Genomics in science and clinical care

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Institut National du Cancer – October 8, 2012

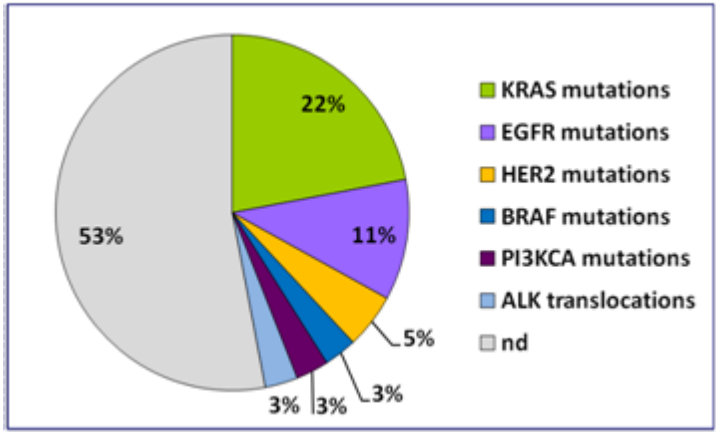
Institut national du cancer (INCa)

- The French National Cancer Institute is a health and science agency dedicated to oncology.
- INCa was created through the Public Health Act of 9 August 2004
- INCa is involved in all aspects of the fight:
  - **Public health :** Observation – Prevention - Screening
  - **Care**: Improve the quality of care for all cancer patients
  - **Research**: Orient the national cancer policy towards international competition
  - **Information**: Give every individual the means to help fight cancer

The shift of paradigm for cancer treatment

- **Towards molecular subsets of cancers**

⇒ Molecular genetics deciphers severe frequent cancers into specific rare cancers



Molecular subsets of **non small cell lung cancer** : 20,000 patients

- **Molecular alterations shared in several cancers**

⇒ Some drugs are <u>now</u> efficient for the treatment of several « rare cancers »

- Imatinib for LMC (*BCR-ABL* translocation) and GIST (*KIT* mutations)
- Trastuzumab for HER2 overexpressing breast and gastric cancer

Predictive tests for targeted therapies prescription

Biomarker	Cancer type	Targeted therapies
***BCR-ABL* translocation**	Chronic Myeloïd Leukemia/ Acute Lymphoblastic Leukemia	Imatinib, nilotinib, dasatinib
***KIT* and *PDGFRA* mutations**	GIST	Imatinib, nolotinib, dasatinib
***HER2* amplification**	Breast and gastric cancers	Trastuzumab, lapatinib (breast)
***KRAS* mutations**	Colorectal cancer	Panitumumab and cetuximab
***EGFR* mutations**	Lung cancer	Gefitinib and erlotinib
***ALK* translocations**	Lung cancer	Crizotinib
***BRAF*V600 mutation**	Melanoma	Vemurafenib

Drugs approvals for molecularly-stratified tumour subgroups make molecular testing mandatory

Measure 21.

Guarantee equal access to innovative and existing treatments.

21.2 Develop cancer molecular genetics hospital platforms and expand access to molecular testing.

The Cancer Plan 2009-2013:

- follows on from the Cancer Plan 2003-2007
- 5 areas : research/observation/prevention-screening/ patient care/ life during and after cancer
- 30 measures/ 118 actions

Ensuring equity of access to innovation: France organisation of molecular centres for personalized medicine

Provides nationwide molecular diagnostic tests

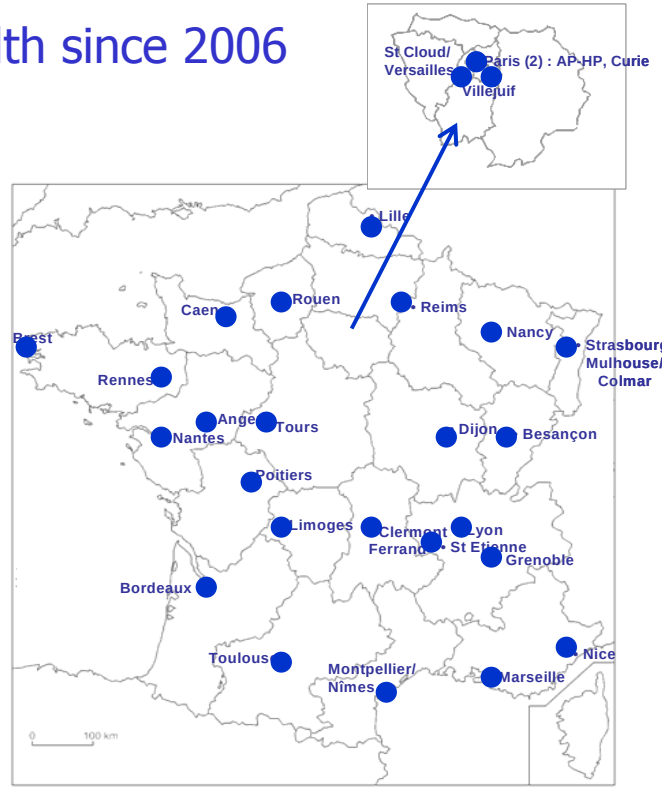
The programme is operated by the INCa/Ministry of Health since 2006

➢ Objectives

- Perform molecular testing for all patients;
- Whatever the healthcare institution status (public hospitals, private hospitals…);
- Perform high quality tests;
- leukemia, solid tumours

➢ 28 regional centres

- Partnerships between several laboratories located in University hospitals and cancer centres
- Regional organization
- Cooperation between pathologists and biologists

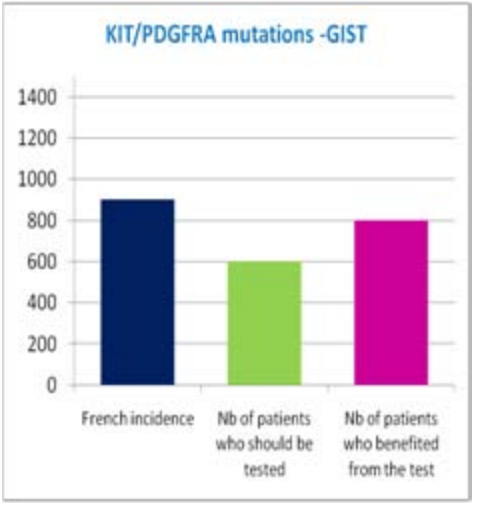


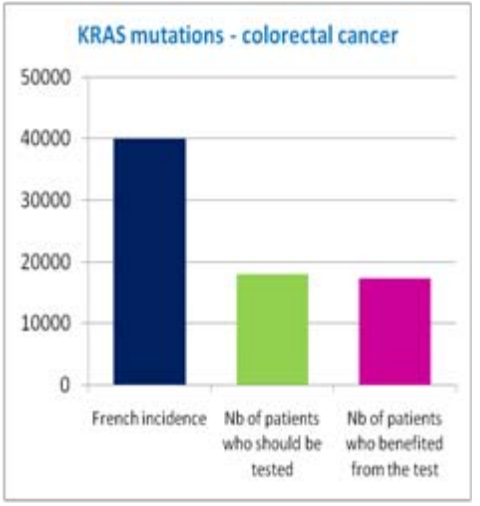
Benefit for all patients

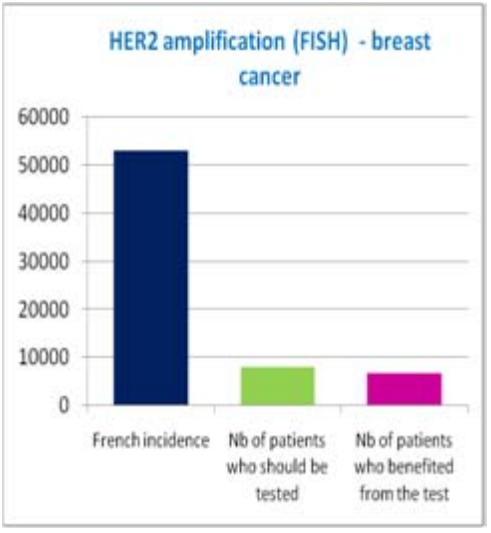
Molecular tests are performed :

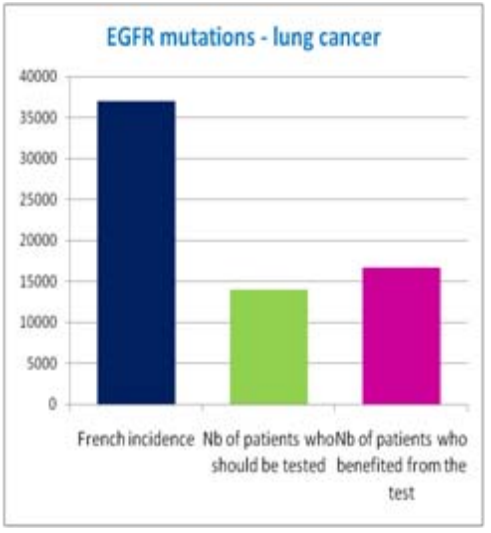
- For all patients
- free of charge for patients & hospitals
- With compensation of local pathologists for sample shipments

⇒ Ensure that all patients effectively benefit from molecular testing







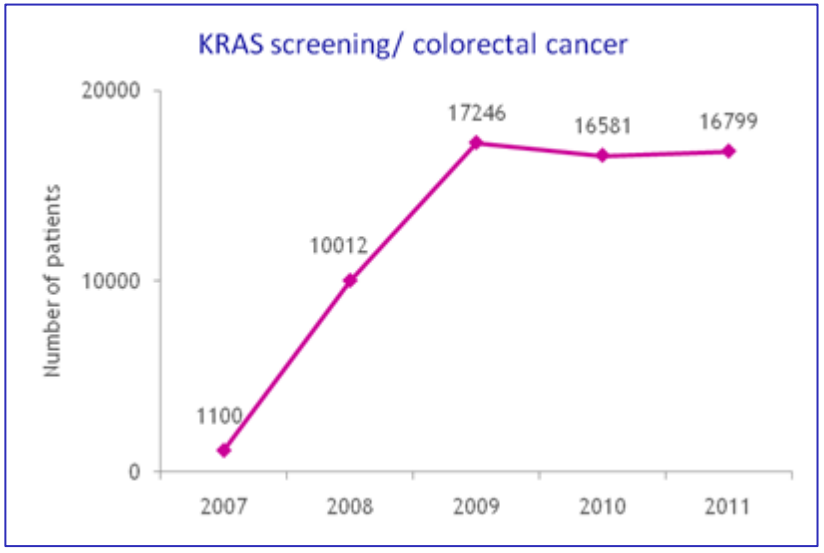


Rapid access to innovation

Offer each patient in France an equal access to molecular tests as soon as a new targeted therapy is available

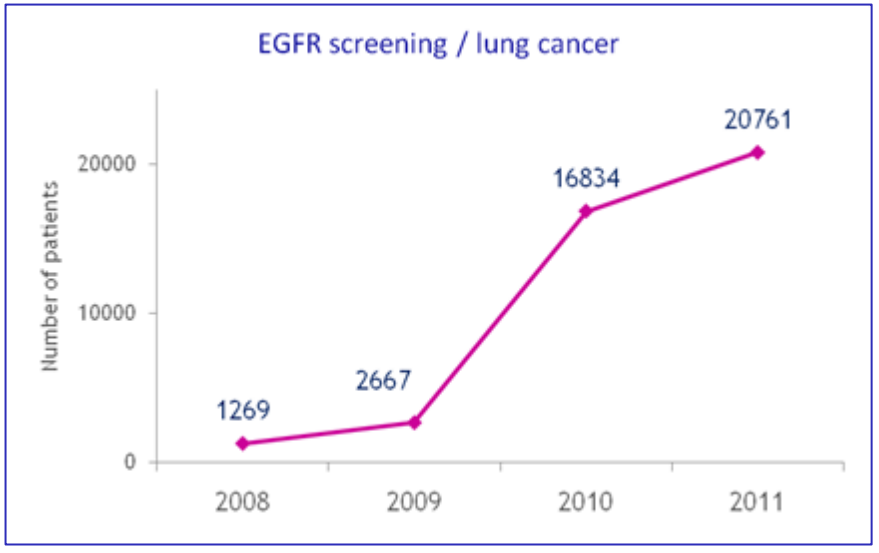
Mid 2008 : EMA approvals for panitumumab and cetuximab for patients with wild type KRAS tumours

⇒ INCa started to allocate €2.5M to the 28 centres at the end of 2008



June 2009 : gefitinib approvals by EMA for patients with activating mutations of EGFR in their tumors

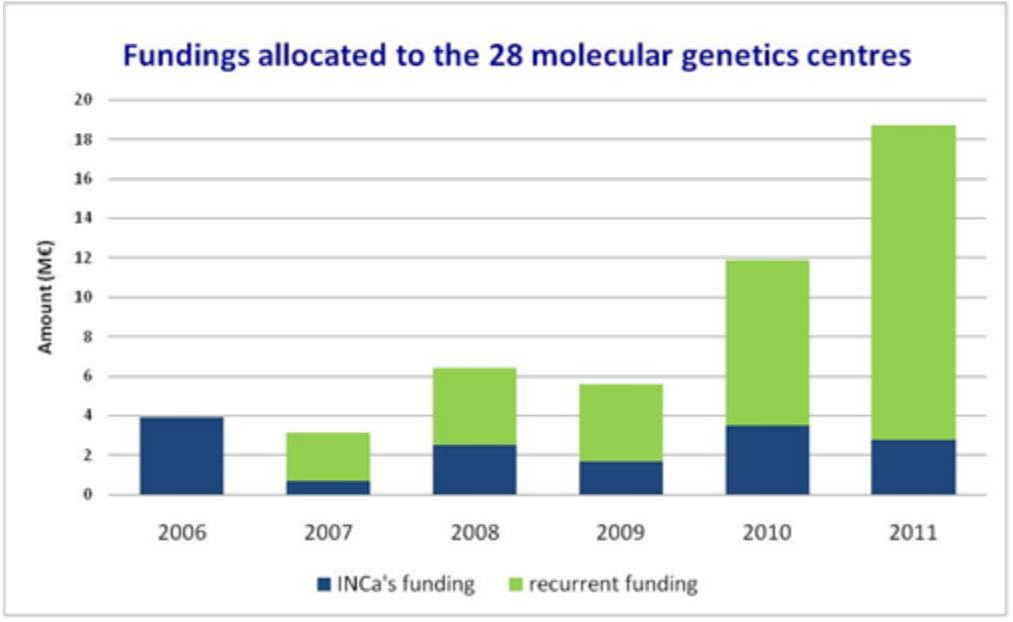
=> INCa started to allocate €1.7M to the 28 centres at the end of 2009



Funding mechanisms

Offer the best treatment to patients considering the cost – effectiveness ratio

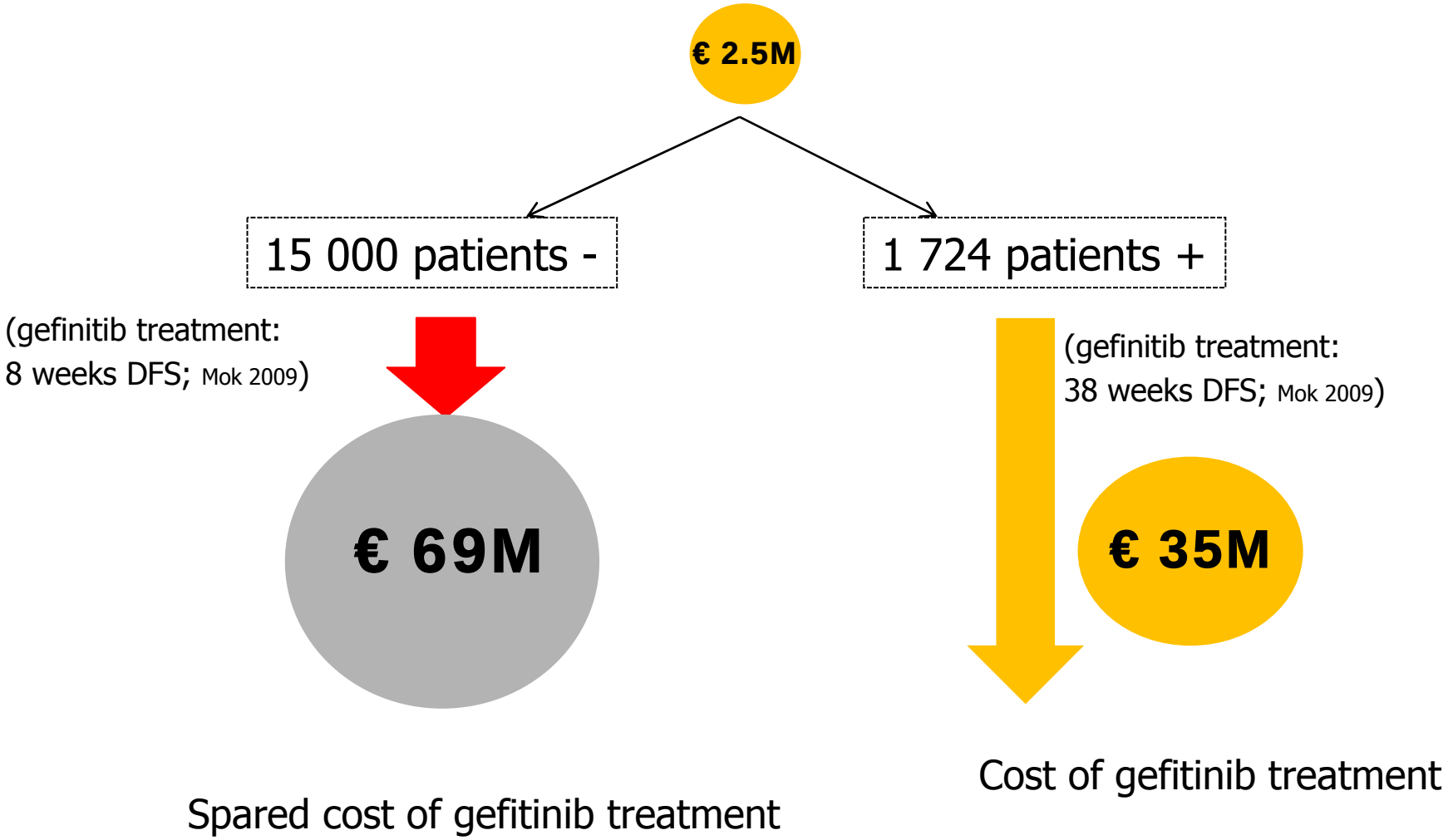
- Seed fundings from INCa for the test set-up
- Performance and cost evaluation
- Recurrent annual fundings from the French Ministry of Health insurance



This programme benefits also from INCa/private partnerships

Example of gefitinib treatment : €69M spared cost for the health insurance

EGFR testing for lung cancer patients



Challenges ahead

- **Maintain the quality of molecular tests**
- **Anticipate the launch of new molecules** : reduction of time-to-access to molecule
- **Improve translational and clinical research interfaces**
- **Public/private partnerships** to optimize the implementation of new tests and sustain innovation.

Ensure the best quality for molecular tests

Implementation of a quality assurance programme

- Elaboration of guidelines for:
  - the detection of mutations in solid tumors;
  - the organization of molecular testing;
  - reports of molecular tests

- Implementation of a national External Quality Assessment for the 28 centres :
  - 2011 : *BCR-ABL* quantification, *KRAS* and *EGFR* mutation screening ;
  - 2012: *BRAF* mutation screening

⇒ Assurance quality optimization

⇒ Guide the molecular genetics centres to becoming accredited to ISO 15189 standard as soon as possible

Anticipate the launch of new molecules

The INCa allocated €3.5M in 2010 and €2.8M in 2011 for the prospective detection of emerging biomarkers

- **For the 20,000 patients with lung adenocarcinoma, additional analysis of :**
  - *EGFR* mutations conferring resistance to TKI-EGFR;
  - *KRAS*, *HER2*, *PI3KCA* and *BRAF* mutations;
  - *ALK* translocation.
- **For the 17,000 patients with colorectal cancer, additional analysis of :**
  - *BRAF* mutation;
  - MSI test.
- ***BRAF* and *KIT* mutations for patients with melanoma**

⇒ Be ready to perform the test as soon as the therapy is available

Anticipate the launch of new molecules

What's new in 2012?

- NSCLC : ***ROS1* translocation**/crizotinib; **RET translocation**/vandetanib
- Squamous NSCLC : ***DDRE2* mutations**/dasatinib
- Melanoma : ***NRAS* mutations**/ MEK inhibitor
- Breast cancer and other solid malignancies: ***FGFR1* amplification**/FGFR inhibitors
- Papillary thyroid cancer: ***BRAF*** mutations/ vemurafenib
- RAI-refractory thyroid cancer : ***BRAF*** mutations/ BRAF or MEK inihibitors for re-acquisition of RAI uptake…

=> Towards the implementation of Next Generation Sequencing (NGS) for clinical use

- First step : analysis of a panel of genes (short term)
- Second step : analysis of whole exome or genome (medium term)

Improve interface with research

Make the most of the generated data : implementation of a lung cancer database

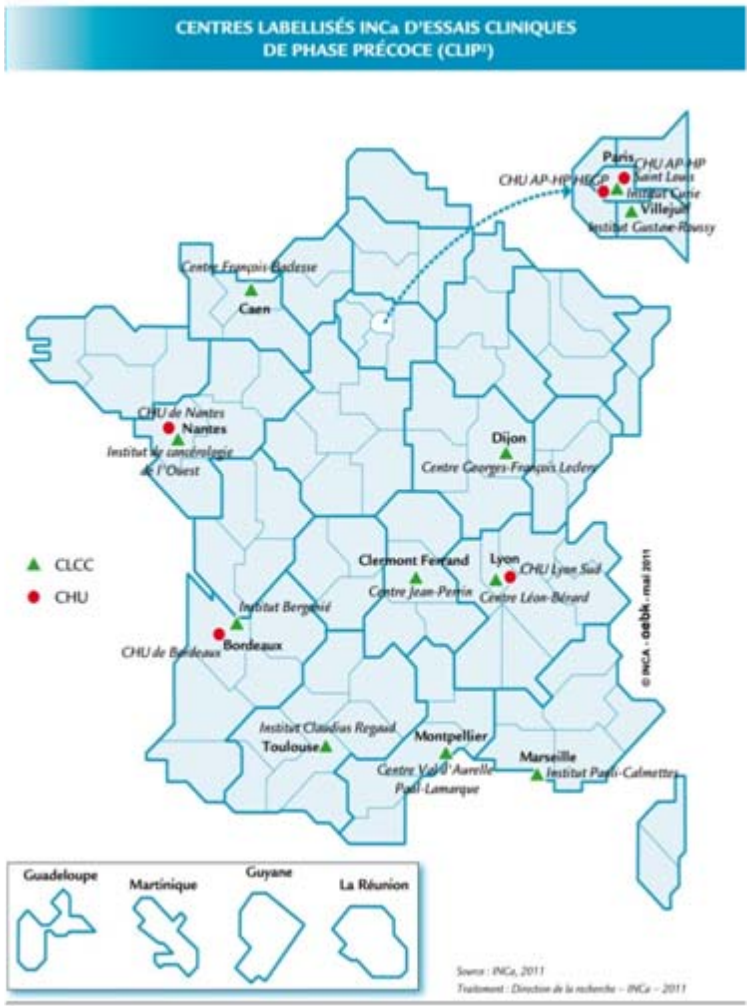
- funded by INCa, coordinated by IFCT (Intergroupe Français de Cancérologie Thoracique) and molecular genetics centres representatives
- evaluate the correlation between molecular alteration identification and targeted therapy prescription
- collect both clinical data, molecular data and clinical follow up of patients

Improve interfaces with clinical research

Extension of the mission of the molecular genetics centres:

- they may perform molecular tests for clinical trials
- more particularly for the screening of rare mutations (1 to 2% of patients)

16 accredited early phases clinical trials centers selected by an international committee



The 16 CLIP² work in close interface with the 28 molecular genetics centres for personalized medicine

CLIP² clinical activity - 2011
166 early phase trials
1788 patients included

The 16 CLIP² cover all pathologies (including Hematology, Pediatric, Rare diseases…)

ACSE STUDY: secured access for patients to innovative anticancer treatments

- Programme INCa- ANSM- Unicancer – pharma companies
  - A targeted therapy in a molecularly defined subgroup of patients
  - The same type of abnormality in other tumour types
  - Promote access for all patients in all authorized cancer treatment centers (835)
  - No clinical trial under way

- One trial for each targeted treatment selected
- 2 pilot studies : - vemurafenib/BRAFV600 mutation
  - crizotinib/ALK, ROS1, MET and RON alterations

- Simple clinical protocol aiming at detecting efficacy and safety
- Stratification for Go – Stop in the different tumour types
- Not a substitute for the essential development trials
- Molecular screening performed in the molecular genetics centres

International cancer genomics consortium: ICGC

Main objectives

- Collect ≈ 500 tumours/ normal pairs from each of 50 different major cancer types;
- Comprehensive genome analysis of each pair: genome, transcriptome and methylome
- Make the data available to the research community and public
- The French contribution to this programme is coordinated and funded by INCa (liver, breast, and prostate cancer, Ewing sarcoma).

First results of ICGC:

- 47 projects are ongoing
- Commitments for 22,179 tumor genomes
- 12 tumors types for which data have been shared with the scientific community

Conclusions and perspectives

- This initiative for targeted cancer treatment in France shows that molecular stratification:
  - can be successfully integrated into the healthcare system ;
  - is cost effective.
- Its expansion to other European countries could be possible.
- These molecular genetics centres are:
  - instrumental to facilitate access to the best care and improve patient's survival and quality of life;
  - key to help develop translationnal and clinical research and to sustain progress.
- A strong integration must be established between translational research, clinical research and patients care.