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MELCAYA

NOVEL HEALTH CARE STRATEGIES FOR MELANOMA IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

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Executive Summary

The aim of this deliverable is to describe the strategy to register the participation of patients referred by external French clinical partners in the MELCAYA initiative. A new bioethics law had been adopted in France on 2 August 2021 to update the previous national bioethics law. However, the new rules governing personal data protection and facilitating access to genetic information already foreseen required re-examination of how and which French clinicians could contribute resources from their patients to support MELCAYA. This report provides a preliminary approach that will be continuously updated as the project progresses, and a benchmark for enrolment of French and eventually other national partner CAYA cases in the distinct clinical studies.

Contents

Acronyms & Abbreviations

Term	Description
CAYA	Children, Adolescents and Young Adults
CMN	Congenital Melanocytic Nevi
GDPR	General Data Protection Regulation
CPP	Comité pour la Protection des Personnes
CNIL	Commission Nationale de l'Informatique et des Libertés
FIMARAD	Filière Maladies Rares en Dermatologie

1 Introduction

The scope of this document is to describe a current list of procedures to implicate secondary partners in France associated with work package 2 of the MELCAYA project. This may serve as an example for studying similar but nationally specific constraints in other countries or for managing the participation of partners from European countries not currently represented in the consortium to date.

2 Registration of participants as collaborators

2.1 Identification of clinical stakeholders in France

This report on registration of participants makes a cursory description of the impact of the French regulatory landscape in bioethics and how this impacts recruitment of biological samples from patients for clinical studies, be they local, national or international.

Research on human subjects in France is subject to multiple legal constraints:

- The bioethics laws of 1994 (revised by the bioethics law 2011-814 from 7 July 2011).
- The Huriet-Sérusclat law, which created national review boards to protect the interests of participants, called CPP (*Comités de Protection de Personnes*) that had been further modified in 2012 by the Jardé law 2012-300 from 5 March 2012 and its implementing decree.
- The provisions therein were further tempered by an obligation to respect the 2004 law devoted to the protection of personal data, that modified an earlier version from 6 January 1978 and is known as the Computing, Files and Liberties law. This gave rise to the regulatory authority that oversees compliance in France, the Commission Nationale de l'Informatique et des Libertés (National Commission of Data Protection, CNIL). It is an independent commission from ministries, composed of elected representatives and appointees selected by various state councils as well as some parliamentarians. Among its other roles, it can impose sanctions on data controllers who do not comply with the law and in particular with the GDPR.

All research in France that makes use of any human materials, such as blood draws explicitly for research purposes or taken during medical care, buccal swabs, or any other tissues destined for diagnostic purposes or left over after medical procedures, must follow the legislation pertaining to the preservation and use of human materials for scientific research purposes. Its intent is to protect the interest of the donors of such materials.

In order for a biomedical research study to be promoted by a teaching hospital, private company, university or national non-profit research organization to obtain ethical approval from a CPP and

registration of that study, it is also necessary to declare the collection and storage conditions of the samples to be used in that study, as well as the necessary safeguards put in place to protect sample donors from unforeseen consequences of use of any personal data associated with said collection.

A declaration of the collection is made for each site through a form known as CODECOH ("*Conservation d'Éléments du Corps Humain*) through a portal to a database managed by the French Ministry for Higher Education and Research. The participants' data protection must also be declared under the terms of the General Data Protection Regulation (GDPR) to the CNIL. Biomedical research studies must have a beginning and defined end date, although it is also possible to constitute a collection that is then managed in entries and cessions by an approved biobank after the end of a study, if such terms have been anticipated and specified in the informed consent form for participants.

2.1.1 Relative to large/giant congenital melanocytic nevi

The large and giant congenital melanocytic nevus (CMN) is a rare congenital lesion known to predispose to children, adolescents and young adults (CAYA) melanoma, itself an even rarer condition before the age of 18. It is a non-hereditary malformation of the skin that arises from a cell that acquires the predisposing ("driver") mutation during gestation. Its proliferation in the developing foetus leads to a particularly large, superficially pigmented birthmark present at birth, in contrast to small pigmented moles that frequently arise after birth. An estimated 2-5% of children with these large forms of CMN will develop primary melanoma starting in the skin or brain. This malignant cancer is frequently lethal following metastasis.

Certain French clinicians and a few researchers have been regularly publishing work particularly over the last decade based on cohorts from around France or from patients having consulted in a centre affiliated with the French national healthcare network devoted to rare skin diseases (the FIMARAD alliance, Filière Maladies Rares en Dermatologie, founded in 2011) [1].

At least one earlier multicentric study had been promoted by INSERM (French National Institutes of Health), conducted by Dr. Heather Etchevers (ref. DC-2013-1769 approved by the CPP Sud-Méditerranée). These prospectively consented materials, including germline DNA derived from blood draws, CMN tissue, adjacent unaffected skin and primary cell cultures thereof were not repurposed from samples taken for diagnosis, but collected between 2014 and 2017 and used exclusively for research purposes thereafter. A collaborating study from approximately the same period is ongoing in the Paris region. It is co-ordinated by Professors Sarah Guégan-Bart and Sélim Aractingi, pediatric dermatologist at the national Rare Disease Reference Center MAGEC at the Cochin Hospital (approved by the CPP Ile-de-France Paris V). This reference centre, affiliated with the European Reference

Network (ERN-SKIN), further coordinates other sources of familial melanoma. Prof. Guégan has been funded in a pilot study for this work called “THERANEVUS” initially in 2021 (project PPRC-2021-29) but that has been extended until the end of 2024.

Other cohorts, for example subsets with proliferative nodules or other complications, have been the subject of case reports from other public teaching and research hospital centres in Toulouse, Nantes, Paris, Lyon and Marseille. The materials were drawn from samples originally taken for diagnostic purposes and further explored

2.1.2 Relative to paediatric melanoma

A biomedical research project pertaining specifically to paediatric melanoma, including familial predisposition cases, has been ongoing in the Paris region and directed by Professor Brigitte Bressac de Paillerets, member of the completed GenoMEL project [1], as had been Prof Puig (MELCAYA general coordinator). The project of Prof. Bressac de Paillerets was funded by the private non-profit cancer research charity “Ligue Nationale Contre le Cancer”, call AAP-EAC2019.LCC/ST “Enfants, Adolescents et Cancer” project PRAME20617, identification of the genetic bases of childhood melanoma, from 2019 to 2022.

2.2 Measures of contact of potential partners

Potential partners in pathology, dermatology and plastic surgery departments around the country were contacted directly by Dr. Etchevers (WP2 leader) by telephone, Zoom or e-mail. An additional call was put out by Dr. Stéphanie Mallet, pediatric dermatologist at the Marseille Timone Hospital and chair of the Research Commission of the French Society for Pediatric Dermatology to fellow members. A further call was disseminated by Dr. Isabelle James, general secretary based at the Section for Pediatric Plastic Surgery (SFCPP) which will be renewed in the spring.

2.3 Positive responses

As of the time of writing of this report, Dr. James and a renowned pediatric pathologist in Paris (Dr. Sylvie Fraitag) have committed respectively to making prospective or both retrospective and prospective contributions to the MELCAYA consortium. Dr. Fraitag had previously also been contacted by Prof Daniela Massi (WP3 leader), to participate in MELCAYA’s second opinion platform, as she is a reference in the field of analysis of ambiguous pediatric skin lesions.

2.4 Further opportunities

The European Society for Pigment Cell Research annual conference will be held in October 2024 in Marseille (France). Dr. Etchevers chairs the organizing committee. As the meeting features sessions

devoted to melanoma diagnosis, therapy and precursor lesions in both children and adults, potential secondary partners may be recruited from other European institutions during the year and the publicity around this conference, where MELCAYA will naturally be promoted.

Other MELCAYA-related networking activities close to this time may also be undertaken by representation at the European Academy of Dermatology and Venereology (EADV) Congress in Amsterdam from 25-28 September 2024, the 27th French Pediatric Dermatology Day on 7 November 2024 in Lyon, or the Bordeaux Pediatric Dermatology Day on 8 November 2024.

3 Conclusions

In this report, we have reviewed some difficulties in registering additional project partners in one of the member countries of the MELCAYA consortium as an example. The additional ethical constraints in France, relative to those outlined in the MELCAYA data management plan, mean that restricted types of clinical and molecular data, rather than biological samples themselves, are most straightforward to share through the secure centralized database envisaged in the project. The extreme rarity of CAYA melanoma means that it continues to be relevant to contact potential new collaborators with the teams already participating in MELCAYA until the end of the project.

References

Websites

[1] https://fimarad.org/

[2] https://genomel.org/