Current status of personalizing diagnosis and treatment in oncology: realities and future hopes

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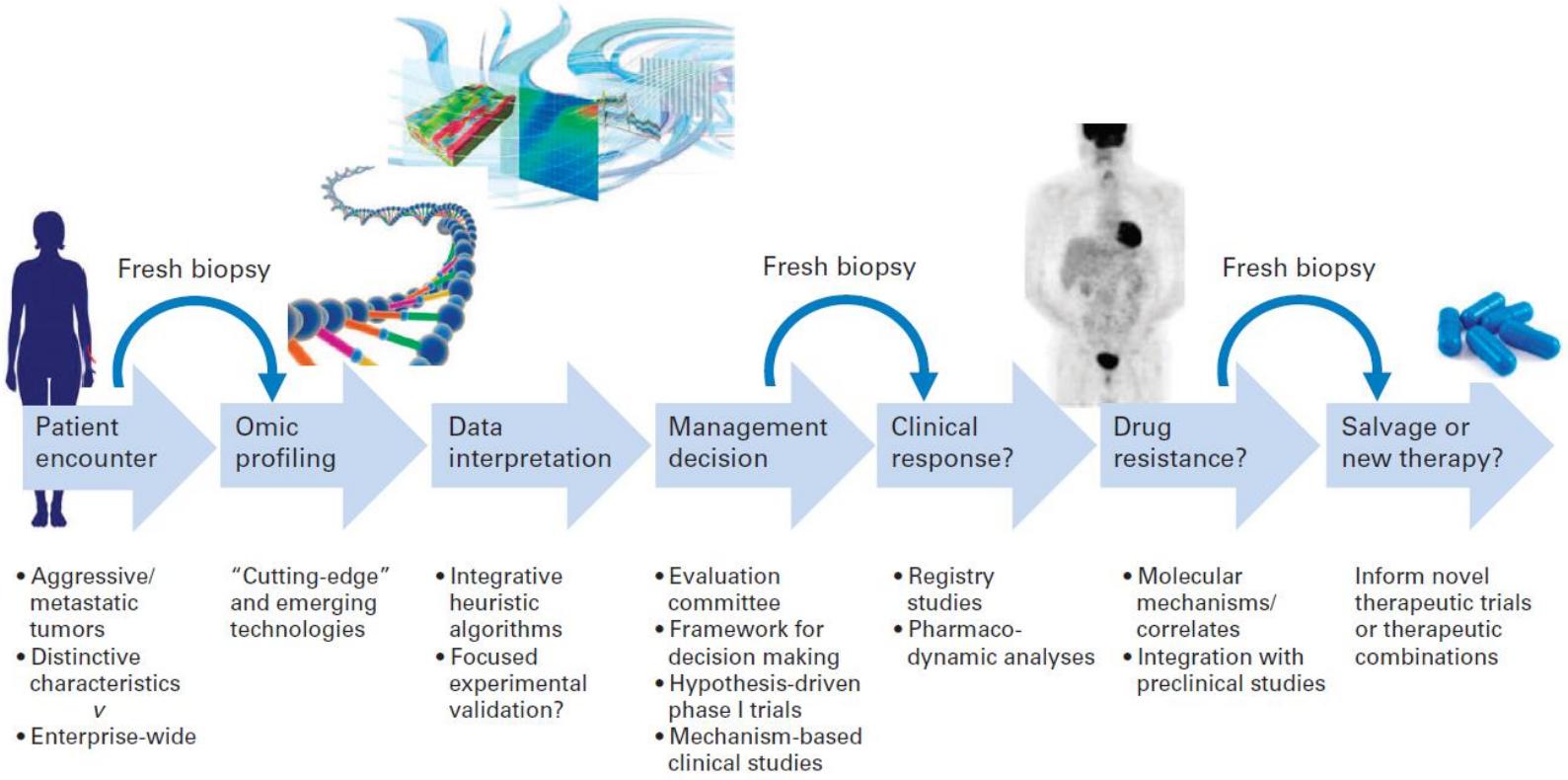
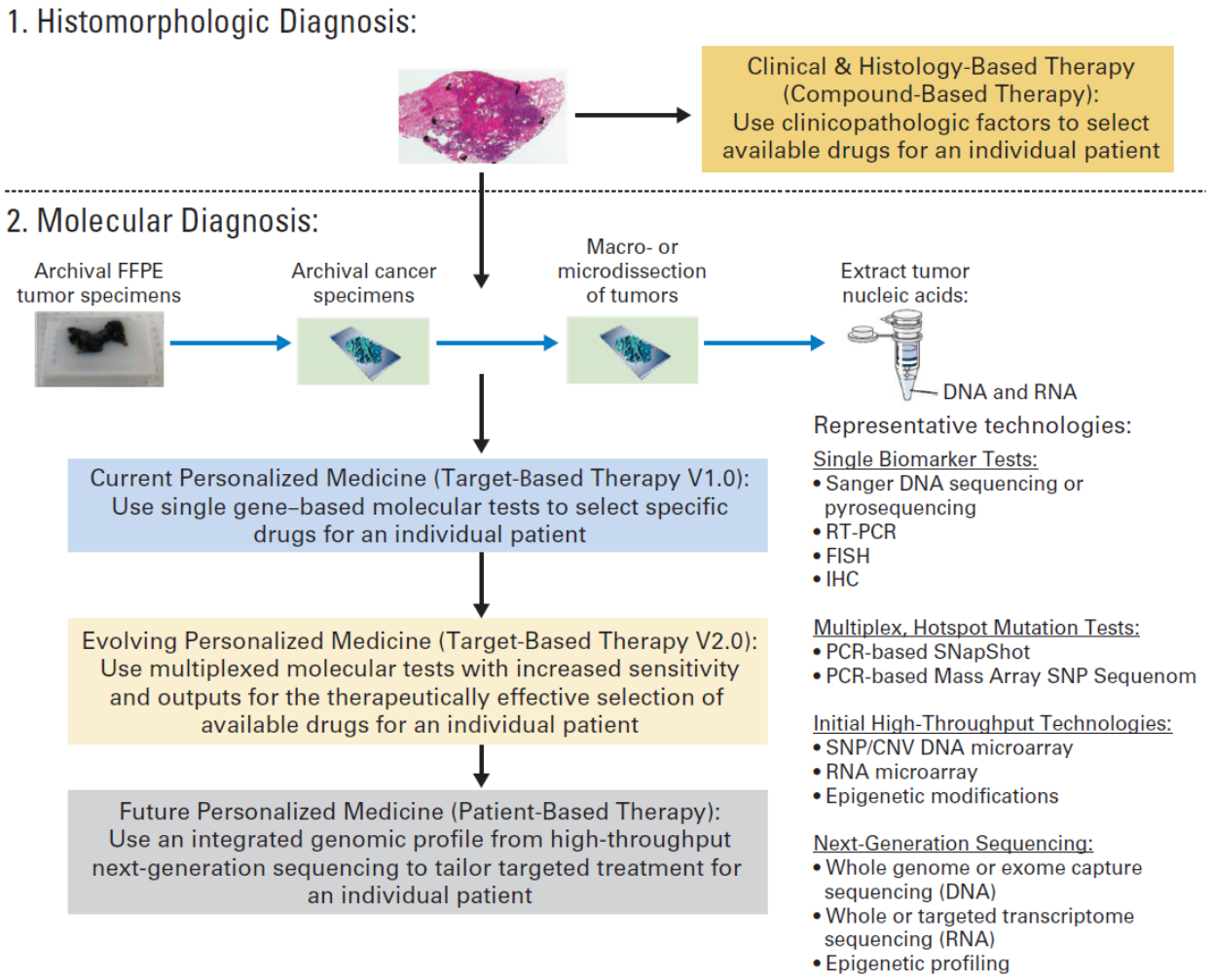
Genomics-Driven Oncology



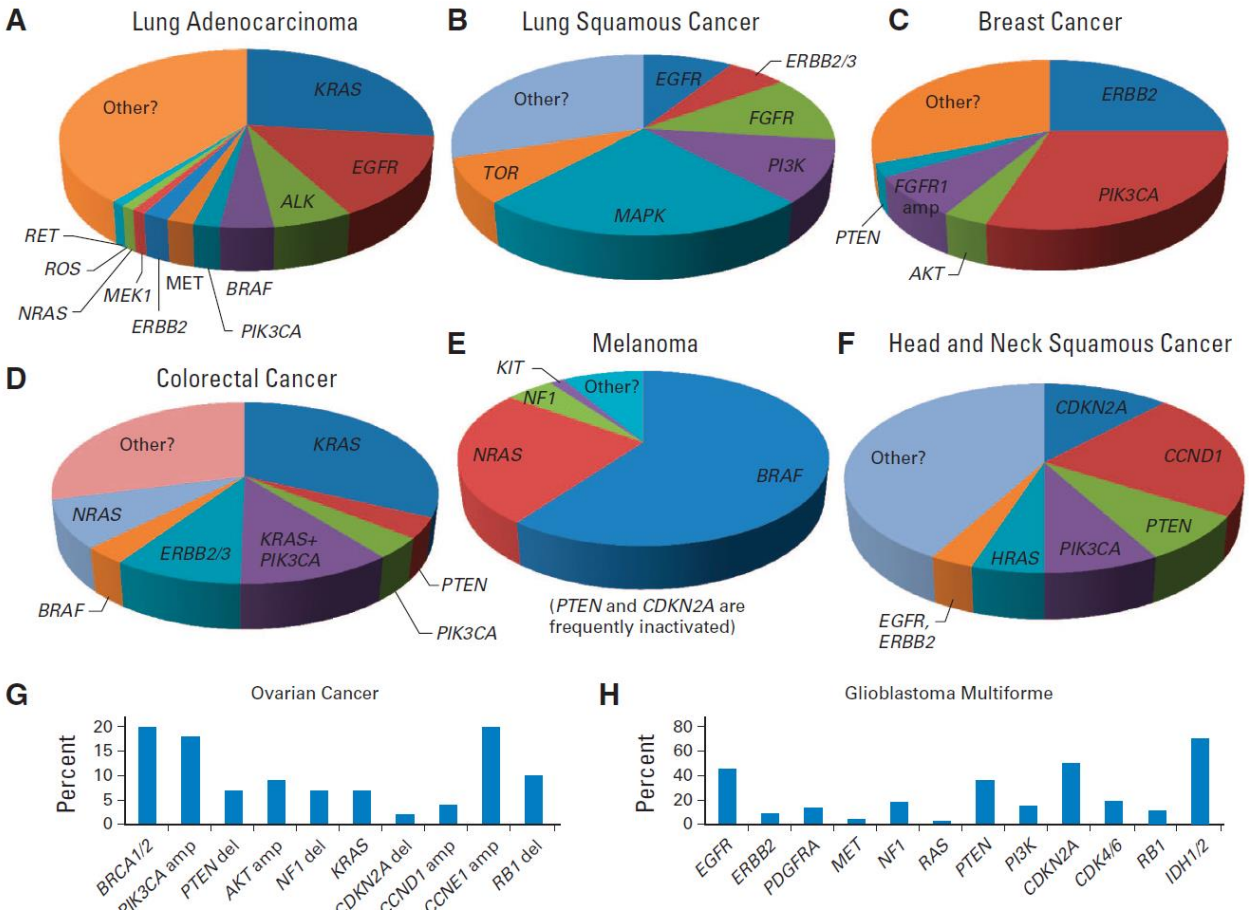
Garraway JCO 2013

Genotyping and genomic profiling in personalized medicine



Li JCO 2013

Genomic alterations affecting actionable signaling pathways



Garraway JCO 2013

Issues for the development of molecular targeted therapies in cancer

- Identify a relevant molecular target for cancer development and/or progression.
- Develop anti-targeted agents which could be used as drugs.
- Identify patients whose cancers depend on the molecular target for growth and/or progression.
- Define one or more biomarkers for patient selection before treatment.
- Define optimal strategies for the use of the molecular targeted drug in combination and/or in sequence with conventional treatments (radiotherapy, surgery, chemotherapy).
- Manage novel side effects and toxicities.
- Identify and possibly overcome mechanisms of acquired resistance to molecular targeted therapies.

The ideal predictive biomarker

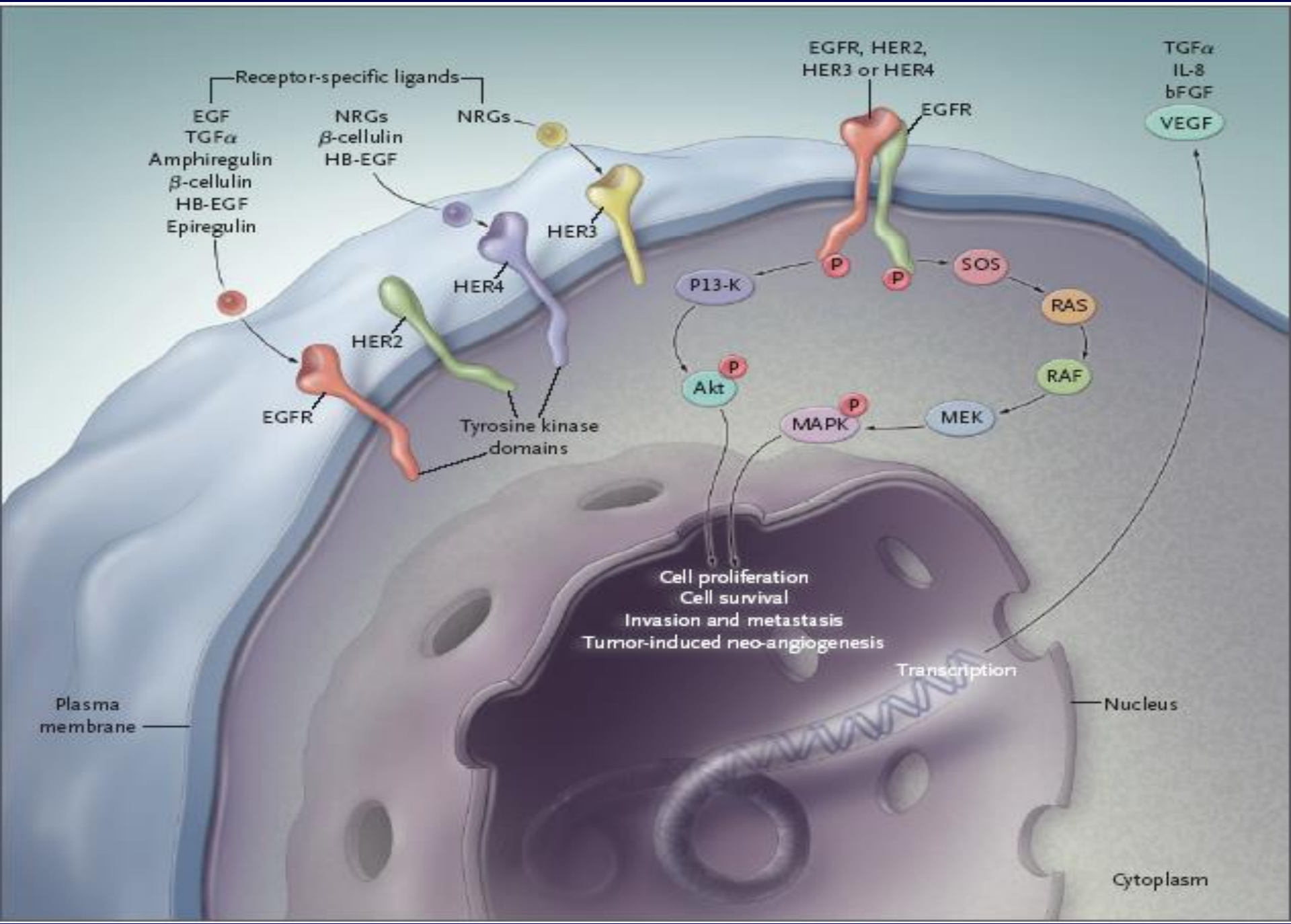
- Should be based on scientific evidence and should be understood mechanistically
- Should be measured reproducibly with high sensitivity and specificity using the patient material before selecting the treatment
- Should have a clinically relevant impact on treatment

The era of personalized medicine for medical oncology

- **Anti-EGFR monoclonal antibodies have been approved for the treatment of patients with EGFR-expressing, KRAS wild-type metastatic colorectal cancer by EMA in 2008**
- **Gefitinib has been approved for the treatment of patients with EGFR mutant metastatic NSCLC by EMA in 2009**
- **Vemurafenib has been approved by EMA in 2012 for treatment of matastatic melanoma patients with BRAF mutations**
- **Crizotinib has been approved for the treatment of patients with ALK positive metastatic NSCLC by EMA in 2012**
- **The use of Anti-EGFR monoclonal antibodies has been restricted to RAS wild-type metastatic colorectal cancer by EMA in 2013/2014**

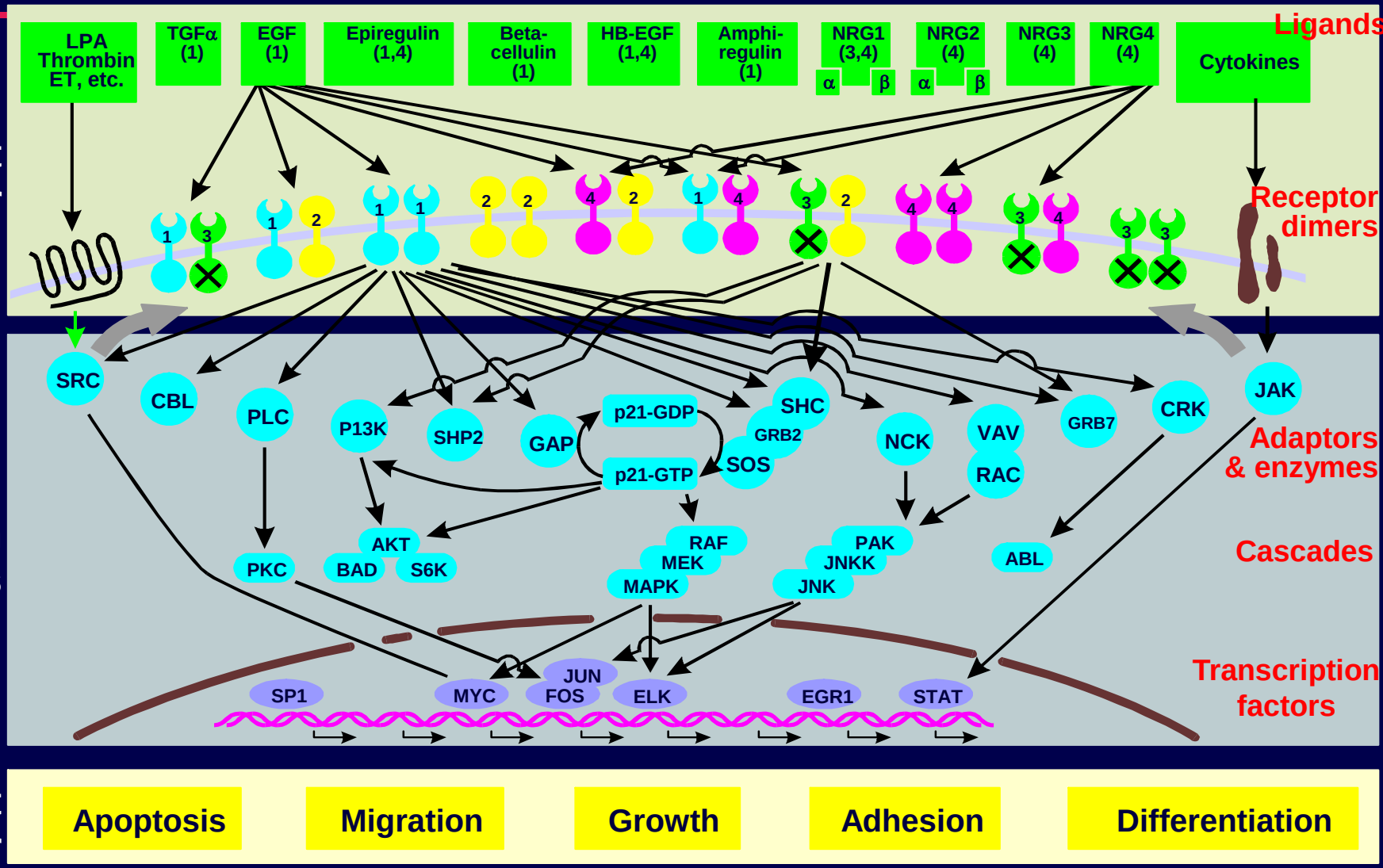
An example of a predictive biomarker for therapy:

RAS mutations and the use of anti-EGFR monoclonal antibodies in metastatic colorectal cancer (mCRC)

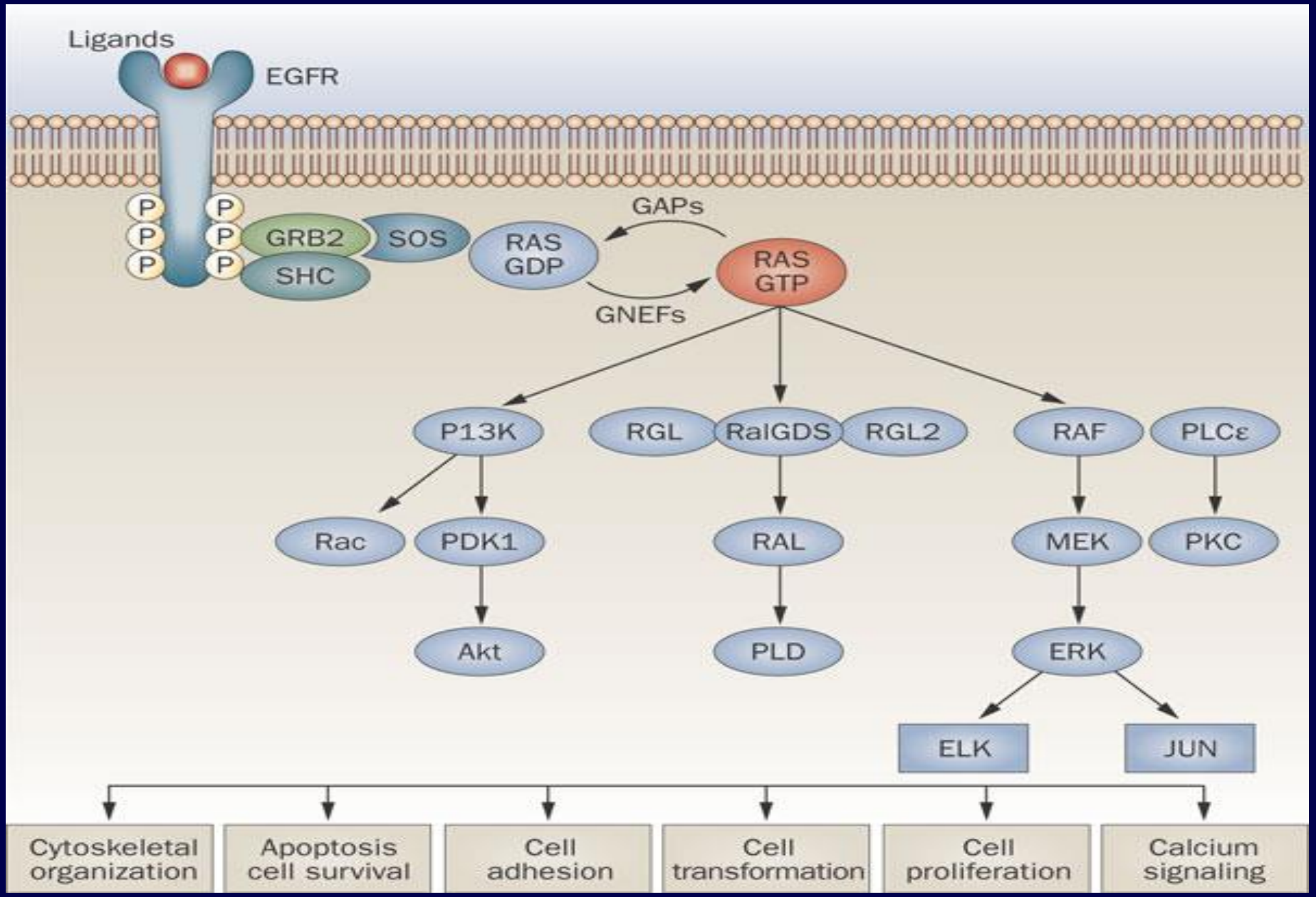


Ciardiello F and Tortora G. New Engl J Med 2008;358:1160–74.

ErbB Family Members Collaborate Within a Framework of a Layered Signaling Network

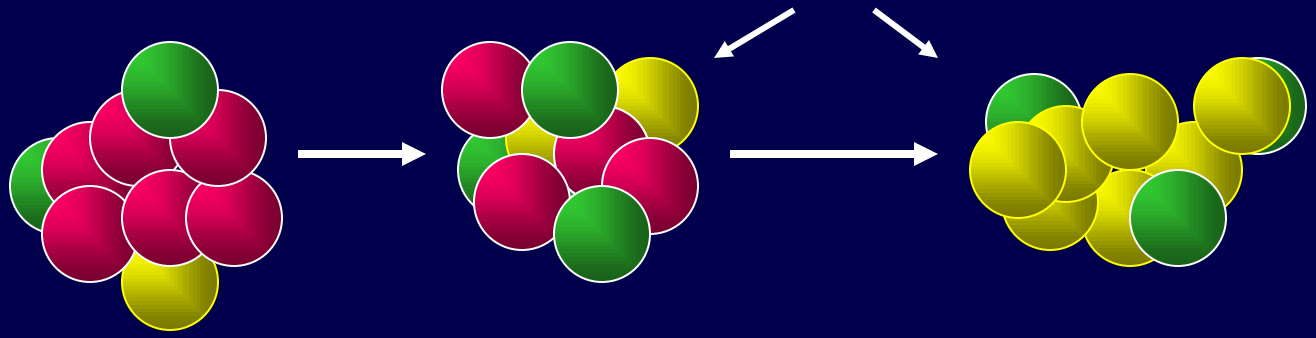


Yarden and Sliwkowski (2001) Nature Rev. Mol. Cell Biol, 2,127-137.



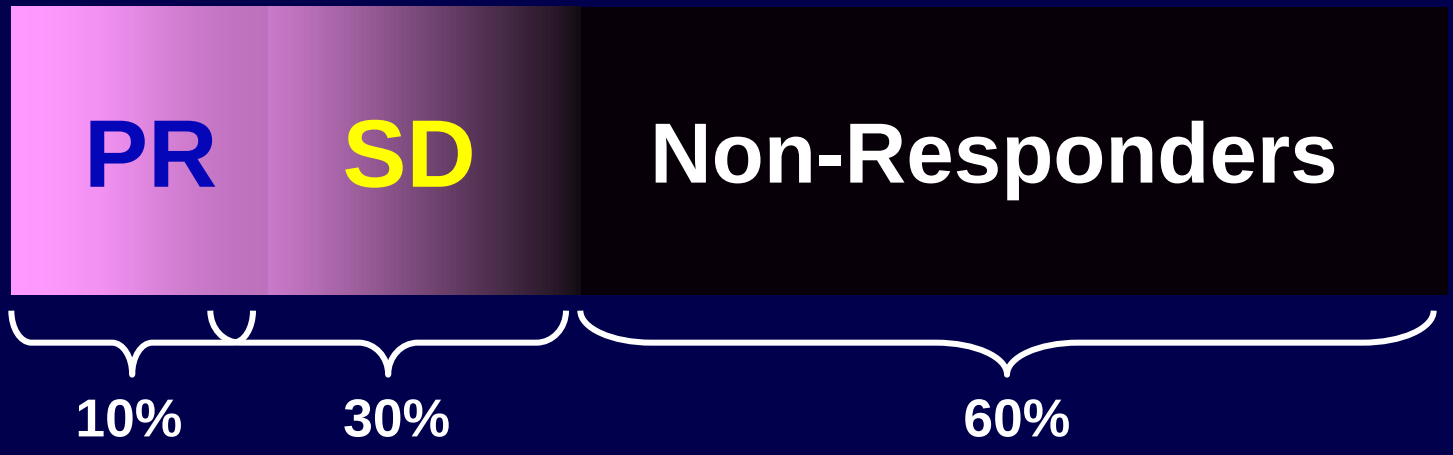
Normanno N et al. Nat Rev Clin Oncol 2009

Anti-EGFR drugs as monotherapy in unselected chemorefractory metastatic CRC : clinical results



EGFR-dependent Growth

Non-EGFR-dependent Growth



EGFR inhibitors: Potential positive predictive factors

Predictive of efficacy:

- **Markers of EGFR activation**
  - **Immunohistochemistry (IHC)**
  - **Fluorescence in situ hybridization (FISH)**
  - **Gene mutations**
  - **Gene expression levels**
  - **Gene polymorphisms**
- **Markers of EGFR ligand (amphiregulin, epiregulin) activation**
  - **Immunohistochemistry (IHC)**
  - **Gene expression levels**

EGFR inhibitors: Potential negative predictive factors

Predictive of lack of efficacy:

- **Markers of activation of EGFR-independent signalling pathways in cancer cells:**
  - **Intrinsic resistance to EGFR inhibitors.**
  - **Acquired resistance to EGFR inhibitors.**

Possible Mechanisms of Intrinsic and Acquired Resistance to EGFR Inhibitors

- Target changes in cancer cells (selection of cancer cell clones with somatic EGFR gene mutations which confer resistance, i.e. the T790M mutation in lung adenocarcinoma, the S492R mutation in colon adenocarcinoma).

- Activation of downstream signaling pathways through EGFR-independent mechanisms:
  - Other cell membrane growth factor receptors (IGF1-R; ErbB2; ErbB3; MET);
  - PTEN-PI3K-AKT pathway;
  - RAS-RAF-MEK-ERK pathway;
  - Pro-angiogenic growth factors (VEGF) production;
  - Expression of VEGFRs in cancer cells.

- Epithelial to mesenchimal cancer cell transition (loss of E-Cadherin expression; acquisition of Vimentin expression).

KRAS and NRAS are involved in the EGFR pathway in CRC

- Activating KRAS or NRAS gene mutations are early events in the multi-step CRC carcinogenesis process:
  - Detected as early as in aberrant crypt foci
  - Detected in approximately 50 to 55% of patients with CRC
- Hot spot point mutations mainly within exon 2, 3 or 4 of the RAS genes result in the translation of a constitutively active RAS protein
- A constitutively active RAS protein is able to promote cancer cell growth and survival through the RAF-MEK-ERK and PI3K-AKT pathways independently from EGFR signaling

Table 2 | Influence of *KRAS* status on cetuximab efficacy in single-arm studies of chemorefractory mCRC

Treatment regimen	Number of patients with *KRAS* mutation out of total number of patients (%)	ORR (CR+PR) in patients with *KRAS* mutations (%)	ORR (CR+PR) in patients with wild-type *KRAS* (%)	Comments
Cetuximab with or without chemotherapy or panitumumab	10 of 31 (32%)	2 of 10 (20%)	8 of 21 (38%)	First exploratory analysis[30]
Cetuximab and chemotherapy	13 of 30 (43%)	0 of 13 (0%)	11 of 17 (65%)	Better median OS in patients with wild-type *KRAS* (P=0.016)[31]
Cetuximab with or without chemotherapy or panitumumab	16 of 48 (33%)	1 of 16 (6%)	10 of 32 (31%)	Better median TTP in patients with wild-type vs mutant *KRAS* (P=0.044)[22]
Cetuximab and chemotherapy	10 of 27 (37%)	1 of 10 (10%)	9 of 17 (53%)	Wild-type *KRAS* correlated with ORR (P=0.05)[32]
Cetuximab and chemotherapy	22 of 59 (37%)	0 of 22 (0%)	12 of 37 (32%)	*KRAS* mutations associated with progressive disease (P=0.0005) and with worse TTP (3.0 vs 5.5 months, P<0.015)[33]
Cetuximab	30 of 80 (38%)	0 of 30 (%)	5 of 50 (10%)	Disease control rate (PR+ stable disease) higher in patients with wild-type vs mutant *KRAS* (10% vs 48%, P=0.0003)[43]
Cetuximab and chemotherapy	42 of 108 (39%)	0 of 42 (0%)	27 of 66 (40%)	Longer median OS in patients with wild-type vs *KRAS* mutations (43 vs 27.2 weeks, P=0.02)[35]
Cetuximab and chemotherapy	24 of 89 (27%)	0 of 24 (0%)	26 of 65 (40%)	Longer median DFS (31.4 vs 10.1 weeks, P=0.0001) and median OS (14.3 vs 10.1 months, P=0.0001) in patients with wild-type *KRAS* vs *KRAS* mutations[36]
Cetuximab and chemotherapy	27 of 64 (42%)	1 of 27 (4%)	10 of 37 (27%)	Wild-type *KRAS* correlates with improved ORR (P=0.02) and with longer PFS (5.3 vs 3.0 months, P=0.024)[37]
Cetuximab with or without chemotherapy or panitumumab: summary of the above studies	194 of 536 (36%)	5 of 194 (2.5%)	118 of 342 (34.5%)	Total numbers should be interpreted with caution as they derive from the sum of data from retrospective analyses of studies; however, all the studies show similar results

Abbreviations: CR, complete response; DFS, disease-free survival; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; TTP, time to progression.

Normanno N et al., Nature Reviews Clinical Oncology, 6:519-27, 2009

Molecular pathology in Italy

- **A few Italian laboratories were equipped for molecular pathology in 2008.**
- **Uneven distribution of laboratories in the country (Nord>Center>South).**
- **Health system organized on a regional basis, with significant differences between regions.**
- **No guidelines or EQA programs from regional or national Departments of Health.**

Italian project for the molecular characterization of cancers for therapeutic intervention

- **To provide to each Italian cancer patient a validated test for a biomarker of clinical use.**

- **Aims:**
  - **Appropriate clinical indication**
  - **Appropriate methodology**
  - **Appropriate results for clinical practice**

Activity of the AIOM-SIAPEC Board

Aims	KRAS CRC	EGFR NSCLC	ALK NSCLC	BRAF Melanoma
Organize working groups on specific topics	Meeting Sept 2008	Meeting Oct 2009	Meeting June 2011	Meeting Sept 2011
Outline guidelines	February 2009 – November 2010	May 2010	June 2012	June 2012
EQA programs	Completed 2010, 2012. Ongoing 2014	Completed 2011	Completed 2013	Completed 2012
Training	3 Courses 2011, 2012, 2013	3 Courses 2011, 2012, 2013	3 Courses 2012, 2013	3 Courses 2012, 2013

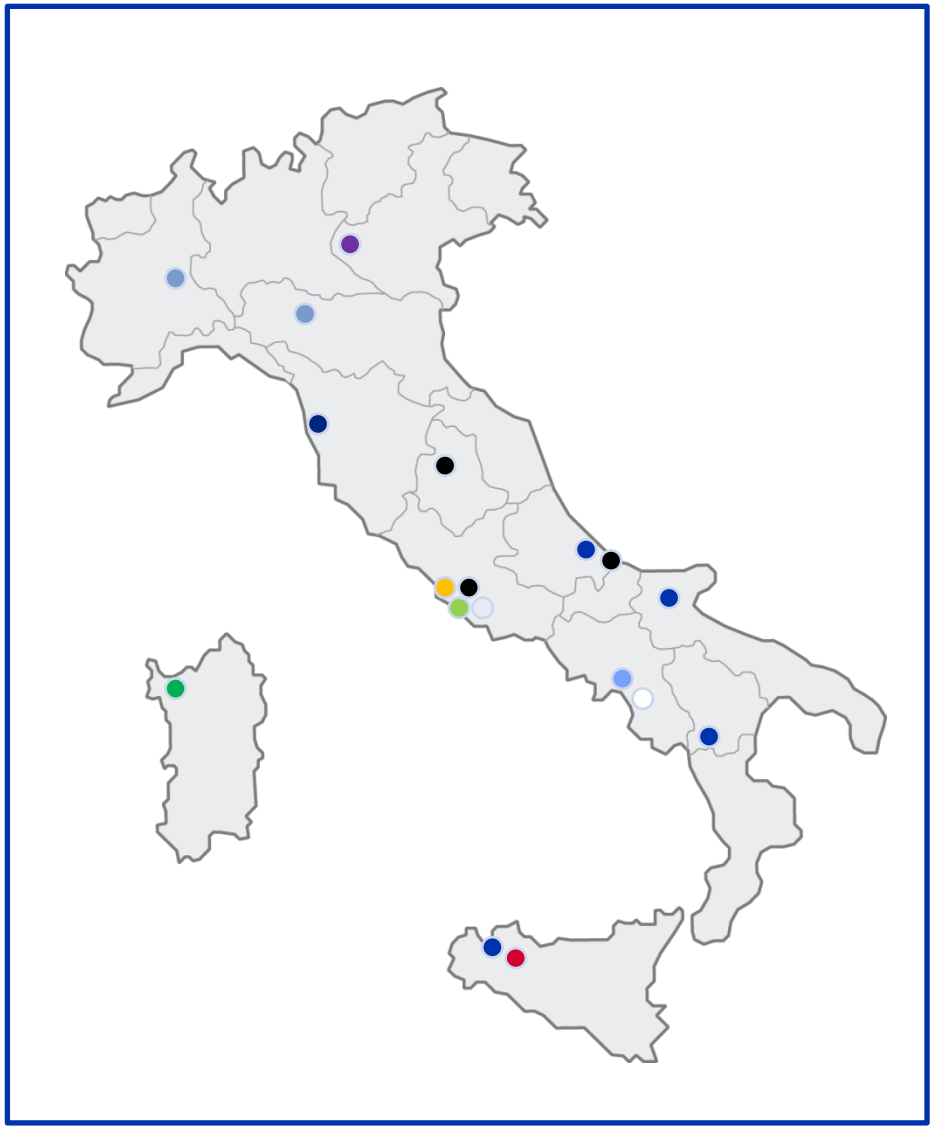
KRAS-Active Network

Involved:

18 Referral Laboratories

570 oncologists
and 190 pathologists

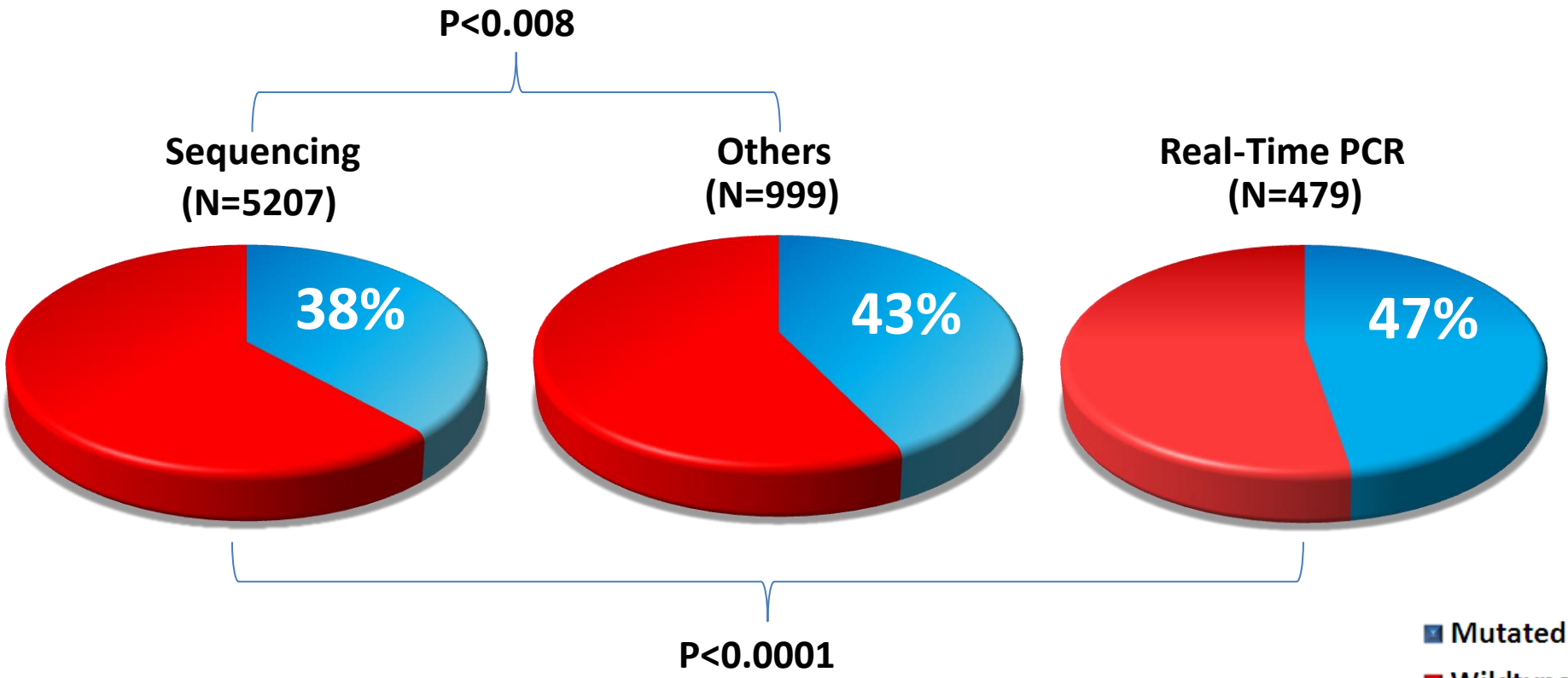
More than 15.000 samples
were examined
(March 2009 – March 2014)



KRAS αKtive

Mutations by Techniques

***KRAS* mutation analysis was performed by PCR-Sanger sequencing, real time PCR or other techniques (Pyrosequencing, Strip Assay).**



Marchetti et al. AIOM 2011


Raccomandazioni
sui requisiti minimi
e gli standard di refertazione
e sull'utilizzo di metodiche
per la determinazione
dello stato di HER2
nel carcinoma mammario
A cura del gruppo di lavoro AIOM-SIAPEC-IAP


Raccomandazioni
per la determinazione
dello stato di HER2
nel carcinoma gastrico
A cura del gruppo di lavoro AIOM-SIAPEC-IAP


Raccomandazioni
per l'analisi mutazionale
del gene KRAS
nel carcinoma del colon-retto
Aggiornamento, 10 Novembre 2010
A cura del gruppo di lavoro AIOM - SIAPEC-IAP


Raccomandazioni
per l'analisi mutazionale
del gene EGFR
nel carcinoma polmonare
Antonio Marchetti e Nicola Normanno
A cura del gruppo di lavoro AIOM - SIAPEC-IAP


Raccomandazioni
per la determinazione
dello stato mutazionale
di BRAF nel melanoma
A cura del Gruppo di Lavoro di AIOM e SIAPEC-IAP


Raccomandazioni per l'analisi
dei riarrangiamenti del gene
ALK nel carcinoma polmonare
non a piccole cellule
A cura del Gruppo di Lavoro di AIOM e SIAPEC-IAP

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December 2011 | Volume 6 | Issue 12 PLoS one

KRAS Mutations Testing in Colorectal Carcinoma Patients in Italy: From Guidelines to External Quality Assessment

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Abstract

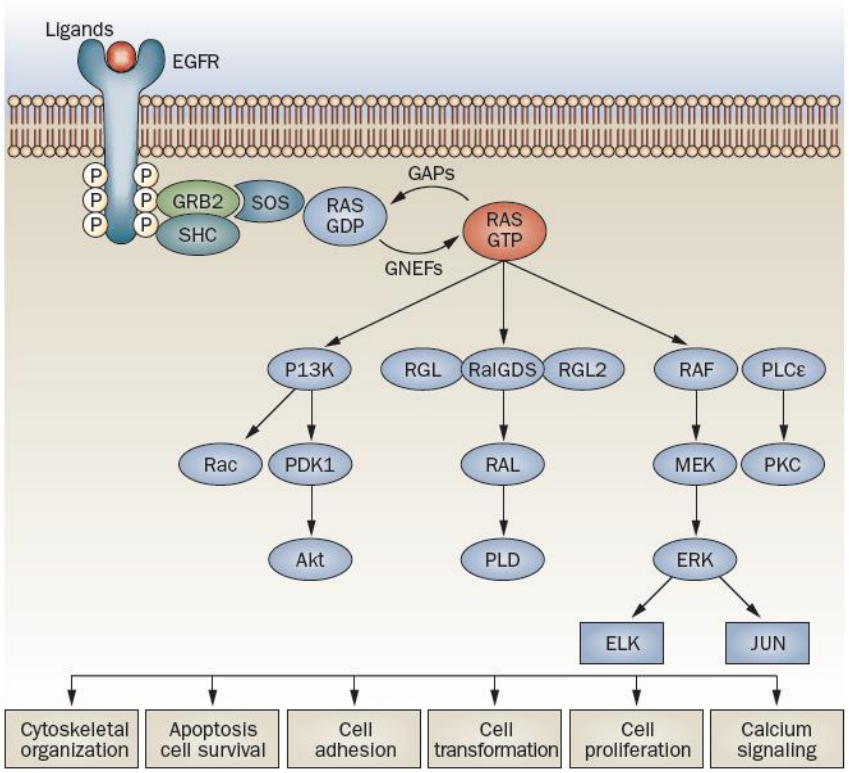
Background: Monoclonal antibodies directed against the epidermal growth factor receptor (EGFR) have been approved for the treatment of patients with metastatic colorectal carcinoma (mCRC) that do not carry KRAS mutations. Therefore, KRAS testing has become mandatory to chose the most appropriate therapy for these patients.

Methodology/Principal Findings: In order to guarantee the possibility for mCRC patients to receive an high quality KRAS testing in every Italian region, the Italian Association of Medical Oncology (AIOM) and the Italian Society of Pathology and Cytopathology -Italian division of the International Academy of Pathology (SIAPEC-IAP) started a program to improve KRAS testing. AIOM and SIAPEC identified a large panel of Italian medical oncologists, pathologists and molecular biologists that outlined guidelines for KRAS testing in mCRC patients. These guidelines include specific information on the target patient population, the biological material for molecular analysis, the extraction of DNA, and the methods for the mutational analysis that are summarized in this paper. Following the publication of the guidelines, the scientific societies started an external quality assessment scheme for KRAS testing. Five CRC specimens with known KRAS mutation status were sent to the 59 centers that participated to the program. The samples were validated by three referral laboratories. The participating laboratories were allowed to use their own preferred method for DNA extraction and mutational analysis and were asked to report the results within 4 weeks. The limit to pass the quality assessment was set at 100% of true responses. In the first round, only two centers did not pass (3%). The two centers were offered to participate to a second round and both centers failed again to pass.

Conclusions: The results of this first Italian quality assessment for KRAS testing suggest that KRAS mutational analysis is performed with good quality in the majority of Italian centers.

EGFR MoAbs in CRC

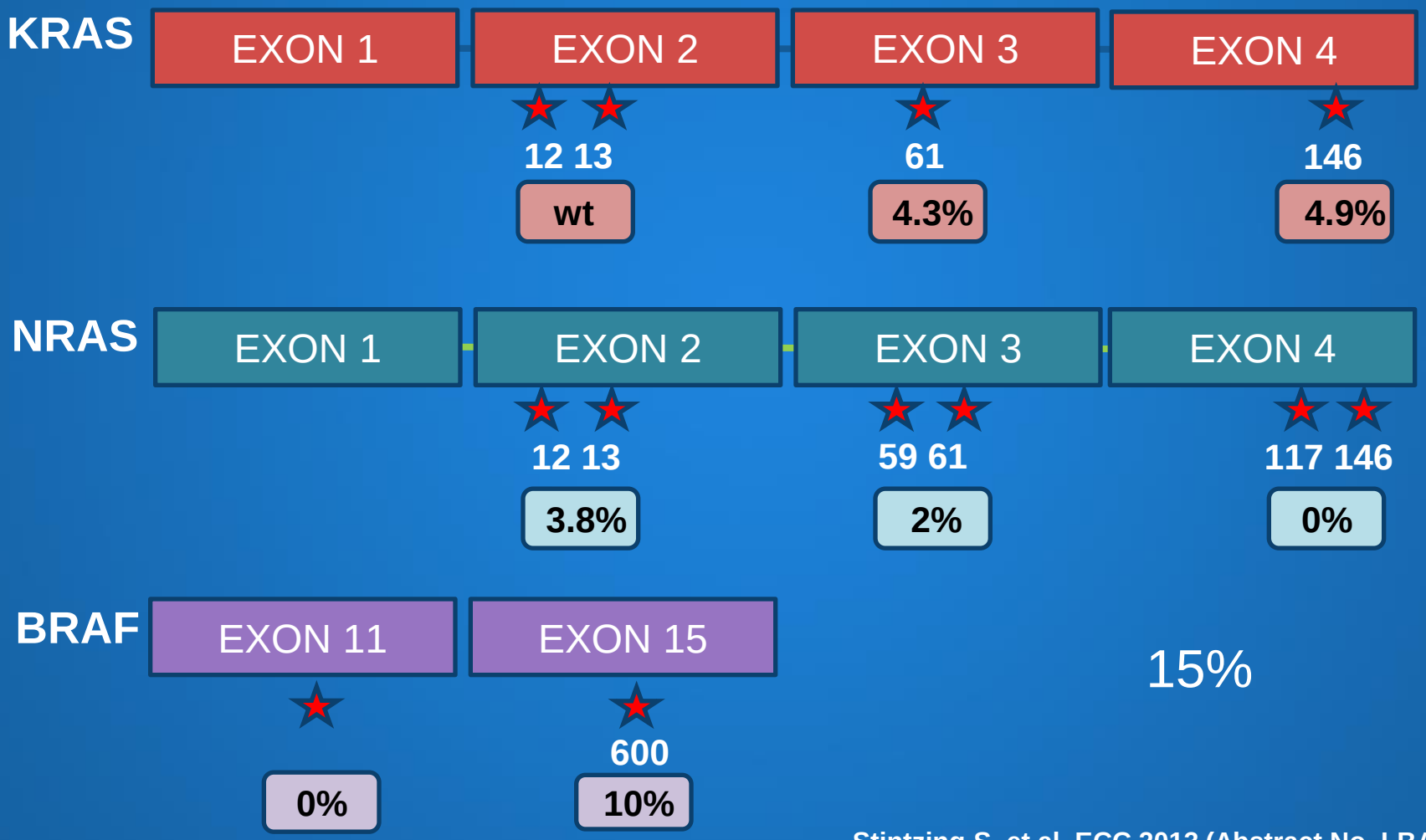
- **EGFR monoclonal antibodies have been approved for the treatment of patients with wild-type RAS metastatic colorectal cancer by EMA**
- **Therefore, RAS testing should be performed only in metastatic colorectal carcinoma patients undergoing treatment with EGFR monoclonal antibodies**



Normanno Nat Rev Clin Oncol 2009

FIRE-3: Mutations tested

KRAS wt (exon 2) subset



Stintzing S, et al. ECC 2013 (Abstract No. LBA17)

Comparison of methodologies

Study	Method	Sensitivity*	RAS mutant
FIRE-3[1]	Pyrosequencing	≤5%[2]	15%
OPUS[3]	Inostics BEAMing technology (detection cut-off 0.1%)	0.01%[4]	32.2%
CAPRI[5]	Next-generation sequencing: Ion AmpliSeq™ Colon and Lung Cancer Panel	2%[5]	15.9%
PRIME[6]	Bidirectional Sanger sequencing and WAVE-based SURVEYOR® Scan Kits (Transgenomic)	10−20% (Sanger sequencing)[8]	17%
PEAK[7]		1% (WAVE-based SURVEYOR®)[9]	22%
20020408[8]	Next-generation sequencing, Sanger sequencing, and independently conducted WAVE-based SURVEYOR® Scan Kits (Transgenomic)	10–20% (Sanger sequencing)[8]	18.1%
De Roock et al[10]	Sequenom MALDI-TOF MassARRAY multiplex PCR and genotyping	5–15%[10]	11%**

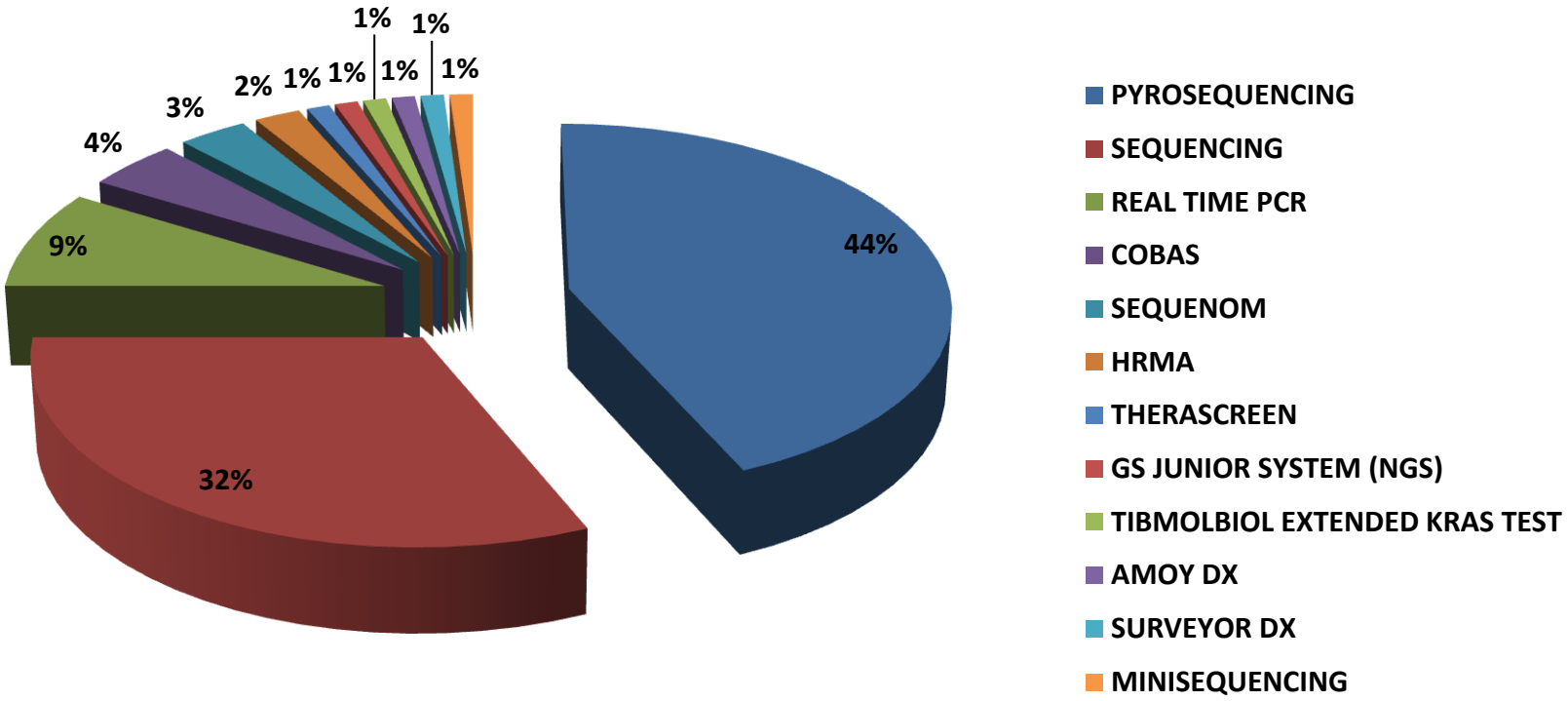
*Values refer to the lowest percentage of mt sequence that is detectable; **selected mutations

1. Stintzing S, et al. ECC 2013 (Abstract No. LBA17); 2. Anderson SM. Expert Rev Mol Diagn 2011;11:635–642; 3. Data on file; 4. Aung KL, et al. Hugo J 2010;4:11–21; 5. Ciardiello F, et al. ECC 2013 (Abstract No. LBA31); 6. Douillard J-Y, et al. N Engl J Med 2013;369:1023–1034; 7. Karthaus M, et al. ECC 2013 (Abstract No. 2262); 8. Peeters M, et al. WCGC 2013 (Abstract No. PD-0008); 9. Jänne PA et al. Clin Cancer Res 2006;12:751–758; 10. De Roock W, et al. Lancet Oncol 2010;11:753–762

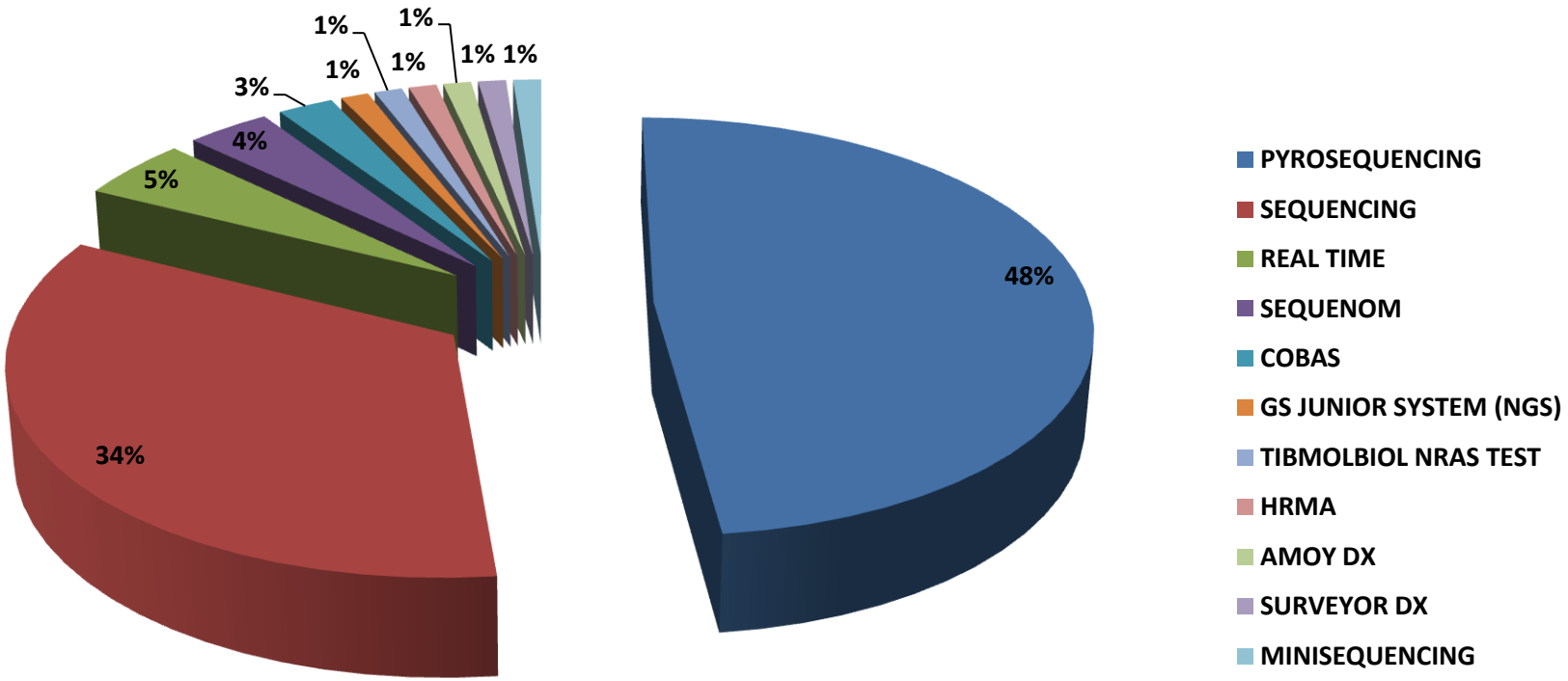
AIOM-SIAPEC RAS scheme 2014

- **RAS EQA 2014 Board: M. Barberis, F. Castiglione, C. Clemente, G. De Rosa, F. Fenizia, G. Fontanini, A. Marchetti, N. Normanno, C. Pinto, G. L. Taddei**
- **EQA programs aimed to assess only genotyping: samples do not require dissection (>70% neoplastic cells; >20% mutant alleles as assessed by NGS)**
- **10 cases for each round, validated by: pyrosequencing, Sequenom, Sanger sequencing and/or NGS (Ion Ampliseq Colon and Lung Cancer Panel)**
- **Centers are asked to run the molecular analysis with the technique that they routinely use within a 3-week timeframe**

Methods used for KRAS testing



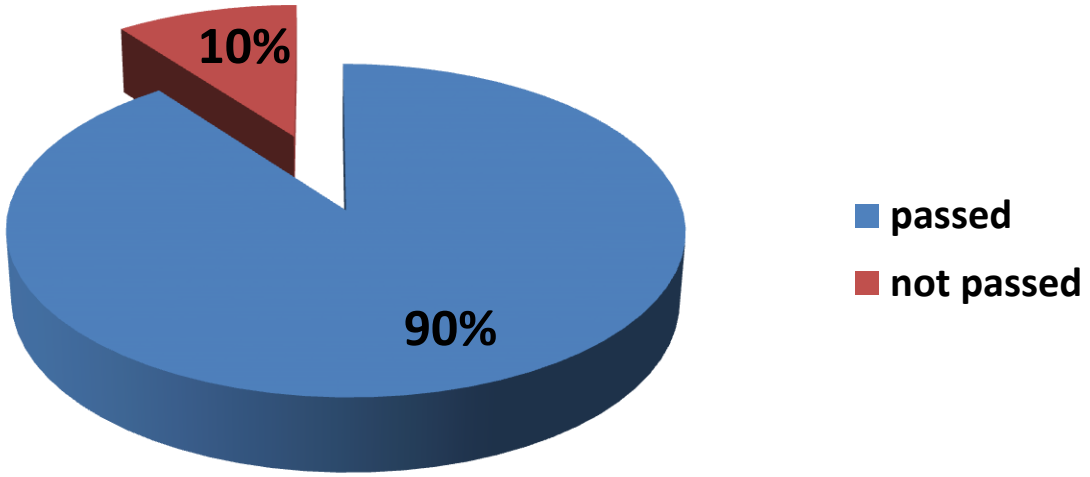
Methods used for NRAS testing



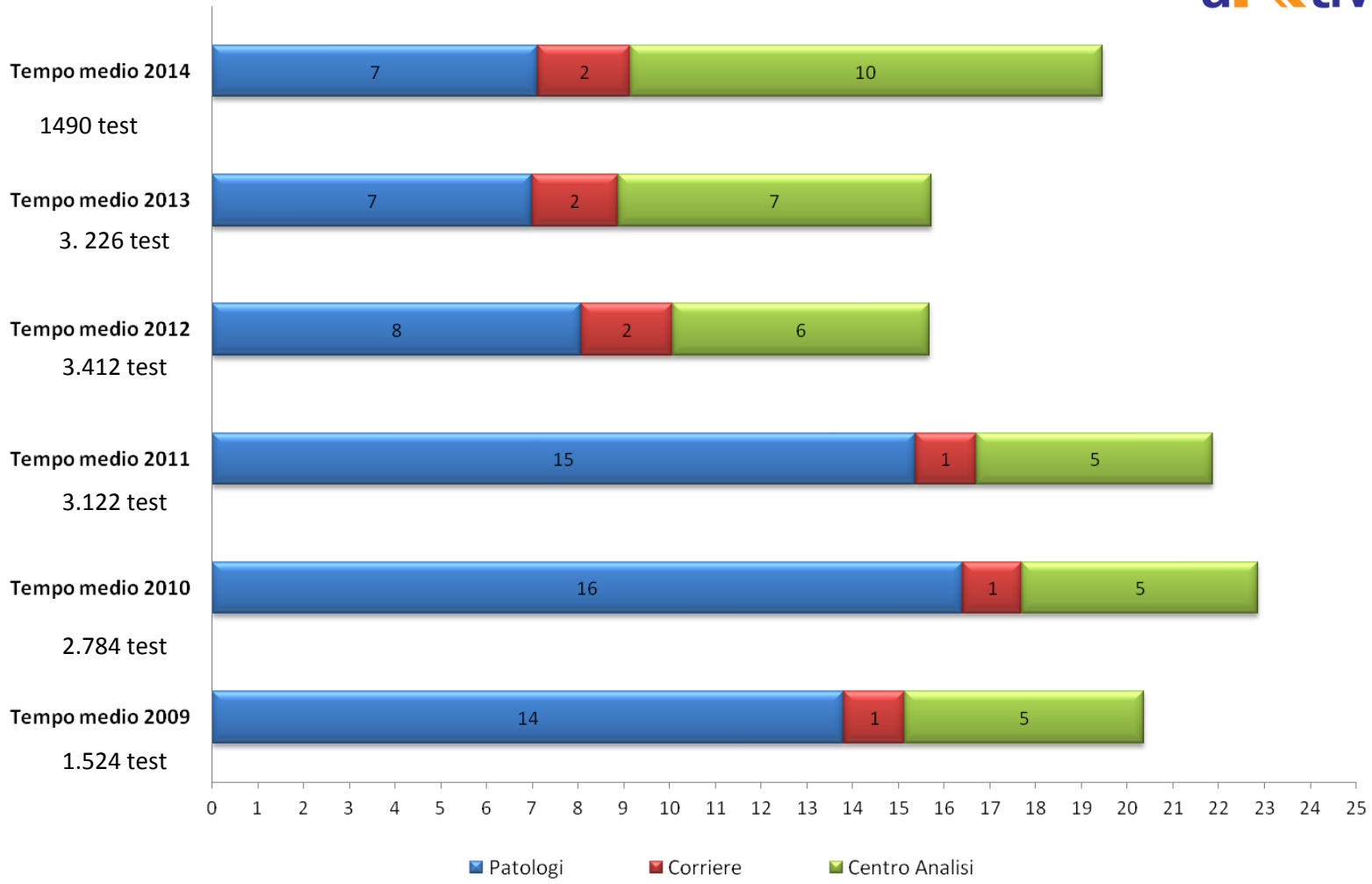
Error rate in *III Italian EQA Program for RAS mutations*

- **2 rounds within the same year**

- **9/88 centers failed in total, while 79/88 passed the *III Italian National EQA Program for RAS mutations***



Global time (days) from the request of the test to the results of the test for RAS in mCRC



Fonte: Aktive – Aprile 2014

Organization models and critical points

PARAMETERS	CRITICAL POINTS
Amount of biological material	Surgical specimen, biopsy, citological sample, Tissue-Cells Saving/storage
Quality of biological material	Pre-analitical phase
Representativeness of the sample	Tissue dissection. DNA extraction
Appropriatness of the methods	Availability of different technologies
Quality of the report	Immediate interpretation by the clinician according to drug registration
Total time of testing	≤ 7-15 days
Workflows	Pathology lab/Referral Center (Centralizzation) /Network
Costs	250-800 Euros

European Journal of Cancer (2013) **49**, 2126–2133

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

The *KRAS* mutation detection within the initial management of patients with metastatic colorectal cancer: A status report in France in 2011

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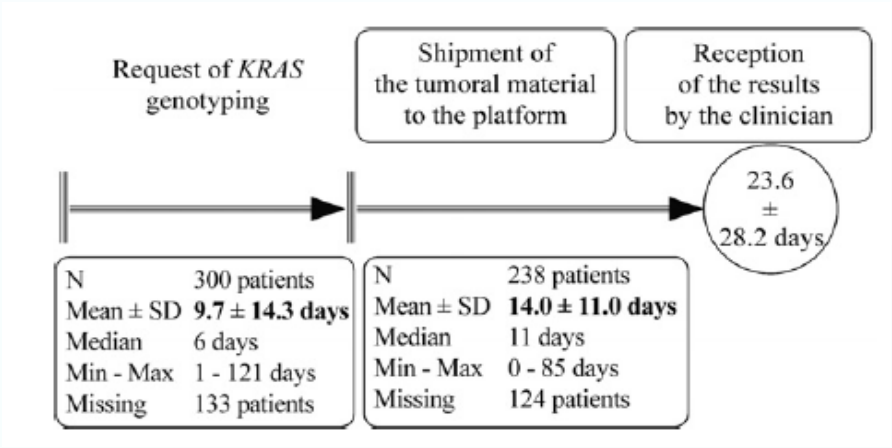
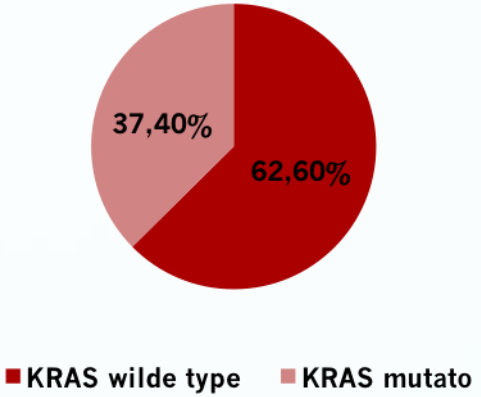
Available online 6 March 2013

FLASH KRAS Study (France in 2011)

Duration of the whole process of KRAS testing

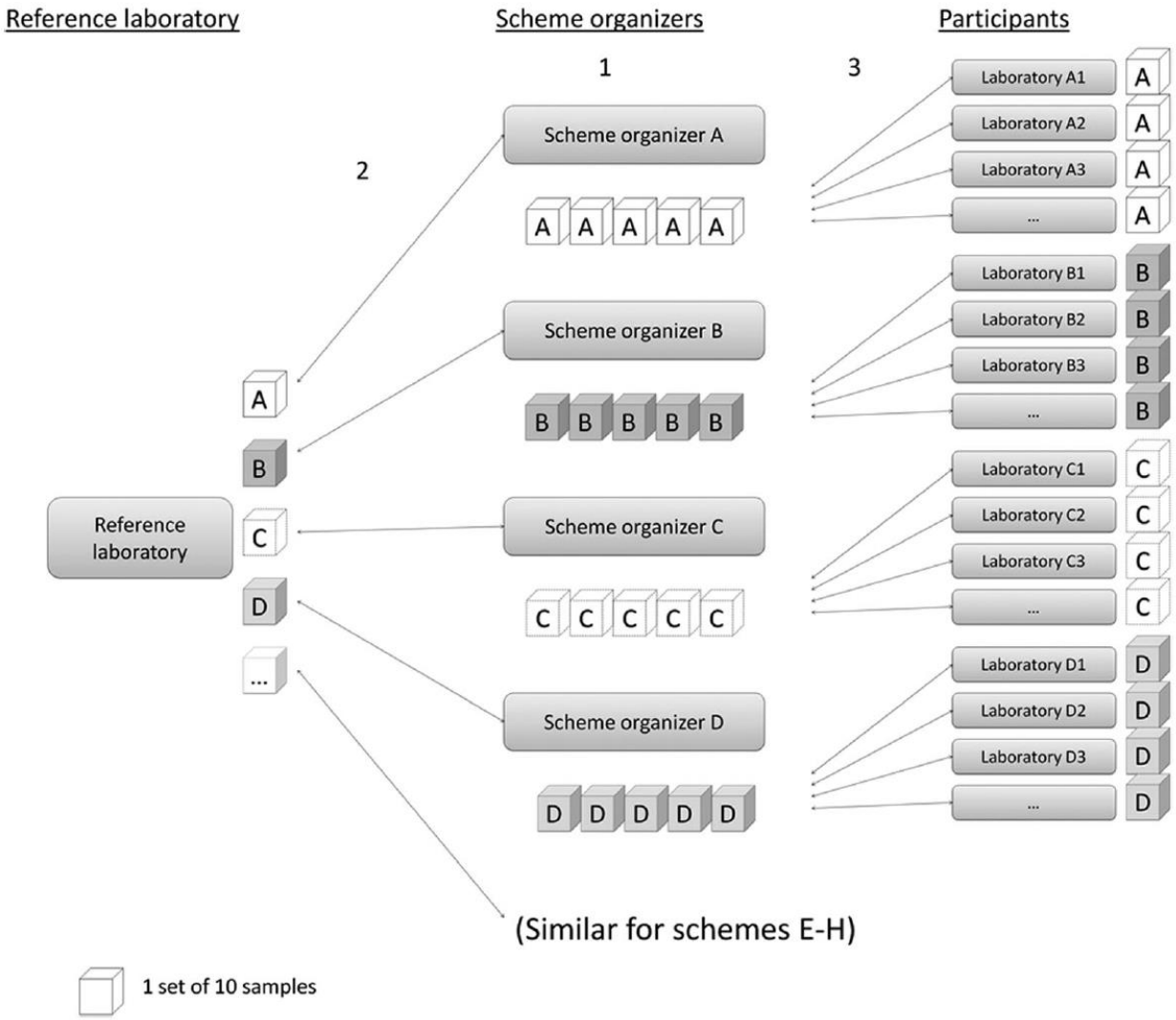




- **Time from diagnosis of mCRC : 40% within one month; median, 15 days**
- **Time to send the sample to the lab: median, 6 days**
- **Time from sample shipment to the result: median, 11 days**
- **Global time to obtain the results: median, 19 days**
- **KRAS test results available before first line: 43,4% of patients**

Lièvre et al, Eur J Cancer 2013

Organization of the European KRAS scheme



In total, 59 labs from 8 different European countries participated in the regional *KRAS* EQA scheme in 2009.

Bellon Oncologist 2011

Results of the ESP KRAS schemes

- 2009
- 59 laboratories
- 22% made genotyping errors
- 8% technical failures
- The majority of the errors were false-positive (3) or false-negative results (6)

Bellon Oncologist 2011

- 2012
- 105 laboratories
- 27% made genotyping errors
- 20% reported a technical error
- 9 false positives and 29 false negatives occurred; 10 cases with an incorrect mutation reported.

Tembuyser J Mol Diagn 2014

European External Quality Assurance in Molecular Pathology

Virchows Arch (2013) 462:27–37
DOI 10.1007/s00428-012-1354-4

MEETING REPORT

Guideline on the requirements of external quality assessment programs in molecular pathology

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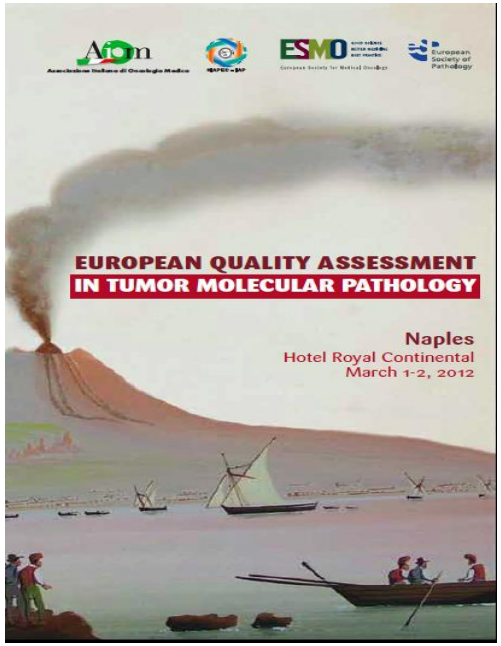

reviews

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European Consensus Conference for external quality assessment in molecular pathology

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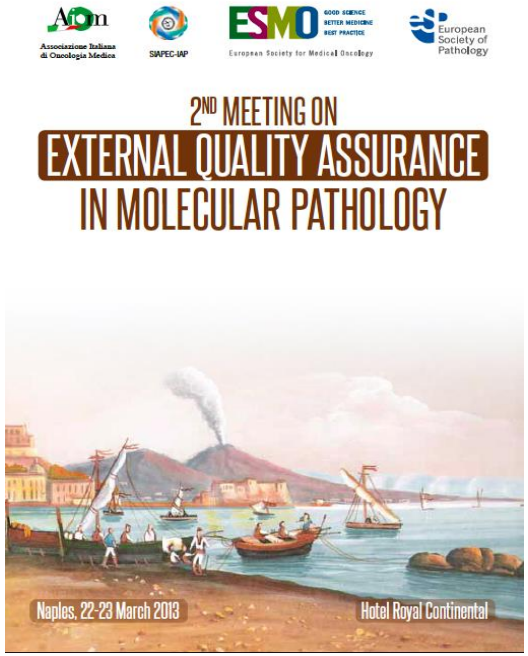

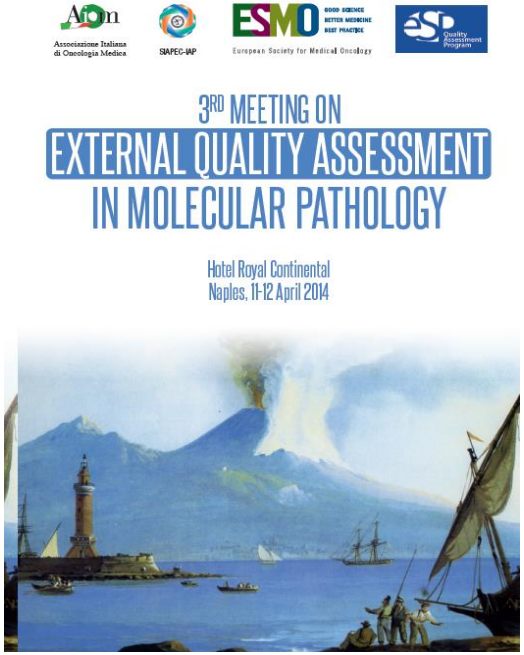

Tumour molecular profiling for deciding therapy—the French initiative

Frédérique Nowak, Jean-Charles Soria and Fabien Calvo

Abstract | The use of tumour molecular profiles for therapeutic decision making requires that molecular diagnostics be introduced into routine clinical practice. To this end, the French National Cancer Institute and French Ministry of Health have set up a national network of 28 regional molecular genetics centres. These facilities perform selected molecular tests, free of charge, for all patients in their region, regardless of the institution where they are treated. A specific programme has also been implemented to anticipate the launch of new targeted treatments and reduce time-to-access to new drugs and experimental therapies. In 2011, 55,000 patients with cancer in France benefited from molecular predictive tests. The French nationwide initiative for tumour molecular profiling is a tool to fight inequalities in access to molecular testing and targeted therapy, and demonstrates that molecular stratification of tumours for therapeutic decisions is a cost-effective strategy that can be successfully integrated into the health-care system.

Nowak, F. et al. Nat. Rev. Clin. Oncol. 9, 479–486 (2012); published online 10 July 2012;
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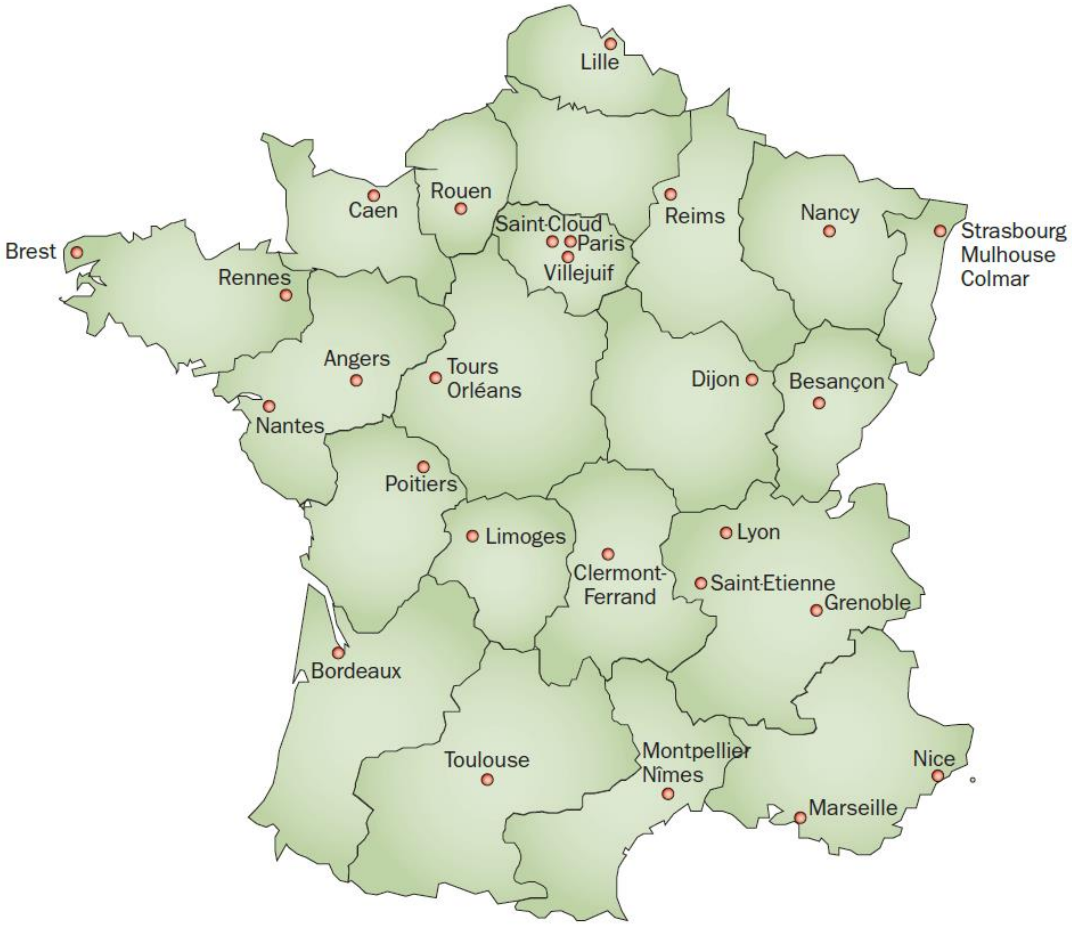
Molecular genetics platforms in France



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- **The 28 molecular genetics centers are regional hubs for expert molecular testing. The centers were selected through competitive calls for proposals.**
- **The centers are located throughout the country, with an average of one center per administrative region; their number is not expected to increase.**
- **Each molecular genetics center is a partnership between several university hospital and cancer center laboratories with complementary expertise**

Table 3 | Molecular tests performed in France in 2011 by the 28 molecular genetics centres

Biomarker	Cancer	Clinical indication or application
Predictive		
BCR–ABL translocation	Chronic myeloid or acute lymphoblastic leukaemia	Prescription of imatinib, dasatinib or nilotinib
ABL mutation	Chronic myeloid or acute lymphoblastic leukaemia	Predicts resistance to tyrosine kinase inhibitor therapy and aids second-line treatment decisions
KIT and PDGFRA mutations	Gastrointestinal stromal tumours	Prescription of imatinib
HER2 amplification	Breast cancer	Prescription of trastuzumab and lapatinib
HER2 amplification	Gastric cancer	Prescription of trastuzumab
KRAS mutations	Metastatic colorectal cancer	Prescription of panitumumab and cetuximab
EGFR mutations	Lung cancer	Prescription of gefitinib and erlotinib
Diagnostic		
JAK2 V617F mutation	Suspected myeloproliferative syndrome	Differential diagnosis
Microsatellite instability	HNPCC spectrum cancers	Diagnosis of suspected hereditary forms
Specific chromosomal abnormalities	Sarcomas	Aids diagnosis and/or subtype classification
Specific chromosomal abnormalities	Non-Hodgkin lymphomas	Aids diagnosis and/or subtype classification
Specific chromosomal abnormalities	Haemopathies	Aids diagnosis and/or subtype classification
1p/19q co-deletion	Brain tumours	Aids diagnosis and/or subtype classification
B-cell or T-cell clonality	Non-Hodgkin lymphomas	Aids diagnosis of lymphoma and/or reactional lymphoproliferation
Prognostic		
MYCN amplification	Neuroblastoma	Contributes to treatment guidance
FLT3 and NPM mutations	Acute myeloid leukaemia	Contributes to treatment guidance
Specific chromosomal abnormalities	Haemopathies	Contributes to treatment guidance
BCR–ABL transcript level of expression	Chronic myeloid or acute lymphoblastic leukaemia	Monitoring of minimal residual disease

Abbreviation: HNPCC, hereditary nonpolyposis colorectal cancer.

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Table 4 | Tumour molecular profiling in France in 2011

Cancer	Biomarker	Number of patients tested	Number of positive results* (% of patients tested)
Chronic myeloid or acute lymphoblastic leukaemia	BCR–ABL translocation	6,497	1,228 (18.9)
Chronic myeloid or acute lymphoblastic leukaemia	BCR–ABL transcript level of expression	13,750 (total of 28,607 tests)	Not determined
Chronic myeloid or acute lymphoblastic leukaemia	ABL mutations	861	202 (23.4)
Gastrointestinal stromal tumours	KIT mutations	944	532 (56.4)
Gastrointestinal stromal tumours	PDGFRA mutations	880	111 (12.6)
Breast cancer	HER2 amplification	8,545	1,820 (21.3)
Gastric cancer	HER2 amplification	443	115 (26.1)
Colorectal cancer	KRAS mutations	17,003	6,626 (39.0)
Lung cancer	EGFR mutations	20,750	2,085 (10.0)

* Data are missing for some molecular genetics centres; estimations are based on available data.

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Molecular pathology in Europe: the need of the medical oncologist

- **Establish common rules for reporting i.e. medical oncologists should find in the report a minimum level of information independently from the country in which the test was performed:**

  - **The percentage of neoplastic cells in the specimen**
  - **The technique used for testing**
  - **The sensitivity of the test**
  - **The mutation identified (nucleotide and amino acid change)**

An European form for reporting in molecular pathology?

Conclusions

- Biomarker assessment for the use of molecular targeted therapies is being performed in Europe in clinical practice.

- However, several critical issues need to be solved for an appropriate use of predictive molecular biomarkers:
  - Cost and reimbursement policies
  - Methodology and reproducibility of the results
  - European-driven quality control schemes
  - Availability of the results in time before starting treatment
  - Major differences in different European countries