

Accelerating
Understanding
Summit 2016

Welcome from Institut Gustave Roussy

Professor Eggermont, The Director General - Institut Gustave Roussy

Gilles Bloch, President - Université Paris-Saclay

Professor Vassal, Professor of Oncology - University Paris-Sud



Precision Cancer Medicine and Big Data with a focus on children with cancer

Gilles Vassal



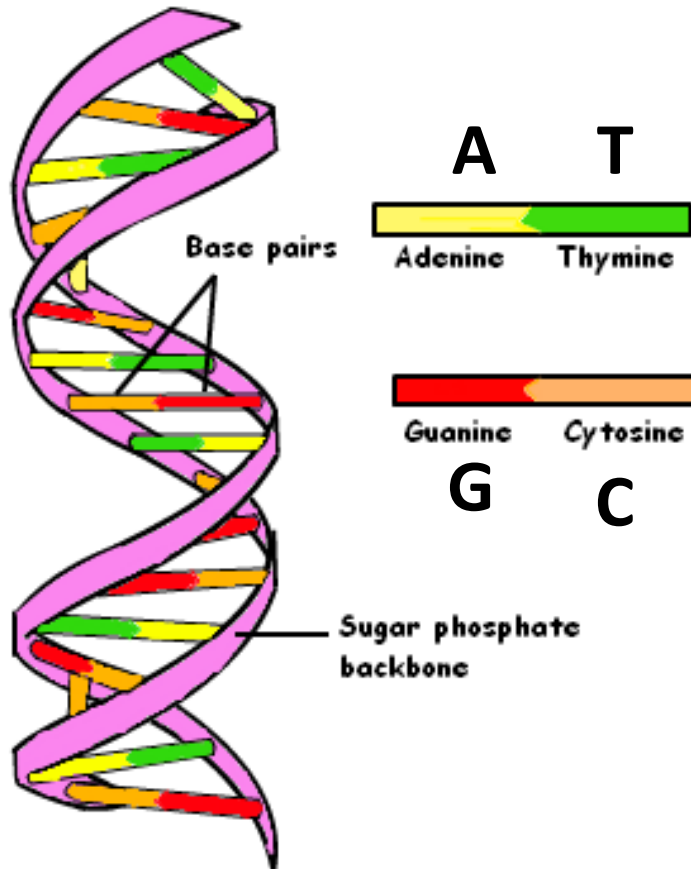
Accelerating Understanding
Summit 2016

31 May - 1 June 2016, Paris, France



Each human being is unique





4 bases

1 human genome
=
 3×10^9 basepairs

25,000 to 30,000 genes

DNA sequencing of the First Human Genome

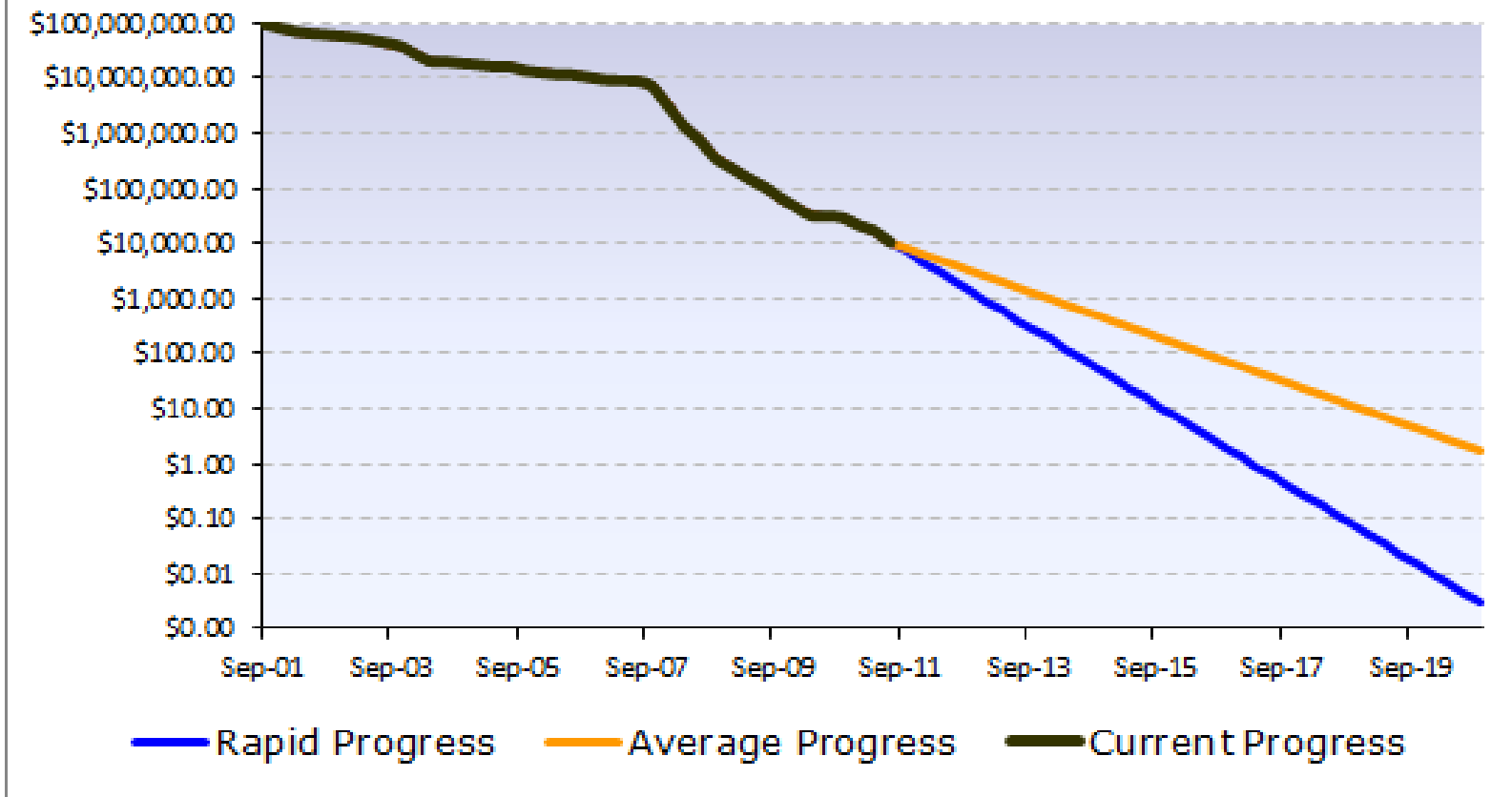
Started 1990

13 years, \$2.7 bn

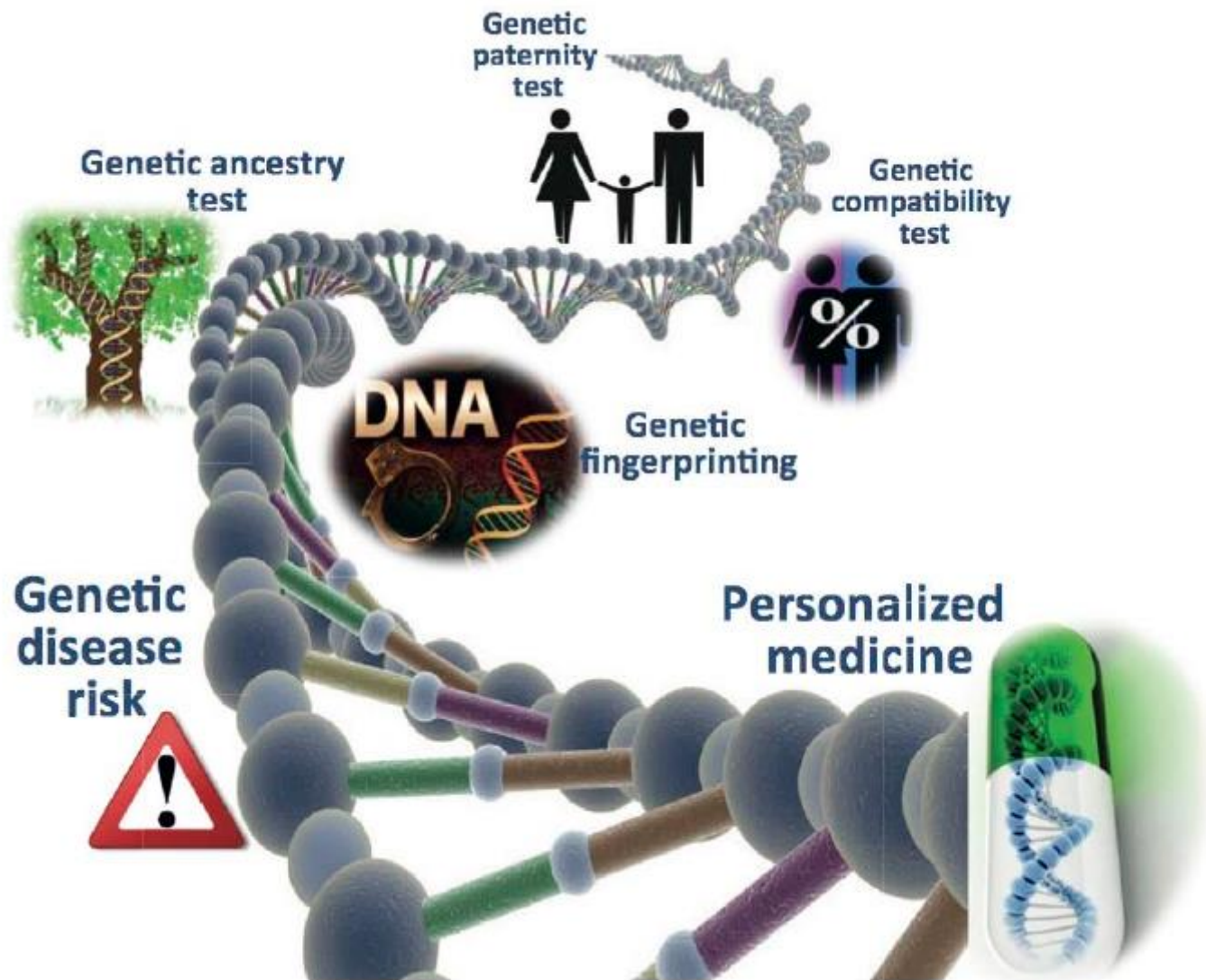
Completed on April 14, 2013



Sequencing Cost per Genome: 2001 to 2020



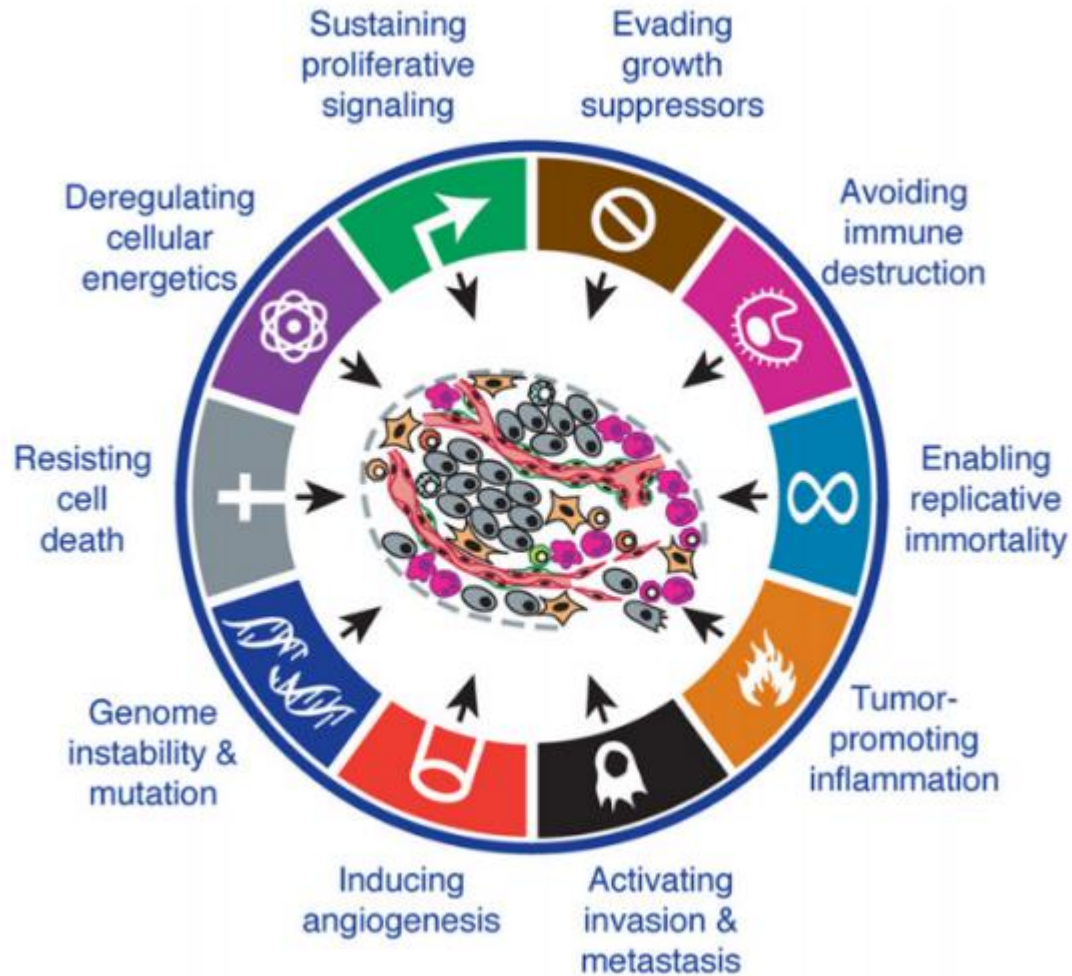
Sources: National Human Genome Research Institute and author's calculations.



Cancer

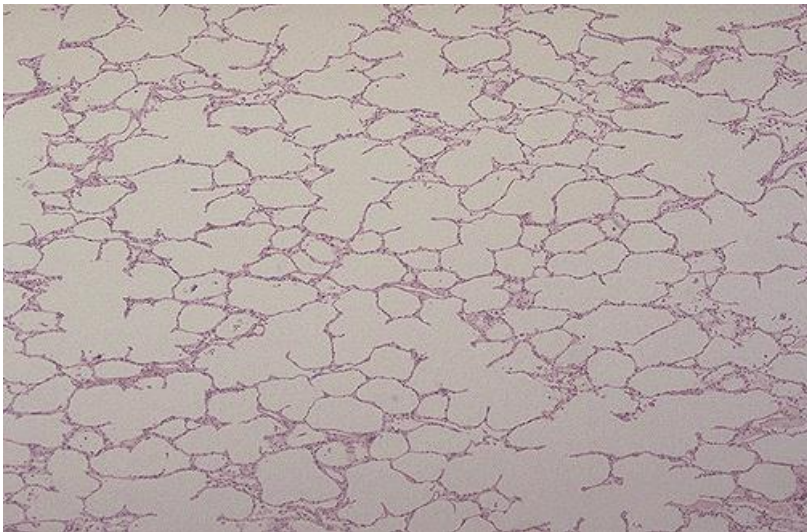
- Interaction between Genome and Environment
 - Eg, Tobacco, UV, virus,.....
 - Somatic alterations
- Genetic predisposition
 - Eg Breast cancer (BRCA)
 - Constitutional DNA

Cancer

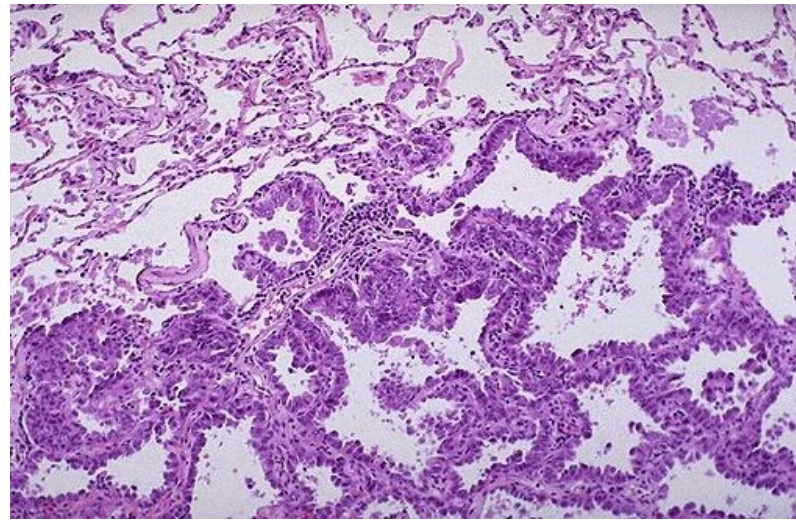




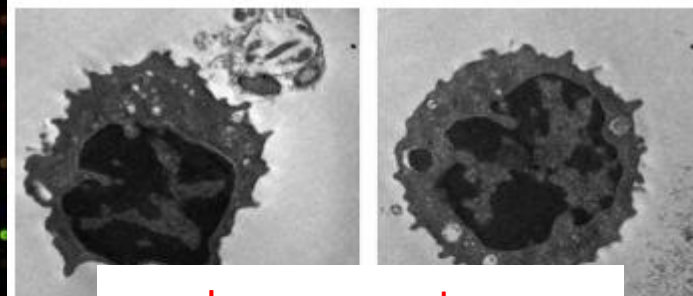
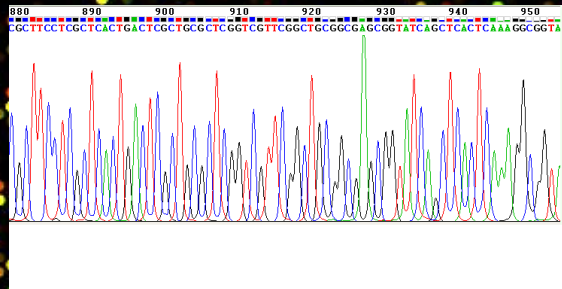
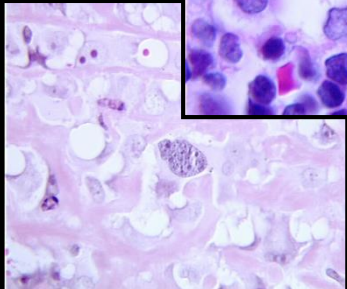
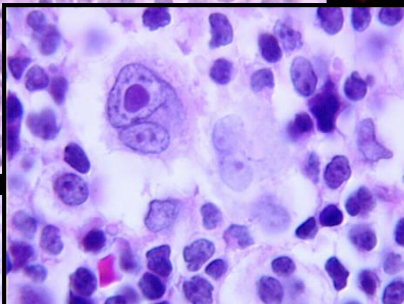
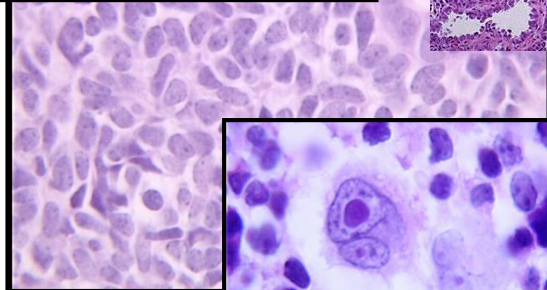
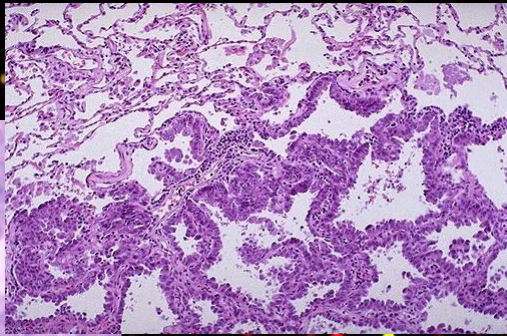
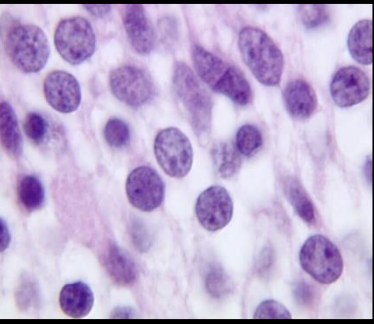
Normal Lung



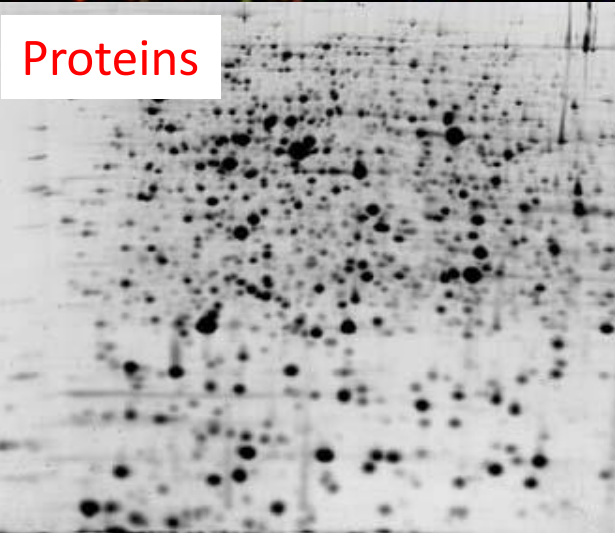
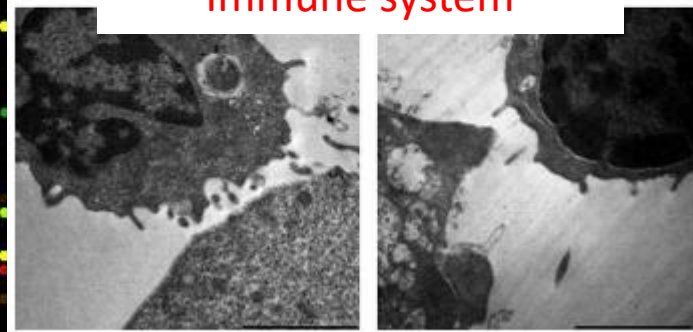
Lung cancer



Cancer Molecular alterations Heterogeneity

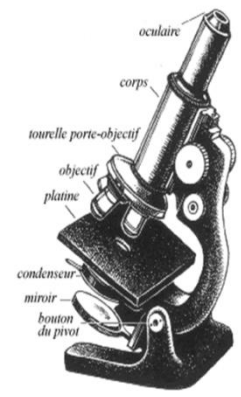


Immune system



Genes

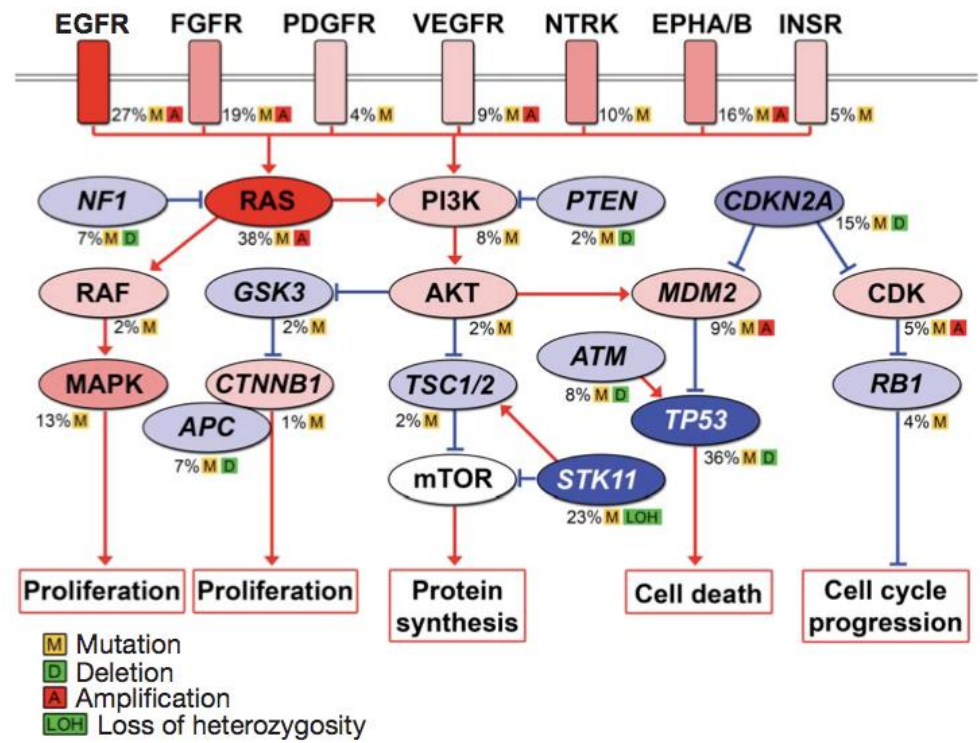
definition of cancer



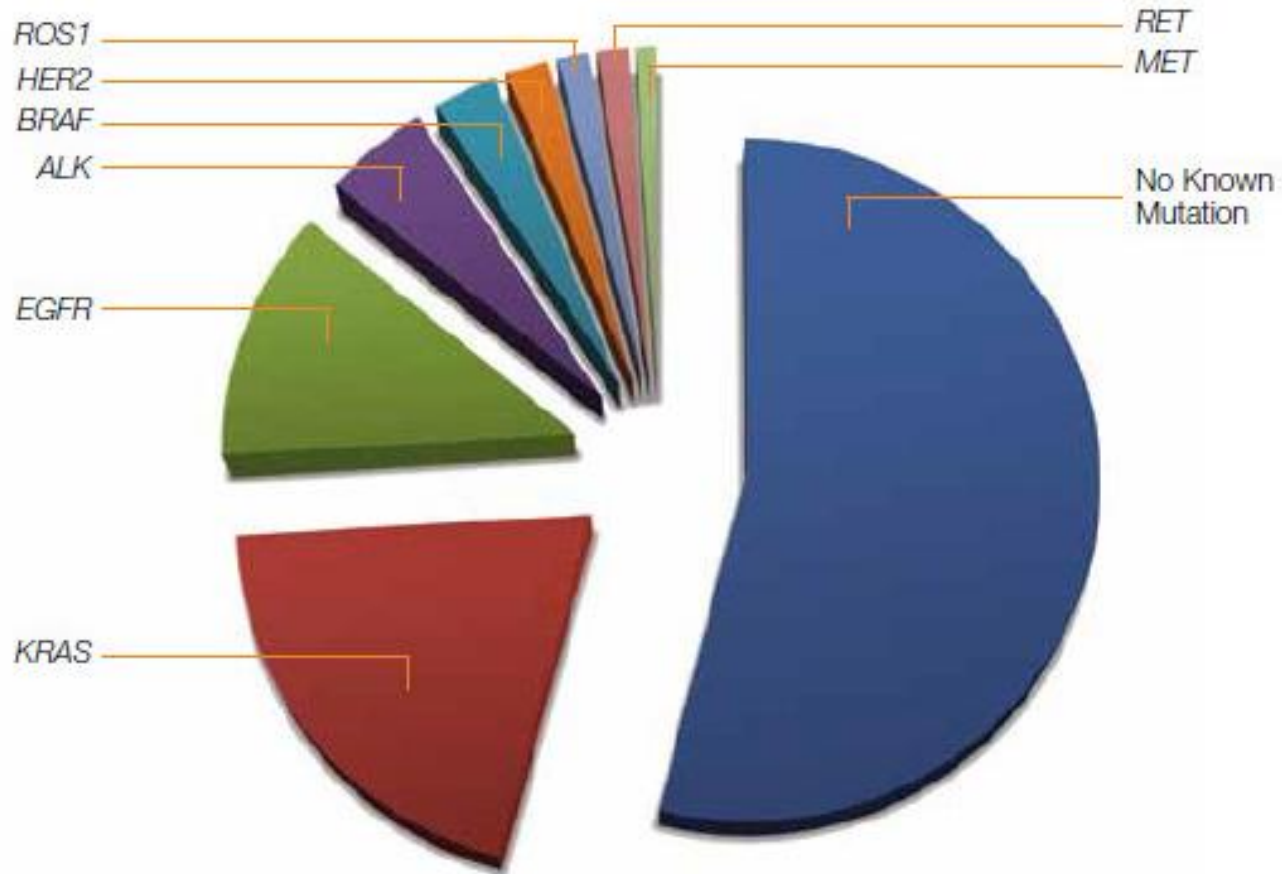
a tumor
an organ
a pathological sample
=
A definition from
the XIXth century

A definition from
the XXth century

Significantly mutated
pathways in adenocarcinoma
of the lung



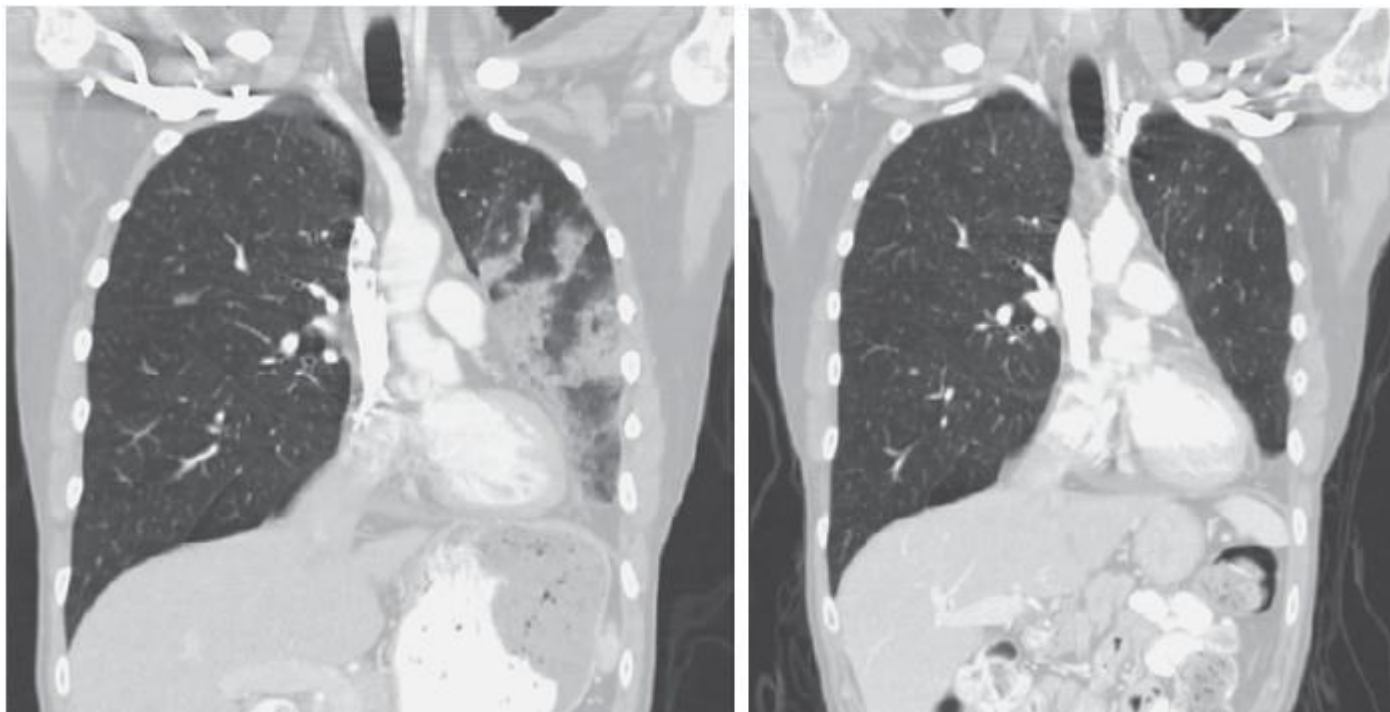
Lung Cancer Molecular Subtypes



Cancer signaling is not linear.... It is a highly inter-connected and redundant network...



Development of oral crizotinib, ALK MET inhibitor



Phase I
48 y old female
NSCLC
with EML4-ALK

Enrichment of phase 1 with EMLA4-ALK patients

RR = 1CR + 46PR/82 (57%) with a PFS at 6 months = 72%

EML4-ALK fusion gene = 2 to 7% of NSCLC

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

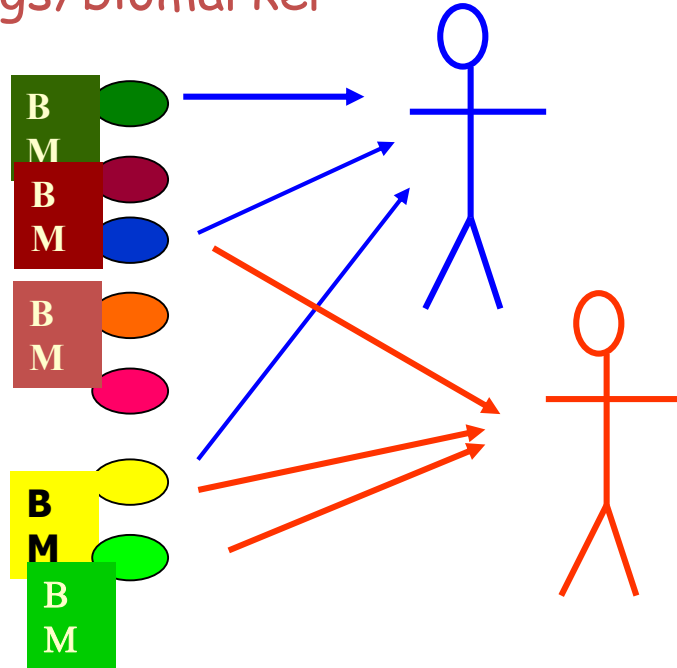
Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell
Lung Cancer

NEJM 363, 2010

Which drug(s) for Mister X?

Tailored medicine

Drugs/biomarker



Algorithms
for decision making

Challenge

To prescribe
the right drug combination
At the right time

Precision Medicine

A public health and societal
issue

To Increase survival
using expansive drugs
only for patients who will
benefit

Precision cancer medicine

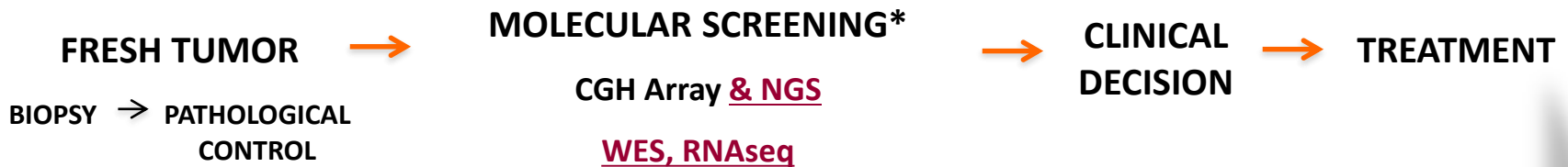
At least for a first step : Stratified Medicine

1. Moving away from empirism and serendipity to a biology-based therapy
2. Matching the right drug with the right cancer type
3. Defining the right response biomarker on each patient's tumor
4. Organizing molecular follow up of patients under therapy

☞ **The Ultimate goal**
individual biology-guided treatment decision

MOSCATO 01 trial:

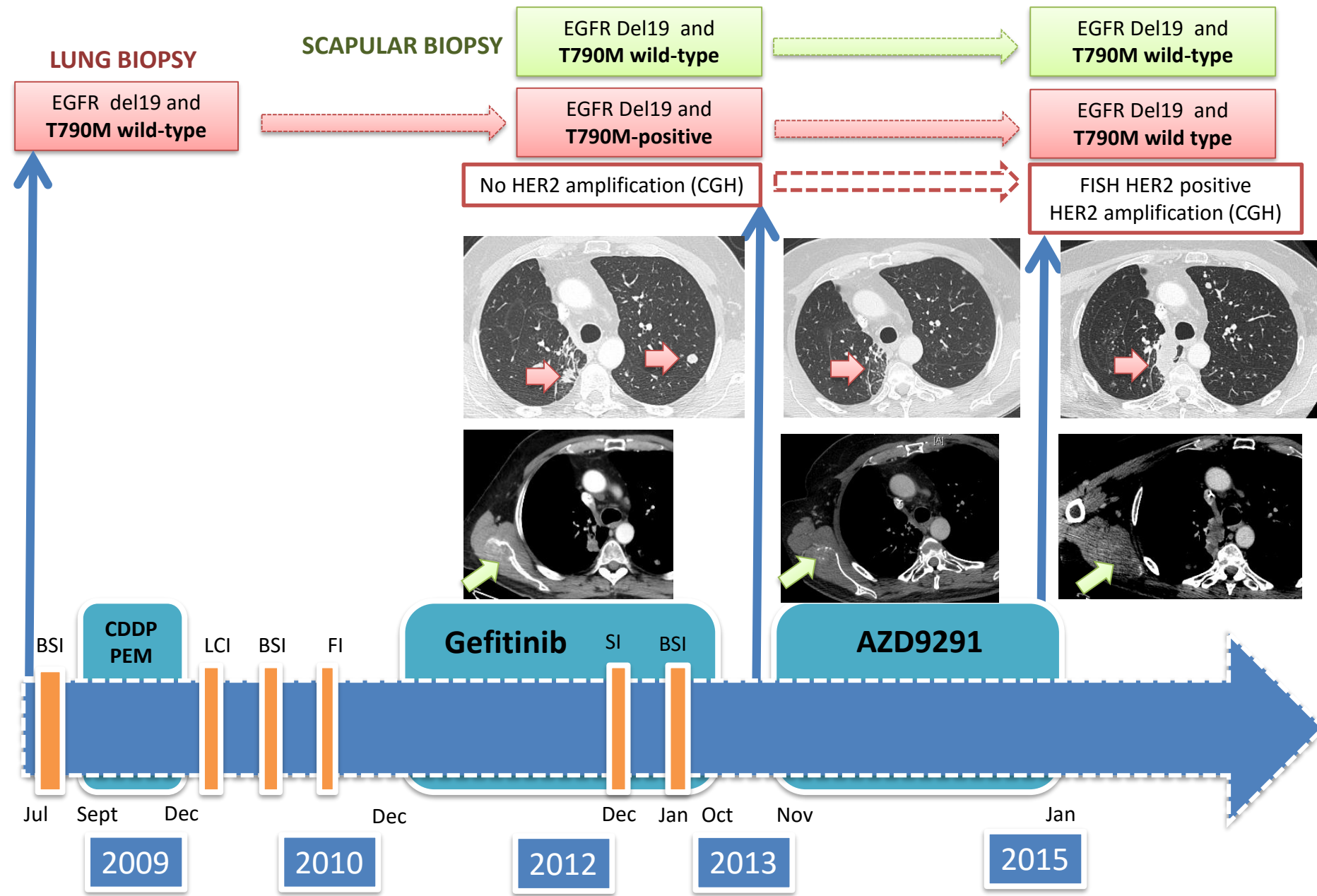
- **Monocentric**
- **1200 patients – 2011-2015**



Max <21 calendar days

***From 15 genes to 25000 genes In 4 years
Per tumor sample**

Figure 1. Patient I Clinical Course Including Treatment History and Relevant Imaging Studies and Tumor Biopsy Specimens



Legend: Biopsy Irradiation

BSI: brain stereotaxic irradiation; LCI:lung conformational irradiation; FI:Femoral irradiation; SC: scapula irradiation

Applications of Liquid Biopsy

Monitoring & Early Detection

Brain cancer DNA blocked by blood-brain barrier

MULTIPLE TUMOR TYPES

Breast cancer

Pancreatic cancer

Colon cancer

Many tumors release DNA fragments that circulate in the bloodstream

ctDNA & TUMOR CELL ANALYSIS

ctDNA

Detection of Resistance Mutations

Targeted therapy

Response to therapy

Selective pressure

Resistance mutations

ctDNA of resistance mutations collected in blood sample

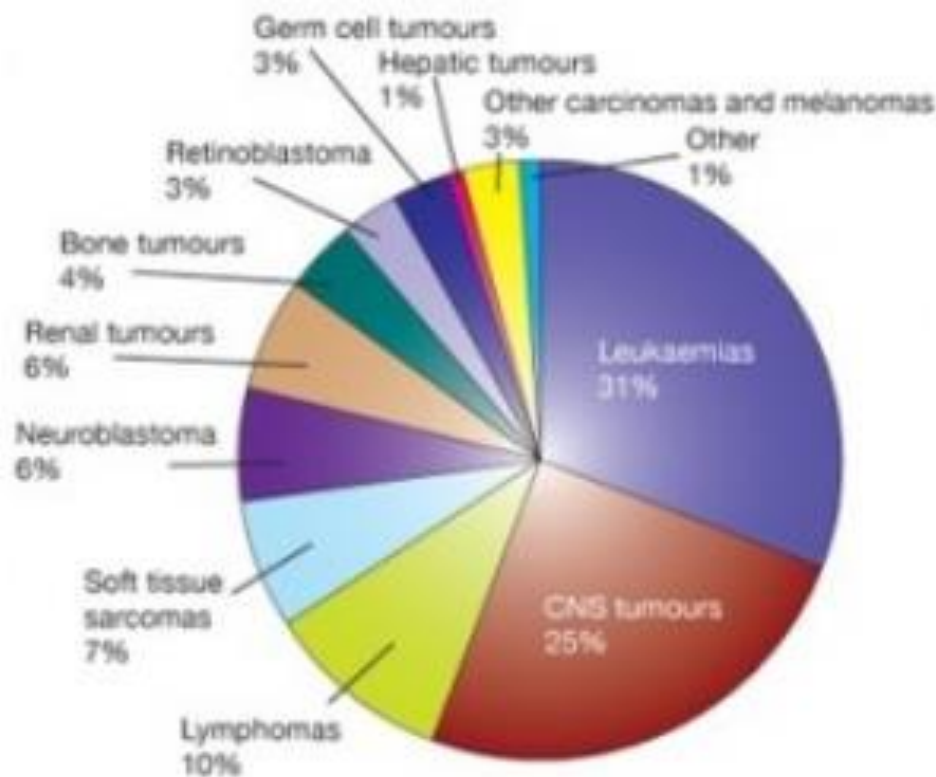
Cancer in Young People in Europe

- **Each year: 35 000 new cases**
 - 15,000 <15 years and 20,000 15 -24 years
- **80% are disease-free at 5 years with multidisciplinary treatments**
 - 300,000 EU citizens are childhood cancer survivors
 - 2/3 have long-term side-effects
- **6,000 young people die each year**

Cancer: first cause of death by disease beyond one year in EU

STILL A PUBLIC HEALTH ISSUE

Pediatric malignancies are different from malignancies in adults



THE SIOPE STRATEGIC PLAN

A European Cancer
Plan for Children and
Adolescents



SIOPE
SIOPE Europe
the European Society for Paediatric Oncology

http://www.siope.eu/SIOPE_StrategicPlan2015/

SIOPE Strategic Plan

SIOPE-ENCCA
Conference 2014

Brussels 18-19 September
Belgium 2014

Joining Efforts for a Brighter Future for
Children and Adolescents with Cancer

The European Roadmap
to Horizon 2020



By 2025:

- To increase cure rate in patients with poor prognosis malignancies
- To increase quality of life (cure) in survivors
- To tackle inequalities

A long term sustainable strategy

Designed within the FP7





Created in 2003, ITCC is a consortium of 49 institutions in 12 countries

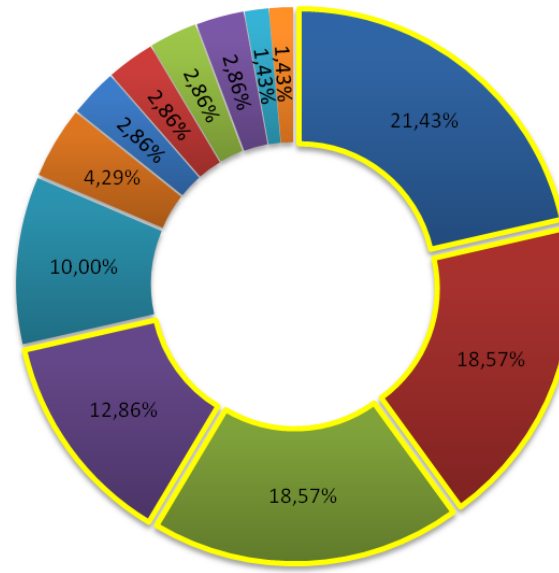
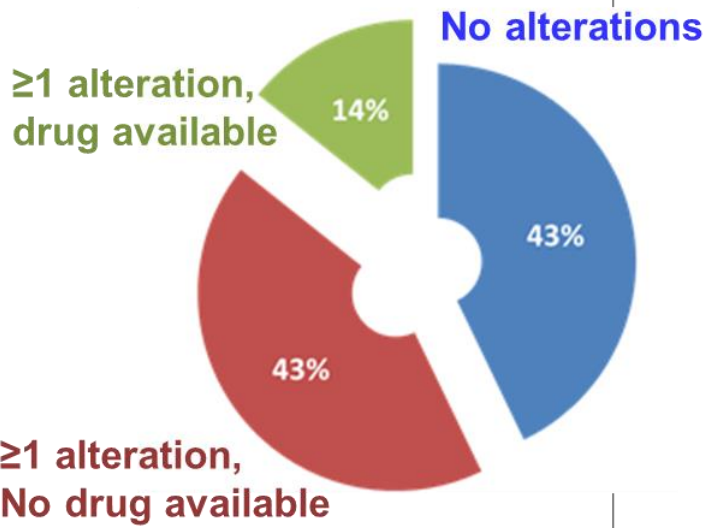
- ✧ ITCC runs a **comprehensive clinical and biological early evaluation program of anticancer drugs** for children and adolescents.
- ✧ Each year, **4 500 patients** with cancer are diagnosed in ITCC centers.
- ✧ **20% of them experience recurrence** of their disease and are offered to participate in ITCC trials.

Austria Belgium Denmark
France Germany Ireland
Israel Italy Spain
Switzerland The UK
The Netherlands

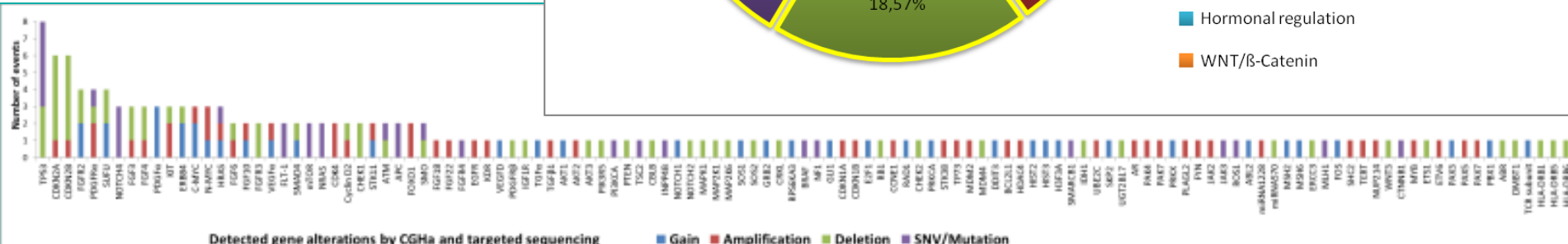


MOSCATO-01 (pediatric cohort)

- 78 patients included; Data from 60 with results from 65 interventions
 - 62% solid tumors; 38% CNS tumors
 - Median age: 11.1 years (range, 0.8-24.3y)
- 56/60 patients had a molecular analysis done
- 32 of 56 (57%) had at least 1 actionable target



- Growth factors & receptors
- Cell cycle
- MAPK pathway
- PI3K pathway
- Transcription factors (NMYC, CMYC)
- Apoptosis regulation
- DNA damage response
- Epigenetics
- Non-receptor tyrosine kinases
- SHH
- Hormonal regulation
- WNT/β-Catenin



Bioinformatics of Precision Cancer Medicine

Speed and storage are essential!

- Raw data for one sample and calculation = 300 Go
- One patient = Tumor + constitutional DNA
- quality control+mapping+variant calling+annotation
- DELL Cluster* (since 215) [servers + storage+network]
 - 96 samples in parallel per day versus 12 per day
- Acceleration = x11
- 1000 patients = 600 To duplicated = 1,2 Po

*dedicated to the pediatric programm

The Innovative Therapies & PCM Programme

1

A tumour molecular profile for patients at relapse*

*WES, RNAseq, Immuno

Molecular Matching Trials

M
A
T
C
H

2

New targeted and immune therapy drugs

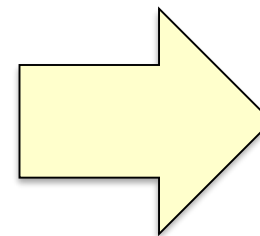
Trials w single agents and combinations

SHARE



With ECTGs

EU Clinico Biological Database



Paediatric New Drug Development

3

New knowledge, targets, pathways

4

The ITCC Precision Cancer Medicine program

1. Generate molecular profiling for each patient

Molecular Matching Trials at relapse

WES, RNA seq, methylome
immunophenotype

INFORM (Germany)



MAPPYACTS

(France, Spain, Denmark, Italy)



iTHER (Netherland)

S- PED (UK)

2. M A T C H

3. Evaluate drugs and combinations

Phase 1 & 2 ITCC Trials

(sponsored by industry and ISTs)

MATRIX trial (Genentech/Roche)

(2 drugs – atezolizumab ; cobimetinib)

eSMART trial

IST multi-agent from multi-company



4. Create

**European clinico –
biological database**

5. New knowledge

*new druggable pathways
for specific pediatric drug development*

1000 children
and adolescents
4 years



Projet National MAPPYACTS

PI B Geogerger

Molecular Profiling for Pediatric and Young Adult Cancer Treatment Stratification

Enfant et adolescent, en rechute, tumeur solide et leucémie

Biopsie à la rechute



Portrait Moléculaire Tumoral (WES/RNAseq)



RCP moléculaire



Traitement

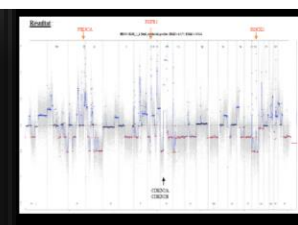
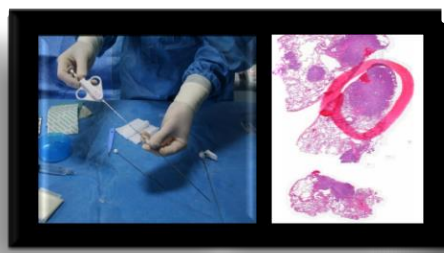
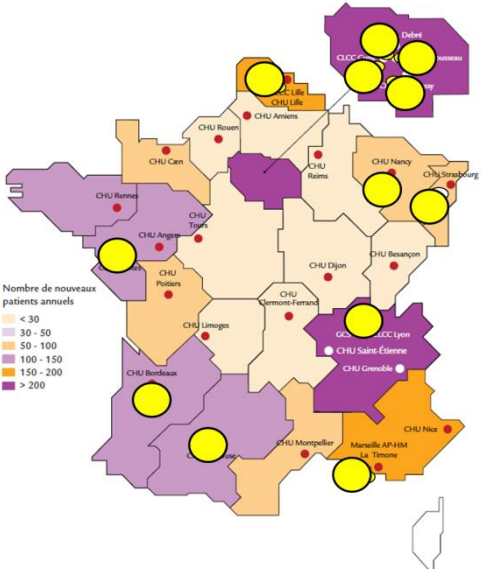


FIG. 4 : CARTOGRAPHIE ET ACTIVITÉ DES 29 CENTRES SPÉCIALISÉS VISITÉS ENTRE 2006 ET 2009



GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

institut Curie
Together, let's beat cancer.

RCP moléculaire Nationale

INSTITUT NATIONAL DU CANCER

**300 enfants en 3 ans
PHRC 2015
Fondation ARC
Ouverture décembre 2015**

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

Innovative Therapies
for Children with Cancer



Children and their parents
need to travel to
investigating centers
to access early innovation





A multistakeholder platform
(Academia, Parents, Industry, Regulatory)

Vassal, Eur J Cancer, 2015, 51, 218



Accelerating Understanding Summit 2016

31 May - 1 June 2016, Paris, France



Precision Cancer Medicine Programm

Thanks to the patients and their family

Thanks to:

FONDATION GUSTAVE ROUSSY



MINISTÈRE
DES AFFAIRES SOCIALES
ET DE LA SANTÉ

ANR



Genentech

AstraZeneca 