Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Technical and scientific challenges in biomedicine: an European perspective.

CS3
Esade Forum-Pedralbes Campus

Alfonso Valencia. Ph.D.

ICREA Prof.

Dir. Life Sciences Dept. BSC/CNS

Dir. INB / ELIXIR-ES / IMPaCT-Data

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Research Institute & Europena Infrastructure

MareNostrum 4

Total peak performance 13.9 Pflops

- Disk capacity 14 Pbytes
- Total storage capacity 115 Pbytes

800 scientist and engineers

4 Departments: Earth, Engineering, Computer Science & Life

The third Spanish Institution in EU funding

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

Generalitat de Catalunya
Departament de Recerca i Universitats

UPC
UNIVERSITAT POLITÈCNICA DE CATALUNYA
BARCELONATECH

MareNostrum5

GPP - General Purpose

Intel Sapphire Rapids

Peak performance: 45,4 Pflops
Sustained HPL: 35,4 Pflops

April 2023

InfiniBand NDR 200 Fat Tree

Spectrum Scale File System
248 PB HDD
2,81 PB NVMe
402 PB tape

January 2023

ACC – Accelerated

Intel Sapphire Rapids
NVIDIA Hopper

Peak performance: 260 Pflops
Sustained HPL: 163 Pflops

June 2023

NGT GPP - Next Generation

NVIDIA Grace
Peak performance: 2,82 Pflops
Sustained HPL: 2 Pflops

June 2023

Consortium

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

NGT ACC - Next Generation

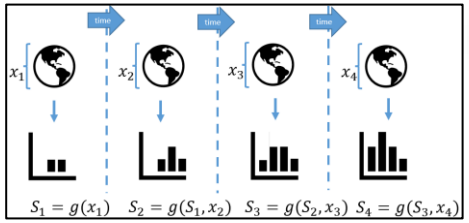
Intel Emerald Rapids
Intel Rialto Bridge

Peak performance: 6 Pflops
Sustained HPL: 4,24 Pflops

December 2023

BSC – EARTH Sciences

Code development



Data workflows

Computational Earth Sciences

Digital Twin Earth

Climate Modelling

Big data

ORCA 2
550 MB of memory
8 CPU hours
10 Gigabytes of output (daily)

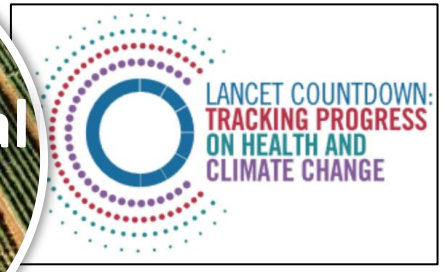
ORCA 1/12
414 Gigabytes of memory
90 000 CPU hours
1 Terabyte of output (daily)

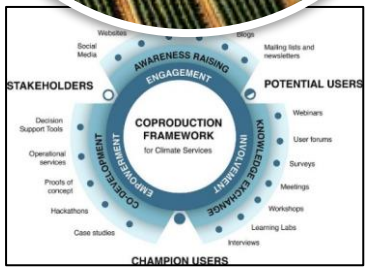
Process understanding

Visualisation

Environmental Services

Climate impacts





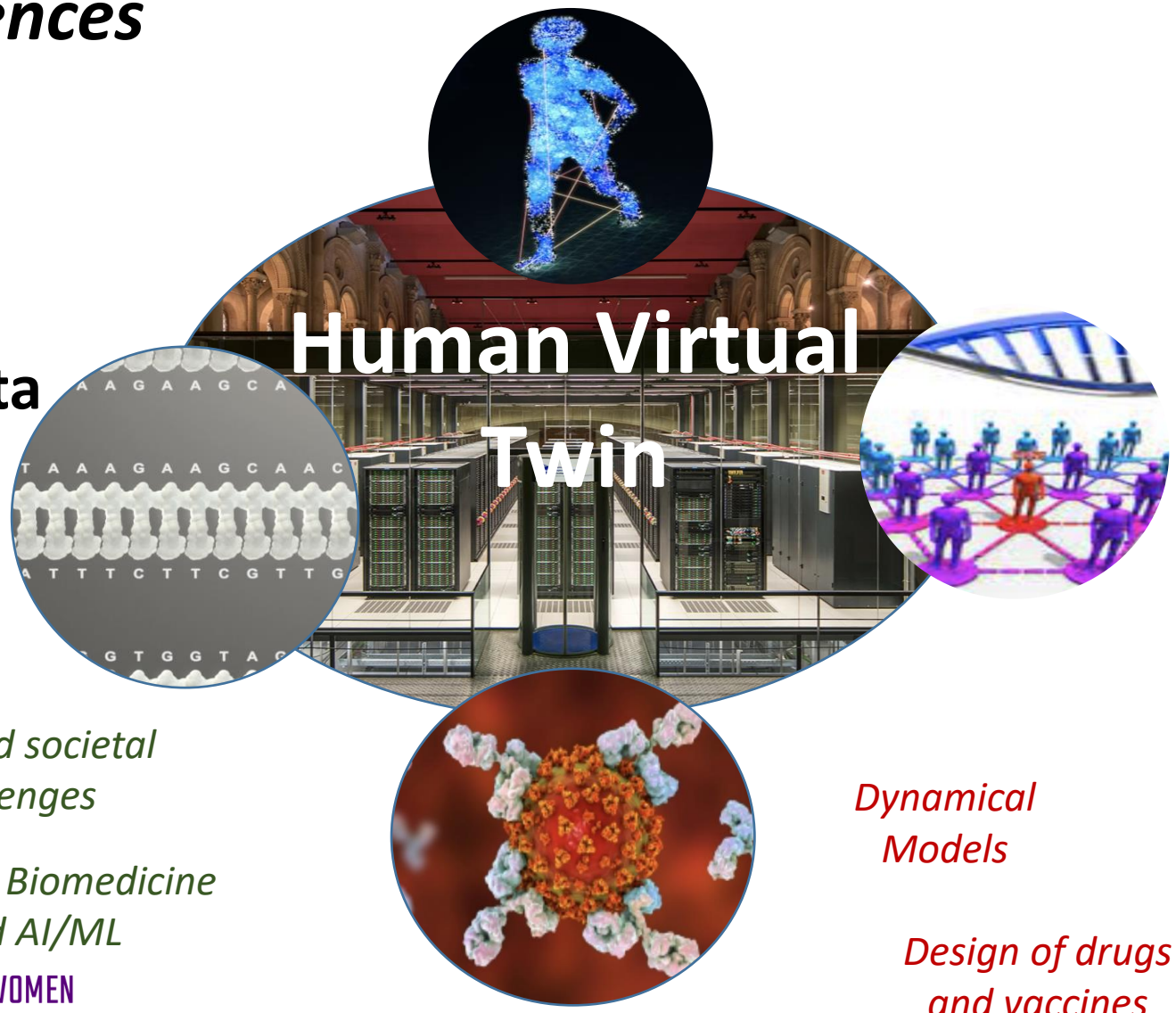
User engagement

BSC – LIFE Sciences

170 scientists/engineers

6 research groups

7 Support Units



Bio-Data management & data infrastructures

NLP: Large Language Models & BioNLP

Bioinformatics Methods & workflows

Data and societal challenges

Biases in Biomedicine and AI/ML

BIOINFO 4 WOMEN

Personalised Medicine

Rare Diseases

Cancer Research

Genome Regulation

Genome Wide studies

Molecular & Cellular Modelling and Design

Dynamical Models

Design of drugs and vaccines

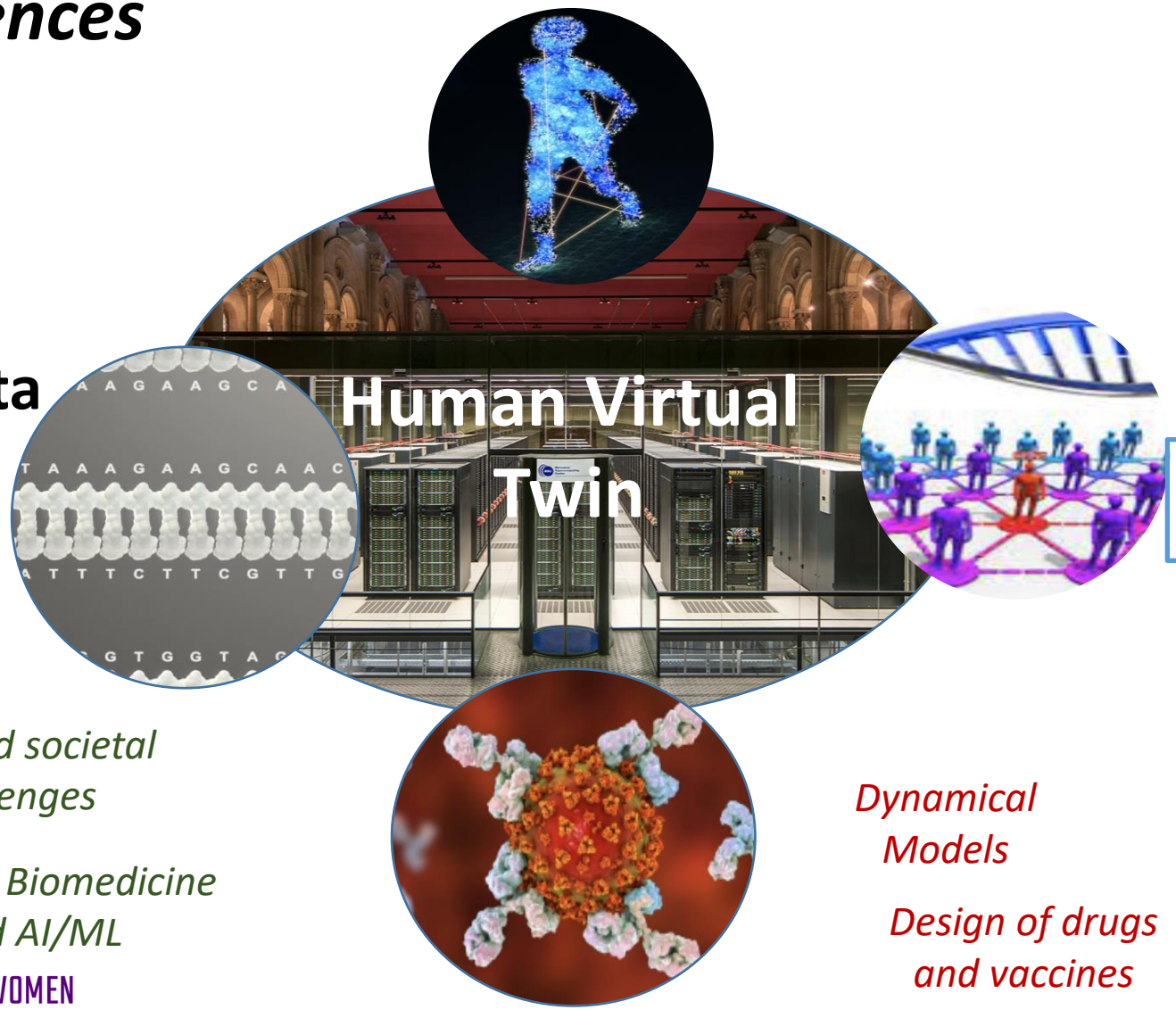
Language Models and AlphaFold

BSC – LIFE Sciences

170 scientists/engineers

6 research groups

7 Support Units



Bio-Data management & data infrastructures

NLP: Large Language Models & BioNLP

Bioinformatics Methods & workflows

Data and societal challenges

Biases in Biomedicine and AI/ML

BIOINFO 4 WOMEN

Personalised Medicine

Rare Diseases

Cancer Research

Genome Regulation

Genome Wide studies

Molecular & Cellular Modelling and Design

Dynamical Models

Design of drugs and vaccines

Language Models and AlphaFold

- **BioMedical Data**
  - **IMPaCT-Data**

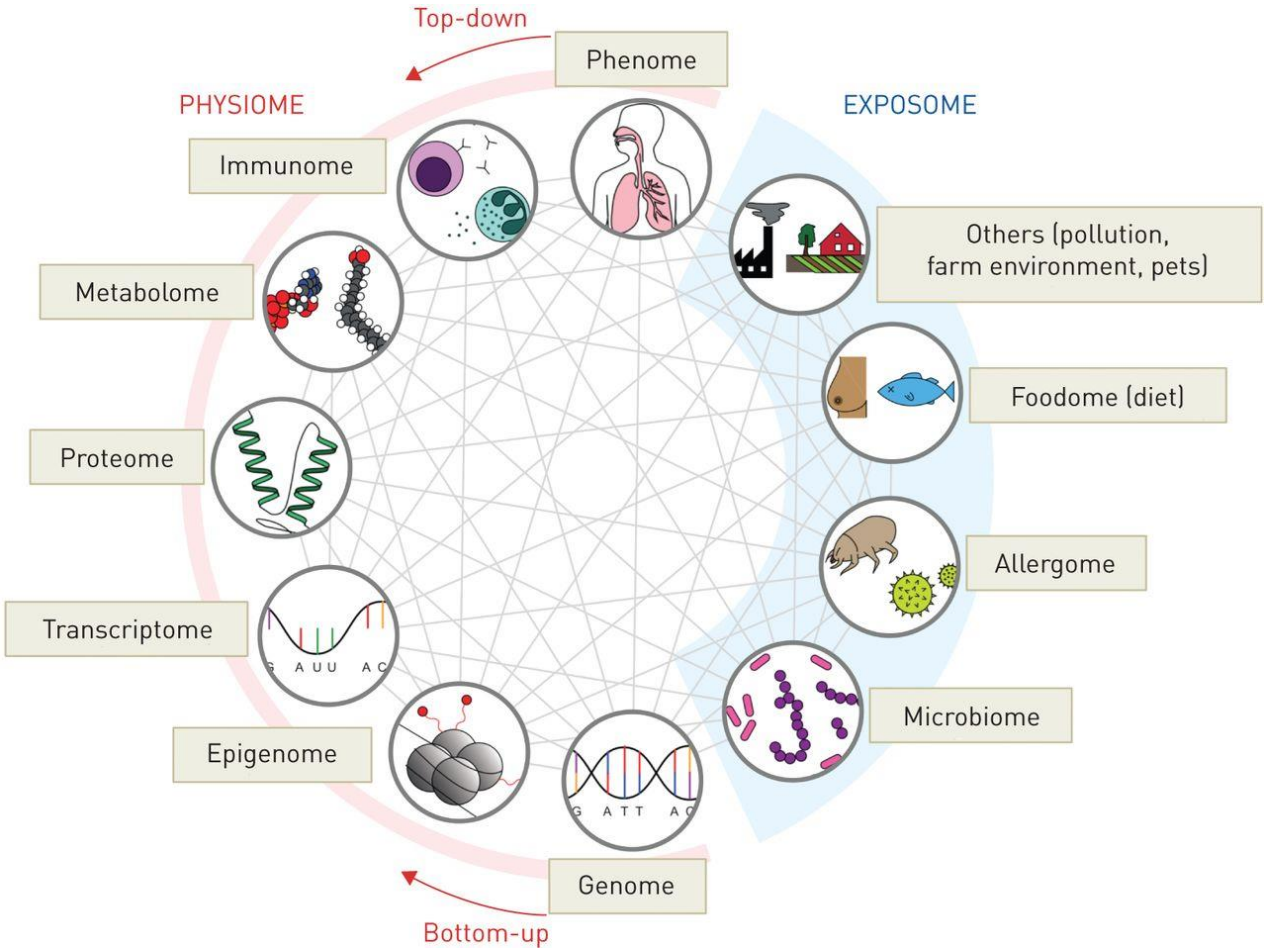
- **AI/ML in Biomedicine**
  - **bioNLP + NLP in Spanish**

- **Digital Twins (Virtual Human Twins)**

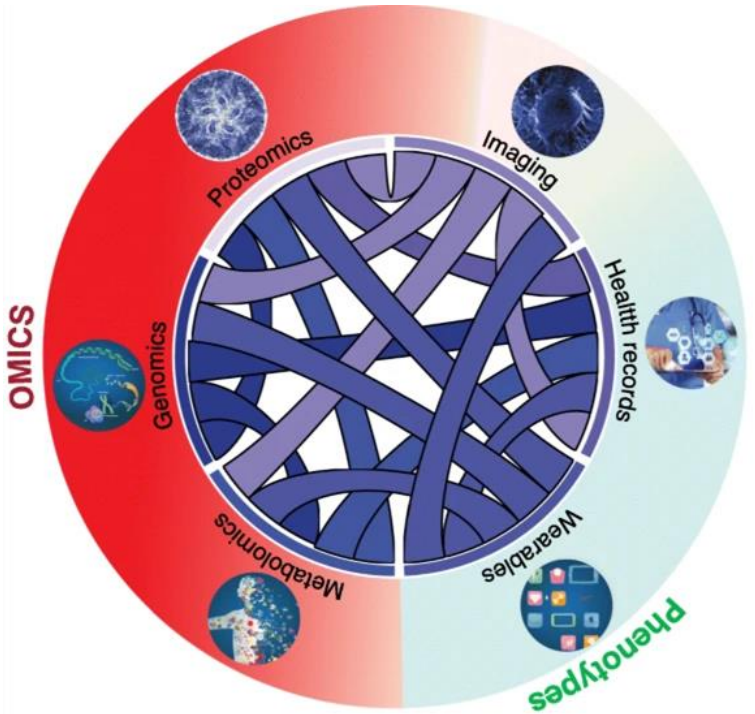
- ***Rare Diseases a Computational Approach***

- **Sex and Gender biases in biomedicine and AI**

Integration of multiple biomedical data sets



Howard H.F. Tang, et al.European Respiratory Journal 2020



Navarro, F.C.P., Mohsen, H., Yan, C. et al. Genomics and data science: an application within an umbrella. Genome Biol 20, 109 (2019)

The European Health Data Movement - for Research

European Health Data Space

This initiative is a commitment of **23 European countries** to give **cross-border access** to one million sequenced genomes by 2022

B1MG Beyond one Million Genomes

European Genomic Data Infrastructure

Beacon

EUROPEAN GENOME-PHENOME ARCHIVE

Global Alliance for Genomics & Health
Collaborate. Innovate. Accelerate.

ELIXIR - Nodes of European infrastructure for biological information

Data infrastructure for Europe life-science research:
- Data
- Interoperability
- Tools
- Compute
- Training

- ELIXIR Nodes build local bioinformatics capacity throughout Europe
- Over 180 institutes involved in ELIXIR Nodes

www.elixir-europe.org @ELIXIREurope

elixir

Instituto de Salud Carlos III

IMPaCT

Eje 1

Spanish Cohort

Eje 2

IMPaCT-Data

Eje 3

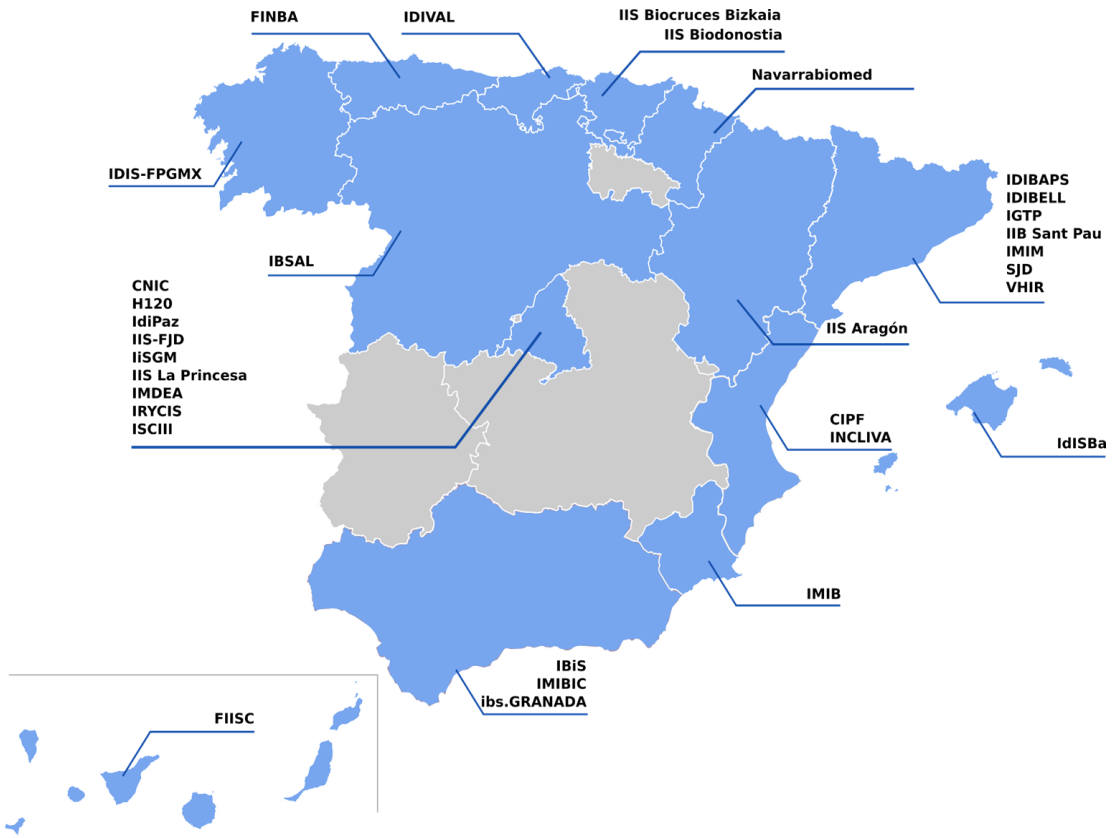
Genomics

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

IMPaCT-Data

TRANSBIONET
Translational Bioinformatics Network



Bioinformática INB/ELIXIR-ES

BSC
CRG
FPS
CNIO
CSIC
IRB Barcelona
UMA
UPF

Informática Médica & imagen

H12O
HCB
IACS
IDIAPJGol
IIS La Fe (II)
Navarrabiomed -
SAS-HUVR
ISCIII
FISABIO
IIS La Fe
INIBICA

Agencias Evaluadoras

RedETS
CTI-SEIS –
AQuAS
AEMPS

Demostradores Tecnológicos (Empresas

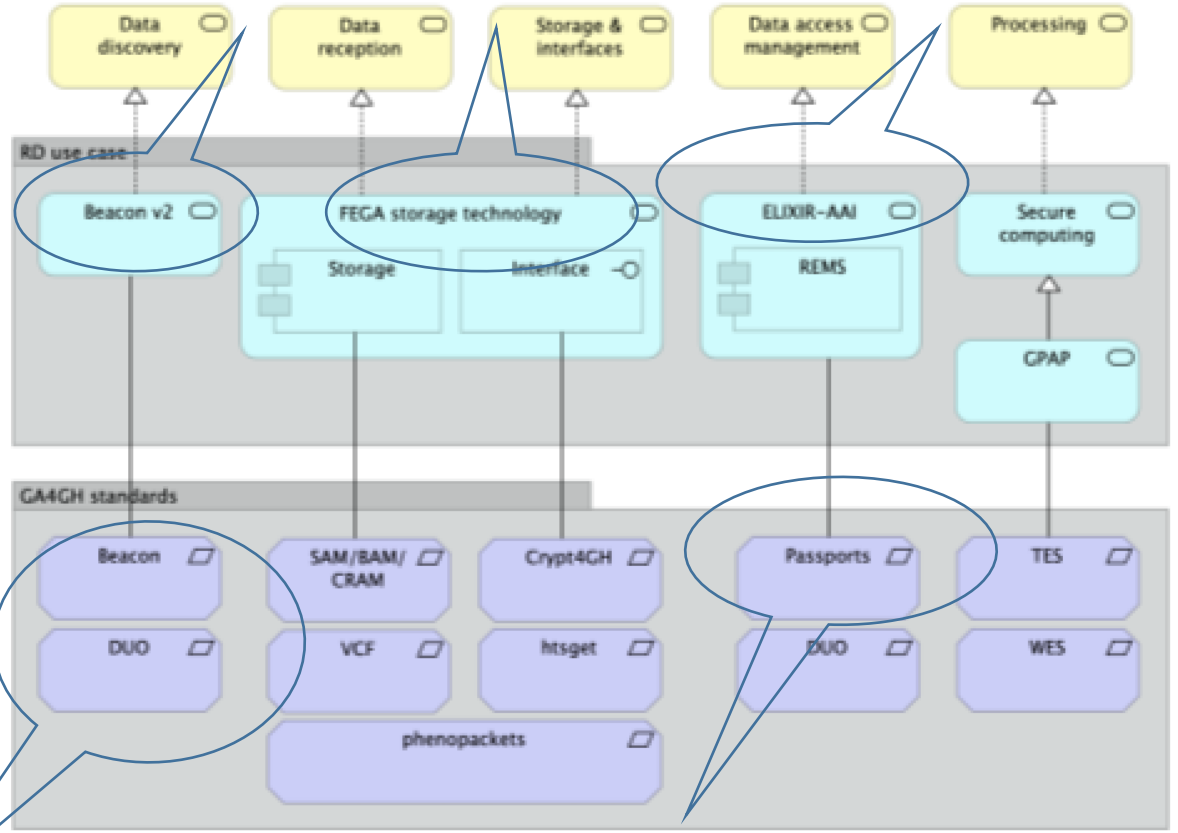
BITAC
IBM
IVA/OpenCGA
Ilumina
Roche Pharma
Fujitsu

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Caso de uso de B1MG: enfermedades raras

Rare Diseases activities at ELIXIR FI – B1MG PoC

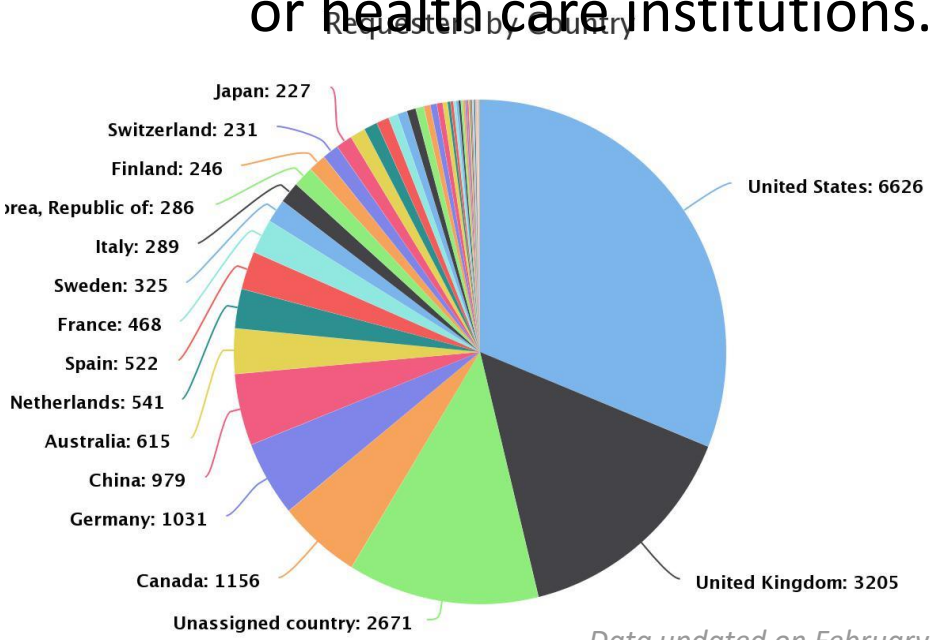
- Links GA4GH Standards and RD services
  - Federated EGA, Beacon, REMS, RD-Connect GPAP
- Using PoC to investigate ELSI issues
- Uses synthetic dataset
  - Aim to dope the genetic data with clinically relevant monogenic variants and associated phenotypes
- Building links with EJP-RD and Solve-RD



EGA

Federated European Genome-phenome Archive

- Data is provided by **research centers** and **health care institutions**.
- Access is controlled by Data Access Committees.
- Data requesters are researchers from other research or health care institutions.



Data updated on February 2nd, 2022

EMBL-EBI · CRG Centre for Genomic Regulation · Barcelona Supercomputing Center · Centro Nacional de Supercomputación · elixir SPAIN · Fundación "la Caixa"

European institutes commit to data access across borders

Research institutes from five European countries have committed to improving the way researchers discover and access sensitive human data across national borders to enable more efficient health research.

Credit: Karen Arnott/EMBL

Finland, Germany, Norway, **Spain**, Sweden

Ciencia / Materia — EL PAÍS

JESSICA MOUZO
Barcelona - 23 SEPT 2022 - 05:20 CEST

INVESTIGACIÓN CIENTÍFICA >

El almacén invisible que guarda datos genómicos de un millón de personas

El Archivo Europeo de Genomas y Fenomas, que dispone de 16 petabytes de datos de salud muy sensibles para investigación científica, está custodiado en el superordenador MareNostrum de Barcelona y en Cambridge

Barcelona Supercomputing Center · Centro Nacional de Supercomputación

The EGA allows going from data to therapy all around the world

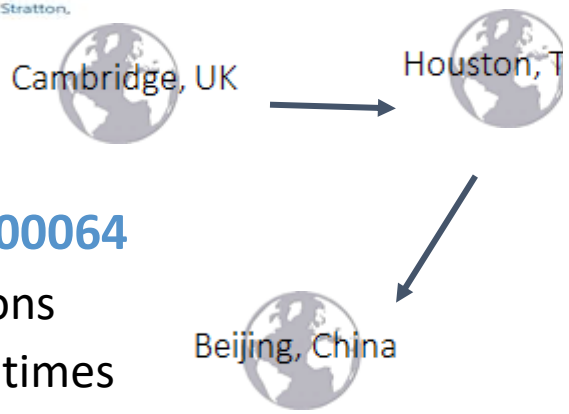
Published: 27 October 2010

The patterns and dynamics of genomic instability in metastatic pancreatic cancer

Peter J. Campbell, Shinichi Yachida, Laura J. Mudie, Philip J. Stephens, Erin D. Pleasance, Lucy A. Stebbings, Laura A. Morsberger, Calli Latimer, Stuart McLaren, Meng-Lay Lin, David J. McBride, Ignacio Varela, Serena A. Nik-Zainal, Catherine Leroy, Mingming Jia, Andrew Menzies, Adam P. Butler, Jon W. Teague, Constance A. Griffin, John Burton, Harold Swerdlow, Michael A. Quail, Michael R. Stratton, Christine Iacobuzio-Donahue & P. Andrew Futreal

Nature **467**, 1109–1113(2010) | Cite this article

3186 Accesses | **885** Citations | **29** Altmetric | Metrics



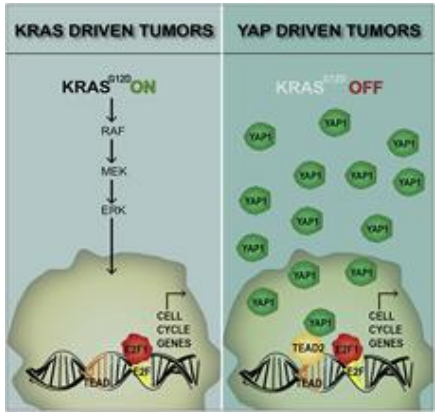
(1) Study deposited EGAS00000000064

- ★ The paper has over 700 citations
- ★ Datasets re-used many, many times

Cell

Yap1 Activation Enables Bypass of Oncogenic Kras Addiction in Pancreatic Cancer

Avnish Kapoor, Wantong Yao, Hanqiang Ying, Sujun Hua, Alison Liewen, Qiuyun Wang, Yi Zhong, Chang-Jiun Wu, Anguraj Sadanandam, Baoli Hu, Qing Chang, Gerald C. Chu, Ramsey Al-Khalil, Shan Jiang, Hongai Xia, Eliot Fletcher-Sananikone, Carol Lim, Gillian I. Horwitz, Andrea Viale, Piergiorgio Pettazzoni, Nora Sanchez, Huamin Wang, Alexei Protopopov, Jianhua Zhang, Timothy Heffernan, Randy L. Johnson, Lynda Chin, Y. Alan Wang, Giulio Draetta, and Ronald A. DePinho



(2) Molecular mechanism identified

(3) New therapeutic strategy shaped

Cancer Lett. 2017 Aug 28;402:61-70. doi: 10.1016/j.canlet.2017.05.015. Epub 2017 May 30.

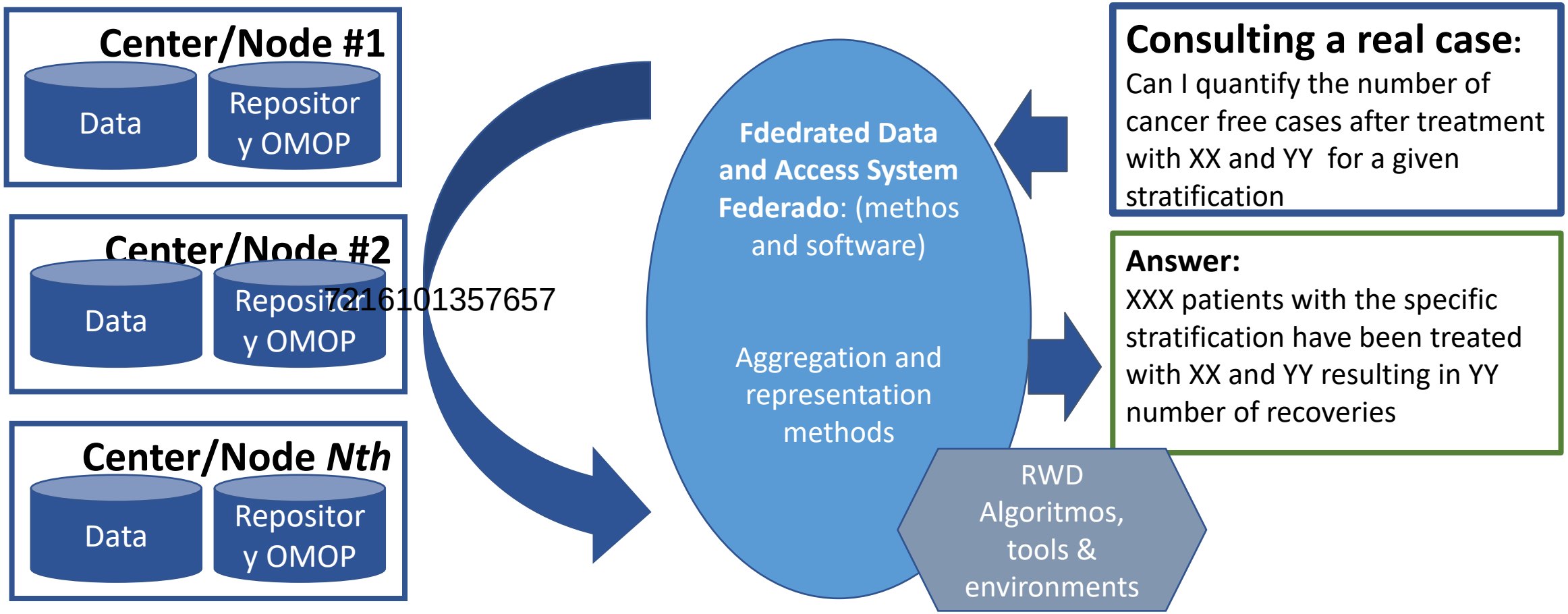
A combinatorial strategy using YAP and pan-RAF inhibitors for treating KRAS-mutant pancreatic cancer

Xiao Zhao [1], Xiuchao Wang [2], Lijun Fang [3], Chungen Lan [2], Xiaowei Zheng [2], Yongwei Wang [1], Yinlong Zhang [4], Xuexiang Han [1], Shaoli Liu [4], Keman Cheng [1], Ying Zhao [1], Jian Shi [1], Jiayi Guo [1], Jihui Hao [2], He Ren [5], Guangjun Nie [6]

Affiliations + expand

PMID: 28576749 DOI: 10.1016/j.canlet.2017.05.015

Example of potential use: Building a Virtual Cohort in a Federated Environment



A federated operation is executed in each of the centers / nodes on their private OMOP repositories – after consultation with the ethic committee(s). ***Requires interoperable data***

1.- Compartir datos clínicos para investigar

1.- **A basic standardized model of clinical data** organized in ISO13606 archetypes agreed between HCB, H12dO and HVdR, with maximum granularity

- Patient (non-identifying demographics)
- Episodes and movements (care actions)
- Laboratory determination
- Clinical observation (signs, symptoms, states)
- Limitation of therapeutic effort
- Health problems
- Diagnoses and Procedures
- Medication prescribed, administered and accumulated

2.- ADL file and its representation in **owl for each archetype**

3.- **A standardized terminological** reference for the elements of the archetype (CIM10-MC, SNOMED-CT, LOINC)

4.- A **repository of ISO13606 extracts**

5.- **Optimized transformation tools** from raw formats to archetypal extracts (LinkEHR®-Veratech)

6.- Processes to **convert archetyped data in ISO13606 to OMOP**: Extracts 13606 API ontology instances SPARQL queries OMOP tables.

7.- **OMOP repository.** Successful proof of concept carried out with a small subset of patients. Pending to populate it definitively.

8.- **Availability of views (templates)** on databases based on the definition of archetypes to model ad hoc extractions of data from primary data sources that do not necessarily have to be medical records

Federated Secure Access and Software Execution

- **Single password access to distributed data hubs**
- **Distributed computing in secure sites under a federated protocol**
- **Implementing GA4GH and ELIXIR technology**
- **Aligned with the EHDS and GDI developments**

Demo: restricted access to allowed data sets for users with different access rights.

https://www.youtube.com/watch?v=gDN_3ktHYuE

Demo: computing (variant calling) in 4 sites with private genomic data, collect data and provide summary of detected mutations.

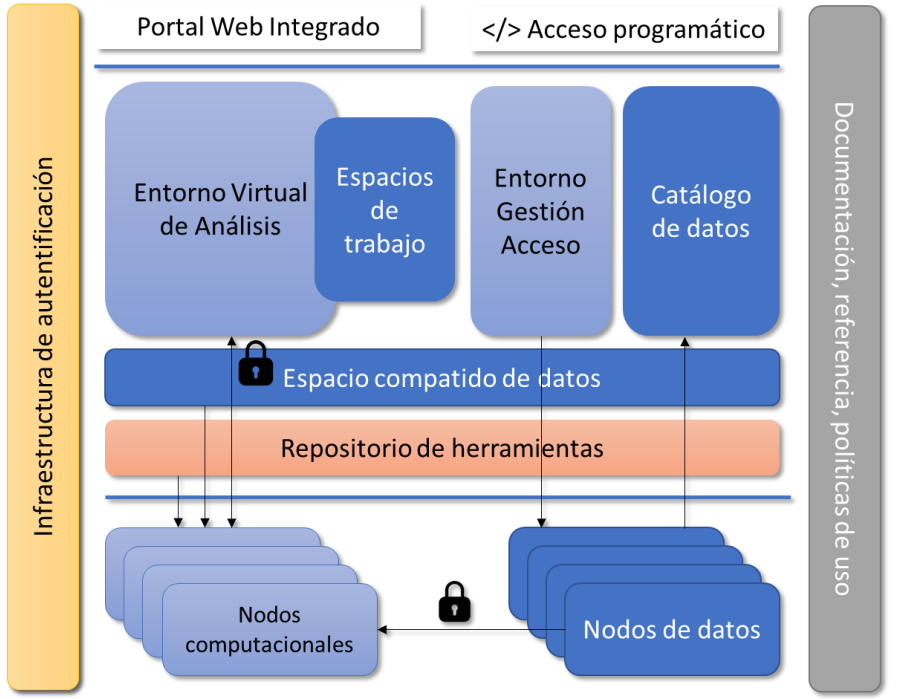
https://www.youtube.com/watch?v=vzb6uUyY-AQ

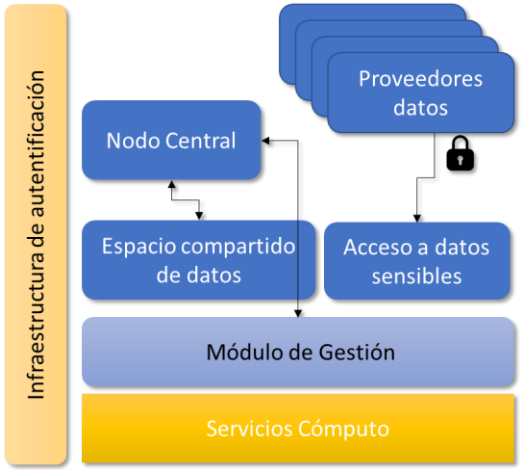
La infraestructura computacional federada

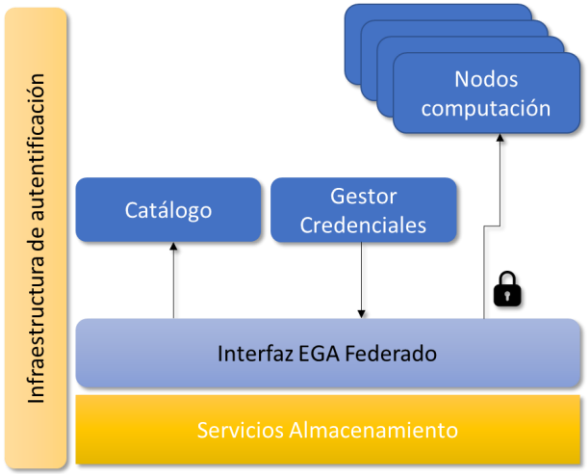
Distributed infrastructure ("IMPaCT-Data cloud")

- Unified computing and data Access control/authentication
- Nodes with different attributions
  - Central Node
    - Single access point users
    - Virtual environment with private workspaces
    - Data server and tools
    - Execution Orchestrator
    - Access credentials management
  - Computational nodes
    - Analysis execution
  - Data nodes
    - Data providers (omics, phenoclinics, etc.

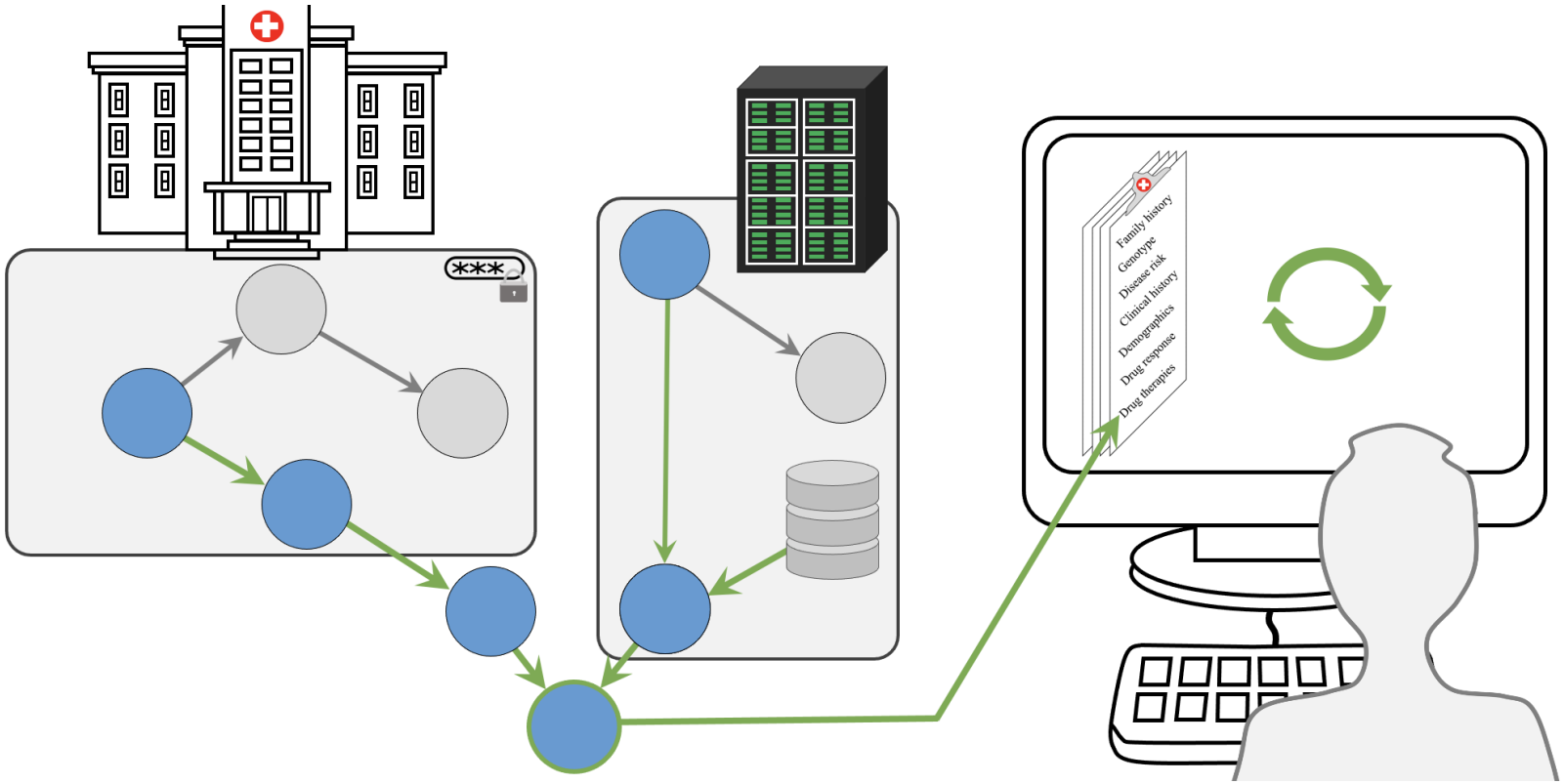
- Management of sensitive data based on the federated EGA model







Transparent acces to normalised and interoperable data and the appropiate compute



PERSPECTIVE

Patient Dossier: Healthcare queries over distributed resources

October 17, 2019

Miguel Vazquez[1,2], Alfonso Valencia[1,3]*

PLOS COMPUTATIONAL BIOLOGY

- **BioMedical Data**
  - **IMPaCT-Data**

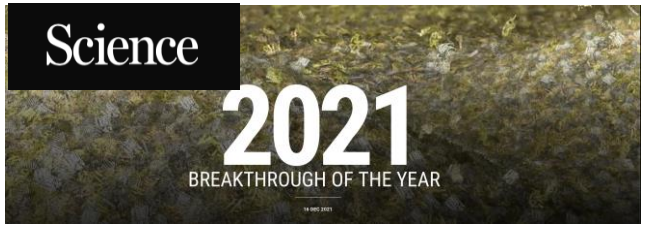
- **AI/ML in Biomedicine**
  - **bioNLP + NLP in Spanish**

- **Digital Twins (Virtual Human Twins)**

- ***Rare Diseases a Computational Approach***

- **Sex and Gender biases in biomedicine and AI**

Predicción de estructura de proteínas.
El mayor logro de la IA – y un cambio paradigmático en ciencia.



Premio Princesa de Asturias de Investigación Científica y Técnica 2022

Geoffrey Hinton, Yann LeCun, Yoshua Bengio y Demis Hassabis

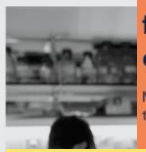
Premio Fronteras del Conocimiento

Demis Hassabis, David Baker y John Jumper.

Stories by DeepMind

Matthew Higgins is unlocking a new path to stop malaria in its tracks

AI is helping Matthew Higgins and his team develop a vaccine that could dismantle the malaria parasite's ability to infect humans, potentially saving hundreds of thousands of lives every year



"We need to help people start fighting osteoporosis before it's even begun"

Melissa Formosa is unlocking new ways to predict and fight the onset of osteoporosis

Unlocking a decade of data to fight antibiotic resistance

Marcelo Sousa and Megan Mitchell solved a ten-year problem in minutes

"For me, AlphaFold is transformative"

Pedro Beltrao is unlocking the secrets of our evolutionary past

BSC Supercomputing Center
Centro Nacional de Supercomputación

"It took me two days to do something that could have taken me years"

Vilde Leipart is helping to protect honeybees

Luigi Vitagliano is paving the way to solving a 60-year-old genetic mystery

His team at the Institute of Biostructure and Bioimaging IBB, in Naples, Italy, are researching how the function of a family of disease-causing proteins has evolved over time

Unlocking the mystery of the demon-duck of doom

Beatrice Demarchi, Josefin Stiller and Matthew Collins solve an eggshell controversy with palaeoproteomics

Unlocking the nuclear pore complex

Pietro Fontana is part of a global effort piecing together one of biology's hardest puzzles

Accelerating the fight ag plastic pollution

John McGeehan and Rosie Graham's breakth with an email

Making AlphaFold's predictions available to scientists around the world

Prof Dame Janet Thornton and Mihaly Varadi are helping transform biology

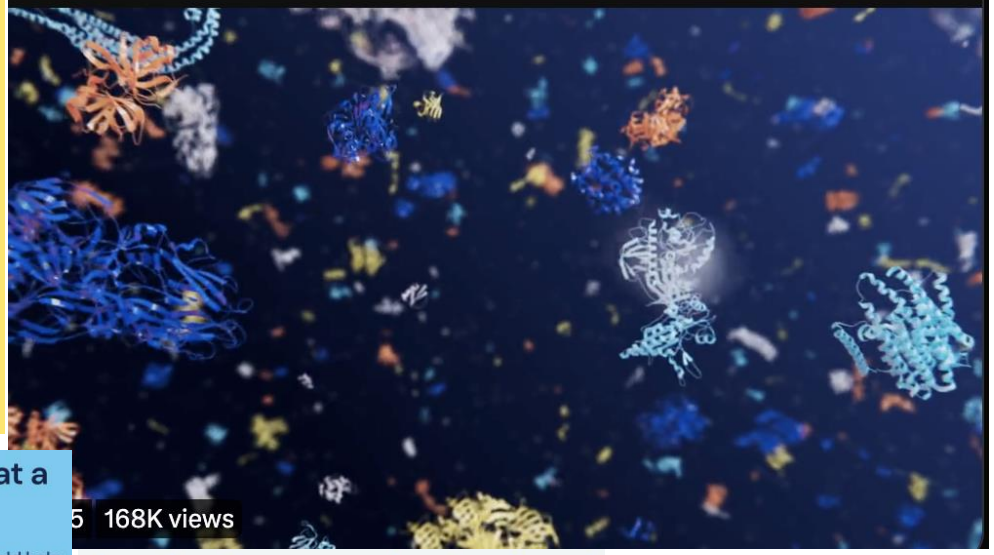
Accelerating the race to treat a deadly parasitic disease

Benjamin Perry is closing in on a treatment that could help millions

Demis Hassabis @demishassabis · Feb 1

Big milestone: 1M+ researchers have now made use of #AlphaFold in their vital work, in the 18 months since we made it freely available.

From antibiotic resistance to crop sustainability, it's been amazing to see the impact of 'Science at Digital Speed': unfolded.deepmind.com/#stories



Accelerating our understanding of early onset Parkinson's

Zhong Yan Gan uncovers crucial insights into the molecular basis of the neurological disorder

"This could accelerate drug discovery in a way that we've never seen before"

Karen Akinsanya is searching for transformative new medicines

AlphaFold has changed the field of structural bioinformatics forever, with immediate implications for biotechnology and drug development.

AlphaFold covers the protein universe >200M proteins

Article

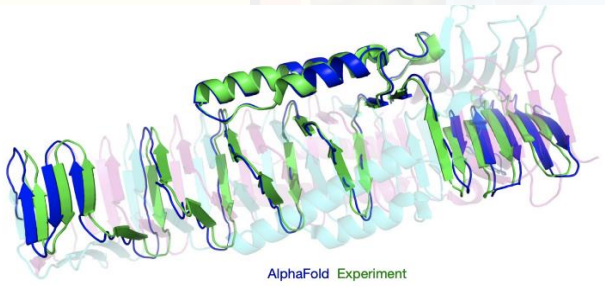
Highly accurate protein structure prediction with AlphaFold

Nature | Vol 596 | 26 August 2021 |

Article

Highly accurate protein structure prediction for the human proteome

Nature | Vol 596 | 26 August 2021



Making AlphaFold's predictions available to scientists around the world

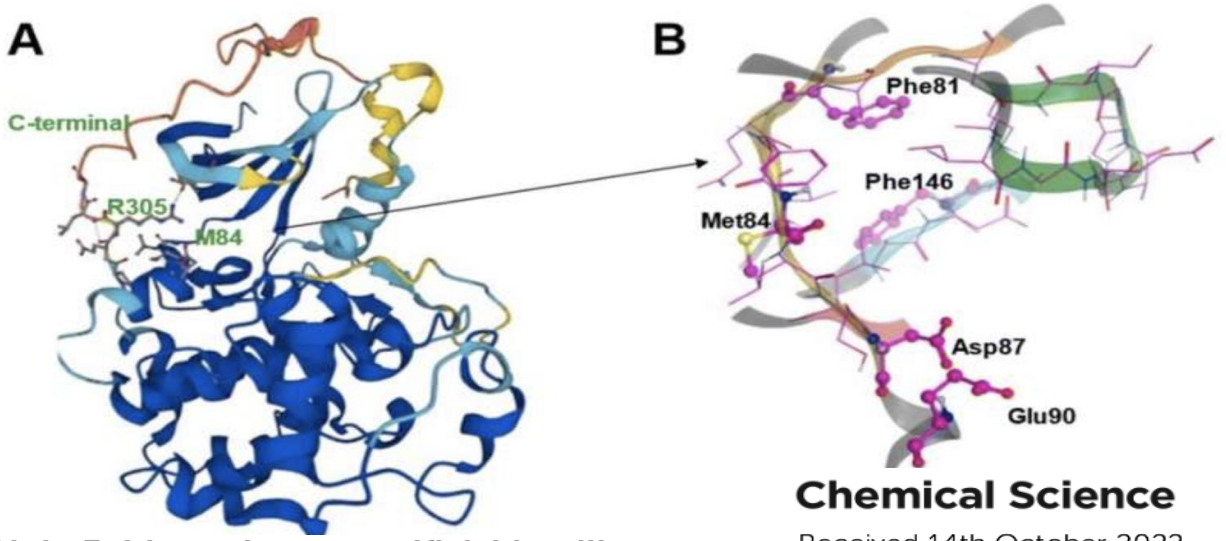
Prof Dame Janet Thornton and Mihaly Varadi are helping transform biology

see the impact of 'Science at Digital Speed':
unfolded.deepmind.com/#stories

JANUARY 19, 2023

New study uses AlphaFold and AI to accelerate design of novel drug for liver cancer

by University of Toronto



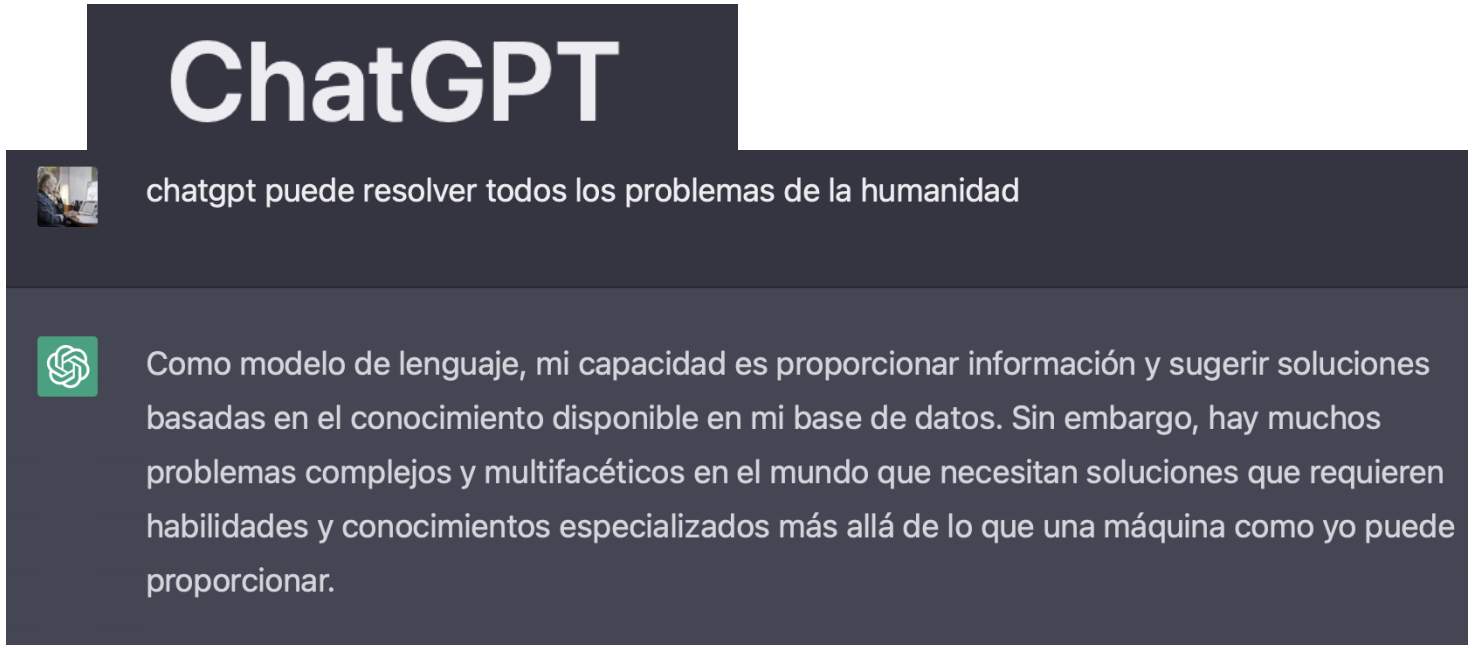
AlphaFold accelerates artificial intelligence powered drug discovery: efficient discovery of a novel CDK20 small molecule inhibitor†

Chemical Science

Received 14th October 2022
Accepted 5th January 2023

DOI: 10.1039/d2sc05709c

ChatGPT. GPT3 - Intelligencia Artificial - Machine Learning



Traducción automàtica	Asistentes de voz	Resumen automático
Sistemas de pregunta respuesta	Extracción de información	Descripción de imatges
Generación de voz y texto	Sistemas conversacionales	Análisis de sentimientos

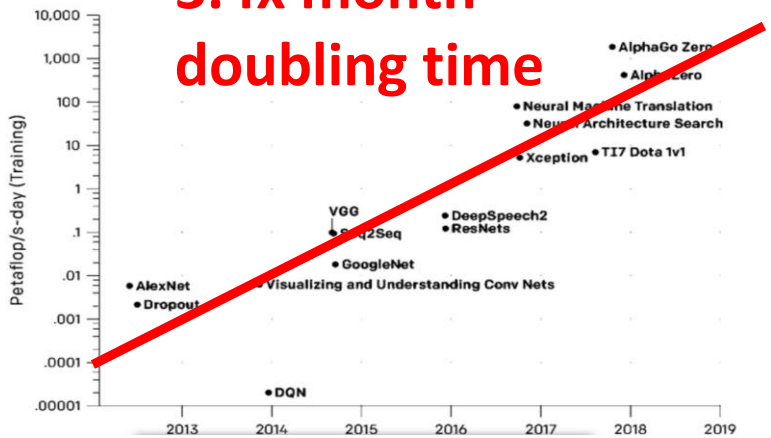
- **MarIA** - Corpus Biblioteca Nacional de España. 120 mM tokens. **GPT-2-large.** *(192 GPUs - 16gb / GPT-2 takes 32*4 GPUs for a weak)*
- **AINA** - Corpus catalán, 1.7 mM tokens. 1st **RoBERTa**

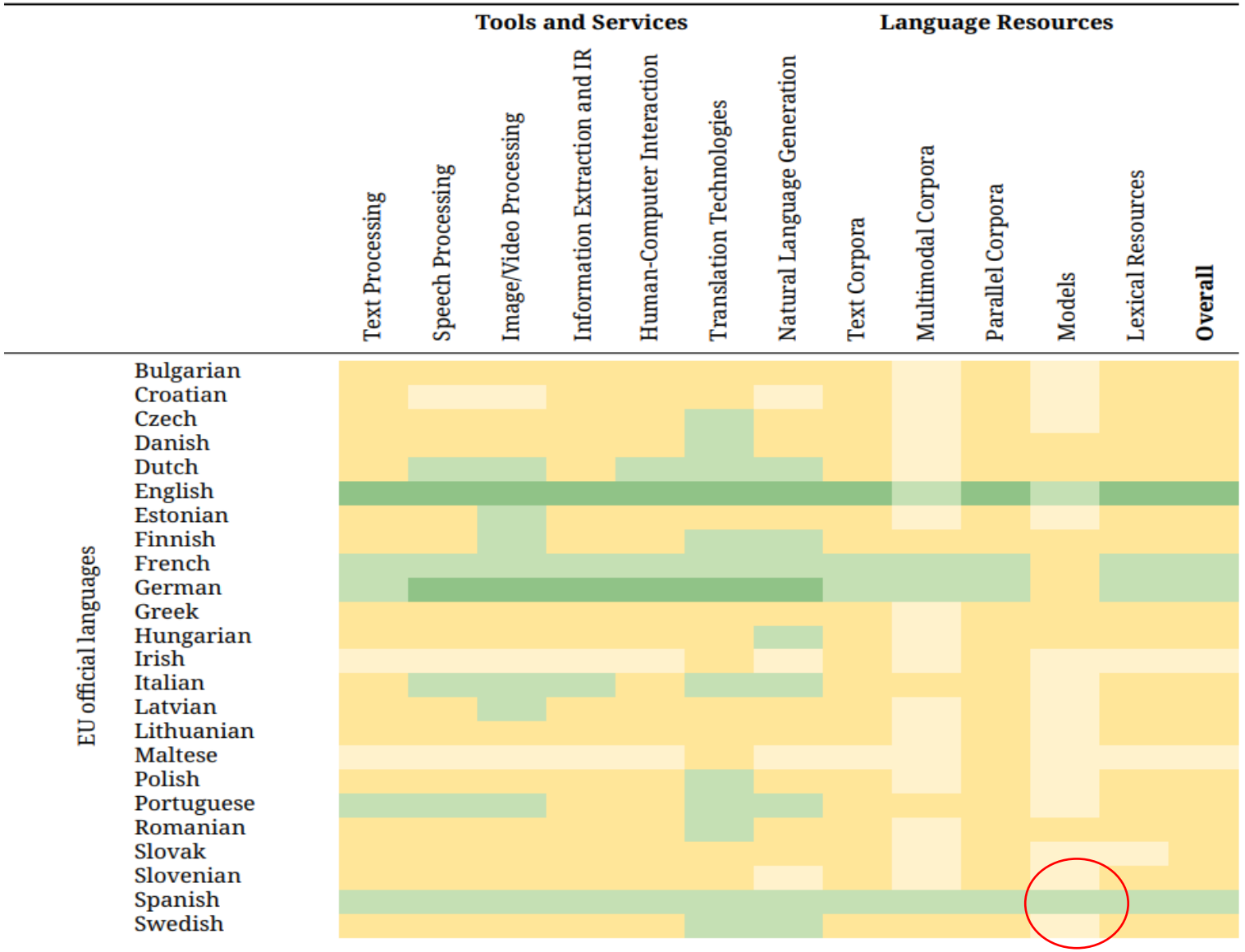
gencat politiquesdigitals.gencat.cat

Europe Needs Language Specific Model

Technological Support for the European Official Languages

3.4x month doubling time





Marta Villegas et al. BSC

La adaptación de los modelos a lengujaes específicos con los expertos de dominio

Plan TL
Plan de Impulso de las Tecnologías del Lenguaje

SECRETARÍA DE ESTADO DE DIGITALIZACIÓN E INTELIGENCIA ARTIFICIAL

CLÍNIC BARCELONA
Hospital Universitari

A **Medical document selection and automatic annotation**

Paciente con fiebre ingresa en neumología *Patient with*

Unannotated Medical Documents

Artificial Intelligence baseline systems

Paciente con fiebre ingresa en neumología

Automatically Annotated Documents

B **Medical Experts correct the automatic annotations**

Automatically Annotated Documents

Multilingual Terminologies

Medical Experts

SCTID: 386661006

Paciente con fiebre ingresa en neumología

"tag a little, train a

Iterative correction of automatic annotations until system is perfected **powered by HPC resources**

use human knowledge automatically → to learn

C **Automatic Annotation of new medical documents**

El paciente con disnea fue colocado en decúbito prono.

Unannotated Medical Document

INPUT

Artificial Intelligence Systems powered by HPC resources

OUTPUT

SCTID: 2670360073

El paciente con disnea fue colocado en decúbito prono.

Record #01		
Affirmed	Negated	Uncertain
fever	dyspnea	COVID-19

Structured medical records

Use Cases

Detecting similar patients

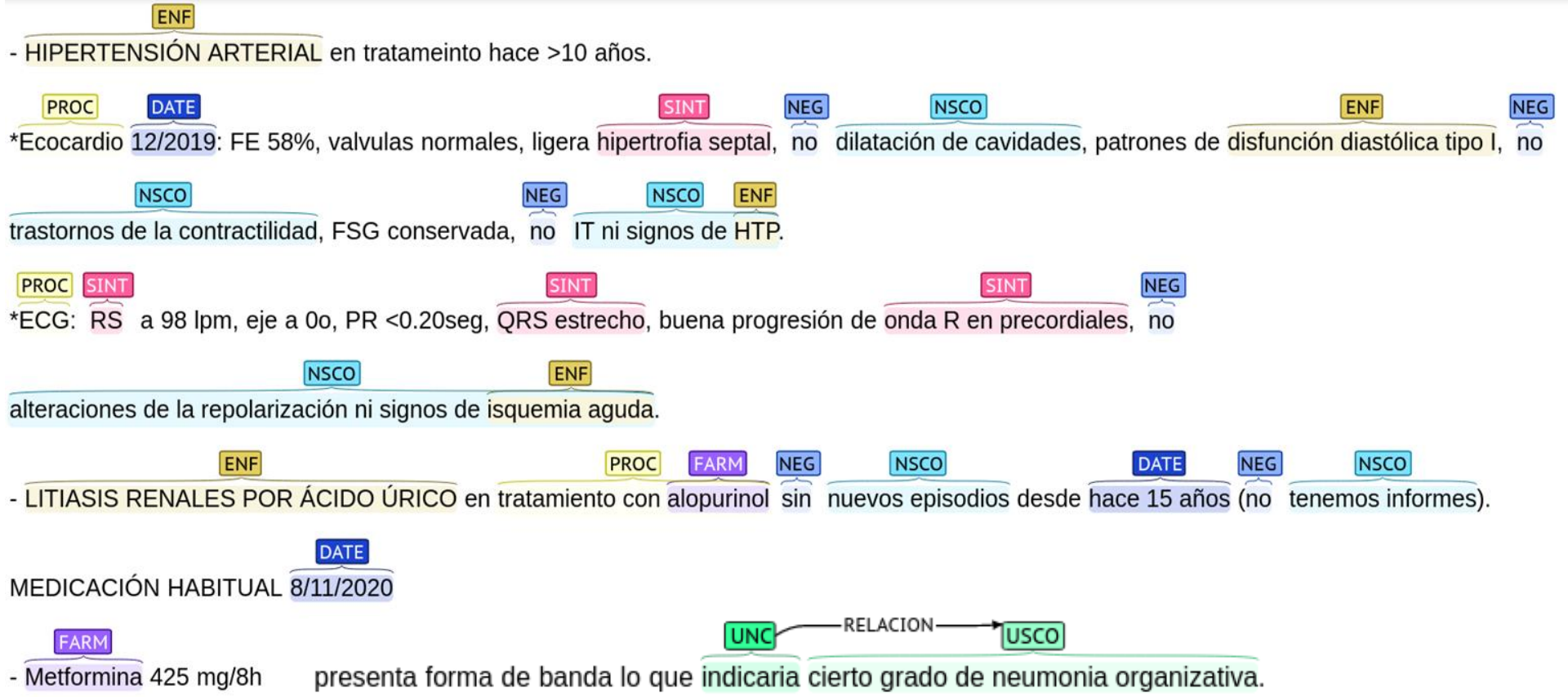
Identifying successful treatments

Doc. indexing - Power complex searches

This graphic has been designed using resources from Freepik.com

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Ejemplo de anotación de un curso clínico del Hospital Clinic



ENTIDADES CLÍNICAS

- **SINT**: Síntoma
- **ENF**: Enfermedad
- **PROC**: Procedimiento
- **FARM**: Fármaco
- **SPECIES**: Organismo Vivo

ENTIDADES TEMPORALIDAD

- **DATE**: Fechas
- **TIME**: Horas
- **DURATION**: Duraciones
- **SET**: Frecuencia

ENTIDADES LINGÜÍSTICAS

- **NEG**: Marcador Negación
- **NSCO**: Alcance Negación
- **UNC**: Marcador Especulación
- **USCO**: Alcance Especulación

Casos Reales Hospital Clinic : anotación curso clínico

Varón de 50 años, transportista de alimentos empaquetados. Exfumador, hipertenso en tratamiento con Enalapril sin otros antecedentes de interés o hábitos tóxicos. Ingresa por cuadro de 4 días de evolución de astenia, hiporexia, dispepsia, cefalea, mialgias, prurito, coluria y acolia. Niega fiebre. Niega consumo de drogas, productos de parafarmacia, setas silvestres o nuevos fármacos. Niega

Presentamos el caso de una mujer de 38 años, sin antecedentes personales ni familiares de interés y de profesión pescadera desde los 17 años. Acude a urgencias por un cuadro de prurito generalizado y lesiones habonosas confluentes por todo el cuerpo, precisando dosis altas de corticoides y antihistamínicos para su cese. Un mes más tarde vuelve a reproducirse idéntica sintomatología, acompañada además en esta ocasión de poliartralgias y rigidez, sobre todo en rodillas y tobillos, con buena respuesta a indometacina. En la anamnesis, la paciente refería

Varón de 53 años, empresario, sin alergias medicamentosas conocidas ni hábitos tóxicos. Acudía a nuestra consulta acompañado por su mujer. Estaba diagnosticado de una miastenia gravis con afectación ocular y bulbar de 20 años de evolución, timectomizado y en tratamiento con azatioprina 100 mg al día y piridostigmina 180 mg al día. No seguía controles rutinarios por parte de Neurología.

23 clases de conceptos

Personas

- PACIENTE-PROFESION
- FAMILIAR-PROFESION
- SANITARIO-PROFESION
- PACIENTE-SITUACION_LABORAL
- FAMILIAR-SITUACION_LABORAL

Conceptos clinicos

- SINTOMA — *symptoms*
- ENFERMEDAD — *diseases*
- FARMACO — *drugs*
- PROCEDIMIENTO — *procedures*
- ORG_VIVO — *living beings*

Modificadores

- NEG NSCO — *negation trigger and scope*
- UNC USCO — *uncertainty trigger and scope*

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

A. Estructuración de datos

JSON

```
{
    "INPUTTEXT": [
        {
            "A-ID": "T1",
            "B-TYPE": "PROCEDIMIENTO",
            "C-START": "576",
            "D-END": "594",
            "E-text": "exploración física",
            "F-snomed": "425044008+129432007+5880005"
        },
        {
            "A-ID": "T2",
            "B-TYPE": "PROCEDIMIENTO",
            "C-START": "643",
            "D-END": "668",
            "E-text": "auscultación respiratoria",
            "F-snomed": "NIL"
        },
```

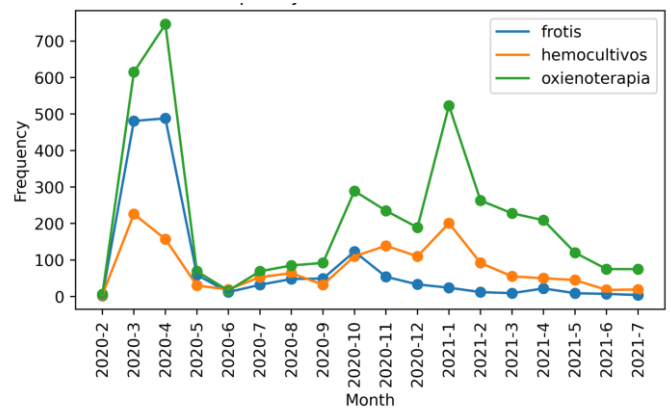
CSV

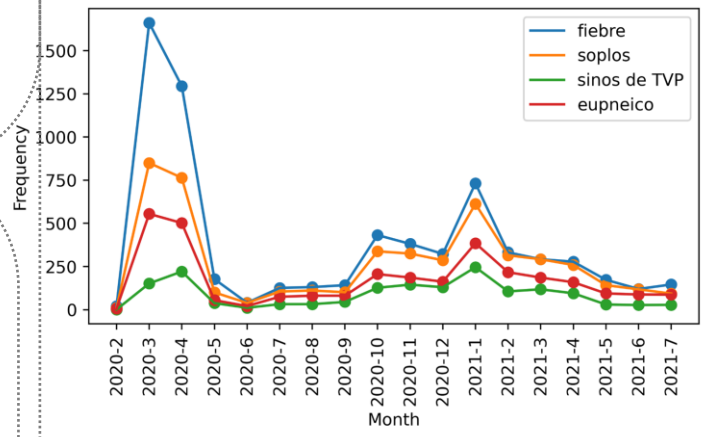
```
ID,TYPE,START,END,TEXT,SNOMED
T1,PROCEDIMIENTO,576,594,exploración física,425044008+129432007+5880005
T2,PROCEDIMIENTO,643,668,auscultación respiratoria,NIL
T3,PROCEDIMIENTO,843,861,electrocardiograma,29303009
T4,PROCEDIMIENTO,947,967,radiografía de tórax,55587003
T5,PROCEDIMIENTO,1099,1118,frotis nasofaríngeo,NIL
T6,PROCEDIMIENTO,1541,1556,ecocardiografía,40701008
T7,PROCEDIMIENTO,2035,2050,coronariografía,NIL
```

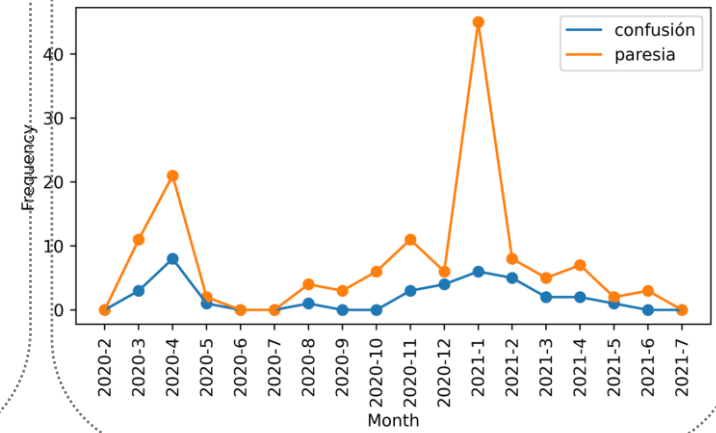
TSV

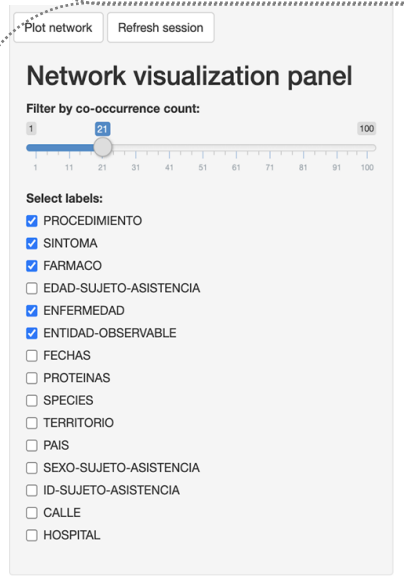
ID	TYPE	START	END	TEXT	SNOMED
T1	PROCEDIMIENTO	576	594	exploración física	425044008+129432007+5880005
T2	PROCEDIMIENTO	643	668	auscultación respiratoria	NIL
T3	PROCEDIMIENTO	843	861	electrocardiograma	29303009
T4	PROCEDIMIENTO	947	967	radiografía de tórax	55587003
T5	PROCEDIMIENTO	1099	1118	frotis nasofaríngeo	NIL
T6	PROCEDIMIENTO	1541	1556	ecocardiografía	40701008
T7	PROCEDIMIENTO	2035	2050	coronariografía	NIL
T8	PROCEDIMIENTO	2150	2176	de un catéter de Swan-Ganz	NIL
T9	PROCEDIMIENTO	2284	2310	reanimación cardiopulmonar	89666000
T10	PROCEDIMIENTO	2312	2340	pericardiocentesis emergente	NIL

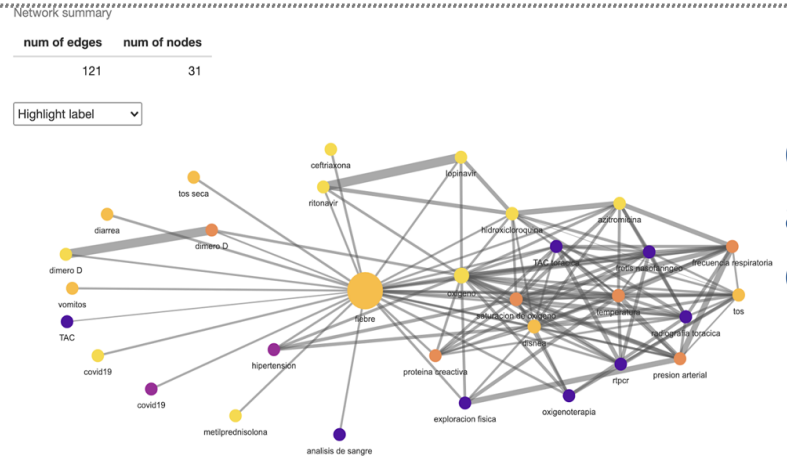
B. Timeline/panel de control











C. Red de conocimiento, análisis de datos, grafo de relaciones clínicas

Co-occurrence | Node ranking | Communities

word1	word2	count word1	count word 2	count of co-occurrences	PMI
lopinavir	ritonavir	38	40	38	2.32
dimero D (entidad-observable)	dimero D (farmaco)	38	29	27	2.29
frecuencia respiratoria	presion arterial	50	52	33	1.34
exploracion fisica	presion arterial	43	52	25	1.16
azitromicina	hidroxicloroquina (farmaco)	47	69	35	1.11
frecuencia respiratoria	temperatura	50	74	36	0.96

- **BioMedical Data**
  - **IMPaCT-Data**

- **AI/ML in Biomedicine**
  - **bioNLP + NLP in Spanish**

- **Digital Twins (Virtual Human Twins)**

- ***Rare Diseases a Computational Approach***

- **Sex and Gender biases in biomedicine and AI**

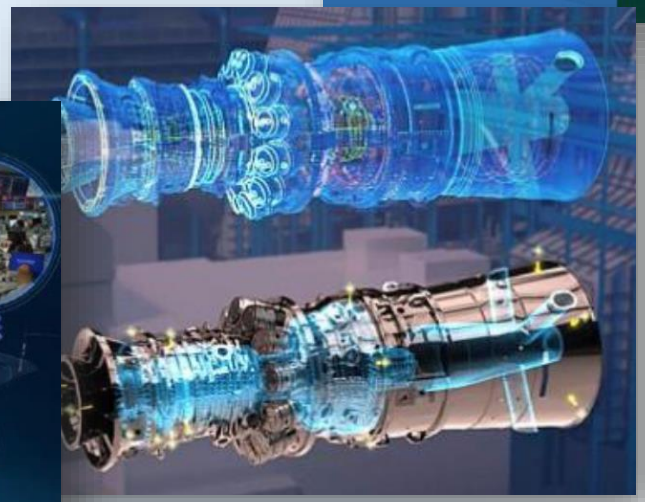
Digital twins

HORIZON
The EU Research & Innovation Magazine

INDUSTRY SCIENCE IN SOCIETY ICT

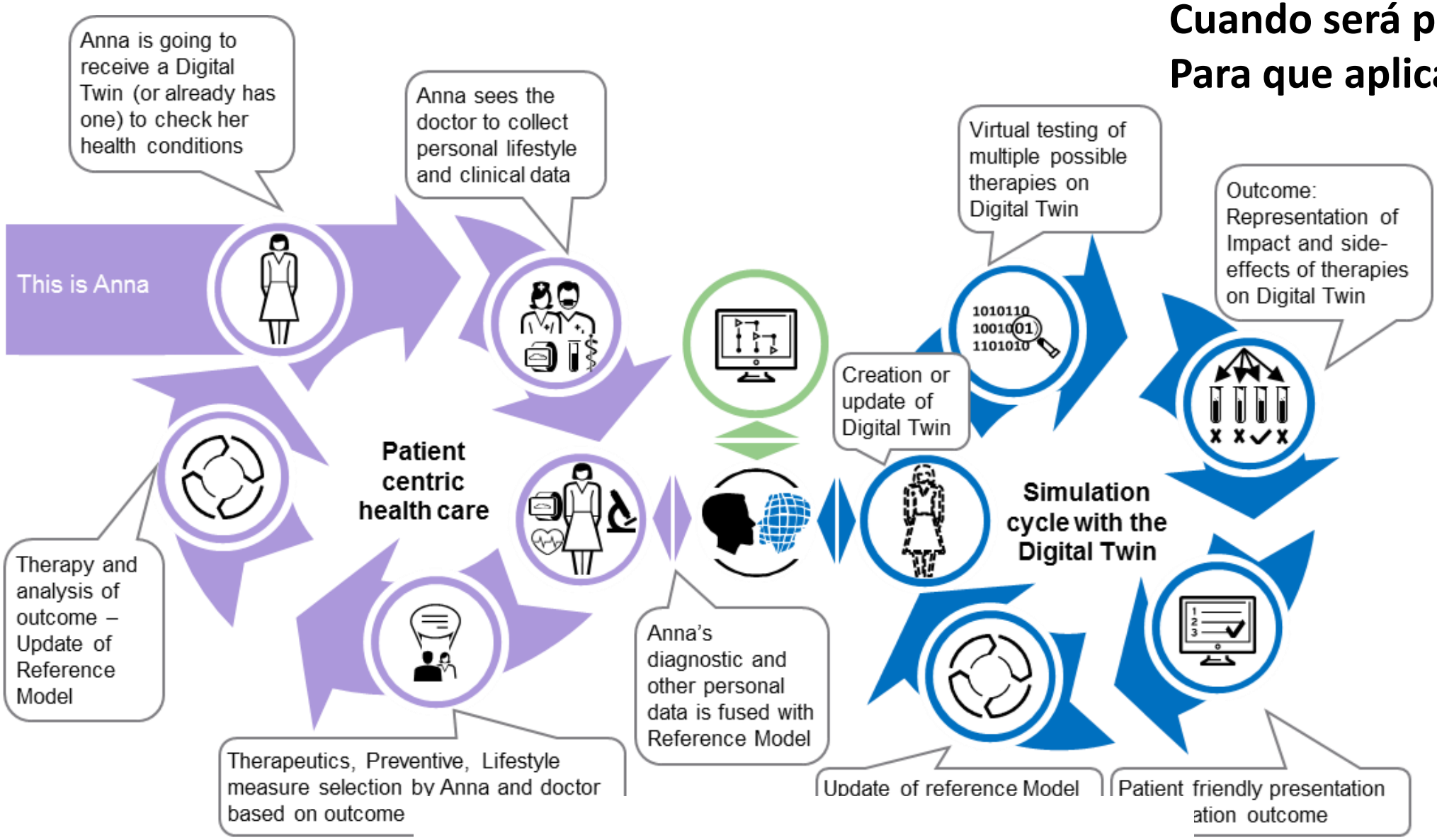
How digital 'twins' are guiding the future of maintenance and manufacturing

15 November 2019



Gemelos Digitales para la Medicina del Futuro

Cuando será posible?
Para que aplicaciones?



Simulations & FDA

FDA U.S. FOOD & DRUG ADMINISTRATION

Model-Informed Drug Development Paired Meeting Program

Congress Approves Landmark Measure to Reduce Animal Testing

FDA Modernization Act promises to spare animals, bring safer and better treatments to patients, and drive down drug prices

December 23, 2022 18:48 ET | Source: Animal Wellness Action

fda.gov
https://www.fda.gov › drugs › mo... · Traducir esta página

Model-Informed Drug Development Paired Meeting Program

31 oct 2022 — Provide an opportunity for **drug** developers and **FDA** to discuss the application of MIDD approaches to the development and regulatory evaluation of ...

What is the FDA Modernization Act 2.0, and what does it mean?

The U.S. Food and Drug Administration (FDA) are the federal agency tasked with approving new drugs for use within the United States (U.S.). On the 29th of September 2022 the U.S. Senate unanimously passed Bill S. 5002, the "FDA Modernization Act 2.0." On Dec 23rd 2022, the U.S. House gave its **final approval**. This has subsequently been signed into law by President Biden. In this landmark measure, the Federal Food, Drug, and Cosmetic Act dating back to 1938 will now be updated to reflect the advances of modern science. But why is this such a big deal?

GATC Health Welcomes the FDA Modernization Act 2.0, Allowing New Drug Candidates to Bypass Animal Testing Using Computer Modeling

NEWS PROVIDED BY
GATC Health Corp →
Jan 25, 2023, 09:55 ET

IC sees expanding role for computational modeling and ulation in med tech

...McCarty Jan. 31, 2023

Computational modeling and simulation (CM&S) isn't the new flavor of the month in the medical device industry, but it hasn't exactly achieved the status of a buzzword, either. However, the Medical Device Innovation Consortium (MDIC) has published a report which makes clear that these software tools are continuing to open new frontiers in device development, a trend that seems certain to continue to expand in the decades ahead as to-market costs continue to grow.

February 14, 2023

Medical Device Computational Modeling and Simulation Reports Highlights Best Uses and Barriers to Adoption

By MedTech Intelligence Staff

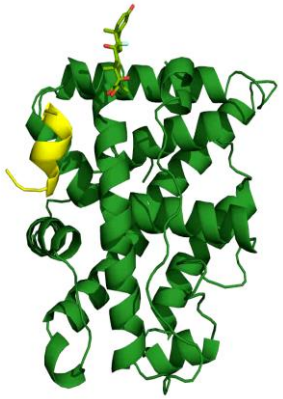
No Comments

MDIC MEDICAL DEVICE INNOVATION CONSORTIUM

"This report validates the broad applicability—and true value—of computational modeling and simulation as a critical engineering discipline. Tangible cost, quality and performance improvements are being realized by the early adopters."

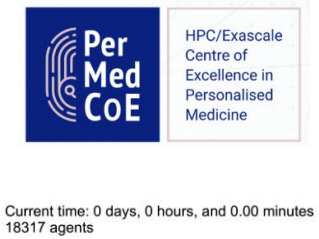
Towards a Human Digital Twin

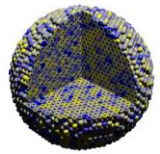
Simulations from molecules, to cells, to organs …



By Victor Guallar ICREA & BSC

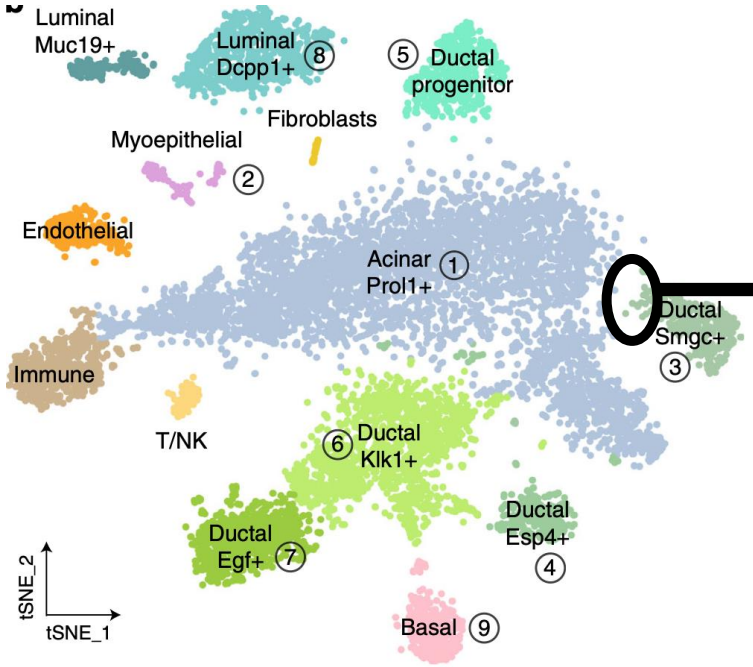
By Mariano Vazquez, CASE - BSC

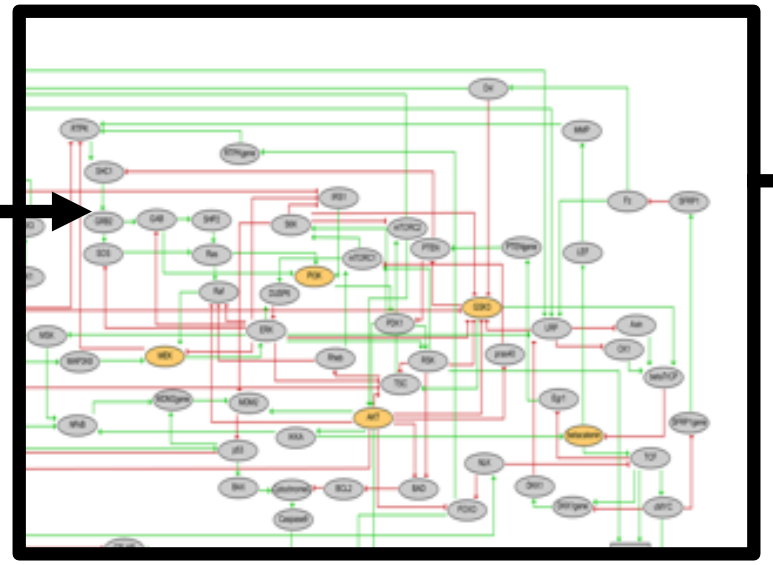


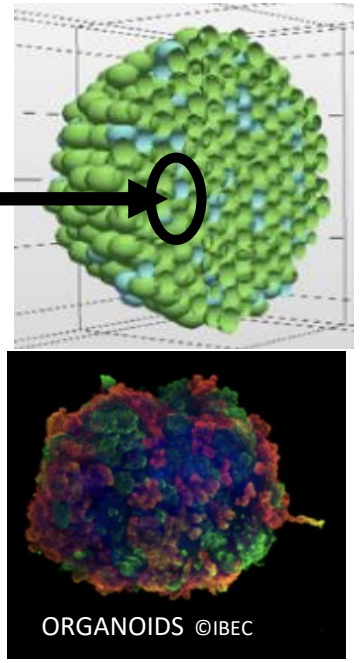


By Arnau Montagud
MABOSS Cell Modellng Framework
Col Physicell by P Macklin, Indiana U

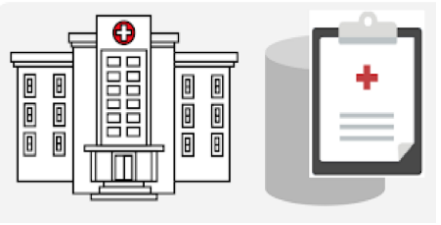
Introducing simulations in the genomic world







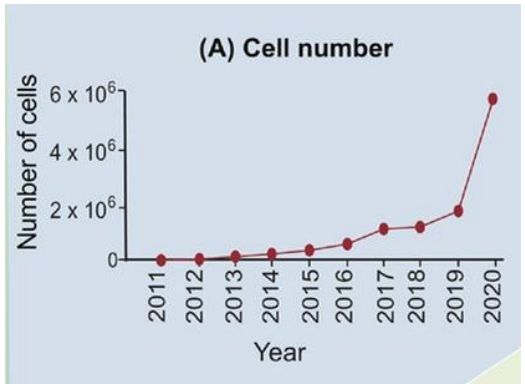
End Users Communities

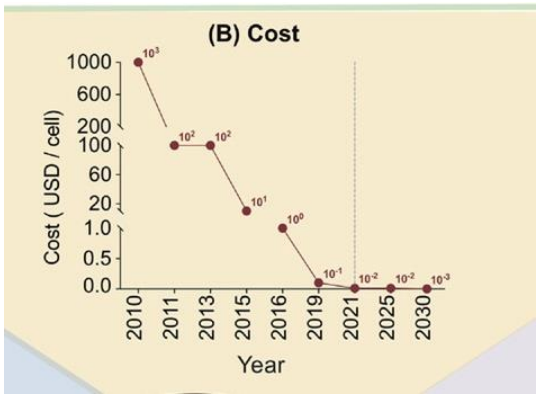


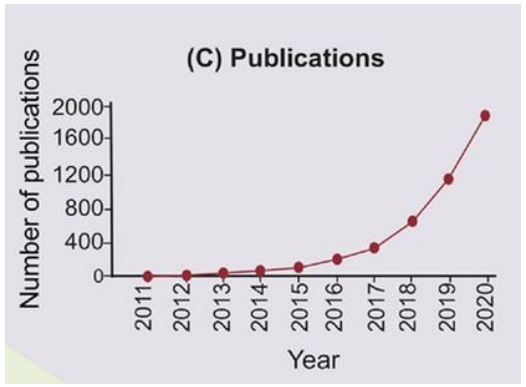
HUMAN CELL ATLAS

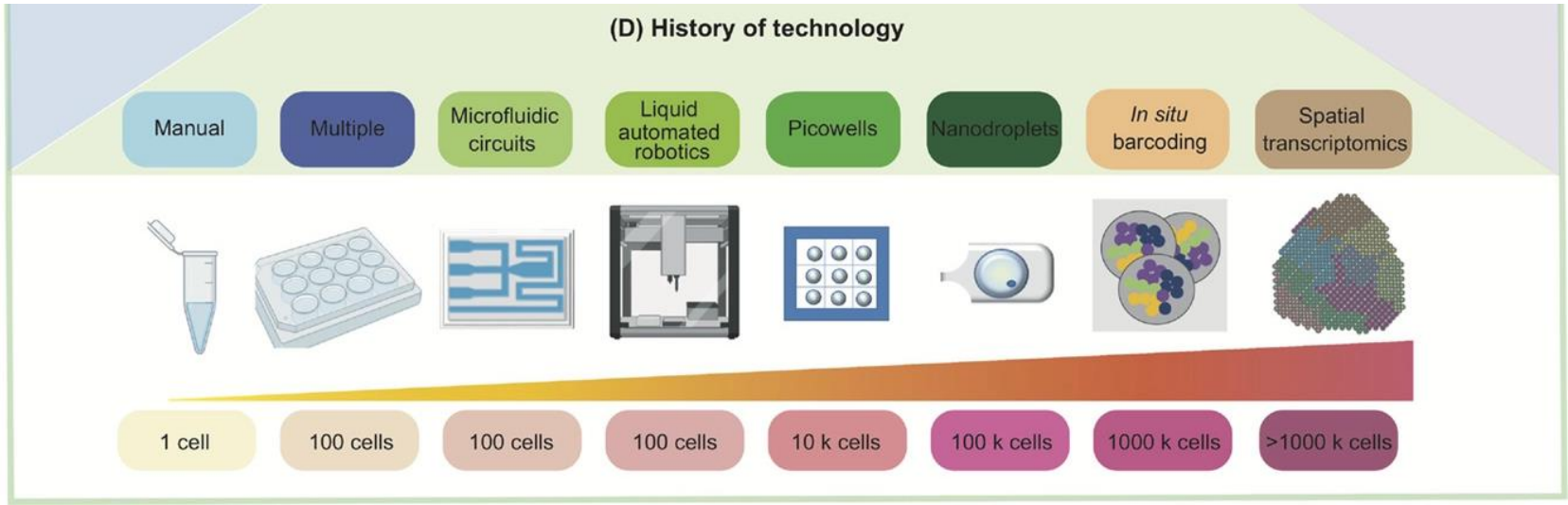
”Reemplazar la generación actual de métodos bioinformáticos con modelos celulares, proporcionando descripciones mecanicistas e hipótesis comprobables, en lugar de las actuales aproximaciones estadísticas y descripciones intuitivas”

From Bulk to Single-cell sequencing



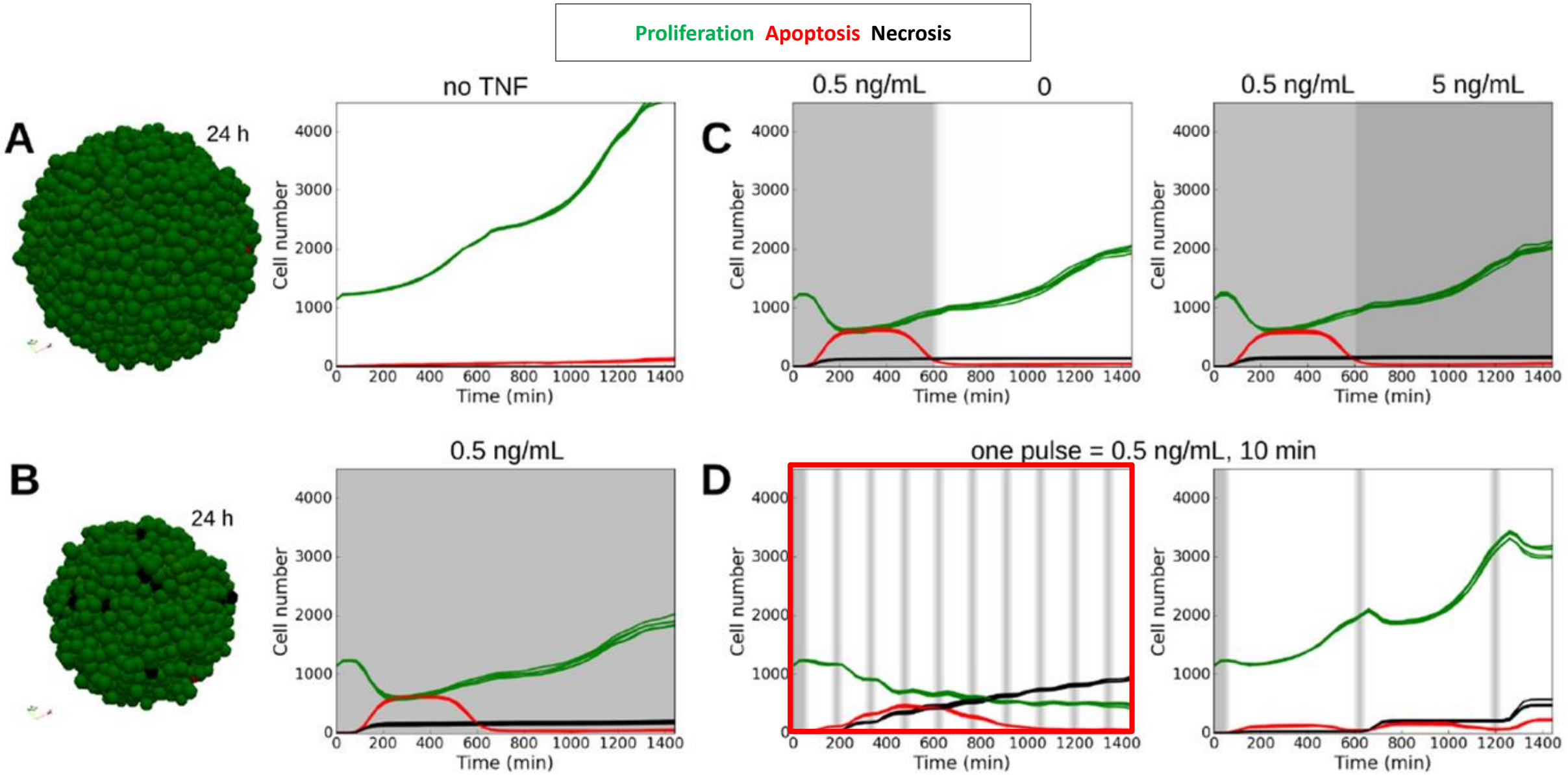






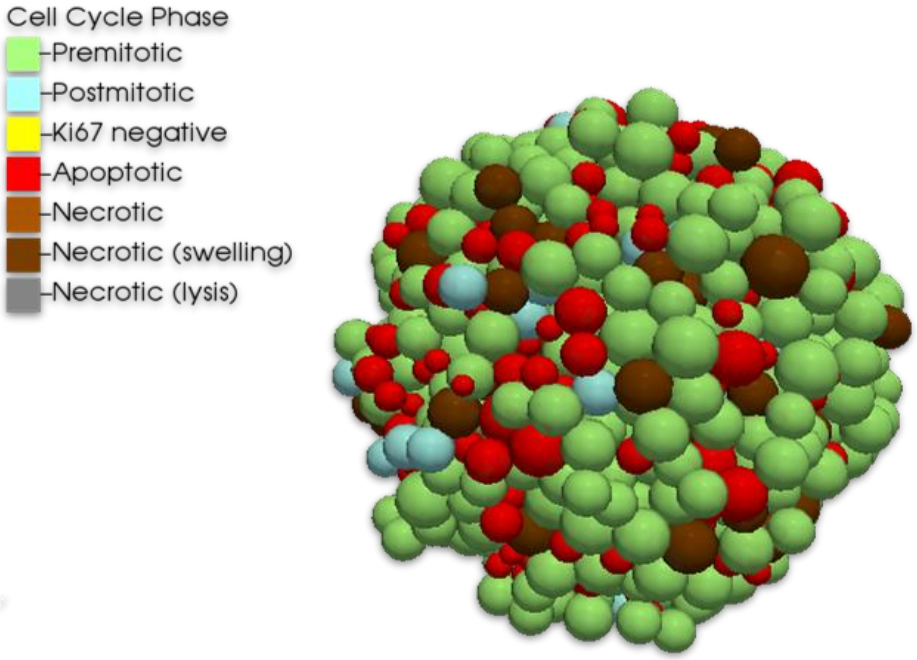
Jovic D et al. Single-cell RNA sequencing technologies and applications: A brief overview. Clin Transl Med. 2022 Mar;12(3):e694

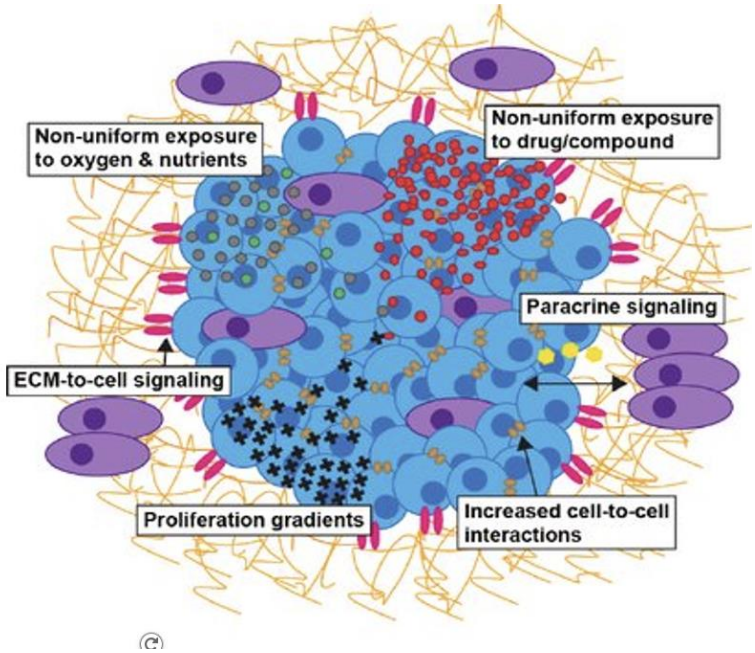
Agent-based with probabilistic logical model allows for finding optimal drug regimes



Letort et al., *Bioinformatics*, 2018, bty766

Simulaciones de tumores & microambiente – tumores simulados NO SON como tumores reales …pero pueden ser útiles





La historia elabora un concepto encontrado en *Silvia y Bruno* de Lewis Carroll: un mapa ficticio que tenía una escala de "una milla por milla". Uno de los personajes en la historia de Carroll hace notar varias de las dificultades prácticas con el mapa y asegura que "ahora usamos el país mismo como su propio mapa, y [le] aseguro que funciona casi igual de bien".

La historia de Borges, citada ficcionalmente como de "Suárez Miranda, Viajes de varones prudentes, Libro IV, cap. XLV, Lérida, 1658", imagina un imperio en el que la ciencia de la cartografía se vuelve tan exacta que sólo un mapa a escala del imperio mismo será suficiente: "las Generaciones Siguientes entendieron que ese dilatado Mapa era inútil y no sin impiedad lo entregaron a las inclemencias del Sol y los Inviernos. En los desiertos del Oeste perduran despedazadas Ruinas del Mapa, habitadas por Animales y por Mendigos".[1]

Inteligencia Artificial y Simulaciones Dinámicas

IA>SM Exploración Espacio de parámetros

SM>IA Generar datos para entrenar modelos de ML

IA>SM Predecir el curso de las simulaciones

SM>IA Interpretar en términos mecanísticos los resultados de AI

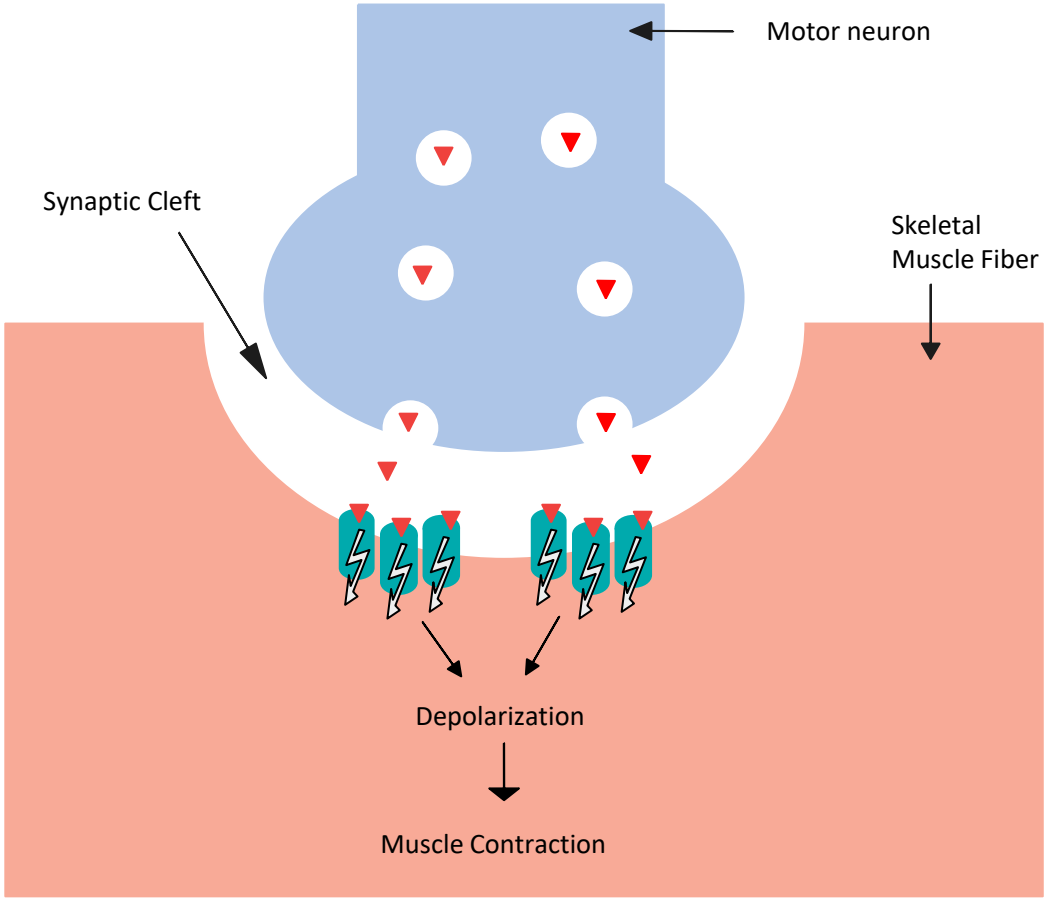
IA>SM Analizar los grandes conjuntos de resultados de las simulaciones

SM>IA Inteligencia artificial informada con leyes físicas

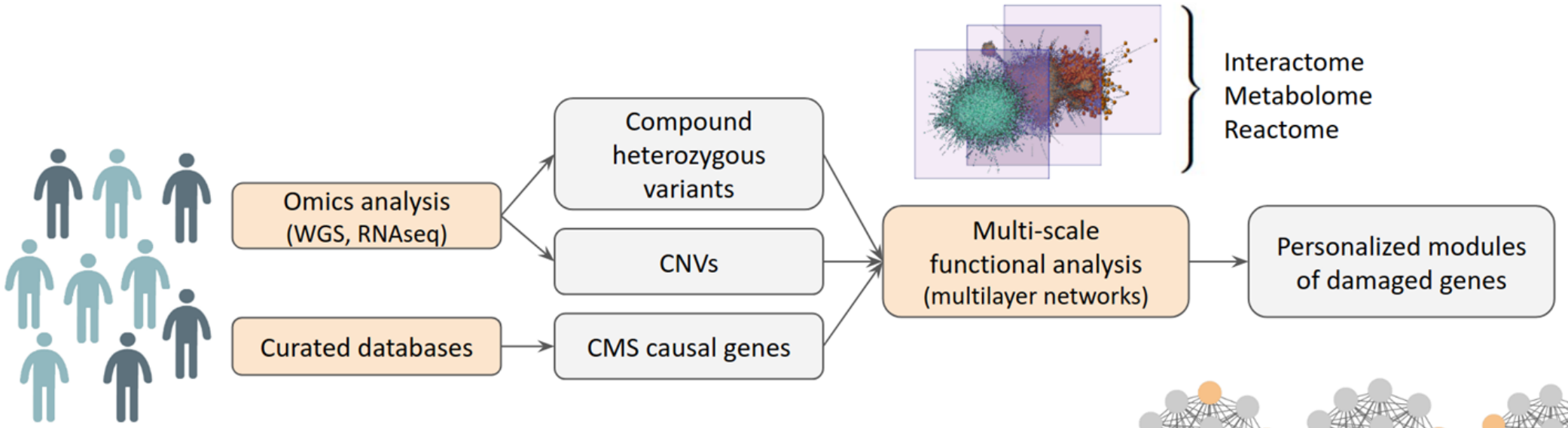
<> Modelos mixtos AI/Simulación

- **BioMedical Data**
  - **IMPaCT-Data**
- **AI/ML in Biomedicine**
  - **bioNLP + NLP in Spanish**
- **Digital Twins (Virtual Human Twins)**
- ***Rare Diseases a Computational Approach***
- **Sex and Gender biases in biomedicine and AI**

Congenital myasthenic syndrome project

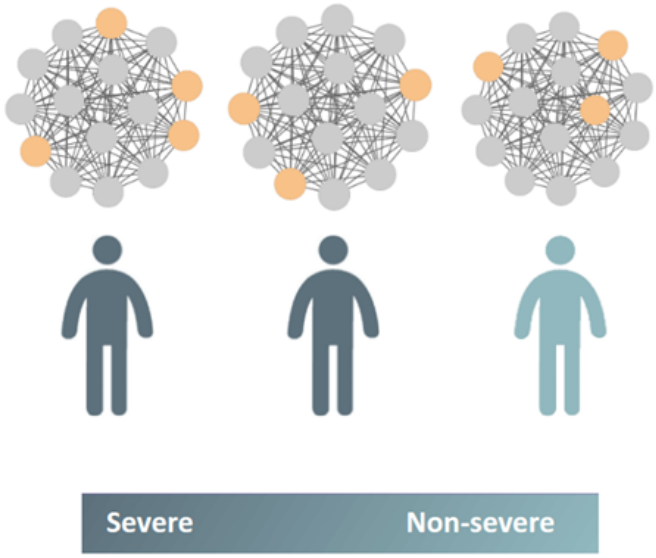


A Personalized medicine approach

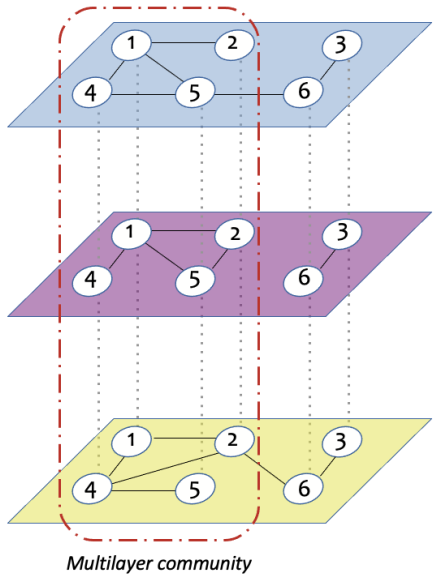


Cohort Characteristics
20 patients:
8 severe
12 non-severe

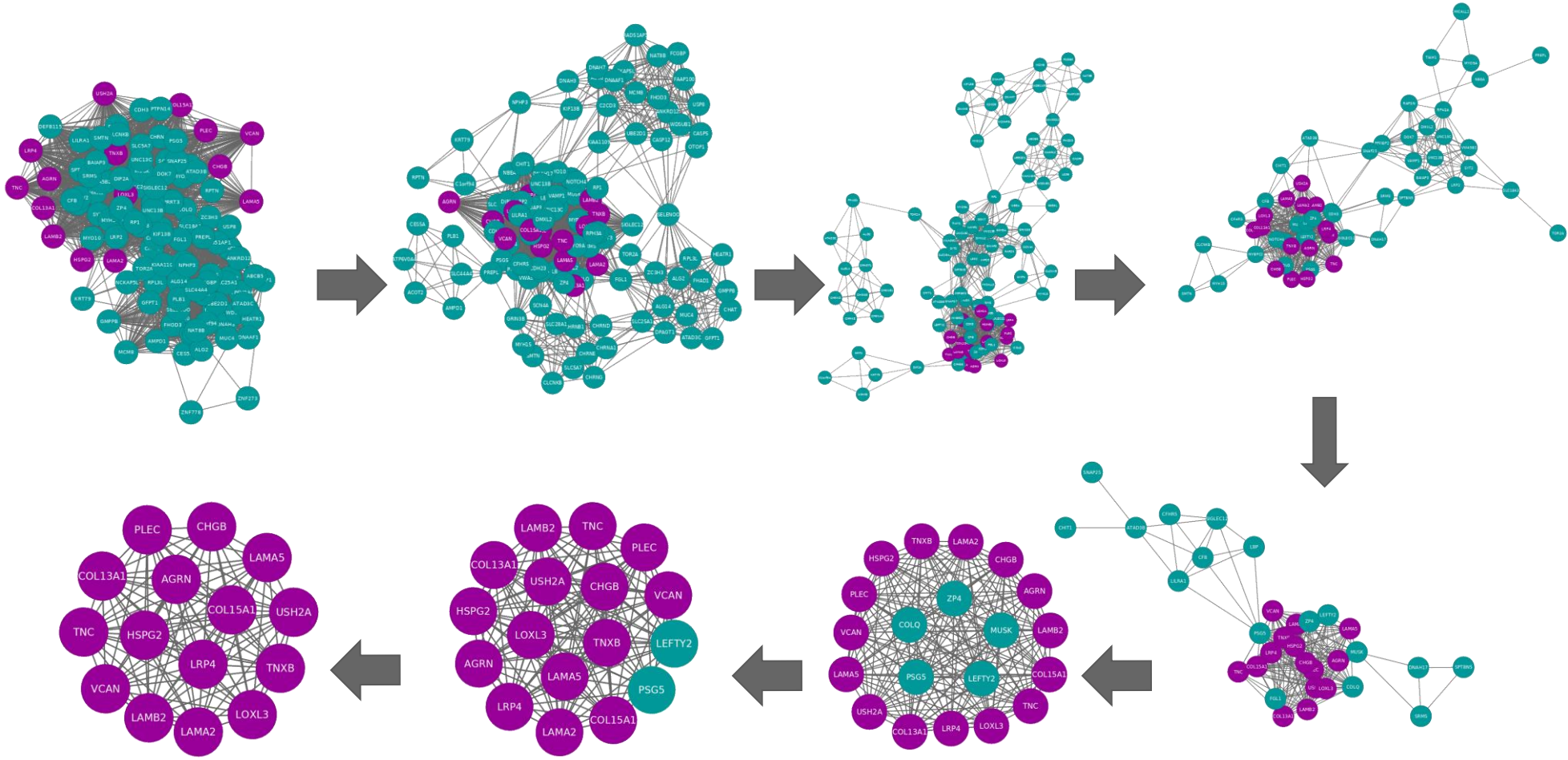
Same causal homozygous mutation in the CHRNE gene (CHRNE c.1327delG)



Severity in Congenital Myasthenic Syndromes



Multilayer community



Algorithm clustering in multilayers networks

Nuñez et al. (in preparation)

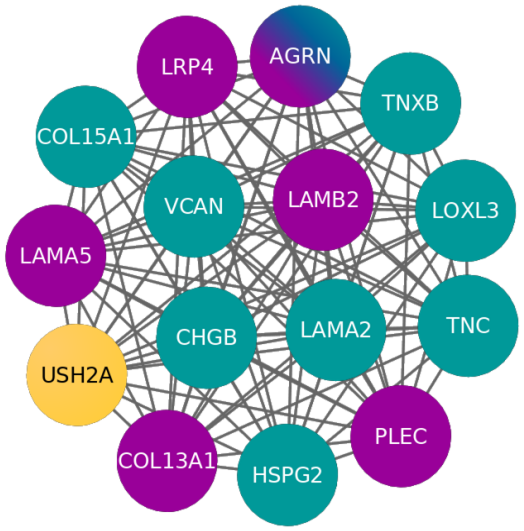
Severe and non-severe communities have different actors and functions

Compound heterozygous variants

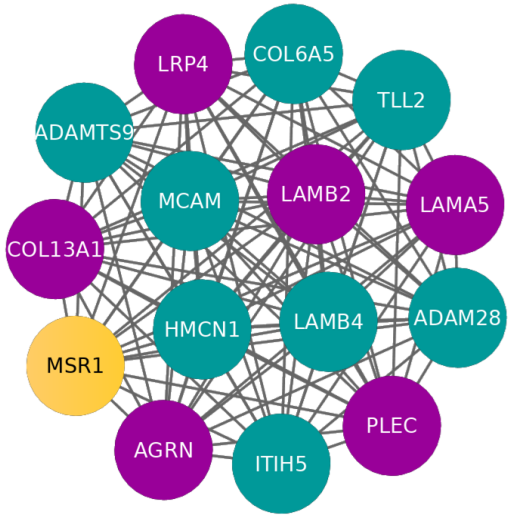
Copy number variants

Known CMS gene

Severe



Non-severe



Activity localization	Class	CMS causal gene	Phenotype group		Function	Synaptic localization (Manual curation)	Localization (UniProt)
			Not-severe	Severe			
ECM (ECM)	Proteoglycans	AGRN	-	AGRN	Cell hydration and growth factor trapping	Pre- and post-synaptic (PMID:29462312)	Synaptic basal lamina / ECM
		-	-	HSPG2		Basement membrane (PMID:30453502)	Basement membrane / ECM
		-	-	VCAN		ECM (PMID: 29211034)	ECM
		-	-	COL15A1		Basement membrane (PMID:26937007)	ECM
	Collagens	COL13A1	-	-	Structural support	Basement membrane, post-synaptic (PMID:30768864)	Post-synaptic cell membrane
		-	COL6A5	-		Basement membrane (PMID:23869615)	Extracelullar matrix
	Laminins	LAMA5	-	-	Web-like structures	Pre-synaptic (PMID:28544784)	Basement membrane / ECM
		LAMB2	-	-		Basement mebrane (PMID:27614294)	Basement membrane / ECM / Synaptic cleft
		-	LAMB4	-		Myenteric plexus basement membrane (PMID:28595269)	Basement membrane / ECM
		-	-	LAMA2		Pre-synaptic (PMID: 9396756)	Basement membrane / ECM
		-	-	USH2A		Neuronal projection of stereocilia (PMID:19023448)	Stereocillium membrane / Secreted (Extracelullar region)
	Fibulins	-	HMCN1	-	Scaffolding	Glomerular Extracelullar matrix (PMID:29488390)	Basement membrane / ECM
	Tenascins	-	-	TNC	Anti-adhesion	Basement membrane (PMID:29466693)	ECM / Perisynaptic ECM (Ensembl)
				TNXB		Basement membrane (PMID:23768946)	ECM
	Enzymes	-	-	LOXL3	Collagen assembly	Basement membrane (PMID:26954549)	Secreted (extracellular region)
			ADAMTS9	-	Proteoglycan cleavage	Secreted to ECM (PMID:30626608)	ECM
			ADAM28			ECM (PMID:24613731)	Cell membrane / Secreted (extracellular region)
	Neuropeptides	-	-	CHGB	Regulatory peptides precursor	Pre- and post-synaptic (PMID:7526287)	Secreted (extracellular region)
	Others	-	ITIH5	-	Hyaluronic acid binding	ECM (PMID:27143355)	Secreted (extracellular region)
Cell surface	Receptors	-	MSR1	-	Proteoglycan and collagen binding	Macrophage surface Scavenger Receptor (PMID:12488451)	Plasma membrane
			MCAM			Plasma membrane (PMID:28923978)	Plasma membrane
		LRP4	-	-	Laminin binding	Post-synaptic (PMID:25319686)	Post-synaptic cell membrane
Cytoplasm	Cytoskeleton	PLEC	-	-	Structural support	Post-synaptic (PMID:20624679)	Post-synaptic cytoskeleton

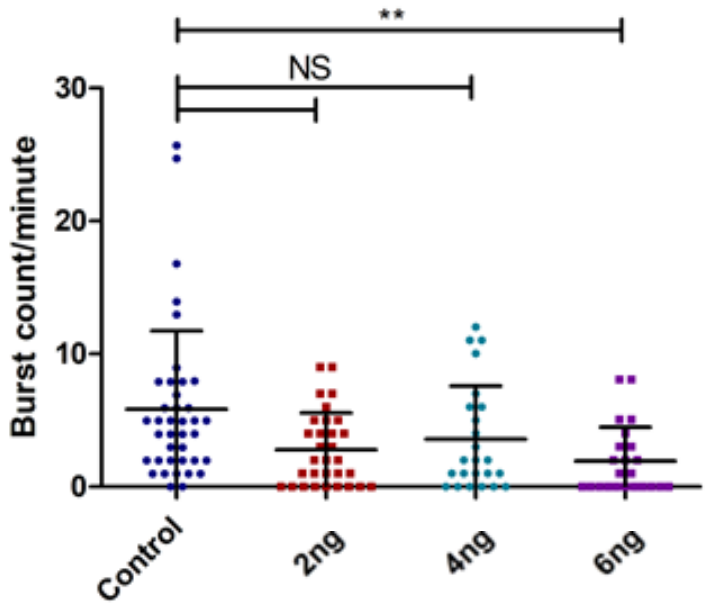
Slide from D. Cirillo, BSC

CHEO RESEARCH INSTITUTE
INSTITUT DE RECHERCHE

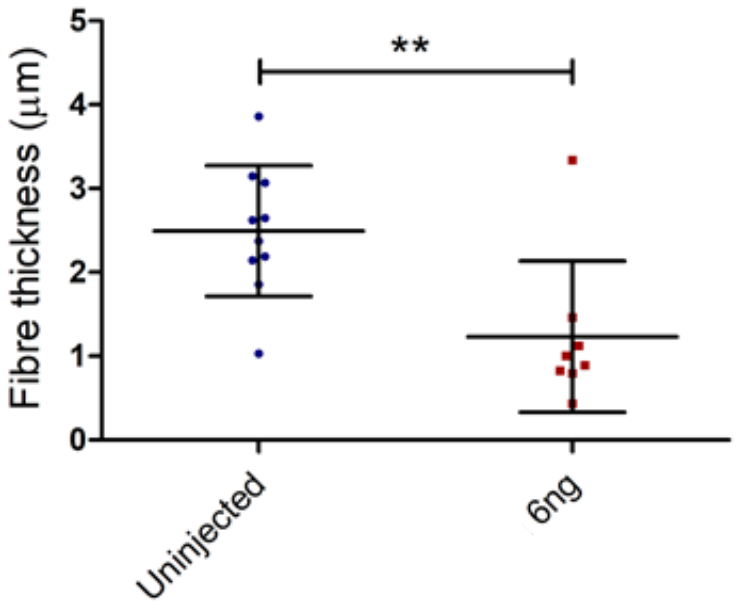
RD Connect

Lochmüller's lab, Ottawa

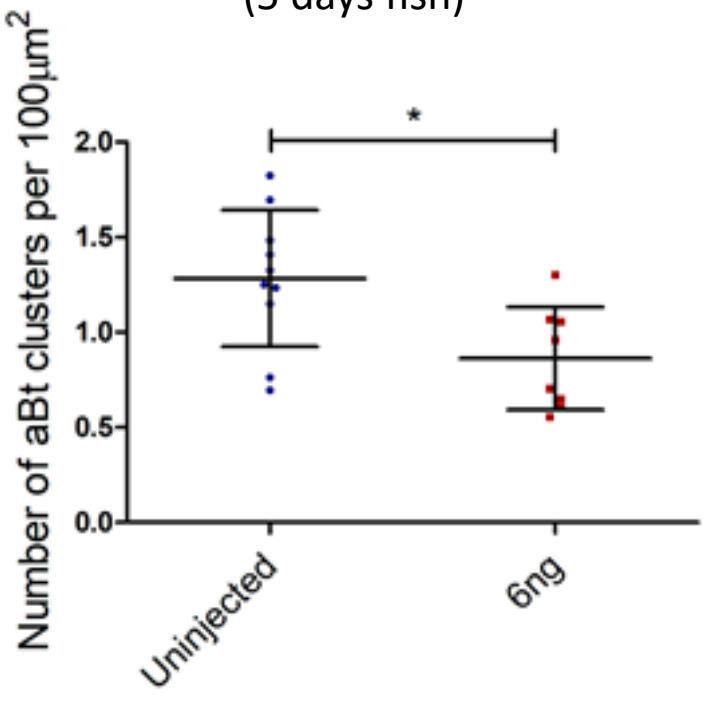
Decreased chorion movement
(1 day post fertilisation)



Decreased muscle fibre thickness
(5 days fish)



Decreased number of AChR clusters
(5 days fish)



Data Aggregation and Interpretation

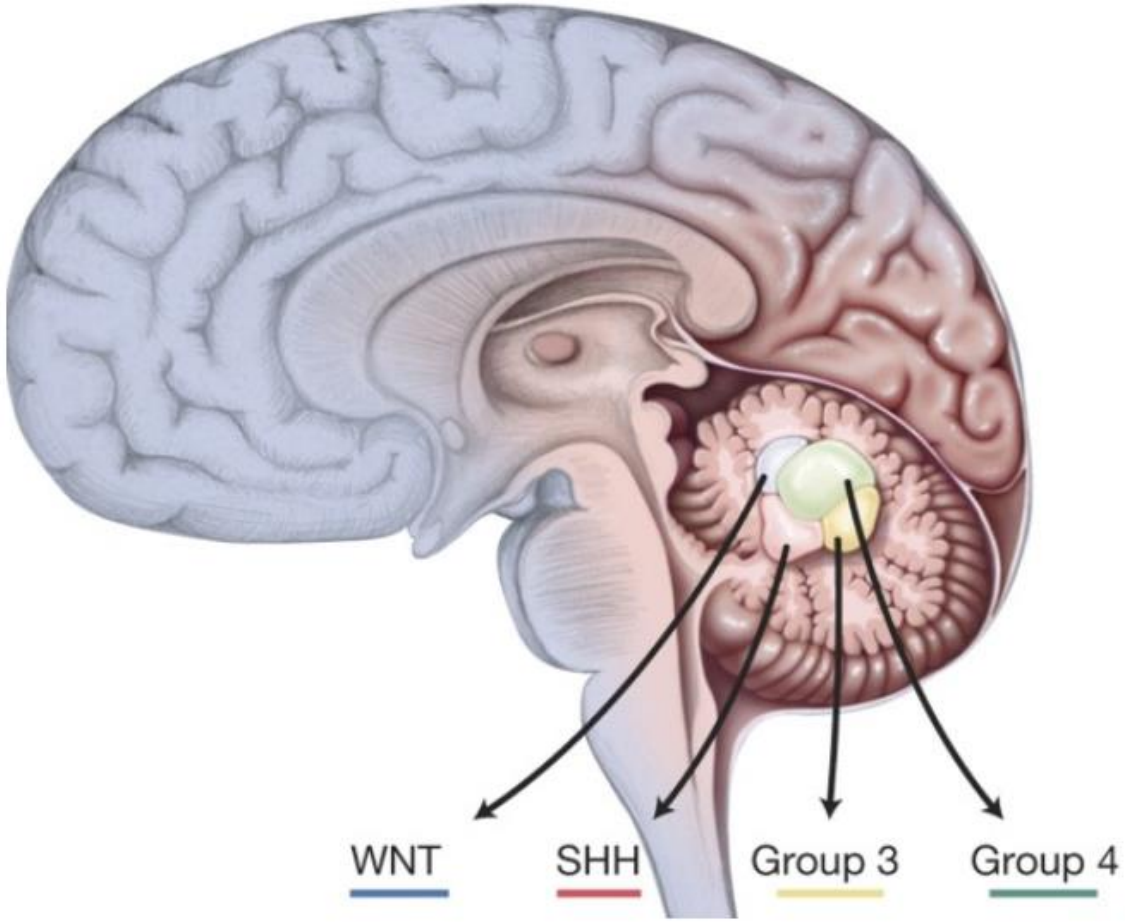
European Commission
Horizon 2020
European Union funding
for Research & Innovation

Individualized PaediatricCure

Cloud-based virtual-patient models
for precision paediatric oncology

5 Paediatric cancers

- **Medulloblastoma (MB)**
- Ewing Sarcoma (ES)
- Neuroblastoma (NB)
- Hepatoblastoma (HB)
- Acute Lymphoblastic Leukemia (ALL)



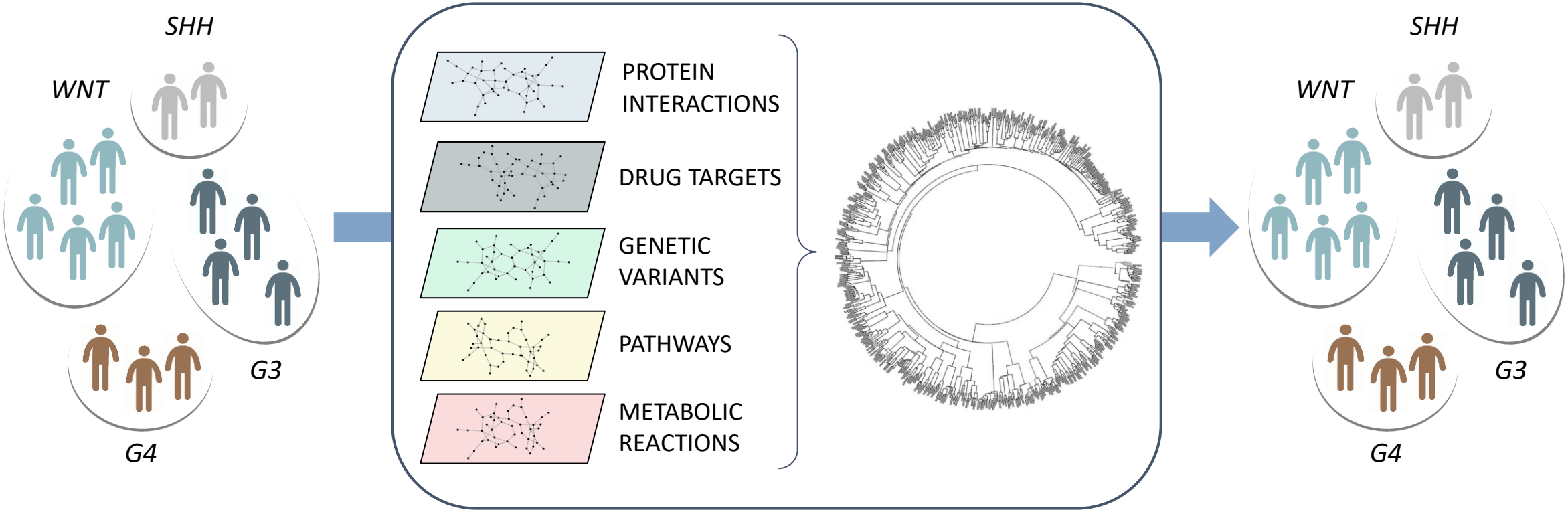
Northcott et al. *Nature*. 2017
Taylor et al. *Acta Neuropathol.* 2012

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Patient stratification in medulloblastoma

(~14,000 altered genes per patient)

(~1,800 altered genes per patient)



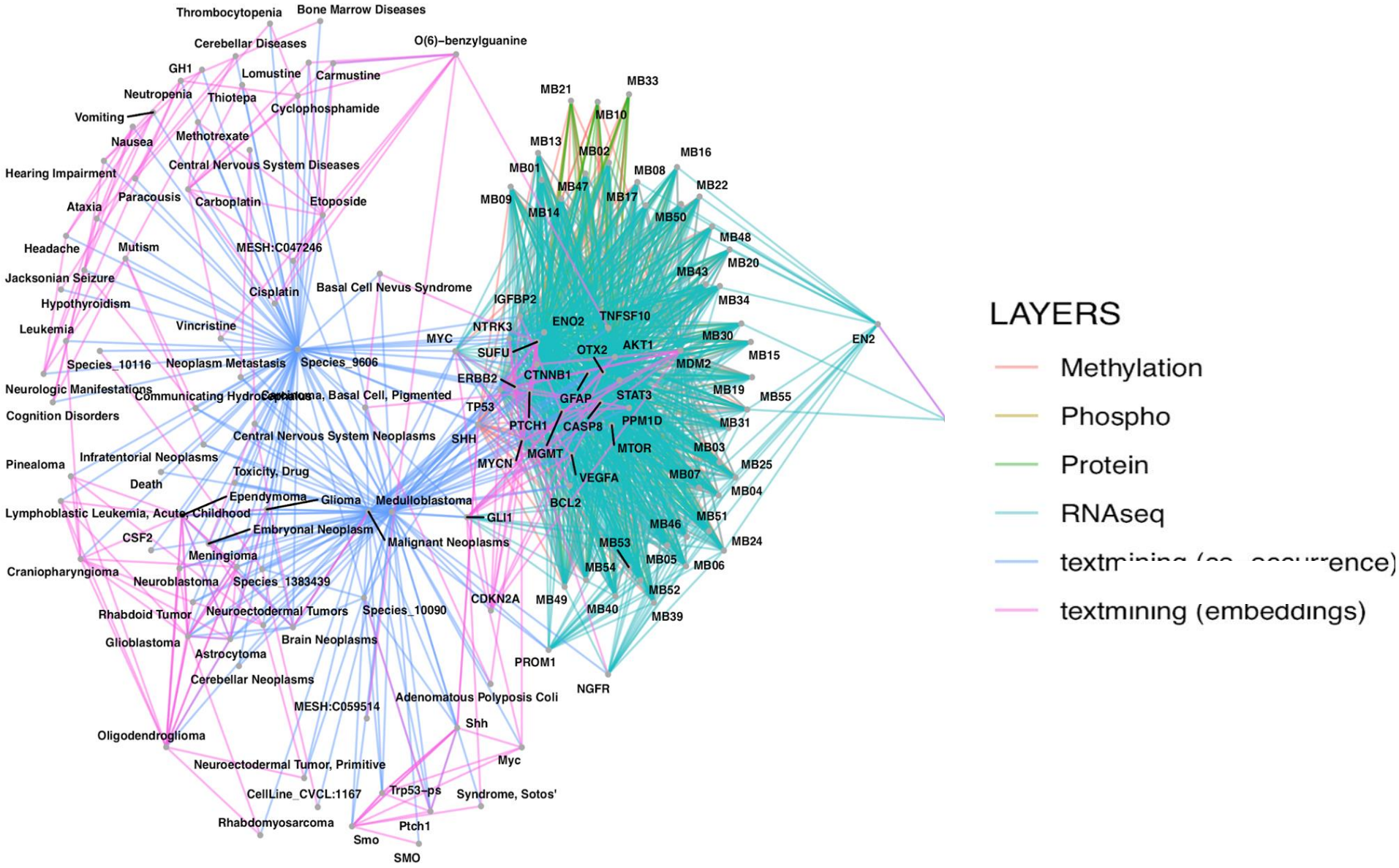
95% accuracy

87% dimensionality reduction

Forget et al. *Cancer Cell*. 2018
Nuñez et al. *Cell iScience*. 2021

Methylation: 54 nodes
Phospho: 42 nodes
Protein: 46 nodes
RNAseq: 60 nodes
Textmining: 100 nodes

A multilayer network to combine gemomics and real world data in medulloblastoma



Interpretability: Multilayer community labelling

ClusterID:1||
Syndrome_Sotos
GLI1
PROM1
MTOR
PTCH1
MB54
MB15
MB13
MB07
MB17
MB09
MB43
MB24
MB53
VEGFA
MB47
AKT1
MB02
TNFSF10
OTX2
MB01

ClusterID:2||
EN1
EN2
CTNNB1
MB30
MB21
MB48
MB39
MB20
MB25
MB06
MB04
MYCN
MDM2

ClusterID:6||
MESH:C059514
MESH:C047246
Thiotepa
Carboplatin
Cisplatin
O(6)-benzylguanine
Etoposide
Cyclophosphamide
Methotrexate
Carmustine
Lomustine
Vincristine

ClusterID:3||
CDKN2A
Basal_Cell_Nevus_Syndrome
Adenomatous_Polyposis_Coli
Carcinoma_Basal_Cell_Pigmented
GFAP
SUFU
MB34
MB33
MB31
MGMT
MYC
MB08
MB40
MB51
MB14
MB03
TP53
CASP8

ClusterID:4||
Rhabdoid_Tumor
Rhabdomyosarcoma
Craniopharyngioma
Lymphoblastic_Leukemia_Acute_Childhood
Neuroectodermal_Tumors
Glioma
Neuroblastoma
Oligodendroglioma
Neuroectodermal_Tumor_Primitive
Meningioma
Ependymoma
Pinealoma
Embryonal_Neoplasm
Central_Nervous_System_Neoplasms
Malignant_Neoplasms
Glioblastoma
Astrocytoma
Brain_Neoplasms

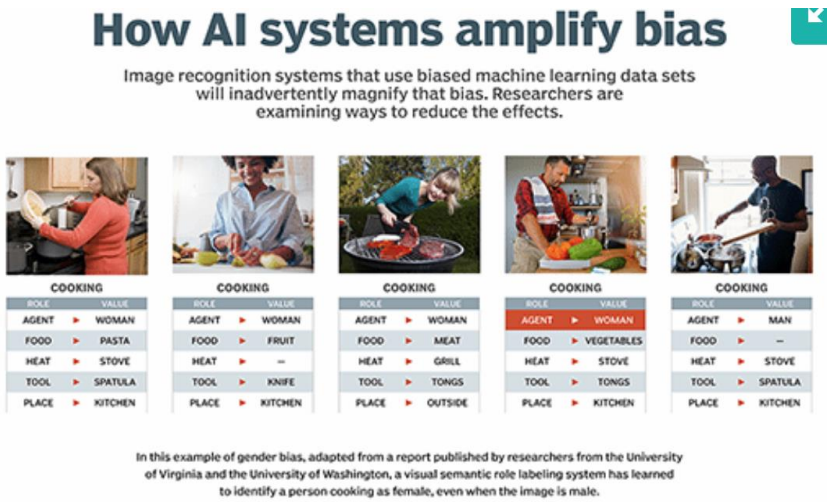
ClusterID:5||
Nausea
Hearing_Impairment
Thrombocytopenia
Paracousis
Cognition_Disorders
Mutism
Vomiting
Ataxia
Headache
Neurologic_Manifestations
Jacksonian_Seizure
Neutropenia
Hypothyroidism
Neoplasm_Metastasis
Leukemia
Bone_Marrow_Diseases
Communicating_Hydrocephalus
Cerebellar_Diseases
Infratentorial_Neoplasms
Central_Nervous_System_Diseases
GH1
Species_9606

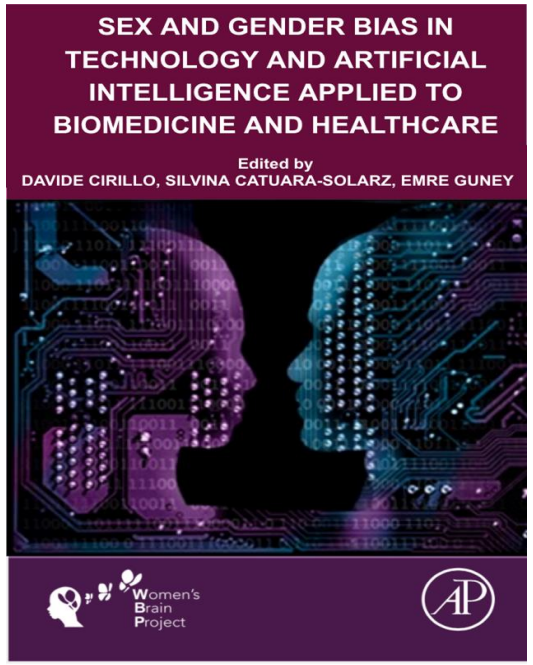
ClusterID:7||
Myc
SMO
Trp53-ps
Smo
Ptch1
Shh
CellLine_CVCL:1167
Toxicity_Drug
Species_1383439
Death
Cerebellar_Neoplasms
Species_10116
Species_10090
CSF2
Medulloblastoma
NGFR
BCL2
PPM1D
ENO2
MB22
MB16
MB10
MB55
MB49
MB46
ERBB2
NTRK3
MB05
MB52
MB50
STAT3
MB19
SHH
IGFBP2

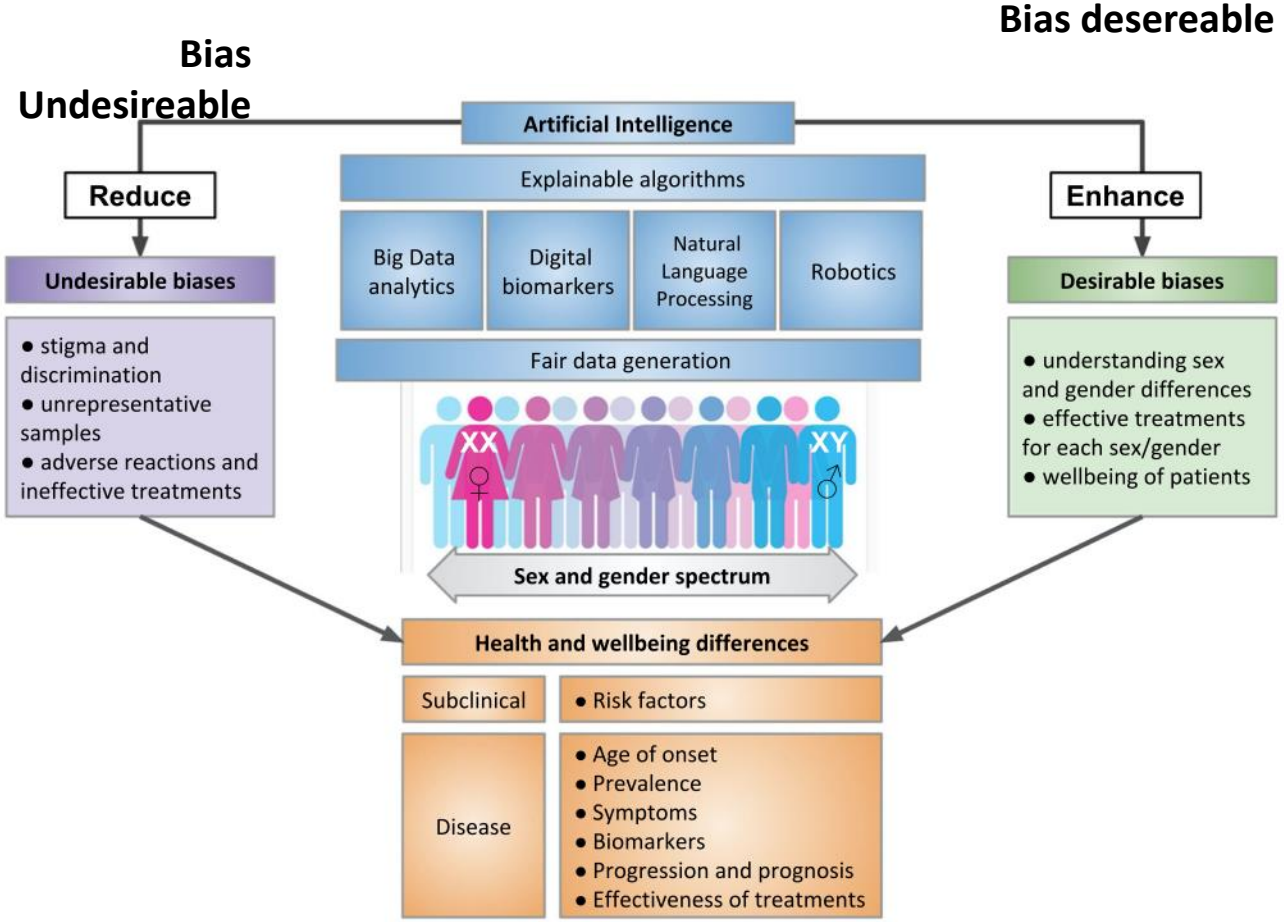
- **BioMedical Data**
  - **IMPaCT-Data**
- **AI/ML in Biomedicine**
  - **bioNLP + NLP in Spanish**
- **Digital Twins (Virtual Human Twins)**
- ***Rare Diseases a Computational Approach***
- **Sex and Gender biases in biomedicine and AI**

Sex & Gender Biases in Biomedicine, AI and NLP

bioinfo 4women







Barcelona Supercomputing Center
Centro Nacional de Supercomputación

Davide Cirillo et al. BSC

.. Part of the research line of bioinfo4women

CON SUPERCOMPUTACIÓN

Identifican qué genes hacen a cada persona única y cómo esa diferencia cambia con la edad

• Las principales diferencias entre hombres y mujeres residen en los genes expresados en la tiroides y el tejido mamario

Los humanos compartimos el 99,9% de nuestro genoma (Getty)

CRISTINA SÁEZ
BARCELONA

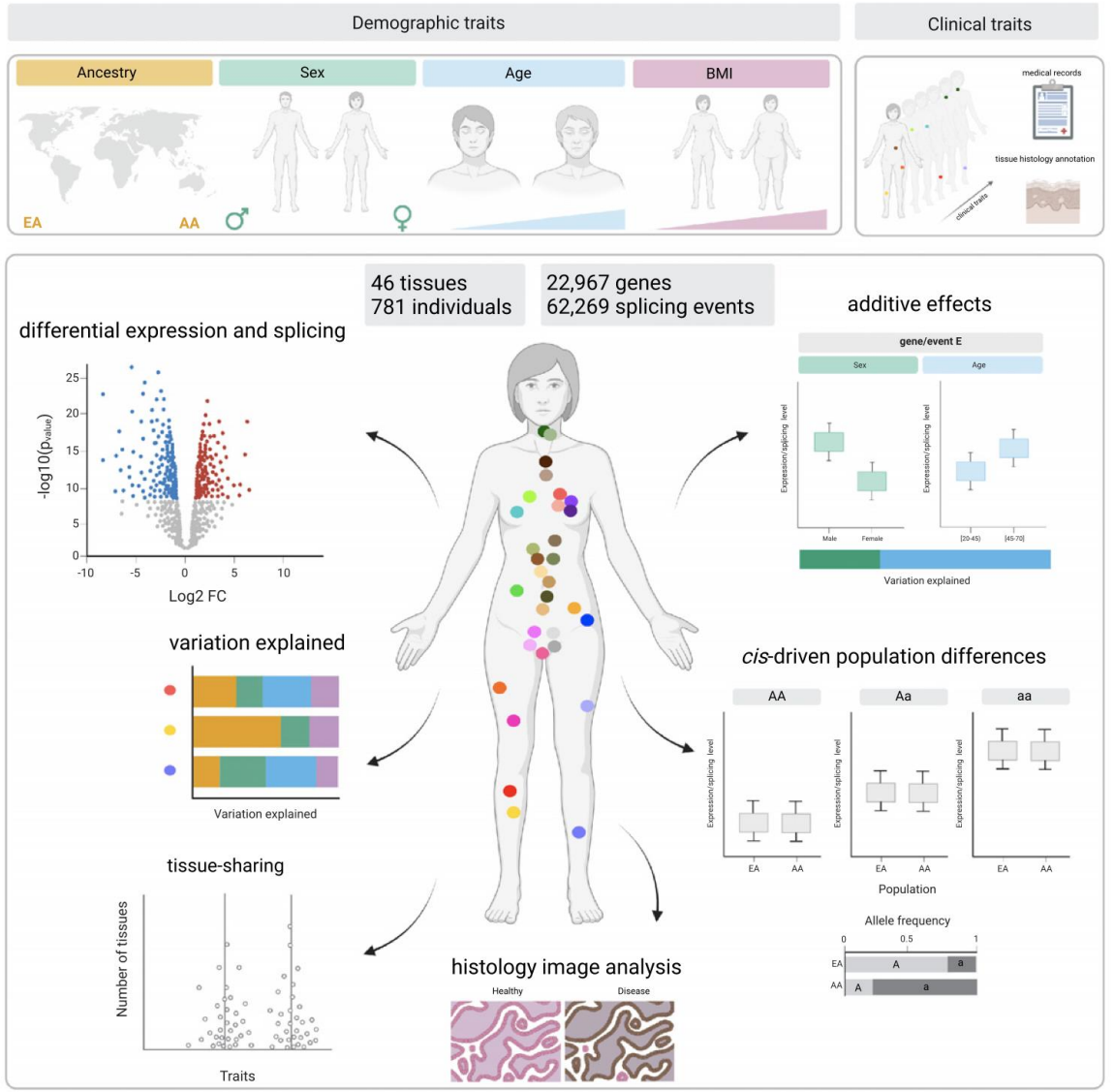
Cell Genomics

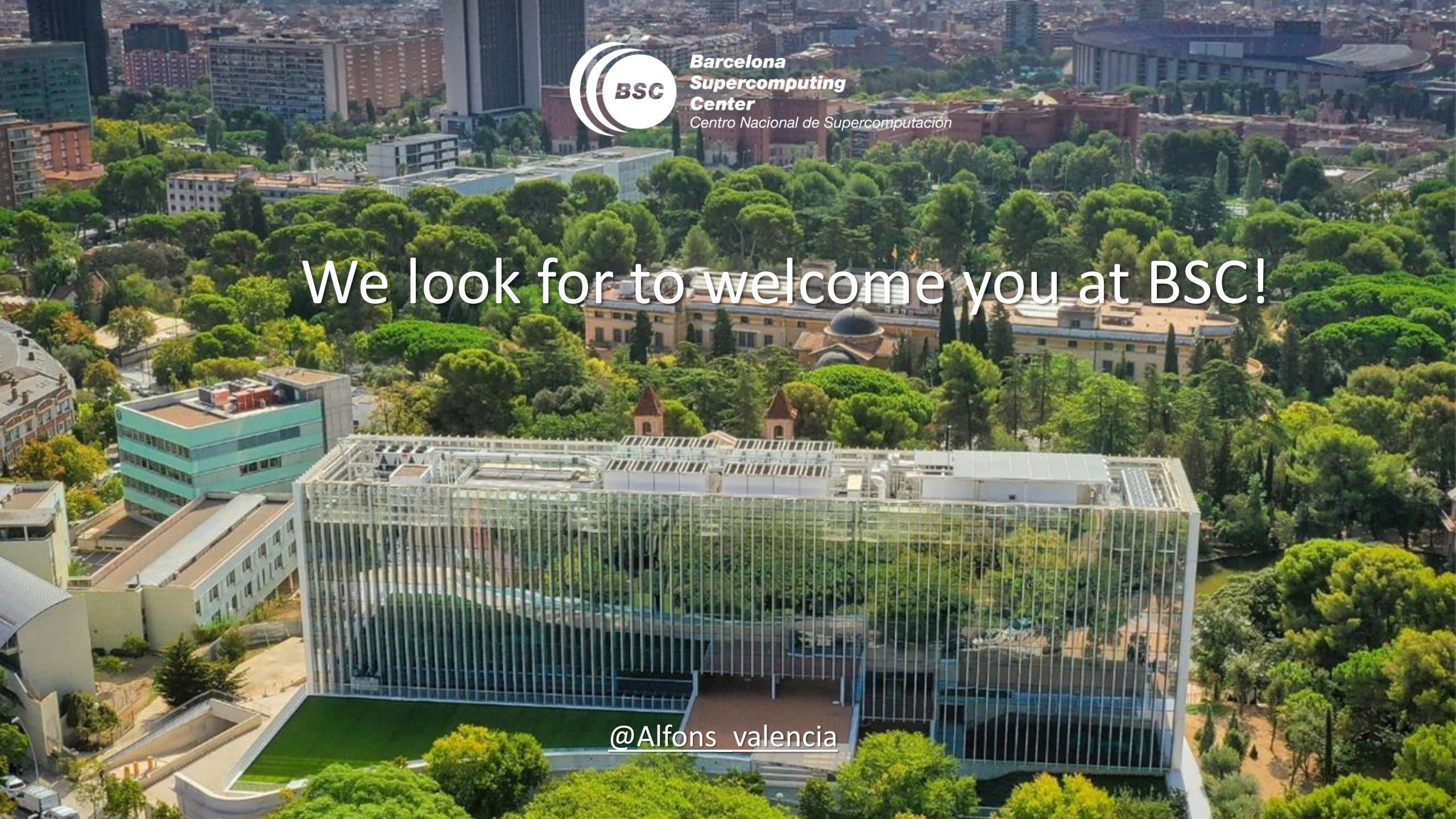
CellPress
OPEN ACCESS

Article

The landscape of expression and alternative splicing variation across human traits

Raquel García-Pérez,[1] Jose Miguel Ramirez,[1] Aida Ripoll-Cladellas,[1] Ruben Chazarra-Gil,[1] Winona Oliveros,[1] Oleksandra Soldatkina,[1] Mattia Bosio,[1] Paul Joris Rognon,[1,2,3] Salvador Capella-Gutierrez,[1] Miquel Calvo,[4] Ferran Reverter,[4] Roderic Guigó,[5] François Aguet,[6,10] Pedro G. Ferreira,[7,8,9] Kristin G. Ardlie,[6] and Marta Melé[1,11,*]




BSC
Barcelona
Supercomputing
Center
Centro Nacional de Supercomputación
We look for to welcome you at BSC!
@Alfons_valencia