STUDY SYNOPSIS

Study title	**MULTICENTER, NON-INTERVENTIONAL STUDY, DESCRIBING PATIENTS WITH INHERITED RETINAL DISEASE (IRD) IN FRANCE**
Short title	EPI-GenRet
Sponsor	Strasbourg University Hospitals
Coordinating/Principal Investigator	**Pr Hélène DOLLFUS**
Collaborative partner	**Novartis Pharma SAS**
HUS n°	8173
ID RCB n°	2021-A01786-35
NCT	NCT05122442
Study rationale	Genetic diagnostic testing becomes increasingly important for enhancing our understanding of the disease notably the genetics and providing the best care to the patients*("Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations - 2016," 2016)*, and several initiatives seek to gather more data in order to better understand and treat those diseases. **Within this context, Novartis and SENSGENE/Strasbourg University Hospitals (HUS) want to set up, through a research collaboration, a non-interventional study in France to better understand the epidemiology of IRDs, particularly the distribution of pathogenic variants in patients.** This study aims to serve as a starter study to implement an IRD national registry led by SENSGENE/Strasbourg University Hospitals (HUS). The data collected might also be used to populate global European registries (cf ERN-EYE initiatives). The primary objective has been defined in a sufficient broad way to address this perspective of registries. As IRDs can present from birth to late middle age, this study will include both children and adult patients regardless of age, sex, and the type of IRD.
Primary Objective	**The primary objective of this study is to describe the type of IRD of patients clinically diagnosed and who attended a consultation at one of participating centers from SENSGENE network over the inclusion period.**

Secondary Objectives	The secondary objectives are stated for patients with IRD who attended a consultation at one of the participating centers from SENSGENE network over the inclusion period.
	
	• To describe the genetic diagnosis
	  ○ To describe the genetic testing characteristics
	  ○ To describe the distribution of genes and pathogenic variants (class 4 and class 5) associated with IRDs
	  ○ To describe the distribution of variant of uncertain significance (VUS - class 3 variants) in IRD-associated genes
	  ○ To describe the proportion of unsolved patients
	  ○ To describe the type of pathogenic variants in each IRD-associated gene identified

	• To evaluate the potential correlation between the patient's genotype and the IRD phenotype • To describe the clinical characteristics • To describe the diagnosis pathway • To describe the socio-demographic characteristics of patients • To describe the therapeutic care of patients
Primary endpoint	**Proportion of patients by type of IRD (based on ORPHA classification for IRD)**
Secondary endpoints	• Proportion of patients by type of analysis performed for definitive molecular genetic diagnosis • Proportion of each type of genetic analysis performed and duration between clinical diagnosis and definitive molecular genetic diagnosis • Proportion of genes with at least 1 pathogenic variant identified (classified as class 4 likely pathogenic and class 5 pathogenic) according to transmission mode • Proportion of variants according to their classification (class 4 and 5) in a specific gene and in all IRD genes • Proportion of variants of uncertain significance (VUS-class 3 variants) • Proportion of unsolved patients • Proportion of pathogenic variants according to the: o Mutation's nomenclature o Nature of gene mutation o Allelic status o Origin of the allele • Proportion of patient with family segregation assessment • Proportion of similar genotype in other family members • Proportion of "classic cases", i.e. patients whose clinical phenotype is associated with the expected genotype • Proportion of "atypic cases", i.e. patients whose clinical phenotype is associated with unusual/unexpected genotype • Proportion of patients whose type of IRD (ORPHA classification) was modified after definitive molecular genetic diagnosis • Proportion of patients by: o Age at first symptom onset o Circumstances of discovery o Type of clinical assessments to confirm the clinical diagnosis o Age at date of clinical diagnosis o Type and number of current symptoms related to IRD at consultation o Associated clinical signs

	○ Medical history of interest • Proportion of patients according to the values of visual acuity (VA) and visual field (VF) by patients' clinical characteristics • Proportion of patients with a cystoid macular oedema (CME) on last coherence tomography (OCT) done • Proportion of patients with preserved macular area appearance by autofluorescence at consultation • Proportion of patients according to lens status • Proportion of patients with cataract at consultation • Proportion of patients with posterior capsular opacification • Proportion of patients with cataract (phakic and pseudophakic) with an impact on VA • Proportion of patients by type of clinical assessments performed • Diagnostic odyssey (Length of time from the first symptoms onset to the clinical diagnosis and Length of time from the previous molecular genetic test and the definitive molecular genetic diagnosis for patient who already had a molecular genetic test) • Proportion of patients by age class, gender, type of occupation and geographical origin • Proportion of patients by type of treatments administered for IRD
Study design	This study is a multicenter, cross-sectional non-interventional study that aims to set up a registry of patients with IRD in France. This study relies on primary data collection and a cross sectional design. Data will be collected for both patients with prevalent IRD (patients who were already clinically diagnosed with IRD before the inclusion in the study) and patients with incident IRD (patients who were clinically diagnosed with IRD upon their inclusion in the study). To address the primary objective, all patients seen by the physician over the inclusion period following site initiation will be included into the study, on a consecutive and exhaustive basis until a maximum of 1000 patients is reached (registry starter). Given the capacity of sites to screen patients over one year (around 3000 patients), the inclusion of patients into the study will be limited to the first 1000 patients in order to favor the data collection quality by limiting the sites workload. This will also encourage the inclusion of the patients exhaustively, especially for high volume sites for which this registry represents a deep work. However, it should be reminded that this study is a starter study that is planned to be extended to a larger national registry. Since this study is non-interventional, nor clinical interventions neither genetic tests, imaging and assessment schedule will be

	required as part of this study, and all data will be collected as per physicians' routine practice. Patients included in this study must have either available genetic results upon their inclusion in the study (whether the result of this test is positive or negative) or a genetic testing prescription for IRD (genetic testing through PFMG platform or from a traditional reference public laboratory). Given the delay for obtaining genetic results, the data may be available within approximately 12 months after the test prescription.
Inclusion and non-inclusion criteria	Only the patients who meet **all** the following inclusion criteria can be included in this study: • All patients, whatever age or gender, clinically diagnosed with IRD or with high suspicion for IRDs based on clinical examination and functional tests (such as fundus exam and ERG), regardless of genetic testing • Patients who attended a consultation at one of the participating centers from SENSGENE network over the inclusion period starting from sites initiation • Patients who had been prescribed a genetic test for IRD prior to or at the date of inclusion. • Patients who present **at least one** of the following non-inclusion criteria cannot be included in this study: • Patients/Parents/Legally authorized representatives (LAR) opposed to the collection and processing of their medical data/the medical data of their children/the medical data of the person for whom they are LAR; • Patients who are suffering from any other retinal disorder or optic neuropathy that may clinically or genetically overlap with IRD or non-genetic (phenocopy); • Patients/parents/Legally authorized representatives (LAR) refusing genetic testing; • Patients lacking decision-making capacity: Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation.
Conduct of the study	French reference and competence centers for rare eye diseases are gathered within the SENSGENE network. The Filière de santé maladies rares (FSMR) SENSGENE fulfills national missions around rare sensory diseases with the aim of improving the care of patients, coordinating and encouraging research and developing training and information. Seven French reference and competence centers from the SENSGENE network will be contacted to participate in the study. • Five coordinating or constitutive reference centers for rare eye diseases: **HU-Necker-Enfants Malades-APHP (Paris), CHNO XV-XX (Paris), CHI Créteil, HU Strasbourg, CHU Montpelier.** • Two competence centers for rare eye diseases: **CHU Nantes** and **CHU Lille**
Required sample size	This study will set up a registry that will include all eligible patients with IRD who attended a consultation at one of the participating centers from SENSGENE network.

For the Cross-sectional registry no sample size calculation is required as this registry will record patient fulfilling the sets of criteria defined and will allow to have an estimation of the target population at the national level.

Given the capacity of sites to screen patients over one year (around 3000 patients), the inclusion of patients into the study will be limited to the first 1000 patients in order to favor the data collection quality by limiting the sites workload. This will encourage the inclusion of the patients exhaustively, especially for high volume sites for which this registry represents a deep work. However, it should be reminded that this study is a starter study that is planned to be extended to a larger national registry.

The precision can be estimated for a sample size of 1000 patients while considering 5% loss (patients not evaluable for the primary objective or not meeting all selection criteria).

The following table presents the precision and the corresponding 2-sided 95% confidence interval (CI) to describe the distribution of IRD type (proportions varying from 10% to 50% for each modality) and a sample size of 1000 patients.

Table. Precision and corresponding 2-sided 95% CI given the proportion of a modality varying from 10% to 50% and a sample size of 1000 patients (5% of non-evaluable patients)

	Proportion				
	10%	20%	30%	40%	50%
n	Precision	Precision	Precision	Precision	Precision
Précision (%)	1.9	2.5	2.9	3.1	3.2
95% CI	8.1; 11.9	17.5; 22.5	27.1; 32.9	36.9; 43.1	46.8; 53.2

The precision (e) is calculated based on the normal approximation using the following formula:

$$e = \sqrt{\frac{1{,}96^2 * (p - p^2)}{n}}$$

where p is the proportion of a given modality and n is the number of patients.

Statistical method

A descriptive analysis will be conducted on all study endpoints for which data has been collected both for the overall study population and per subgroups of interest where relevant (e.g. patients' clinical characteristics, classification (class 4 and 5), nature of the mutation, the values of visual acuity (VA) and visual field (VF), date of genetic testing, clinical phenotype, type of genetic analysis performed and unsolved patients) as long as that the sizes of the sub-groups are relevant for statistical estimations. The subgroups' modalities and associated endpoints will be detailed in the Statistical Analysis Plan.

The following statistics will be provided for quantitative variables: number and proportion of patients with non-missing and missing

	values per variable, mean, standard deviation (StD), median, first quartile (Q1), third quartile (Q3), minimum and maximum value, the mode (especially for discrete quantitative variables with limited variability). For qualitative variables, the number and proportion of each variable modality will be provided together with the number of missing values. Proportion will be computed based on the population with non-missing data. Exploratory comparison between study subgroups might be considered. Statistical tests will be based on the type and distribution of the variables. All comparison tests will be two-tailed with a standard type 1 error threshold of 5% (significance level). The enrollment of patients in the study will be limited to a maximum of 1000 patients, registered over a variable period of time limited to 12 months. This study design therefore presents bias related to the heterogeneous duration of patients' inclusion which depends on the activity size of each participating physician. In order to take into account the biases associated with this study design and be able to extrapolate results at the national level, an adjustment is planned for descriptive analyses over the registry using a weight applied at center level.
Expected benefits	Implementation of an IRD national registry including all data related to IRD and presenting their clinical features may help to deepen the epidemiologic and genetics knowledge of IRDs. No direct benefit to the participating patient is expected from this study but the knowledge generated from this study may benefit future patients.
Provisional schedule	-Maximum duration of the inclusion phase: 12 months or themaximum of 1000 patients is reached, whatever occurs first (a) -Maximum duration of participation of each patient: 12months (b) -Maximum total duration of the study: 24 months (= a+b) -Exclusion from other interventional studies while patientsparticipate to the present clinical trial: None -End of trial: The study end corresponds to the end of thecollection of gene testing results of the participation of the lastsubject in the study.