENTO general principles and path to follow for data and biospecimen access, ancillary project and publication submission
- **The biobank is opened to a large scientific community (academic and industrial), without any restriction regarding the nature of the biospecimens and in accordance with the charter terms**
- Industrials wishing to access to the MEMENTO biobank have to submit a research project to the Steering and the Scientific Committees for review
- **Transfer of biological samples** to public or to private/industrial teams is possible **upon granted access and after following specific rules of the charter**
- Biological samples may be shareable with a foreign company under conditions depending on the purpose, the analysis...

BIOLOGICAL SAMPLE ANALYSES

- The collected samples are **used for the validation of disease diagnosis**
- The biological sample **analysis-derived data are accessible** to the scientific community, **according to the charter rules**
- Industrial research team proposing a project are **invited to identify the laboratory able to perform sample analyses** and find the **specific funding** for biological measurements

COST

- A **financial estimation** of the MEMENTO biological samples is not yet available but is underway

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- **Identification and validation of new biomarkers** or combination of biomarkers **for the early diagnosis** of Alzheimer's disease and associated disorders
- **Identification of prognosis factors** for transition from isolated cognitive complaints to mild cognitive impairment to dementia
- **Validation of surrogate markers** of Alzheimer's disease for future clinical trials
- **Validation of preclinical and pre-dementia stages** of Alzheimer's disease

CLINICAL DEVELOPMENT

- **Definition phenotypes of patients at high risk** of clinical dementia that should be the target of future clinical trials
- **Structuration of clinical research** in the field of Alzheimer's disease
- **Platform** for clinical research

OUTCOMES RESEARCH

- **Better characterization** of etiologies of dementia
- **Pharmaco-economic studies** cost/benefit of new biomarkers for Alzheimer's disease and associated disorders
- **Provide data to health authorities** on the added value of biomarkers for care and treatment of patients
- **Assess the impact of early diagnosis** of Alzheimer's disease and associated disorders on the patient and its family

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OFSEP:

Observatoire Français de la Sclérose en Plaques

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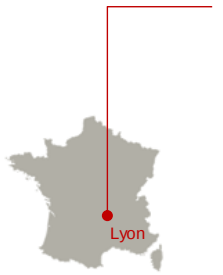

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OVERVIEW

AT A GLANCE

> **Neurology**
> **Multiple Sclerosis** (MS) and **MS-related diseases**
> Coordination: Pr S. Vukusic & Pr F. Guillemin
> **Academic partners**: Claude Bernard Lyon 1 University, Lyon University Hospital & EDMUS Foundation
> **Funded by** the Investissements d'Avenir Cohort program and private funds
> **Keywords:** multiple sclerosis, registry, imaging, biobanking, pharmaco-epidemiology, medico-economic data

KEY FACTS & FIGURES

> **OFSEP**: **> 60 000 included** patients with **MS and related diseases** (50 % of French patients) by December 2017
  > 26 380 (43%) patients followed during the last 2 years
> **OFSEP-HD**: a specific **OFSEP High Definition Cohort** developed as an **ancillary study** since 2018 and **is being opened** for inclusion
  > Inclusion objective: **5 000 patients** with MS in the next 2 years
> **OFSEP & OFSEP-HD:**
  > National multicentric cohorts with more than 40 expert MS centers in France participating to OFSEP and OFSEP-HD
  > Certified biobanks : serum, plasma, DNA, PBMC, urines, CSF and feces, for all patients or for subgroups only
  > Development of a web based platform to centralize clinical, biological and MRI data Linkage to SNDS is expected

OFSEP aims to **improve the clinical, biological and imaging systematic longitudinal follow-up of patients with MS** and makes it available to the research and industrial communities as well as health authorities.
The purpose of the OFSEP ancillary study, OFSEP-HD, is to **determine prognostic factors** of MS, to study the **effectiveness of treatments in real life, and to create patient-centered prognostic tools.**

Positioning

> **One of the largest MS cohort** worldwide and a **unique epidemiological tool** with a such standardized and systematic collection of clinical, imaging and biological data
> OFSEP is currently involved in **international collaborations** with other registers, pharmaceutical companies and EMA as well as in academic projects using collected or to be collected data
> **OFSEP HD** is accessible, as OFSEP, to both the public and private research communities

LEADERSHIP

Sandra VUKUSIC, M.D., Ph.D., *Professor of Neurology at the Lyon University Hospital*

- Neurologist and epidemiologist working since 1998 on the description of the natural history of MS, prognosis, vaccines and pregnancy
- Head of Department of Neurology A – Neurological Hospital – Lyon University Hospital
- Scientific Coordinator of the French MS Registry
- Research expertise and animation
  - > Member of the board of French neurology teachers since 2013
  - > Inter-regional coordinator (Auvergne-Rhône-Alpes area) of the neurology teaching for interns and residents 2013-2016
  - > President of the Eugène Devic EDMUS Foundation against Multiple Sclerosis since 2014
  - > Member of the Medico-scientific committee of the ARSEP Foundation since 2013
  - > Member of the executive board of the Société Francophone de la Sclérose en Plaques
  - > Founding member and treasurer of the Réseau Rhône-Alpes SEP
  - > Head of the EDMUS coordinating center since 2013
  - > Member of the International Advisory Committee on Clinical Trials in MS since 2015
  - > Member of the ECTRIMS Council, representing France, since October 2016
  - > Elected member of the ECTRIMS Executive Committee, since October 2016
- Current collaborations
  - > Principal Investigator of industrial clinical trials in MS
- Publications
  - > More than 130 peer-reviewed publications

Francis Guillemin, M.D., Ph.D., *Professor of Public Health at Université de Lorraine – Faculté de Médecine, Nancy*

- Head of Inserm CIC 1433 Clinical epidemiology – Hôpital de Brabois – Nancy University Hospital
- Director of EA 4360 APEMAC, Université de Lorraine
- Director of School of public health, Université de Lorraine – Faculté de Médecine, Nancy
- Scientific Associated Coordinator of the French MS Registry
- Research expertise and animation
  - > President of the Epidemiology section of the French society of rheumatology
  - > Secretary (1991-2000), president (2000-2006), vice-president (since 2007) of the Quality of life in Rheumatology committee of the French society of rheumatology since 1991
  - > Chairperson Standing Committee of Epidemiology and Health Service Research of EULAR 2003-2005
  - > Member of Committee of medical research and public health of the University hospital of Nancy 2008-2014
  - > Member of the National committee of clinical research (Ministry of Health) 2004-2006
  - > Member of the CSS 9 scientific commission of INSERM Public health, population health 2012-2016
  - > Coordinator of the national Platform Quality of life and cancer, since 2008
  - > Member of the Scientific Board of the National League against cancer since 2012
  - > Coordinator of the INSERM national RECaP network since 2014
- Publications
  - > More than 380 peer-reviewed publications

SCIENTIFIC NETWORK & MANAGEMENT

- OFSEP and OFSEP-HD gather a network of French neurologists, neuro-radiologists and biologists
- OFSEP is organized around **four working groups** including experts from all OFSEP centers in France:
  - > **Clinical** Working Group
    - > Leader: Pr. Jérôme de Sèze, neurologist (Strasbourg)
    - > + 1 neurologist per OFSEP Clinical center
  - > **Biological** Working Group
    - > Leader: Pr. David Laplaud, neurologist (Nantes)
    - > + 1 neurologist and 1 biologist of each OFSEP Biological Resource Center (BRC)
  - > **Neuro-Imaging** Working Group
    - > Co-leaders: Pr. François Cotton (Lyon) and Pr. Vincent Dousset (Bordeaux), neuro-radiologists
    - > + Neurologist and neuro-radiologists from OFSEP Imaging centers and engineers from INRIA (Rennes)
  - > **Methodology** Working Group
    - > Leader: Pr. David Laplaud, neurologist (Nantes)
    - > Statisticians, epidemiologists and neurologists, support on the methodological aspects of research projects
- Their role mainly consists in defining the variables to be collected in their own thematic which could be reconsidered in the light of changes in scientific knowledges and needs
- The National Coordinating Center organizes the OFSEP and OFSEP-HD data collection and centralization, and ensures the data quality
- The Scientific and Strategic Committees are common organs for both the cohorts with the following missions:
  - > To define the scientific orientations of the OFSEP project in general and the scientific operational objectives in particular
  - > To propose the adapted changes in the inclusion criteria of the new cohort, the collection of data and the statistical analyses
- Final decisions of the Scientific and Strategic Committees are reported to the Steering Committee to be validated considering the available resources and the respect of the OFSEP missions and key values

PROJECT DESCRIPTION

OPERATIONAL OBJECTIVES

- To maintain and expand the **nationwide cohort of patients with MS** in France
- To **enrich the existing clinical data** with imaging and medico-economic data and with biological samples
- To allow all researchers worldwide **to access the collected data and biological samples** (through research project submitted to OFSEP governance)

SCIENTIFIC OBJECTIVES

- **For OFSEP Cohort**
  - To **describe the patients with MS or MS associated diseases** included in the cohort
  - To agree on a minimal standardized dataset for the clinical, imaging, therapeutic, medico-economic data and biological samples in order to **harmonize data collection**
  - To conduct research on priority projects (**nested cohorts**)
- **For OFSEP HD cohort**
  - To better appreciate the **causal factors of disease progression**
  - To obtain **reliable predictive tools** that could be applied on the individual level and at different key moments in the disease course (landmarks)
  - To merge with high standard of quality data related to clinical dimension, QoL, socio-demographic context, imaging results from MRI, biological data and treatments received

Its overarching objective is to determine, at specific **landmarks over the disease course**, the prognostic factors of the evolution of disability in MS and the **care practices** that can modify this predicted evolution in real-life settings.

METHODOLOGY QUALITY

- **EDMUS software** enforces a **level of data consistency and automatic cross-check** of data. EDMUS uses a standardized nomenclature, a requisite for efficient data exchange and analysis.
- Biological Resource Centers are all certified
- Quality management system set up based on **ISO 9001 standard**

INNOVATIVE SCIENTIFIC FEATURES

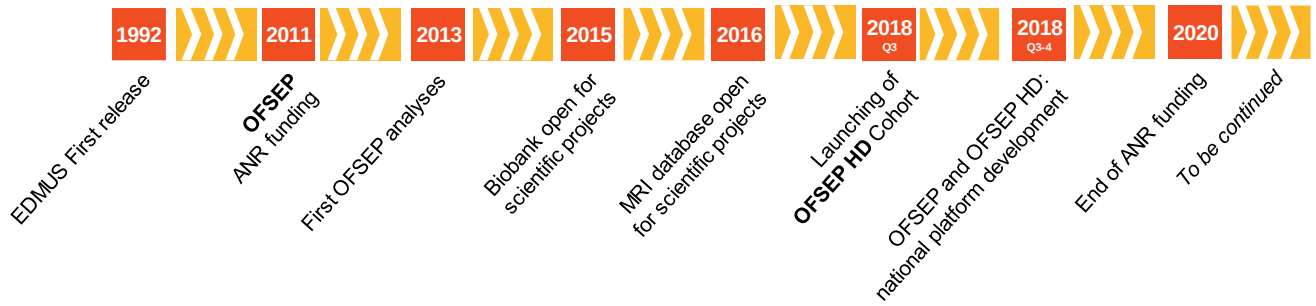
- Clinical data collected since 1992, standardized collection since 2013
- Data collected routinely during medical visits
- Almost half of French MS patients are included in the OFSEP database
- A specific software dedicated to MS (EDMUS) used in daily practice by neurologists
- Separate anonymized clinical, MRI and biological databases linked by a national unique identifier

PROJECT DESCRIPTION : ARTIFICIAL INTELLIGENCE TOOLS

LINKAGE TO HEALTH DATABASE

- Linkage to SNDS is planned:
  - For both the OFSEP and OFSEP HD cohorts
  - Research projects using these data have been already designed in the context of the OFSEP HD cohort
- Linkage to health databases will allow to carry out medical economic studies, cost-effectiveness studies, and pharmaco-epidemiological studies
- OFSEP is involved in **the Big MS Data project** gathering 5 big MS registries (Sweden, Italy, Denmark, France and an international registry, the MSBase). Common research projects are on going with **data sharing.**

DESIGN, METHODOLOGY & TIMELINE



OFSEP mother Cohort

Recruitment objectives:	All patients consulting at least once in a clinical OFSEP center. To date, more than 60 000 patients included.
Sites:	All clinical centers using EDMUS in daily practice and willing to participate (to date: 40), Biological Resource Centers (to date: 12), and nearly 100 MRI centers expected
Inclusion criteria:	Multiple Sclerosis (MS) and MS-related diseases (RIS, CIS), Neuromyelitis Optica Spectrum Disorders (NMOSD)
Exclusion criteria:	None of the inclusion criteria

INCLUSION

Database:
Clinical data: MS history (neurological events and disability scale), MRI results, disease modifying treatments history, SAE
Imaging collection: MRI exam
Biobank:
1 OFSEP kit at inclusion (blood, urine, CSF, feces)

FOLLOW-UP

Database:
Clinical data : at every visit (usually at least once a year)
Imaging collection : MRI brain at least once every 3 years ; spinal cord at least once every 6 years
Biobank:
1 OFSEP kit during follow-up for patients in nested cohorts according to specific inclusion criteria

OFSEP HD Cohort

Recruitment objectives:	5 000 patients annually followed in French OFSEP expert centers (2018-2020)
Sites:	All French OFSEP clinical centers certified CRC-SEP in the national plan for neurodegenerative diseases
Inclusion criteria:	Patients with a diagnosis of MS and an EDSS score ≤ 7.0
Exclusion criteria:	None of the inclusion criteria

INCLUSION

Database:
Clinical data: OFSEP core minimal clinical data, MFSC (T25FW, 9HPT, CSCT), comorbidities, quality of life (5Q5D, SF12, MusiQoL), extended socioeconomic data and risk exposition data
Imaging collection: Brain MRI
Biobank :
Blood

FOLLOW UP

Database:
Clinical data: OFSEP core minimal clinical data, MFSC (T25FW, 9HPT, CSCT), comorbidities, quality of life (5Q5D, SF12, MusiQoL), extended socioeconomic data and risk exposition data
Imaging collection: Brain MRI
Biobank :
No biobanking during follow up

DATABASE & BIOBANK CONTENTS

DATABASE

Clinical Database (EDMUS software)

- EDMUS is a software dedicated to MS that allows to collect demographic and longitudinal clinical data, prospectively and retrospectively, at each neurologist's visit and can be used for both medical follow-up and research purposes.
- A minimal set of data was implemented in June 2013 in order to standardize data collection
- **Type of collected data in OFSEP**: socio-demographic data, neurological episodes, disability, disease modifying treatments, serious adverse events (since January 2017)
- **Type of collected data in OFSEP HD:** OFSEP core minimal clinical data (disability, neurological episode, treatment…), MFSC (T25FW, 9-HPT, CSCT), comorbidities, quality of life (EQ-5D, SF12, MusiQoL), socioeconomic indicators, alcohol and tobacco consumption, in addition to serum neurofilament light chains and biocollection at T0

During the follow up period: disease diagnosis, disease progression, recent disease activity and absence of disease activity in the past 5 years

Magnetic Resonance Imaging data (Shanoir platform)

- A standardized brain and spinal cord acquisition protocol defined and validated by a group of experts, largely diffused and published
- A minimal MRI follow-up consisting in at least one brain MRI every three years and one spinal cord MRI every six years
- **MRI data collection** based on standardized MS specific protocol implemented in a large number of MRI centers in France
- MRI manufacturers have agreed to implement an "OFSEP box" on any new or updated MRI machine
- Routinely OFSEP acquired MRIs centralized in a unique MRI platform (Shanoir)
- MRI from 659 patients to date: 1 023 exams corresponding to 11 408 sequences (83% cerebral, 17% spinal)

BIOBANK

- **Originality**
  - OFSEP is a large scale nationwide biobank with 500 patients sampled per year (800 patients already sampled, about 350 expected each year)
  - In the context of the OFSEP HD cohort, **5 000 MS patients** (RRMS, SPMS and PPMS**) will be sampled** (serum, plasma EDTA)
- **Scientific objective**
  - Biobanks aim to carry out future studies on MS and related diseases (Neuromyelitis Optica)
  - To date, 7 nested cohorts in the OFSEP are ongoing. Theses cohorts have specific objectives requesting dedicated data collection (i.e through *ad hoc* questionnaires) and/or particular biospecimens analysis:
    - Clinically Isolated Syndrome (CIS)
    - Radiologically Isolated Syndrome (RIS)
    - NeuroMyelitis Optica (NMO) also known as Devic's disease, Primary-progressive multiple sclerosis (PPMS)
    - Progressive Multifocal Leukoencephalopathy (PML)
    - Acute Disseminated Encephalomyelitis (ADEM)
    - Untreated PPMS
    - Untreated RRMS since March 2018
- **Samples**
  - Serum, plasma, DNA, PBMC & urines
  - Additional samples (optional) : cerebrospinal fluid & feces
  - Number of samples per **OFSEP patient at the inclusion**
    - Serum: 10 aliquots
    - Plasma: 6 aliquots
    - Total blood for DNA : 2 samples
    - PBMC: 2 to 4 aliquots
    - Urines: 2 to 6 aliquots
  - Total number of samples expected : **50 000 blood** (plasma, serum, blood, PBMC) and **5 000 urines samples**

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Biobank is **spread over 12 certified BRCs** linked to clinical sites which enroll patients; 19 are expected in December 2018
- Biological sample collection, treatment and short-time **storage** is organized and performed by BRCs
- Each BRC provides the long-term conservation of biological samples
- Each biological sample is identified with a patient-specific barcode

SPECIFICATIONS

- Patients already included in OFSEP cohort and presenting one of the following specificities: Clinically Isolated Syndrome (CIS), Radiologically Isolated Syndrome (RIS), NeuroMyelitis Optica (NMO) also known as Devic's disease, Primary-progressive multiple sclerosis (PPMS), Progressive Multifocal Leukoencephalopathy (PML), Acute Disseminated Encephalomyelitis (ADEM)
- First sampling in November 2013
- Biobank is **supervised by the biological working group** leads by Pr David Laplaud and Nathalie Dufay, including neurologists committed in sampling and BRC leaders. The biological working group aims to set-up the multi-site biobanking, **defines sampling strategies** and follows biobank enrollment.
- **A standardized biological protocol** exists for basic- (serum, plasma EDTA, DNA, PBMC, urine) and additional samples (cerebrospinal fluid, feces) collection
- Biobank is being constituted according to standardized protocol for sampling, **Standard Operating Procedure** for ensuring the homogenization in terms of treatment and storage quality and **high standards with quality checking procedures**
- **A minimum dataset** for each sample is available comprising Edmus ID (to link with clinical database), BRC ID (to follow sample in each site), patient information, date of the written inform consent, basic clinical data and basic data on treatment at sampling date. Two times per year, export of biobank database is performed to implement OFSEP general database.
- **Label of quality:** All BRCs have been AFNOR certified, according to French biological research center standard NF S 96-900. Biobank procedures have been developed by the biological working group in order to **apply standardized methods for sample collection, treatment and conservation** (Standard Operating Procedure).
- Biological samples are available for academic and industrial research projects

BIOLOGICAL SAMPLE COLLECTION & ACCESS

OFSEP Biological specimens	Origin	Quantity available per aliquot	No. of aliquots	No. of subjects expected to sampled per year	Storage conditions
At Baseline before treatment :					
Serum	Blood (dry tubes)	500 µL	10	500	-80°C
Plasma	Blood (EDTA tubes)	500 µL	6	500	-80°C
PBMC	Blood (CPT tubes)	$10x10^6$ cells/mL	2 to 4	500	-196°C
DNA	Whole blood	*not available*	2	500	Half at 4°C & half at -20°C
Urines	Urines	500 µL	2 or 6	500	-80°C
Cerebrospinal Fluid (CSF)	Lumbar Puncture	500 µL	10	100	-80°C
CSF cells	CSF	200 µL	2	100	-196°C
Feces	Feces	2-3 g	2	100	-80°C

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A charter has been drawn up to govern relationships between OFSEP and any person using the cohort resources, in accordance with the ethical guidelines for the collection of human products, laws as well as regulatory rules governing the collection of samples, their treatment and storage, and all related provisions
- Biological samples, including DNA, **are accessible** to academic as well as to industrial research teams
- Specific biological sample **access** will be granted upon a **collaborating request form** for research projects available on OFSEP website
- Biological samples can be transferred to academic or private teams according to modalities defined in a material transfer agreement
- Biological samples **are shareable with a foreign company**

BIOLOGICAL SAMPLE ANALYSES

- Projects are already ongoing on the biobank to:
  - > Find biomarkers that predict the evolution of the disease in early years according to immunological treatments received
  - > Patient risk stratification
  - > Improve disease-specific antibody detection, determine its diagnostic added value and its predictive value

COST

- Costs related to sample release and sample transport to be borne by the requesting team
- An **estimation of the cost of each sample** that composes the biological collection has been made in close collaboration with BRC and University Hospital

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Investigation of diffusion tensor imaging metrics of deep grey matter nuclei and their potential **association with mobility and neuropsychological function**
- Characterization of late onset (≥ 50 years) of neuromyelitis optica and neuromyelitis optica spectrum disease, and to analyze their **predictive factors** of disability and death
- Optimization of aquaporin-4 (AQP4) antibody detection and assessment of the influence of the increased **sensitivity** of the **assay** on the demographic and disease-related characteristics of a group of AQP4-Ab-negative patients
- Assay of biological markers with the aim of identifying new markers of disease progression and new markers of therapeutic response
- Genotyping and identification of new factors of susceptibility to the disease and of gene associated to therapeutic response
- Automatic calculation of markers of disease progression derived from standardized MRI

CLINICAL DEVELOPMENT

- Determine the **prognostic value** of intrathecal synthesis in a cohort of patients with relapsing-onset MS taking into consideration demographic and imaging parameters
- Definition of standards for routine MRI follow-up
- Characterization of the **development** and **natural history** of contrast-enhanced **lesions** by weekly following relapsing remitting MS patients

OUTCOMES RESEARCH

- **Real-life use** of a dedicated drug: Observational follow-up of patients treated in France
- Pediatric MS: evaluation of **prognostic factors** of socio-professional performances in young adults
- **Survival estimation** of MS patients and mortality comparison with that of the French general population
- **Assessment** of rituximab as a maintenance therapy in refractory neuromyelitis optica
- **Evaluation of the impact** of early redosing of natalizumab after delivery on the risk of post-partum relapses in women with very active multiple sclerosis
- **Evaluation of the efficacy** of mitoxantrone on clinical and neuroradiological parameters of patients who had a relapse of neuromyelitis optica spectrum

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RAMSES:

Recherche sur l'AsthME SEvère

ITMO Santé publique

Pr Camille Taillé
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OVERVIEW

AT A GLANCE

> Evaluation of **pharmacological and non pharmacological asthma** treatments
> **Severe asthma** (GINA STEP 4-5 treatments)
> **Multicentric cohort** headed by Pr Taillé
> Sponsorship: AP-HP and Société de Pneumologie de Langue Française (SPLF)
> Funded by SPLF and by industrials actors

KEY FACTS & FIGURES

> First **inclusions expected in September 2018**
> At least **2 000 patients** will be enrolled
> **5 years follow up**
> Linkage to **SNDS**: application in progress
> **Associated-biobank** expected in 2020 (blood, DNA, bronchial biopsies)
> All French lung physicians are invited to participate

RAMSES is a project leaded by the Société de Pneumologie de Langue Française and AP-HP.
Because many new biologics in severe asthma are or will be available in the future, it seems important to **assess severe asthma treatments effects** in real life conditions and **evaluate their cost effectiveness.**

Many questions related to **the use of biologics** will soon appear, such as best choice for 1st line therapy, 2nd line, best treatment duration.

Positioning

> Part of the F-CRIN **CRISALIS network** program, created in 2017
> Collaboration with the **French COBRA cohort** (INSERM)
> Collaboration with the **SHARP cohort** (European Respiratory Society)
> **Protocol validated by the Haute Autorité de Santé** as suitable for post-marketing studies
> **Partnerships** with pharmaceutical companies mainly for post marketing studies. Partnerships are on going with other companies.

LEADERSHIP

RAMSES's leadership team is set up with a team of severe asthma experts from the SPLF and epidemiologists from the AP-HP Pharmaco-Epidemiological Center (CEPHEPI).

Pr Camille Taillé, *Head of the Severe Asthma Clinic in Bichat Hospital, AP-HP*

- Investigator for the COBRA cohort for 10 years
- Member of the F-CRIN CRISALIS network
- Head of the Asthma and Allergy (G2A) working group for 4 years
- More than 80 peer-reviewed publications

Dr Candice Estellat, *CEPHEPI, AP-HP*

- Member of REDSIAM network
- Member of Inserm network Recherche en Epidemiologie Clinique et en santé Publique (RECaP)
- More than 30 peer-reviewed publications
- CEPHEPI:
  - > Evaluation of the SOPHIA-asthma program (funded by the CNAMTS)
  - > Methodology and Coordination of several multicentric cohorts (Psobioteq, SAFIR, RATIO observatory, PréCARE cohort)
  - > Methodology center for F-CRIN IMIDIATE network (inflammatory disease)
  - > Certified by the European Network of Centers for Pharmaco epidemiology and Pharmacovigilance (ENCePP)

SCIENTIFIC NETWORK & MANAGEMENT

- **The Steering Committee is composed of** Pr C.Taillé, Pr A.Bourdin, Pr C.Chenivesse, Pr G. Devouassoux, Pr G.Garcia and a representative of the CEPHEPI platform
  *Its role is **operational** and mainly consists to monitor the progress and to apply and implement the Charter.*

- **The Scientific Committee is composed of well-known experts:** the Steering Committee members, representatives of from university hospitals (7), general hospitals (7) and liberal practice (7), a member from the Endoscopic Working group (GELF). The Presidents of both the SPLF and the F-Crin CRISALIS network are also members.
  *Its role is **Strategic** aiming to define the scientific strategy and communication of the program.*

- **The Industrial Committee** has an advisory role and may propose change or new data to be included in the cohort, comment publications, follow-up of inclusions, in connection with the Scientific Committee.

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- Main objective : **description of the severe asthma population** in France, according to the treatment they receive
- Secondary objectives:
  - > Comparison of different **medical strategies** (choice of 1st line, 2nd line, best treatment duration...)
  - > Evaluation of **treatment safety**
  - > Evaluation of **asthma medical costs**

INNOVATIVE SCIENTIFIC FEATURES

- RAMSES will be **associated with a biobank in 2020**
- Linkage with **SNDS for pharmaco-epidemiological** studies and to validate some medical data such as **exacerbations**
- Investigators with **different medical activity** : private practice, university centers and general hospitals **to capture different medical practices**
- **Educational tool eCRF** for the private doctors to **improve the patient consultation and follow-up**
- RAMSES **protocol has been validated by the Haute Autorité de Santé in October 2017** suggesting RAMSES as the **high-quality tool for providing real life data** in the field of Severe Asthma

METHODOLOGY QUALITY

- Data collected with **eCRF**
- The RAMSES database is housed by AP-HP and managed by **CEPHEPI** (the AP-HP Pharmaco-Epidemiological Center). The **CEPHEPI is certified by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance** (ENCePP).
- On-site data monitoring **training for clinical research technicians** at study initiation
- eCRF filling guide
- Periodic data management and queries issues

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	At least 2 000 patients
Sites:	40 sites (lung physicians with private practice, general and university hospitals)
Inclusion criteria:	Adults with severe asthma, according to GINA guidelines (receiving **STEP 4-5 treatments**)
Exclusion criteria:	Patients without Health Insurance

INCLUSION

Database:
- Asthma history
- Asthma control (ACT score, exacerbations, hospitalizations, FEV1, FeNO…)
- Blood eos and IgE
- Comorbidities (allergy, CVD, GRED, chronic rhinosinusitis, obesity…)
- Asthma treatments. For **STEP 5** treatments, reasons for change, stop or continuation

Biobank:
Serum, DNA and bronchial biopsies

FOLLOW-UP : at least 6 mo and 1 year, then every 6 months, and at each unscheduled visit for asthma exacerbations and until 5 years follow-up

Database:
- Asthma control (ACT score, exacerbations, hospitalization, FEV1, FeNO…)
- Comorbidities (allergy, CVD, GRED, chronic rhinosinusitis, obesity…)
- Asthma treatments. For **STEP 5** treatments, reasons for change, stop or continuation

Biobank:
Serum every 6 months

DATABASE CONTENTS

- **Patient characteristics and clinical data**
  - Administrative and demographics data
  - **Asthma history**
  - **Asthma control**
    - ACT score, exacerbations, hospitalizations, medical visits
- **Biological and functional Data**
  - Blood eos and IgE
  - FeNO
  - Lung function test
- **Comorbidities and treatments**
  - Comorbidities
    - Allergy, CVD, GRED, chronic rhinosinusitis, obesity…
  - Anxiety Depression score, SGRQ, EQ5D
  - Asthma treatments
    - For **STEP 5** treatments: reasons for change, stop or continuation
- **Quality of Life**
  - St George Respiratory questionnaire
- **Medico-administrative via SNDS**
  - Sick leave days
  - Treatments delivered
  - Hospitalizations
  - Costs

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Study the value and stability of blood eosinophils in real life
- Development and validation of novel measurement scales (activity, handicap, dyspnea..) based on PRO **with connected objects**
- **Mobile App development for educational therapy**, treatment management, asthma control treatment measure…

CLINICAL DEVELOPMENT

- **Validation of eosinophils** to predict response to treatment and improve therapeutic guidance
- **Optimization of clinical studies** (timing, measures and scales, sub population characterization, design….)
- Developing scores to better define “good clinical response” to biologicals
- Support clinical enrollment
- Epidemiological studies to **support market access**
- Ancillary study for **RAMSES sub-groups**

OUTCOMES RESEARCH

- Pharmaco-epidemiological studies : drug safety, “real-world” use, effectiveness, adherence to treatments, treatment escapement
- Medico-economic studies cost/benefit : measure of asthma costs and treatment-related costs, before and after **STEP 5** treatment initiation
- **Quality of life studies, evaluation of handicap**
- **Study on current practices** (best treatment duration, best 1st line therapy in the overlap population…)

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REALYSA:

REal world dAta in LYmphoma and Survival in Adults

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OVERVIEW

AT A GLANCE

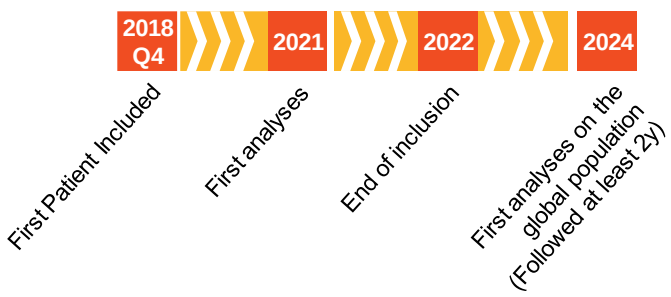
> Hematology
> **Lymphomas**
> Target population: newly diagnosed patients
> Coordinated by Prof. H. Ghesquières & Dr A. Monnereau
> Coordination Institution: **LYSARC** (the Lymphoma Academic Research Organization), Lyon
> Sponsorship: Hospices Civils de Lyon (HCL)
> **Cohort in preparation**
> **Funded by private funds**

KEY FACTS & FIGURES

> Status: **inclusions will start in October 2018**
> **6 000 expected enrolled patients** during a 4-5 years period
> **9 years follow-up**
> **Multicentric cohort** with 13 LYSA clinical sites
> **Biobank:** serum, plasma, constitutional DNA collected from 2 500 patients
> **Linkage to the FRANCIM and LYMPHOPATH databases** is planned
> Linkage to administrative databases (SNDS, PMSI) might be asked for the need of specific studies

REALYSA cohort is a **population-based epidemiological platform** in real-life for lymphomas designed to enrich prognostic data **by integrating together epidemiological, clinical and biological data**.
The **REALYSA cohort** is a program developed by **the LYSA (the Lymphoma Study Association)** whose main objective is to improve prevention, management and treatment of lymphoma patients. For the operational aspects, the LYSA relies on the expertise of its **academic partner, LYSARC**, a fully integrated research organization in charge of setting up and running the projects designed by the LYSA. In this context, the LYSARC is in charge of all operational aspects of the REALYSA cohort.
REALYSA is a platform perfectly set up to:

> **Study prognostic factors** using integrated epidemiological and biological data (genetics), to **better characterize the determinants of refractoriness and relapse** in patients with lymphoma, to follow the **growing number of survivors** and to describe median to long-term sequela, second cancer, quality of life (QoL)…
> Document **treatment effectiveness** in real life and **observance**
> Address **socio-economical questions**



Positioning

> Close collaboration with the **Lymphoma Epidemiology and Outcome Cohort** (LEO, Mayo Clinic) and **InterLymph consortium**
> Close relationship between REALYSA program and the FRANCIM cancer registry network
> **Experiences of PIs** in population sciences, epidemiology programs and on genetic or prognostic studies **at international level**
> Partnership has been initiated with one pharmaceutical laboratory; others are in discussion with several companies as well as academic institutions

LEADERSHIP

REALYSA's leadership team is set up with a tandem of epidemiologist, Dr Alain Monnereau, and clinician, Pr Hervé Ghesquières, who are committed to the lymphoma field for more than 15 years.

Alain Monnereau,
Epidemiologist, Université de Bordeaux, Inserm (U1219), Public health & epidemiology

- Head Hematological Malignancies Registry
  - > 12 000 patients included in C. Registry followed for their vital status
- Coordination of national and international level database on descriptive, clinical, and etiological epidemiology and outcome research
- Head FRANCIM network (French Cancer Registries) and ENCR member
- Chairman of International Coord. Committee InterLymph Consortium
- More than 170 peer-reviewed publications; H Index Web of Science: 25

Hervé Ghesquières,
Physician in Hematology, Centre Hospitalier Lyon Sud. Professor in Hematology, Claude Bernard Lyon 1 University

- Experience in clinical care in lymphoma patients since 2003
- Experience in clinical research in lymphoma field since 2003 (phase I, I, III) and genetic epidemiology since 2010
- Member of scientific and administrative council of the Lymphoma Study Association (LYSA)
- Research activity at Centre de Recherche en Cancérologie de Lyon - INSERM U 1052/CNRS UMR 5286
- Research Collaborator Mayo Clinic, Rochester, MN, USA
- Active member of Interlymph Consortium
- More than 120 peer-reviewed publications; H Index Web of Science: 30

SCIENTIFIC NETWORK & MANAGEMENT

- **REALYSA collaborates with other cohorts through European and International projects and consortiums**:
  - > REALYSA has been presented to the **French national cancer institute** (INCa)
  - > REALYSA is linked to **Mayo Clinic Cohort project** (LEO)
  - > The project is partly involved in a **TRANSCAN2** call for grant submitted in 2018 (EU call for grant)
  - > REALYSA is in close relationship with other initiatives within the **InterLymph consortium** as well as the **FRANCIM cancer registry network** for a formal evaluation of the representativeness of patients included in this prospective cohort compared to the general population

- The Scientific Committee will be composed of well-known experts (*nomination in progress*):
  - > Clinicians experts in Lymphoma subtypes
  - > Biologists and pathologists from the LYSA network
  - > Epidemiologists from INSERM and Cancer registries
  - > Experts in processing such a large amount of data

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- To study **the prognostic value of epidemiological, clinical and biological factors** with a prospective 9-year follow-up by setting up an **integrative epidemiological platform** in real-life for lymphomas in France
- Secondary objectives:
  - **Clinical:** analyze various **outcome indicators** such as survival data or patients reported outcomes such as the **quality of life**, or the **social support**, **and specific geriatric** questionnaire
  - **Epidemiological:**
    - **From patient**: analyze the **prognosis impact of epidemiological exposure factors** and **comorbidities, the frequency** and type of new morbidities and **second cancers** during follow-up, the health behavior (use of alternative medicine, care consumption..)
    - **From health structures:** access to healthcare and expertise…

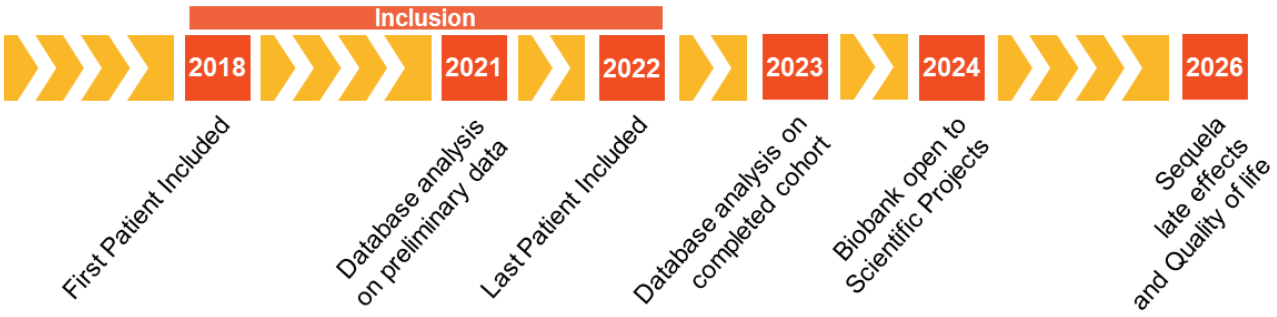
INNOVATIVE SCIENTIFIC FEATURES

- REALYSA will **provide real-life data** from **lymphoma patients**, included those regarding their **routine care management**
- **Representativeness** will be assessed using the population-based cancer registry gold-standard
- REALYSA has been designed as a **research platform for ancillary studies**. Academic and industrial partners will be encouraged to submit analysis proposals.

METHODOLOGY QUALITY

- **Project coordinated by LYSARC**, specialized institution in interventional clinical trials in lymphoma
- LYSARC proposes a biometry department which has been labeled **"Data Processing Center"** by INCa
- Clinical data collected on the basis of a **gold-standard eCRF** with **audit trail and query system**
- Guide of data collection and manual for **biological sample** collection to insure standardized methods between the LYSA centers, with similar reliable and proven processes as those used in interventional research

DESIGN, METHODOLOGY & TIMELINE



Recruitment objectives:	**6 000 patients**
Sites:	**13 LYSA hematology centers in France (12 CHU and 1 CHG) in the first instance**
Inclusion criteria:	Aged over 18, diagnosed with lymphoma in the last 6 months (180 days), lymphoma subtype belonging to at least one of the 7 histological subtypes: diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt lymphoma (rare exceptions)
Exclusion criteria:	Anti-lymphoma treatment already received (except pre-phase: typically corticosteroids, vincristine, cyclophosphamide, etoposide, alone or in combination), documented HIV infection, other lymphoma subtype not included in the list outlined in the protocol

INCLUSION

Database:
Demographics, care pathway, clinical and pathological diagnosis, biological, history of residences and occupations, medical history, professional and domestic exposures, lifestyle and women health
quality of life, social support, geriatric screening

Biobank:
Plasma, serum and constitutional DNA sampling. Information on the availability of tumor biopsies

FOLLOW-UP: twice per year for 3 years then once a year

Database:
Status, treatment received (adverse event in case of treatment discontinuation), response to treatment, progression/relapse, death.
In rotation : new morbidities (including new malignancy), QoL, social support, impact on the professional life, on lifestyle, on fertility, on health behaviors

Biobank:
Plasma and serum at Day 1 of cycle 3 of first line treatment

DATABASE & BIOBANK CONTENTS

DATABASE

- Type of collected data:
  - **eCRF** (data extracted from patient medical files)
    - Demographics
    - Care pathway (type of health facility for the first medical contact, the diagnosis, the therapeutic decision, the treatment; review in RCP, …)
    - Clinical (with detailed diagnostic)
    - Documentation of all treatment lines at the chemotherapy cycle level, interruption of treatment, dose modification, main toxicities, response and its modalities, progression & relapse
  - **Questionnaires** :
    - Residencies and employment
    - Exposures
    - Medical history, G8 (>70 y-o)
    - New morbidities (incl cancer)
    - Impact of the disease on lifestyle
    - Professional or fertility
    - Quality of life (QLQ-C30 + specific modules for NHL (high/low grade), HL)
    - Social support: SSQ6
    - Health behavior (use of alternative medicine, screening, care consumption…)
  - **Imagery (Pet scan, scanner):**
    - Are not routinely collected but could be accessed at a later stage for specific project
    - The LYSA-Imagery platform could be solicited to perform a central imaging review for PET, CT and/or MRI scans by experts
  - **Central Diagnostic Data Reviews:**
    - The reviewed diagnostic data are collected from LymphoPath (>80% of lymphom cases reviewed nation-wide) and LYSA-Pathology (for patients also included in clinical trials run by LYSARC)
- Linkage to other databases
  - FRANCIM, LYMPHOPATH
  - PMSI, SNDS, CéPiDC: access could be asked for specific projects

BIOBANK

- **Originality**
  - **Large prospective biobank** on a variety of **lymphoma subtypes** (including rare subtypes)
- **Scientific objective**
  - **Biological prognostic factor** identification at diagnosis and during treatment
  - Identification of **theranostic biomarkers**
- **Samples**
  - Nature of the samples: serum, plasma, constitutional DNA. Tumor biopsies can also be made available:
    - Number of samples per patient: 5
    - Number of patients who will be sampled: 2 500
    - Total number of samples: 12 500
- **Associated resources**
  - Human resources:
    - **Coordination by LYSA-Biology**: biological project officer and biological sampling technician to assist the centers. LYSA-Biology has a longstanding expertise in managing biological resources for biobanking: providing sampling material, reminders for sample collections, close contact with the CRB
    - **CRB**: dedicated full-time technician
  - **Longstanding know-how** in sample collection at LYSARC

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- Biological samples will be **centralized**
  - > CRB Lyon Sud, under the supervision of Dr Pierre Sujobert
  - > CRB Créteil (at a later stage)
- A **dedicated biological project officer,** experienced in the transport of medical samples**,** is responsible for ensuring the safe transport of the biological samples from each center to the central lab
- Samples will be labeled with -80 compatible labels indicating the patient ID number, date, protocol name and sample type
- Samples will be centralized and tracked with **a traceability form**
- On the biobank, they will be registered in a **specific sample-management software Tumorotek®**

BIOBANK-ASSOCIATED DATABASE

- Each sample will be linked to the clinical database

SPECIFICATIONS

- All patients enrolled in the cohort can be sampled
- Sampling frequency: **at diagnosis and at D1C3**
- Responsible for the biobank: Dr Pierre Sujobert
- Institution responsible for the biobank: HCL
- Manual for the biological sample collection will be available for the investigating centers
- Label of quality: **NFS 96-900 for CRB Lyon Sud**
- **Standard Operating Procedures** will ensure that standardized methods are applied for the sample collection, treatment and storage
- Biological samples **will be made available in 2024**

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biological sample	Origin of the sample	Quantity of the sample/ concentration available	Number of aliquot	Number of patients who have been sampled (expected/ ongoing	Preservation or storage conditions
At Baseline: ***Baseline samples are collected before the start of the first treatment line*** • **Date of the first sampling: October 2018**					
Plasma	Blood	10mL	2	2 500 expected	-80°C
Serum	Blood	10mL	2	2 500 expected	-80°C
DNA	Blood	8,5mL	1	2 500 expected	-80°C
During the follow-up • **Date of the first sampling: December 2018** • **Sampling frequency: at D1C3 of first line treatment**					
Plasma	Blood	10mL	2	2 500 expected	-80°C
Serum	Blood	10mL	2	2 500 expected	-80°C

BIOLOGICAL SAMPLE ACCESS MODALITIES

- A document specifying biobank access (charter) will be made available (in preparation)
- Biological samples, including biological derivatives (i.e. DNA, RNA), will be **accessible to public as well as to private/industrial teams through partnership**
- Access will be granted **based on a detailed research protocol** reviewed by the Scientific Committee and approved by the Steering Committee

BIOLOGICAL SAMPLE ANALYSES

- The protocol only specifies the banking of the samples
- Specific project will have to be proposed to perform analysis
- Biological sample analysis-derived data could be made accessible to public teams and to private/industrial teams through partnerships

COST

- A price list for biological samples will be set up

RESEARCH COLLABORATION OPPORTUNITIES

Phase IV Product approval Phase III Phase II Phase I Pre-clinical Proof of concept

TRANSLATIONAL RESEARCH

- Identification of biomarkers for the development of diagnostic or prognostic tests based on the correlation of biological and clinical data, such as:
  - Circulating tumoral DNA
  - Constitutional SNP (GWAS)
  - Cytokines/chemokines
  - ATACseq profiling in tumor
- Pathophysiology studies for the understanding of disease history (etiology), such as:
  - Deciphering new/rare lymphoma entities
  - Molecular definition of lymphoma (NGS)
- Development and validation of novel measurement scales and disease models, such as:
  - Development of artificial intelligence based on large databases

CLINICAL DEVELOPMENT

- Epidemiological studies to support market access, including on refractory patients
- Identification lymphoma patients with an early event (EFS24, POD24)
- Prognostic factors related to early predictors
- Validation of biomarkers to define clinical stages and improve therapeutic guidance
- Biological prognostic factors linked to outcomes
- Guide therapeutics based on imaging (PET), ctDNA

OUTCOMES RESEARCH

- Pharmaco-epidemiological studies: drug safety, “real-world” use, effectiveness, practices patterns, acceptance, risk/benefit, risk management
- Survival and prognostic studies in the general population (epidemiological predictors)
- Comparative studies to assess product efficiency
- Prognostic studies using alternative outcomes: Quality of life and other Patient-Reported Outcome studies
- Pharmaco-economic studies cost/benefit; Health economic outcomes

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  - Journées du LYSA 9 février 2018: Etudes en vie réelle : Principes, avantages inconvénients
  - ASH 2017
  - Interlymph: June 25-28, 2018 (Chicago)
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SFDT1:

Study in France on the health Determinants in patients with Type 1 diabetes

Jean-Pierre Riveline, MD, PhD
Professor in endocrinology, Lariboisière Hospital, AP-HP, Paris

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OVERVIEW

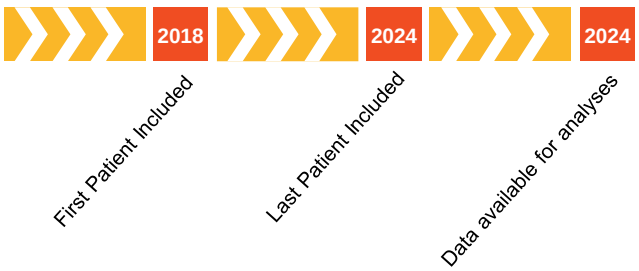
AT A GLANCE

> **Diabetes** (type 1, without age limit)
> Coordinated by Dr Anouar Fanidi, Pr Jean-Pierre Riveline and Pr Emmanuel Cosson
> Sponsor: **Fondation Française pour la recherche en Diabétologie**
> In preparing the inclusion phase
> **Associations as Project Partners**: Association d'Aide aux Jeunes Diabétiques (AJD), Association Française des Diabétiques (AFD)
> Funded by pharmaceutical partners

KEY FACTS & FIGURES

> **Inception of the inclusion phase** expected by the end 2018
> **15 000** included patients expected
> **A 10 years follow-up** period is planned
> **A National multicentric cohort** with 6 centers during the pilot phase and 50 expected for the national phase
> **Biobank expected** with blood (plasma-serum-DNA), urine, hair and saliva
> **SNDS linkage** expected as soon as the first patient is included

SFDT1 will serve to improve our understanding on the biological, clinical, psychosocial and health care system determinants of T1D, more specifically linked to the cardiovascular events.



Positioning

> SFDT1 **is unique in France** while other similar cohorts exist in Europe
> **Academic collaborations** discussed with:
  > **Hypo-RESOLVE**: newly started European research project for investigating Hypoglycemia and its impact in Diabetes
  > The **ComPaRe** platform (Patient Community for Research)
  > The **French Retinal Clinical Research Network** project: a national ophthalmologic cohort (FCrin)
> The SFDT1 cohort aims **to be opened to scientific community** at European and International levels for academic as well as industrial researchers
> SFDT1 has already 2 industrial partners and 4 partnerships are ongoing

LEADERSHIP

SFDT1's leadership team, led by Prof Jean-Pierre Riveline, brings together renown endocrinologists, epidemiologist and clinician who have been committed in the field of diabetes care over 20 years.

Jean-Pierre Riveline, ***Professor in Endocrinology at Lariboisière Hospital***

- **Chief of the CUDC** (Centre universitaire du diabète et de ses complications), at Lariboisière Hospital
- **Member of the Metabolic Inflammation in Diabetes and its Complications unit**, Cordeliers Research Centre, INSERM U 1138, Paris, France
- **Participation or elaboration of many cohorts in diabetes** on patients with T1D treated with insulin pump (2003-2010), Evadiac (T1D treated with implantable pump), Gragil (T1D treated with islet transplantation), Angiosafe 2 (D2T patients)
- **PI of the Sensor-Evadiac Study:** multicentric study on the efficacy of Continuous Glucose Monitoring (2007-2012)
- **Investigator of several cohorts** : General secretory of the french diabetologist association SFD (2015-2017)
- Several study ongoing (Panex, Revadiab…etc)
- More than 67 peer-reviewed publications; H Index Web of Science :18 (Sigaps: 771)

Emmanuel Cosson, ***Professor in Endocrinology and Metabolism at Jean-Verdier Hospital***

- **Head adjunct of Diabetology-Endocrinology-Metabolism Department** of Avicenne, Jean Verdier and René Muret hospital, AP-HP
- Research Unit: Equipe de Recherche en Epidémiologie Nutritionnelle (EREN) UMR U1153 Inserm/U1125 Inra/Cnam/Univ Paris 13 Centre de Recherche en Epidémiologies et Biostatistiques Sorbonne Paris Cité
- **Current general secretary of SFD**, Member of the working group « Epidemiology and Diabetes » of the SFD
- Current collaborations: **ComPaRe, Constances, Santé Publique France**
- More than 89 peer-reviewed publications; H Index Web of Science :27 (Sigaps: 1151)

SCIENTIFIC NETWORK & MANAGEMENT

- SFDT1 gathers a network of French and International epidemiologists
- The SFDT1 Scientific Boards (international and internal) are organized around six work packages including well-known experts:
  - T1D phenotypes
    - Leader: Etienne Larger
  - Assessment of glycaemic control
    - Michael Joubert
  - Treatment of T1D
    - Pierre-Yves Benhamou
  - Diabetes complications
    - Bruno Verges
  - Psychosocial
    - Caroline Guillot
  - Health economics
    - Bruno Detournay

PROJECT DESCRIPTION

SCIENTIFIC OBJECTIVES

- The primary objective of the SFDT1 study is to develop a research platform to evaluate clinical, biological, and environmental determinants associated with cardiovascular events among T1D
- Secondary objectives:
  - > To identify and characterise **novel biomarkers and metabolic pathways** associated to T1D outcomes (complications, QoL, mortality)
  - > To identify **determinants of glycaemic variation** and evaluate **the relation between glycaemic instability and health events of T1D outcomes**
  - > To identify **psychosocial factors** associated with T1D outcomes
  - > To evaluate **costs associated to T1D outcomes** and identify their determinants

INNOVATIVE SCIENTIFIC FEATURES

- **Nationally representative** samples of T1D patients
- Large sample of patients (15 000) **associated with high-quality biological samples**
- **Long-period follow-up** with repeated measurements
- **Connected to the French Health Insurance Databases** (SNDS)
- Provide an **unbiased view of routine T1D care** in a wide variety of settings while collecting standardized data
- **Exhaustive data from the Free Style** with millions of data
- **A developed IA tools**: the "Real-world flash glucose monitoring » allows to display interstitial glucose data collected by the sensor and to download records during 90 days maximum with the following characteristics:
  - > The sensor lasts 14 days; No capillary glycemia; Capture and store data; Quick scan
- The **platform ComPaRe (e-questionnaires)** is used to gather and process a large amount of patient data (mainly **psychosocial and lifestyle items**)
- The cohort can serve for ancillary studies

METHODOLOGY QUALITY

- **A web-based data collection system** will be developed for the SFDT1 study, using a **secure web portal**
- Confidentiality, security and integrity of the data will be covered by **a certified Agency**
- Biosamples will be stored in **certified biological resource centers** (BRCs)

DESIGN, METHODOLOGY & TIMELINE

Recruitment objectives:	15 000 participants (about 10% of the French T1D population)
Sites:	About 50 participating centers will spread out in France with University hospitals, general hospital, and GPs
Inclusion criteria:	Patients with T1D, clinically and biologically diagnosed
Exclusion criteria:	Patients unable to give written informed consent and speak French language

INCLUSION

Database:
Clinical, biological, treatment, environmental and psychosocial data integrated trough clinicians and self-reporting

Biobank:
Blood, urine, saliva, and hair sampling

FOLLOW-UP every 3 years (3, 6, 9 years follow-up)

Database:
Blood, urine, saliva, and hair sampling combinaison of systematic follow-up visit with using a variety of different national administrative database (SNDS) and e-questionnaires (ComPaRe)

Biobank:
Blood, urine, saliva, and hair sampling

DATABASE & BIOBANK CONTENTS

DATABASE

- **Patient characteristics:** demographics, lifestyle, history of diabetes
- **Cardiovascular:** ATCD cardio, blood pressure, dyspnea, cardiovascular diseases, FC, endothelial function…
- **Nephrology:** MDRD, disease classification, creatinine…
- **Ophthalmology:** retinopathy, macular edema, cataract…
- **Neurology:** ulcerations, Achille reflexes, dysautonomia…
- **Glycemic variability:** Hb1Ac, severe hypoglycemia, CGM…
- **Hypoglycemic treatment:** insulin, injection modes, pomp, doses…
- **Non-hypoglycemic treatment:** antihypertensive, hypolipidic…
- **Education/evaluation of the patient:** therapeutic education, functional insulinotherapy
- **Psychosocial:** quality of life, anxiety, depression, precariousness..
- **Imagery data** (number of patients to determine): retinal images
- **Free Style Libre**

- Linkage with the **SNDS** database

BIOBANK

- **Originality**
  - > A large scale biobank with 15 000 patients sampled; serum, plasma, DNA, urines, saliva and hair; with a conservation -80°C for blood samples
- **Scientific objective**
  - > Biobank aims to carry out future studies of progression, inflammation and oxidative stress biomarkers, genetics and proteomics, and cardiovascular risk markers and factors

*The collected samples are planned to be primary used for the **validation of the cardiovascular disease diagnosis and prognosis in T1D**: the identification of new biomarkers to predict CVD progression and metabolic complications & the validation of the CVD disease diagnosis*

- **Samples**
  - > Blood, serum, plasma, DNA (extracted from blood), urine, hair, saliva *(and maybe feces)*
  - > At baseline: 15 000 patients will be sampled
  - > For follow-up, number of patients who will be sampled still to be determined
- **Associated resources**
  - > 2 national certified BRCs (Biological Resource Centers)
  - > BRCs ensure the availability of well qualified and competent personnel, at all levels
  - > SFDT1 has skills to manage the operational and scientific aspects associated to the biobank

TECHNICAL MODALITIES & SPECIFICATIONS

ORGANIZATION

- The biological samples will be centralized in 2 main BRCs (Lille and Paris):
  - DNA samples in the BRC of Lille
  - Serum and plasma samples in the BRC of Paris
- The biological samples might be identified by bar codes

SPECIFICATIONS

- **Date of the first sampling** : by December 2018
- Sampling at **baseline** and at **3, 6 and 9-years** during the follow-up period
- Responsible for the biobank: Pr Samy Hadjad
- **Protocol** for the biological sample collection exists but confidential at this stage
- Label of quality: certified BRC
- Biobank procedures to apply standardized methods for sample collection, treatment and conservation (**SOPs**) are developed and will be soon finalized
- The **availability of the biological samples** is expected **by 2024** (15 000 sampled patients)

BIOLOGICAL SAMPLE COLLECTION & ACCESS

Biospecimens	Origin	Quantity / concentration available	No. of aliquot	No. of subjects expected to be sampled	Storage conditions
First sample collection expected in 2018 (At baseline)					
Serum	Blood		75 000	15 000	-80°C
Plasma	Blood		150 000	15 000	-80°C
DNA	Blood		15 000	15 000	-80°C
Urine	Urine		45 000	15 000	-80°C
Hair	Hair		15 000	15 000	T° ambiante
Saliva	Saliva		15 000	15 000	-80°C

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ANR	Stands for Agence Nationale de Recherche -or French National Research Agency. The ANR is a research funding organisation. The Agency was established by the French government in 2005 to fund research projects, based on competitive schemes giving researchers the best opportunities to realise their projects and paving the way for groundbreaking new knowledge. The role of the Agency is to bring more flexibility to the French research system, foster new dynamics and devise cutting edge-strategies for acquiring new knowledge. By identifying priority areas and fostering public-private collaborations, the ANR also aims at enhancing the general level of competitiveness of both the French research system and the French economy. Project-based research funding is well established in many countries where it is known to stimulate research organisations and strengthen their synergies. The ANR's approach to funding allows French research to reinforce its international position and better integrate the framework of European cooperation.
ANSM	Stands for Agence Nationale de sécurité du médicament et des produits de santé - or French National Agency of Medicine and Health Products Safety. As a public body under the supervision of the Ministry of Health, the ANSM conducts expert assessment of healthcare products and acts as a decision-making body in the field of sanitary regulation. Their aim is to reconcile patient safety with access to therapeutic developments. In France, the Agency works in close collaboration with many institutional partners: other healthcare agencies, Regional Health Agencies (ARS), the French National Health Insurance Fund for Salaried Workers (Caisse nationale de l'assurance maladie des travailleurs salariés – CNAMTS), the French National Authority for Health (Haute Autorité de Santé – HAS), etc.
Aviesan / ITMO Santé Publique	The French National Alliance for Life and Health Sciences (Aviesan) Aviesan has been set up in response to the commitment to further step up these French research performances by fostering its consistency, creativity and excellence. This mission calls for scientific coordination of the main research themes – which concern all organizations – as well as operational coordination of projects, resources and funding. The purposes of Aviesan are to: • coordinate the strategic analysis, scientific programming and operational implementation of life and health science research; • give a fresh boost to translational research by speeding up the transfer of fundamental knowledge to clinical application; • increase cross-disciplinarity by opening biology and medicine up to contributions from mathematics, physics, chemistry, information technology, engineering sciences, human and social sciences; • ensure that projects are consistent in thematic and infrastructure terms; • carry out clinical, economic and social promotion of knowledge, particularly by facilitating industrial partnerships; • define shared standpoints in terms of European research and international cooperation; • harmonize and cut down on red tape for laboratories so as to free up the creativity and excellence of teams. These objectives will be performed within 10 thematic multi-organization institutes (ITMOs) whose primary role will be to chair the strategic debates within their own scientific community. The ITMO Public health works on facilitating and coordinating the activity of research teams who develop studies on public health or clinical research.
Biomedicine Agency	The French Biomedicine Agency is a public organisation under the supervision of the Minister of Health, operating in four key areas of human biology and medicine: assisted reproductive technologies, prenatal and genetic diagnosis, embryo and stem cell research, and the procurement and transplant of organs, tissues and cells, previously entrusted to L'Etablissement français des Greffes (the French Transplant Agency) between 1994 and 2005. These medical activities present major therapeutic, health and ethical issues. Interacting with society, the agency's mission is to provide professionals and researchers with collective answers to the questions they encounter. Its underlying goal is to improve care for patients. The French Biomedicine Agency was created by virtue of the Bioethics Law of August 6, 2004. It guarantees equity, ethics and transparency for the activities under its responsibility, and for anticipated developments.
BRC	Stands for Biological Resource Centers. BRCs are both service providers and repositories of culturable organisms (e.g. micro-organisms, plant, animal and human cells) replicable parts of these (e.g. genomes, plasmids, viruses, cDNAs), viable but not yet culturable organisms, cells and tissues, as well as databases containing molecular, physiological and structural information relevant to these collections and related bioinformatics.
CepiDc	Stands for Causes Médicales de Décès: Medical Causes of Death
CHU	stands for Centre Hospitalier Universitaire: University Hospital
CIC	stands for Centre d'Investigation clinique: Clinical Center of Investigation
CNAM	Stands for La Caisse nationale de l'assurance maladie des travailleurs salariés: Health Insurance
Cnav	Stands for Caisse Nationale d'Assurance Vieillesse: Old-Age Insurance
CRA	Stands for clinical research associate
EFS	Stands for Etablissement Français du Sang [French National Blood Service], EFS is the only civilian blood transfusion organization in France. Blood transfusion, to which the EFS has held exclusive rights since 2000, includes blood donation, plasma donation and platelet donation. The Etablissement Français du Sang guarantees the safety of the transfusion chain, from the donor to the receiver.

GLOSSARY

ERC	Stands for European Research Council
European Commission FP7 (EU FP7)	FP7 is the short name for the 7th Framework Programme for Research and Technological Development. This is the EU's main instrument for funding research in Europe and it will run from 2007-2013. FP7 is also designed to respond to Europe's employment needs, competitiveness and quality of life.
GWAS	Stands for Genome-wide association study
H2020	Horizon 2020 is the biggest EU Research and Innovation program ever with nearly €80 billion of funding available over 7 years (2014 to 2020) – in addition to the private investments that this program will attract. It promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market.
HAS	Stands for The Haute Autorité de santé (HAS) - or French National Authority for Health. Its activities range from assessment of drugs (including reimbursement level definition), medical devices, and procedures to publication of guidelines to accreditation of healthcare organisations and certification of doctors.
INCa	The French National Cancer Institute Created by the Public Health Law of 9 August 2004, INCa has two core objectives: To develop expertise in the field of cancer To provide scientific planning, evaluation and funding for projects.
Inserm	Founded in 1964, the French National Institute of Health and Medical Research (Inserm) is a public scientific and technological institute which operates under the joint authority of the French Ministry of Health and French Ministry of Research.
Santé publique France - InVS	Stands for Institut de veille sanitaire; The French Institute for Public Health Surveillance, a governmental institution reporting to the Ministry of Health, is responsible for surveillance and alert in all domains of public health.
ISPED	Stands for Institut de Santé Publique, d'Epidémiologie et de Développement - or Bordeaux School of Public Health ISPED, within the Université Bordeaux Segalen, is the first University-based School of Public Health ever created in France. Distinct, though very close to a medical faculty, ISPED aims to help meet the great challenges of contemporary public health: increasing life expectancy, the reform of health systems, the resurgence of infectious diseases worldwide, the impact of industrialisation and globalisation on the environment and the population's health.
MRC	Stands for Medical Research Council
NIH	Stands for National Institutes of Health
PHRC program	Stands for Programme Hospitalier de Recherche Clinique: Hospital Clinical Research Program
PIA	Stands for "Programme Investissement d'Avenir"; With €35 billion in funding for 10 years, the "Investments for the future" program should provide funding for profitable assets and research and innovation infrastructures which promote economic development. The goals are to develop biotechnology, stimulate progress in laboratories of excellence, and promote industrial applications of research. Research credits are allocated through seven priority actions: Technological Research Institutes, Health and biotechnology, Laboratories of excellence, Equipment of excellence, Hospital-University Institutes, Technology transfer acceleration companies, and Carnot Institutes. For each of these actions, cancer research received direct funding from the State that is complementary to the INCa investments.The global "investments for the future" made by the State to projects in the field of cancer are estimated at €315 million.
PMSI	Stands for Programme médicalisé des systèmes d'information: Healthcare information systems program. French national medico administrative database which collects data from all hospital stay either medical surgical or obstetrical stay
RNIPP	Stands for Répertoire National d'Identification des Personnes Physiques - or National Directory for the Identification of Natural Persons RNIPP is the model for public service registers. It is regularly updated through statistical bulletins on civil status changes, drawn up and sent to INSEE by municipalities and containing details of births, deaths, recognitions and marginal notes made in birth certificates for persons born in metropolitan France or the overseas departments (DOM).
SNDS	Stands for Système National des Données de Santé: Health Data National System. The SNDS is created since 2017 (April 18th) in the context of the modernization and renewal of the French healthcare system. It Includes - data from National Health Insurance Database (SNIIRAM Database) - data from Healthcare Information Systems Program (PMSI Database) - data from Medical Causes of Death Database (CepiDC Database) - data concerning the handicap - a sample of data from complementary private Health Insurances
SOP	Stands for Standard Operating Procedure
UCL	Stands for University College London
UCSF	Stands for University of California, San Francisco