

Seminario

CNE, 15 Febrero 2018

# El Exposoma Humano y la Epidemiología: hacia la Salud de Precisión

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&

Professorial Fellow (Honorary), The University of Melbourne

Chair, IMIA Working Group on Exposome Informatics

# Contenidos

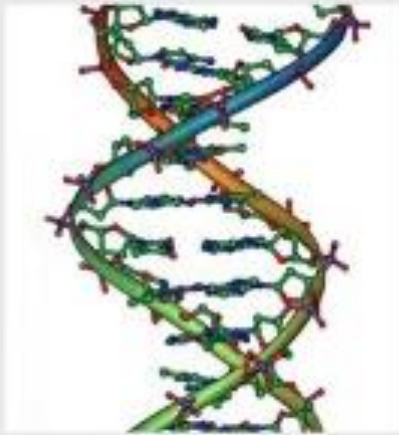


- Historia y definición del concepto Exposoma
- Exposoma y Epidemiología
- Retos en el procesamiento de datos
- Áreas de investigación
- Hacia la Salud de Precisión



# Historia y definición del concepto Exposoma

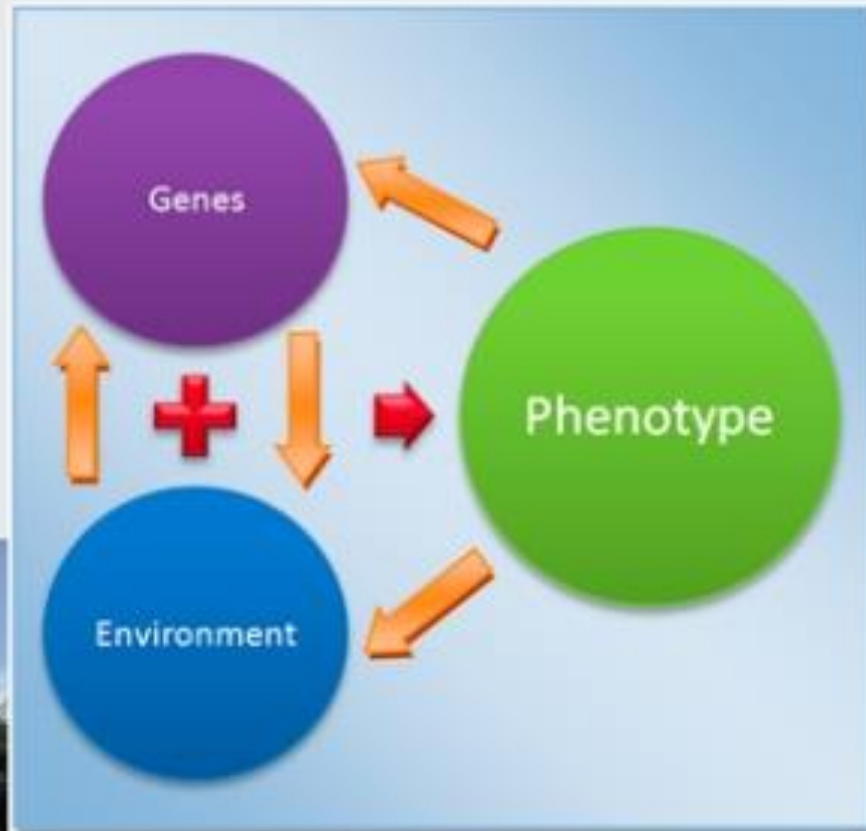
$$P = G * E$$



Genome



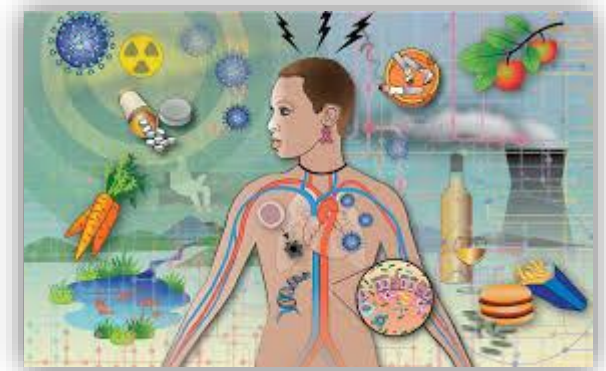
Exposome

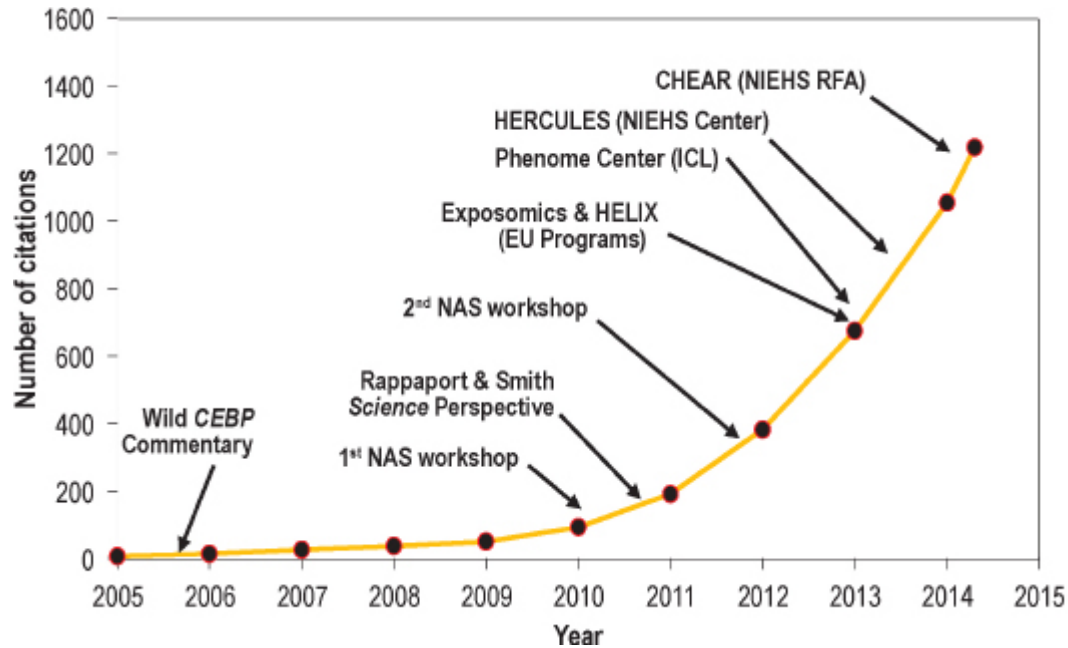


Phenome

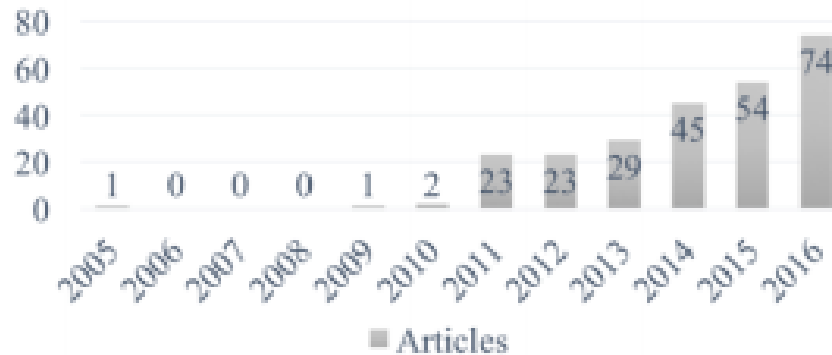
# Evolución

- 2005 - Christopher Wild - Director de IARC, (International Agency on Cancer Research), acuña el término “exposome” – Una llamada a realizar **aproximaciones sistemáticas de alto rendimiento** al estudio del impacto del ambiente en la salud.
- Hasta 2010 (paper Rappaport) no tiene eco.
- El Exposoma incluye la totalidad de las exposiciones de una persona a lo largo de su vida.
- Los avances tecnológicos hacen posible medir el Exposoma a mayor escala y con mejor resolución que nunca.
- Complemento del genoma



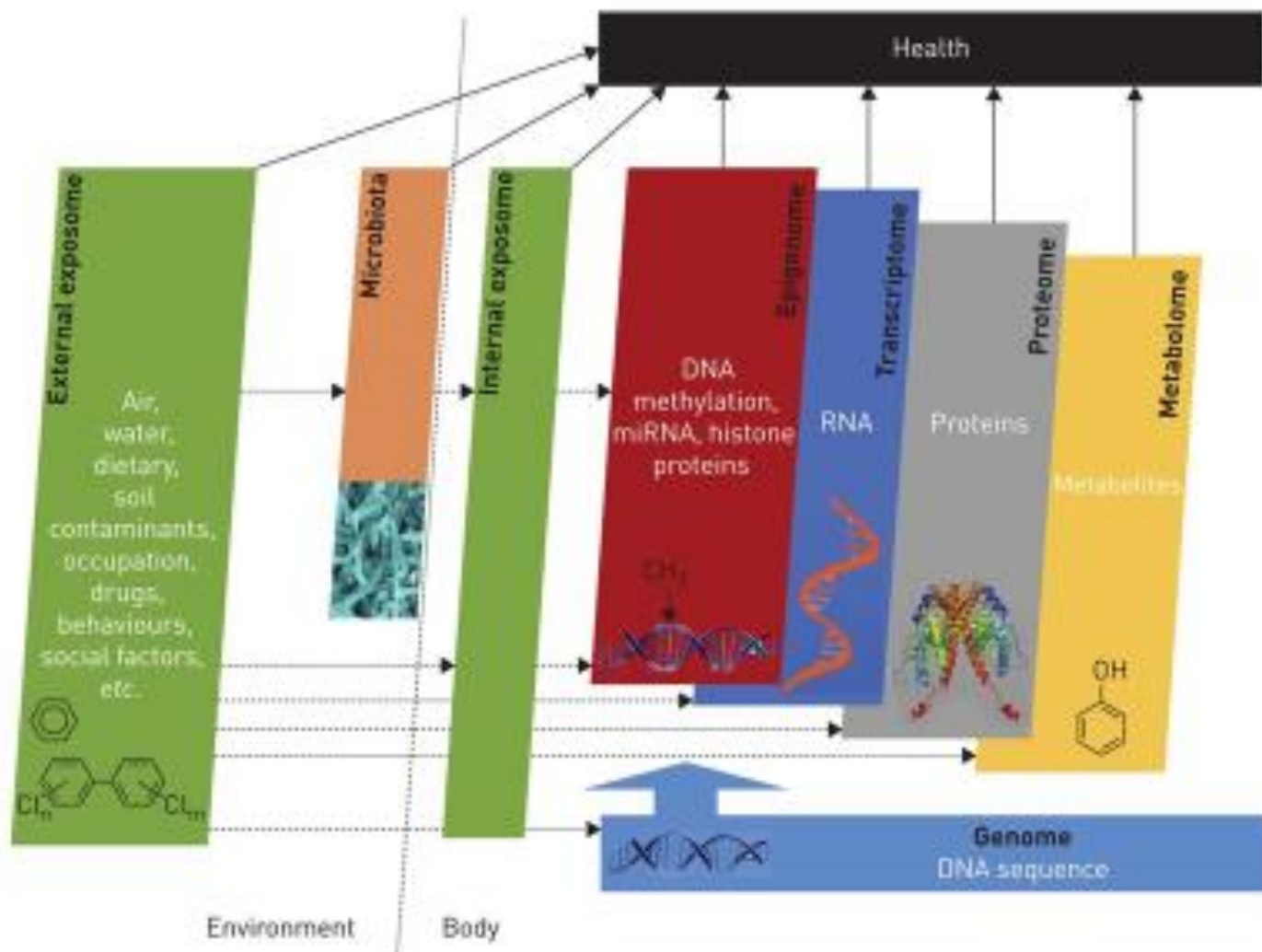


PubMed “Exposome” articles (per year)



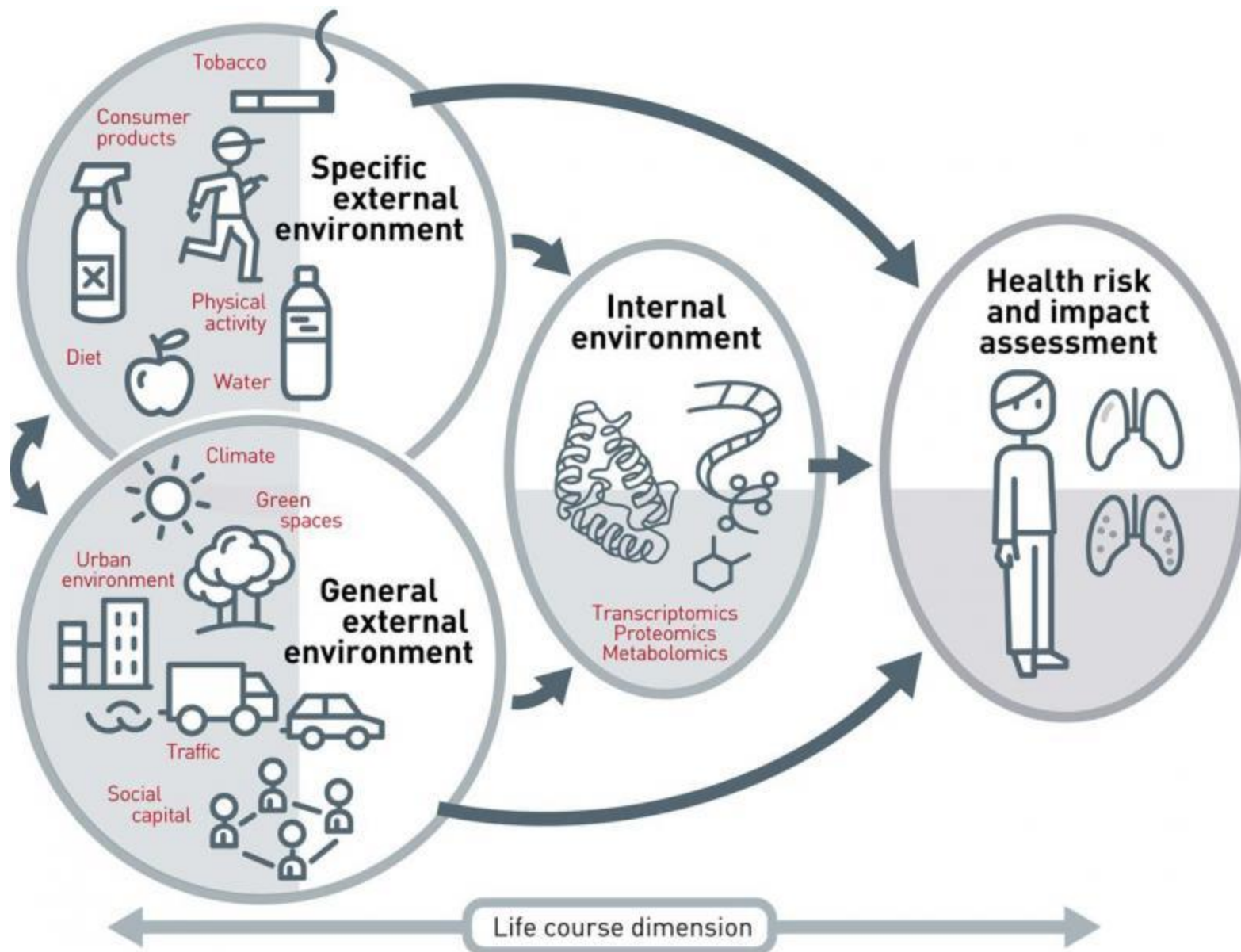
311 papers MEDLINE 2018

**Schematic diagram of some of the 'omics layers and pathways of influence of the exposome on health.**



Valérie Siroux et al. Eur Respir Rev 2016;25:124-129







# Marco unificador?

- Salud ambiental – Exposición, toxicología
- Servicios de salud – SDOH - Socioexposoma
- Urbanismo – “Built environment”
- Salud laboral – exposoma ocupacional
- Ecología - EcoExposoma
- Epidemiología
- Sociología
- Nanomedicina -
- Infecciones
- Medicamentos
- Tecnología –exposoma digital
- ...



**NIH** National Institute of Environmental Health Sciences  
Your Environment. Your Health.

Health & Education | Research | Funding Opportunities | Careers & Training

Research Exposure Biology and the Exposome



**HEALS**  
Health and Environment-wide Associations  
based on Large population Survey

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

The National Institute for Occupational Safety and Health (NIOSH)

Workplace Safety and Health Topics

Exposome and Exposomics

[NIOSH](#) > [Workplace Safety and Health Topics](#)



**HERCULES**  
Exposome Research Center

**HELIX** BUILDING THE EARLY-LIFE EXPOSOME

#exposome

**Icahn School of Medicine at Mount Sinai**

ABOUT THE SCHOOL | EDUCATION

Home > Research > The Institute for Exposomic Research

**The Institute for Exposomic Research**

**exposomics**

**ADVANCING EXPOSOMICS RESEARCH**  
Integrating workflows and bioinformatics



**Agilent**

**JECS**  
Japan Environment and Children's Study

**I<sub>3</sub>CARE** INTERNATIONAL EXPOSOME CENTER

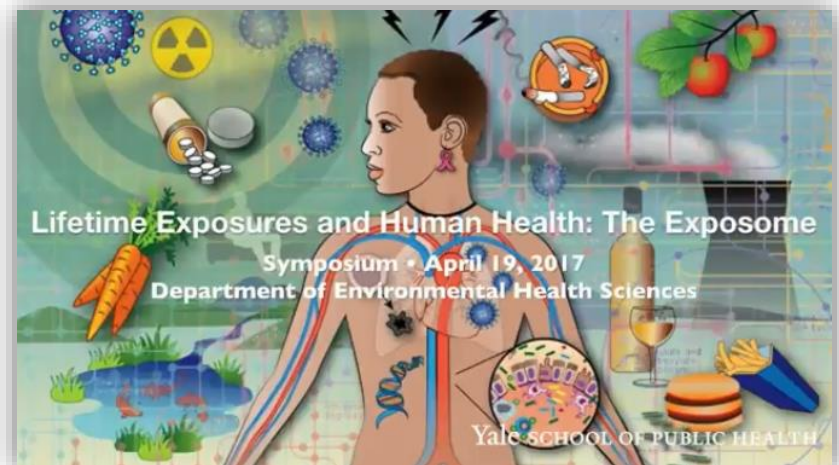
**CHEAR** Children's Health Exposure Analysis Resource



**Emory Exposome  
Summer Course  
June 12-17, 2016**



**HELIX Scientific Symposium  
Oct 2017  
Barcelona**





# Exposoma y Epidemiología



# Exposome + Epidemiology

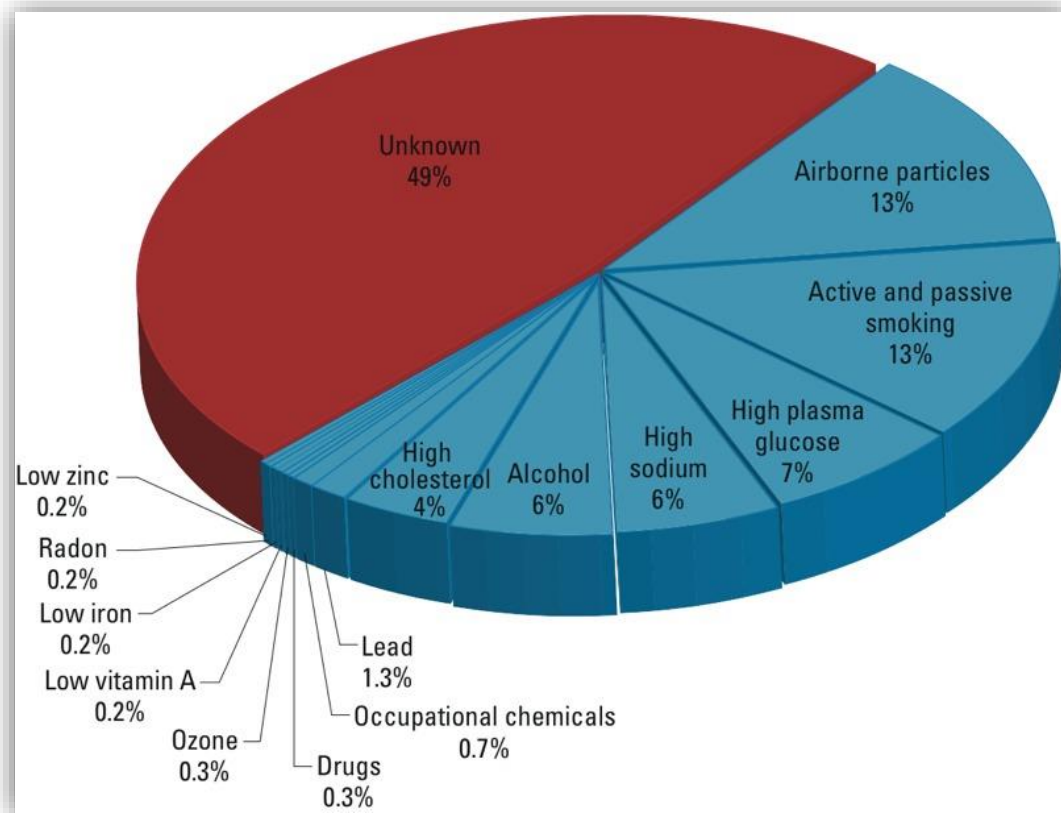
- **Kim KN, Hong YC. The exposome and the future of epidemiology: a vision and prospect. Environ Health Toxicol. 2017 May 3;32:e2017009.**
- **Stingone JA, et al. Toward Greater Implementation of the Exposome Research Paradigm within Environmental Epidemiology. Annu Rev Public Health. 2017 Mar 20;38:315-327.**
- **DeBord DG, et al. Use of the "Exposome" in the Practice of Epidemiology: A Primer on -Omic Technologies. Am J Epidemiol. 2016 Aug 15;184(4):302-14.**
- **Siroux V, Agier L, Slama R. The exposome concept: a challenge and a potential driver for environmental health research. Eur Respir Rev. 2016 Jun;25(140):124-9.**
- **Khoury MJ, et al. Transforming epidemiology for 21st century medicine and public health. Cancer Epidemiol Biomarkers Prev. 2013 Apr;22(4):508-16**
- **Future of environmental research in the age of epigenomics and exposomics. Rev Environ Health. 2017 Mar 1;32(1-2):45-54**
- **Buck Louis GM, et al. The exposome--exciting opportunities for discoveries in reproductive and perinatal epidemiology. Paediatr Perinat Epidemiol. 2013 May;27(3):229-36.**
- **Vineis P, et al. Advancing the application of omics-based biomarkers in environmental epidemiology. Environ Mol Mutagen. 2013 Aug;54(7):461-7.**
- **Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1847-50.**
- **Patel CJ, Ioannidis JP. Studying the elusive environment in large scale. JAMA. 2014 Jun 4;311(21):2173-4.**
- **Patel CJ, Ioannidis JP. Placing epidemiological results in the context of multiplicity and typical correlations of exposures. J Epidemiol Community Health. 2014 Nov;68(11):1096-100.**

# Desafíos para la Investigación en salud pública en el siglo XXI

- Contaminación del aire y calentamiento global,
- Uso generalizado de productos químicos nocivos, incluidos plaguicidas, plastificantes, y otros disruptores endocrinos,
- Cambios radicales en nutrición y estilo de vida

## CONSECUENCIAS

- Defectos congénitos
- Déficits en el neurodesarrollo
- Mayor riesgo de cáncer
- Otras enfermedades multifactoriales: cardiovasculares, asma, diabetes y obesidad



Risks factors  
for exposures  
that  
contribute to  
chronic-  
disease  
mortality  
*Rappaport et  
al, EHP, 2014*

28 de enero de 2018:

- 661.563 citas de PubMed para “disease causes AND genetics”
- 83.201 citas para “disease causes AND exposure”,

una relación de aproximadamente ocho a uno.



# Una nueva aproximación

- En lugar de caracterizar exposiciones "una por una", o por exposición combinada a dos o tres sustancias químicas a la vez, el objetivo es dar cuenta simultáneamente de numerosos factores que van desde químicos a nutricionales, conductuales y ambientales
- Mejorar la comprensión de las interrelaciones entre un amplio abanico de factores de riesgo y condiciones de salud para diseñar nuevos sistemas de control y prevención de enfermedades

## Khoury et al. Cancer Epidemiol Biomarkers Prev. April 2013

- Visión del NCI para la epidemiología del cáncer
- 7 recomendaciones:
  - 4) Develop, evaluate and use novel technologies
  - 5) Integrate 'big data' into the practice of Epidemiology

Stingone JA, et al. Annu Rev Public Health.  
2017 Mar 20;38:315-327.

*The Exposome represents a complement to, not a replacement for, the hypothesis-driven research that has successfully advanced the field of epidemiology.*



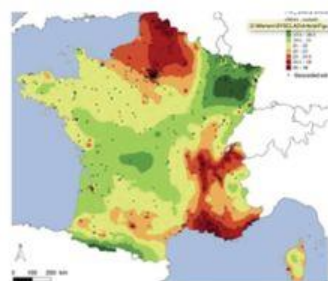
# Retos en el procesamiento de datos

**Questionnaires**  
Residential,  
occupational,  
smoking history,  
*etc.*

EMA



**GIS-based environmental model**  
Air pollution  
Green space  
Noise, *etc.*



**Pictures**  
Cosmetic use  
Food  
Cleaning products,  
*etc.*




**Mobile devices**  
Smartphone  
Accelerometre  
Environmental sensor, *etc.*




**Integrated tools and technologies for exposome assessment**


**Biomarkers in different tissues**  
Urine  
Blood  
Exhaled breath condensate, *etc.*




**Electronic Health Records**  
Socio-demographic  
Infection  
Procedures  
drugs



**High-throughput 'omics technologies**  
Epigenomics  
Transcriptomics  
Proteomics  
Metabolomics, *etc.*

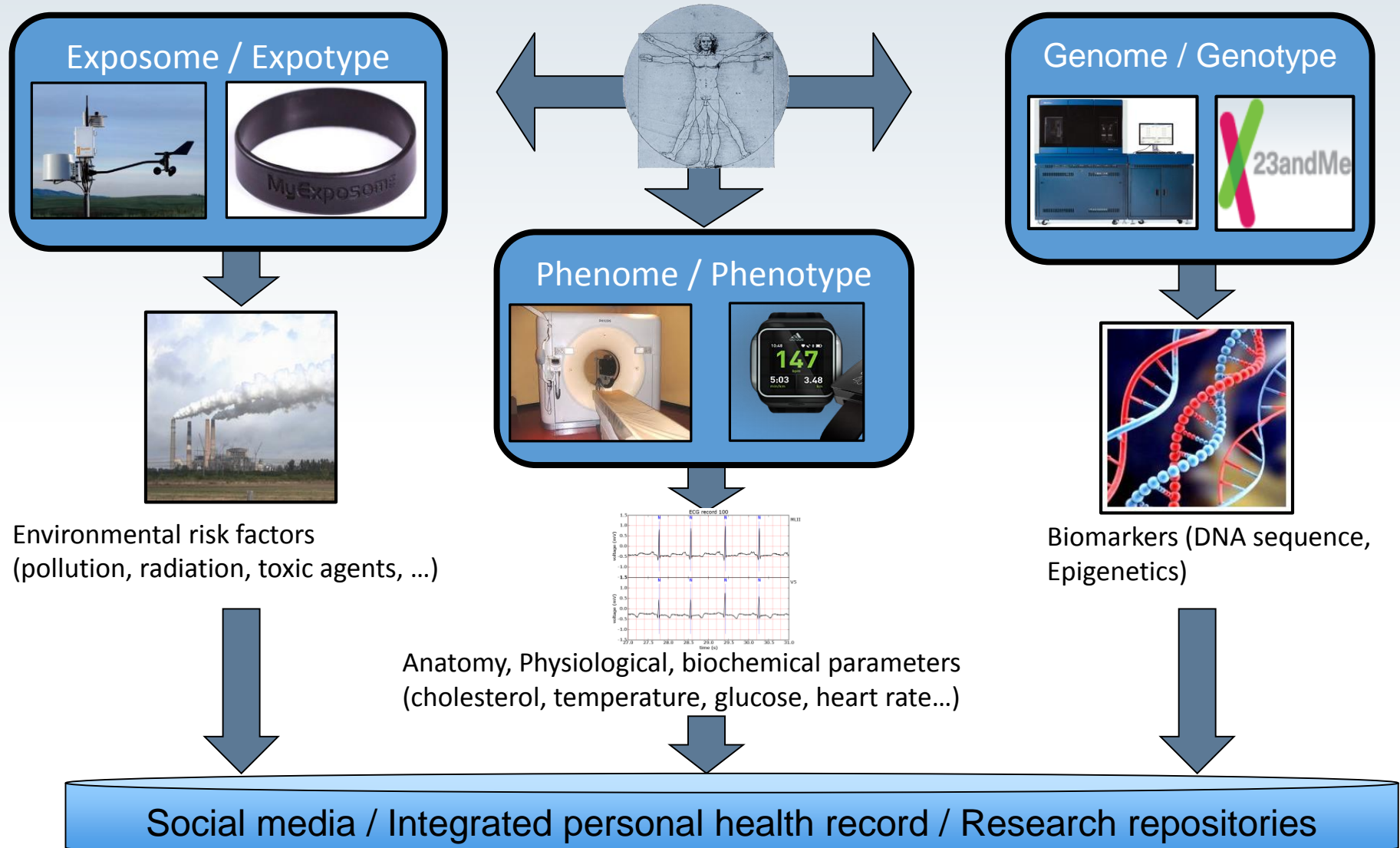


**Reality mining**  
Social networks  
Online Searches



# Recogida de datos

Surveys, GIS, biomarkers, smartphones, sensors, wearables, Electronic Health Records, ...

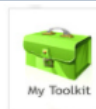




# PhenX Toolkit



# PhenX Toolkit



Log In  
Register

## My Toolkit

Hide Tree

- PhenX Toolkit (3)
- Domains (24)
- Measures (23)
- Collections (6)
- Substance Abuse and Addiction
- Mental Health Research (7)
- Tobacco Regulatory Research
- Sickle Cell Disease (4)
- Risk Factors (12)
- Behaviors and Attitudes (4)
- Social Factors (3)
- Participant Medical History
- Body Size and Composition
- Development (8)
- By Disease (3)
- Chemical and Physical Exposure
- Diet and Nutrition (3)
- Family Health History (13)
- Health Status (4)
- Personal and Household Characteristics
- Family Health History
- Health Conditions (7)

« Return to last visited browse page

Download Report

Download Data Collection Worksheet

Download Data Dictionary

Download  Instrument Zip

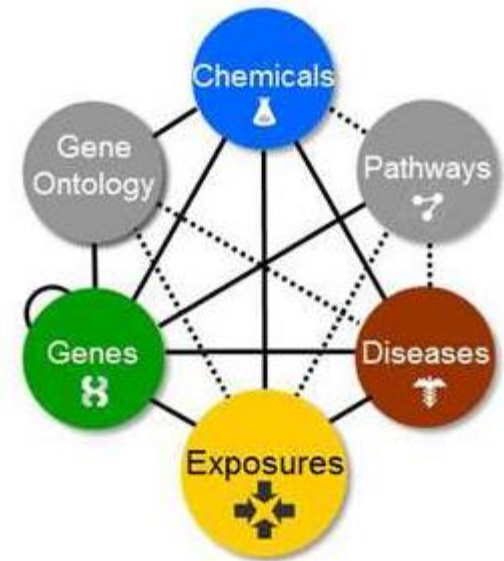
Empty My Toolkit

Measure	Protocol	Requirements <sup>2</sup>	Essential Measures <sup>2</sup>
Air Contaminants in the Home Environment <a href="#">Remove</a>   <a href="#">Related Measures</a>	Air Contaminants in the Home Environment <a href="#">Remove</a>		
✓ All Essential Measures have been added to your Toolkit			
<a href="#">Share this Toolkit »</a>			

Measures: 1 Protocols: 1

# Bases de datos

- [The Comparative Toxicogenomics Database](#)
- [Toxicant and Disease Database](#)
- [Exposome Explorer](#) - biomarkers of exposure
- [Toxin and Toxic-target database](#)





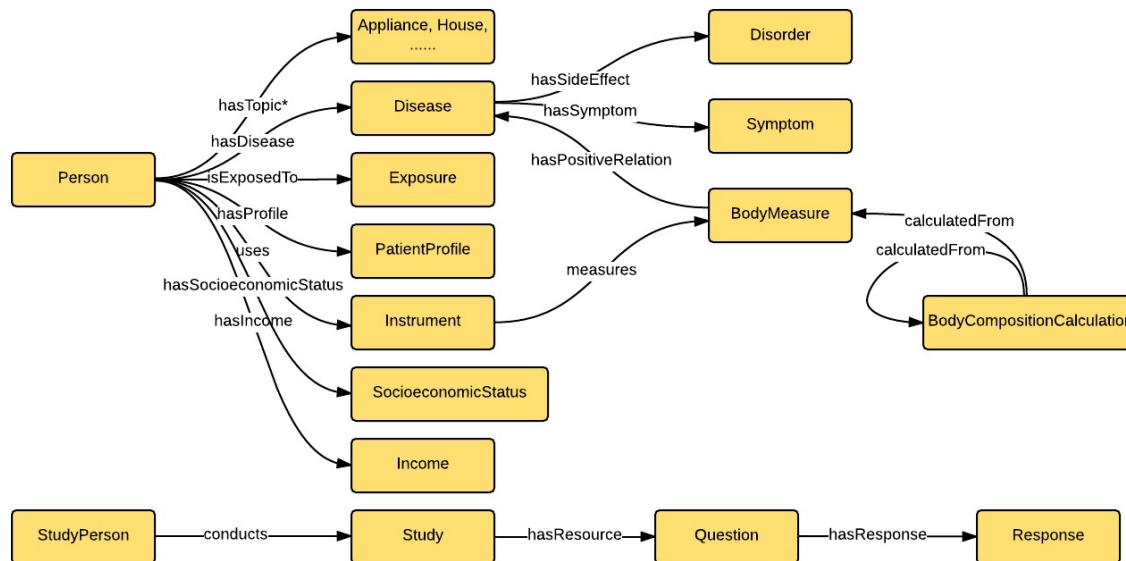
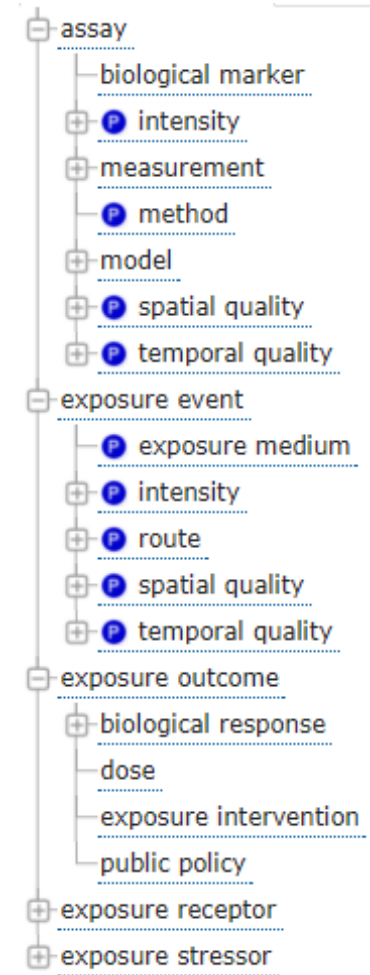
# Ontologías

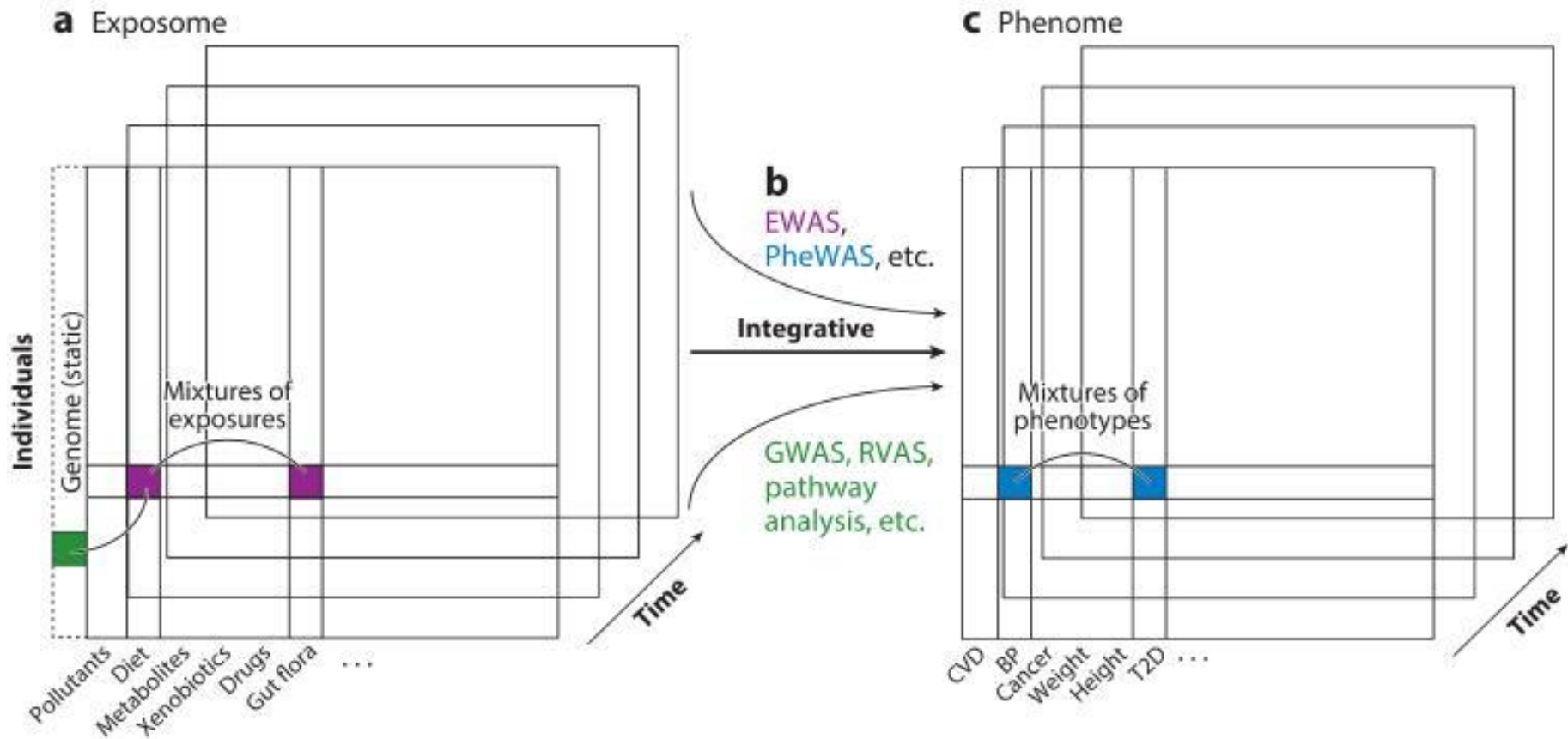
- ExO – Exposure Ontology

<https://www.ebi.ac.uk/ols/ontologies/exo>

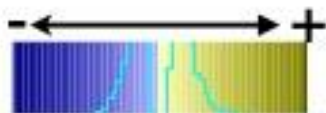
- CHEAR - Children's Health Exposure Analysis Resource –

<http://purl.bioontology.org/ontology/CHEAR>

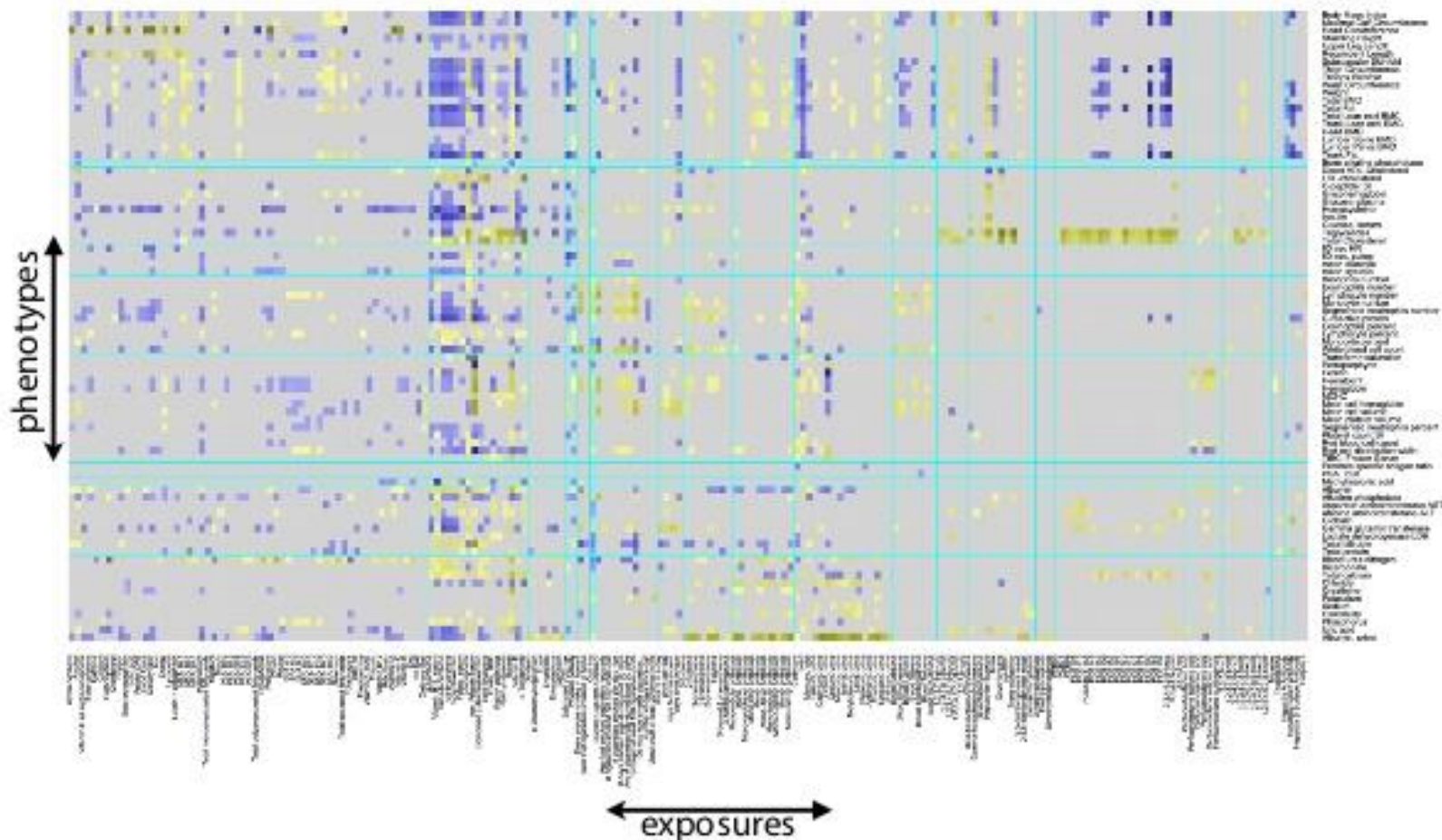




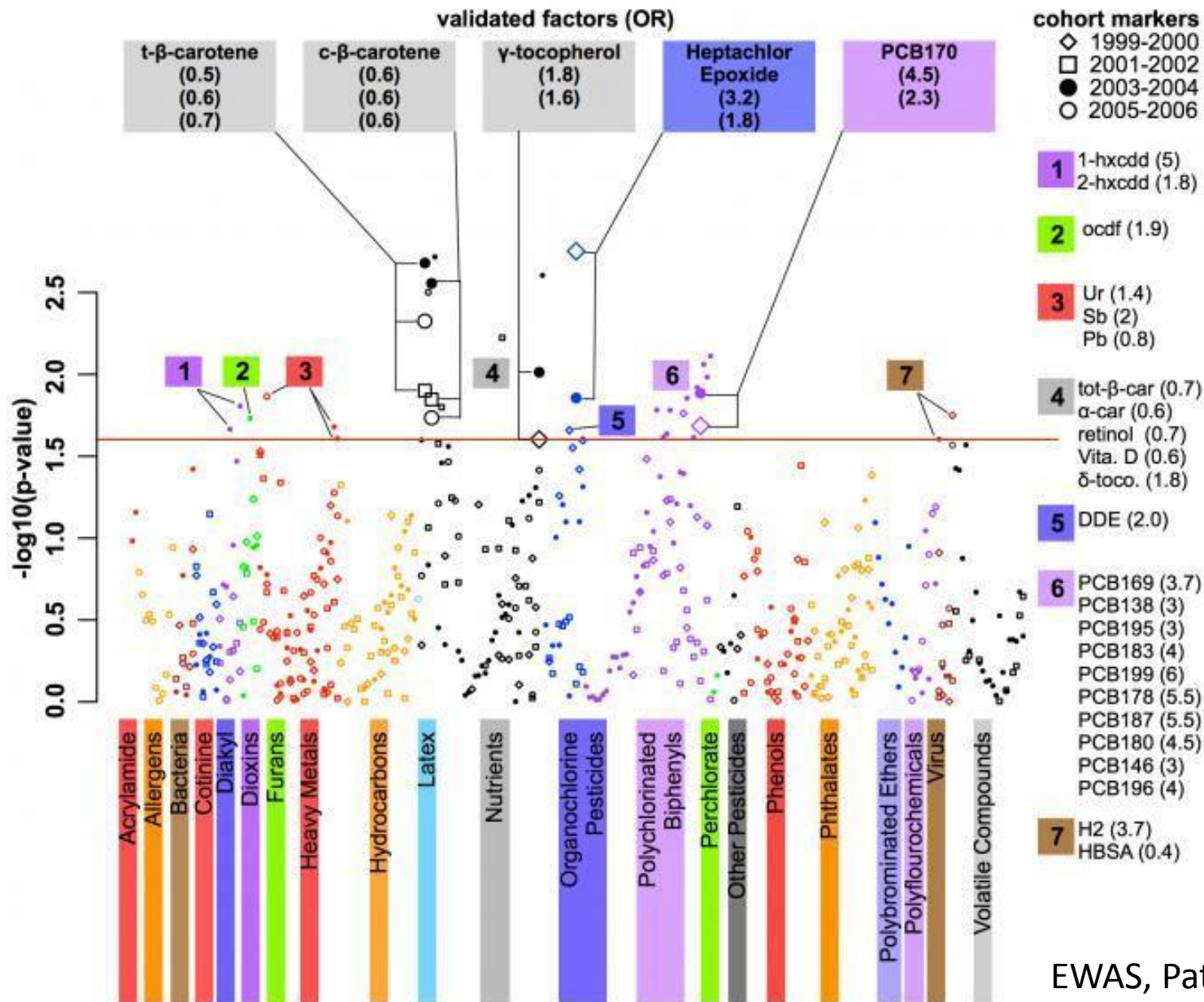
[Annu Rev Public Health. 2017 Mar 20; 38: 279–294.](#)



*EWAS*-derived phenotype-exposure association *map*:  
A 2-D view of 86 phenotype by 252 exposure associations

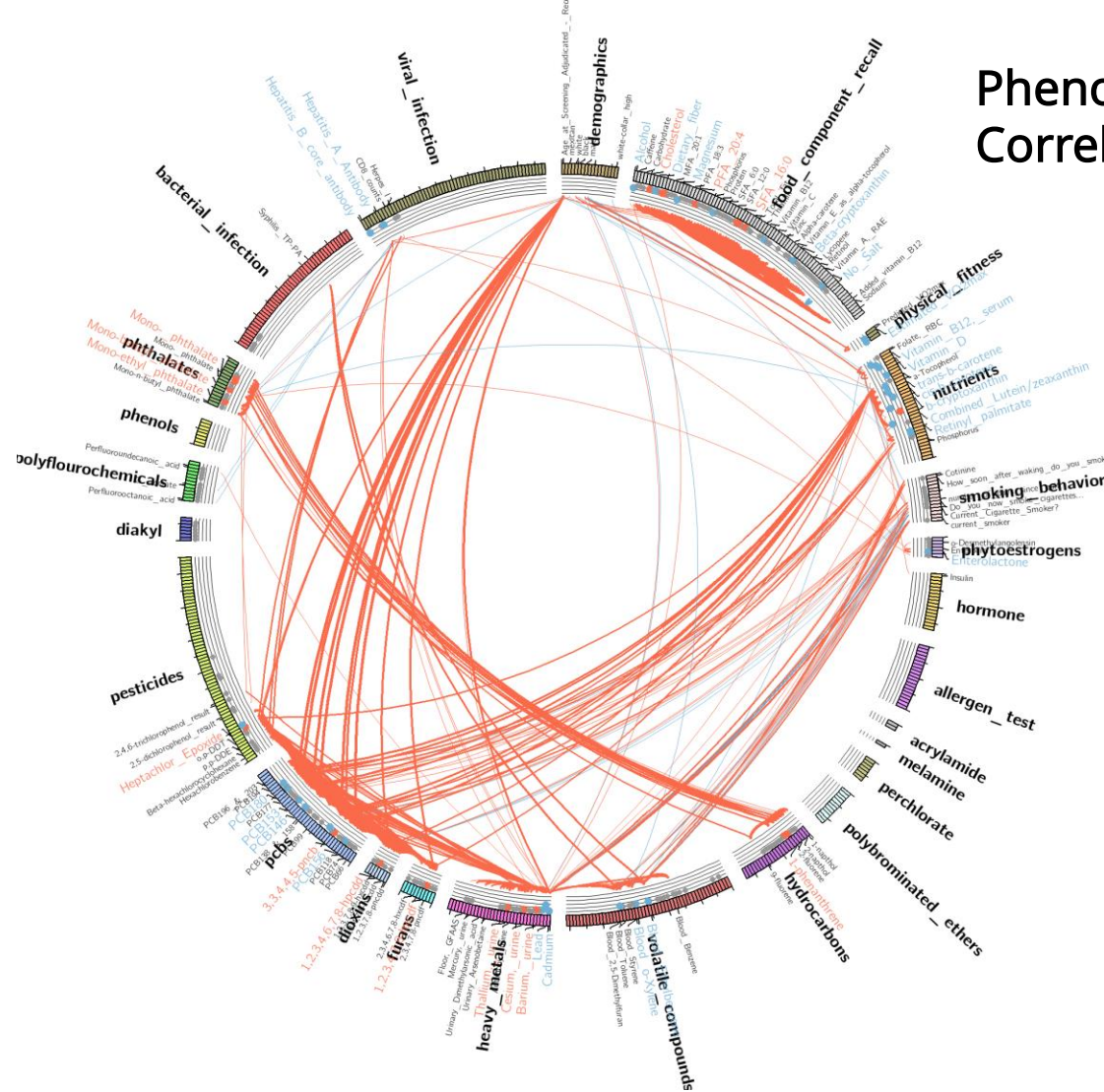


<http://bit.ly.com/pemap>





# Phenotype-Exposome Correlation Globe Browser



Waist Circumference

The [exposome correlation globes](#) display the correlation between pairs of environmental exposures where at least one of the exposures is associated with a clinical phenotype. (Patel C. JAMA, 2014)

# Comparación con Bioinformática

Mientras que los datos genómicos consisten en secuencias lineales estables, los datos del exposoma son variables heterogéneas no lineales que cambian en el tiempo y el espacio.

- Infraestructura de información (Genome browsers)
- Métodos analíticos (GWAS)
- Repositorios centralizados (dbGaP, GEO)
- Estándares (Gene Ontology)
- Arrays – NHANES
- Secuenciación – metabolómica
- Haplotipo: Correlation globes





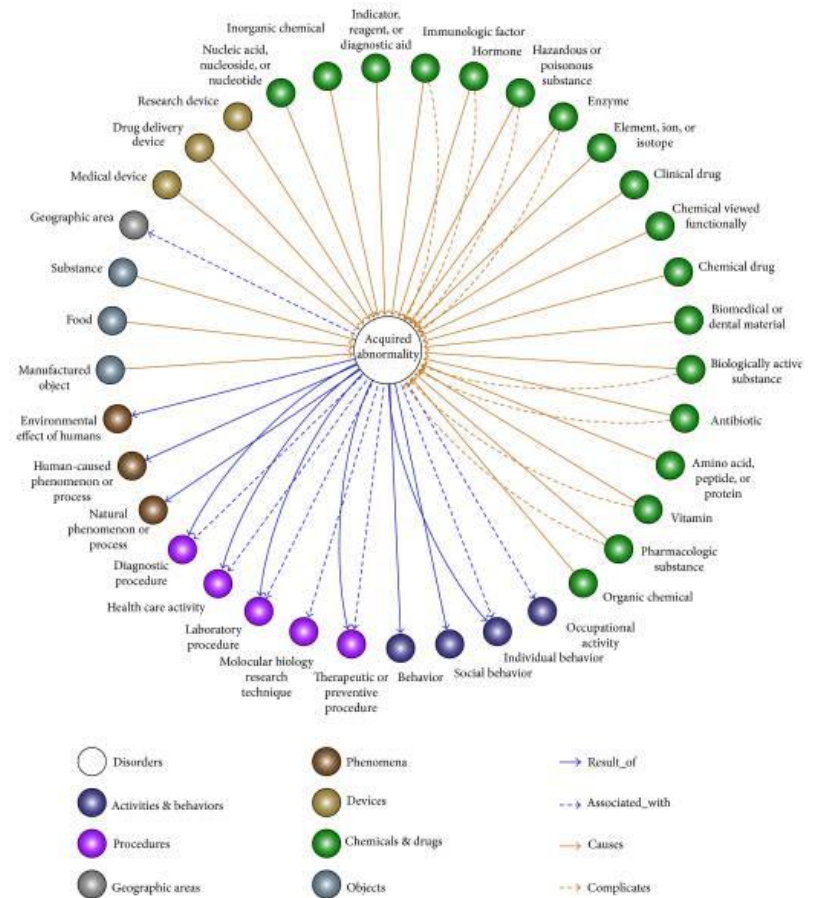
# Áreas de investigación



- Exposoma  $\leftrightarrow$  HCE
- Gestión datos salud digital (sensores individuales de exposoma)
- Exposoma en la literatura
- Ontologías y SDOH
- Componente digital del exposoma
- Expotipo

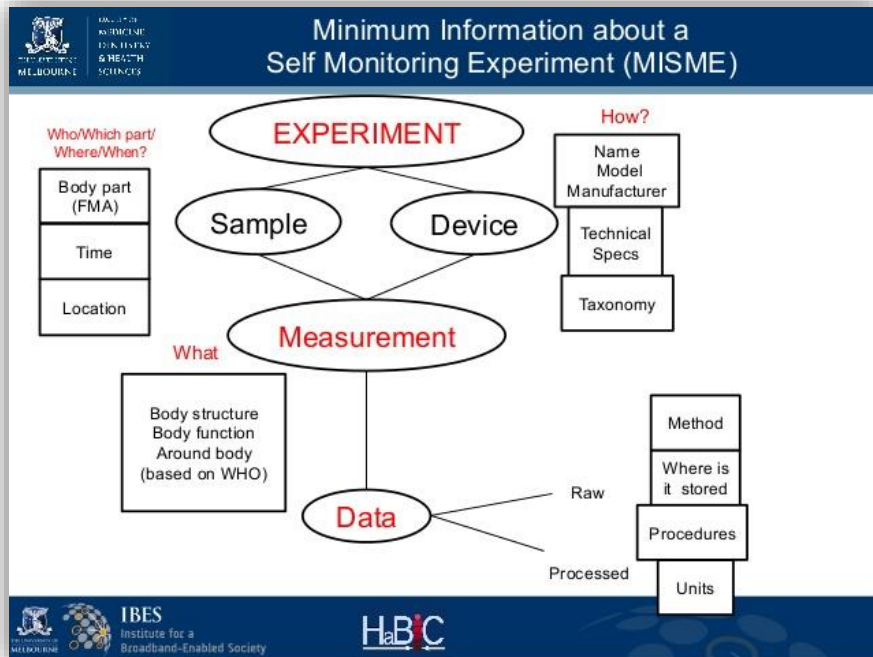
# Exposoma $\leftrightarrow$ HCE

- Datos en la HCE incorrectamente considerados fenotipo (infección, medicamentos, procedimientos medicos, vacunas)
- El US Institute of Medicine recomendó una batería de 11 items que deberían ser incluidos en la HCE. (tabaco, actividad física, educación, etnia, domicilio y conexiones sociales)

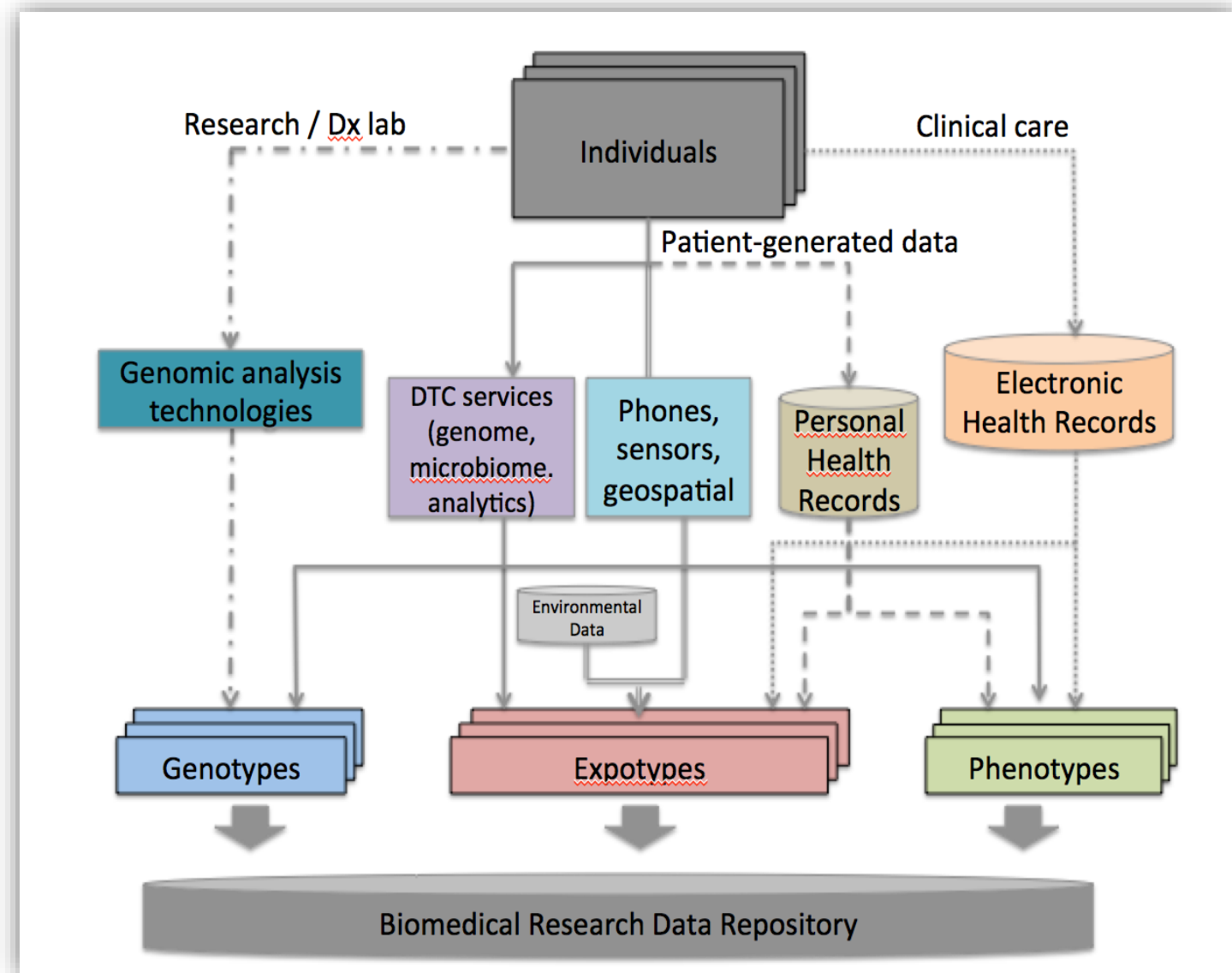


# Gestión datos salud digital (sensores individuales de exposoma)

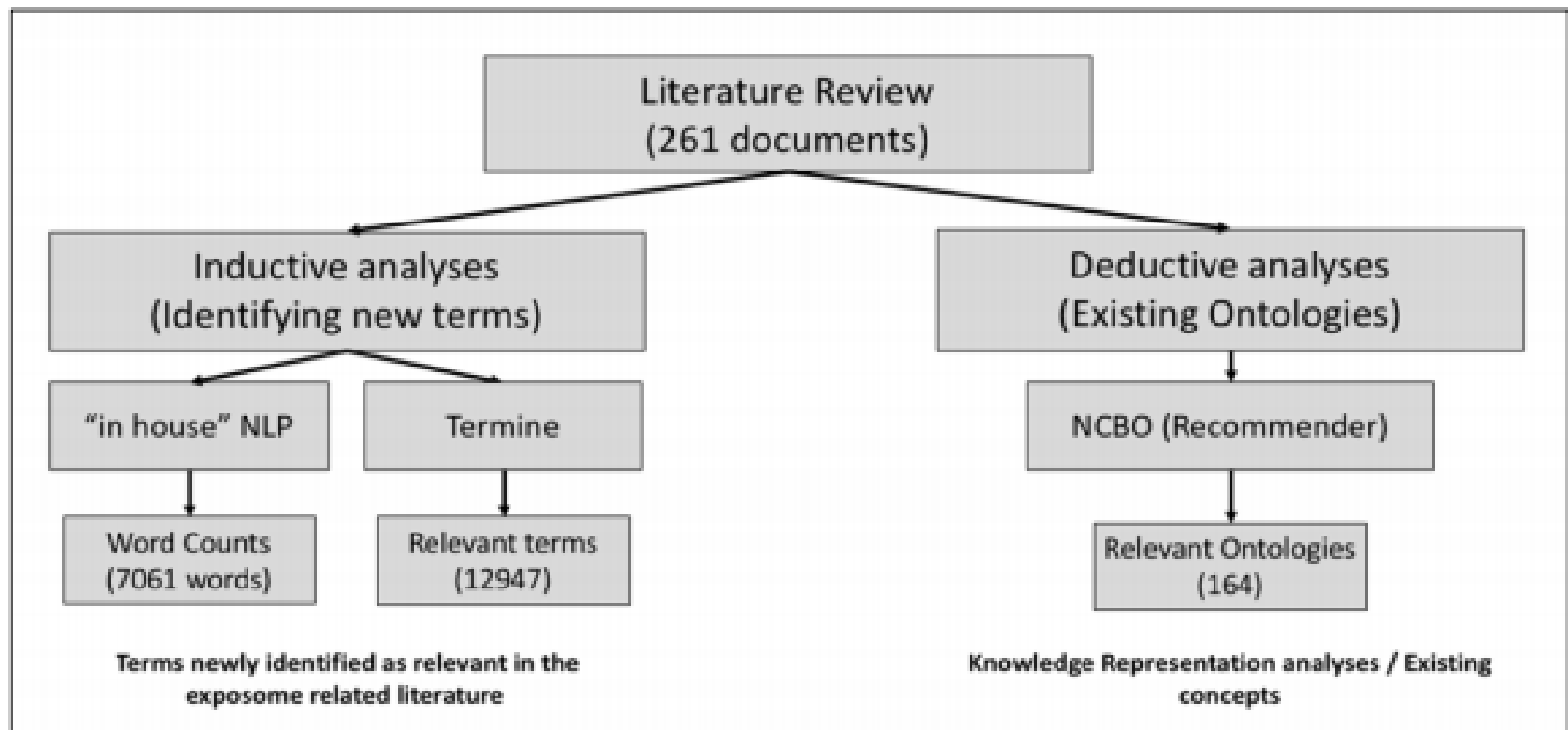
- MISME (Minimum Information about a Self-Monitoring Experiment)
- Wearables
- Mobile apps
- DTC services
- Social media



# Flujos de datos



# Exposoma en la literatura



*Figure 2 – Methodology for Characterising Exposome Research through Inductive and Deductive Analysis of the Literature.*

How Well Do Existing Ontologies Represent Exposome Literature?

# Ontologías y SDOH

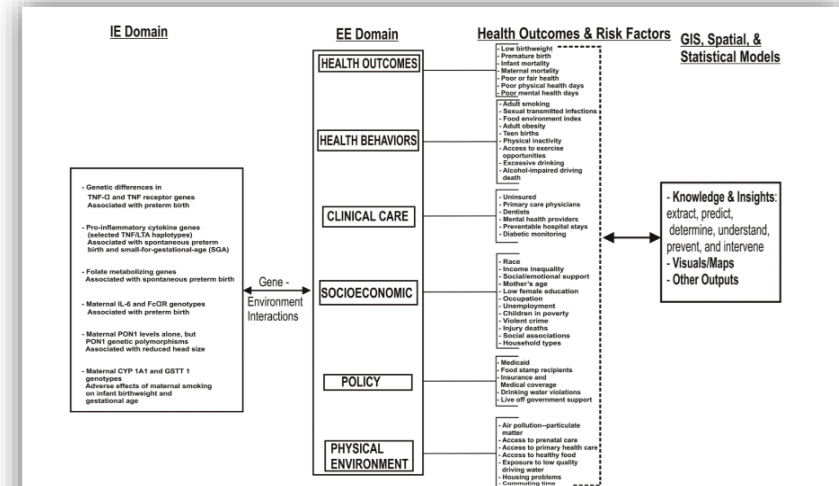
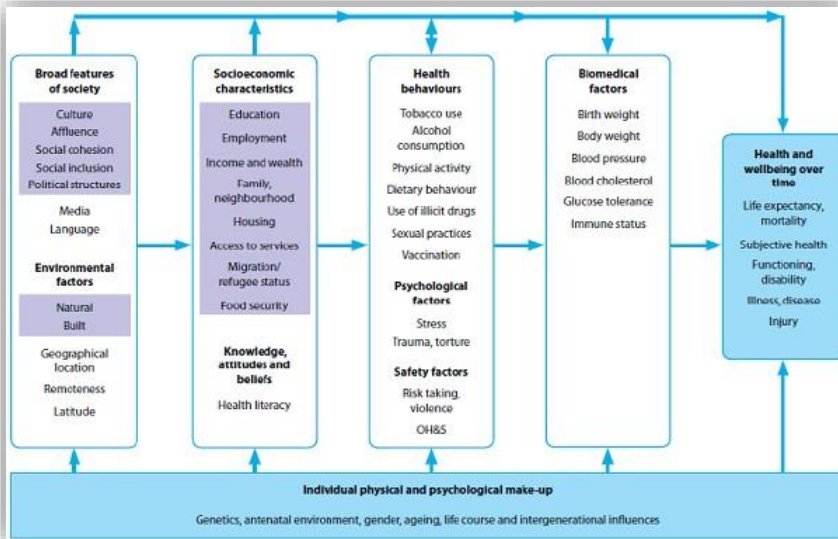
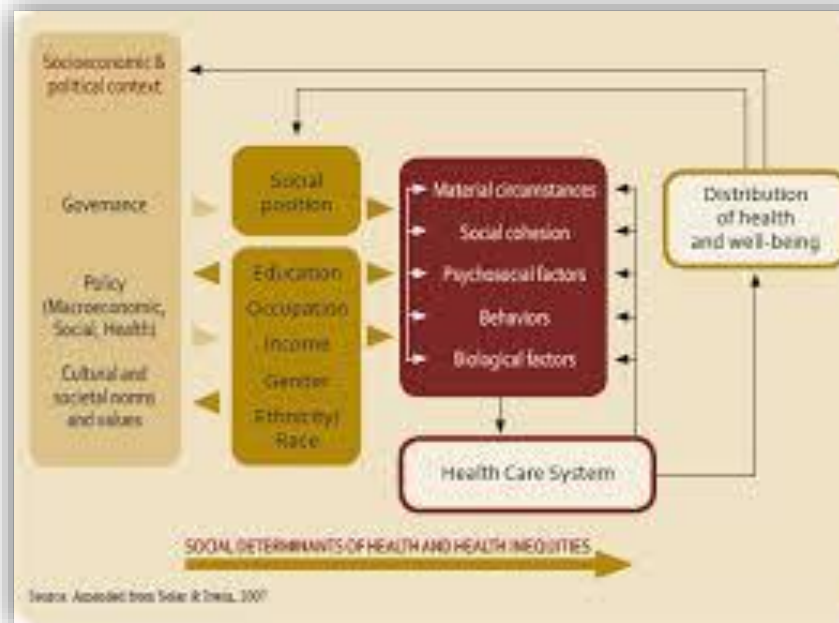


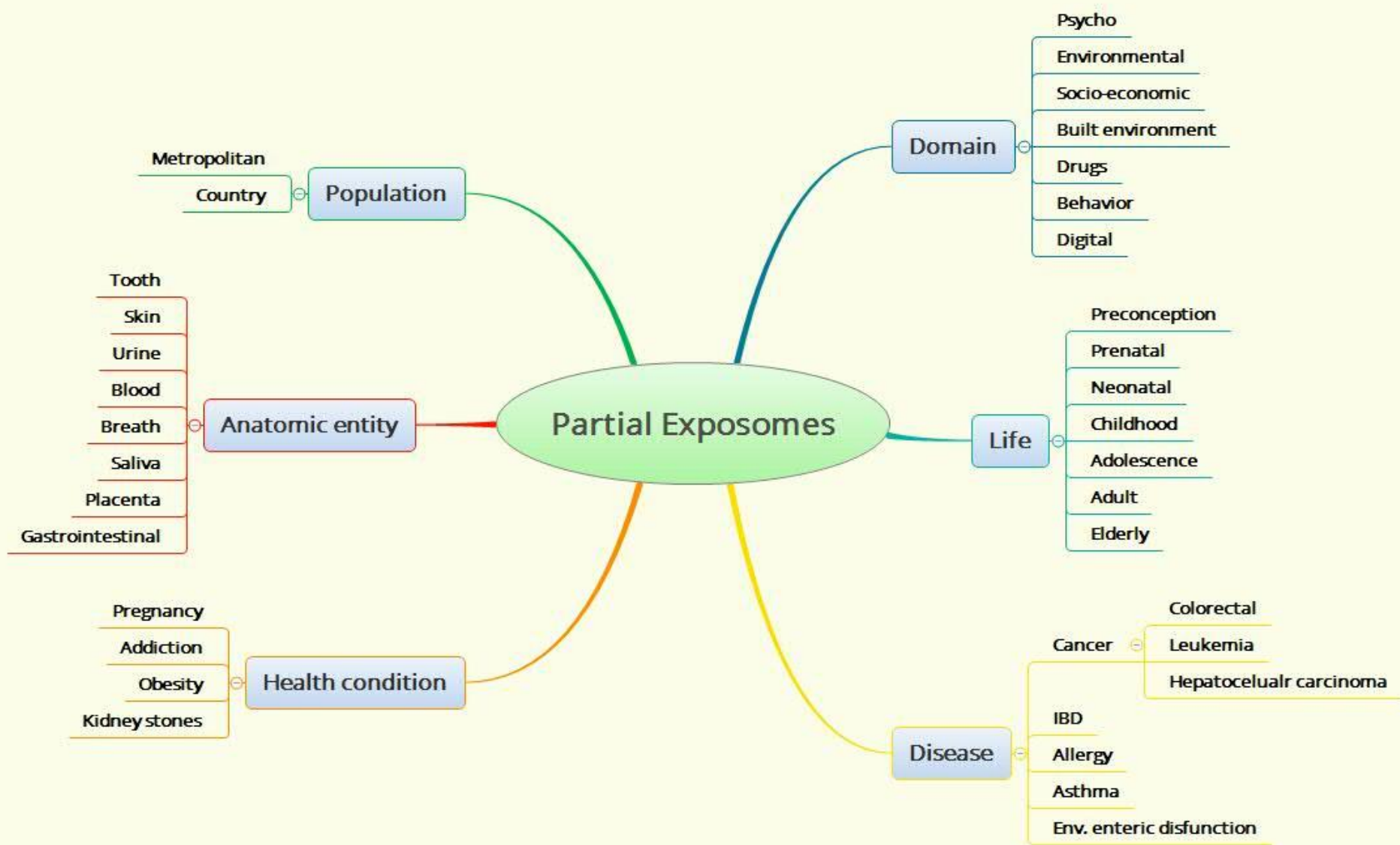
Figure 1. A conceptual framework for understanding adverse birth outcomes synthesized from over 50 research articles. IE refers to internal exposome while EE is the external exposome.

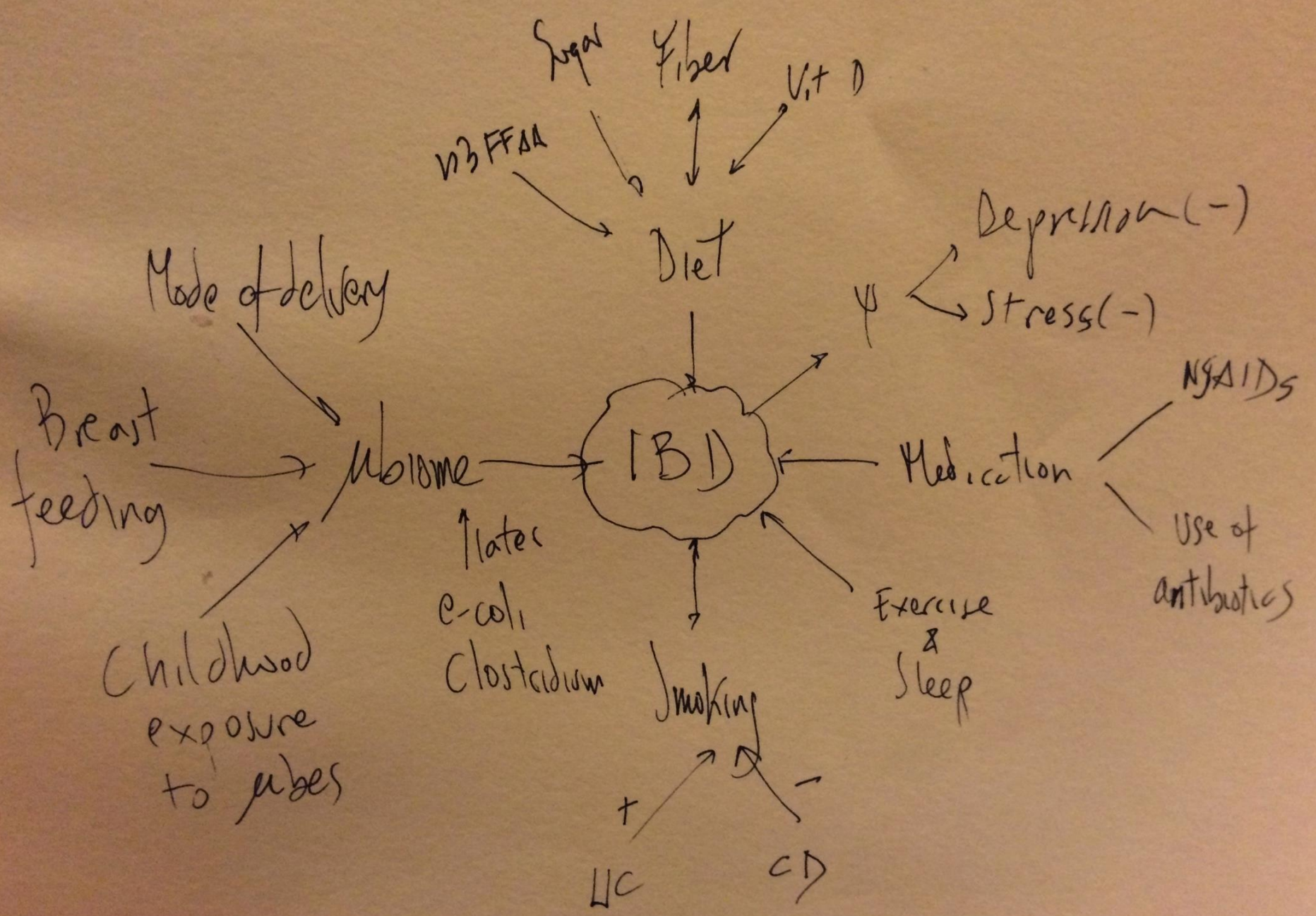




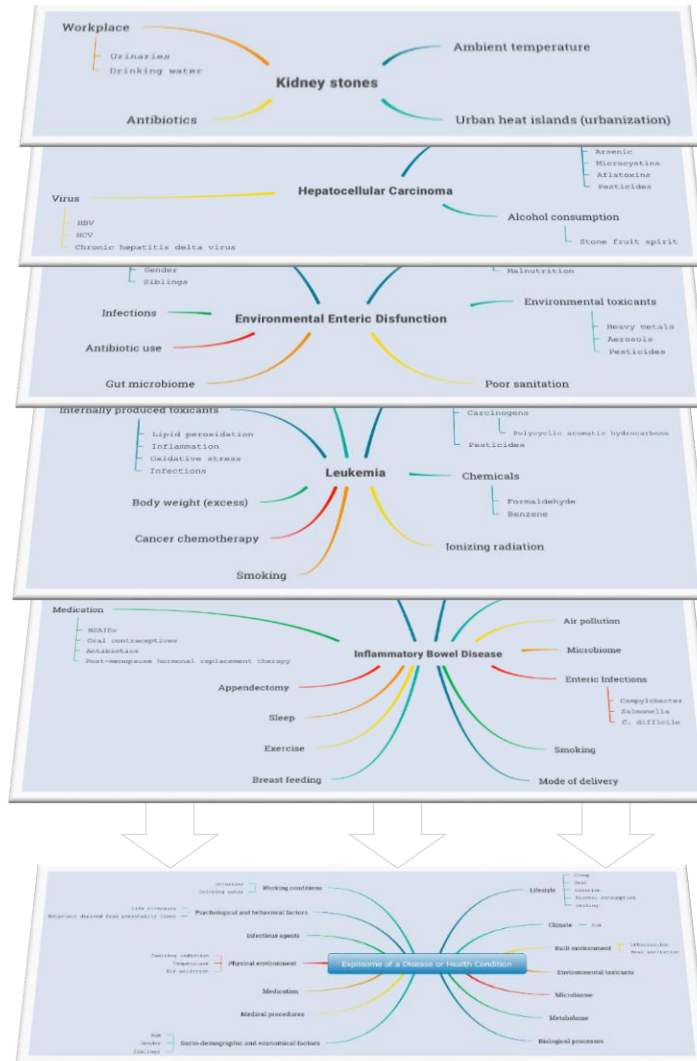








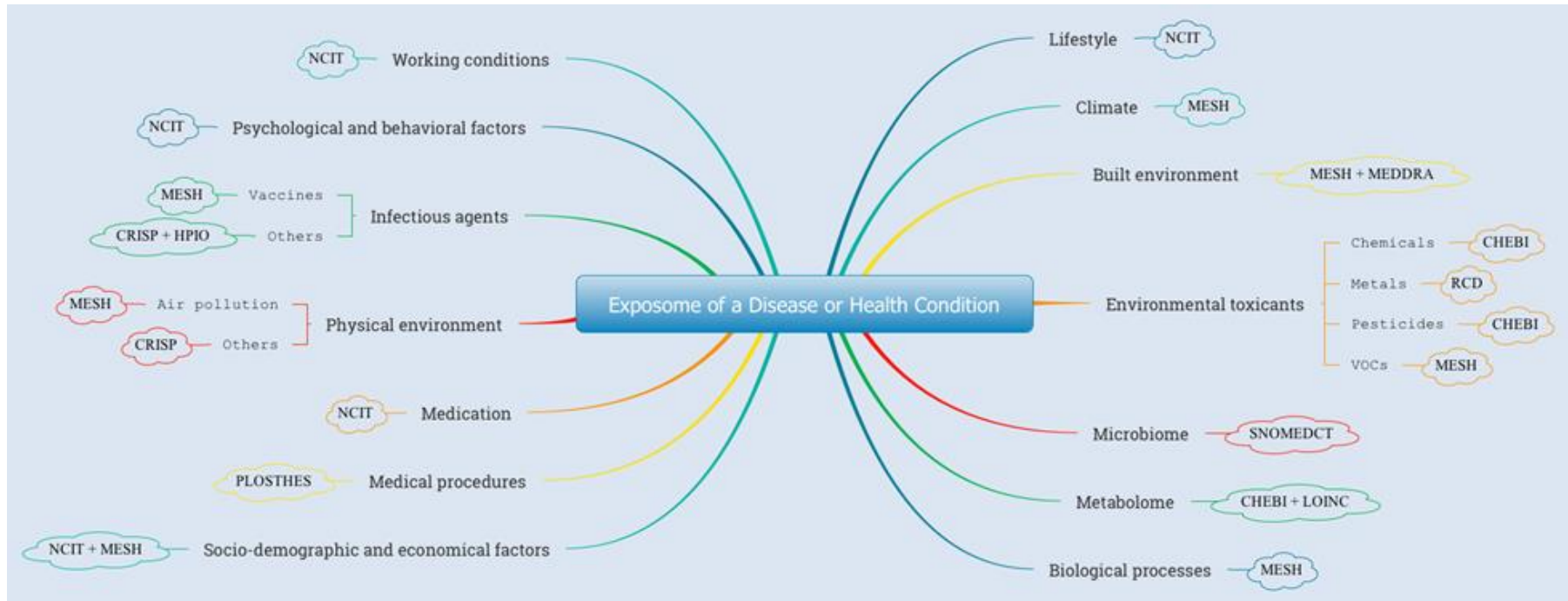
# Mapping disease exposomes



Colaboración with  
Dr Aguiar-Pulido  
(Weill Cornell)

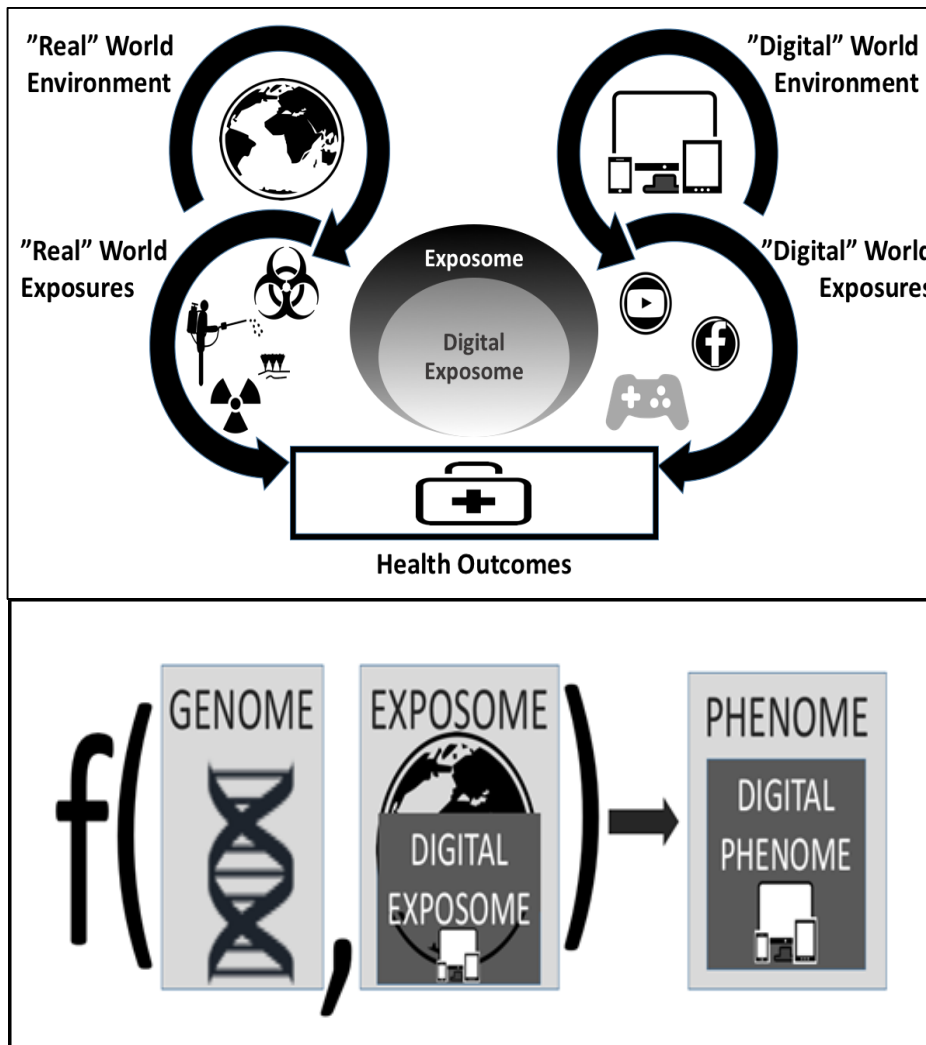


# Choosing the best ontology or vocabulary



Colaboración with  
Dr Aguiar-Pulido  
(Weill Cornell)

# Componente digital del Exposoma



*'the whole set of tools and platforms that an individual use and the activities and processes that an individual engage with as part of his/her digital life'*

Lopez-Campos G, Merolli M, Martin-Sanchez F. Biomedical Informatics and the Digital Component of the Exposome. *Stud Health Technol Inform.* 2017;245:496-500.

Children are 27% more likely to suffer from depression when he or she frequently uses social media

# Exposome and Exposure

Genotype \* Exposure → Phenotype



**Exposome** is the totality of all environmental (meaning all non-genetic) exposures of an individual over his or her lifetime (*Wild, 2005*)

**Exposure** is the specific set of exposome elements of an individual accumulated during a certain time/space and responsible for a particular phenotype (*Martin-Sanchez and Lopez-Campos, 2016*)

# Expotype

Variable	Value	Coding system
Person ID	M-123456	
Category	Behavior	Exposome Ontology
Subcategory	Physical activity	Classification of data and activity in self-quantification systems (CDA-SQS)
Timeframe	01/01/2018 - 31/01/2018	Internet time range
Geolocation	Madrid	GPS coordinates
Method	Mobile app XYZ	
Measurement	Steps	
Value	342.000	
Error	3%	

*Martin-Sanchez FJ, Lopez-Campos GH. The New Role of Biomedical Informatics in the Age of Digital Medicine. Methods Inf Med. 2016 Oct 17;55(5):392-402.*



# New IMIA Working Group

<https://exposomeinformatics.wordpress.com>

The screenshot shows the homepage of the Exposome Informatics website. At the top, there is a dark red header with the text "EXPOSOME INFORMATICS" in large white letters. Below this, a subtitle reads "International Medical Informatics Association - Working Group on Exposome Informatics". A dark navigation bar contains links for HOME, FOCUS, ACTIVITIES, DATA RESOURCES, REFERENCES, NEWS, MEMBERSHIP, and CONTACT, along with a search icon. The main content area has a light beige background. On the left, a large heading reads "WELCOME TO THE INTERNATIONAL MEDICAL INFORMATICS ASSOCIATION (IMIA) WORKING GROUP ON EXPOSOME INFORMATICS". Below this is the IMIA logo, which features the letters "IMIA" in blue and a black caduceus symbol. To the right of the logo, a paragraph of text describes IMIA as the world body for health and biomedical informatics. On the right side of the page, there are sections for "TAGS", "SEARCH" (with a search input field), and "TIMELINE DE TWITTER". The Twitter section shows a tweet from @exposome\_imia that has been retweeted by "Exposor".

Mis sitios Lector Escribir

# EXPOSOME INFORMATICS

International Medical Informatics Association - Working Group on Exposome Informatics

HOME FOCUS ACTIVITIES DATA RESOURCES REFERENCES NEWS MEMBERSHIP CONTACT

## WELCOME TO THE INTERNATIONAL MEDICAL INFORMATICS ASSOCIATION (IMIA) WORKING GROUP ON EXPOSOME INFORMATICS



The **International Medical Informatics Association (IMIA)** is the world body for health and biomedical informatics. As an 'association of associations', IMIA acts as a bridging organisation, bringing together the constituent organisations and their members. IMIA provides leadership and expertise to the multidisciplinary, health focused community and to policy makers, to enable the

### TAGS

### SEARCH

Search ...

### TIMELINE DE TWITTER

Tweets by @exposome\_imia

Exposor Retweeted Personalizar Editar Estadísticas

# Publicaciones

Lopez-Campos G, Merolli M, Martin-Sanchez F. Biomedical Informatics and the Digital Component of the Exposome. *Stud Health Technol Inform.* 2017;245:496-500. PubMed PMID: 29295144.

Kiossoglou P, Borda A, Gray K, Martin-Sanchez F, Verspoor K, Lopez-Campos G. Characterising the Scope of Exposome Research: A Generalisable Approach. *Stud Health Technol Inform.* 2017;245:457-461. PubMed PMID: 29295136.

Martin-Sanchez FJ, Lopez-Campos GH. The New Role of Biomedical Informatics in the Age of Digital Medicine. *Methods Inf Med.* 2016 Oct 17;55(5):392-402. Epub 2016 Aug 15. PubMed PMID: 27523651.

Martin Sanchez F, Gray K, Bellazzi R, Lopez-Campos G. Exposome informatics: considerations for the design of future biomedical research information systems. *J Am Med Inform Assoc.* 2014 May-Jun;21(3):386-90. doi: 10.1136/amiajnl-2013-001772. Epub 2013 Nov 1. PubMed PMID: 24186958; PubMed Central PMCID: PMC3994854.

Lopez-Campos G, Bellazzi R, Martin-Sanchez F. INDIV-3D. A new model for INdividual Data Integration and Visualisation using spatial coordinates. *Stud Health Technol Inform.* 2013;190:172-4. PubMed PMID: 23823413.

Comunicación oral: “Beyond Bioinformatics: contributions from Medical Informatics to Exposome Research” HELIX – Exposome conference. Barcelona. Oct 2017.

Poster “How Well Do Existing Ontologies Represent Exposome Literature?”. AMIA Summit on Translational Bioinformatics. San Francisco, March 2017.

Poster Analysis of Disease Enrichment in Exposome-related Data Resources AMIA Informatics. Summit San Francisco, March 2018

Kiossoglou P, Tran E, Martin-Sanchez F, Lopez-Campos G. (2016). How Are Exposome Data Annotated in Major Genotype-Phenotype Data Repositories? Poster presented at AMIA Summit on Translational Bioinformatics 2016. San Francisco.

Aguiar-Pulido V, Martin-Sanchez F (2016). From published examples to knowledge representation: an inductive approach for exposome data mapping (Invited talk). Emory Exposome Summer Curso at Atlanta, GA (USA).

“Self-Quantification Systems as sources of Big Data and individual sensors

for the Exposome: A proposal for a Minimum Information About a Self-Monitoring Experiment” Presentation at IBM-UoM Annual Research Meeting. March 2014. Melbourne.

Aguiar-Pulido V, Martin-Sanchez F (2016). Towards disease characterization: The Exposome as a new challenge for Bioinformatics (Poster). Intelligent Systems for Molecular Biology (ISMB) at Orlando, FL (USA).



# Hacia la Salud de Precisión

The implications for precision medicine:  
By itself, the genome is a *poor to modest* diagnostic

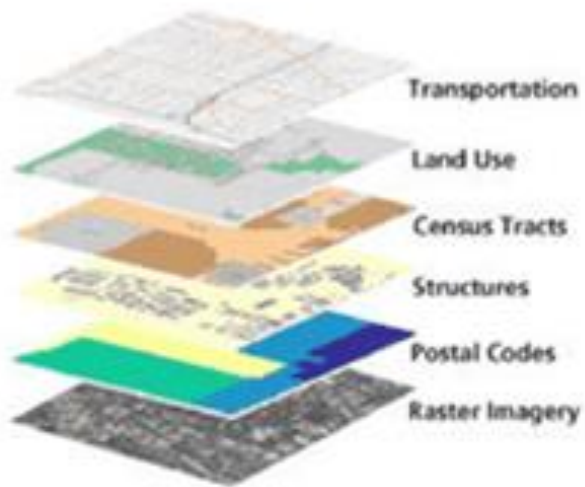
## The Predictive Capacity of Personal Genome Sequencing

Nicholas J. Roberts,<sup>1\*</sup> Joshua T. Vogelstein,<sup>2\*</sup> Giovanni Parmigiani,<sup>3</sup> Kenneth W. Kinzler,<sup>1</sup>  
Bert Vogelstein,<sup>1†</sup> Victor E. Velculescu<sup>1†</sup>

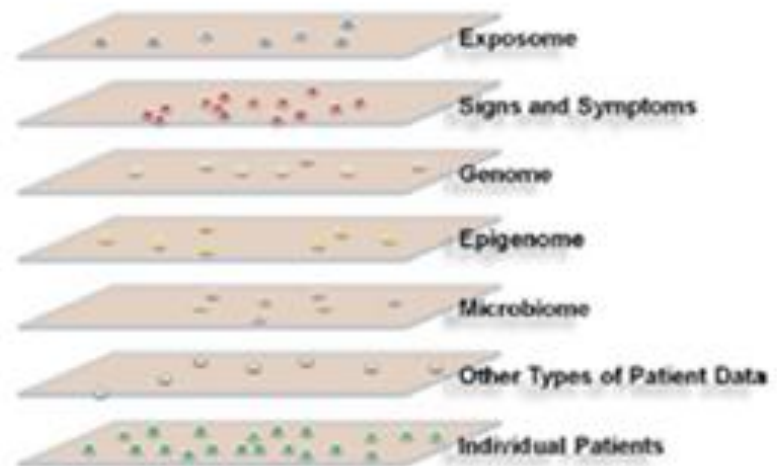
New DNA sequencing methods will soon make it possible to identify all germline variants in any individual at a reasonable cost. However, the ability of whole-genome sequencing to predict predisposition to common diseases in the general population is unknown. To estimate this predictive capacity, we use the concept of a "genomotype." A specific genomotype represents the genomes in the population conferring a specific level of genetic risk for a specified disease. Using this concept, we estimated the maximum capacity of whole-genome sequencing to identify individuals at clinically significant risk for 24 different diseases. Our estimates were derived from the analysis of large numbers of monozygotic twin pairs; twins of a pair share the same genomotype and therefore identical genetic risk factors. Our analyses indicate that (i) for 23 of the 24 diseases, most of the individuals will receive negative test results; (ii) these negative test results will, in general, not be very informative, because the risk of developing 19 of the 24 diseases in those who test negative will still be, at minimum, 50 to 80% of that in the general population; and (iii) on the positive side, in the best-case scenario, more than 90% of tested individuals might be alerted to a clinically significant predisposition to at least one disease. These results have important implications for the valuation of genetic testing by industry, health insurance companies, public policy-makers, and consumers.

*Science Translational Medicine*, 2012

### Google Maps: GIS layers Organized by Geographical Positioning



### Information Commons Organized Around Individual Patients



**Figure 1-2:** The proposed, individual-centric Information Commons (right panel) is somewhat analogous to a layered Geographical Information System (left panel). In both cases, the bottom layer defines the organization of all the overlays. However, in a GIS, any vertical line through the layers connects related snippets of information since all the layers are organized by geographical position. In contrast, data in each of the higher layers of the Information Commons will overlay on the patient layer in complex ways (e.g., patients with similar microbiomes and symptoms may have very different genome sequences). Source: FPA 2011 (left panel).

# Definición

La Medicina de Precisión es un enfoque para descubrir y desarrollar medicamentos, vacunas o intervenciones (nutrición, etc.) que permiten la prevención de enfermedades y ofrecen resultados terapéuticos superiores para los pacientes, mediante la integración de "Big Data", clínicos, moleculares (multi-ómicas incluida la epigenética y microbiómica), información ambiental y de comportamiento para comprender las bases biológicas de la enfermedad.

*Thomas Wilckens MD, Coordinador y fundador  
PRECISION MEDICINE INSIGHT Linkedin group (>8500 miembros)  
<https://www.linkedin.com/groups/5180384>*





La Medicina de Precisión requiere **vistas longitudinales** de datos individuales (patient journey) para la estratificación de los pacientes; no solo instantáneas estáticas de genomas y estado clínico

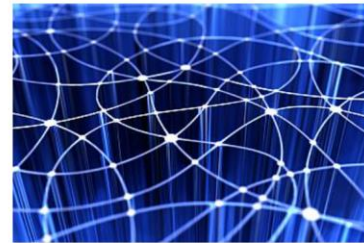
(PMI >10 años)

Recontact!!!



## Program Components

Through a set of [funding awards](#), NIH has established the essential components of the *All of Us* Research Program to build a research cohort of one million or more U.S. volunteers to advance precision medicine. Click the images below to learn more about each of these components.



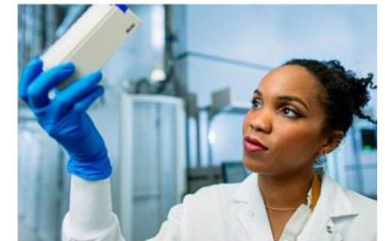
Data and Research Center



Participant Technologies Center



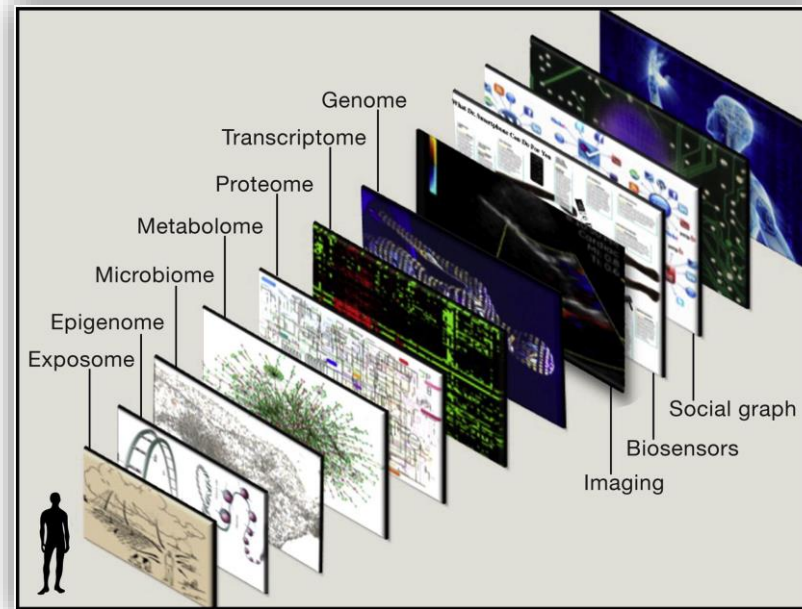
Health Care Provider Organizations



Biobank

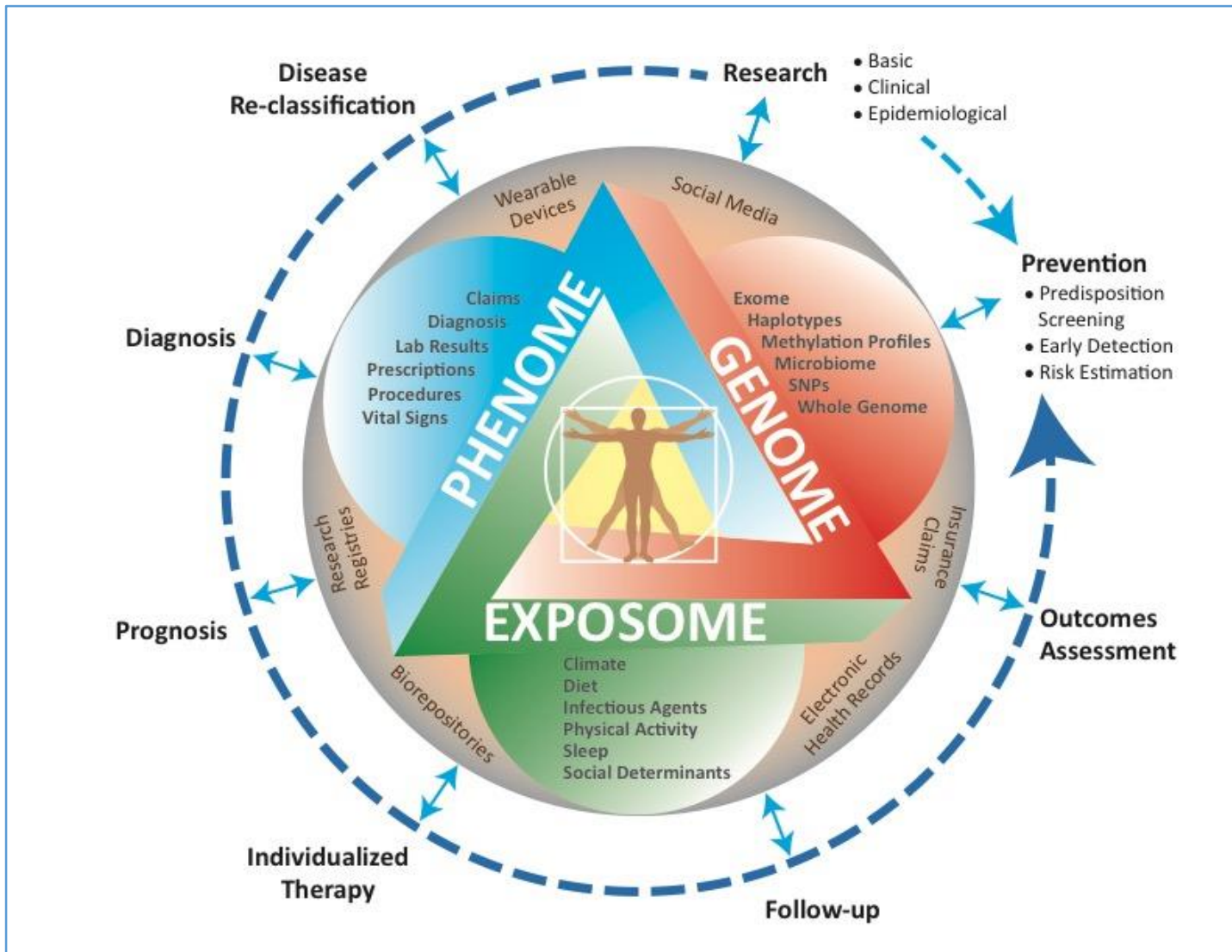
[joinallofus.org](https://joinallofus.org)

*La medicina de precisión permite una medicina más segura, más eficiente, preventiva y preventiva, **pero necesita abordar la complejidad y diversidad de la información de salud personal, más allá de la secuencia del genoma.***



*Topol E. Cell 2014*

# Key role of Exposome research in Precision Medicine



# Salud de Precisión

- The goal is **to provide patients** with more informed choices that include such health determinants as **environmental exposures** and **socio-economic status**, based on **real-world data**.
- "How I think we go **from precision medicine to population health** is to extend beyond our historical data streams of clinical medicine and genetics".



*Dr. Sachin Kheterpal, associate dean for research information technology at the University of Michigan Medical School and co-director of its Precision Health initiative.*

# Participatory Technologies (Digital Health)

mHealth, Wearables  
Social Media, Direct to Consumer Services

Biomedical  
Research

Healthcare &  
Prevention

Environmental  
Health  
Informatics

Participatory  
Health  
Informatics

EXPOSOME  
CHARACTERIZATION

- Ontologies
- Resources
- Expotyping

EVIDENCE  
GENERATION

- Therapeutic affordances of social media
- Essential characteristics of Self Quantification Systems

Precision Medicine Informatics



Muchas  
gracias  
por vuestra  
atención!!!