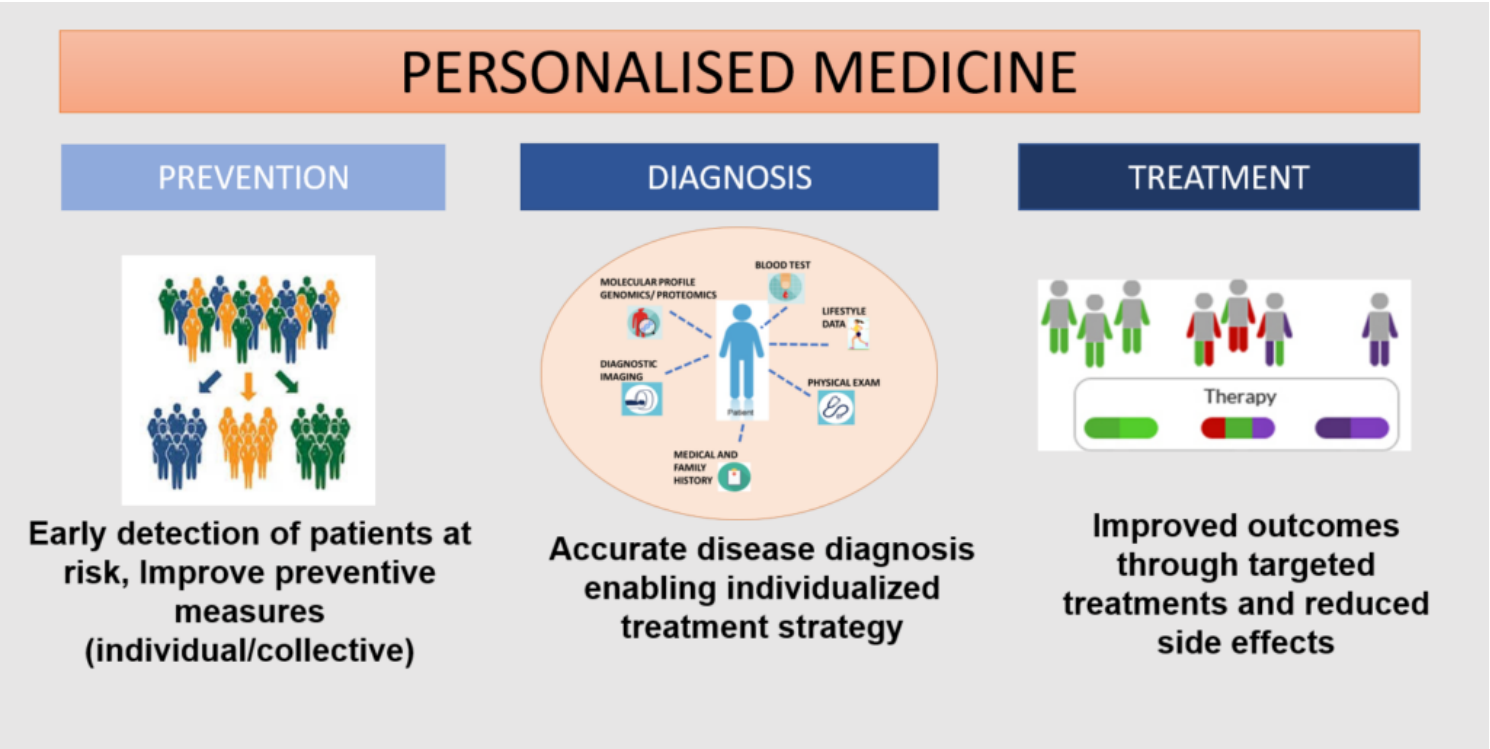
Retos de traslación de la medicina personalizada: El programa IMPaCT

Angel Carracedo

Universidad de Santiago de Compostela

Fundación Pública Gallega de Medicina Genómica- SERGAS



5P Medicine is:

•**Personalized:** Specific for each patient in diagnosis, therapy, and monitoring.

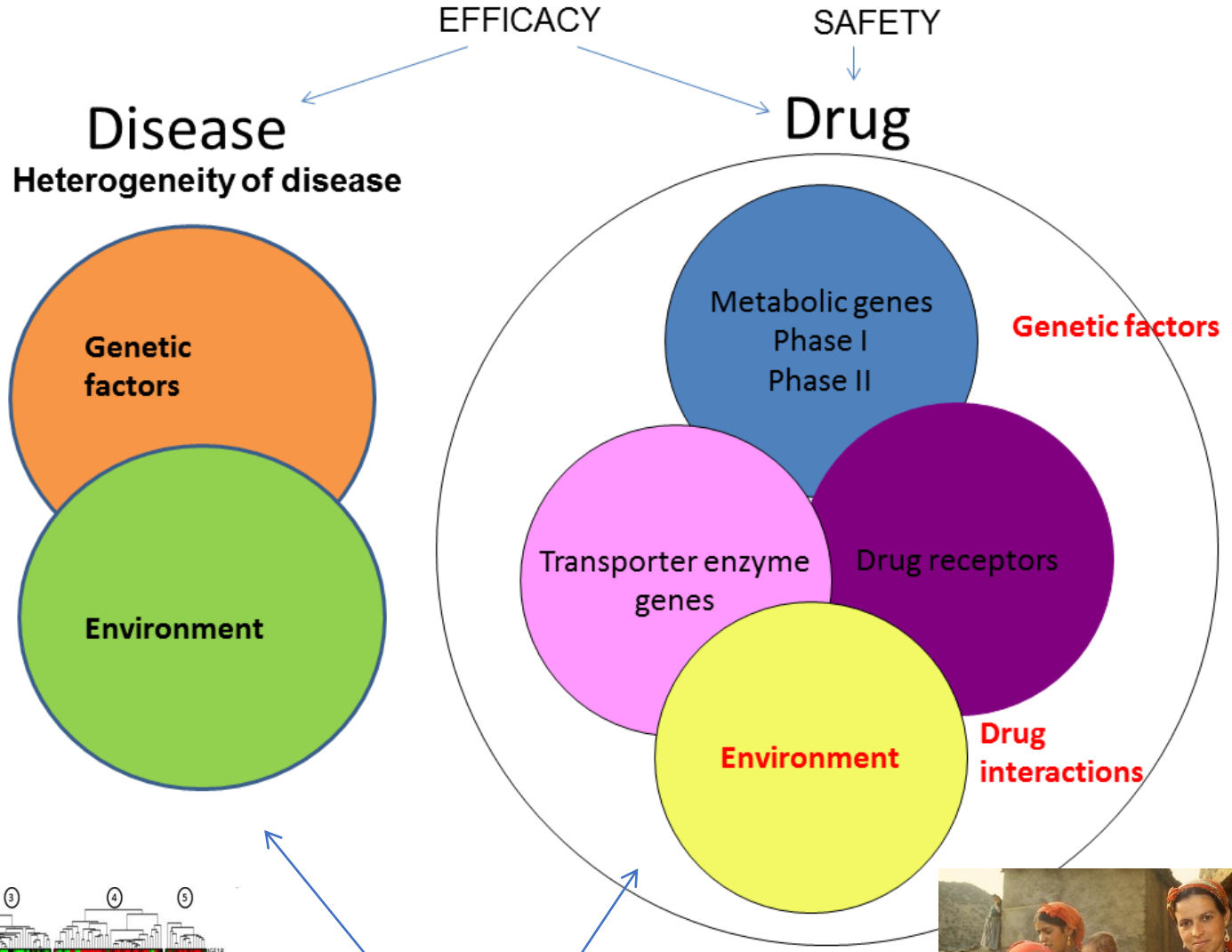
•**Predictive:** Analyzes and calculates the risk that a person will develop a disease.

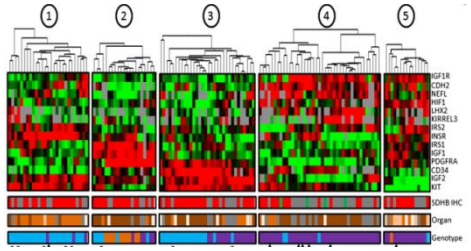
•**Preventive:** Helps make decisions that prevent the appearance of diseases.

•**Participatory:** Tries to put the patient at the center of the healthcare system, teaching and providing appropriate tools so the patient can participate in the responsibility for his or her health care.

•**Populational:** Must assure access to healthcare for the entire population.

The concept of personalized medicine





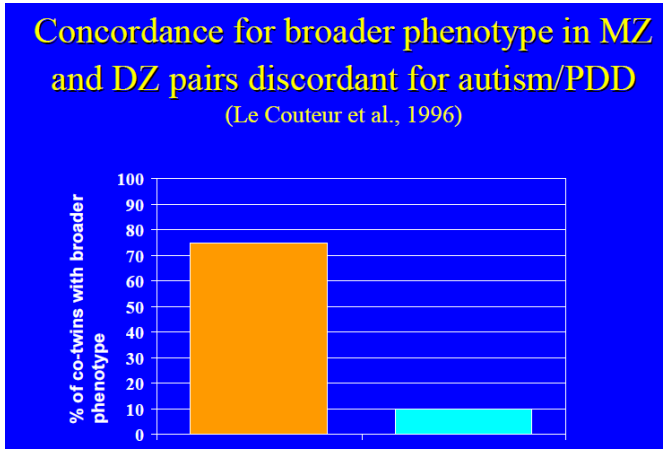
Biomarkers

CYPs
Important pop. differences

Heritability

Heritability: Genetic variance/Total variance

Colorectal cancer: 35%
Breast cancer: 28%
Lung cancer: 5%
ASD: 80%
ADHD: 70%
Schizophrenia: 80%
Bipolar disorder:80%
Average disease: 50%

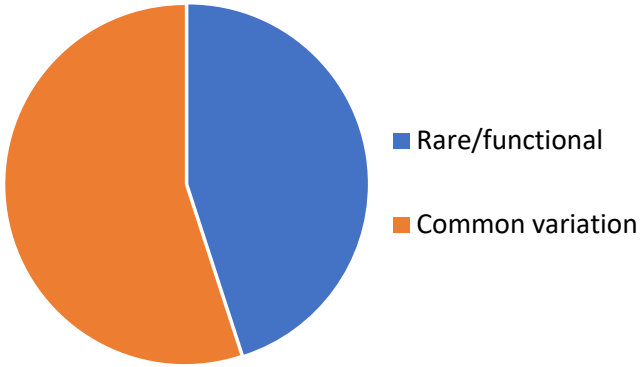


Heritability estimates:
Based in family studies: Overstimated (shared enviroment in some studies)
Based in GWAS: Underestimated (the total genetic variance is not captured)

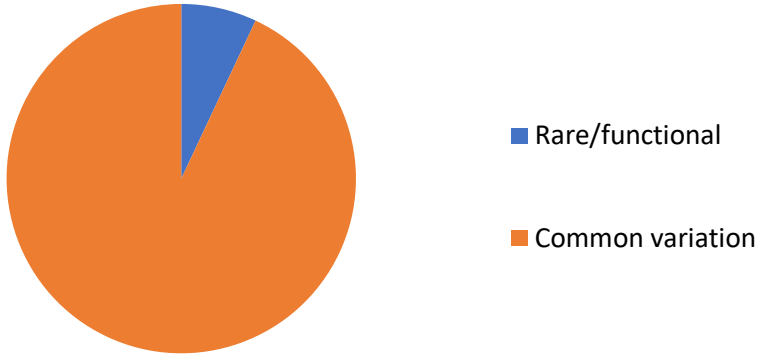
The study included 37 570 twin pairs, 2 642 064 full sibling pairs, and 432 281 maternal and 445 531 paternal half-sibling pairs. Of these, 14 516 children were diagnosed with ASD. The model including additive and nonadditive genetic, shared and nonshared environmental parameters.
0.83 general, 0.87% using only twins

Common and rare functional variation (H: 0.80)

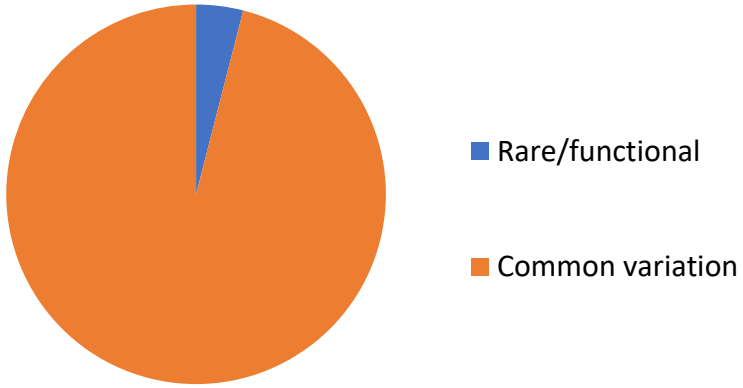
ASD



Schizophrenia



BD



Rare/functional forms

-Early onset
-More syndromic (co-morbility)


nature genetics

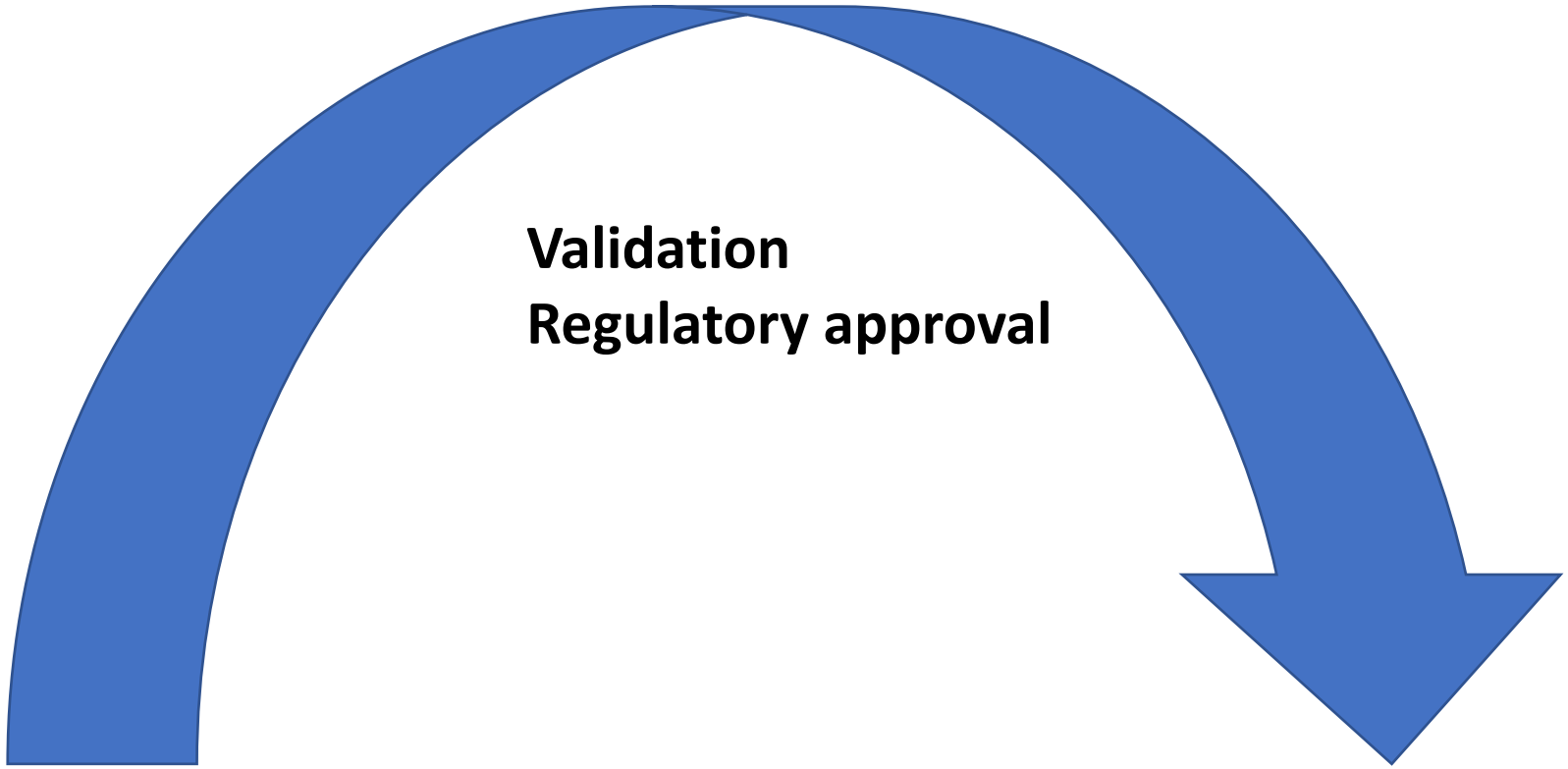
Letter | Published: 20 July 2014

Most genetic risk for autism resides with common variation

Trent Gaugler, Lambertus Klei, Stephan J Sanders, Corneliu A Bodea, Arthur P Goldberg, Ann B Lee, Milind Mahajan, Dina Manaa, Yudi Pawitan, Jennifer Reichert, Stephan Ripke, Sven Sandin, Pamela Sklar, Oscar Svantesson, Abraham Reichenberg, Christina M Hultman, Bernie Devlin, Kathryn Roeder & Joseph D Buxbaum

Nature Genetics **46**, 881–885 (2014) | Download Citation

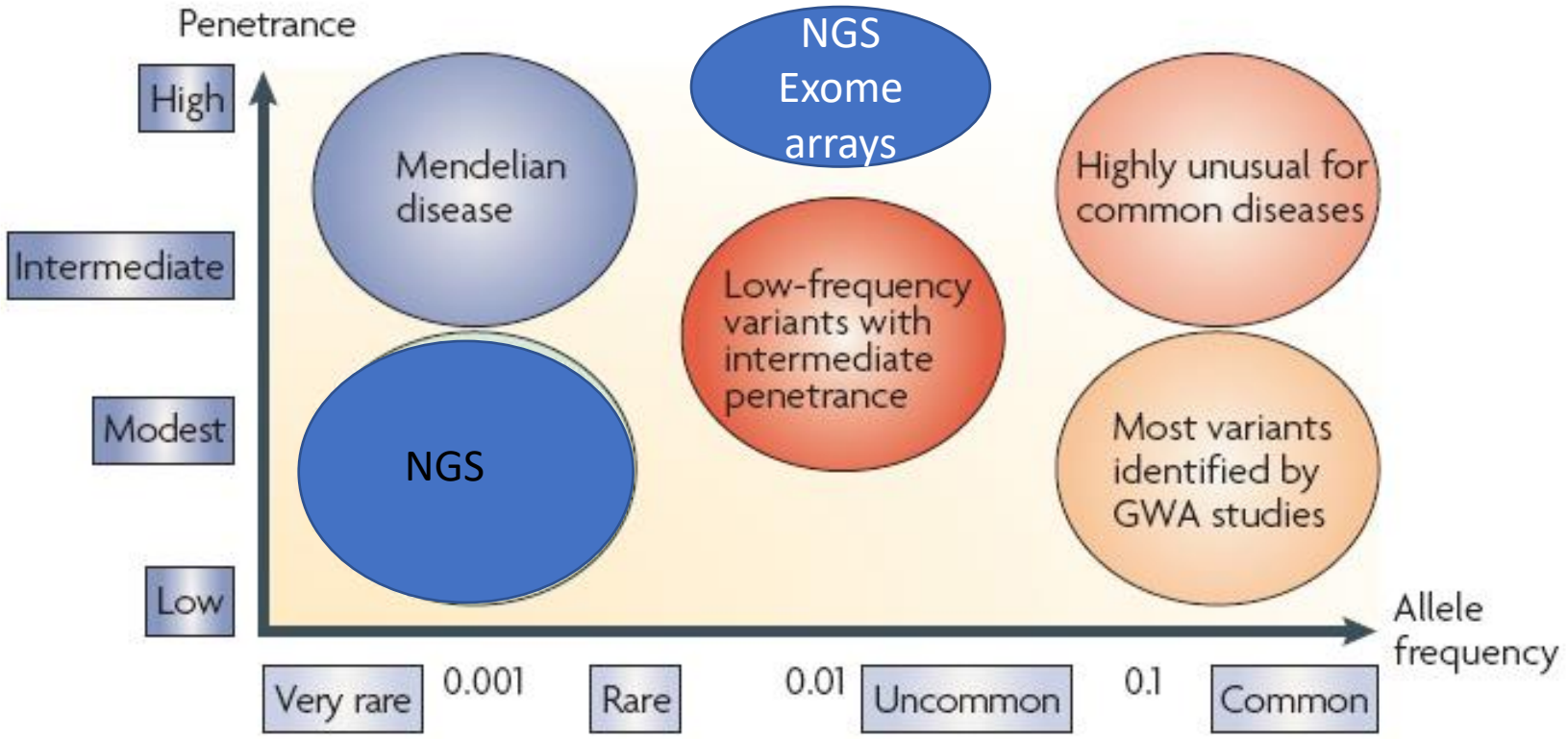
GENOMIC BIOMARKERS FOR PERSONALIZED MEDICINE



Discovery phase:
GWAS and sequencing projects

Translation:
Implementation in clinical applications

Looking for the genetic component of the disease



Secuenciación de nueva generación o secuenciación paralela masiva

Evolución tecnológica rapidísima

Exige capacidad de computación

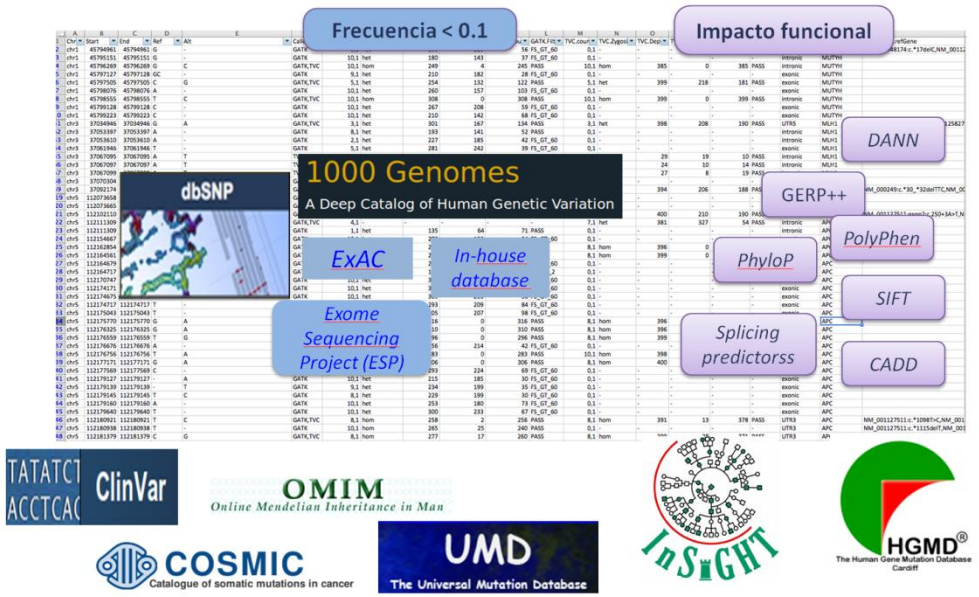
Análisis complejo de la variación: Necesidad de bioinformática

Secuenciadores de primera generación: Sanger

Secuenciadores de segunda generación

Secuenciadores de tercera generación: secuenciación de molécula única

Listado de variantes anotadas NGS: Filtrado



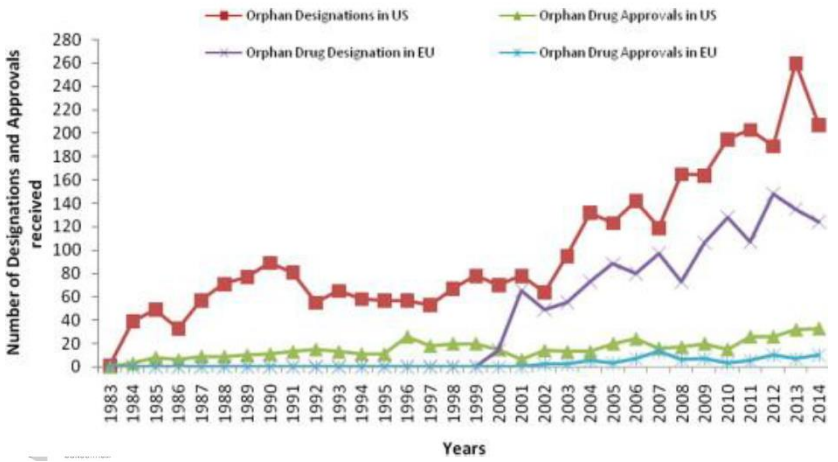
IRDiRC new objectives 2027

Diagnostic of 90% of rare disease within one year from symtoms in 2027

Number of tretaments for rare diseases: Expected to increase x 20 in 10 years (more than 1000 new treatments expected for 2027) (IRDiRC, Paris, 2017)

Fostering Transatlantic Cooperation on Research into Rare Diseases: European Union – USA Bilateral Workshop on Rare Diseases and Orphan Products; 27-28 October 2010, Reykjavik, Iceland

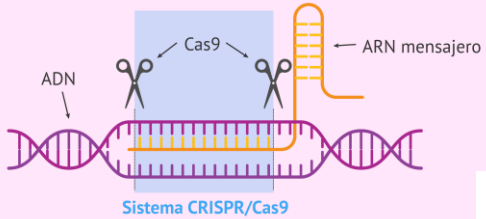
Orphan Drugs in the USA and Europe



Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Premio Nobel Química 2020: Emmanuelle Charpentier y Jennifer A. Doudna



La Comisión Europea aprueba la única terapia génica para la atrofia muscular espinal

Zolgensma ha demostrado un beneficio terapéutico y clínicamente significativo en la AME presintomática y sintomática, incluida la supervivencia libre de eventos prolongada

Dos décadas de notables avances

Gracias a una regulación específica (Reglamento europeo 141/2000)…

2000

Se ha pasado **de 8 fármacos disponibles** para estos pacientes en el año 2000 **a 129**

2022

Hoy, **uno de cada cuatro nuevos medicamentos** aprobados por la Agencia Europea del Medicamento (EMA) tiene **designación de huérfano**

2006 - 2016

Entre 2006 y 2016 el número de **ensayos clínicos** para enfermedades raras **creció en un 88%** en Europa

2000 2005 2010 2015 2022

El acceso en España, un desafío

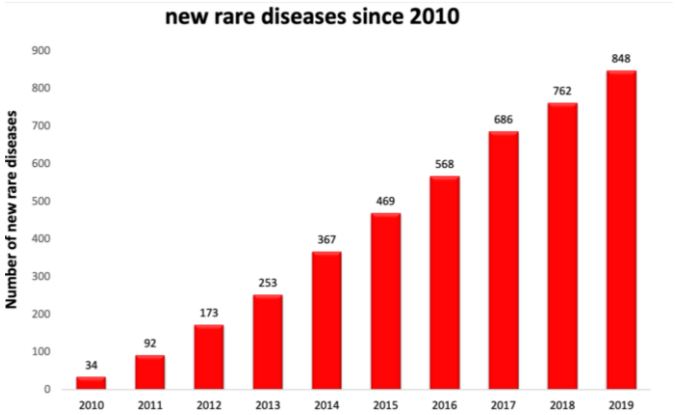
40/100 En nuestro país sólo están **disponibles** 40 de cada 100 medicamentos huérfanos aprobados en Europa, muy por debajo de países de referencia como Alemania, Italia o Francia

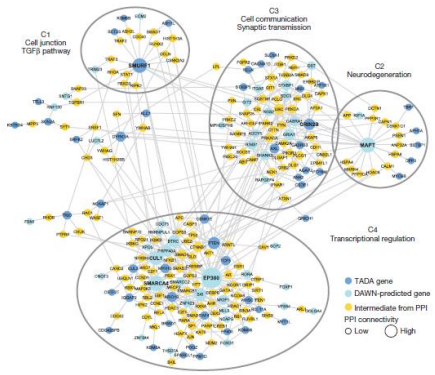
523 Tardan una media de 523 **días en financiarse** por el sistema público

54% Casi la mitad de los que se financian lo hacen con **restricciones terapéuticas**

Nuestro país no dispone de un **procedimiento específico** de financiación pública y fijación de precio para estos fármacos

From gene panels to WES and WGS
The bottleneck is from prioritized variants to the report





EUROPEAN GENOME-PHENOME ARCHIVE

elixir Core Data Resource

Population databases
Disease specific databases
Locus specific dabases (LSDB)
Scientific literature

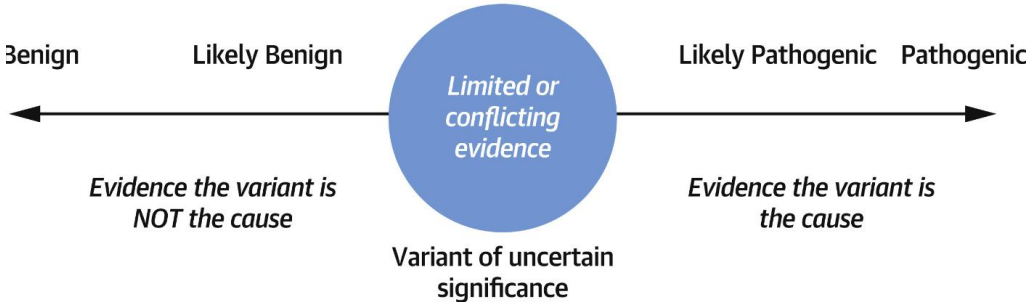
Data mining of clinical data

HPO training
CIBERER-IMPaCT

CHALLENGE: UNCERTAIN VARIANTS

Key evidence for considering pathogenicity

Robust gene-disease association
Sufficiently rare in population reference databases
Seen in other patients with concordant phenotypes
Loss of function variant in a gene where this is an established mechanism
Segregation with affected relatives, de novo occurrence, functional studies



Segregation

Mutation databases
-Level of evidence variable
Functional studies
-Level of evidence variableCell
Cell- Animal models
-CRISPER models

International Collaborative Projects

THE HUMAN VARIOME PROJECT

Science 7 November 2008:
Vol. 322. no. 5903, pp. 861 - 862
DOI: 10.1126/science.1167363

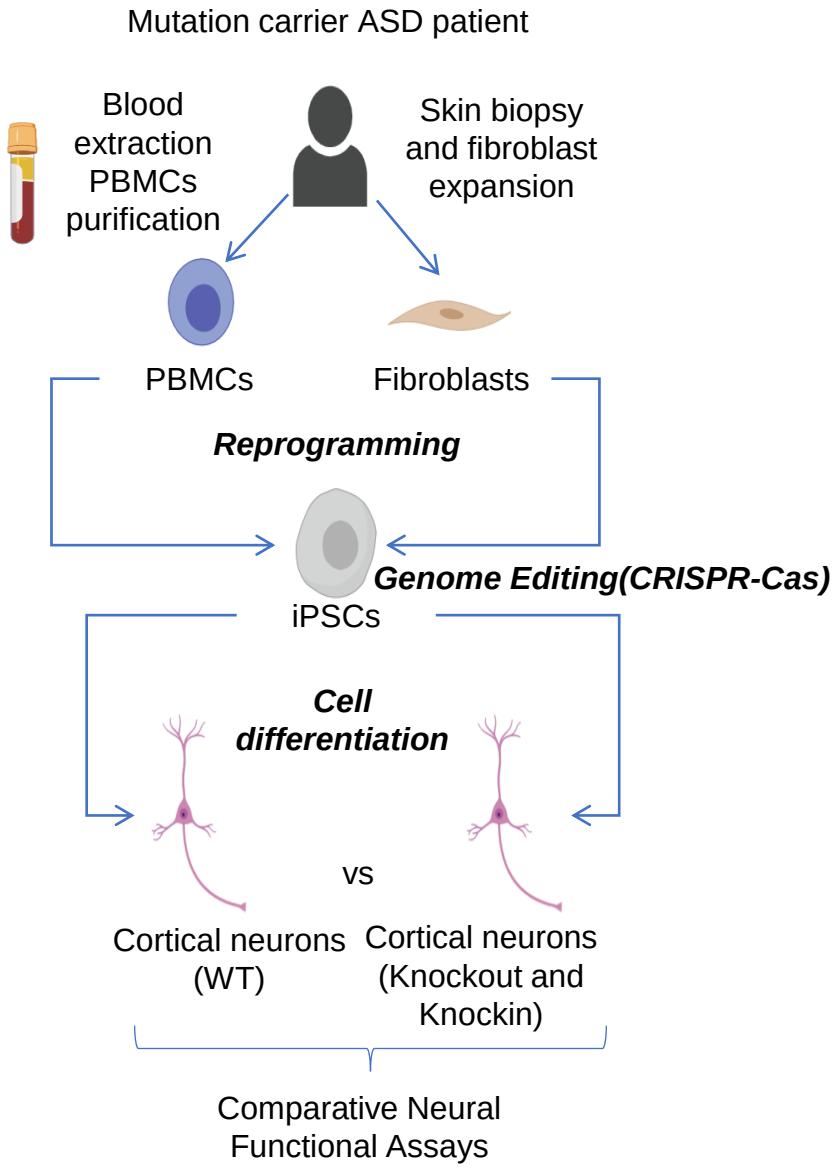
POLICY FORUM

GENETICS:
The Human Variome Project

EXOME DATABASES

IRDiRC
INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Cellular and animal models



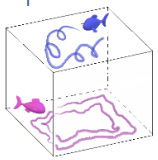
Zebrafish as a model in neurodevelopment

76-82% of human genes involved diseases are conserved

Reduced complexity of the nervous system

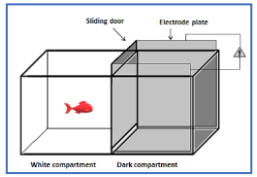
Molecular and structural homology of brain regions

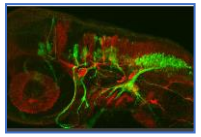
Some **typical ASD repetitive behaviors**



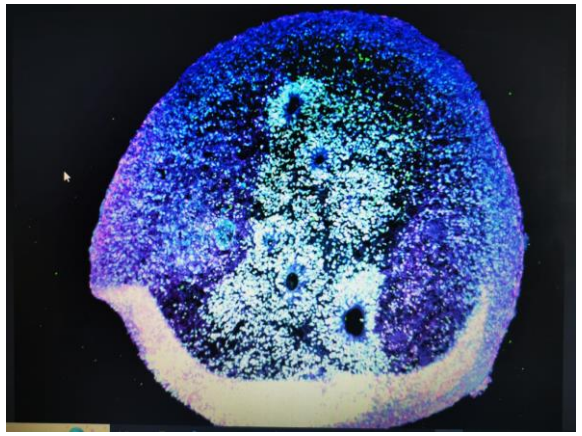
Method

Gene selection;
CRISPR-Cas9 design;
Knock-out procedure
Analyses:
Functional and behavioral anomalities





Medicina Xenómica



Cerebral organoids

Retos

Necesidad de estudios funcionales

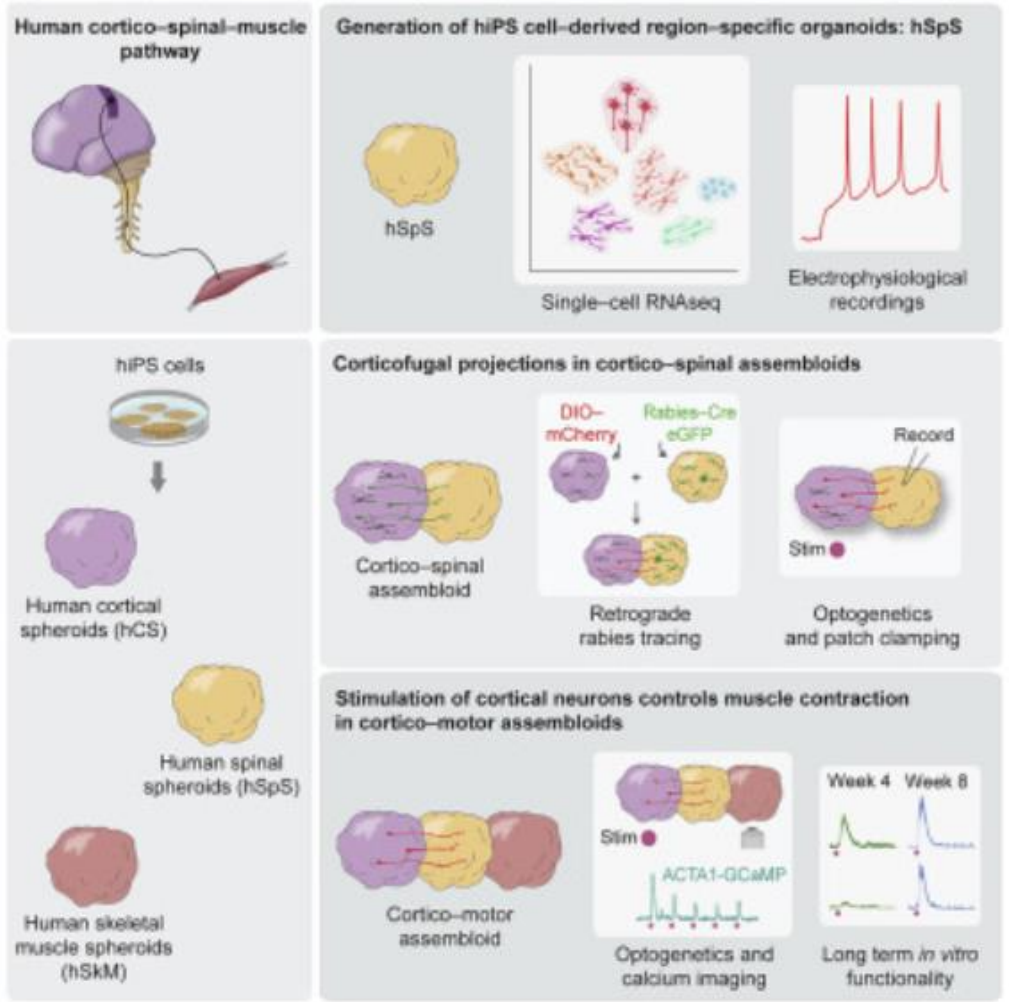
Mapa de recursos a nivel nacional/internacional

Bases de datos de variantes validadas

Cell. 2020 Dec 23;183(7):1913-1929.e26. doi: 10.1016/j.cell.2020.11.017. Epub 2020 Dec 16.

Generation of Functional Human 3D Cortico-Motor Assembloids

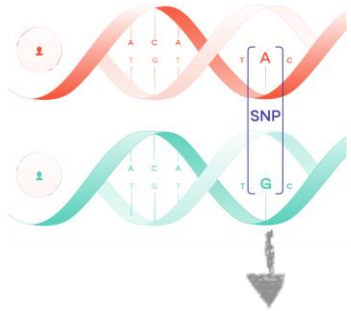
Jimena Andersen [1], Omer Revah [1], Yuki Miura [1], Nicholas Thom [2], Neal D Amin [1], Kevin W Kelley [1], Mandeep Singh [1], Xiaoyu Chen [1], Mayuri Vijay Thete [2], Elisabeth M Walczak [3], Hannes Vogel [4], H Christina Fan [3], Sergiu P Paşca [5]



Genetic architecture of ASD

ASD heritability~ 83%

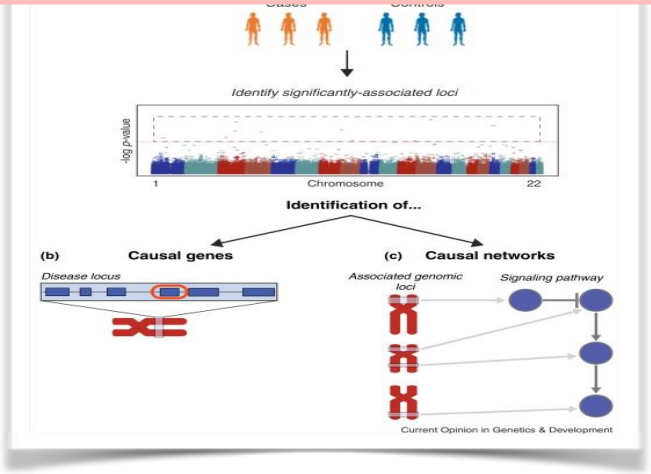
Common variation (SNPs) (55%)



Common missing heritability (? %)

- **Increase GWAS sample size**
- **Reduce phenotype heterogeneity**
- **Causal genes identification— GBA method** (A.Gonzalez et al. 2019)
- **TWAS (Transcriptome Wide Association analysis)**
- (Rodriguez-Fontenla et al. Transl Psych 2021)
- **eQTLs colocalization methods**

Dominguez Alonso et al.(WCongress PG 2022) in review Transl Psych

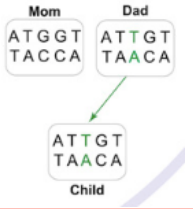


Rare variation (SNVs and CNVs) (25/45 %)

Protein coding genome

De novo

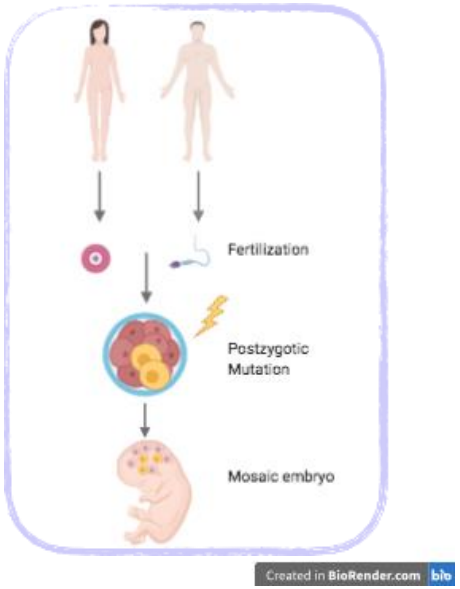
Inherited



-WES (whole-exome sequencing)

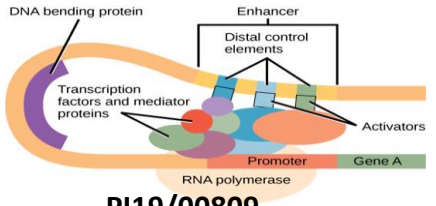
A.Gonzalez et al. 2021. Scientific Reports)

PZM



The non-coding genome

(regulatory regions)



PI19/00809

-Targeted sequencing

-WGS (whole-genome sequencing)

3D Genome

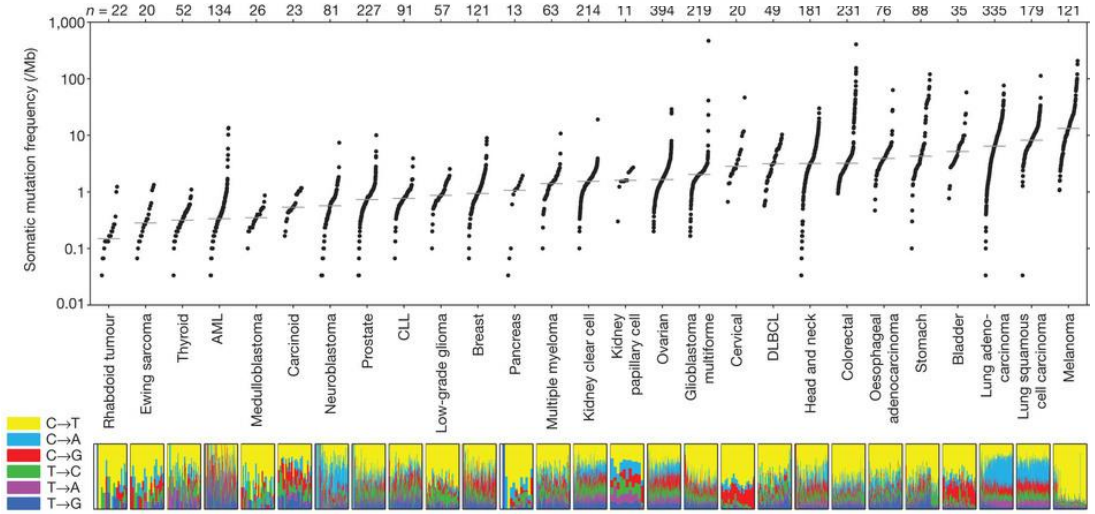
PI22/00208

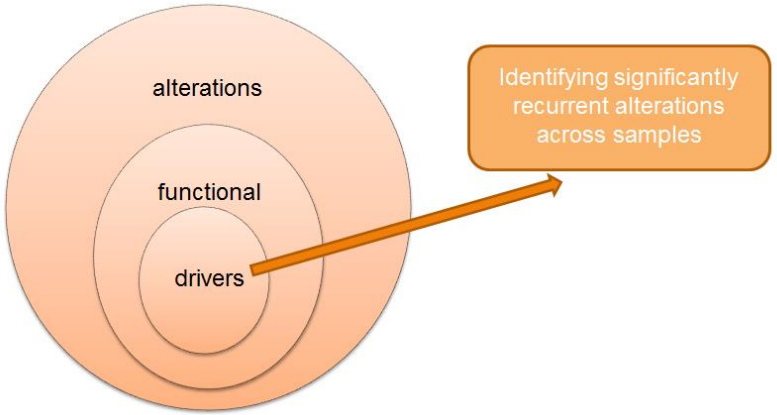
Data modified and updated from Alonso-Gonzalez et al, 2018, Bourgeron et al, 2016.

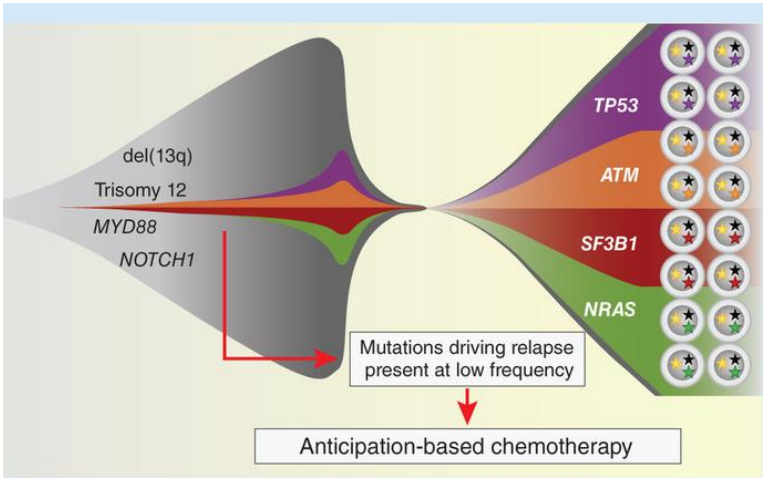
The Cancer Genome Projects

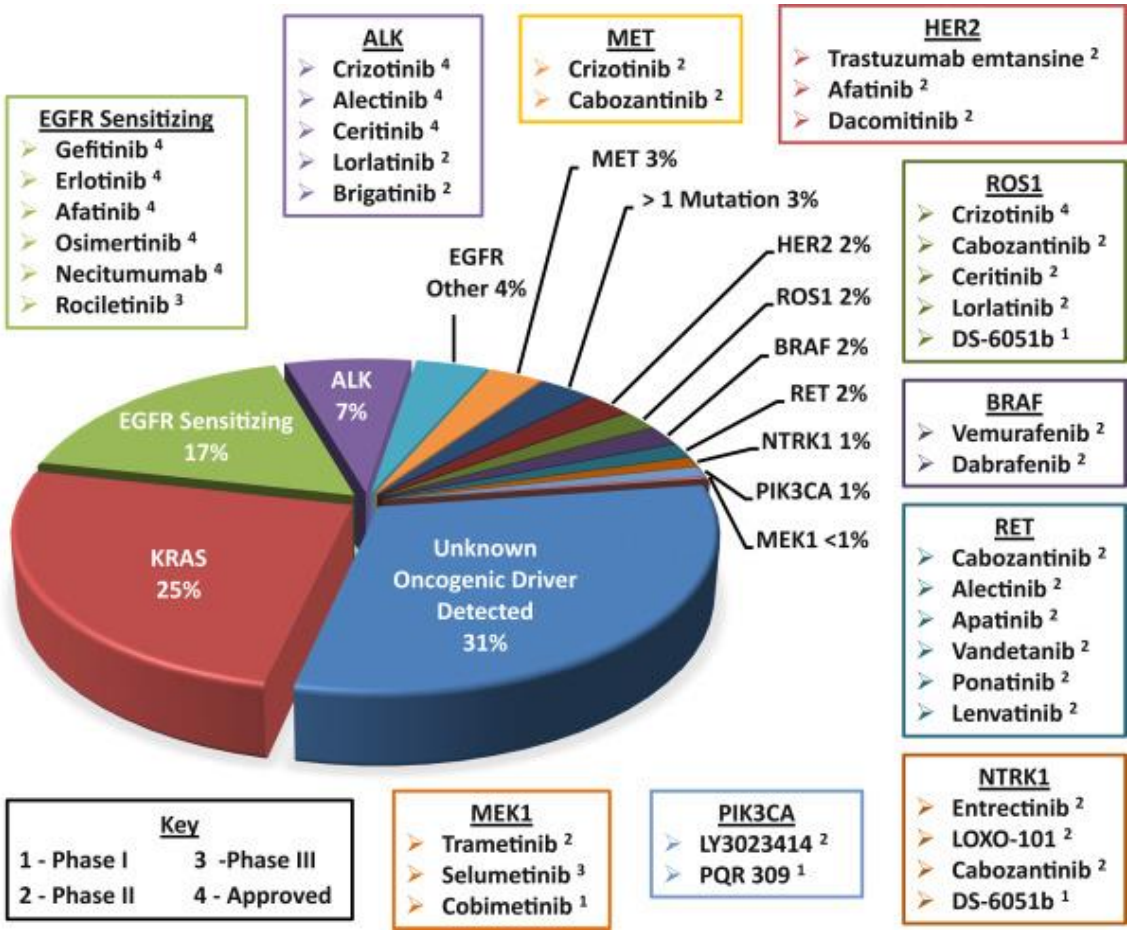
The Cancer Genome Atlas — Understanding genomics to improve cancer care

International Cancer Genome Consortium



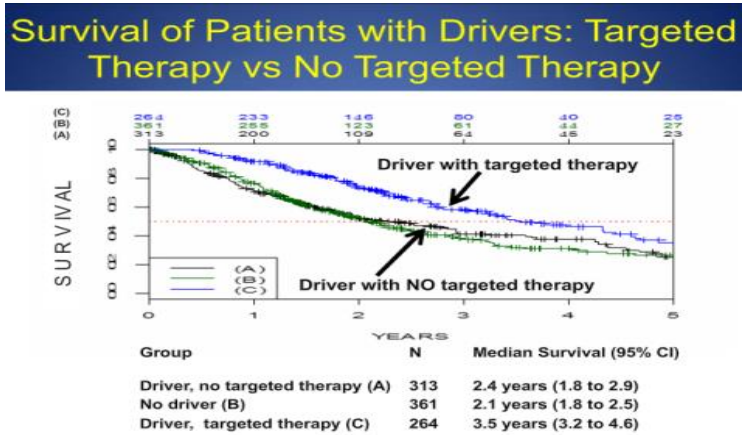




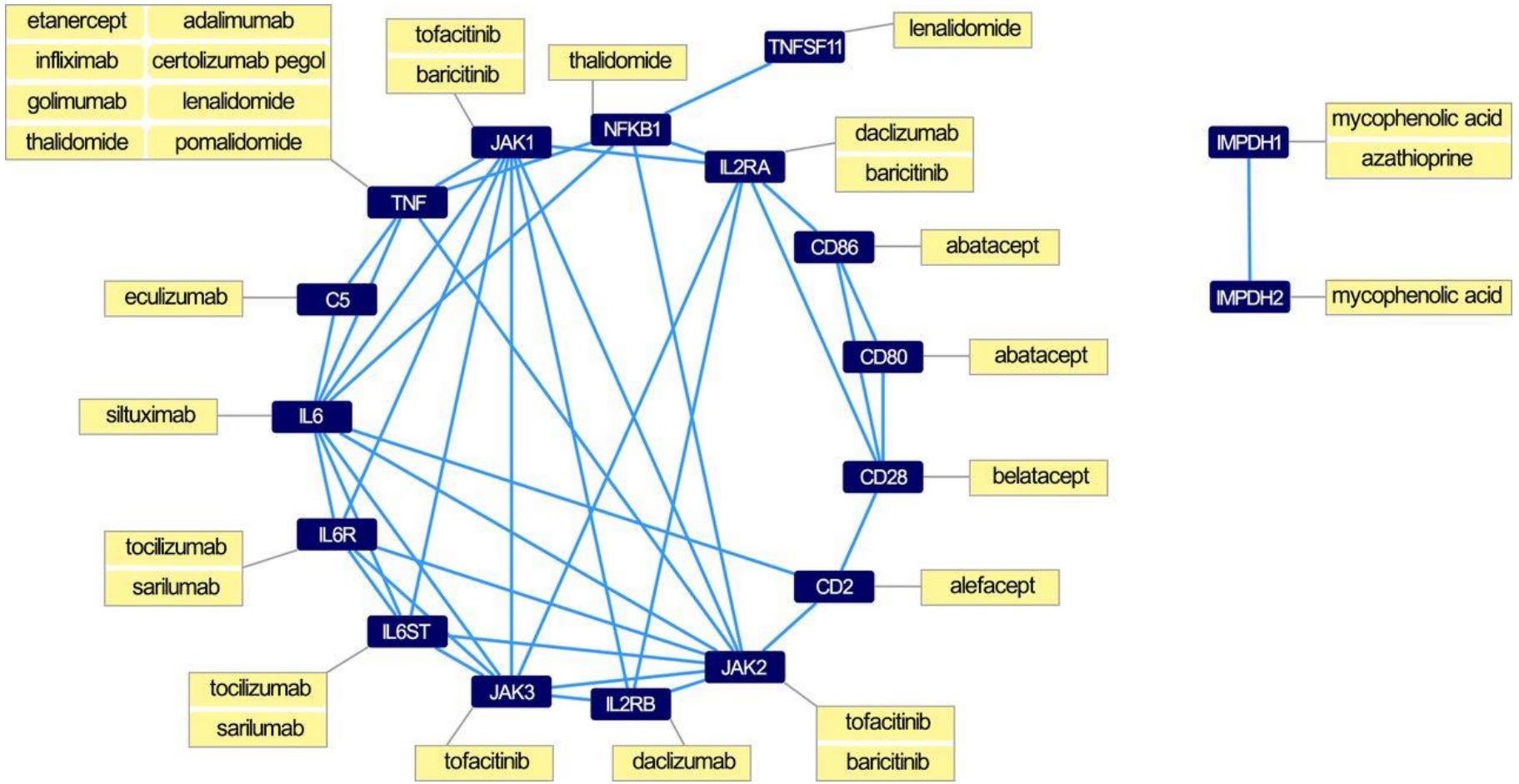


Scientific Advances in Lung Cancer 2015
Tsao et al. 2016, 11(5): 613–638

Kris M, et al. JAMA 2014



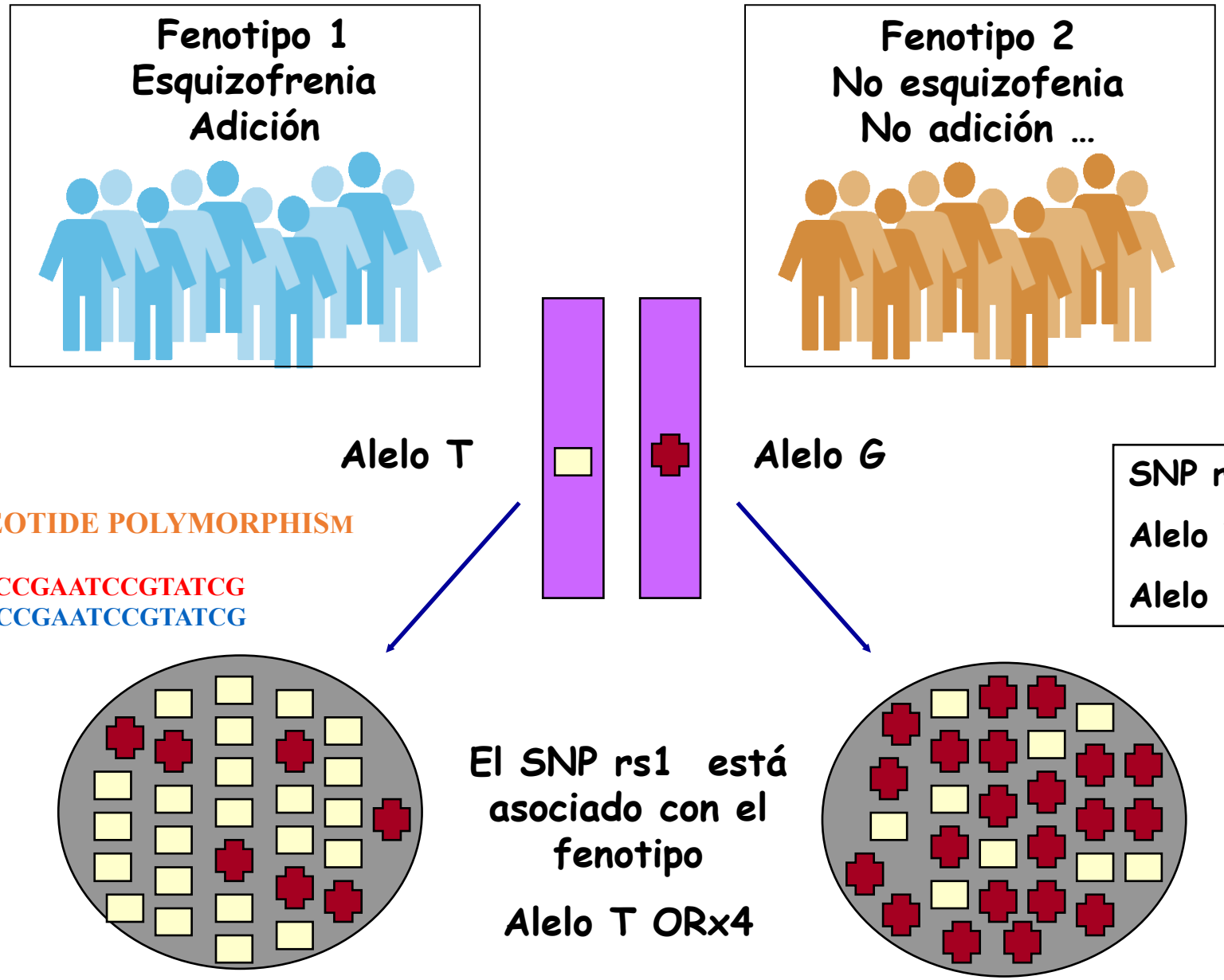
Retos: Muchos tratamientos sin evidencia suficiente.
Estratificación de biomarcadores desde el principio en ensayos clínicos
Gestión y organización de la información clínica y genómica
Real world data



Approved or potentially repurposable immunosuppressants for RA treatment. Existing immunosuppressants (shown in yellow boxes) are connected with drug targets (shown in dark blue boxes) that were extracted from potential RA effector gene products and their interaction partners. A network of the drug targets was retrieved from HumanNet v2-XN and visualised by Cytoscape. RA, rheumatoid arthritis

Ha E, Bae S-C, Kim K. Ann Rheum Dis 2021;80:558–565.

Diseño de un estudio de asociación



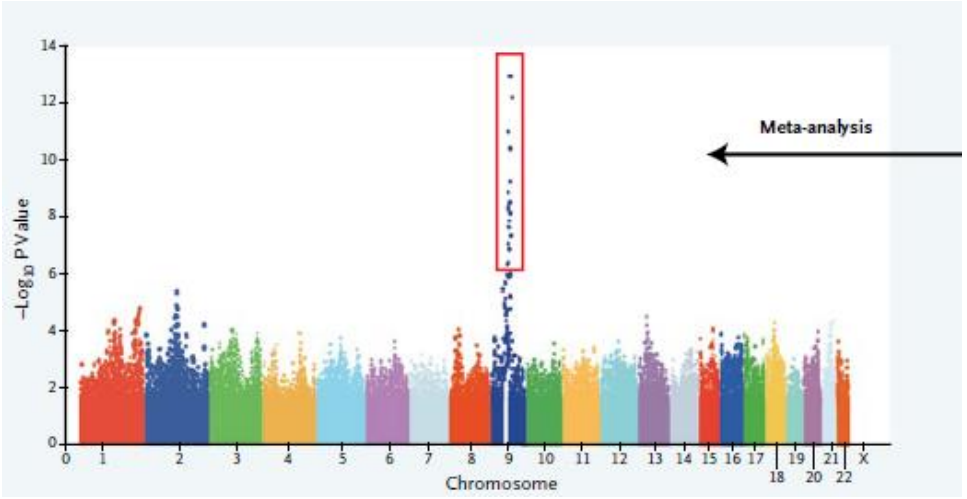
Necesidad de N muy alto para poder tener estadístico para detectar riesgos relativos pequeños

Necesidad de consorcios

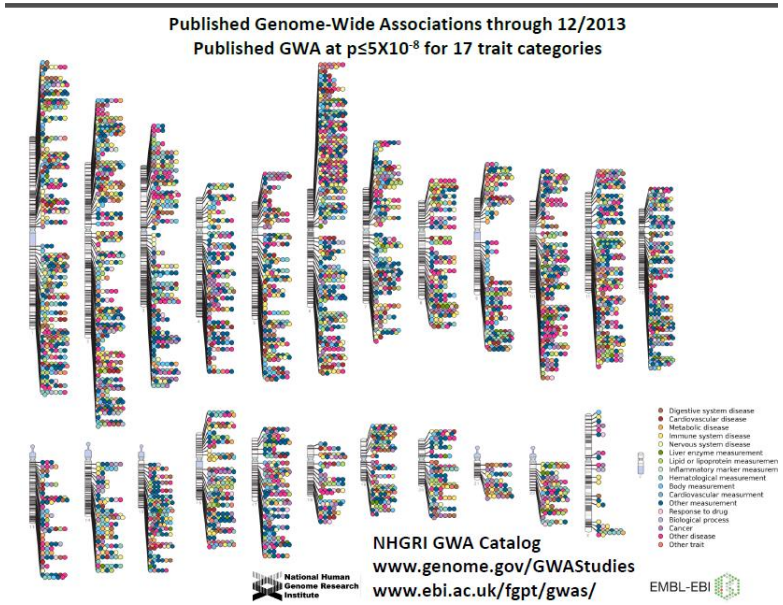
La definición del fenotipo es muy importante. Se puede incrementar el poder con fenotipos extremos

GWAS

Hit $p<5x10^{-8}$ after QC and Bonferroni

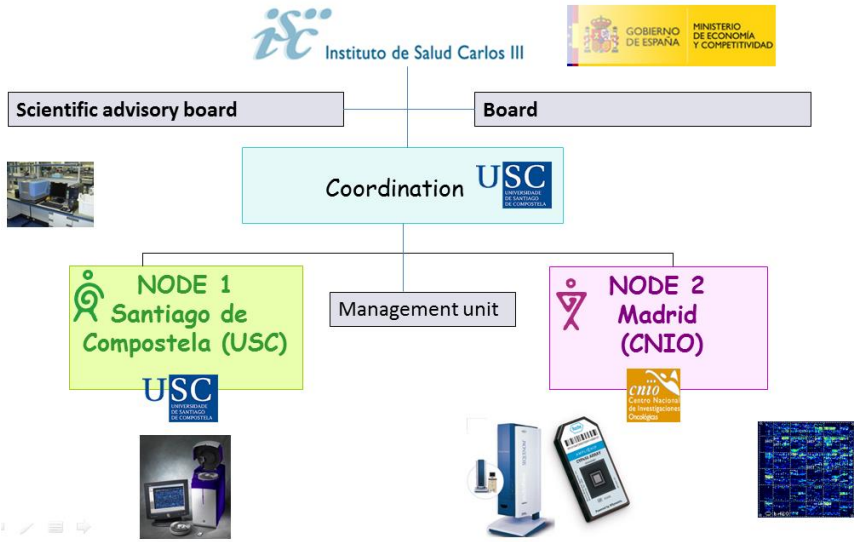


Manhattan plot



Most of biomarkers for ADRs
Most of biomarkers for complex – low heritability disease

CENTRO NACIONAL DE GENOTIPADO CEGEN-ISCIII



Common variants conferring risk of schizophrenia

Nature Stefansonn et al. Aug 2009 (SGENE Consortium)

Genome-wide significant association of seven markers with schizophrenia

ne/ SNP[allele]	Frequency	SGENE-plus* (2,663 cases; 13,498 controls)		Follow-up (4,999 cases; 15,555 controls)		SGENE-plus + follow-up (7,662 cases; 29,053 controls)		SGENE-plus + follow-up + ISC + MGS (12,951 cases; 34,594 controls)		Region/ neighbouring gene
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
rs6913660[C]†☆	0.85	1.22 (1.10, 1.36)	0.00023	1.11 (1.04, 1.19)	0.0021	1.14 (1.08, 1.21)	4.7×10^{-6}	1.15 (1.10, 1.21)	1.1×10^{-9}	MHC/ *HIST1H2BJ*
rs13219354[T]‡☆	0.90	1.25 (1.11, 1.42)	0.00043	1.19 (1.08, 1.30)	0.00022	1.21 (1.12, 1.30)	4.4×10^{-7}	1.20 (1.14, 1.27)	1.3×10^{-10}	MHC/ *PRSS16*
rs6932590[T]§☆	0.78	1.15 (1.05, 1.26)	0.0024	1.17 (1.10, 1.25)	4.9×10^{-7}	1.17 (1.11, 1.23)	4.4×10^{-9}	1.16 (1.11, 1.21)	1.4×10^{-12}	MHC/ *PRSS16*
rs13211507[T]‖☆	0.92	1.24 (1.08, 1.42)	0.0027	1.27 (1.15, 1.40)	3.1×10^{-6}	1.26 (1.16, 1.36)	3.1×10^{-8}	1.24 (1.16, 1.32)	8.3×10^{-11}	MHC/ *PGBD1*
rs3131296[G]¶☆	0.87	1.21 (1.08, 1.36)	0.0011	1.20 (1.11, 1.30)	5.3×10^{-6}	1.21 (1.13, 1.29)	2.1×10^{-8}	1.19 (1.13, 1.25)	2.3×10^{-10}	MHC/ *NOTCH4*
rs12807809[T]	0.83	1.19 (1.08, 1.32)	0.00045	1.13 (1.06, 1.21)	0.00022	1.15 (1.09, 1.22)	5.0×10^{-7}	1.15 (1.10, 1.20)	2.4×10^{-9}	*NRGN*
rs9960767[C]#☆	0.056	1.30 (1.11, 1.51)	0.0011	1.20 (1.08, 1.33)	0.00044	1.23 (1.13, 1.34)	2.2×10^{-6}	1.23 (1.15, 1.32)	4.1×10^{-9}	*TCF4*

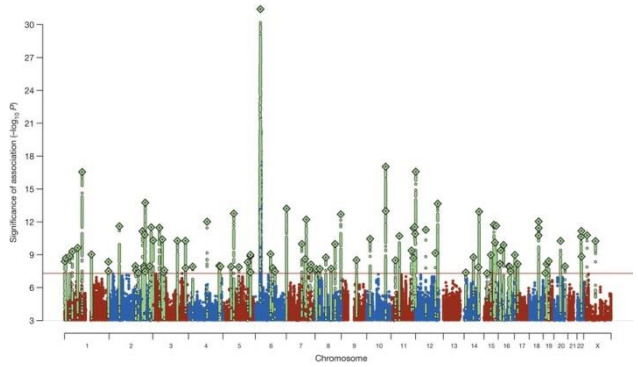
19,000 cases and 35,000 controls from Iceland, Denmark, Denmark, Germany, Hungary,
the Netherlands, Norway, Russia, Sweden, Finland; Spain (Santiago) and Spain (Valencia)

1st 2,663 cases and 13,498 controls

2nd top 1,500 in 4500 cases and 4500 controls

3rd top 25 in 4,999 cases and 15,555 controls

4th top 10 in 14,000 cases and 16,000 controls



Kandhaler et al. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry. 2015 Mar; 2(3): 258–270.

Medicina Xenómica

nature mental health

Explore content · About the journal · Publish with us

nature > nature mental health > articles > article

Article | Published: 22 March 2023

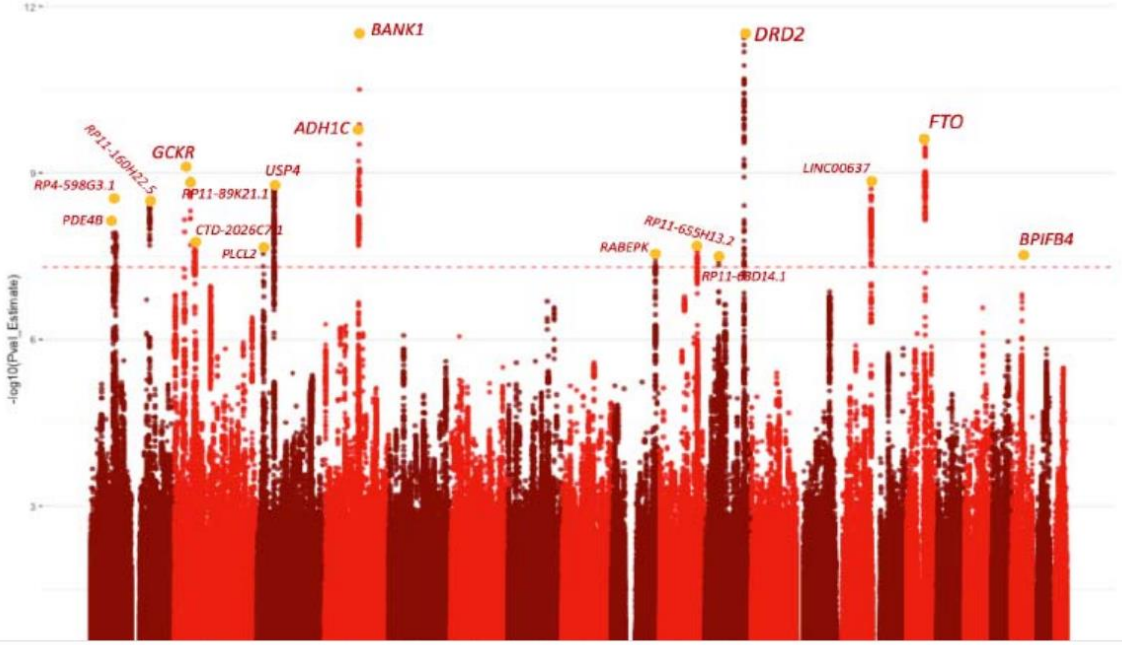
Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders

Alexander S. Hatoum, Sarah M. C. Colbert, Emma C. Johnson, Spencer B. Huggett, Joseph D. Deak, Gita A. Pathak, Mariela V. Jennings, Sarah E. Paul, Nicole R. Karcher, Isabella Hansen, David A. A. Baranger, Alexis Edwards, Andrew D. Grotzinger, Substance Use Disorder Working Group of the Psychiatric Genomics Consortium, Elliot M. Tucker-Drob, Henry R. Kranzler, Lea K. Davis, Sandra Sanchez-Roige,

USC Universidade de Santiago de Compostela

PGC Psychiatric Genomics Consortium

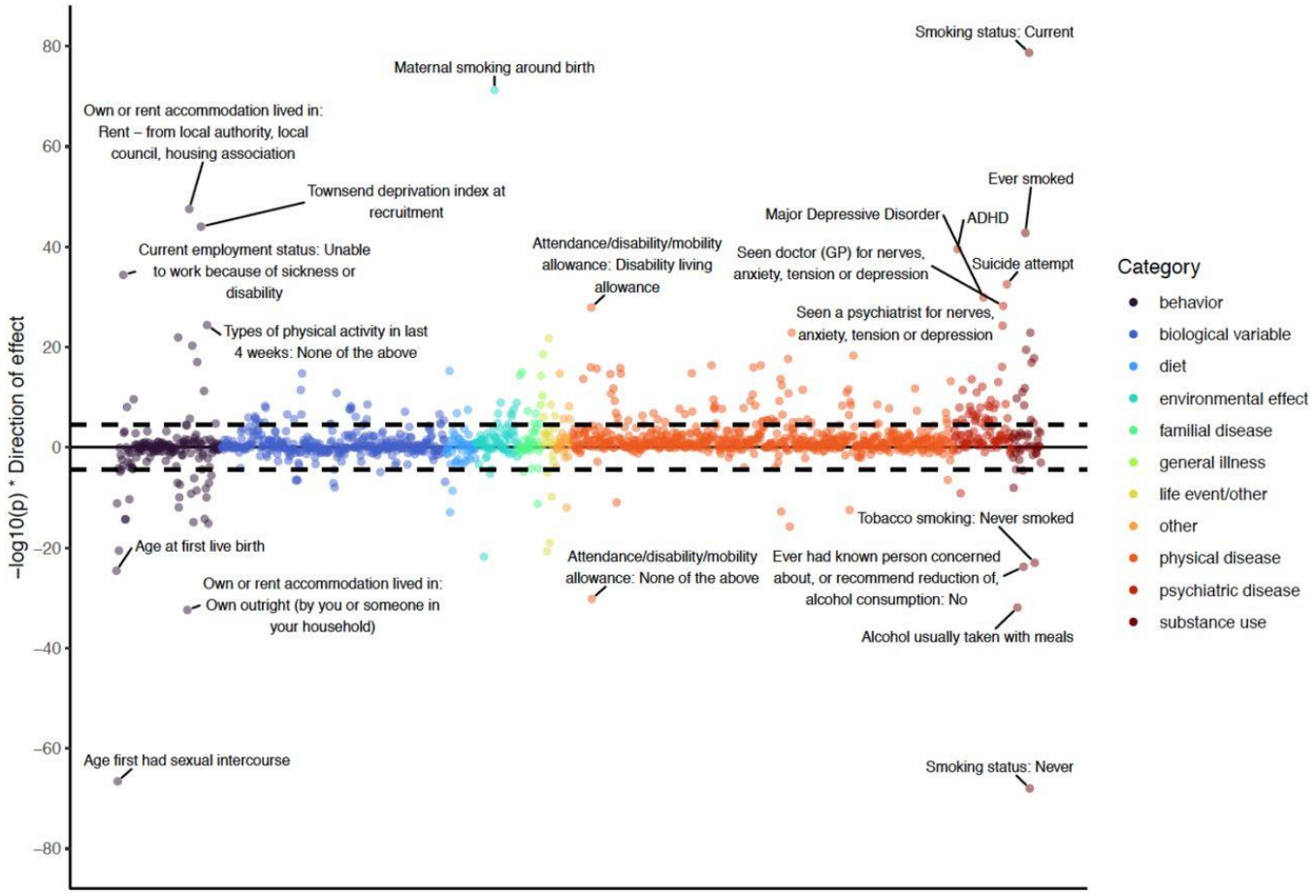
GWAS for prob.alcohol use, problematic tobacco use, and cannabis and opioid use disorders in a sample of **1,025,550** individuals of European and **92,630 individuals of** African descent.



DRD2 plays a **role in reward sensitivity** and may also be central to **executive functioning**

PDE4B, which has been implicated in prior GWASs. The **PDE4 antagonist, ibudilast, has been shown to reduce heavy drinking among patients** with AUD and also shown to reduce inflammation in methamphetamine use disorder. Th

Substance Use Disorder Working Group of the Psychiatric Genomics Consortium



Phenome Wide Association Study (PheWAS) of the *addiction-rf* polygenic risk score (PRS) in the BioVU electronic health record database (N=66,915).

"Our analyses highlight the robust genetic association of the addiction-rf with serious mental and somatic illness. The addictionrf PRS was more **strongly associated with using drugs to cope with internalizing disorder symptoms (anxiety, depression; rG = 0.60–0.62) than with the individual psychiatric traits and disorders themselves** (rG = 0.3), suggesting that genetic **correlations between SUDs and mood disorders** may partially be attributable to a predisposition to use substances to alleviate negative mood states ('self-medication')·

PheWAS is a study design in which the association between SNPs or other types of DNA variants is tested across a large number of different phenotypes

Transcription Wide Association Studies (TWAS) in ASD

Rodriguez-Fontenla and Carracedo *Translational Psychiatry* (2021)11:256
https://doi.org/10.1038/s41398-021-01378-8

Translational Psychiatry

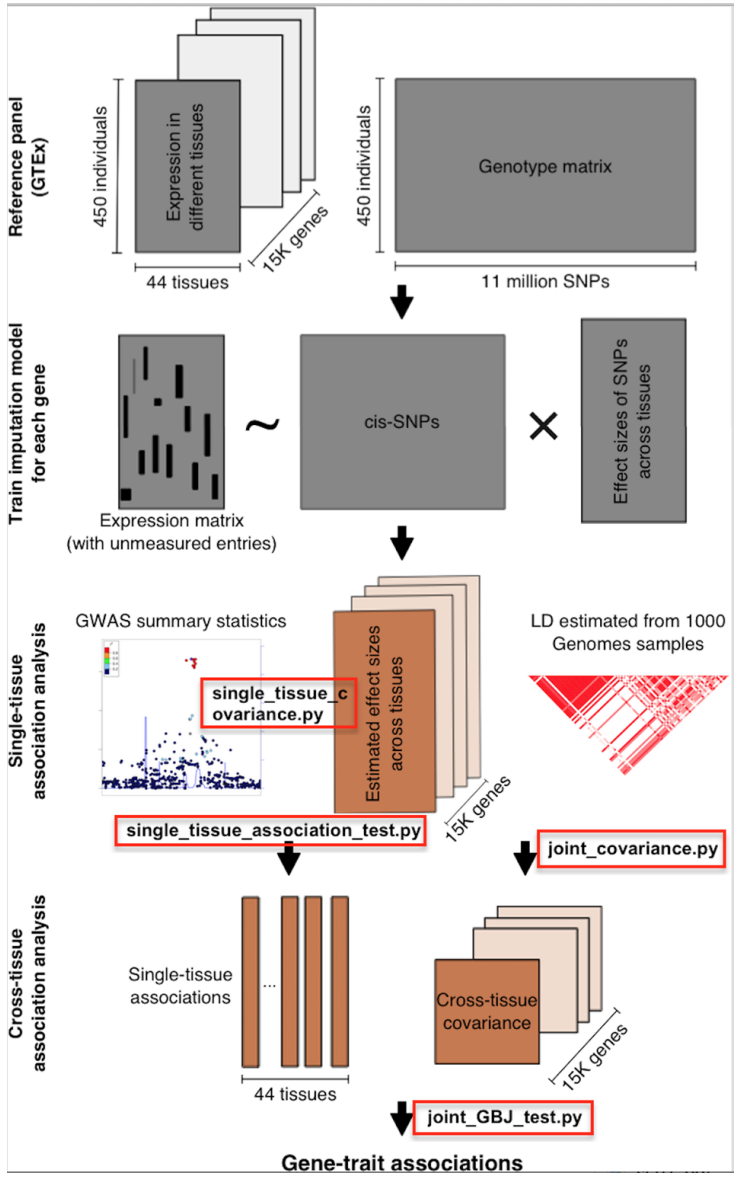
ARTICLE Open Access

UTMOST, a single and cross-tissue TWAS (Transcriptome Wide Association Study), reveals new ASD (Autism Spectrum Disorder) associated genes

TWAS (Transcriptome Wide Association Studies) which integrate tissue expression and genetic data, are a great approach to identify new ASD susceptibility genes.

Loci	Location hg19	MinP (UTMOST)	Tissue	Z score	SNPs in model	Other associations GWAS, GBA and/or TWAS
PTPRE	chr10:129705325-129884164	1.53×10^{-6}	Brain cortex	−4.8	6	–
*CIPC**	chr14:77564601-77583630	3.82×10^{-6}	Brain hipoccampus	−4.62	19	–
NKX2-2	chr20:21491660-21494664	9.38×10^{-9}	Brain nucleo accubens basal ganglia	−5.74	62	Grove et al./Alonso-Gonzalez et al.
*PINX1**	chr8:10622884-10697299	3.82×10^{-6}	Brain nucleo accubens basal ganglia	4.62	14	Grove et al./Alonso-Gonzalez et al. (neighbour gene C8orf74)

NKX2-2, MANBA,ERI1, and *MITF* associated in gastrointestinal tissue
ASD can be a multisystemic disorder involving the participation of other body tissues as the gastrointestinal



EMBAJADA DE ESPAÑA EN BRASIL
CONSEJERIA CULTURAL

cooperación española

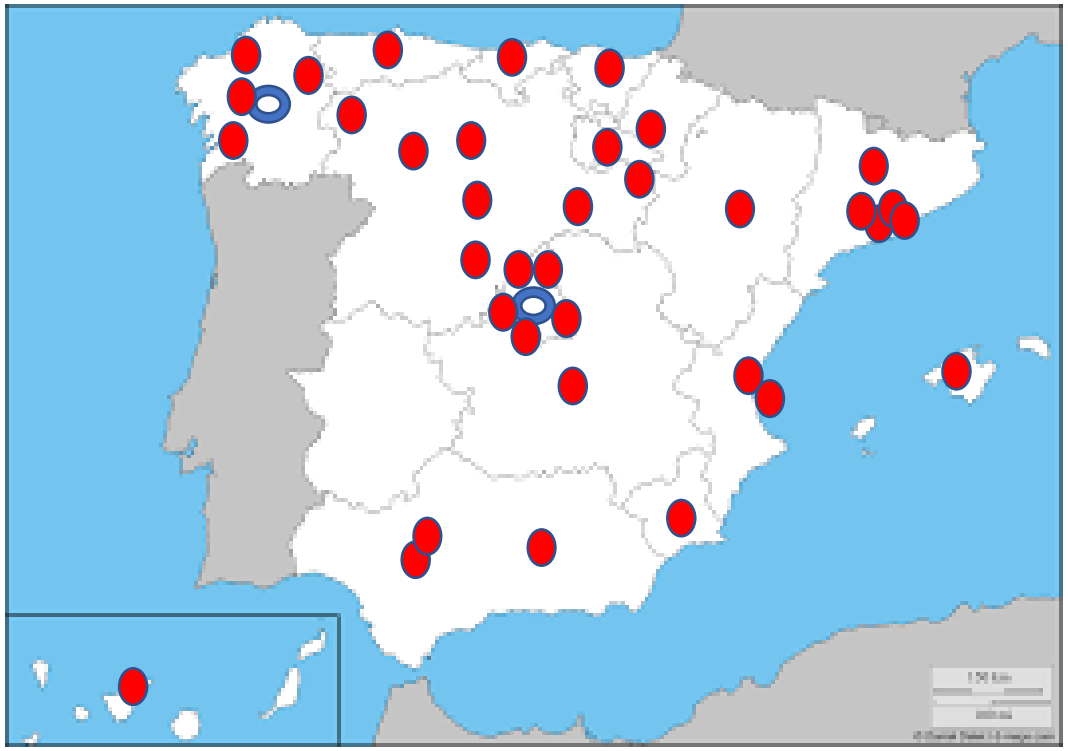
acebra
Asociación de Científicos Españoles en Brasil

SCourGe
Spanish COalition to Unlock Research on host GEnetics on COVID-19

GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA E INNOVACIÓN · isciii Instituto de Salud Carlos III

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

IP: A. Carracedo (USC-FPGMX)
Co-IP: P. Lapunzina (H. La Paz)



Latinoamérica:
22 grupos

España

46 grupos clínicos

14 grupos de investigación

9 biobancos

20,000 España
8,000 LA

Población control (BNADN+CeGEN)**: 8000**

CRD: 174 variables grouped in 8 forms
Minimal set of 17 variables to enter data

EMBAJADA DE ESPAÑA EN BRASIL
CONSEJERIA CULTURAL

cooperación española

acebra
Asociación de Científicos Españoles en Brasil

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

GWAS and meta-analysis identifies 49 genetic variants underlying critical Covid-19

Erola Pairo-Castineira[‡,1,2], Konrad Rawlik[‡,1], Andrew D. Bretherick[2], Yang Wu[3], Ting Qi[4,5], Isar Nassiri[6], Marie Zechner[1], Lucija Klaric[2], Athanasios Kousathanas[7], Anne Richmond[2], Jonathan Millar[1], Clark D Russell[1,8], Tomas Malinauskas[6], Ryan Thwaites, Fiona Griffiths[1], Wilna Oosthuyzen[1], Kirstie Morrice[9], Sean Keating[10], Alistair Nichol[11], Malcolm G Semple[12,13], Julian Knight[6], Manu Shankar-Hari[8], Charlotte Summers[14], Charles Hinds[15], Peter Horby[16], Lowell Ling[17], Danny McAuley[18,19], Hugh Montgomery[20], Peter J.M. Openshaw[21,22], Timothy Walsh[10], Albert Tenesa[1,2,23], GenOMICC Investigators [*], SCOURGE Consortium [*], ISARIC4C Investigators [*], 23andMe [*], Jian Yang[4,5], Chris P Ponting[2], James F Wilson[2,23], Veronique Vitart[2], Alexandre C Pereira[24], Andre Luchessi[25,26], Esteban Parra[27], Raquel Cruz-Guerrero[28], Angel Carracedo[28,29], Angie Fawkes[9], Lee Murphy[9], Kathy Rowan[30], Andy Law[1], Benjamin Fairfax[6], Sara Clohisey Hendry[1], J. Kenneth Baillie[†,1,2,8,10].

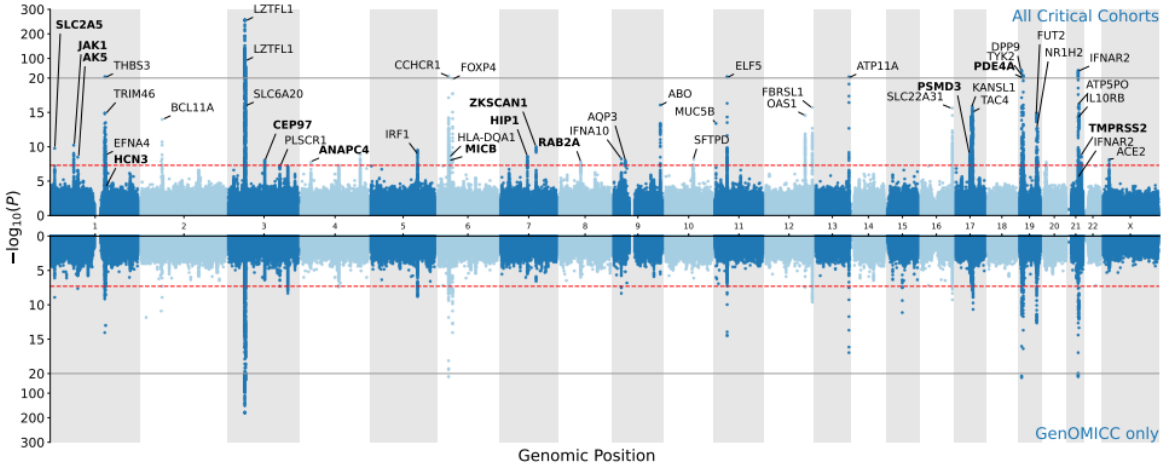
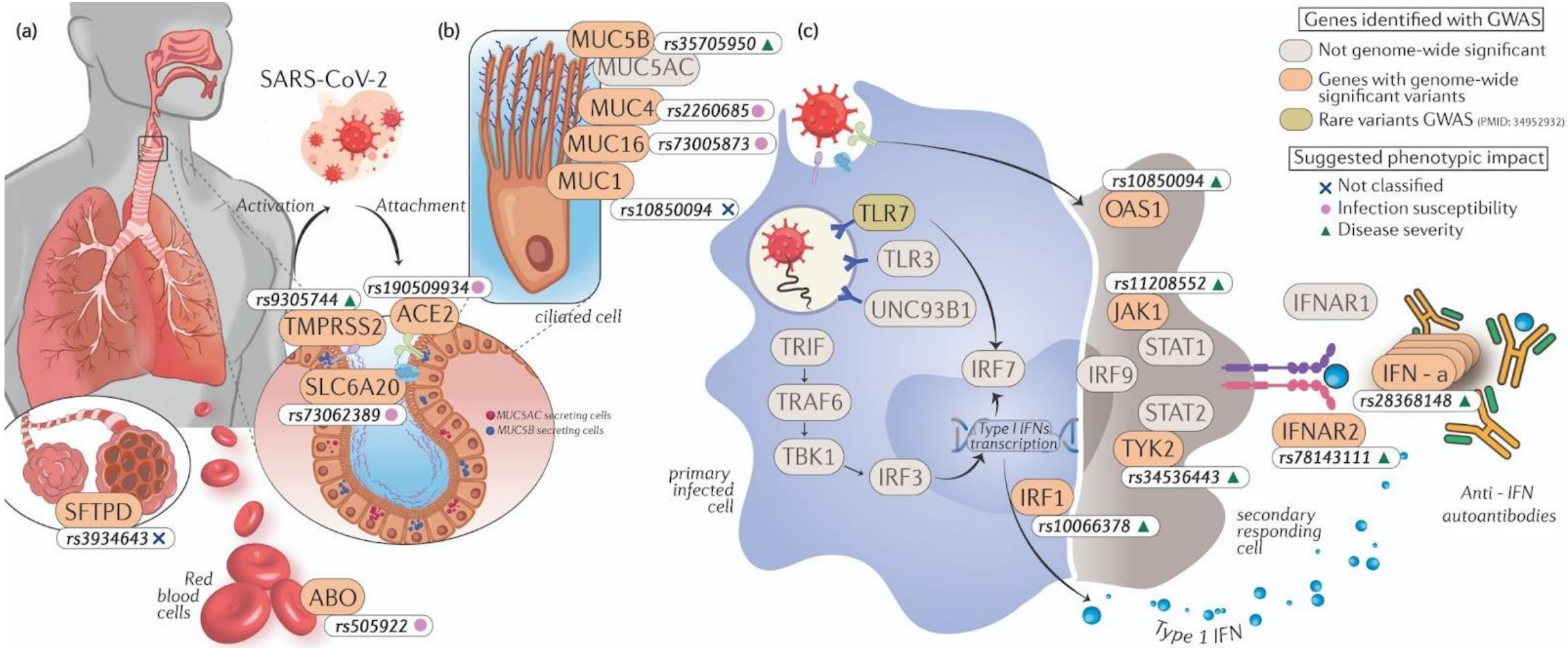


Figure 1: Miami plot showing meta-analysis results obtained using all critical phenotype cohorts (top) and using GenOMICC data only (bottom). Independent lead variants in the all critical cohorts analysis are annotated with nearby or plausible genes, with new associations from the present study in bold.

21519 critically ill cases comprising a combination of microarray genotype and whole genome sequence data from critically ill cases in the GenOMICC UK (11,440 cases)
GenOMICC Brazil (2,186) studies
ISARIC4C (678 cases)
SCOURGE consortium (5,934 cases)

Nature, 2023

Expression of PDE4A in monocytes is associated with critical Covid-19). This phosphodiesterase regulates production of multiple inflammatory cytokines by myeloid cells. Inhibition of PDE4A by several existing drugs is under investigation in multiple inflammatory diseases and has been shown to be safe in small clinical trials in patients with Covid-19. We find a strong association in a key intracellular signalling kinase, JAK1, which is stimulated by numerous cytokines including Type I interferons and IL-6. Along with TYK2, which we previously reported to be associated with severe Covid-19,1 JAK1 is the target for JAK inhibitors, which have recently been shown to be effective therapeutics in Covid-19.11 In addition to ACE2, we see for the first time a genome-wide significant association in TMPRSS2, a key host protease which facilitates viral entry, which we have previously studied as a candidate gene.

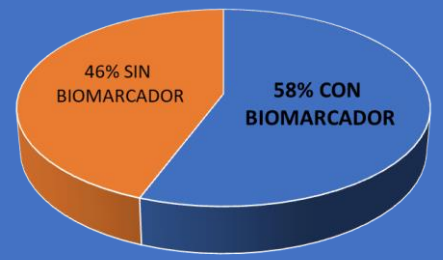


Major COVID-19 biological pathways mapped with susceptibility and severity GWAS loci. Genome-wide significant variants associated with COVID-19 (white circles) and the annotated genes (peach circles) are mapped on to pathways known to be involved in (**a**) viral entry, (**b**) entry defense in airway mucus, and (**c**) type I interferon

Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

PharmGKB
Pharmacogenomics. Knowledge. Implementation.



www.pharmgkb.org

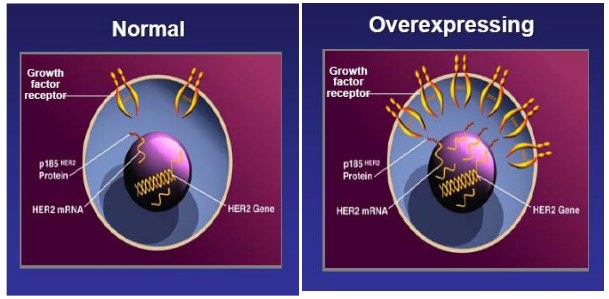
Drugs n=395	FDA n=353	EMA n=134
abacavir	Testing required Alternate Drug Prescribing Info	Testing required Alternate Drug Prescribing Info
abemaciclib	Testing required Alternate Drug Cancer Genome Prescribing Info	Testing required Alternate Drug Cancer Genome Prescribing Info

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

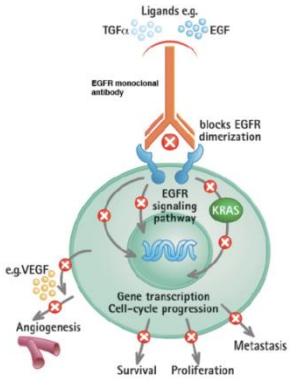
Challenge: Need of translation of ALL valid biomarkers

A new generation of drugs especially for chemotherapy are designed for specific groups of patients requiring specific PGx tests



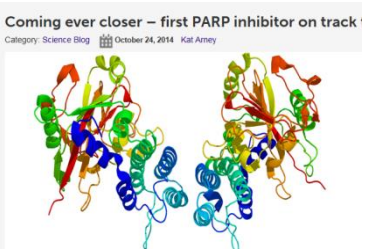
Her2 expression
Trastuzumab

Anti EFGR
Kras mutations



The Translocation of t(9;22)(q34;q11) in CML

BRCA mutations
PARP inhibitors



Disease stratification included in drug pipeline design

Some of the valid biomarkers are widely used

Challenge: Need of translation of ALL valid biomarkers

EMA
FDA

UGT1A Mandatory for EMA and FDA

The impact of increased risk of toxicity attributed the UGT1A variants may be offset by irinotecan in clinical practice by dose reduction or the use of colony stimulating factor.

Table 4: Dose reduction of irinotecan by UGT1A1*28 genotypes

		6/6		UG 6
		n	%	n
Dose	100%	41	(69.5)	19
	80-75%	16	(27.1)	11
	<75%	2	(3.4)	2

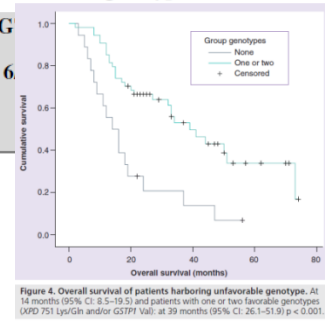
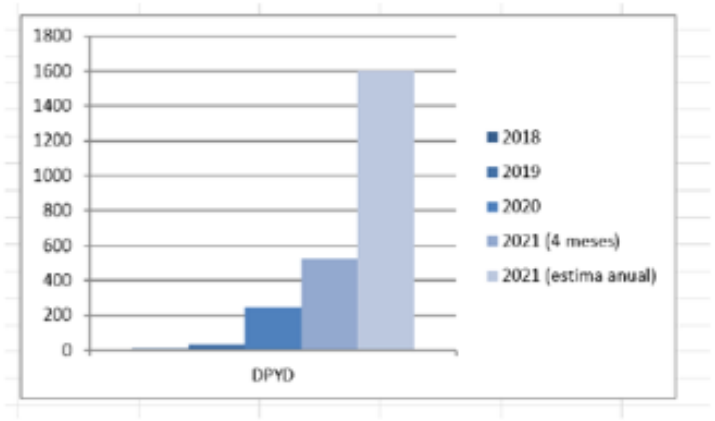


Figure 4. Overall survival of patients harboring unfavorable genotype. At 14 months (95% CI: 8.5–19.5) and patients with one or two favorable genotypes (XPD 751 Lys/Gln and/or GSTP1 Val): at 39 months (95% CI: 26.1–51.9) p < 0.001.

The value of genetic polymorphisms to predict toxicity in metastatic colorectal patients with irinotecan-based regimens. BJCP Lamas et al. 2013



DPYD testing (*2A-1%) -FU Toxicity

Retos:

Mutación somática:

Estándares técnicos y de procedimiento (incluyendo bioinfromática: filtrado, priorización y análisis de variantes)

Esquemas de PT.

Organización de datos genómicos y clínicos

Todavía mucho que hacer en “Discovery para biomarcadores de nuevos medicamentos- Necesidad de redes.

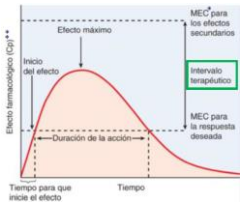
Necesidad de biobancos nacionales para ADRs

Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Translación de biomarcadores obligatorios o recomendados

SERGAS strategy to implement pharmacogenetics in Psychiatry.



Farmacokinetics

Farmacogenetics

ACCI

Action I. Patients treated with depot antipsychotics aripripazole/risperidone)

Action II. Pediatric patients treetad with psycho drugs

Estudios de coste-eficacia para los accionables

Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

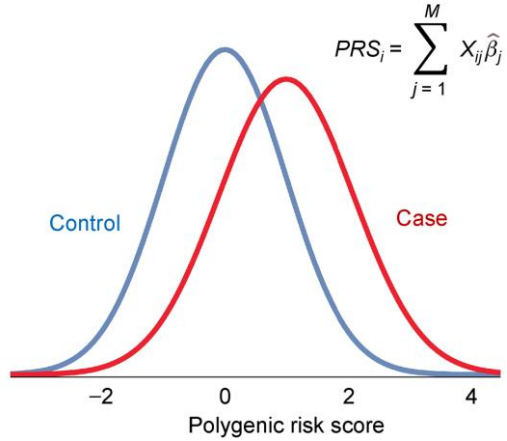
nature genetics

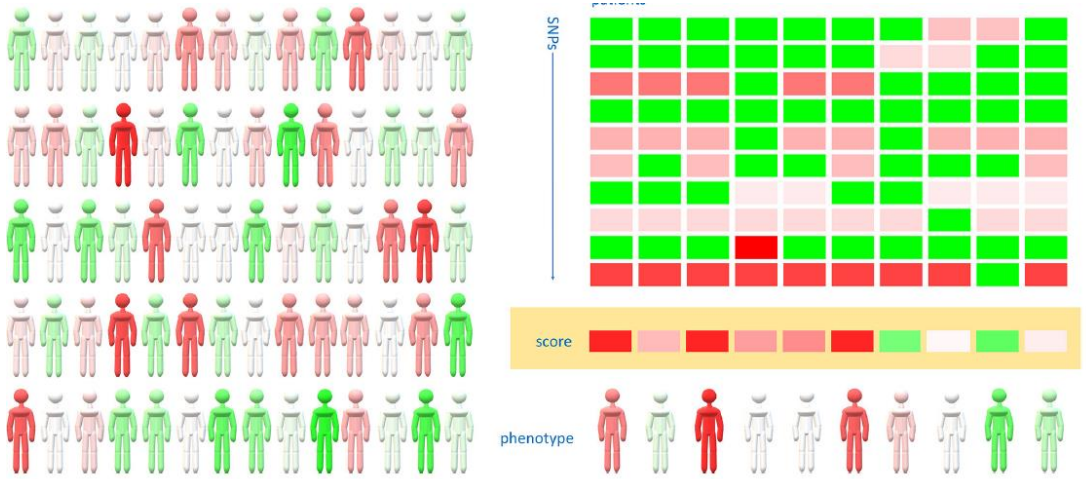
LETTERS

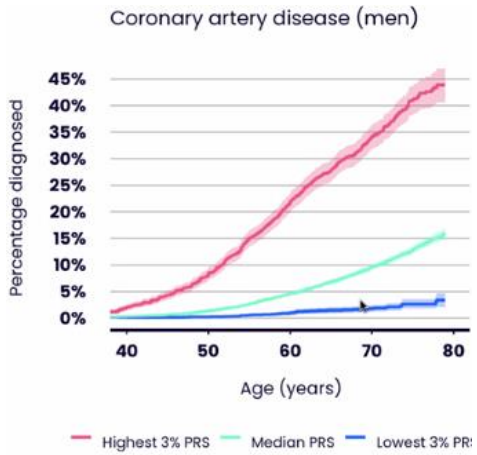
https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

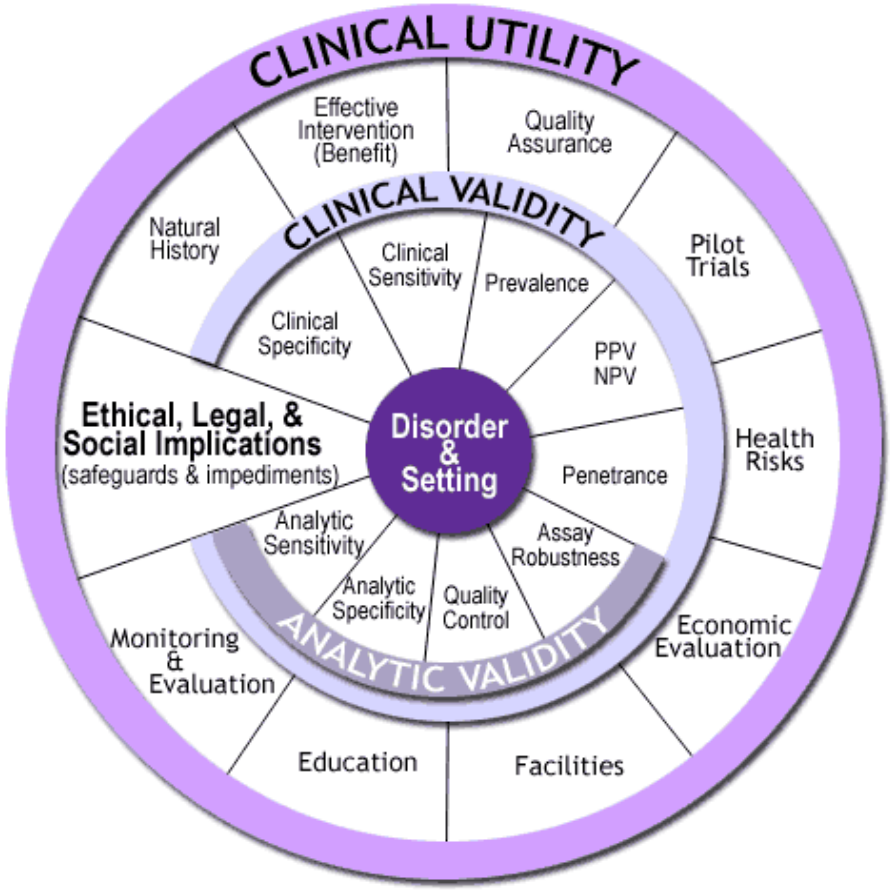






Retos: Estándares, cohortes específicas de enfermedad y organización de las mismas, cohortes poblacionales, validación de modelos.

Challenge: Ethical, legal and social implications



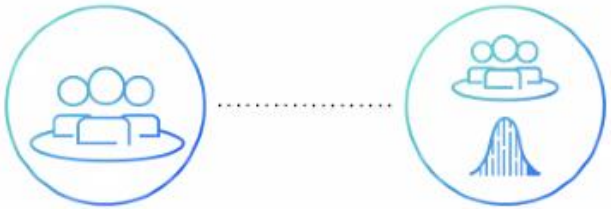
ACCE Model

Ethical aspects
Social aspects
Psychological aspects
Actionability
….

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

PRS as a population health management tool

One test to risk-stratify a population across multiple common diseases



Type 2 diabetes
Use PRS to identify individuals with non-diabetic hyperglycaemia who are more likely to progress to type 2 diabetes

Prioritise these individuals for inclusion in diabetes prevention programmes

Prevention of type 2 diabetes

Prostate cancer
Use PRS to identify men with similar high levels of risk as BRCA2 carriers

Offer PSA measurement to these individuals

Detect cancers at earlier stage

Bowel cancer
(1) Use IRT to identify high risk individuals below screening age
(2) Use IRT to prioritise colonoscopy resources

Offer FIT testing and follow-up, as per the National Screening programme

Detect cancers at earlier stage
Increase colonoscopy effectiveness

Breast cancer
Use PRS to identify high risk and moderate risk women

Offer mammograms earlier and more frequently, as per NICE guidelines

Detect cancers at earlier stage

Cardiovascular disease
Combine PRS with QRISK to identify additional high risk individuals

Offer statins to these individuals

Reduce CVD events and death

Osteoporosis
Combine PRS with FRAX to identify additional high and moderate risk individuals

Offer medication and/or BMD measurement to these individuals

Identify and treat osteoporosis and prevent fracture & resulting morbidity/mortality

Glaucoma
Use PRS to identify high risk individuals below age 60

Offer eye tests to these individuals

Detect glaucoma at earlier stage

1 **Genotype** individuals in the population once.

2 **Use Polygenic Risk Scores (or integrated risk)** to calculate risk for each disease.

3 For each disease, **identify individuals at clinically actionable high risk** who are currently "invisible" to the system.

4 For each disease, plan and execute **interventions** within existing patient pathways in the NHS for these high-risk individuals.

5 **Improve patient outcomes**

Cortesía de Peter Donnelly, 2022

313 variantes= BREAST CANCER POLYGENIC RISK SCORE

ARTICLE

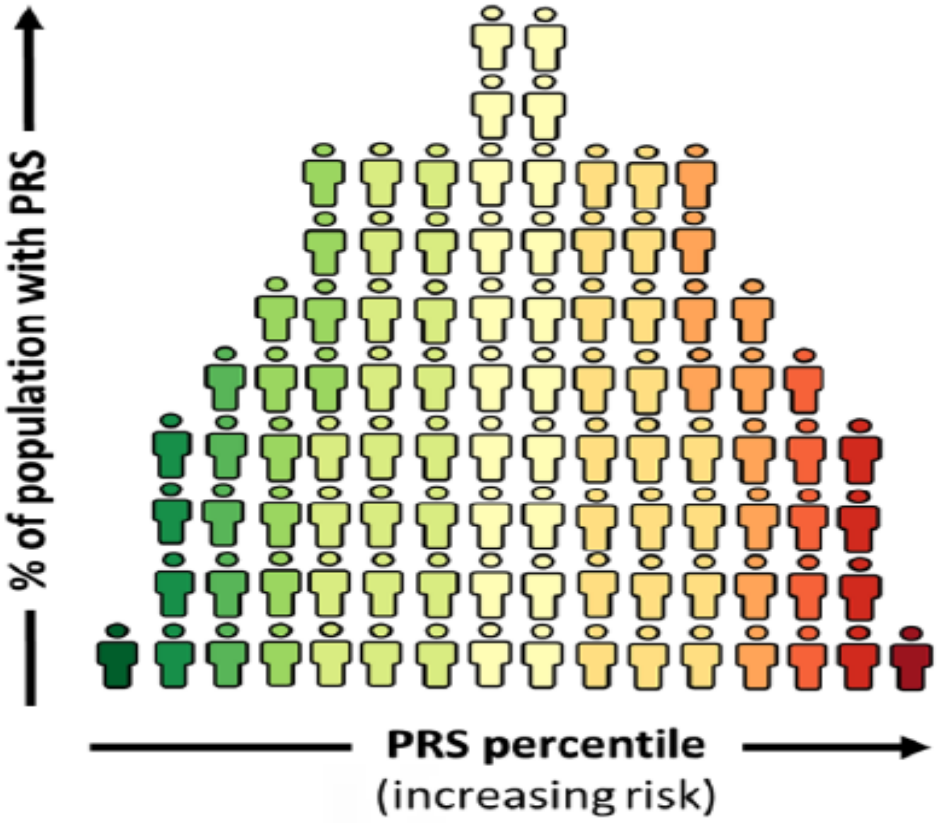
Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes

Stratification of women according to their risk of breast cancer based on polygenic risk scores (PRSs) could improve screening and prevention strategies. Our aim was to develop PRSs, optimized for prediction of estrogen receptor (ER)-specific disease, from the largest available genome-wide association dataset and to empirically validate the PRSs in prospective studies. The development dataset comprised 94,075 case subjects and 75,017 control subjects of European ancestry from 69 studies, divided into training and validation sets. Samples were genotyped using genome-wide arrays, and single-nucleotide polymorphisms (SNPs) were selected by stepwise regression or lasso penalized regression. The best performing PRSs were validated in an independent test set comprising 11,428 case subjects and 18,323 control subjects from 10 prospective studies and 190,040 women from UK Biobank (3,215 incident breast cancers). For the best PRSs (313 SNPs), the odds ratio for overall disease per 1 standard deviation in ten prospective studies was 1.61 (95%CI: 1.57–1.65) with area under receiver-operator curve (AUC) = 0.630 (95%CI: 0.628–0.651). The lifetime risk of overall breast cancer in the top centile of the PRSs was 32.6%. Compared with women in the middle quintile, those in the highest 1% of risk had 4.37- and 2.78-fold risks, and those in the lowest 1% of risk had 0.16- and 0.27-fold risks, of developing ER-positive and ER-negative disease, respectively. Goodness-of-fit tests indicated that this PRS was well calibrated and predicts disease risk accurately in the tails of the distribution. This PRS is a powerful and reliable predictor of breast cancer risk that may improve breast cancer prevention programs.

PRS percentile	Risk of disease vs. reference group
0-1	Lowest
1-5	
5-10	
10-20	
20-40	
40-60 (reference)	**1**
60-80	
80-90	
90-95	
95-99	
99-100	Highest

Source: RGA

Puntuación de riesgo poligénico:
suma ponderada de los alelos de riesgo.



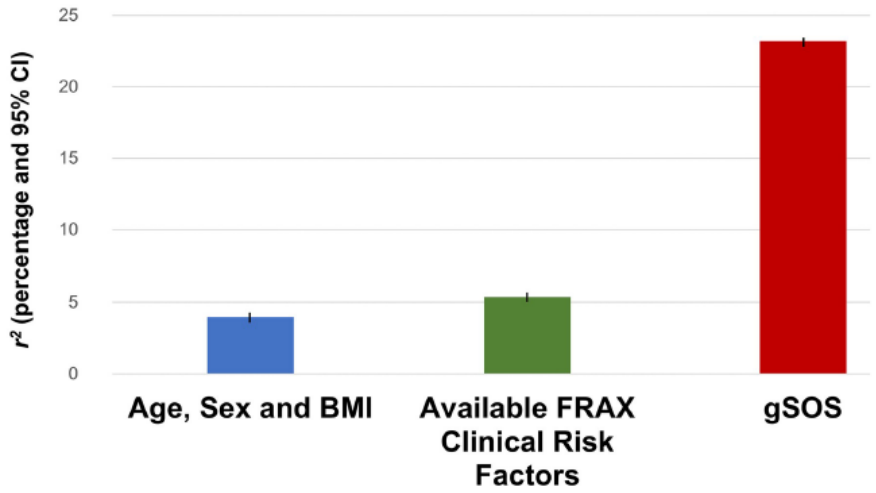


Fig 5. Variance explained in SOS by clinical risk factors and gSOS in the UK Biobank Test Set. Available FRAX clinical risk factors included age, sex, BMI, smoking, previous fracture, use of glucocorticoids, rheumatoid arthritis, and secondary osteoporosis. BMI, body mass index; FRAX, Fracture Risk Assessment Tool; SOS, speed of sound.

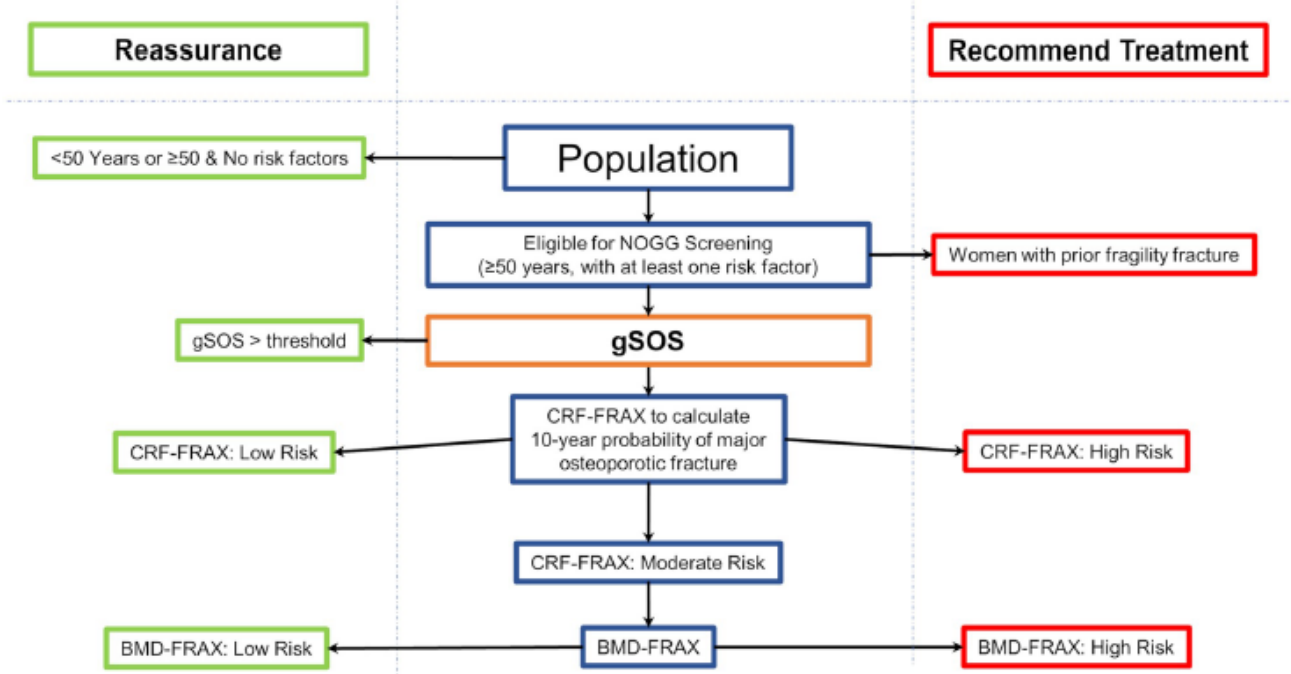
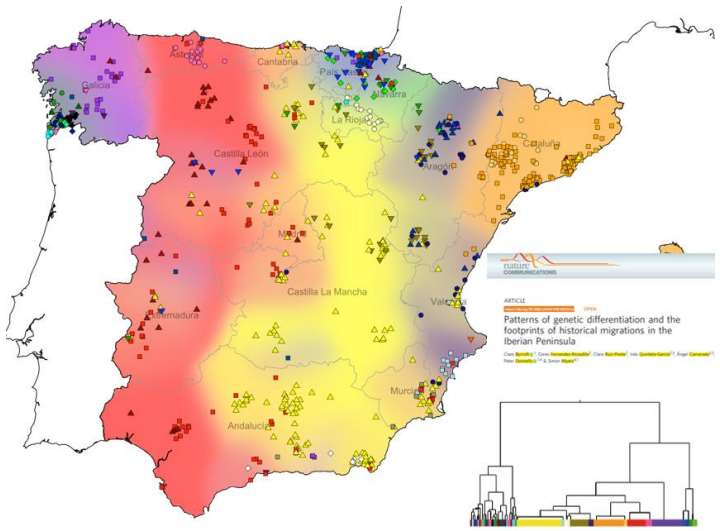


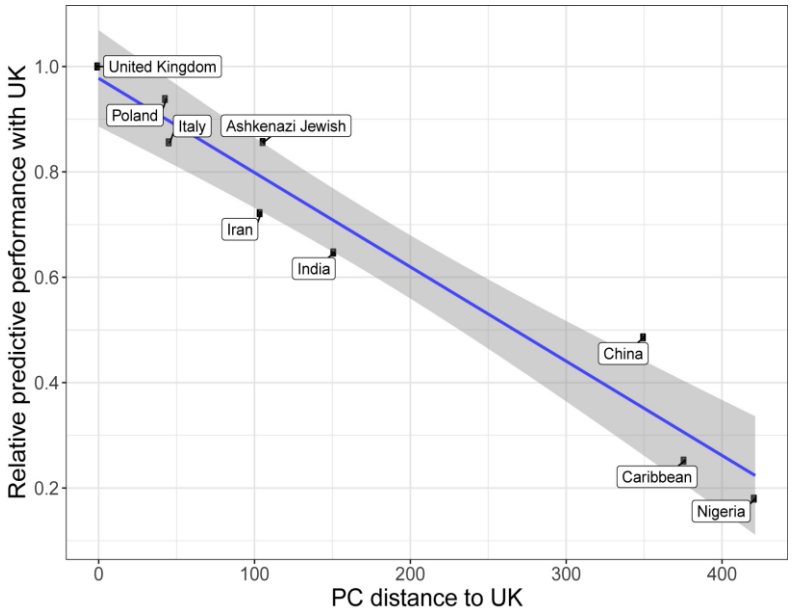
Fig 3. NOGG screening strategy with a gSOS screening step. Both CRF-based FRAX and BMD-based FRAX generate a 10-year probability of major osteoporotic fracture, which is used to designate risk of fracture. gSOS is standardized to have a mean of 0 and standard deviation of 1. BMD-FRAX, bone-mineral-density-based Fracture Risk Assessment Tool; CRF-FRAX, clinical-risk-factor-based Fracture Risk Assessment Tool; NOGG, National Osteoporosis Guideline Group.

Forgetta et al. (2020) Development of a polygenic risk score to improve screening for fracture risk: A genetic risk prediction study. PLoS Med 17(7): e1003152.

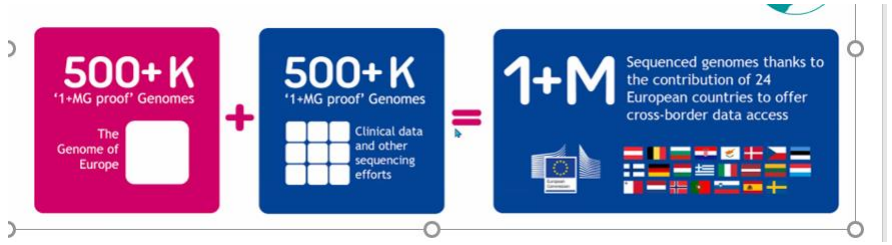
Population stratification

PRS are not easily portable across population subgroups and lose predictive performance >> need to recalibrate PRS locally based on local reference data





Privé F. et al. Portability of 245 polygenic scores when derived from the UK Biobank and applied to 9 ancestry groups from the same cohort. **Am J Hum Genet** Jan 2022 109: 12-23



The Genome of Europe (GoE)

Realising a population genomic reference cohort of at least 500,000 citizens across Europe by 2022

Shared Polygenic Risk Score (PRS)

Estudio de asociación

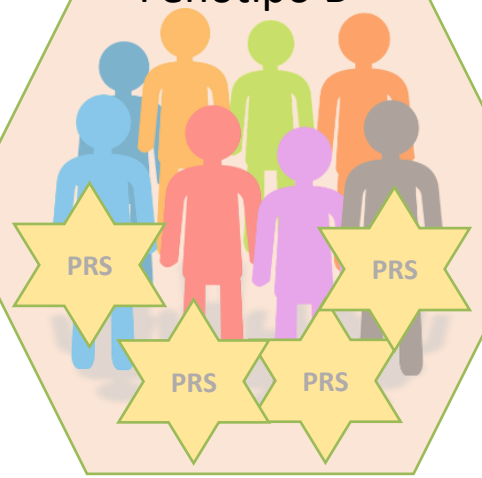
Muestra descubrimiento
Estadísticas resumen de un GWAS

Muestra diana
Datos genotípicos a nivel individual

Fenotipo /A

PRS de Fenotipo A

Fenotipo B



Análisis estadístico

Variable dependiente:
- Fenotipo B

Variables independientes:
- PRS de Fenotipo A
- Otras variables

- *

ARTICLE OPEN

Check for updates

Psychiatric polygenic risk as a predictor of COVID-19 risk and severity: insight into the genetic overlap between schizophrenia and COVID-19

M. Alemany-Navarro[1,2,3,4], S. Diz-de Almeida[2,5], R. Cruz[2,5], J. A. Riancho[6,7,8], A. Rojas-Martínez[9], P. Lapunzina[5,10,11], C. Flores[12,13,14,15], Scourge Cohort Group and A. Carracedo[2,3,4,5]

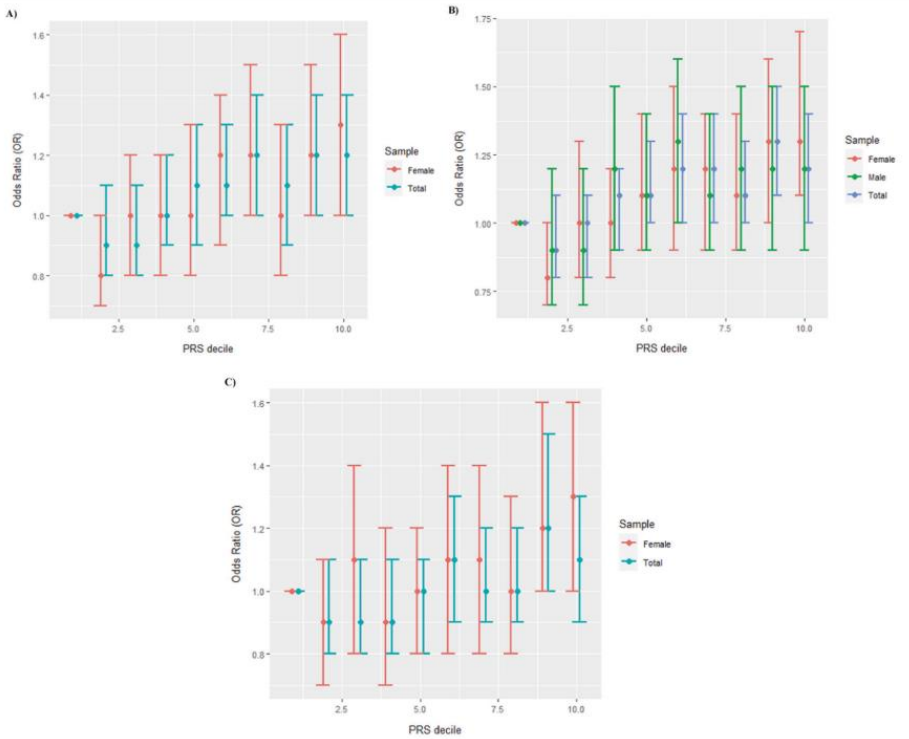
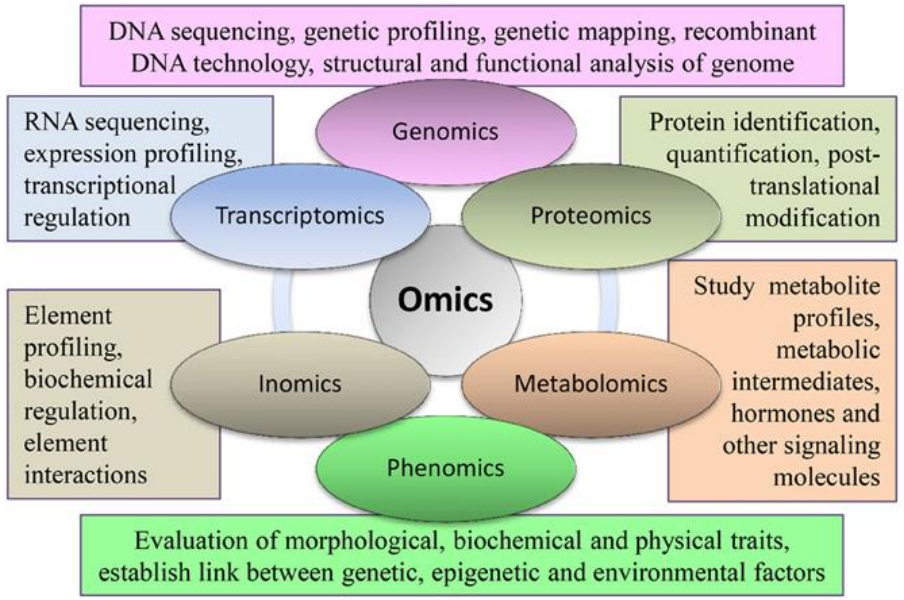


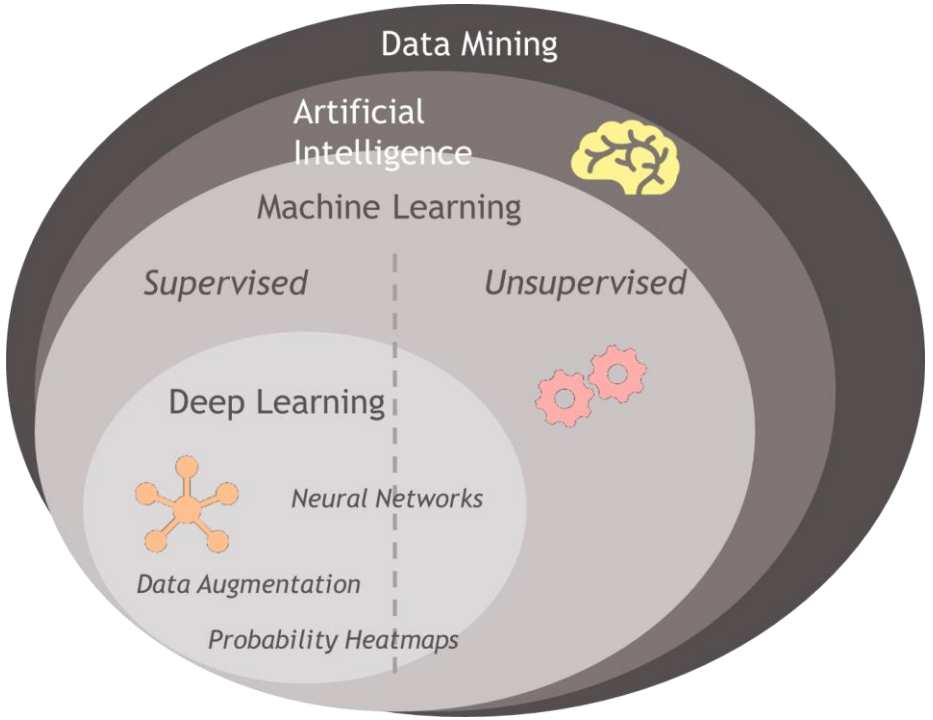
Fig. 1 Odds ratios (OR) by the decile of the global SCZ PRS. OR for **A** COVID-19 cases; **B** symptomatic COVID-19 cases; and **C** hospitalized COVID-19 cases. Error bars represent 95% confidence intervals.

The SCZ PRS was a significant predictor in the case/control, symptomatic/asymptomatic, and hospitalization/no hospitalization analyses in the total and female samples; and of symptomatic/asymptomatic status in men.

The future: Integration of biomarkers and decision models



- Correlación entre todos los tipos de datos
- Interacción entre los datos



Challenges of integration

Lost values and class desequilibrium

Noise and complexity of data

The dimensionality paradox (more variables than samples)

Heterogeinity and redundance of data

Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA


thebmj covid-19 Research Education News & Views Campaigns Jobs

Research Methods & Reporting

Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians

BMJ 2018 ; 362 doi: https://doi.org/10.1136/bmj.k601 (Published 12 July 2018)

Mendelian randomisation uses genetic variation as a natural experiment to investigate the causal relations between potentially modifiable risk factors and health outcomes in observational data.
It is a type of approach that takes genetic variants associated with a risk factor (i.e calcium) as instrumental variants to examine the causality between exposure and outcome (e.g. BMD). Since genes are independent MR analysis are less susceptible to counfunding factors.

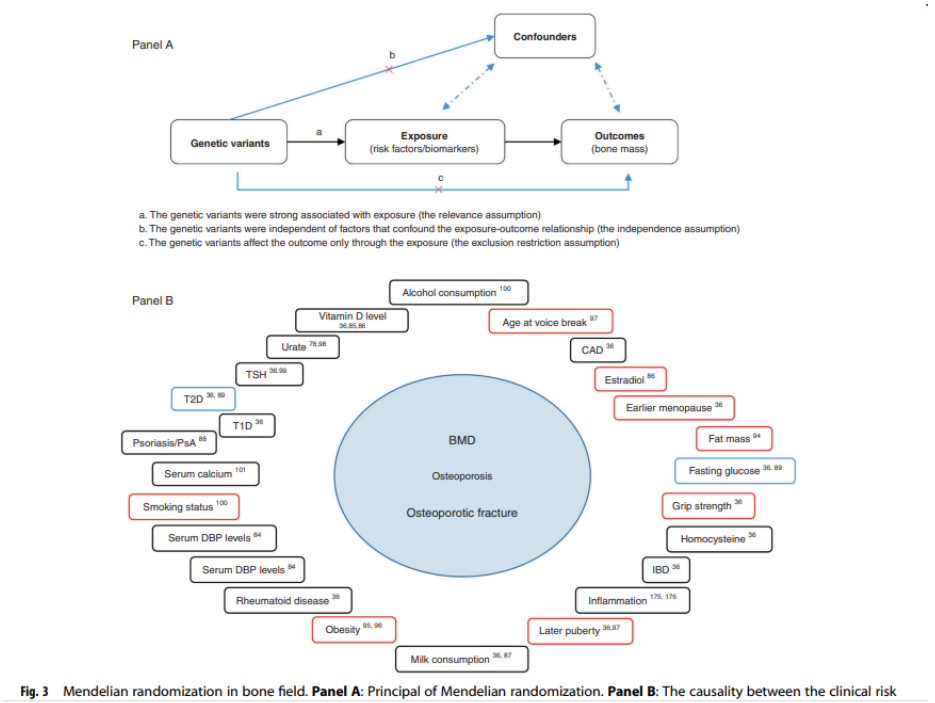


Fig. 3 Mendelian randomization in bone field. **Panel A**: Principal of Mendelian randomization. **Panel B**: The causality between the clinical risk


Use of Mendelian Randomization to Examine Causal Inference in Osteoporosis

Jie Zheng [†], Monika Frysz [2†], John P. Kemp [1,3], David M. Evans [1,3], George Davey Smith [1] and Jonathan H. Tobias [1,2]*

frontiers in Endocrinology

REVIEW
published: 21 November 2019
doi: 10.3389/fendo.2019.00807

To date, the most important findings have been around the lack of causal role of traditional risk factors such as vitamin D in determining variation within the normal range of BMD/fracture risk.

Medicina Xenómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

IMPaCT- Precision Medicine Infrastructure Associated with Science and Technology

INFRAESTRUCTURA DE MEDICINA DE PRECISION ASOCIADA A LA CIENCIA Y LA TECNOLOGIA

IMPaCT

PLAN ESTRATÉGICO

https://www.isciii.es/QueHacemos/Financiacion/IMPaCT/Paginas/Plan.aspx

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

Instituto de Salud Carlos III

ESTRUCTURA ORGANIZATIVA

L.E.T. 1 ÉTICA E INTEGRIDAD CIÉNTIFICA

L.E.T. 2 INTERNACIONALIZACIÓN

Traslación a la práctica clínica

WP1	WP2	WP3	WP4	WP5
Coordinación	Red de Centros de Análisis Genómico de Soporte al SNS	Enfermedades Raras	Cáncer	Farmacogenómica

GdT-T1. Servicios Genómicos: procesos diagnósticos y modelo de informe de laboratorio.

EJE ESTRATÉGICO 02
Ciencia de datos

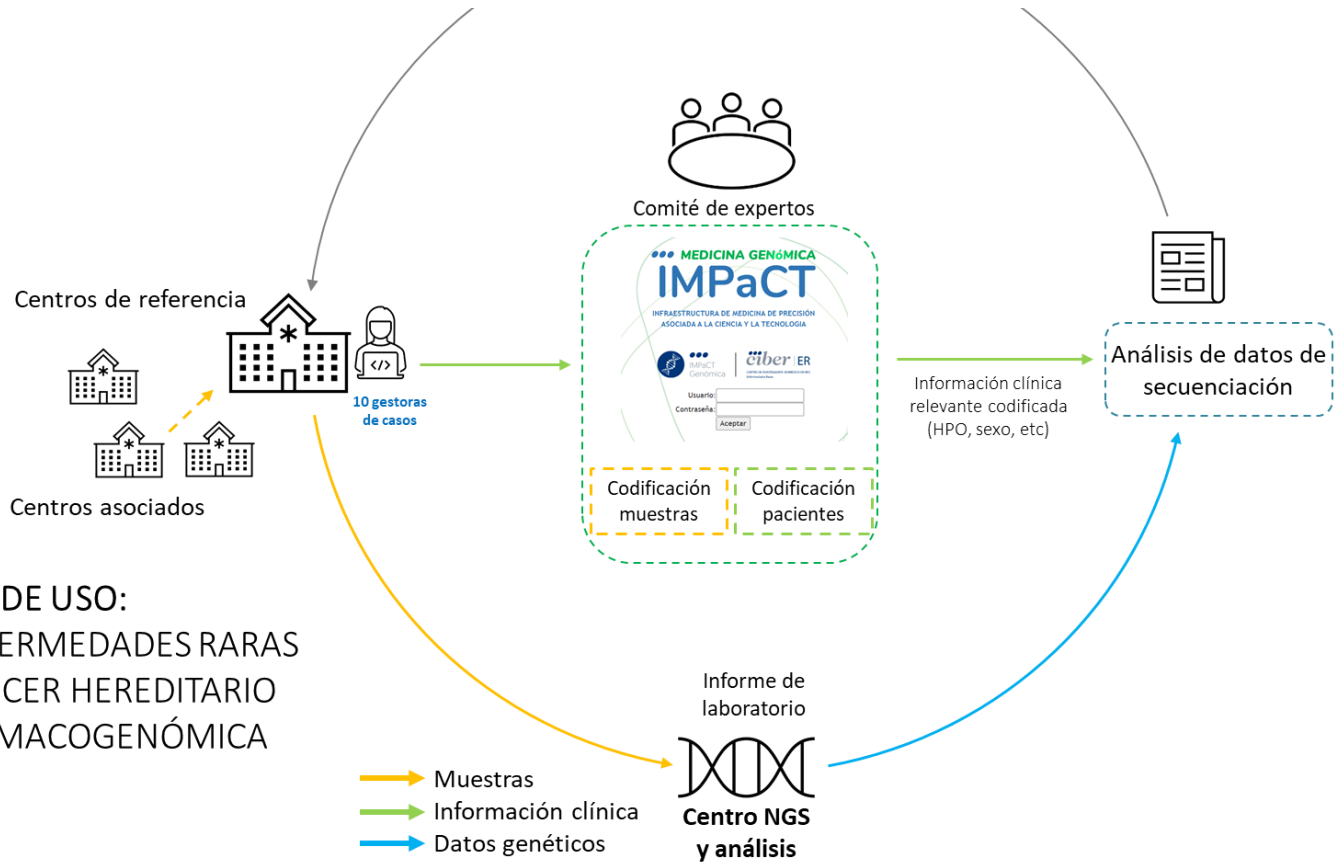
GdT-T2. Herramientas para el análisis, priorización y clasificación de variantes.

GdT-T3. Almacenamiento y Data Sharing.

IMPaCT Genómica

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Circuito 1: infraestructura cooperativa para el análisis genómico de alta complejidad



Circuito 2: uso secundario de datos con fines de investigación científica

EUROPEAN GENOME-PHENOME ARCHIVE

1+MG

IMPaCT Genómica

ciber

CASOS DE USO:

- ENFERMEDADES RARAS
- CÁNCER HEREDITARIO
- FARMACOGENÓMICA

ciber ER CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Enfermedades Raras

IMPaCT Genómica

RED DE CENTROS IMPaCT-GENÓMICA

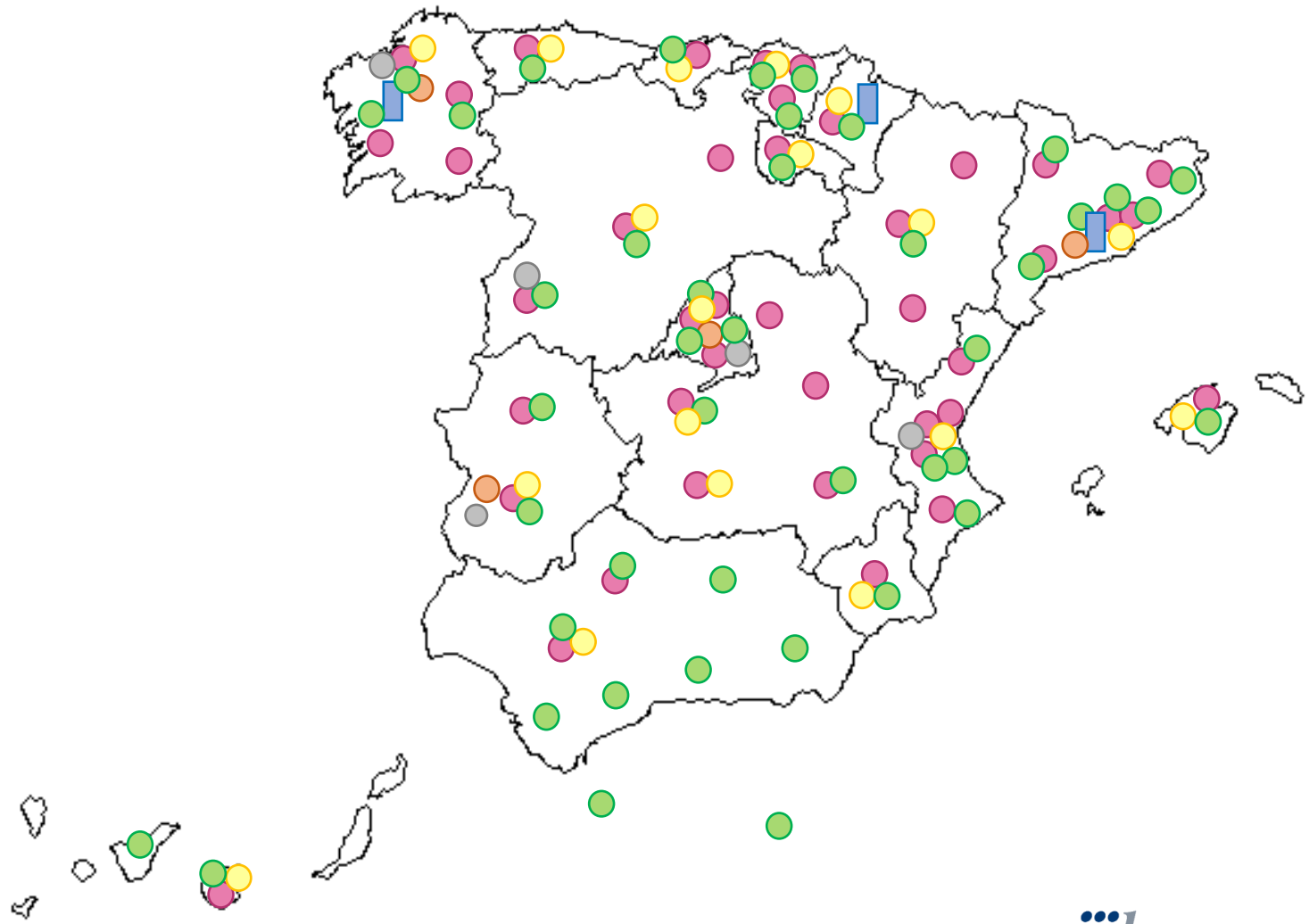
17
Comunidades Autónomas

3
Centros de secuenciación

+100
Hospitales

- Coordinación- gestión
- Centros de Secuenciación
- Hospitales coordinadores

Red de hospitales
- WP3- Raras
- WP4- Cáncer
- WP5- Farmacogenómica



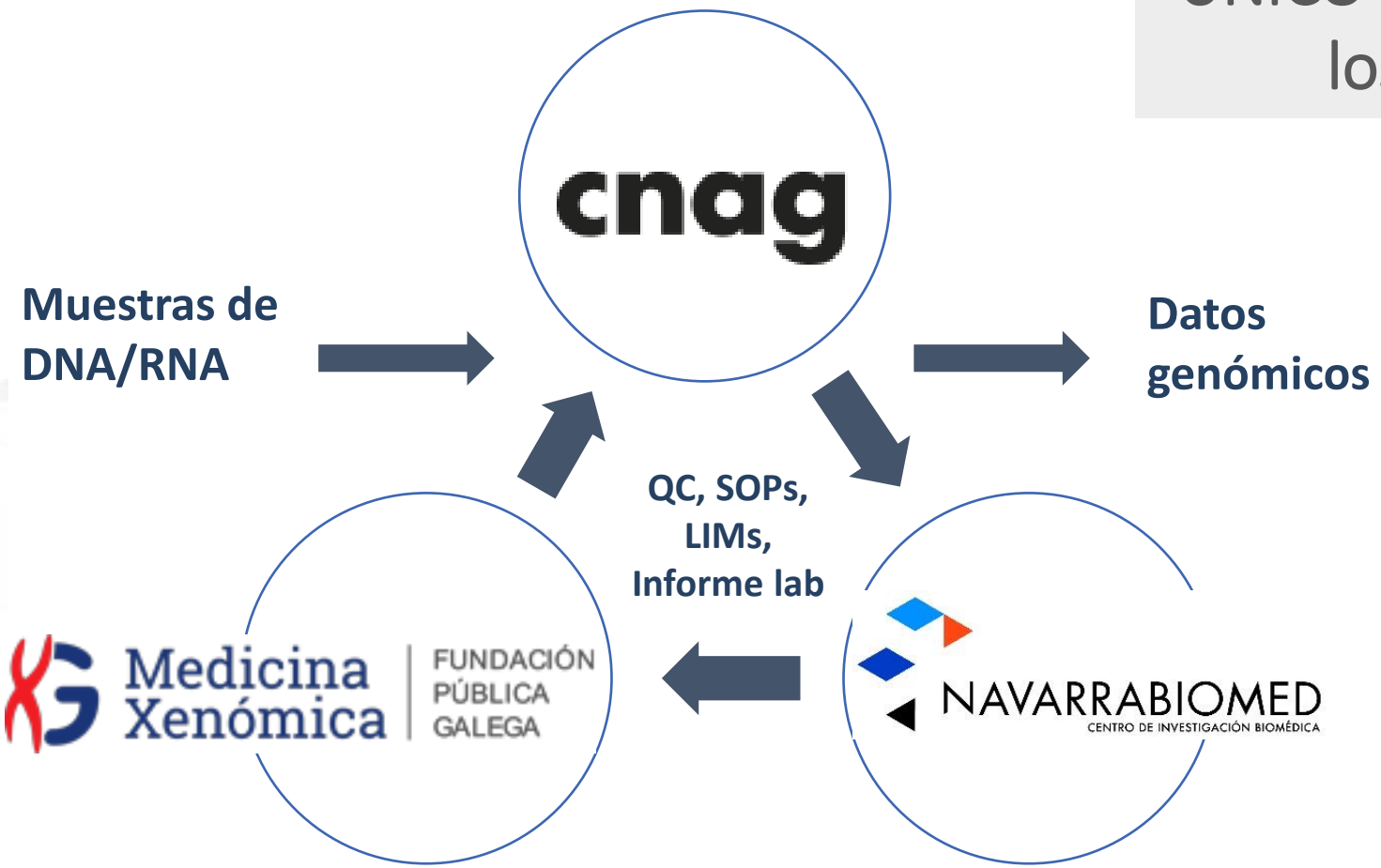
ciber ER CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Enfermedades Raras

RED DE CENTROS DE ANÁLISIS GENÓMICO

Consensuado un modelo ÚNICO de trabajo entre los 3 centros

3

Centros de secuenciación



REQUISITOS ÉTICOS y LEGALES

CONSENTIMIENTOS INFORMADOS

- APROBADOS POR CEI ISCIII
  - CI DIAGNÓSTICO
  - CI USO SECUNDARIO
- Adicionalmente 40 hospitales han requerido evaluación por su propio CEI.

ACUERDO DE TRANSFERENCIA DE MATERIAL Y DATOS (MTA/DTA)

RELEVANCIA:

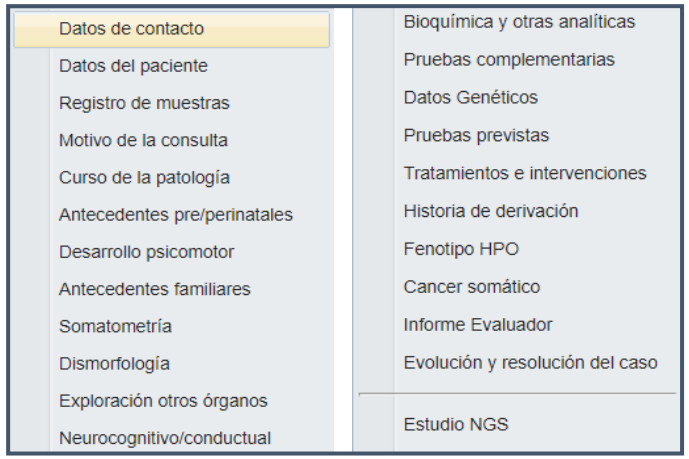
- Posibilita la gestión interna y flujo de muestras y datos.
- Posibilita la cesión de datos para el uso secundario.

Firmado por 5 instituciones

Hospital + CNAG + FPGMX + NB + CIBER

75 MTA/DTA que cubren 110 HOSPITALES

ESTABLECIMIENTO DE LA PLATAFORMA DE FENOTIPADO CLÍNICO



- MODELO DE LA PLATAFORMA DE ENOD-CIBERER
- DATOS INCLUIDOS EN SERVIDOR CIBER

Usos:

- INCORPORACIÓN DE INFORMACIÓN CLÍNICA
- FENOTIPADO HPO (Human Phenotype Ontology)
- EVALUACIÓN Y DISCUSIÓN DE CASOS

- CODIFICACIÓN DE PACIENTES
- CODIFICACIÓN DE LA MUESTRA

ESTABLECIMIENTO DE PLATAFORMA DE ANÁLISIS Y PRIORIZACIÓN DE VARIANTES

- DISCUSIÓN DE REQUERIMIENTOS PARA EL ANÁLISIS DE LOS DATOS (enfermedades raras, cáncer, farmacogenómica).
- Características de las herramientas de análisis disponibles.
- Selección, presentación y discusión de 4 herramientas de análisis.
- SELECCIÓN DE LA HERRAMIENTA COMÚN PARA EL PROGRAMA.

GPAP
Genome - Phenome Analysis Platform

- ENTREGABLE: GUÍA DE FILTRADO Y PRIORIZACIÓN DE VARIANTES.

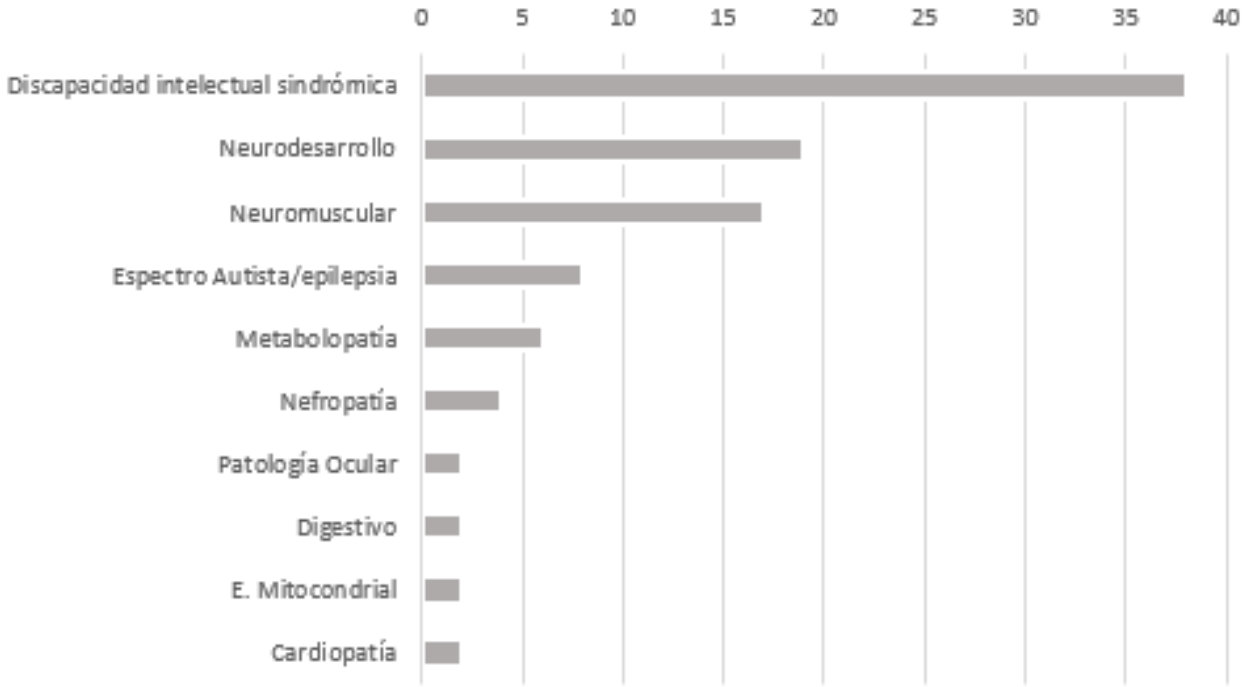
TRASLACIÓN A LA PRÁCTICA CLÍNICA: ENFERMEDADES RARAS

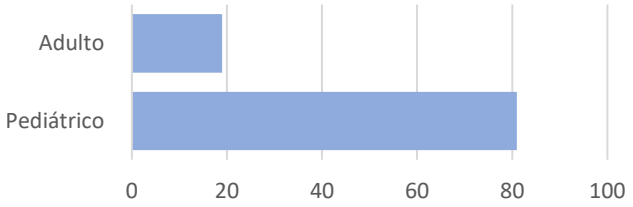
29/05/2023

REVISIÓN DE ESTUDIOS GENÓMICOS PREVIOS PARA MEJORAR EFICIENCIA DEL PROGRAMA

- 750 reanálisis de WES
- 79 pacientes diagnosticados
- Tasa diagnóstica 13-15 %
- 12 casos VALIDACIÓN FUNCIONAL

N° Casos diagnosticados por CCAA





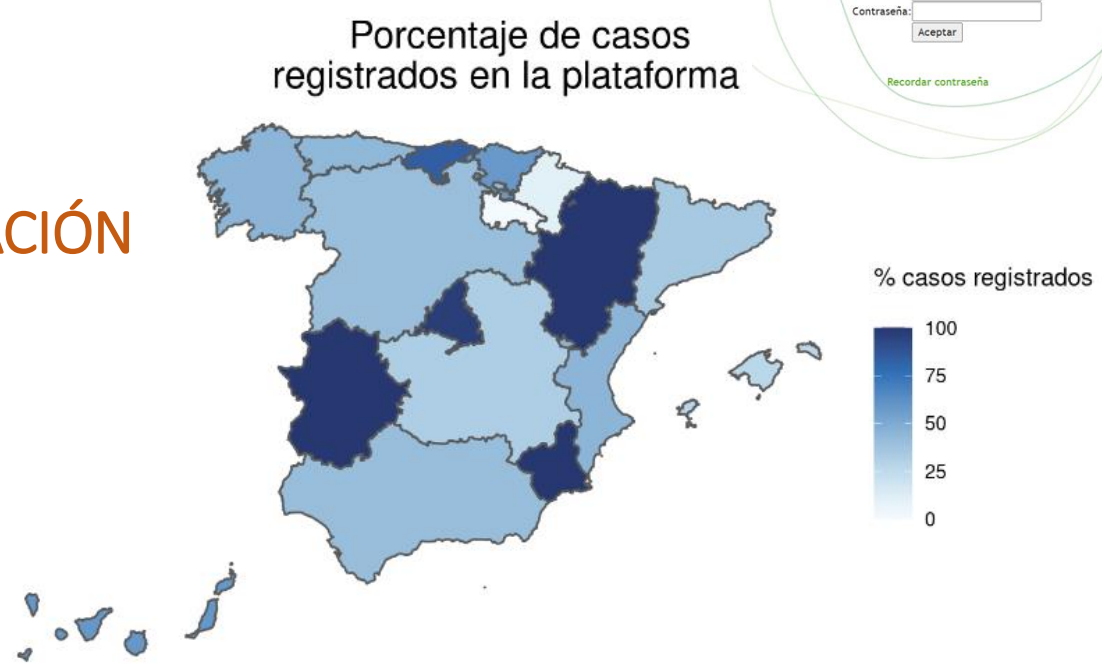
TRASLACIÓN A LA PRÁCTICA CLÍNICA: ENFERMEDADES RARAS

14/04/2023

SELECCIÓN DE PACIENTES y REGISTRO CLÍNICO EN PLATAFORMA

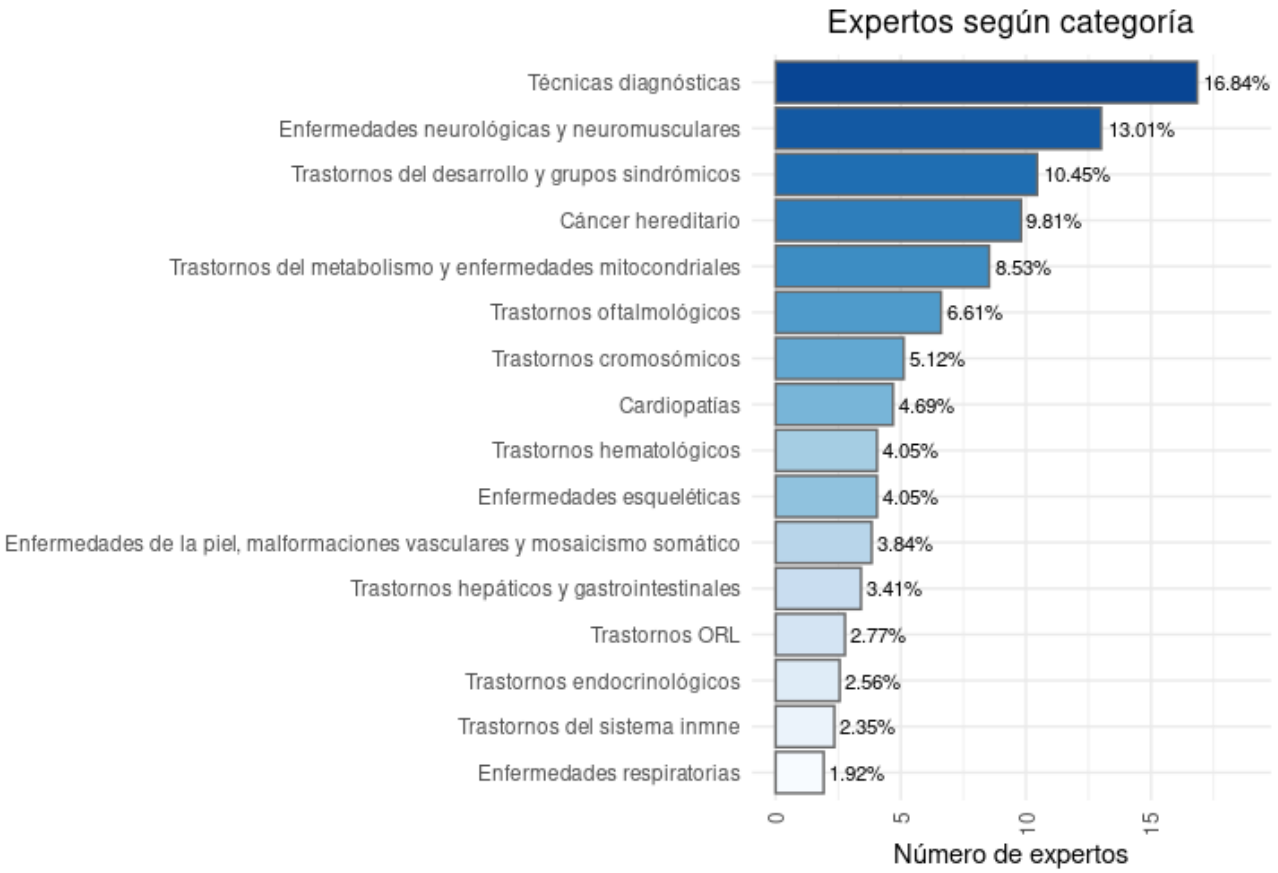
- 2.000 pacientes enfermedades raras
  - 60% de los casos registrados en la plataforma de registro clínico
  - 87% de los casos, seleccionados.
  - PREVISTO COMPLETAR REGISTRO/SECUENCIACIÓN en SEPTIEMBRE.

Previsto 4000 pacientes más 2024-2026



TRASLACIÓN A LA PRÁCTICA CLÍNICA: ENFERMEDADES RARAS

COMITÉS DE EXPERTOS



GENERADA PLATAFORMA BASE DE DATOS

- Categorías de **PATOLOGÍAS, (ORPHA/OMIM)**
- **Genes** (GeneID)
- Técnicas y **PROCEDIMIENTOS DIAGNÓSTICOS**
- Grupos de **VALIDACIÓN FUNCIONAL**

https://expertos.ciberisciii.es/

+ 500 expertos inscritos

- DATOS: + 1300 genes OMIM

  + 1000 enfermedades de 16 categorías

- En proceso

FORMACIÓN

- TALLERES FENOTIPADO HPO PARA CLÍNICOS
- TALLER SOBRE EGA-BEACONS
- TALLER USO DE LA PLATAFORMA DE RECOGIDA DE LA INFORMACIÓN CLÍNICA
- TALLER USO DE LA PLATAFORMA DE ANÁLISIS GENÓMICO
- TALLER ASPECTOS ÉTICOS Y LEGALES

ALIANZAS CON ASOCIACIONES DE PACIENTES

- REUNIONES BILATERALES PERIÓDICAS CON FEDER
- JORNADAS DIVULGATIVAS
- WEBINARIO INCLUSIÓN PACIENTES

- PREMIO Somos FEDER:

  "Proyectos de alto impacto para la mejora del acceso al diagnóstico para personas con enfermedades raras".

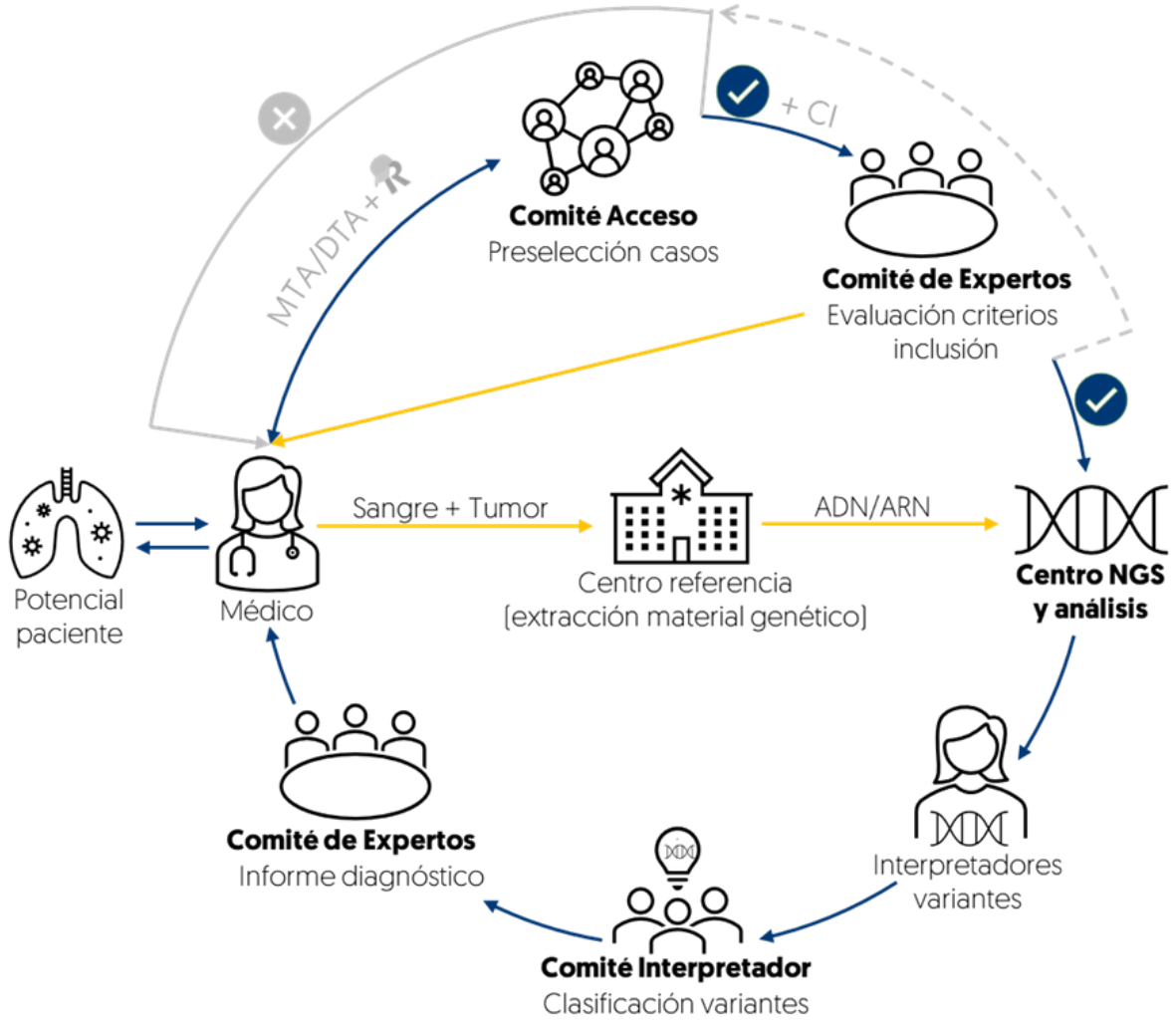
- Protocolo inclusión a petición del paciente:

Revisar criterios de inclusión	• Estudio de secuenciación de **exoma previo no concluyente.** • Disponibilidad de **muestras de familiares.** • **Médico de contacto** interesado en incluir el caso.
Contactar* Autorización tratamiento datos personales	• Se le enviará una **autorización para el tratamiento de sus datos personales,** que tendrá que remitir cumplimentada y firmada para continuar con la tramitación de su solicitud. • En caso de no recibir esta autorización se borrarán los datos recogidos hasta la fecha.
Solicitud de información relacionada con la patología	• Datos personales y **comunidad autónoma** de residencia. • Breve **descripción del caso** (ej: enfermedad neuromuscular). • **Exoma clínico o completo** – SI/NO (indicar cuál). • Otros **estudios genéticos** (ej: cariotipo, panel de genes, etc.). • Hospital y **clínico de referencia interesado** (importante ya que se contactará con él/ella).
Valoración de la solicitud	• Si se cumplen los criterios iniciales la solicitud será trasladada **al coordinador de CCAA para su valoración.**
Resolución	• Desde el programa se le informará de si la **solicitud ha sido admitida/desestimada** y motivos.

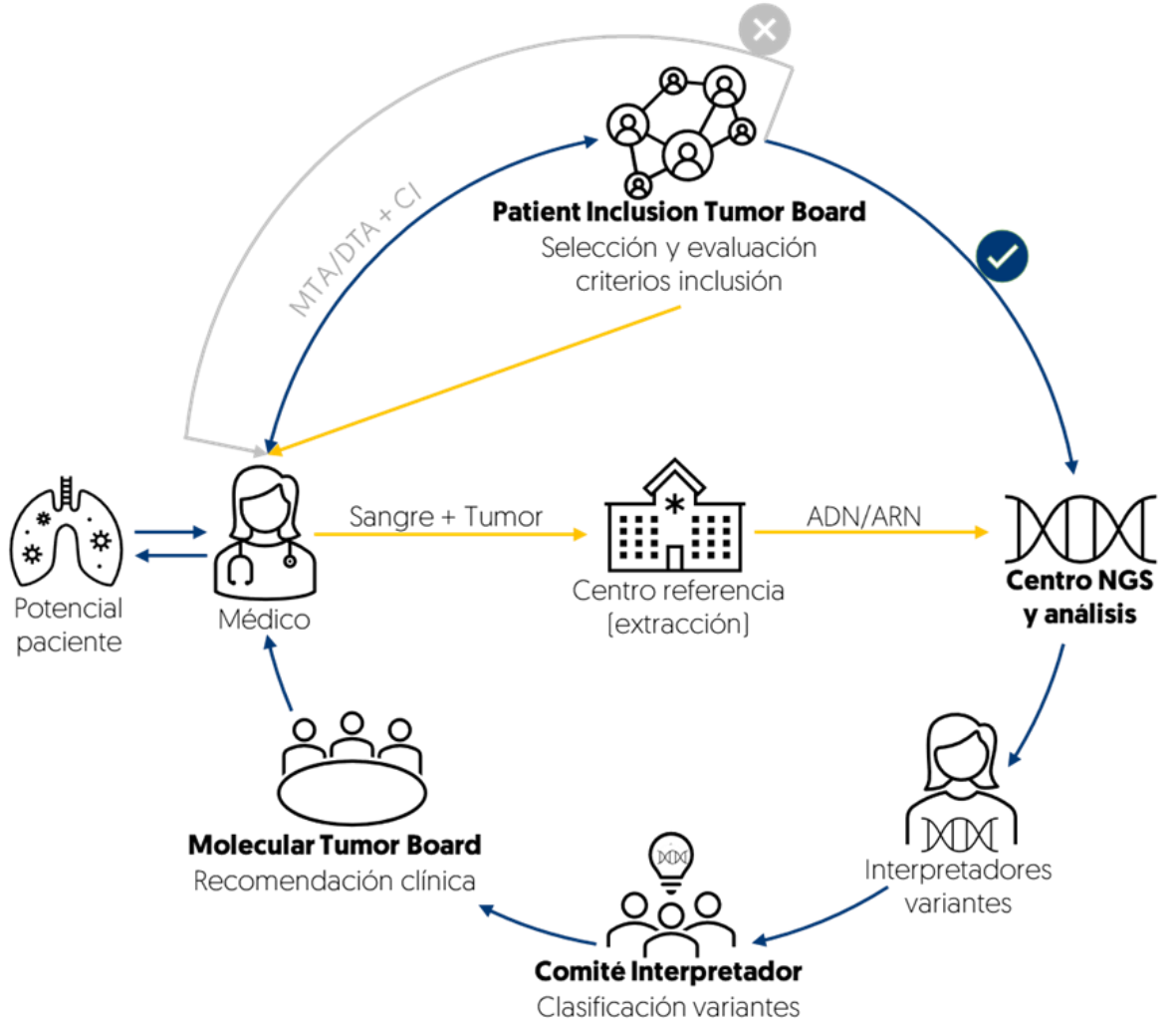
IMPaCT Genómica

Dinámica casos cáncer (WP4)

Cáncer Hereditario



Cáncer Primario Origen Desconocido



WP4 Cáncer Origen Desconocido

COD

Sangre → ADN → WES 100x
Tumor → ADN → WES 200x

- Tiempo entrega resultados:

  a) FPGMX 9-12 días
  b) Nasertic 10 días
  c) CNAG *en estudio*

Estandarización muestra somática

Cáncer Hereditario

Extracción RNA muestra tumor FFPE

- Dra. Miriam Cuatrecasas (H. Clínic)
- Dra. Rita Regojo (H. la Paz)
- Dr. José Palacios (H. Ramon y Cajal)

Cáncer Primario Origen Desconocido

Extracción ADN muestra tumor FFPE

- Dr. Santiago Ramon y Cajal (H. Vall d'Hebron)
- Dr. Xavier Matias-Guiu (H. Bellvitge)
- Dr. José Palacios (H. Ramon y Cajal)
- Dr. Enrique de Álava (H. Virgen del Rocío)

- Se pretenden analizar un total de **140 casos de cáncer origen desconocido**:

  a) 50 casos prospectivos
  b) 90 casos retrospectivos

Previsión de tener el 100 % casos retrospectivos en octubre en NGS

WP5 –Pharmacogenomics and population genomics

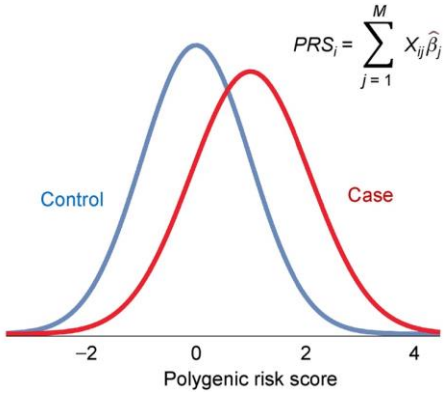
GdT01: FGX TRANSLATION – GUIDELINES- REPORT MODEL

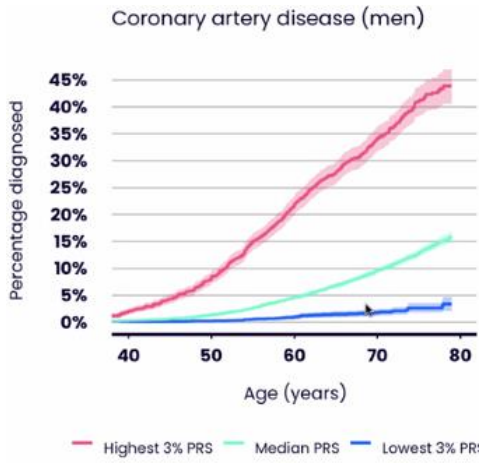
GdT02. PROFICIENCY TESTING – ACCREDITATION

GdT03. IDENTIFICATION OF NEW BIOMARKERS. 2 PILOT PROJECTS (ADRs for vaccines –SARS-CoV-2)

GdT04. POPULATION GENOMICS (GWAS COHORT) - STANDARDS FOR PRS – PILOT PROJECT FOR IMPLEMENTATION OF PRS - (in connection with IMPaCT Medicina Predictiva)

GdTImpact05. DATA SHARING





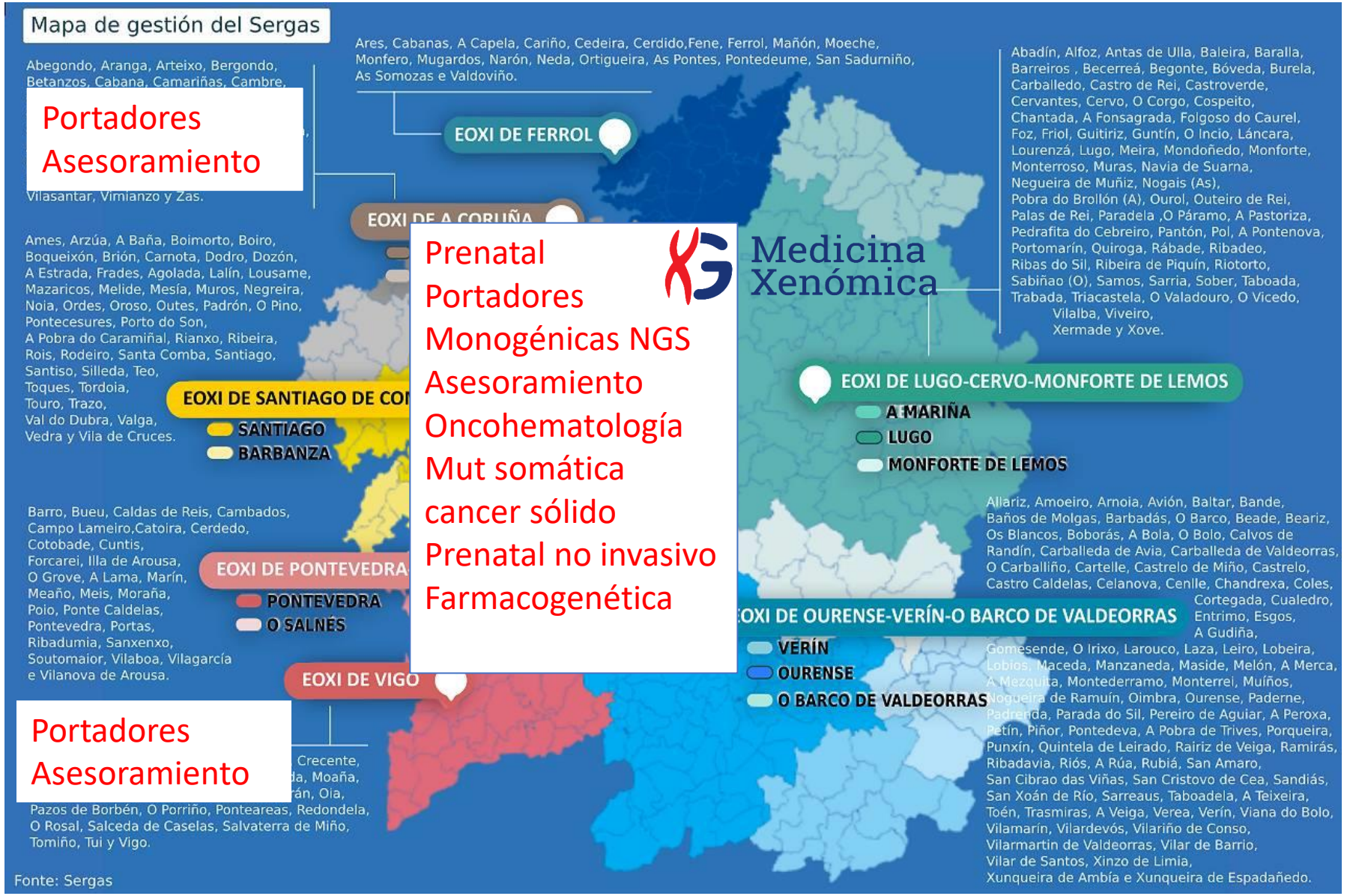
Reto: Modelos de implementación a nivel local, regional y estatal

Fundación Pública Galega de Medicina Xenómica- SERGAS

Medicina Xenómica

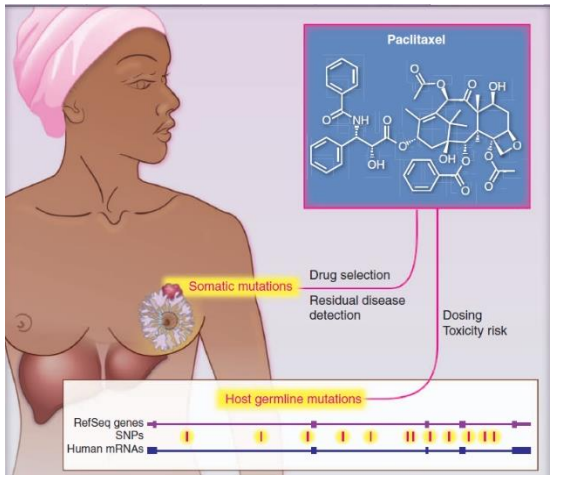
36,500 pacientes/año

2500 PNI
2500 FCX
15,000 Somáticas
15,000 Monogénicas
1500 asesoramiento



Challenge: Education

"Educational framework is needed to improve dialogue between clinicians and patients to provide patients with an accurate assessment of the potential benefits, limitations, uncertainties and toxicities of precision medicine approaches. This could address the trend toward 'treatment anarchy' in which off-label targeted drugs with limited proven value are requested by patients and/or prescribed by their clinicians, compromising the long-term potential of precision medicine to deliver meaningful benefits to patients and health-care systems".



Cancer Pharmacogenomics: Early Promise, But Concerted Effort Needed
McLeod SCIENCE VOL 339 29 MARCH 2013

Salgado et al. Nature Reviews, 2017

> 100 hospitales

Flujo de procesos

3 Centros de secuenciación

20 Grupos de trabajo

Colaboración con IMPaCT Data (G.T. Transversales)

Proficiency Testing

Informe de laboratorio / Protocolos estandarizados

Alianza con pacientes

6 Talleres

Plataforma de registro de información clínica

IMPaCT Genómica

Consentimientos informados

6 Comités de expertos

Selección de casos

Guías clínicas

Análisis de datos

Difusión

Modelo de informe diagnóstico

>300 Reuniones

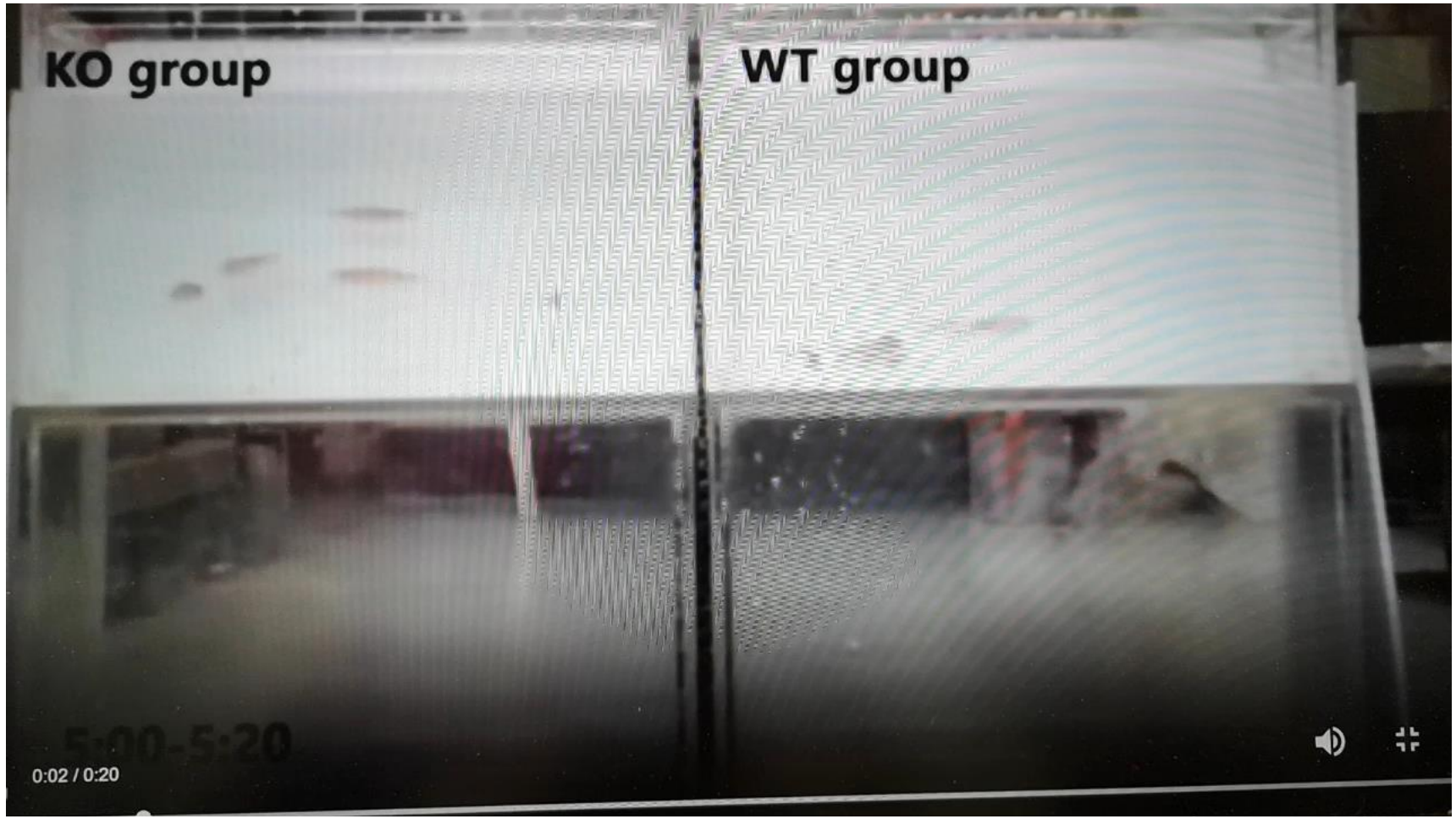
ciber | ER

Equipo de gestión

>500 colaboradores directos

ciber | ER CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED Enfermedades Raras


LA FIESTA CON QUE SE CELEBRA LA LLEGADA DE NUESTROS AMIGOS,ES MAGNIFICA...Y SI ASURANCETURIX NO HUBIERA SUFRIDO UN ACCIDENTE,HABERIA AMENIZADO LA VELADA CON SUS CANCIONES...
FIN



AUTS2