The European House Ambrosetti

LIGURIA 2022

PRESENTAZIONE DI PIER GIUSEPPE PELICCI

Genova, Palazzo Ducale
Martedì, 8 maggio 2018
II Edizione

REGIONE LIGURIA

ERG EVOLVING ENERGIES

Duferco Energia

Compagnia di San Paolo

PSA VOLTRI-PRA

ANSALDO ENERGIA Power together

Gruppo Messina

GO Gruppo Spinelli LOGISTICS PROVIDER

ITALIANA COKE GROUP

MONTALLEGRO

Camera di Commercio Genova

Camera di Commercio Riviere di Liguria Imperia La Spezia Savona

Genova smartcity

Working paper, maggio 2018.

Per gentile concessione dell'Autore.

Per il quinto anno consecutivo, The European House - Ambrosetti è stata nominata - nella categoria "Best Private Think Tanks" - *1° Think Tank in Italia, tra i primi 10 in Europa e nei primi 100 indipendenti su 6.846 a livello globale nell'edizione 2017 del Global Go To Think Tank Index Report dell'Università della Pennsylvania.*

Innovazione, Ricerca e Alta Tecnologia

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Universita' degli Studi
di Milano

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REGIONE LIGURIA

The European House
Ambrosetti

Local Infrastructures in Research and Life Sciences

- **7 Dipartimenti universitari (>100 imprese coinvolte)**
- **5 Poli di Innovazione**
- **27 Dipartimenti CNR**

- **Isitituto Italiano di Oncologia (IIT)**

- **Ospedale Giannina Gaslini (IRCCS; pediatria)**
- **Policlinico San Martino (IRCCS; Oncologia)**
- **Ospedali Gallera (Geriatria)**

Agenda

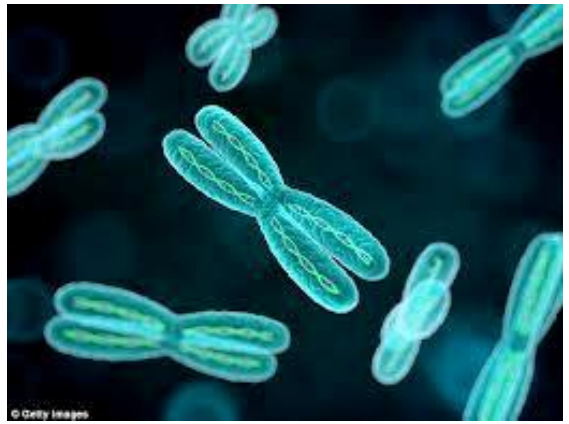
- The ongoing revolution in Life Sciences
  - Biology
  - Medicine (Personalized/Precision Medicine)

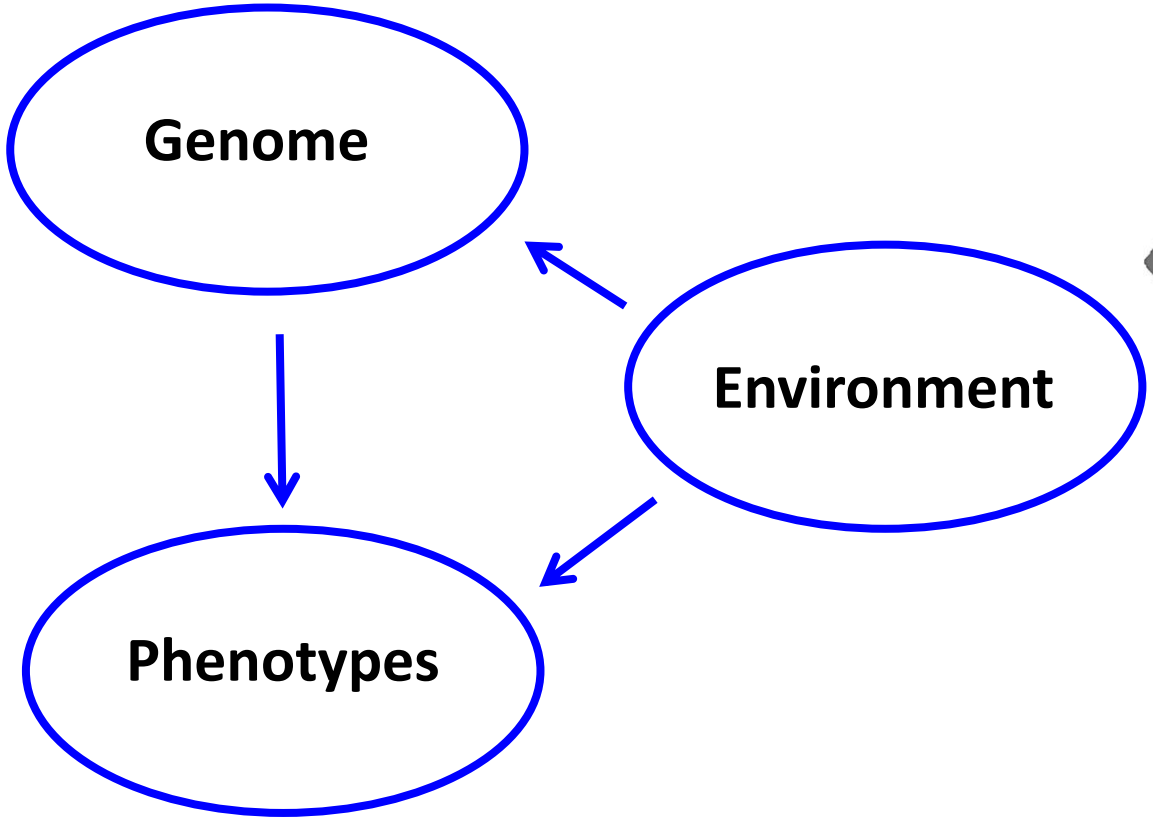
- The national opportunities
  - The ACC network (Ministry of Health)
  - The Human Technopole

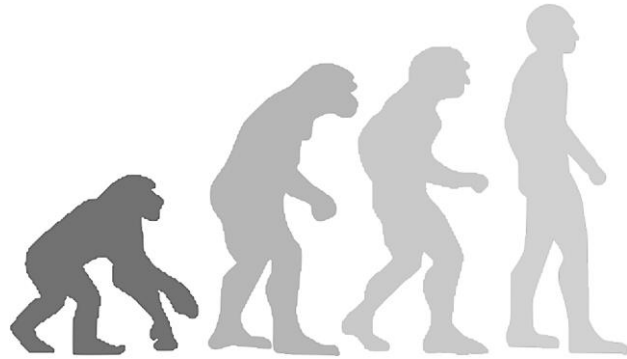
Universal questions in biology :

how the *genome* translates into *phenotypes* (endless forms of living organisms);

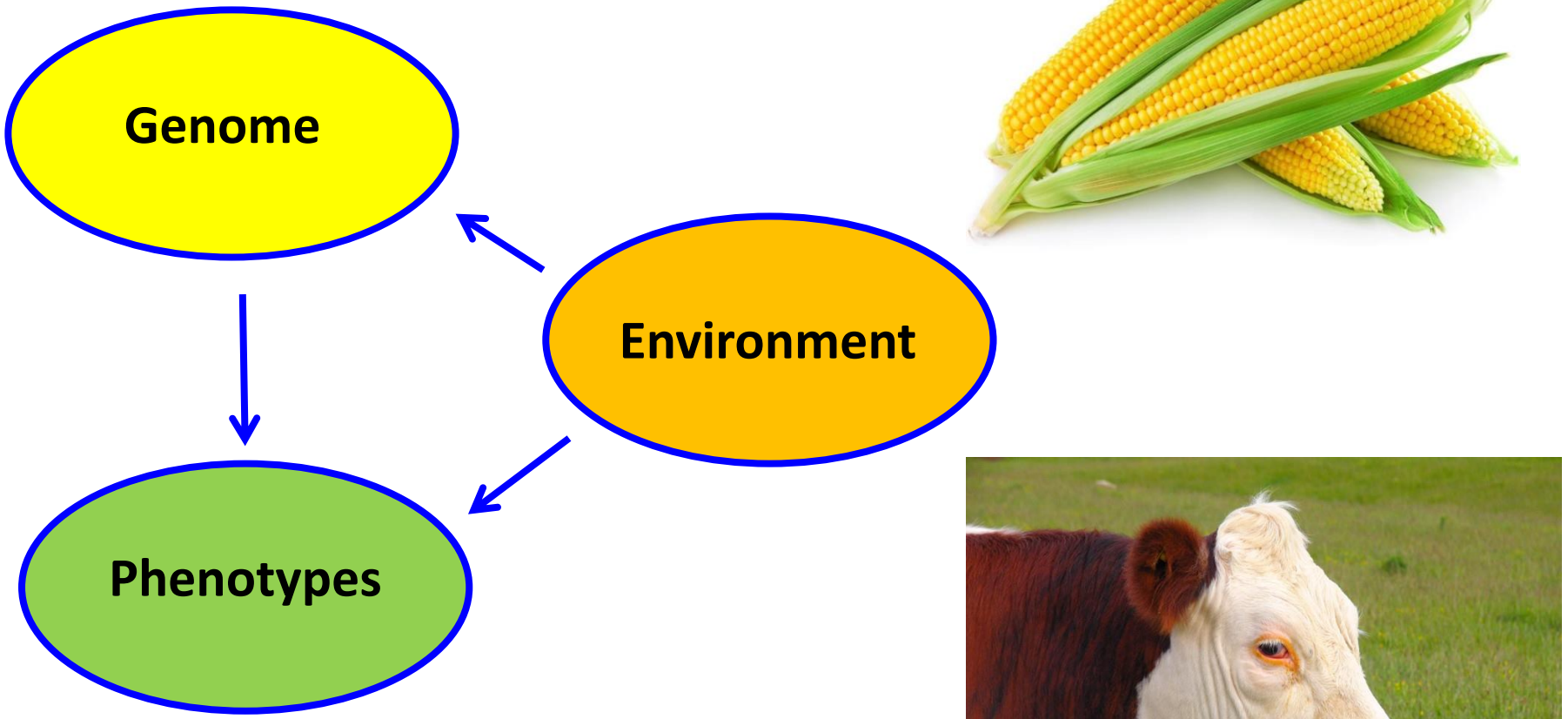
how the *environment* modifies *Genomes and Phenotypes* (millions of species and adaptated phenotypes)







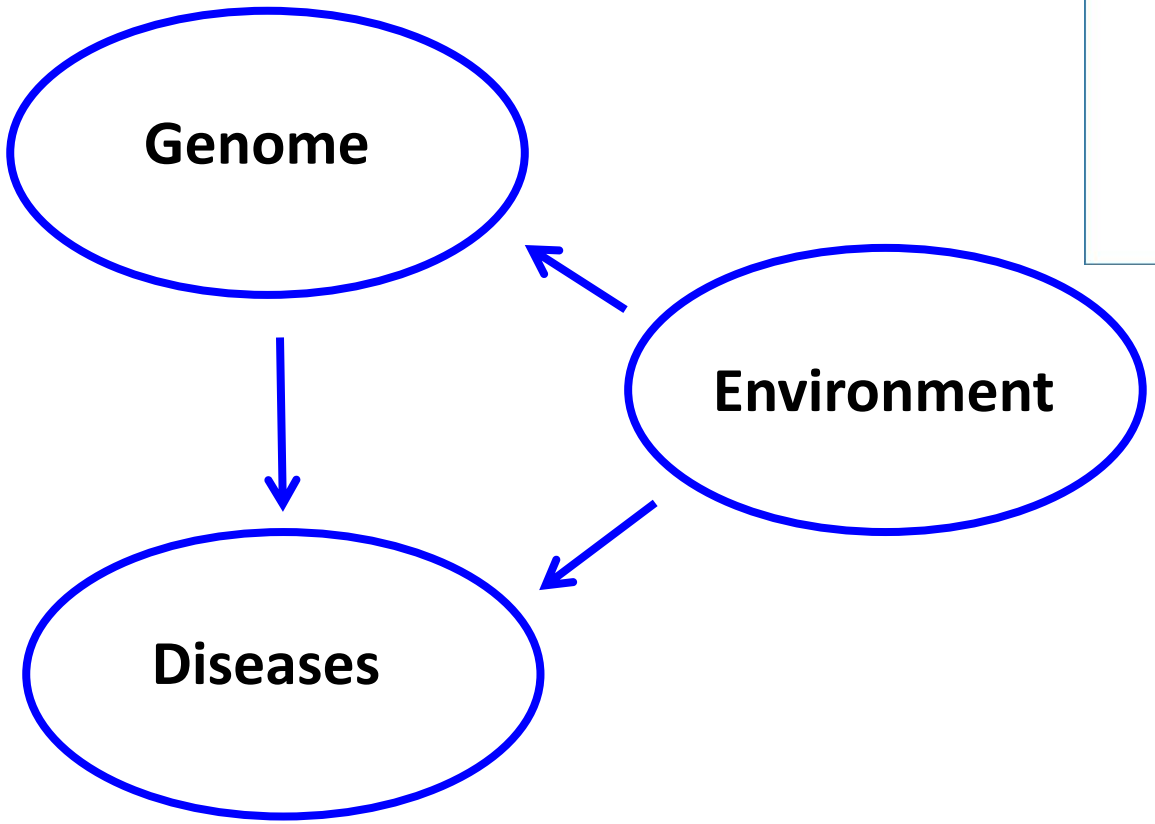
One main goal of biologists:
how to *modify the genome* and the environment to select phenotypes best fitted to the needs of humans



Medicine: **One universal question and One main goal :**

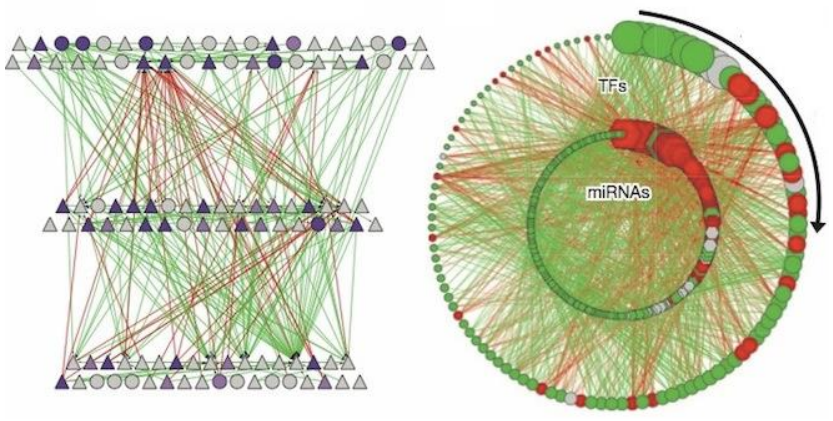
how the genome and the environment contribute to *diseases*

how to *modify the genome and the environment* to prevent and cure diseases



The main problems

1. Complexity



Gene	30,0000
↓	↓
RNA	x10
↓	↓
Protein	x10
↓	↓
Phenotype	x10

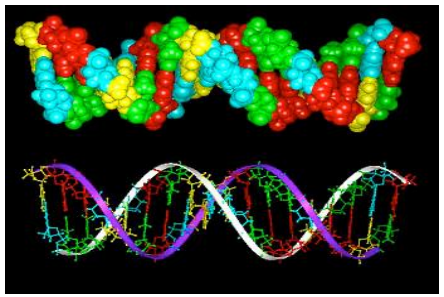
- Genetic Interactions
- Each gene/interaction potentially influenced by environmental factors

2. Genome manipulation

- Gene structure
- Gene Expression

In the past 15 years, biomedical research has radically transformed, leading to unprecedented profound changes in Biology and Medicine

Genomics



3 billions nucleotides per genome

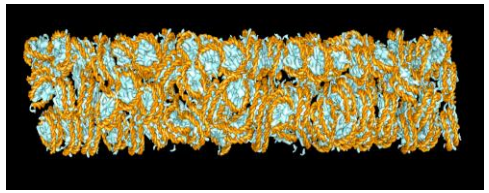
A code with four letters

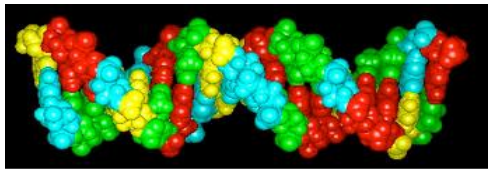
25,000 Genes

0.5% differences among individuals (30 millions bps)

Epigenomics

ENVIRONMENT





A code with hundreds of letters and combination of words Influenced by environment

100's epigenomes per person

Each person with its own epigenomes

DNA Sequencing

Massive parallel sequencing of DNA (NGS)

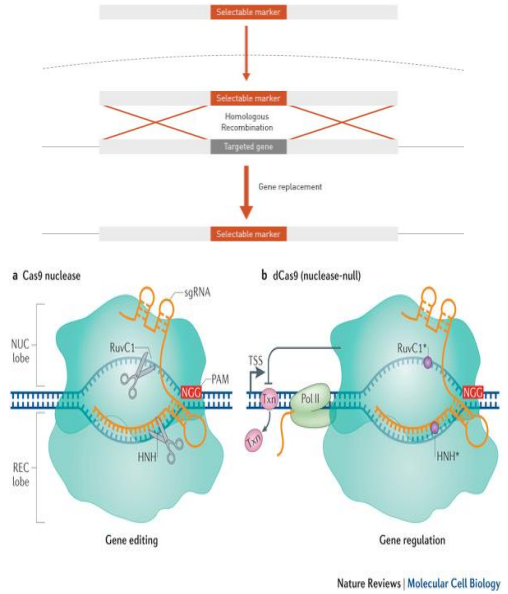
Rapidly evolving

From millions to 100's euros

Time: From years to 1 day

Suitable for population screens

Genome Editing



2004: CRISPR/CAS9

High efficiency

Highly specific

Very easy design (1-3 weeks)

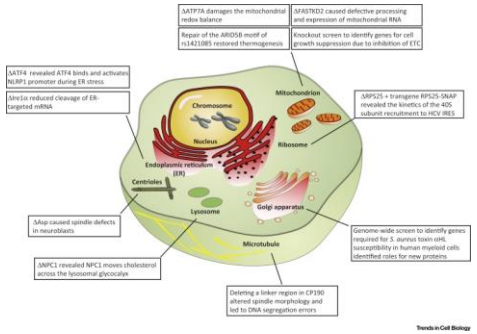
Feasible in any cell type

can be ordered online

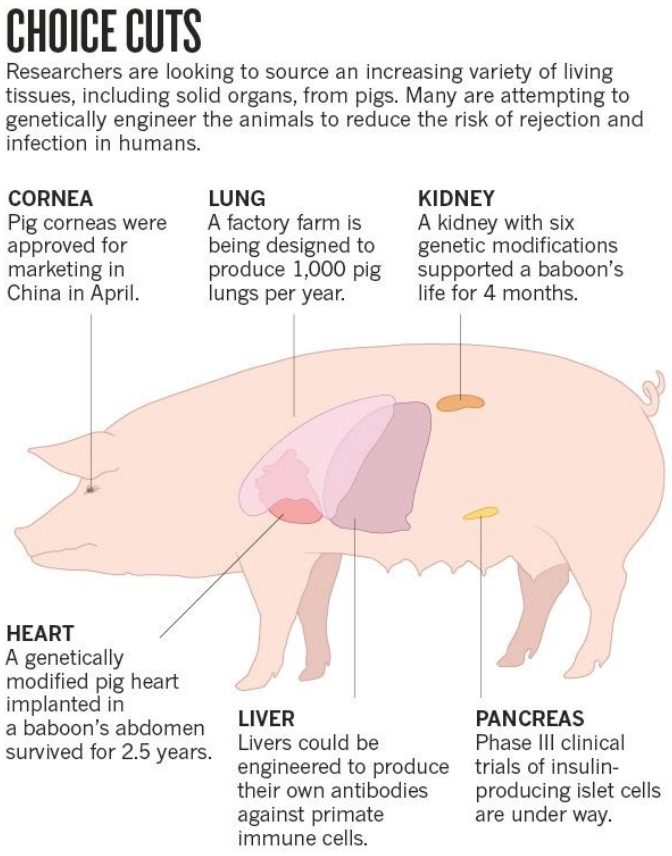
Very cheap (60-100 E one kit)

Genome editing (2014-today):
Endless number of applications in science and technology

Physiology and Mechanisms of diseases

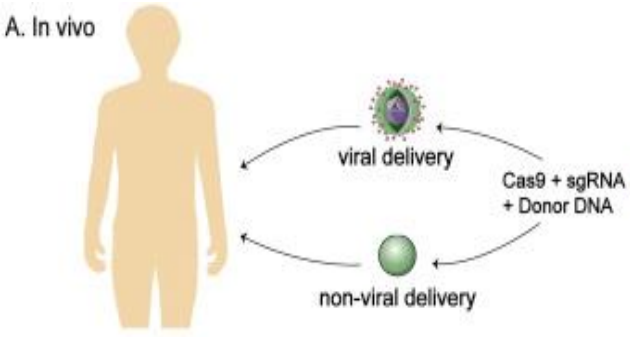


Engineered pigs as organ donors



Engineered chicks for hypoallergenic eggs

Treatment of Genetic diseases and cancer



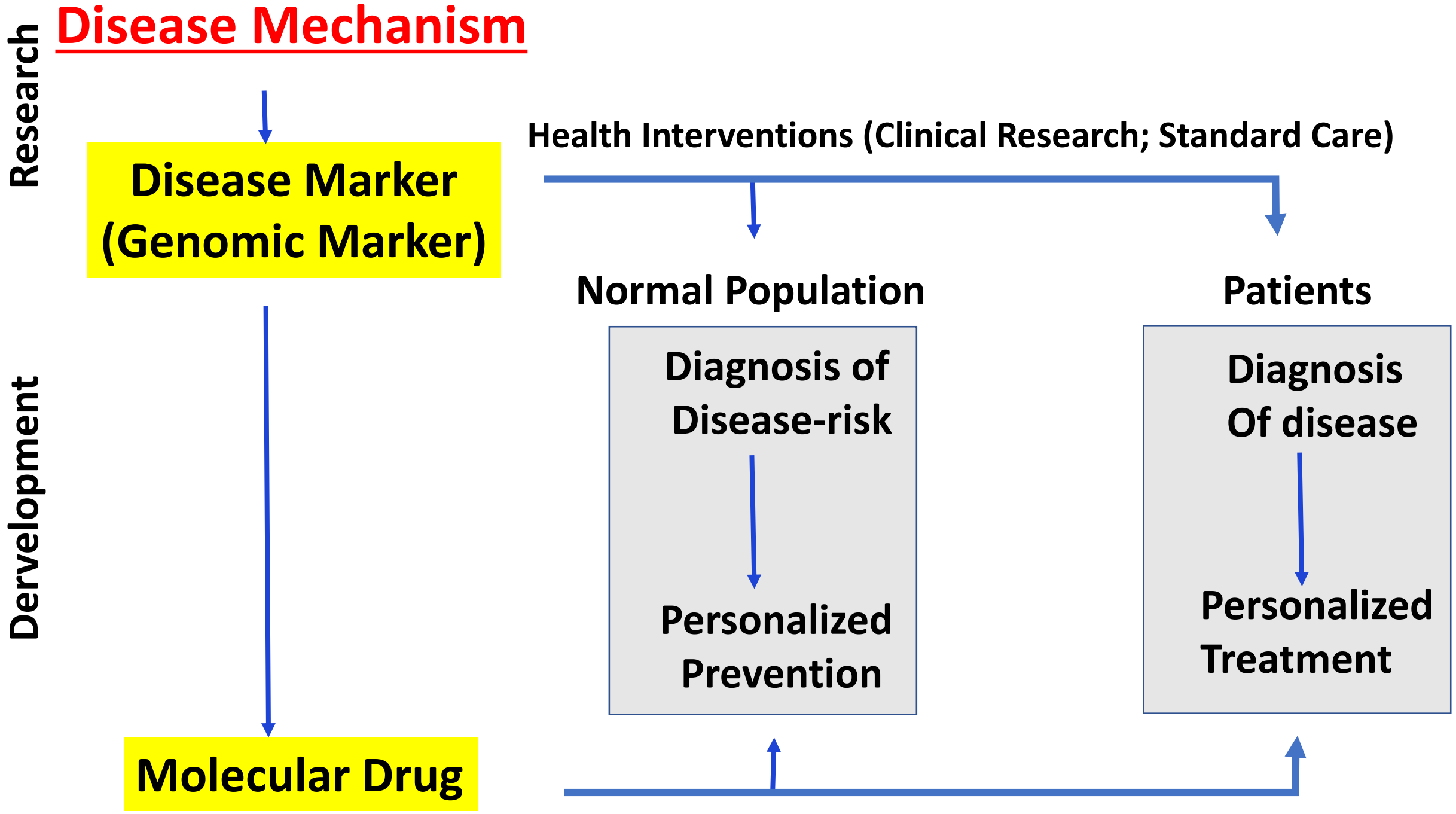
First genome-edited crop (colza) (2015)

Precision /Personalized Medicine

1. Disease re-classification based on causative molecular mechanisms

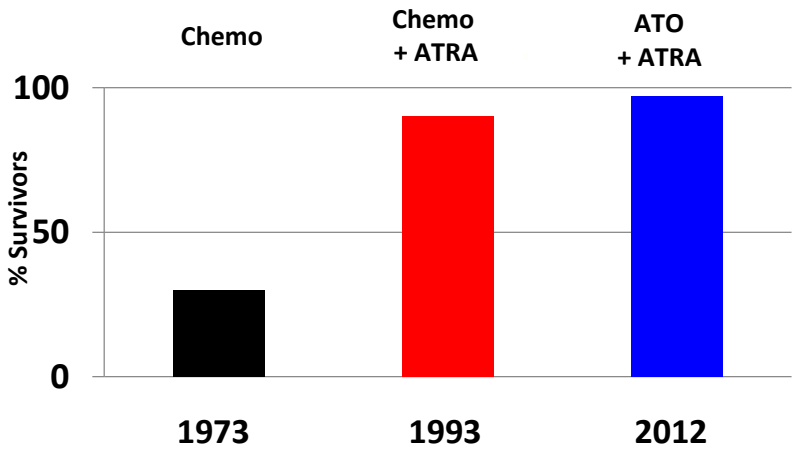
2. Disease-Risk assessment based on molecular mechanisms

3. Disease-Treatment based on molecular mechanisms


Disease Mechanism
Research
Disease Marker
(Genomic Marker)
Dervelopment
Molecular Drug
Health Interventions (Clinical Research; Standard Care)
Normal Population
Patients
Diagnosis of
Disease-risk
Personalized
Prevention
Diagnosis
Of disease
Personalized
Treatment

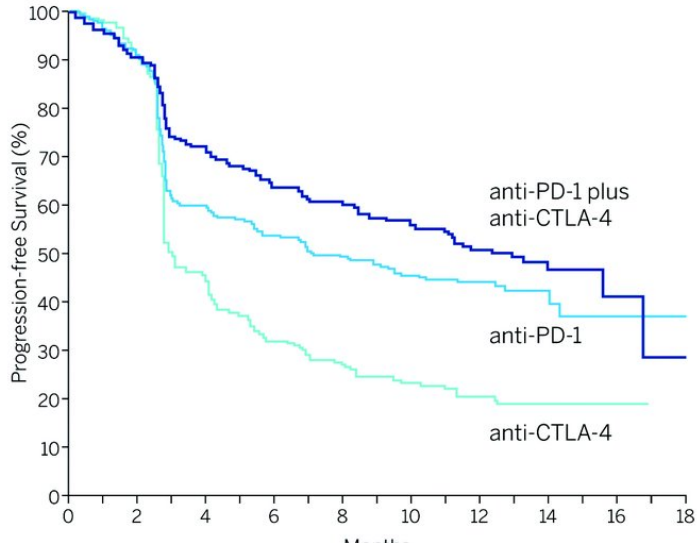
Precision/Personalized Oncology: toward curative treatments

The first example: Combination of Molecular Drugs



Chemotherapy-free cure of Promyelocytic Leukemias

The last example: Immunotherapy with checkpoint inhibitors



Prolonged remissions In metastatic melanomas

Other Molecular Drugs and other Success-Stories

Imatinib mesylate	CML	BCR-ABL translocation	Oncogene addiction (1982)
Imatinib mesylate Sunitinib Nilotinib Dasatinib	GIST Dermatofibrosarcoma protuberans Hypereosinophylic syndrome Melanoma	c-KIT mutation PDGFR mutation	Oncogene addiction (1999)
Trastuzumab Pertuzumab Lapatinib	Breast	HER2 amplification	Oncogene addiction (1985)
Gefitinib, Erlotanib Cetuxumab	Lung cancer Bowel	EGFR mutation	Oncogene addiction (2004)
PKC412, SU11248, CMT53518	AML, ALL	FLT-3 mutation, tandem duplication	Oncogene addiction (1996)
PARP inhibitors	Breast Ovarian	BRCA1/2 mutation	Synthetic lethality (2005)
PLX4032	Melanoma	BRAF (8 years)	Oncogene addiction (2002)
Crizotinib	Lung	EML-4 ALK (4 years)	Oncogene addiction (2007)
PCI 32765	CLL	BTK expression	Lineage (1993)
Tamoxifen, AIs	Breast cancer	ER expression	Lineage (1800s)

Molecular drugs have changed the natural history of different types of cancer

The high potential of Precision /Personalized Medicine

1. General optimism that will ***improve public health***

2. Generally perceived that may be ***economically viable***, due to improved primary and preventive, improved efficacy and reduced toxicity of treatments

3. Anticipated that will induce ***great changes in the health system*** itself, affecting the role people play in health management

The challenges (limits) of Precision Oncology

1. How to extend the benefits of currently available targeted treatments to all patients

- **low number of eligible patients accessing available targeted treatments (<20% in Italy?)**
  - **omic approaches are not standardized for clinical use**
  - **resources required are currently unsustainable in a routine clinical setting, in terms of costs, time and human effort**
  - **limited screening capabilities, drug availability, and training of practitioners**

➢ ***Guarantee access of patients to genomic screenings and to available targeting drugs***

The challenges (limits) of Precision Oncology

2. How to increase the numbers of patients that can be cured with Precision Medicine Medicine approaches

- **Low number of tumors for which approved targeted treatments are available (<20%)**
- **Many drugs in clinical development**

➢ ***Guarantee access of patients to drug testing pipelines (Clinical Trials)***

The challenges (limits) of Precision Oncology

3. How to increase efficacy of targeted treatments (curative treatments)

- **Most not curative; Short responses; Resistance dominant over sensitivity**
- **Poor value of available stratification markers**

➢ ***Urgent need: renewed effort in fundamental-research in oncology***

- **New approaches in Cancer Science (mechanisms of resistance; Tumor heterogeneity; single-cell omics; (micro)environmental interactions)**
- **New treatment approaches, new drugs and stratification markers**

The challenges (limits) of Precision Oncology

4. How to deal with the increasing difficulty in the collection and integration of a huge amount of "personalized data" (-omics, environmental, lifestyle, medical data, etc.)

- **Each patient requires collection and integration of a huge amount of "personalized data" (genomic, epigenomic, environmental, lifestyle and medical history)**
- **"personalized data" needs to be integrated with knowledge from both clinic and basic research**
- **the scale of emerging information is enormous and outpacing our human cognitive capacity**

➢ ***Generation of Large-scale Genomic and Clinical Data Resources (Prescription and Analytical Computational Tools)***

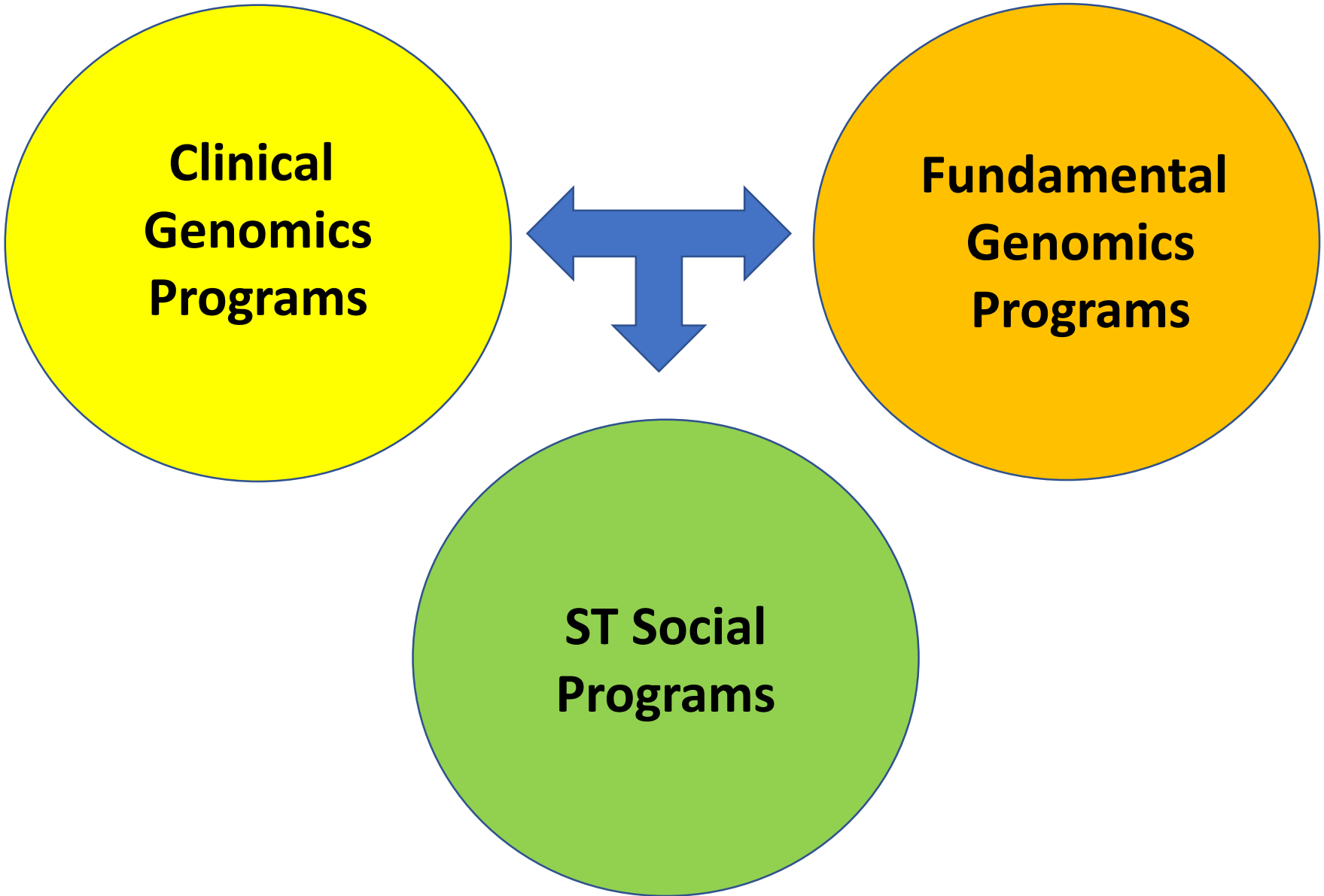
The challenges (limits) of Precision Oncology

5. How to deal with the emerging ethical, legal and social issues connected to Personalized Oncology

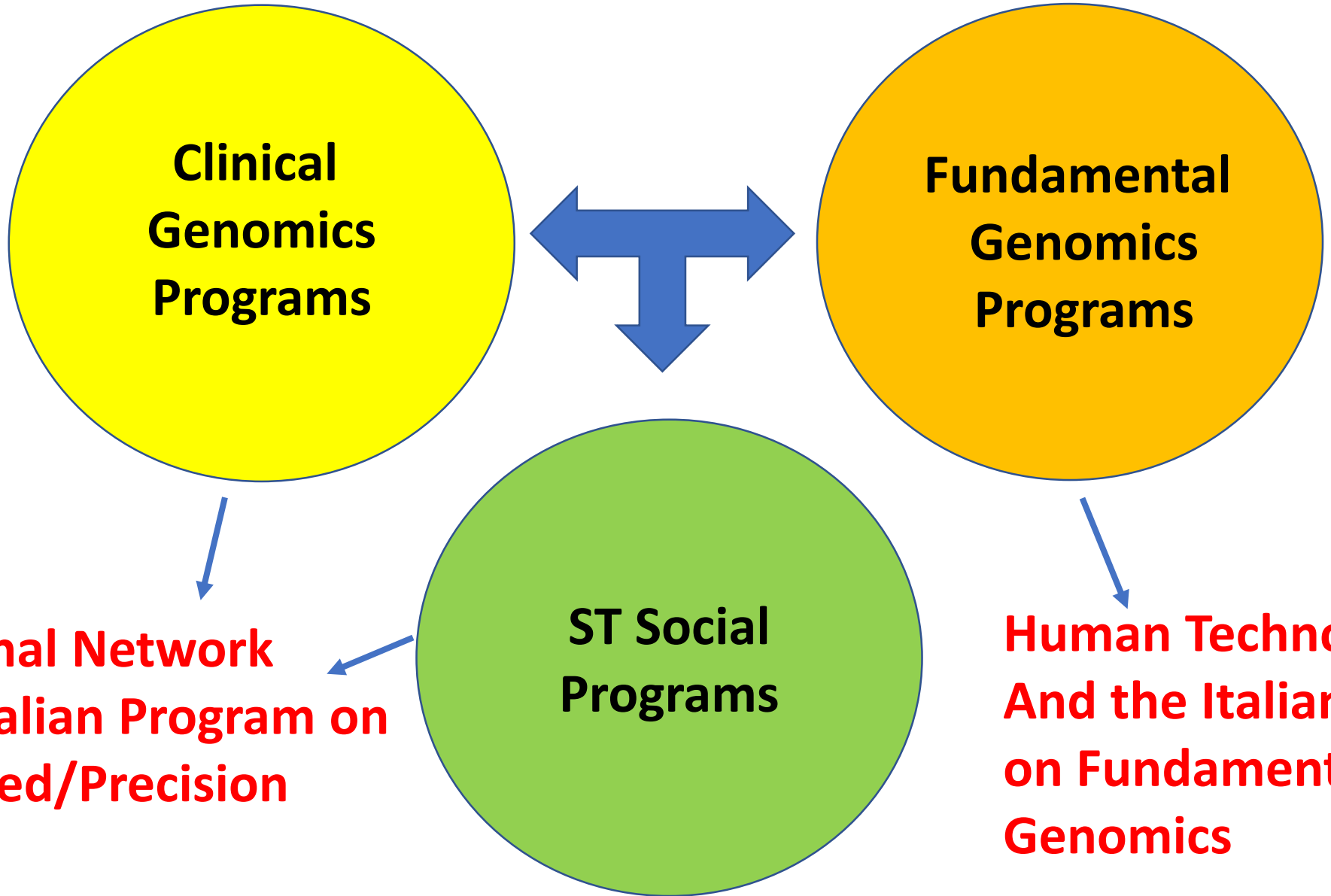
- **Costs**
- **Patient privacy and confidentiality**
- **Implications of data analytics**
- **Patient capacity of data interpretation and management (crowdsourcing, participatory surveillance)**
- **Data acquisition/sharing (social media, and tracking/wearable devices)**

➢ ***Provide patients and doctors with appropriate policies and interpretative tools, and ensure that both benefits and costs are fairly distributed in the society***

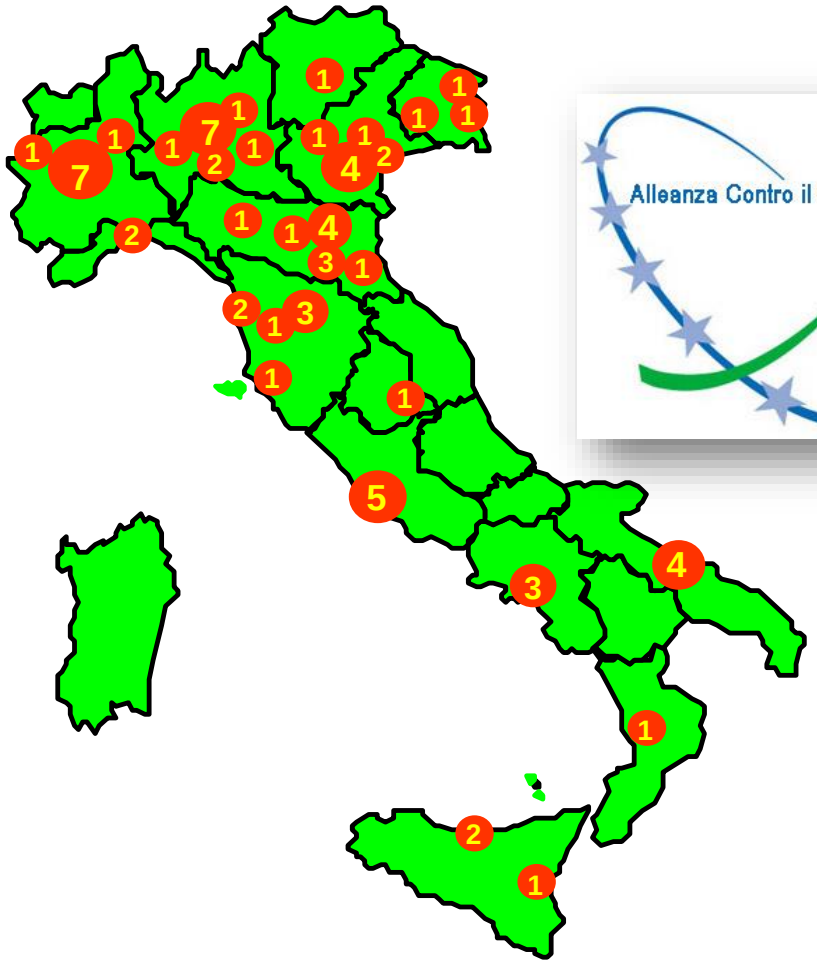
Priorities of Precision/Personalized Medicine



Priorities of Precision/Personalized Medicine



Alleanza Contro il Cancro (ACC)
21 Cancer-Research Hospitals (IRCCS) – Ministry of Health
(+~50 local affiliated Hospitals)



Alleanza Contro il Cancro

The 21 ACC IRCCS Research Hospitals:

Clinical Resources (2014)

- 90k New cancer patients every year
- 70k Patients in Clinical Trials
- 5k Active Clinical Trials

Research performance (2016)

- Number of publications: > 5,000
- Impact Factor: > 20,000
- Research Grants: >200,000,000
- High-Impact Journals

Collaboration with Patients' Associations

Collaboration with the Ministry of Health for NHS regulations

ACC network (started August 2016)

General Goals

Use now all available genomic information to improve treatment for all patients

Continuously transfer new (gen)omic discoveries

Scientific Goals

- Genomic screens of all patients, to guarantee access to the available targeted drugs and to Clinical Trails
- Generation of Large-scale Genomic and Clinical Data Resources *(Prescription and Analytical Computational Tools)*

Infrastructural Goals

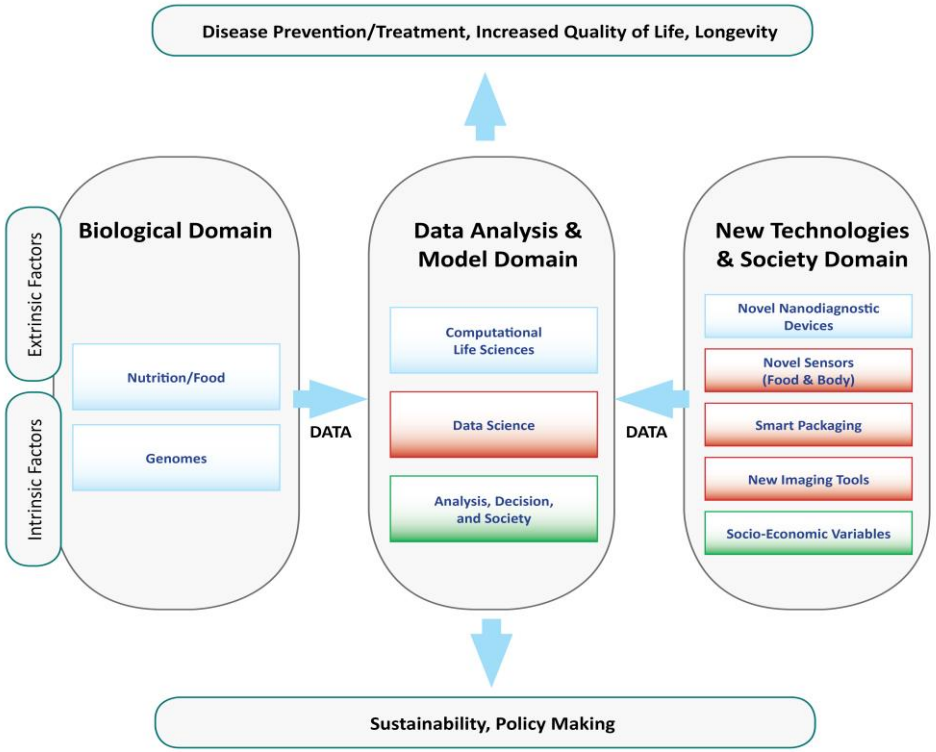
- Dissemination of Genomics-capabilities (e.g. set-up of NGS-facilities at each IRCCS; training of a new generation of genomics technologists and clinical bioinformaticians)
- Set-up of the ACC IT-infrastructure (in coll. with Elixir): storage, pipelines, national database of cancer mutations

Accomplishements (2016-today)

- Created a community of ACC-Bioinformatics and ACC-Genomic-Technologists; common wet and informatic workflows
- Acquired NGS-technology by all the 21 participating IRCCS
- Created a centralized ACC-IT infrastructure shared among all partecipating IRCCS
- Pilot national genome-screening project: lung-cancer (started Febr 2018)

Human Technopole

- A *national research infrastructure* located in Milan, at the EXPO site, and centered on Human Technologies (health, healthy aging)
- Focused on the *cross-disciplinary development* of
  - ✓ Genomics and food/nutrition sciences
  - ✓ big-data analytics and innovative computational methods
  - ✓ advanced technologies
  - ✓ Socio-economic sciences



- *Mission*

✓ new personalized approaches on cancer and neurodegenerative diseases (*preventive nutrition and personalized medicine*)

✓ new opportunities for *industrial development* (food technologies, softwares, diagnostics and therapies)

✓ analytical methods and predictive algorithms to analyze and control, complex *socio-economic scenarios*

Human Technopole

At the Expo Site in Milan:

7 Centers

C1: OncoGenomics Center
C2: Neuro Genomics Center;
C3: Agri-Food and Nutrition Genomics Center
C4: Data Science Center
C5: Computational Life Sciences Center
C6: Center for Analysis, Decisions, and Society
C7: Center for Smart Materials and Devices

3 large-scale Facilities

F1: Central Genomics Facility

F2: Imaging Facility

F3: Data Storage and High-Performance Computing Facility

Collaboration network:

- Research Institutes and Research Hospitals (of the Milan Area and Nationwide)
- National and International Companies

The Oncogenomic Center (C1) at Human Technopole

1. A central research facility at the EXPO site

- **incorporating Several *Joint Laboratories and Outstations* in collaboration with Universities, leading Research Insititutes and Research Hospitals in Lombardy**
- ***Highly-focused and multidisciplinary***
- **Emphasis on a *new organizational model*, designed to allow real-time transfer of new knowledge to clinical and industrial pipelines, and guarantee patients early access to innovative diagnostics and treatments; high integration and mutual dependency of all knowledge-generation levels: preclinical, early clinical and clinical development**

2. A formal joint venture with multi-institutional networks involving the leading Italian Cancer Research Hospitals

- **Example: Alliance Against Cancer (ACC) – a network of 21 italian cancer hospital (IRCCS), with active leadership of the IRCCS of Lumbardy**

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