Medicina personalizada en el sistema público de salud: la experiencia en Andalucía

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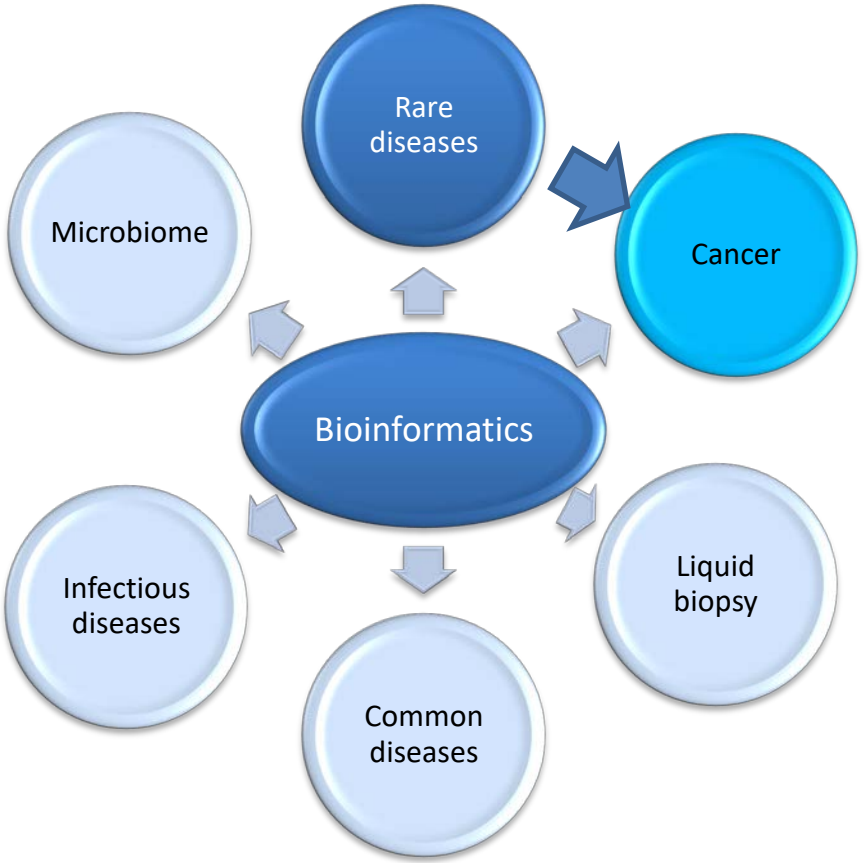
The Personalized Medicine Plan of the Andalusian community

The Program of Personalized Medicine of the Andalusian Community aims to use patient genomic data for precision diagnostic and treatment recommendation, with the long-term idea of converting the whole health system into a prospective clinical study.
Andalusia is the third largest region in Europe with a population of 8.5 M inhabitants

Andalusia is the largest health system in Europe having 8.5M people under a unique, universal electronic health record.

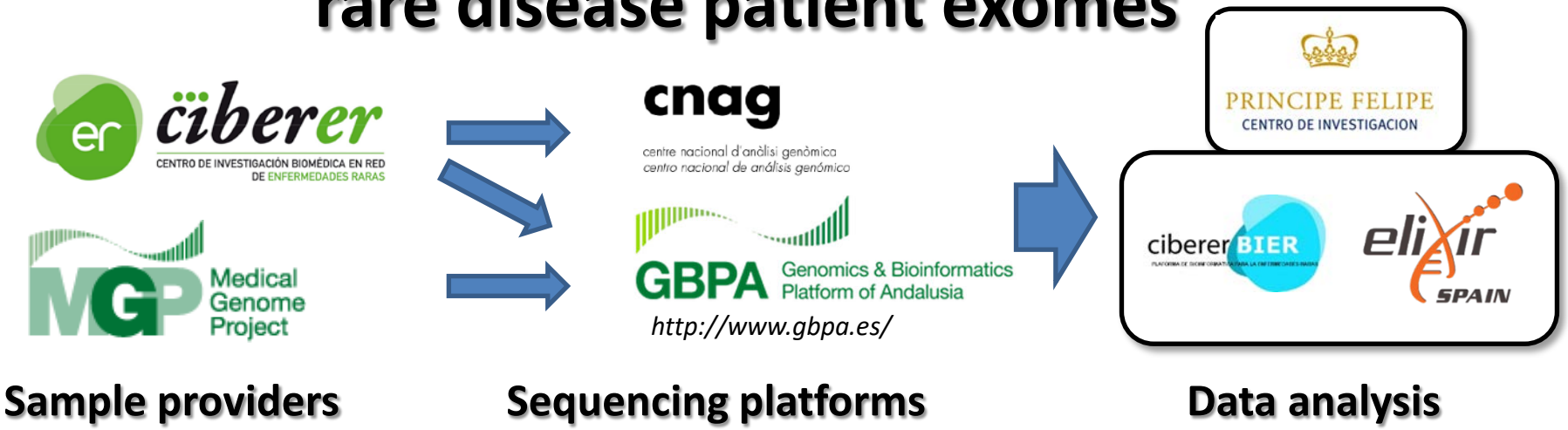
Bioinformatics as a fundamental piece of the Personalized Medicine Plan of Andalucía

The Bioinformatics Area, created in June 2016 in the *Fundación Progreso y Salud*, has as main goal supporting the Program of Personalized Medicine of the Andalusian Community by facilitating the use of genomic data for precision diagnostic and treatment recommendation.
A pilot project in rare diseases will be followed of the progressive implementation in cancer, common diseases, infectious diseases and other emergent, clinically relevant aspects, such as liquid biopsy, microbiome, nutrigenomics.



Previous initiatives

The MGP and CIBERER Initiatives to sequence rare disease patient exomes



Diseases with

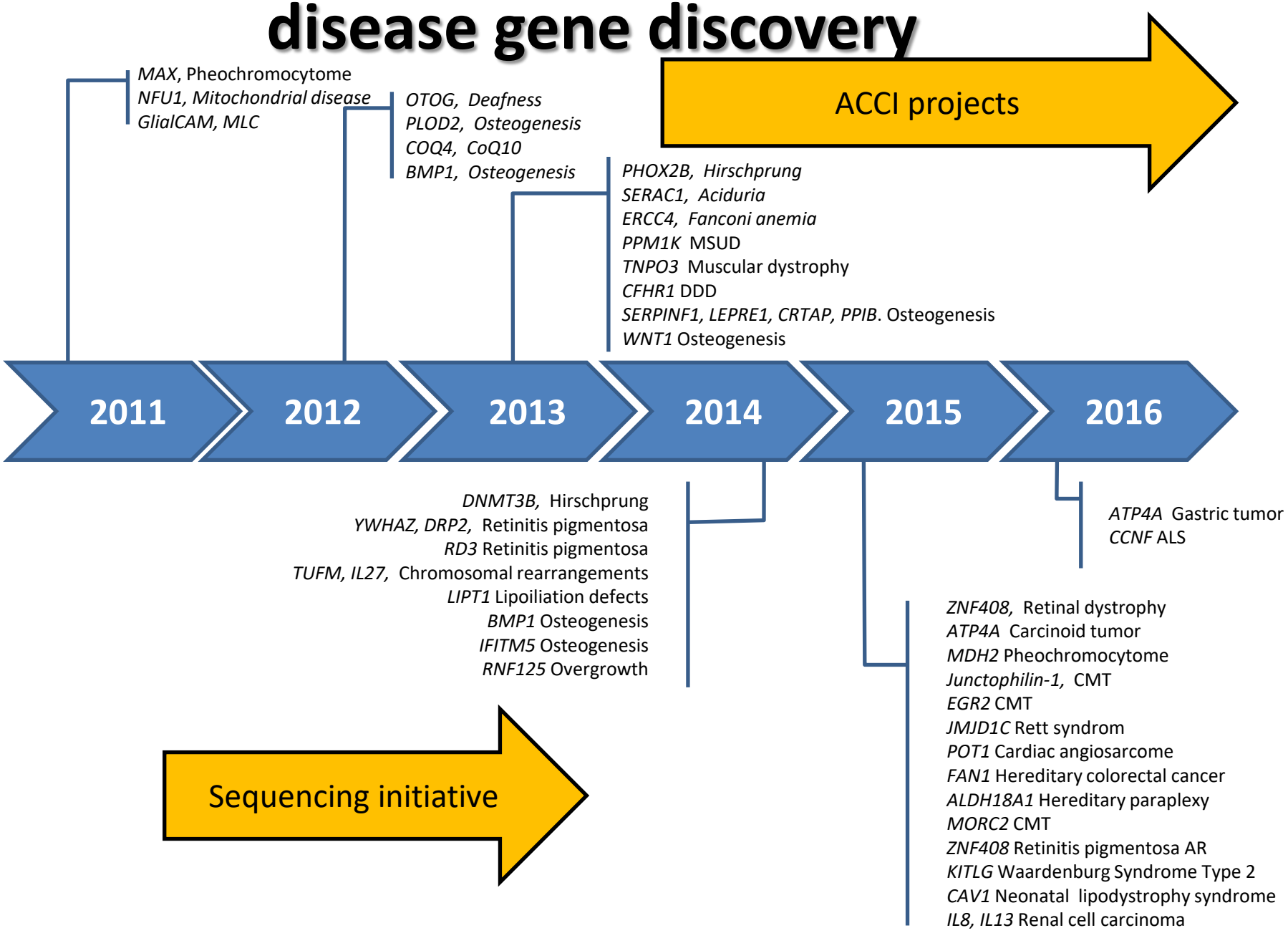
- Unknown causal genes
- No mutations in known genes

Search for:

- New disease genes
- Known genes with unknown modifier genes
- Susceptibility genes

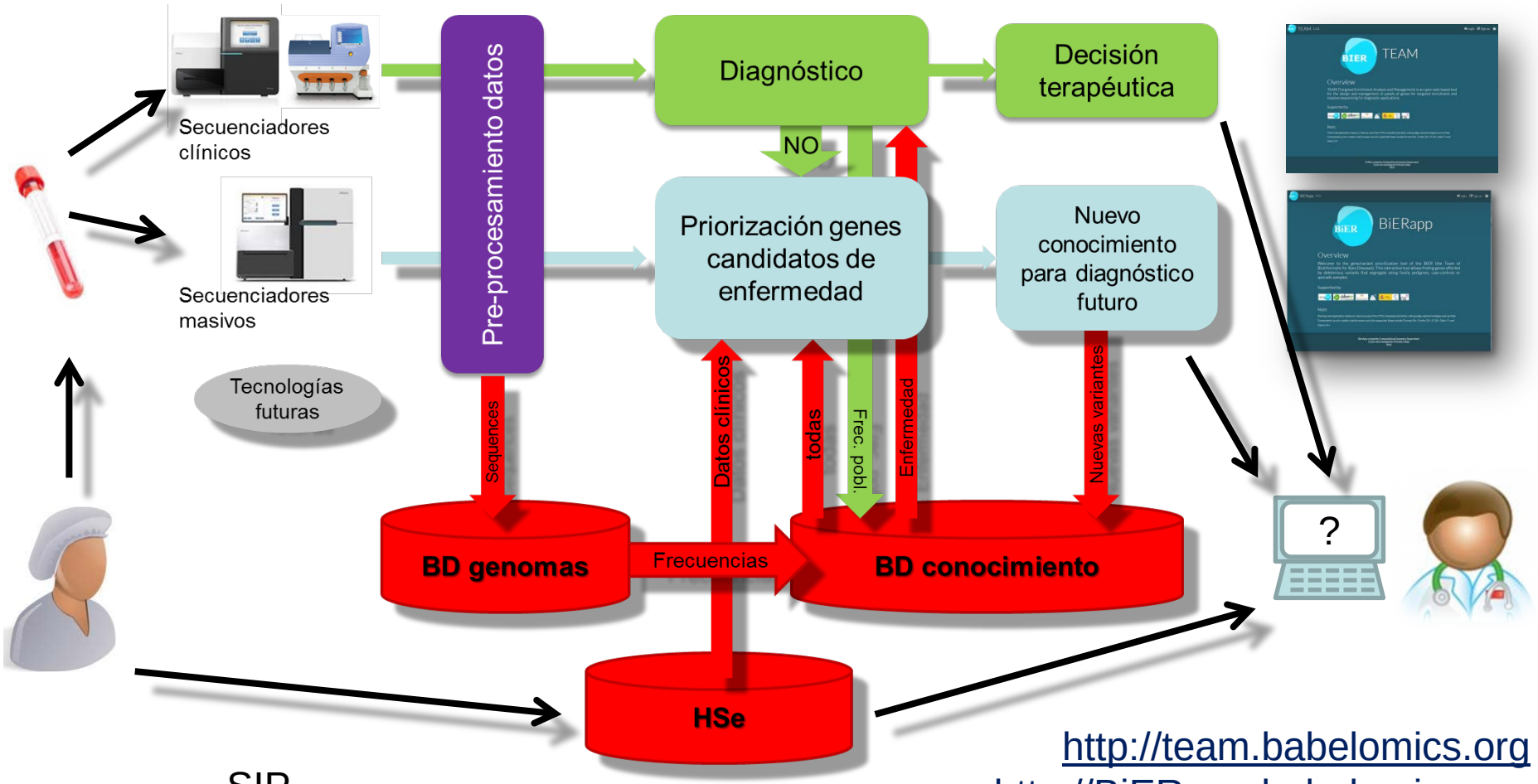
A total of 1044 exomes of 300 healthy controls and patients of more than 30 diseases were sequenced between 2012 and 2013.

Consequence: radical change in the pace of disease gene discovery



CIBERER initiative for diagnosis and biomarker discovery using massive sequencing

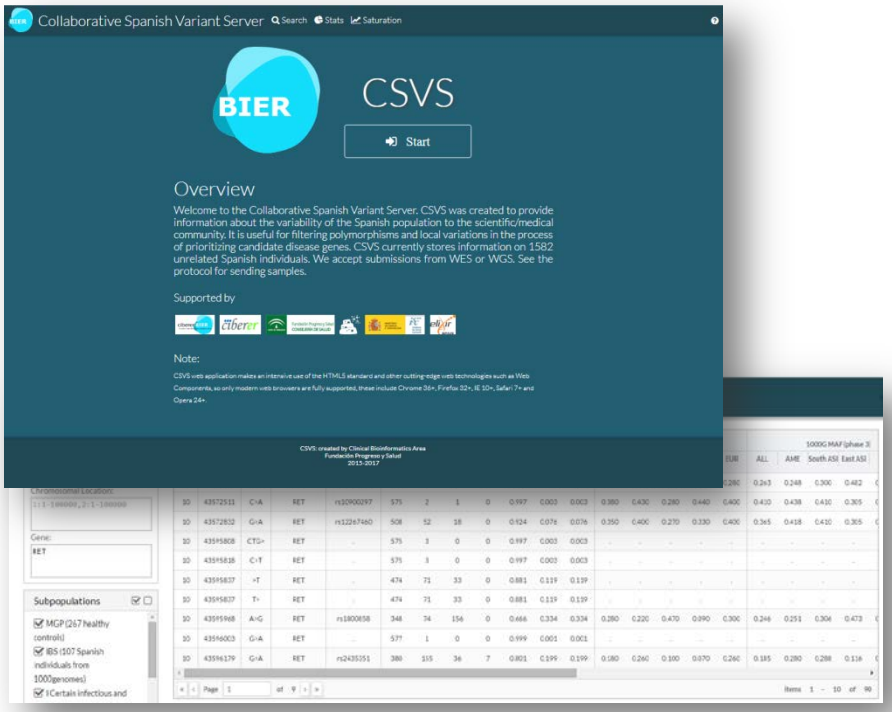
Ongoing (second phase) Project with the collaboration of seven hospitals: La Paz, FJD, Ramón y Cajal, CBM (Madrid), Virgen del Rocío (Sevilla), Hospital del Mar (Barcelona), HU La Fe (Valencia)., **within the context of CIBERER**



SIP

http://team.babelomics.org
http://BiERapp.babelomics.org

The CSVS: a crowdsourcing project



http://csvs.babelomics.org/

Allelic population frequencies obtained from 1,600 exomes are currently available in CSVS

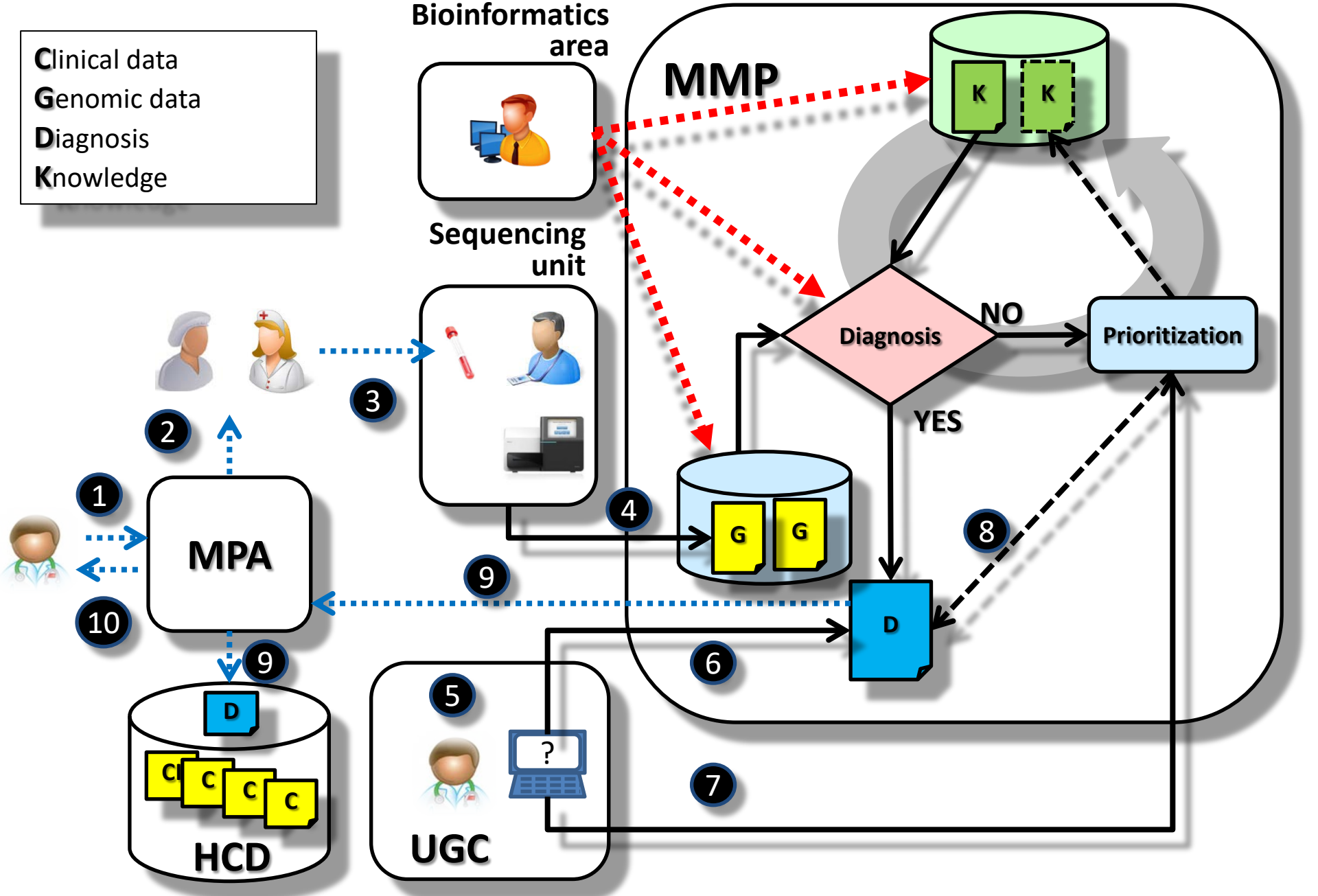
Scenario: Sequencing projects of healthy population are expensive and funding bodies are reluctant to fund them
CSVS Aim: To offer increasingly accurate information on variant frequencies characteristic of Spanish population.
CSVS Main use: Frequency-based filtering of candidate variants
Main data source: Sequencing projects of individual researchers (CIBERER and others)
Problem: Most of the contributions are patient exomes
Idea: Patients of disease A can be considered healthy **pseudo-controls** for disease B (providing no common genetic background exist between A and B)
Beacon: CSVS has a Beacon server

2017 - First phase of the Personalized Medicine Plan of Andalucía: rare diseases

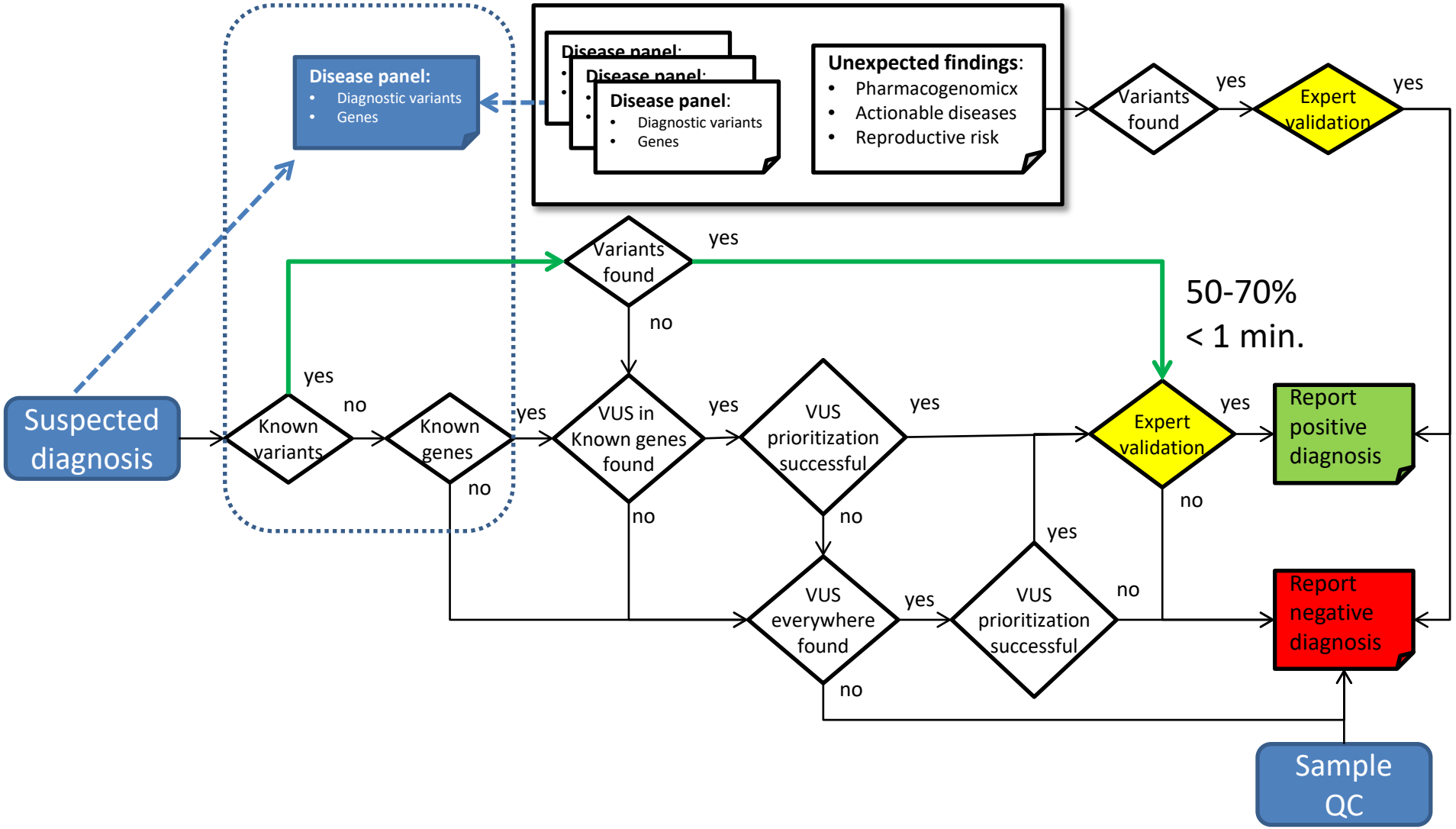
Objectives:

- Implementation of a pilot project to use massive sequencing for high precision diagnostic of rare diseases within the SAS
- Change in the current protocols to introduce of massive sequencing as part of the clinical practice: exome sequencing is cheaper than more than three conventional Sanger sequencing tests and produces much more clinically useful information
- Implementation of a database of genomic data linked to patient's eHR
- Scalability to the dimensions of a whole health system (Andalusia is the third largest region in Europe with >8.5 million inhabitants)
- Setting the foundations for the prospective healthcare paradigm by using the genomic database for prospective clinical studies (e.g. search for adverse response biomarkers…)

First phase: rare disease diagnosis in the SAS

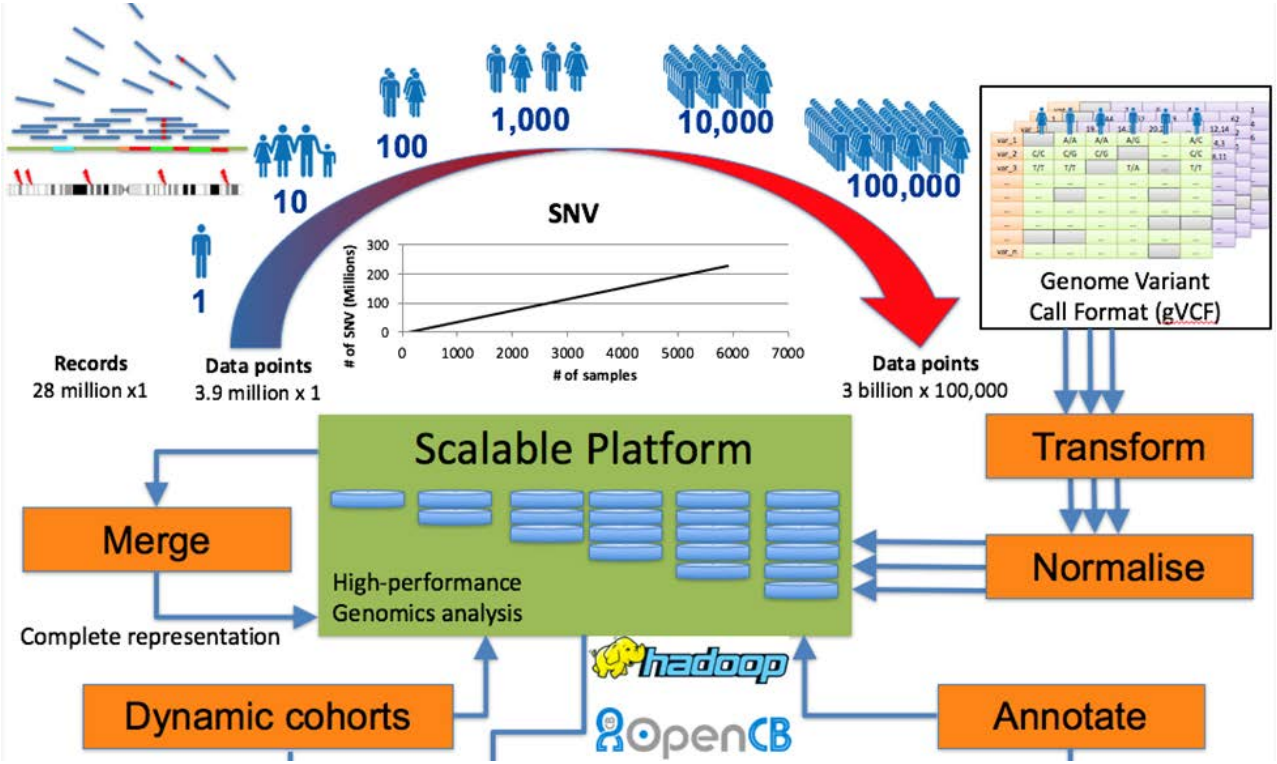


General diagnosis protocol



Back end: OpenCGA, a scalable storage and genomic data management platform

In collaboration with Genomics England (GEL)



Currently, the fastest and more powerful genomic database engine in the world.
Used in the GEL for genomic data management

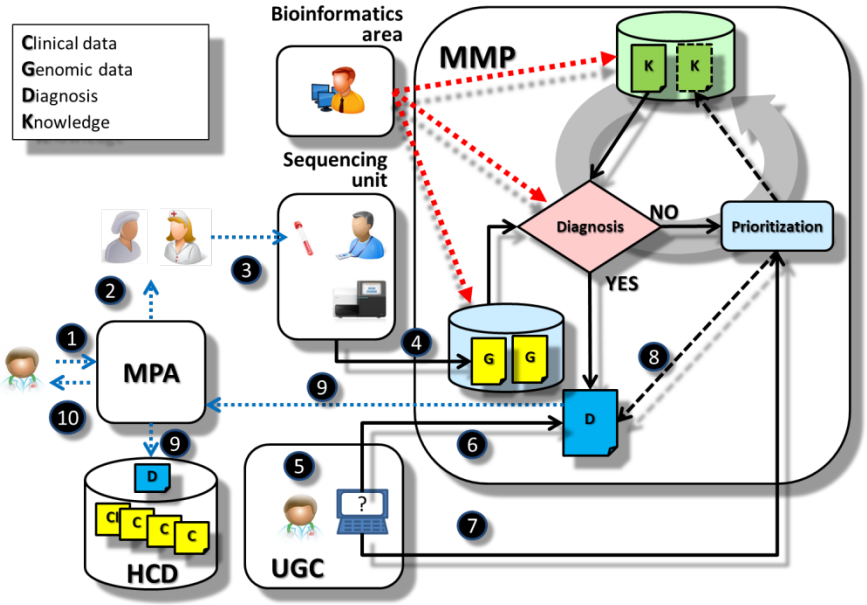
Extensive capabilities to query across genotype and phenotype relationships

https://github.com/opencb/opencga

GDPR compliance

The system has been designed in a way that is compliant with EU and Spanish General Data Protection Regulation

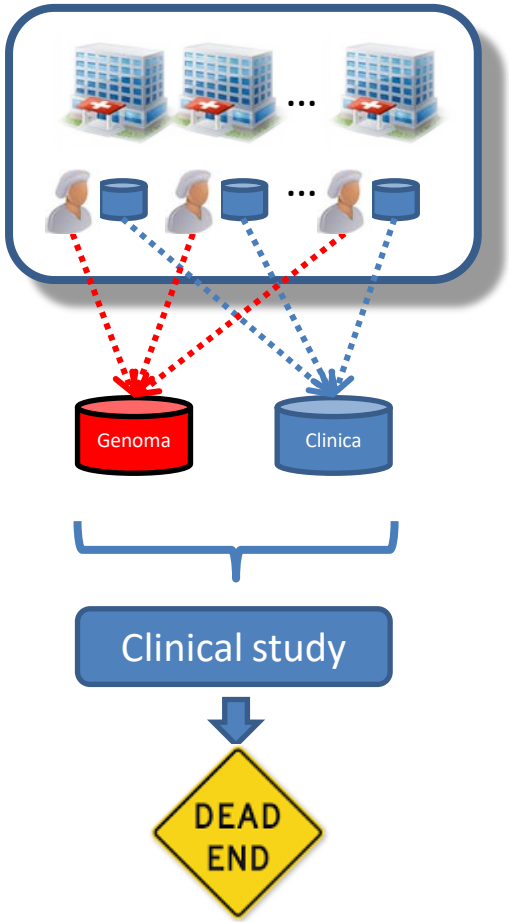
- Clinicians requesting for a genomic diagnostic have access to eHR and get the result of the test.
- Geneticists have access to eHR and can query the genomic data (but never extract them)
- IT have access to de-identified genomic data and no to eHR.



Genomic + clinical data = treasury

- Database of patients with prospective clinical information. Patients sequenced:
  - will have different responses to treatments
  - can have other diseases in the future
  - Today's undiagnosed patients can have a future diagnostic
- More opportunities for precision genomic diagnostic without the necessity of genomic data transfer:
  - Recurrent occurrence of variants in patients of the same disease favors finding new diagnostic disease variants and biomarkers.
  - Variants in patients of unrelated diseases can be taken as population background genomic variability to discard potential disease causal variants.
- Preventive medicine:
  - Prospective discovery of pharmacogenomic relevant variants
  - Prospective discovery of new disease risk variants

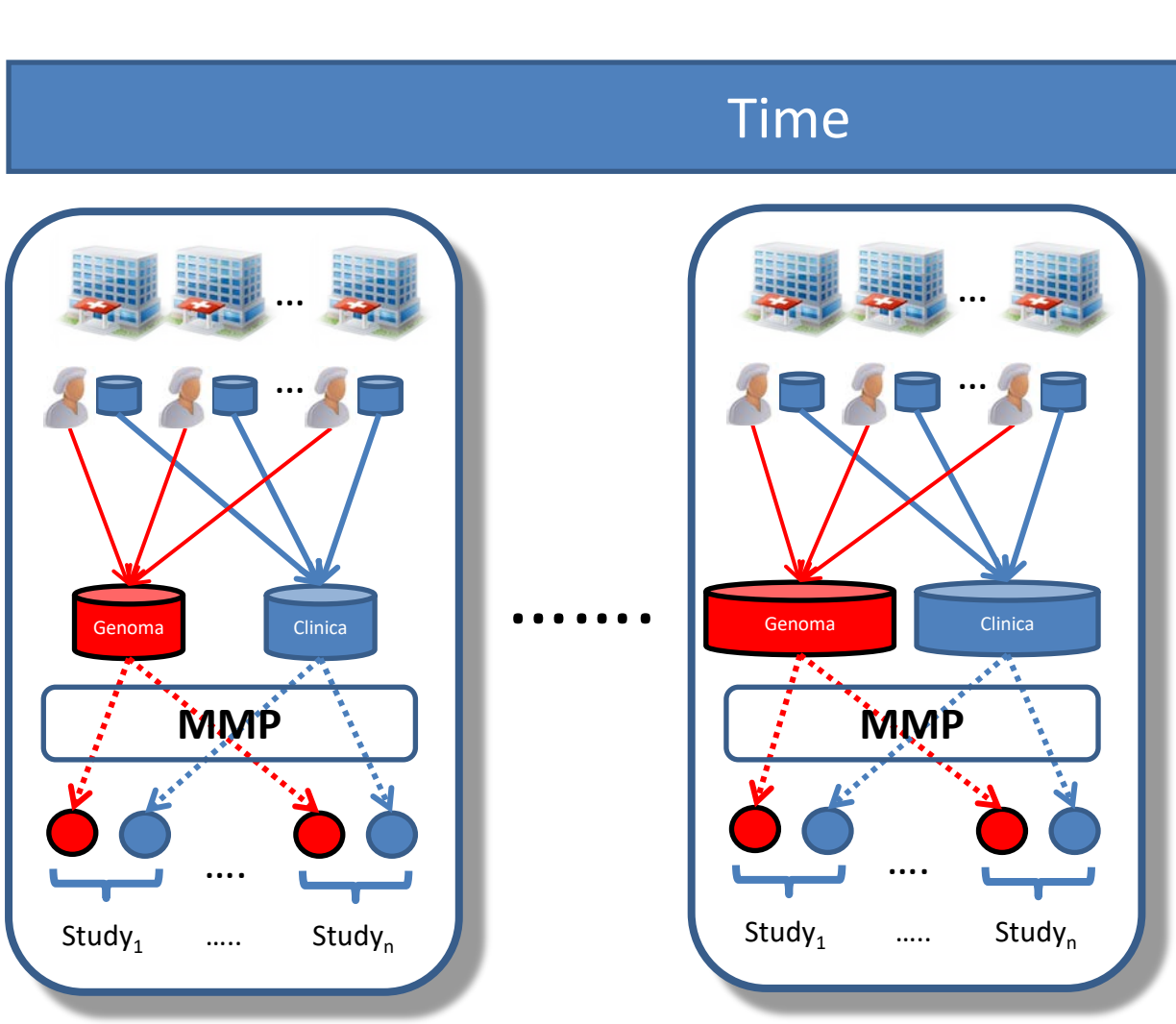
Personalized Medicine Model without universal eHR…



- Each study requires of a specific genomic and clinical data collection into an external database
- Static clinical data (e.g. if a control becomes a case the external DB will not be updated)
- Limited genomic data reuse for purposes different from the original study
- Model of GEL (100,000 genomes) Catalonian Genomic initiative, NaGen, etc.

… is actually only a clinical study

A personalized medicine model must integrate genomic data and universal eHR



- The whole health system becomes a humongous potential prospective clinical study increasingly useful in time
- Clinical data dynamically associated to patients
- Possibility of many clinical studies by reanalyzing genomic data under diverse perspectives (with no extra investment)
- Growing genomic DB with increasing study possibilities

Achievements of the first phase of the Personalized Medicine Plan of Andalucía

- Personalized Medicine Module: Intuitive software for semi-automatic diagnosis using massive sequencing data in a similar way to other clinical tests
- Used for the diagnostic of the 700 more prevalent RDs in Andalusia
- High performance engines for genomic data management and visualization in collaboration with the GEL (100,000 genomes project)
- Change in the current protocols to adopt massive sequencing instead conventional Sanger sequencing tests where possible
- Starting the phase II: Cancer

Clinical Bioinformatics Area
Fundación Progreso y Salud, Sevilla, Spain, and…

…the INB-ELIXIR-ES, National Institute of Bioinformatics and the BiER (CIBERER Network of Centers for Research in Rare Diseases)

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