FRANCE MÉDECINE GÉNOMIQUE 2025

aviesan

GENOMIC MEDICINE IN FRANCE

Pr Yves Levy

INSERM

National Institute for Health and Medical Research

FUNDACION RAMON ARECES
GENOMIC MEDICINE IN SPAIN
Madrid 4th & 5th JUNE 2019

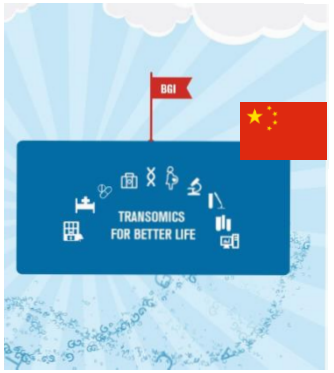
FRANCE MÉDECINE GÉNOMIQUE 2025

aviesan

AN INTERNATIONAL ENDEAVOR

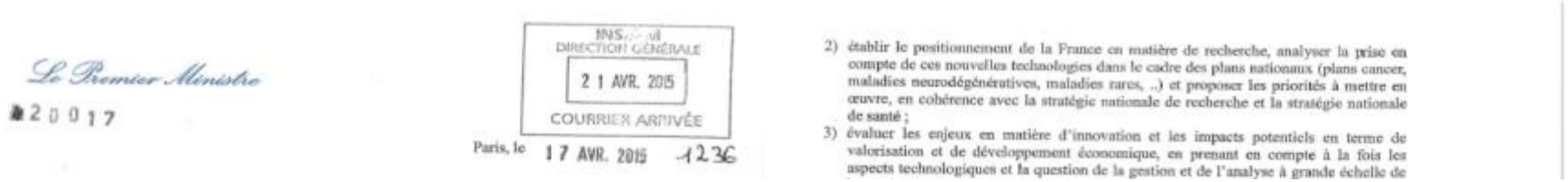
Genomic medicine is a field of international competition supported by national plan where:

- Clinical application is a common goal
- The development of economic sectors is a strategic issue



All started with :

TERMS OF ENGAGMENT LETTER FROM THE PRIME MINISTER



Le Premier Ministre

20017

DIRECTION GÉNÉRALE
21 AVR. 2015
COURRIER ARRIVÉE

Paris, le 17 AVR. 2015 1236

2) établir le positionnement de la France en matière de recherche, analyser la prise en compte de ces nouvelles technologies dans le cadre des plans nationaux (plans cancer, maladies neurodégénératives, maladies rares, ..) et proposer les priorités à mettre en œuvre, en cohérence avec la stratégie nationale de recherche et la stratégie nationale de santé ;

3) évaluer les enjeux en matière d'innovation et les impacts potentiels en terme de valorisation et de développement économique, en prenant en compte à la fois les aspects technologiques et la question de la gestion et de l'analyse à grande échelle de

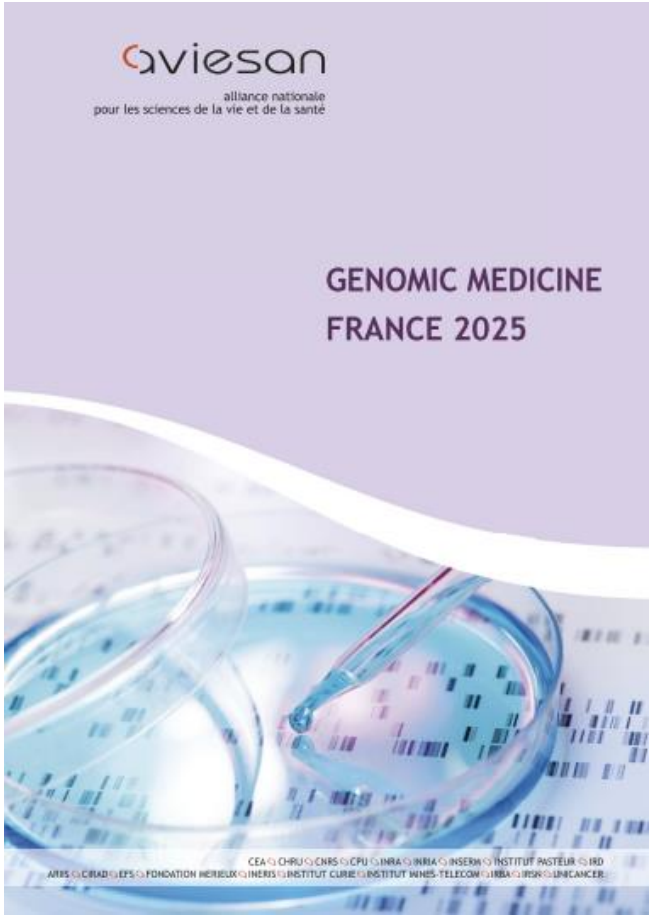
The Prime Minister entrusted Aviesan with the task of examining the current landscape for incorporating genome sequencing in the context of the healthcare pathway by touching on the following four points in his mission statement:

1. Defining the presence and importance of genomic sequencing in current medical practices as well as expected future developments in the coming 10 years.
2. Evaluating France's positioning in the field of genomic research and its role in current health plans and priorities to be implemented in line with national strategies for health and research
3. Evaluating the issues related to innovation and technology transfer and economic growth, taking into account technological aspects, management of large data sets and ethical implications.
4. Proposing a long-term medico-economic model integrating coverage by medical insurance and the establishment of an industrial sector to support such an initiative.

A Co-Constructed National Plan

More than 160 people mobilized under an Aviesan presidency

- Institutional representatives
- transversal competences across fields of research, health and industry
- Research and health agencies
- Central administrations of ministries
- Health industries representatives (Ariis, IT,…)
- National Insurance Fund Salaried Workers (CNAMTS)
- French National Authority for Health (HAS)
- SGPI
- Toulouse School of Economics…



FRANCE MÉDECINE GÉNOMIQUE 2025

Ambition of the French Genomic Medicine Plan 2025

Integrate sequencing into a generic healthcare pathway

Request for exam
Agreement

Patient/doctor dialogue
Shared decisions

Pre-analytic sampling

Clnical data

Support for the therapeutic decision

National database of Clinico-biological Meta-data

Genomic data

Sequences analyzed

Technical validation

Support for the diagnostic decision

Support tools for analysis

Research

Biological validation and interpretation

"Diagnostic Laboratory"

Develop a national genomic medicine sector

A PLAN ORGANIZED AROUND 3 MAJOR OBJECTIVES – 14 ACTIONS

I- SET UP THE TOOLS FOR A GENOMIC HEALTHCARE PATHWAY

II- ENSURE THESE DEVELOPMENTS IN A SAFE TECHNICAL & ETHICAL FRAMEWORK

III - IMPLEMENT MONITORING AND MANAGEMENT TOOLS

GOVERNANCE

Interministerial steering committee

Composition : Prime Minister Office, Ministers' Offices (Research, Health, Industry), National Health Care Insurance system (CNAMTS), French National Authority for Health (HAS), Patient Communities, Health industries representatives.

Mission : To ensure the realization of the plan by mobilizing partners and fundings; to implement and adapt objectives.

Once or twice a year

Monitoring committee

Composition : the pilots of each action and the institutions and agencies involved.

Mission : To follow the main actions of the plan.

Once per trimester

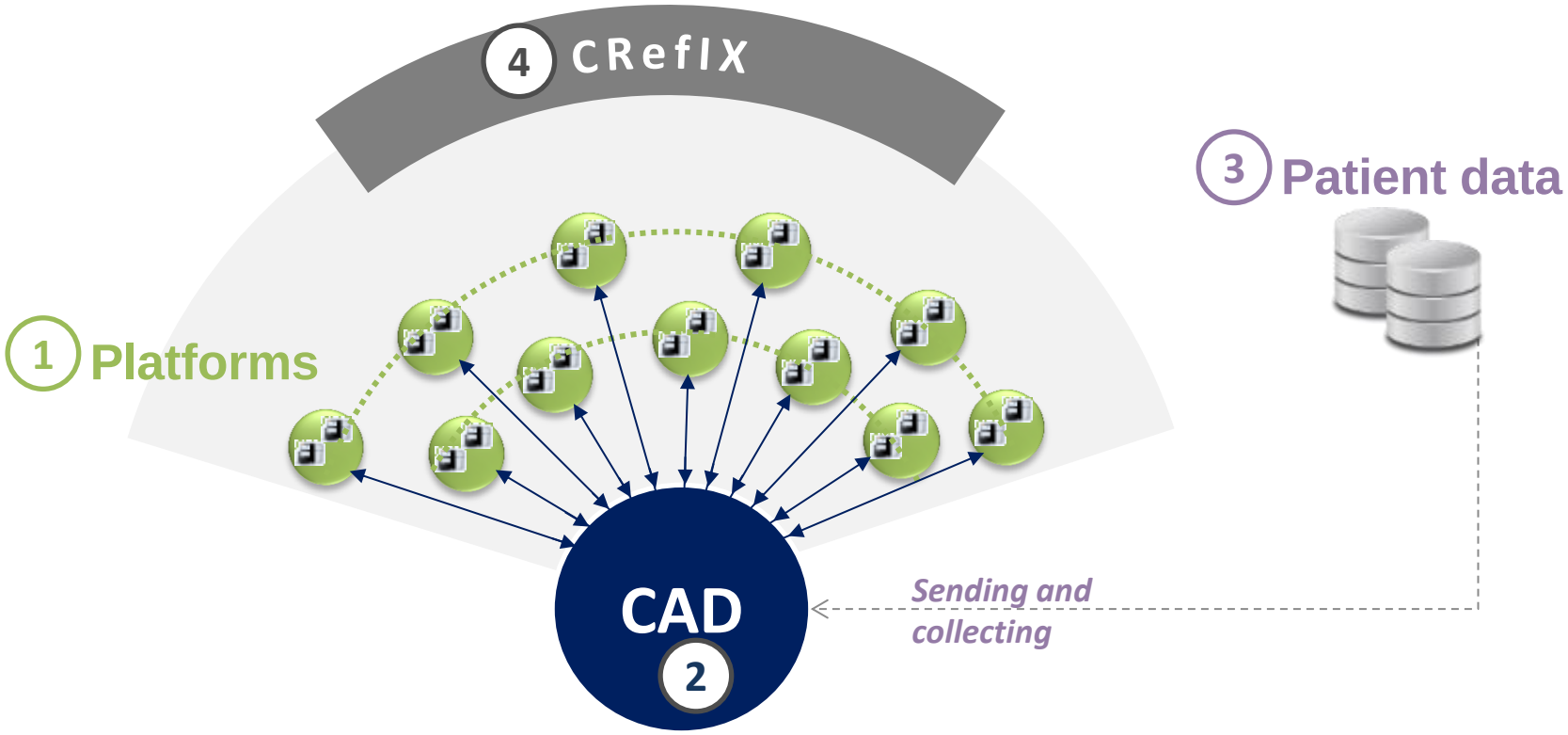
Once a month

Operational committee

Composition : the pilots of each action.

Mission : To conduct individual action in a day-by-day basis

OBJECTIVE I : SET UP THE TOOLS FOR A GENOMIC HEALTHCARE PATHWAY



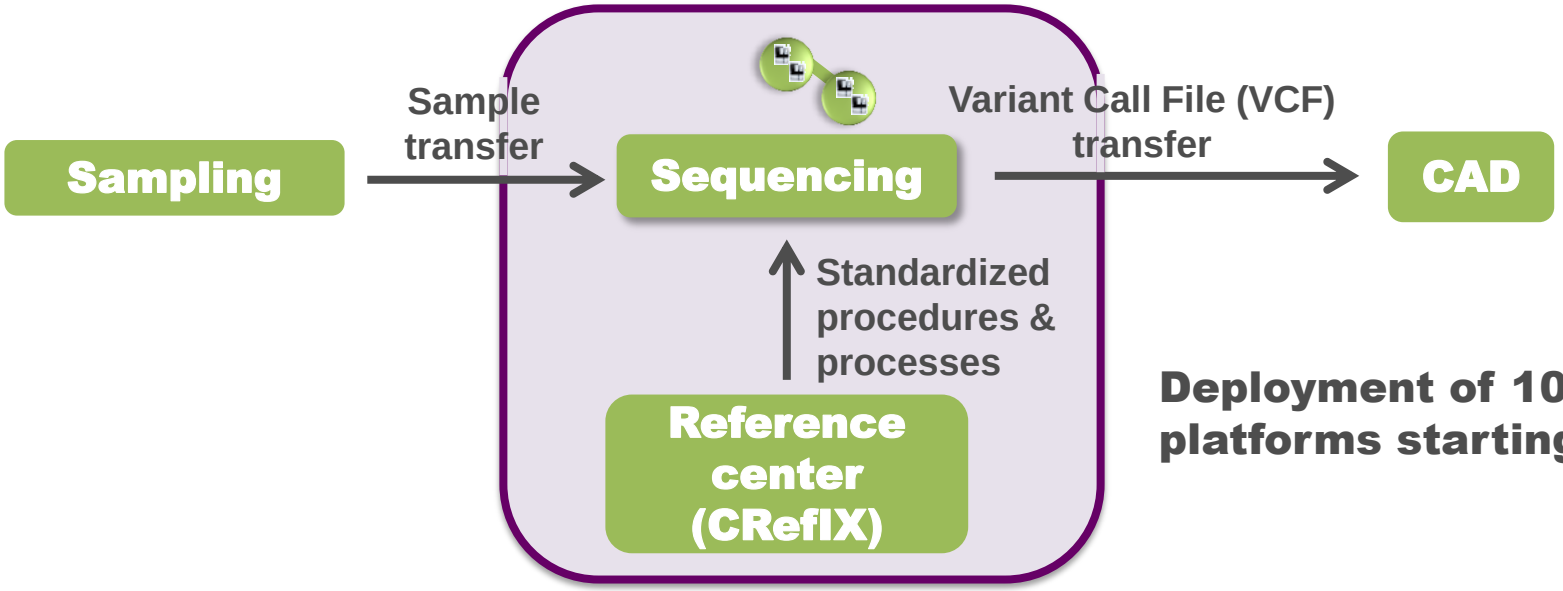
Action ① - Creation of a network of sequencing platforms

Action ② - Creation of a Central Analyzer of Data (CAD) to process and use the volume of data generated

Action ③ - Allow the integration and use of patient data in the healthcare pathway

Action ④ - Set up a center of reference, innovation, expertise and transfer : CREFIX

CREATION OF A NETWORK OF SEQUENCING PLATFORMS

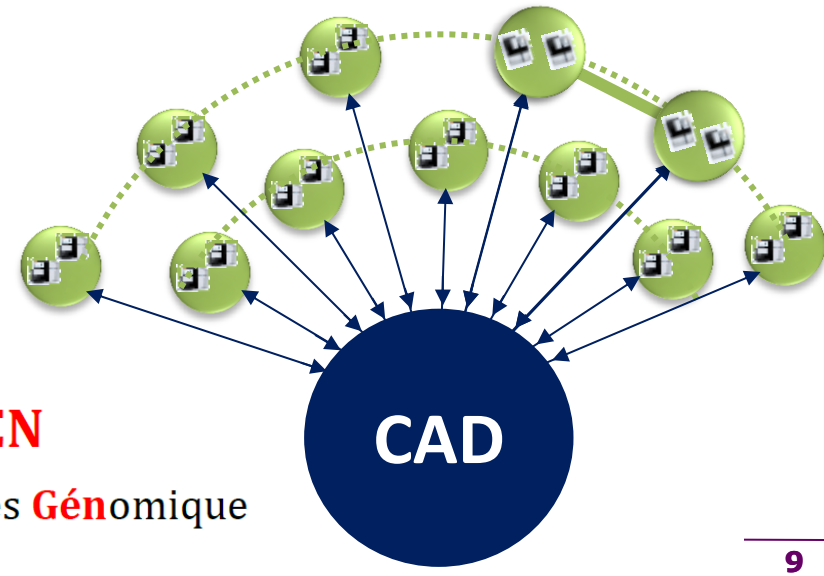


Deployment of 10 other platforms starting in 2019

2018

SeqOIA
LA PLATEFORME GÉNOMIQUE DE PARIS RÉGION

AURAGEN
AUvergne Rhône-Alpes Génomique



CREFIX : CENTER OF REFERENCE, INNOVATION, EXPERTISE AND TRANSFER

➲ **Ensure technogical and informatics developments**

Action ④

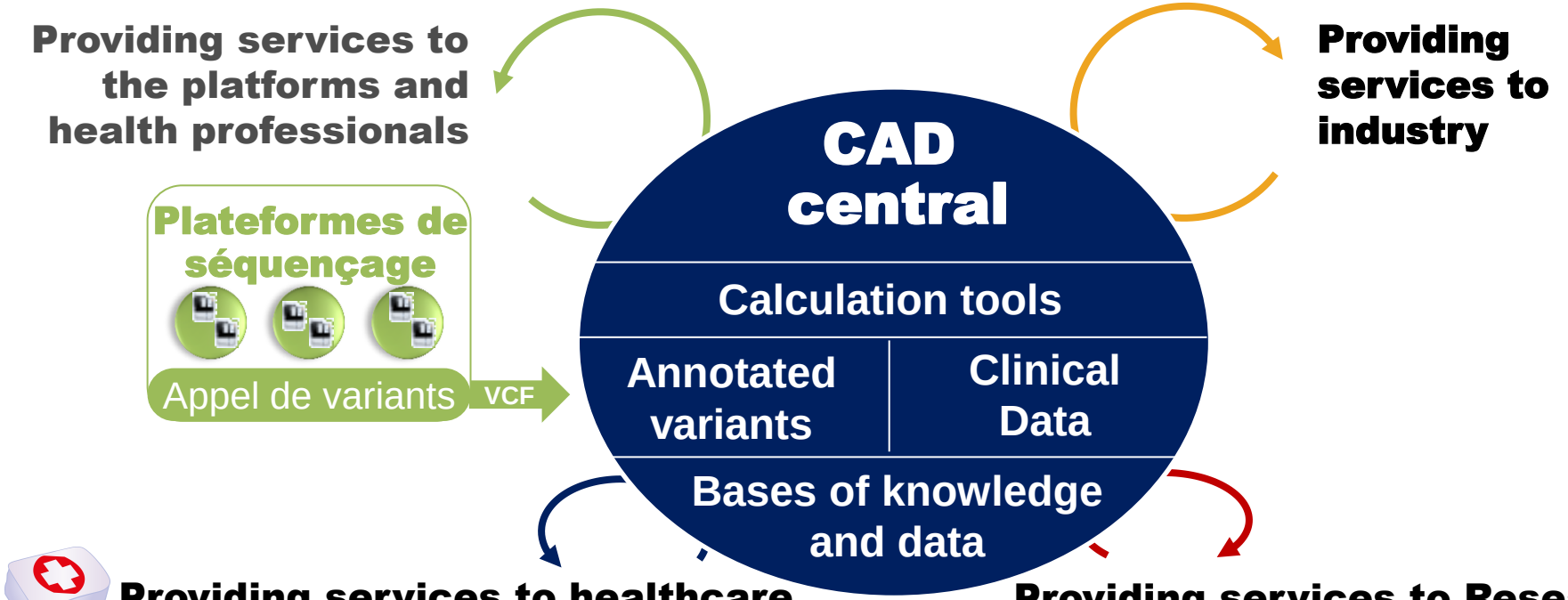
- Center of reference
- R&D
- Ethics and regulation
- Training

Standardized procedures and processes → **CAD** → Industrialization of procedures and deployment → **Network of platforms**

➲ **Ensure deployment and launch on the CAD and platforms**

Process development and harmonization of protocols and methods

CAD : A SERVICE PROVIDER INFRASTRUCTURE



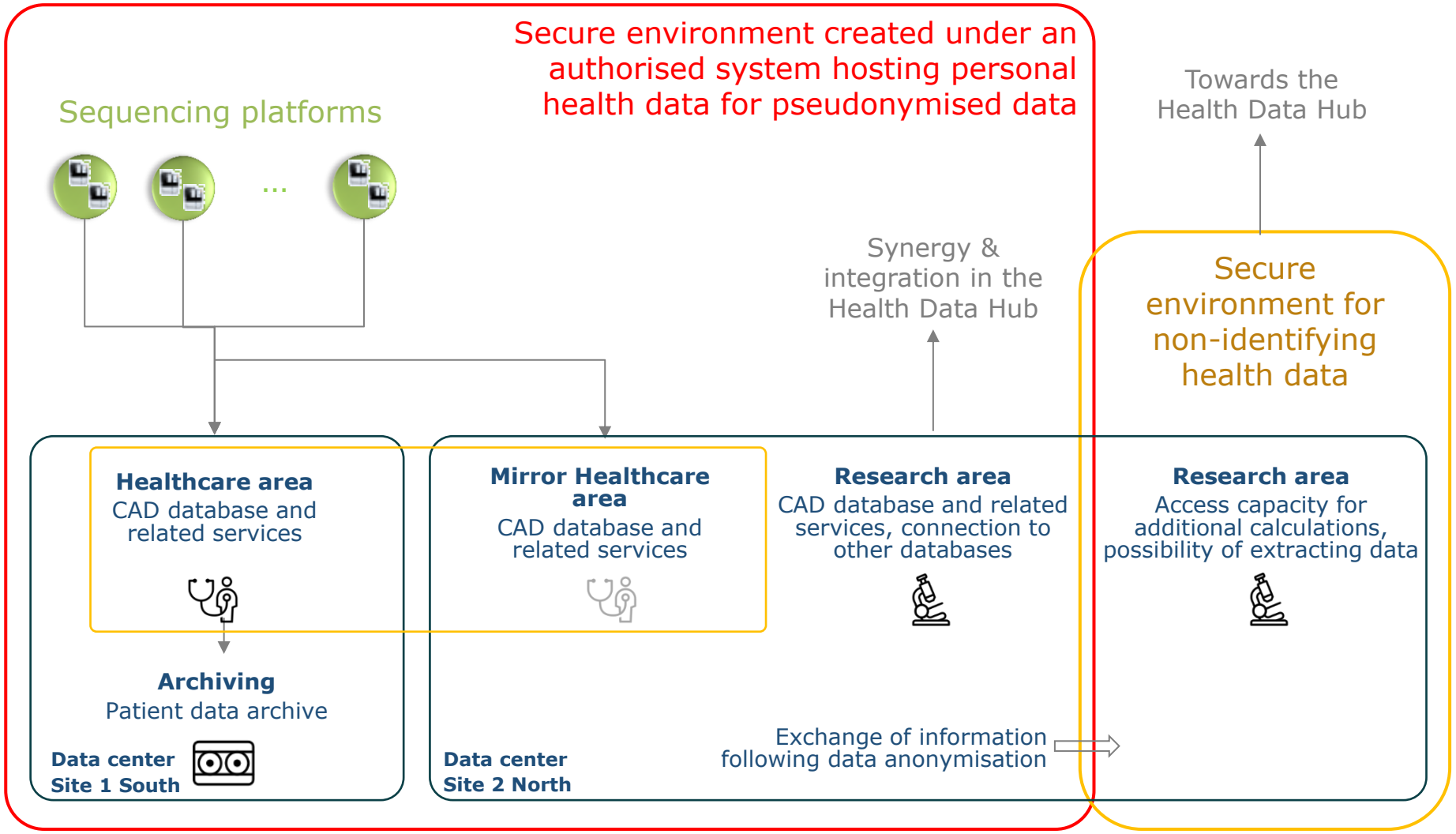
Providing services to healthcare

- Patient Data Access Service
- Access service to databases for the analysis steps
- Access service to analytical tools
- Access service to genome visualization and comparison tools
- Access service to decision support tools
- Data reanalysis service
- Secure web service for interaction between healthcare professionals using the CAD
- Version Management Service

Providing services to Research

- Reception service for research project submissions
- Help desk and project design consultancy
- Access service to data catalogs and datasets
- Service Access to Software Tool Libraries
- Access service to virtual machines
- Re-analysis service for research
- CAD researchers interaction web service
- Monitoring and methodological consulting service

CAD : A SERVICE PROVIDER INFRASTRUCTURE



ETHICS, REGULATORY ASPECTS AND SOCIETY

Patient information and consent

- **Methodology**
  - Hearing of national and international stakeholders
  - Collecting different clinical care/research frameworks (information and consent, including incidental findings)
  - Exchanges/confrontations with pilot projects
- **Working group:** Researchers (included human and social sciences), Ministries (Health, Justice), Patient/user associations, Different institutional levels (Health insurance, Health Agencies), Professional and scientific genetic societies

Data protection : storage, security, privacy and processing modalities of personal data resulting from sequencing

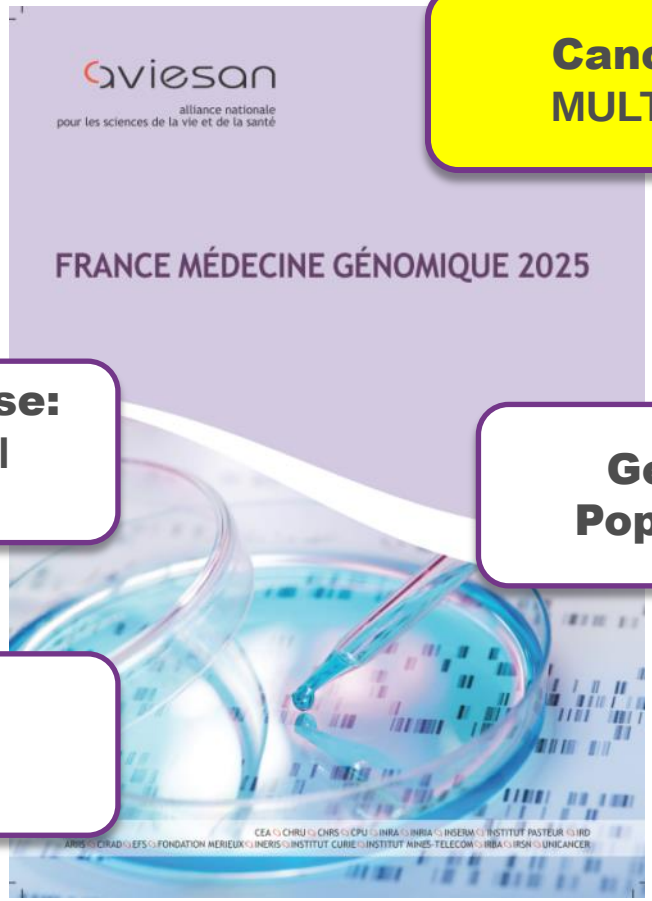
Human and Social Sciences researches

But also

- National advisory bioethics Committee
- Involvement in the structuration of a Precision Medicine observatory
- Dissemination to the public (exhibitions, European Open Science Forum (Toulouse July 2018), website)

Overcome barriers encountered along the pathway

4 Clinical Pilot Projects



Cancer :
MULTIPLI

Rare Disease:
Intellectual Disability

General Population

Common disease:
Diabetes

FRANCE MÉDECINE GÉNOMIQUE 2025 PROGRAMME MULTIPLI

Clinical Pilot Projects

Four pilot projects have been initiated

Methodology and statistics | **Regulatory aspects** | **Initiation of clinical study**

Goal
Investigators identification
Inclusion criteria
WES / WGS Sequencing
Number of patients to be included.
Record of clinical data modalities
Data transfers (in & out) and analysis
Biological specifications : samples taking, labelling and transfer
Clinical reports modalities
Information modalities and informed consent
Quality (Study monitoring, storage, archiving, anonymization and safeguarding data
Regulatory file submission

Soft-tissue sarcomas and advanced colorectal cancer	**Multipli => Cancer**
Intellectual disability	**DefiDiag => Rare disease**
Atypical type 2 Diabetes	**Glucogene => Commun disease**
	PopGen => General population

FRANCE MÉDECINE GÉNOMIQUE 2025

PROGRAMME MULTIPLI

ESSAIS MULTISARC & ACOMPLI

MULTIPLI program

- Previous precision medicine studies:
  - conventional molecular techniques and/or limited sets of gene alterations
  - limited access to innovative drugs

- 1st clinical research program implementing exome seq and RNAseq for therapeutic decision

- Main Objective: **Assess the feasibility of high throughput molecular analyses (NGS)**
  - **Interpretable** results
  - **Validated** genomic results and **clinical recommendation from the Molecular Tumour Board within 6 weeks** after reception of blood and tumor samples on the two platforms

MULTIPLI program

Patients with Advanced Soft Tissue Sarcoma or metastatic Colorectal Cancers
National Cooperative Groups
2,396 patients (960+1,436 patients)

Biopsy

1st line chemotherapy

NGS (Exome, RNA Seq)

Molecular Tumour Board

Targetable alteration,
STS: PD, SD and/or responding
mCRC: SD and/or responding

No targetable alteration,
Not eligible for subsequent trials

Subsequent randomised
MULTISARC
ACOMPLI trials

Standard Treatment and Follow-up

2 Biopathological platforms (INCa)
1 NGS platform (France Medecine Genomic Groups)
1 Bioinformatic Platform

MULTIPLI
International Scientific Advisory Board
Executive Committee
Clinical Monitoring Committee

CONSORTIUM

Public/private partnership

InsermTransfert

Pharma Partners

Project coordination

Inserm
Institut national de la santé et de la recherche médicale

euclid platform for clinical trials A consortium of Inserm CHU Bordeaux université BORDEAUX ICHU

cea DE LA RECHERCHE À L'INDUSTRIE

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229 cours de l'Argonne
CS 61283 - 33076 Bordeaux cedex
www.bergonie.org
CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST
UNICANCER MEMBRE DU GROUPE

CNG CENTRE NATIONAL DE GENOTYPAGE

FFCD CRGA

Clinical Trials Unit
Inserm CIC 1401

euclid platform for clinical trials A consortium of Inserm CHU Bordeaux université BORDEAUX ICHU

Safety Dpt

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Clinical Trial Sites

Laboratories

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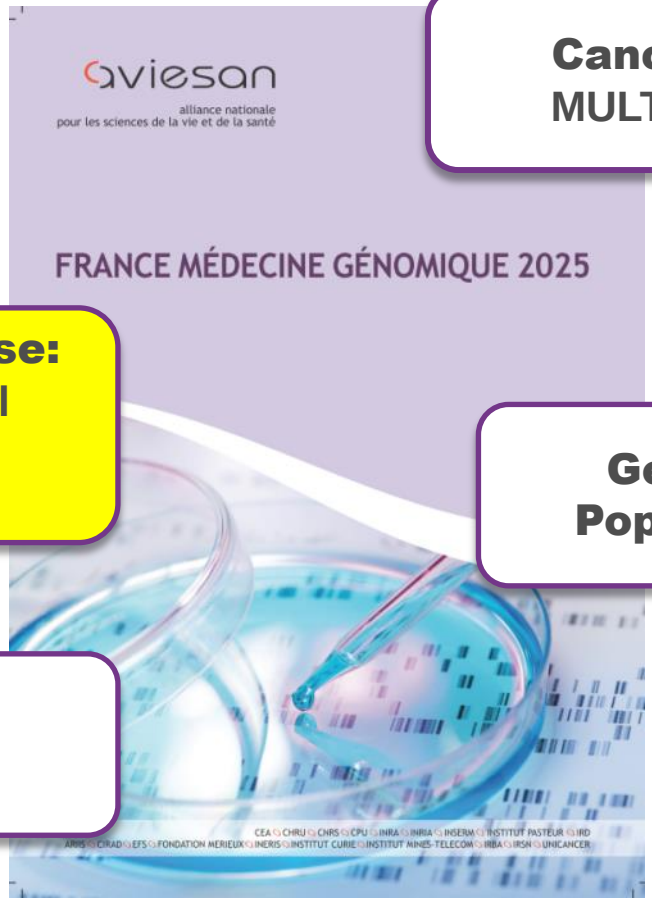
Overcome barriers encountered along the pathway

4 Clinical Pilot Projects



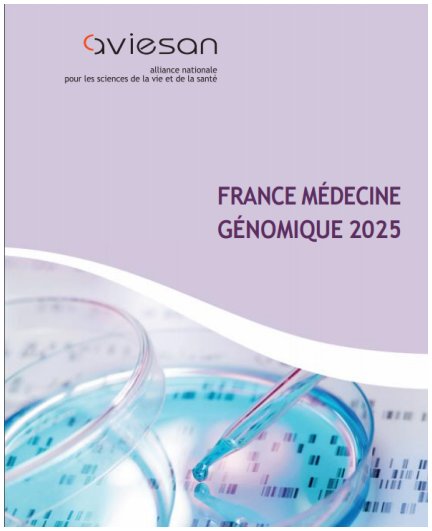
Cancer :
MULTIPLI

Rare Disease:
Intellectual Disability
DEFIDIAG

General Population

Common disease:
Diabetes

PILOT STUDY:



Medical and Economical Evaluation of Whole GENOME Sequencing in Healthcare Pathway of Patients with Rare Diseases

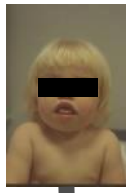
The Intellectual Deficiency Paradigm => the DEFIDIAG « PILOT »:
Frequency ID 1-3% - Most common cause of referral in clinical genetics - High need to cut down patient odyssee - Highly heterogeneous (clinical presentation, numerous genes)

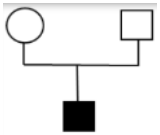
DEFIDIAG OPERATIONAL Steering COMMITTEE

Christine Binquet (INSERM CIC-EC1432), Jean-François Deleuze (CNGRH, Evry), Hélène Dollfus (CHU Strasbourg, INSERM), Hélène Esperou (PRC INSERM), Laurence Faivre (CHU Dijon), Thierry Frebourg (CHU Rouen) , Bénédicte Gérard (CHU Strasbourg) , Delphine Héron (AP-HP Paris) , Catherine Lejeune (INSERM CIC-EC1432), Stanislas Lyonnet (AP-HP, IMAGINE), Sylvie Odent (CHU Rennes), Damien Sanlaville (CHU Lyon, Plateforme AURAGEN)

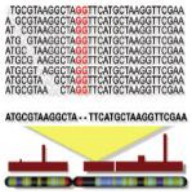
ID Diagnostic yield

Patient

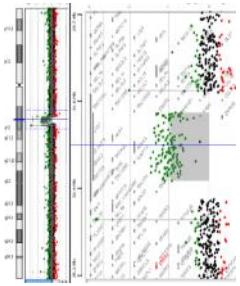




Identification of causal CNVs :



Array CGH



→ **10%**

NGS analyses of gene panels
ID panels (ID 44)

→ **12%**

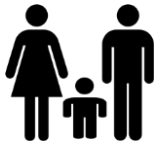
Whole Exome Sequencing
(WES)

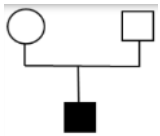
→ **47 %**

Whole Genome Sequencing
WGS

→ **59 %**

DEFIDIAG A PILOT PROJECT





Evaluation of WGS as a first line tool to improve diagnostic performance for ID

DEFIDIAG aims to :

1° Show the **feasibility** of WGS implementation in France with ID as a paradigm for Rare diseases

2° Identify the **best strategy** for optimal and **efficient** genetic diagnosis for ID

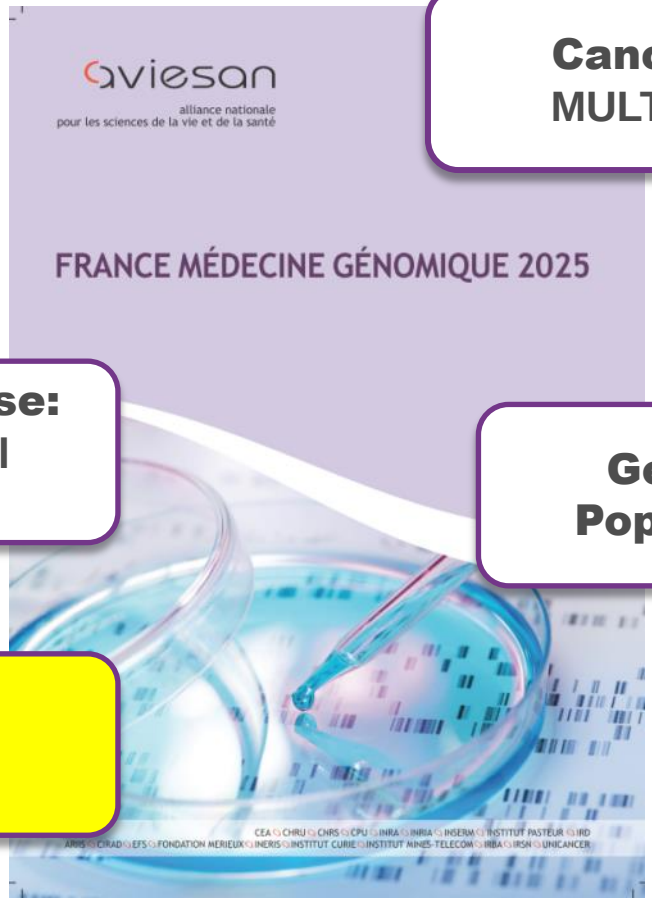
3° Demonstrate the **cost effectiveness** and **cost benefit** of WGS for ID

4° Show the **benefits on the outcome** of patients /parents (including SF)

5° Cut down the **diagnostic odyssey**

Overcome barriers encountered along the pathway

4 Clinical Pilot Projects



Cancer :
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Intellectual Disability

General Population

Common disease:
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DIABETES CLASSIFICATION

World epidemy

2nd diabetes epidemy

DIABETES de type 1

OTHERS

type 2 DIABETES

Autoantibodies
[DNA]
[insulitis]

Biological markers

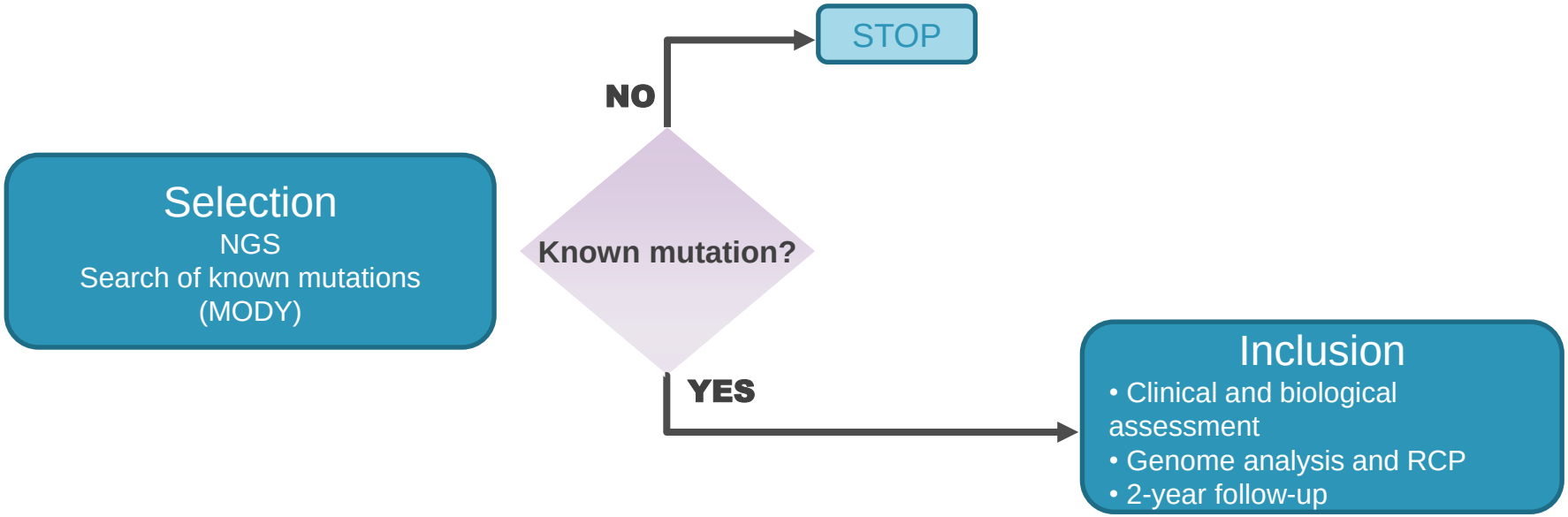
DNA
hormones
insulin secretion
pancreatic imaging

GLUCOGEN - OBJECTIVES

Main objective : to assess the contribution of whole genome sequencing and multidisciplinary meeting (i.e. geneticist + diabetologist) on diagnosis and care of atypical forms of diabetes

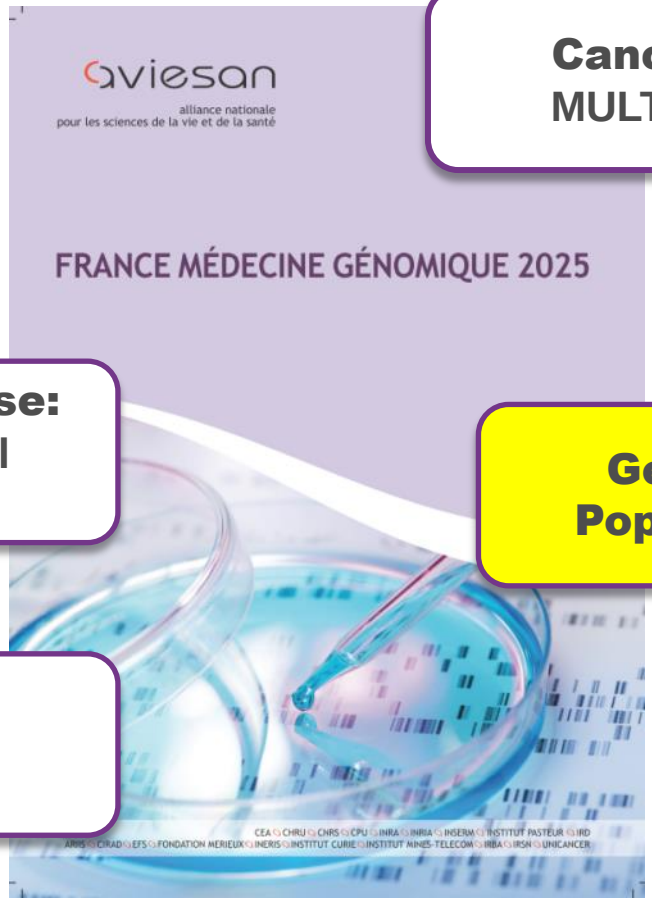
Secondary objectives :

- To assess the feasibility of whole genome sequencing in clinical practice
- To identify new mutations responsible for diabetes development
- To determine phenotypic characteristics according to the presence or absence of identified genomic variation and define phenotype-genotype integrated diagnostic markers.
- To evaluate treatment failure according to patient genotype
- To evaluate the occurrence of long-term complications associated with diabetes according to patient genotype



Overcome barriers encountered along the pathway

4 Clinical Pilot Projects



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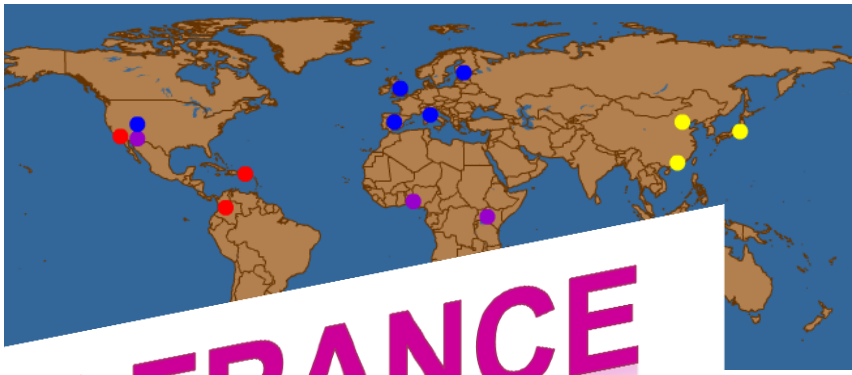
PUBLIC DATABASES

- **1000 Genome Project**
  1092 sequenced individuals
  from 14 populations worldwide
  (low coverage (2-6X) whole-genome sequence data
  targeted deep (50-100X) exome sequence data
  and dense SNP genotype data)



NO DATA FROM FRANCE

- **Exome Variant Se**
  NHLBI GO E
  6,5
  (4, ricans and 2,200 African Americans)
- **Exome Aggregation Consortium (ExAC)**
  Coalition of investigators seeking to aggregate and harmonize exome sequencing data from a wide variety of large-scale sequencing projects, and to make summary data available for the wider scientific community
  60,706 individuals

POPGEN – OBJECTIVES

Inserm Transversal Program

Main objectives:

- To answer the needs in terms of exome and genome « filtering » from common genetic variants in general population
- To provide a reference on the frequency of the genetic variants in a representative sample of the general French population

Questionnaire mailing (parents and grand parents' place of birth)

Geographic distance calculation

Selection of participants

Salivary kits

Whole genome analysis

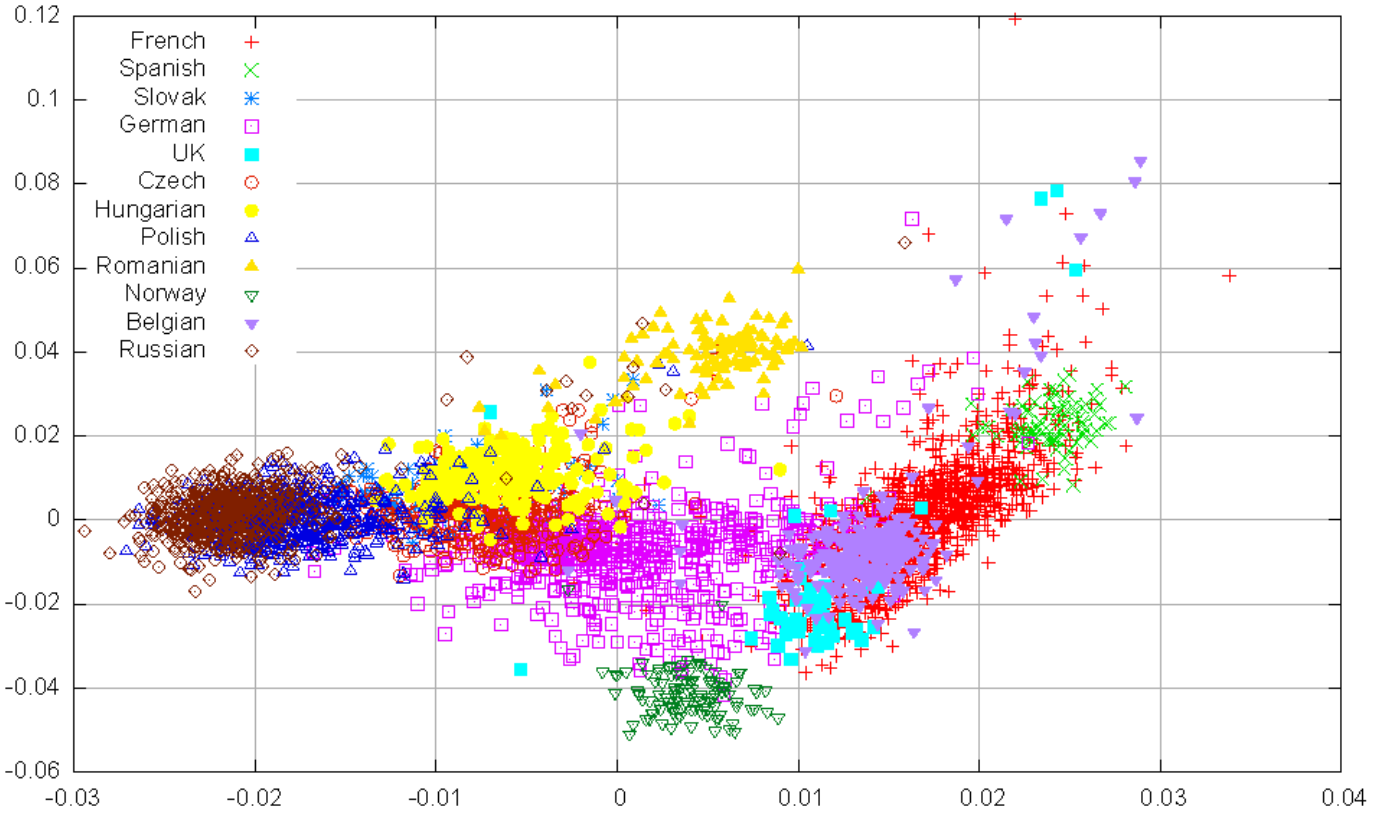
Filter out common/neutral variants from patient WES/WGS

Provide allele frequencies of variants discovered by WGS in a reference panel of individuals representative of the French general population (no selection on disease status)

ALLELE FREQUENCY DIFFERENCES IN EUROPE

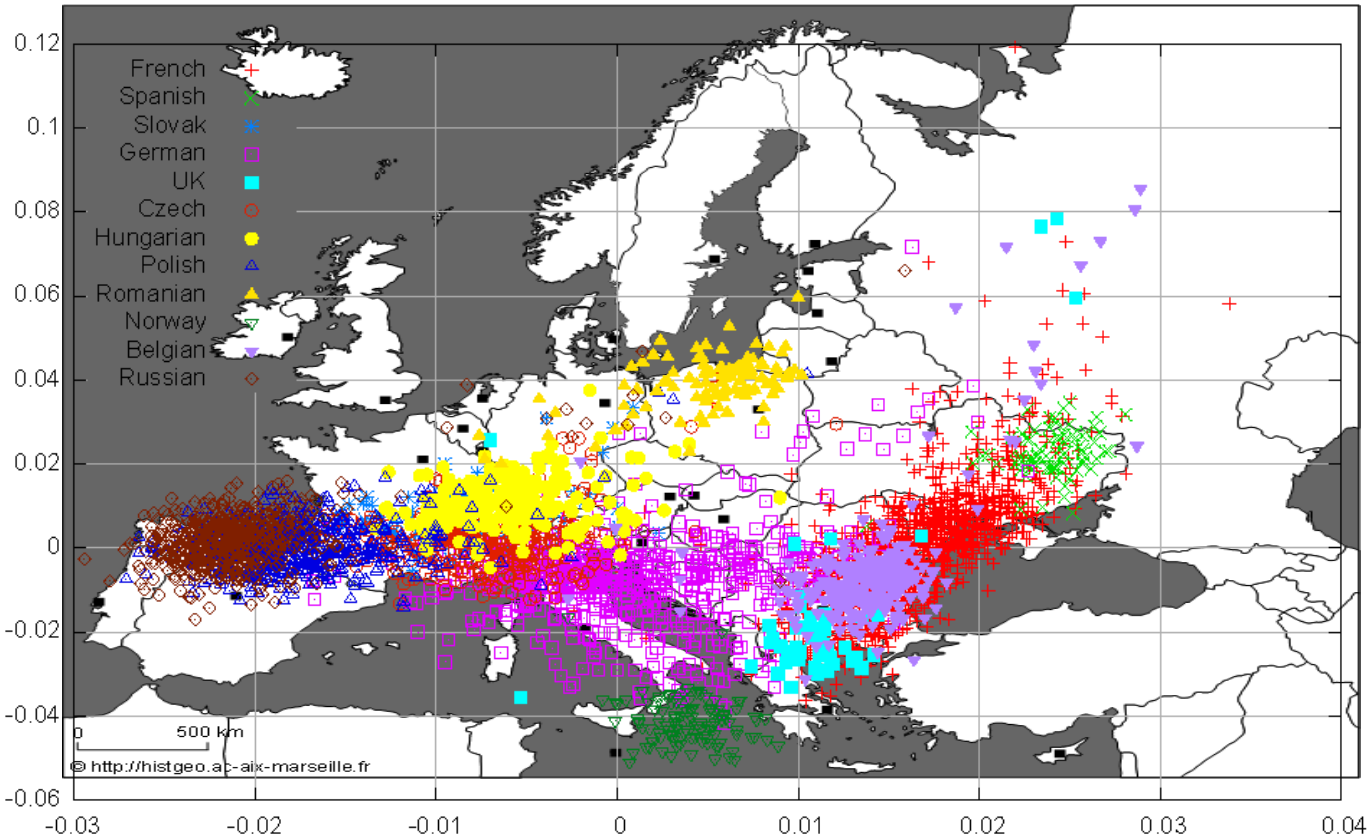
5,811 individuals from 12 European populations

121,242 SNPs



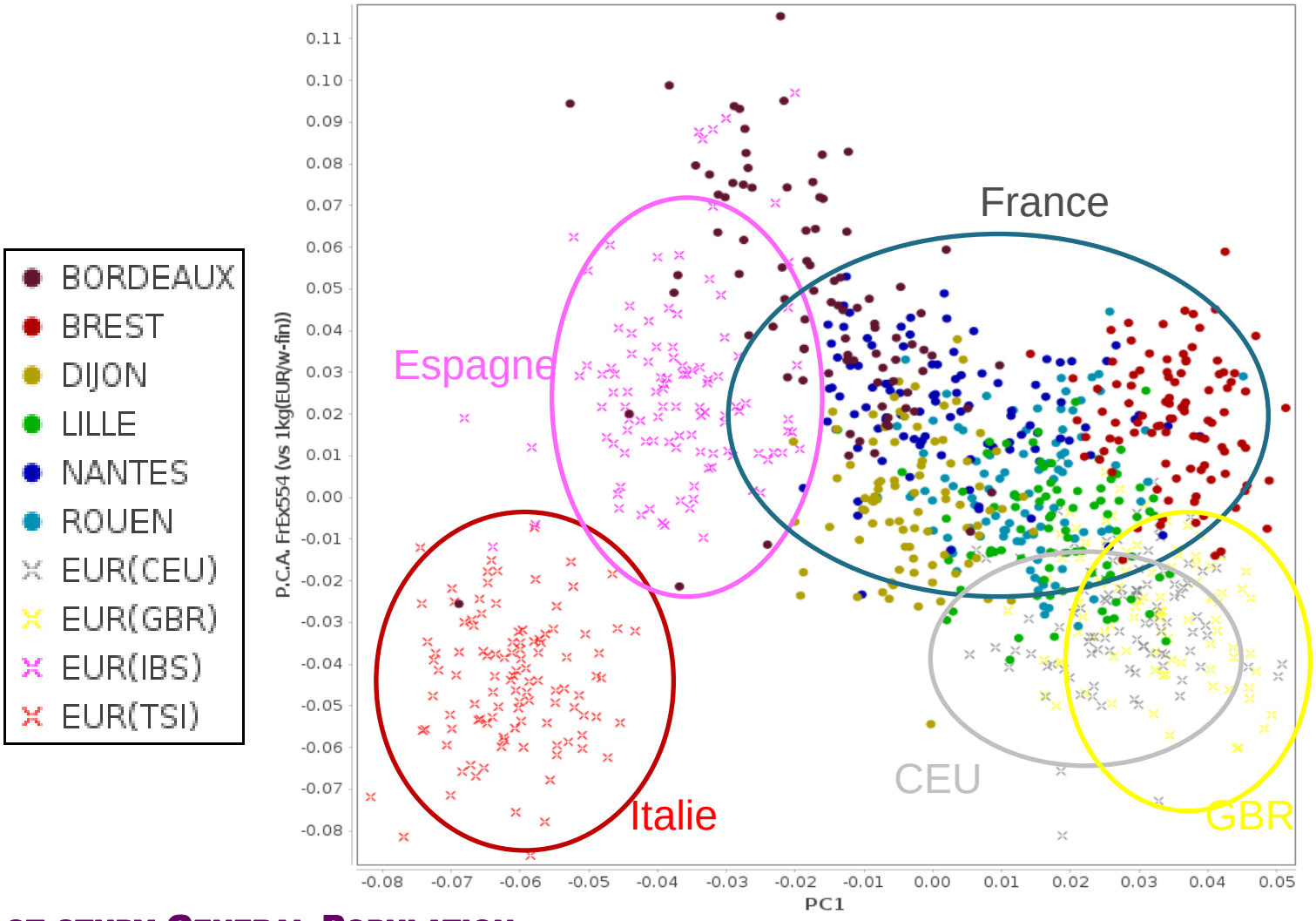
(Heath et al., EJHG, 2008)

ALLELE FREQUENCIES MIRROR GEOGRAPHY



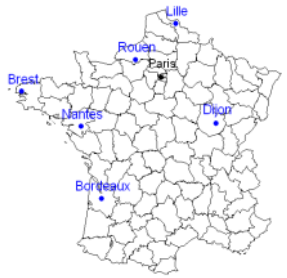
(Heath et al., EJHG, 2008)

THE FREX PANEL COMPARED TO EUROPEAN REFERENCE PANELS



FREX
573 exomes
6 regions

FRANCE GÉNOMIQUE



E. Genin

PROGRESS STATUS OF THE FRENCH INITIATIVE

The 14 action mesures are currently active:

- The first 2 sequencing platforms are in the start-up phase
- The first 14 clinical indications have been defined
- A technical scenario has been defined for the CAD
- The CRefiX recruites & accompanies the future clinical preindications in order to overcome several technological obstacles
- Two Pilot projects have started in 2018
- A mid-term report has been delivered concerning the training action mesure
- WG « ethics, regulatory aspects and society » accompanies the sequencing platforms on the patient consents
- The pharmaceutical industry sector is mobilized and part of this initiative
- Dissemination actions have been implemented
- Medico-economic assessments have been launch are ongoing.

THANK YOU FOR YOUR ATTENTION