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The biological sample collection of the OFSEP French MS registry: An essential tool dedicated to researchers

Guillaume Brocard, Romain Casey, Nathalie Dufay, Romain Marignier, Laure Michel, Michael Hisbergues, Xavier Ayrignac, Sylvain Lehmann, Eric Thouvenot, Geraldine Gallot, Nicolas Collongues, Yves-Edouard Herpe, Christine Lebrun-Frenay, François Cotton, Jérôme De Sèze, Francis Guillemin, Thibault Moreau, Jean Pelletier, Bruno Stankoff, Sandra Vukusic, Hélène Zephir, David Laplaud; on behalf of OFSEP investigators and biobanks

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Abstract:

Today's medicine strives to be personalized, preventive, predictive and participatory. This implies to have access to multimodal data to better characterize patients groups and to combine clinical and imaging data with high-quality biological samples. Collecting such data is one of the objectives of the Observatoire français de la sclérose en plaques (OFSEP), the French MS registry. On December 2022, the OFSEP biocollection includes 4,888 patients with scientific characteristics and about 90,000 samples. Thanks to its richness, this biocollection open for the scientific community, contributes to address unmet needs in MS through identification of multiomics determinants of MS activity, progression, secondary effects.

KEYWORDS:

Multiple Sclerosis, biobank, sample, registry, database, quality

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, for which there are still many unsolved questions including its causes and mechanisms or the prognostic factors of disease progression. In the actual context of personalized, preventive, predictive and participatory medicine, the care of MS requires multimodal data to better characterize patients groups. Through its vast database gathering standardized clinical and imaging data with high-quality biological samples, the main objective of the *Observatoire français de la sclérose en plaques* (OFSEP), the French MS registry, is to provide a powerful epidemiological tool for the worldwide scientific community.¹ The OFSEP biocollection represents a significant and qualitative tool for identifying multiomics determinants of MS activity, progression, secondary effects, etc.² This paper describes the biocollection and the harmonized biobanking processes used to implement this collection.

Setting up of the registry

Data collection

OFSEP is a French national registry in which patients with MS or related disorders can be included by an OFSEP-participant neurologist of an MS expert center (about 80,000 patients on December 2022).¹ Standardized clinical and imaging data are collected during routine follow-up visits and entered into the European database for multiple sclerosis (EDMUS).³ In addition, biological samples are collected in a subset of patients with specific characteristics (called biological cohorts). Samples are processed and stored by the local biobanks of each center. Pseudonymized biological data are stored in TumoroteK[®] database.

Regulatory compliance

Patients enrolled in both the OFSEP registry and OFSEP high definition (HD) cohort ([NCT02889965] and [NCT03603457] on clinicaltrials.gov) signed a consent for participation. OFSEP registry and HD cohort have been authorized by the French data protection agency and an ethical committee.

Biological cohorts description

Inclusion criteria and sampling time

OFSEP has set up seven biological cohorts, gathering subsets of patients from the OFSEP registry. An Expanded Disability Status Scale (EDSS) evaluation at ± 3 months from the sampling date is required. In order to guarantee the non-perturbation of biomarkers and lymphocytes populations, it's recommended to avoid sampling within 30 days of a relapse treatment and less than 12 months of disease modifying treatment. If this general recommendation is not followed the information is collected. Other inclusion criteria are specific for each cohort:

- Radiologically isolated syndromes (RIS): subjects with MRI lesions suggestive of multiple sclerosis, no history of symptoms suggestive of MS, and a normal neurological examination.⁴
- Clinically isolated syndromes (CIS) and single attack (SA): patients fulfilling or not McDonald criteria⁵ with a first inflammatory event of the central nervous system less than six months before sampling.
- Primary-progressive multiple sclerosis (PPMS): PPMS patients⁵ with a disease duration of less than six years and under 65.
- Neuromyelitis optica spectrum disorders (NMOSD) and myelin-oligodendrocyte-glycoprotein antibody associated disease (MOGAD): patients meeting the international NMOSD criteria^{6,7} or MOGAD.
- Acute Disseminated Encephalo-Myelitis (ADEM): patients with ADEM.
- Progressive Multifocal Leukoencephalopathy (PML): patients treated for MS with PML diagnosis confirmed by Polymerase Chain Reaction (PCR); sampling within one month of PML or immune reconstitution inflammatory syndrome diagnosis.
- Covid-19 (stopped): patients with MS/NMOSD/MOGAD and Covid diagnosis; sampling within three months after biological confirmation of the diagnosis by PCR or the symptoms onset.

The HD cohort has been established on a subset of well-defined MS patients with prospective longitudinal follow-up. Patients included in this cohort are SA, relapsing remitting MS, secondary progressive MS or PPMS, not permanently wheelchair users (EDSS ≤ 7) and over 15, treated or not at sampling.

Data management

Twice a year, data from EDMUS and TumoroteK[®] databases are merged into a global OFSEP database, and non-conformity reports are generated to verify and correct data. Upon non-compliance with the inclusion criteria, samples are kept whether the diagnosis remains MS or a related disorder, and can otherwise be kept to serve as negative controls.

Description of the biocollection

On December 2022, 4,888 patients (Table 1) were included in biological cohorts (300 new patients every year) and HD cohort (2,500 new samples every two years).

The OFSEP sample collection

Biosampling

The sampling is carried out by the 27 participating centers, according to OFSEP standardized operating procedures (Figure 1). For the biological cohorts, blood (51.5 mL for serum, plasma, DNA and Peripheral blood mononuclear cells (PBMC)), cerebrospinal fluid (3 mL), saliva (5 mL), urine* and stools* (*stopped in 2022) are collected using inclusion kits. Iterative blood samples (7 mL for serum) can be collected during the patient follow-up visits: for the RIS cohort, annually until the conversion in MS; for the CIS/SA and NMOSD/MOGAD cohorts, at one, three and five years (inclusion kit at 5) and in case of relapse. For the HD cohort, only blood tubes are collected (7 mL for serum, plasma and DNA). Samples are transported at room temperature within 2 hours to each biobank.

Processing

After quality control, biobanks process samples under sterile conditions, according to OFSEP sample management procedure to obtain:

- Serum from Serum-separating clot activator blood tubes
- Plasma and whole blood (for DNA) from K2EDTA blood tubes
- PBMC from Mononuclear Cell Preparation Tube (CPT™) blood tubes
- Cerebrospinal fluid, saliva, urine and stools.

Since 2022, samples are aliquoted into 1D barcoded, biocompatible and suitable to cryostorage ClearLine® cryotubes.

Storage

Aliquots are stored at -80°C within 4 hours following the sampling (or 24 hours for PBMC) to guarantee their integrity and long-term storage. Then, PBMC are transferred to liquid nitrogen within 12 hours.

Data related to bio-sampling processes and non-conformity are recorded in Tumorotek® database to ensure traceability.

Quality management

All biobanks are certified according to biobank standards: NF S96-900 or ISO 20387. OFSEP coordination team undertakes numerous actions to ensure quality and traceability like annual activity reports and biobank audits.

Access to data and samples

The data and samples collected are open to any researcher after positive scientific evaluation of the project by OFSEP (<https://www.ofsep.org/fr/acces-aux-donnees>). Once regulatory and contractual

aspects are solved, OFSEP team organizes the samples distribution from the biobanks to the researcher and the transfer of associated data.

Conclusion

The OFSEP biocollection is a significant and qualitative tool for MS research projects. On December 2022, 4,888 patients were sampled and about 90,000 samples are available. This biocollection is constantly evolving to meet the needs of researchers and adapt to technical improvements. Thanks to its richness and completeness of its associated data, more than twenty research projects have been already carried out.^{8,9,10}

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Declaration of interest

The author(s) declared the following potential conflicts of interest: Guillaume Brocard has no disclosure to declare. Romain Casey has no disclosure to declare. Laure Michel has received honoraria for consulting from Biogen, Teva, Roche, Sanofi Genzyme, Janssen, Novartis and Merck. Eric Thouvenot received consulting and lecturing fees, travel grants or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, BMS, Merck, Novartis, and Roche. Sandra Vukusic has received lecturing fees, travel grants and research support from Biogen, BMS-Celgene, Janssen, Merck, Novartis, Roche, Sandoz, Sanofi-Genzyme. H el ene Zephir has received consulting fees from Alexion, Biogen, Horizon Therapeutics, Merck, Novartis, Sanofi, Roche, and

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Appendix 1

OFSEP Biobanks by number of samples processed on December 2022

Centre de Ressources Biologiques NeuroBioTec (BRIF N° BB-0033-00046), Hospices Civiles de Lyon, Lyon, France; Centre de Ressources Biologiques Santé (BRIF N° BB-0033-00056), CHU Rennes, Rennes, France; Centre de Ressources Biologiques Lorrain – CRBL (BRIF N° BB-0033-00035), CHRU de Nancy, Nancy, France; Centre de Ressources Biologiques du CIC 1403 (BRIF N° BB0033-00030), CHU Lille, Lille, France; Centre de Ressources Biologiques (BRIF N° BB-0033-00059), CHU de Montpellier, Montpellier, France; Centre de Ressources Biologiques (BRIF N° BB-0033-00032), CHU de Nîmes, Nîmes, France; Centre de Ressources Biologiques (BRIF N° BB-0033-00040), CHU Nantes, Nantes, France; Centre de Ressources Biologiques Plurithématique-BBS (BRIF N° BB-0033-00094), CHU de Bordeaux, Bordeaux, France; Centre de Ressources Biologiques Bioressources, CHU Toulouse, Toulouse, France; Centre de Ressources Biologiques (BRIF N° BB-0033-00069), CHU Grenoble-Alpes, Grenoble, France; Centre de Ressources Biologiques Ferdinand Cabanne (BRIF N° BB-0033-00044), CHU Dijon-Bourgogne, Dijon, France; Centre de Ressources Biologiques, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Biobanque de Picardie (BRIF N° BB-0033-00017), CHU Amiens-Picardie, Amiens, France; Biobanque CRB-Tumorotheque (BRIF N° BB-0033-00025), CHU de Nice, Nice, France; Centre de Ressources Biologiques Auvergne (BRIF N° BB-0033-00039), CHU Estaing, Clermont-Ferrand, France; Centre de Ressources Biologiques CRB-T (BRIF N° BB-0033-00013), CHRU de Tours, Tours, France; Plateforme de biomonitoring, UMR Right-EFS-CIC-1431 de Besançon, Besançon, France; Centre de Ressources Biologiques InnovaBIO, CHU de Caen-Normandie, Caen, France; Plateforme de Ressources Biologiques (BRIF N° BB-0033-00021), GHU AP-HP. Hôpitaux Universitaires Henri-Mondor, Créteil, France; Centre de Ressources Biologiques, Hôpital Fondation Adolphe de Rothschild, Paris, France; Centre de Ressources Biologiques BioGenoPole, Hôpital Timone AP-HM, Marseille, France; Centre de Ressources Biologiques (BRIF N° BB-0033-00068), CHU Poitiers, Poitiers, France; Centre de Ressources Biologiques SAT, APHP-Sorbonne Université site Saint-Antoine, Paris, France; Centre de Ressources Biologiques CRBioLim, CHU Dupuytren, Limoges, France; Centre

de Ressources Biologiques de la Martinique CeRBiM (BRIF N° BB-0033-00099), CHU Martinique, France; Banque ADN et cellules - ICM Institut du Cerveau (BRIF N° BB-0033-00042), GH Pitié-Salpêtrière, Paris, France; Service de Biologie Médicale - Biologie moléculaire, Centre hospitalier Intercommunal, Poissy Saint-Germain, France

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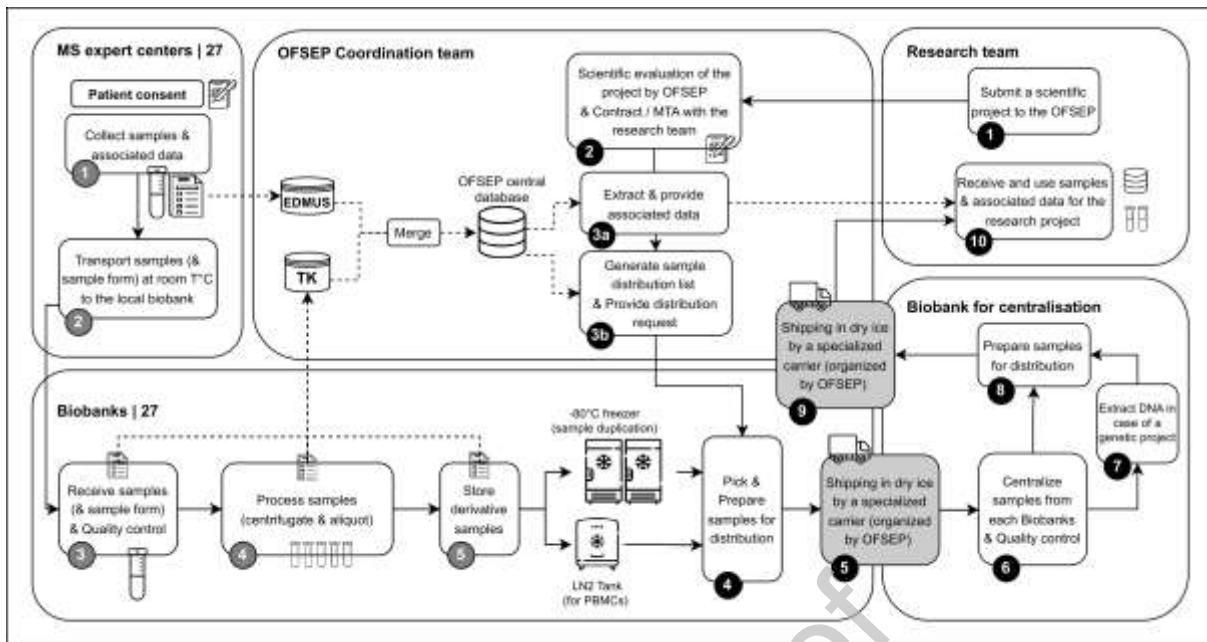


Figure 1: OFSEP Biobank flow chart. *OFSEP: Observatoire Français de la Sclérose En Plaques (French MS Registry) ; EDMUS: European Database for Multiple Sclerosis ; TK: Tumorotek ; LN2: Liquid Nitrogen ; PBMCs: Peripheral Blood Mononuclear Cells ; MTA: Material Transfer Agreement*

Table 1 : Description of the OFSEP biological sample collection on December 2022 (n= 4,888 patients sampled).

	N	Female [%]	Age (years)	Disease duration (years)	Post sample follow-up (years)	Ongoing therapy at sampling	Samples
RIS*	137	107 [78%]	40.5 ± 12.8	na	2.1 ± 2.1	Drug naive: 96% ; Untreated:** 1% ; Other treatment: 3%	Serum=1100 ; Plasma=775 ; DNA=258 ; PBMC=471 ; CSF=398 ; Urines=354 ; Stools=5 ; Saliva=0
CIS (McDo -)	354	248 [70%]	36.6 ± 11.3	0.4 ± 1.2	2.2 ± 2.1	Drug naive: 98% ; Other treatment: 2%	Serum=2834 ; Plasma=2020 ; DNA=731 ; PBMC=1015 ; CSF=1609 ; Urines=1090 ; Stools=21 ; Saliva=15
Single attack (McDo +) ***	835	586 [70%]	36.2 ± 10.6	2.1 ± 3.1	2.8 ± 1.6	Drug naive: 59% ; Untreated:** 1% ; DMF: 8% ; TRF: 8% ; GA: 7% ; INF: 6% ; FNG: 5% ; Other treatment: 6%	Serum=6705 ; Plasma=4392 ; DNA=1546 ; PBMC=1550 ; CSF=2381 ; Urines=1623 ; Stools=39 ; Saliva=12
RRMS *** (at least 2 relapses)	2067	1579 [76%]	40.2 ± 10.9	10.4 ± 7.9	2.7 ± 1.0	Drug naive: 14% ; Untreated:** 4% ; NTZ: 22% ; FNG: 16% ; DMF: 9% ; TRF: 9% ; GA: 7% ; INF: 6% ; RTX: 5% ; Other treatment: 8%	Serum=12044 ; Plasma=7010 ; DNA=2470 ; PBMC=1069 ; CSF=1301 ; Urines=1082 ; Stools=56 ; Saliva=2
SPMS ***	352	241 [68%]	52.4 ± 9.5	20.3 ± 9.9 Progr. dur.=7.7 ± 6.4	2.9 ± 0.9	Drug naive: 8% ; Untreated:** 24% ; RTX: 24% ; FNG: 9% ; MPM: 7% ; NTZ: 7% ; OCZ: 5% ; TRF: 5% ; Other treatment: 11%	Serum=1810 ; Plasma=1029 ; DNA=372 ; PBMC=73 ; CSF=100 ; Urines=86 ; Stools=2 ; Saliva=0
PPMS ***	538	288 [54%]	51.5 ± 10.7	6.4 ± 6.1	2.7 ± 1.8	Drug naive: 56% ; Untreated:** 6% ; RTX: 18% ; OCZ: 11% ; Other treatment: 9%	Serum=6435 ; Plasma=4722 ; DNA=1668 ; PBMC=2661 ; CSF=2330 ; Urines=1745 ; Stools=24 ; Saliva=23
PML	9	5 [56%]	51.2 ± 7.1	17.5 ± 7.6	2.6 ± 2.1	Drug naive: 0% ; Untreated:** 22% ; NTZ: 34% ; FNG: 22% ; DMF: 11% ; MPM: 11% ;	Serum=66 ; Plasma=53 ; DNA=20 ; PBMC=27 ; CSF=8 ; Urines=22 ; Stools=0 ; Saliva=0

NMOSD AQP4+*	217	194 [89%]	50.2 ± 16.5	7.7 ± 8.3	3.0 ± 2.6	Drug naive: 18% ; Untreated:** 3% ; RTX: 41% ; MPM: 22% ; AZT: 12% ; Other treatment: 4%	Serum=2043 ; Plasma=1489 ; DNA=477 ; PBMC=647 ; CSF=22 ; Urines=470 ; Stools=3 ; Saliva=7
NMOSD AQP4-*	69	43 [62%]	43.2 ± 14.5	7.4 ± 6.9	2.4 ± 2.3	Drug naive: 30% ; Untreated:** 9% ; RTX: 30% ; MPM: 14% ; AZT: 12% ; Other treatment: 5%	Serum=583 ; Plasma=425 ; DNA=139 ; PBMC=209 ; CSF=47 ; Urines=137 ; Stools=0 ; Saliva=1
MOGAD*	225	132 [59%]	41.4 ± 16.5	4.9 ± 7.4	2.0 ± 2.1	Drug naive: 56% ; Untreated:** 3% ; RTX: 26% ; AZT: 7% ; Other treatment: 8%	Serum=2033 ; Plasma=1374 ; DNA=439 ; PBMC=653 ; CSF=104 ; Urines=506 ; Stools=8 ; Saliva=0
ADEM	20	13 [65%]	43.4 ± 16.1	1.7 ± 3.6	2.9 ± 2.3	Drug naive: 95% ; TRF: 5%	Serum=151 ; Plasma=120 ; DNA=43 ; PBMC=58 ; CSF=18 ; Urines=54 ; Stools=0 ; Saliva=0
Covid-19	65	44 [68%]	40.0 ± 11.1	9.8 ± 7.8	0.6 ± 0.7	Drug naive: 5% ; Untreated:** 5% ; NTZ: 35% ; OCZ: 18% ; DMF: 12% ; FNG: 6% ; GA: 5% ; RTX: 5% ; TRF: 5% ; Other treatment: 4%	Serum=675 ; Plasma=458 ; DNA=149 ; PBMC=247 ; CSF=35 ; Urines=72 ; Stools=0 ; Saliva=0

*Validated by the RIS/NOMADMUS adjudication committee

**Untreated from 12 months at sample

*** Included in HD cohort : Single attack (McDo+)=376 ; RRMS=1805 ; SPMS=329 ; PPMS=158

AZT: AZATHIOPRINE ; DMF: DIMETHYL FUMARATE ; FNG: FINGOLIMOD ; GA: GLATIRAMER ACETATE ; INF: INTERFERON (BETA 1A + BETA1B + PEG. BETA 1A) ; MPM: MYCOPHENOLATE MOFETIL ; NTZ: NATALIZUMAB ; OCZ: OCRELIZUMAB ; RTX: RITUXIMAB ; TRF: TERIFLUNOMIDE

OFSEP: Observatoire Français de la Sclérose en Plaques ; RIS: Radiologically Isolated Syndromes ; CIS: Clinically Isolated Syndromes ; RRMS: Relapsing Remitting Multiple Sclerosis ; SPMS: Secondary Progressive Multiple Sclerosis ; PPMS: Primary Progressive Multiple Sclerosis ; PML: Progressive Multifocal Leukoencephalopathy ; NMOSD: Neuromyelitis Optica Spectrum Disorders ; MOGAD: Myelin Oligodendrocyte Glycoprotein antibody Associated Disease ; ADEM: Acute Disseminated Encephalo-Myelitis ; PBMC= Peripheral Blood Mononuclear Cells

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Laure Michel reports a relationship with Biogen that includes: consulting or advisory. Laure Michel reports a relationship with Teva Health that includes: consulting or advisory. Laure Michel reports a relationship with Roche that includes: consulting or advisory. Laure Michel reports a relationship with Sanofi Genzyme that includes: consulting or advisory. Laure Michel reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Laure Michel reports a relationship with Novartis that includes: consulting or advisory. Laure Michel reports a relationship with Merck & Co Inc that includes: consulting or advisory. Eric Thouvenot reports a relationship with Actelion Ltd that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Eric Thouvenot reports a relationship with Biogen that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Eric Thouvenot reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Eric Thouvenot reports a relationship with Merck & Co Inc that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Eric Thouvenot reports a relationship with Novartis that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Eric Thouvenot reports a relationship with Roche that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Sandra Vukusic reports a relationship with Biogen Inc that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with Bristol Myers Squibb Co that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with Janssen Pharmaceuticals Inc that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with Merck & Co Inc that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with Novartis that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with Roche that includes: speaking and lecture fees and travel reimbursement. Sandra Vukusic reports a relationship with

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