Accesso ai programmi di molecular screening in Italia: sfide di organizzazione e di finanziamento nel campo della genomic medicine

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- Gene expression profiling
- Hereditary predisposition
- Somatic genetic sequencing

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Test molecolari di espressione nel ca mammella

Nome commerciale	N geni	Classi di rischio	Ref
Mammaprint	70	Basso/alto	van de Vijver 2002
Oncotype Dx	21	Basso/intermedio/alto	Paik 2004
Endopredict	8	Basso/alto	Filipits et akl 2011
Prosigna	50	Basso/intermedio/alto	Parker et al 2009

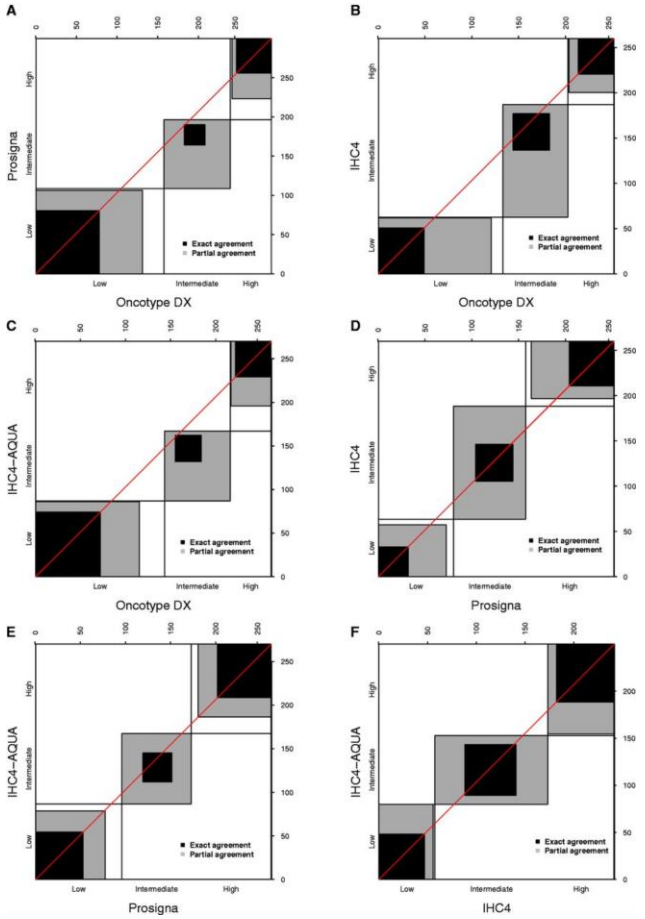
- Tutti hanno dimostrato valore prognostico e predittivo di risposta alla chemioterapia nella malattia St I-III, ER+/HER2-, con alcune differenze
- potenzialmente ~20.000 donne/anno candidabili a ricevere un test con le raccomandazioni attuali

I test molecolari sono economicamente sostenibili

Strategie di trattamento	Costo medio (£)	QALY medio	Beneficio netto in salute (QALYs)
Chemioterapia per tutti	13.961	7.69	6.99
Oncotype DX	13.853	7.89	7.2
MammaPrint	14.156	7.87	7.16
Prosigna ROR_PTa	13.487	7.88	7.2

- Numerosi studi mostrano che l'applicazione a tappeto di test molecolari e' economicamente sostenibile e porta beneficio in salute a parita' di costi (2-5k euro QALY)

Which test?????



From: Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others

J Natl Cancer Inst. 2016;108(9). doi:10.1093/jnci/djw050

Applicazione test molecolari in Italia

- Consiglio Superiore di Sanita' probabilmente suggerira' di includere i test molecolari nella routine clinica rimborsabile
- Restano importanti incognite su come applicare quale test

- Gene expression profiling
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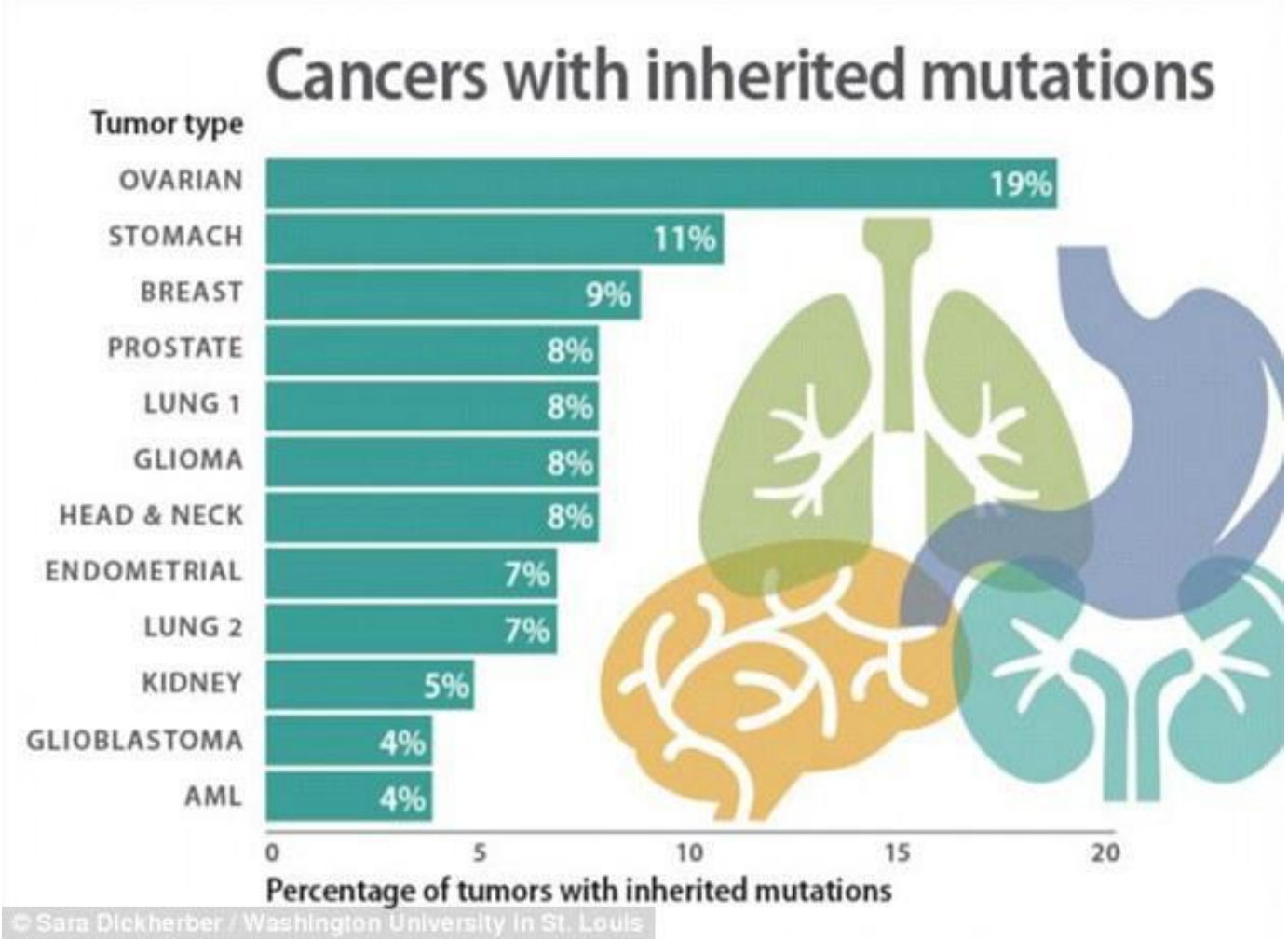
- Somatic genetic sequencing


Cancers with inherited mutations
Tumor type
OVARIAN
STOMACH
BREAST
PROSTATE
LUNG 1
GLIOMA
HEAD & NECK
ENDOMETRIAL
LUNG 2
KIDNEY
GLIOBLASTOMA
AML
19%
11%
9%
8%
8%
8%
8%
7%
7%
5%
4%
4%
0
5
10
15
20
Percentage of tumors with inherited mutations
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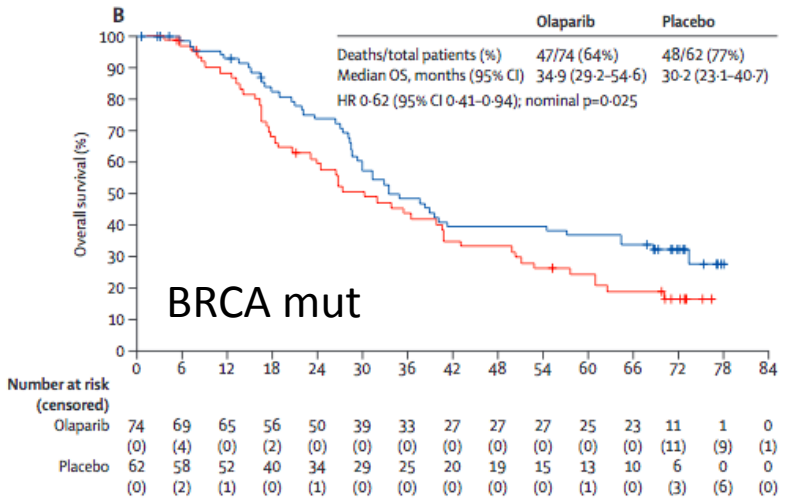
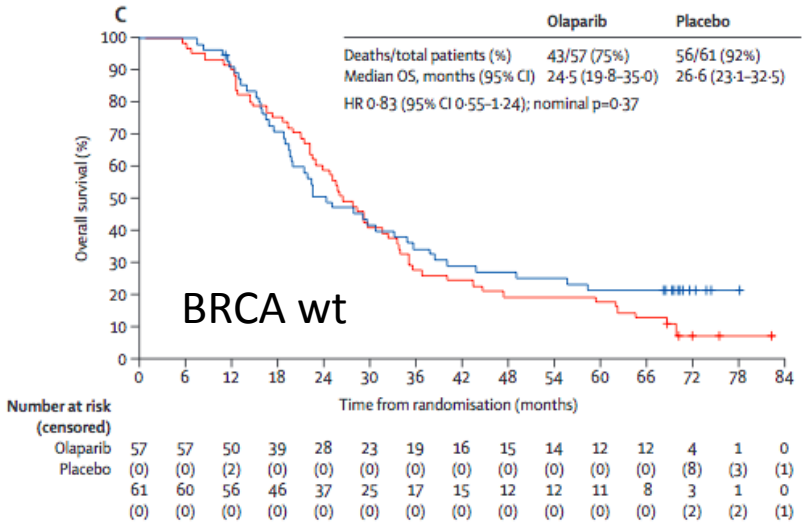
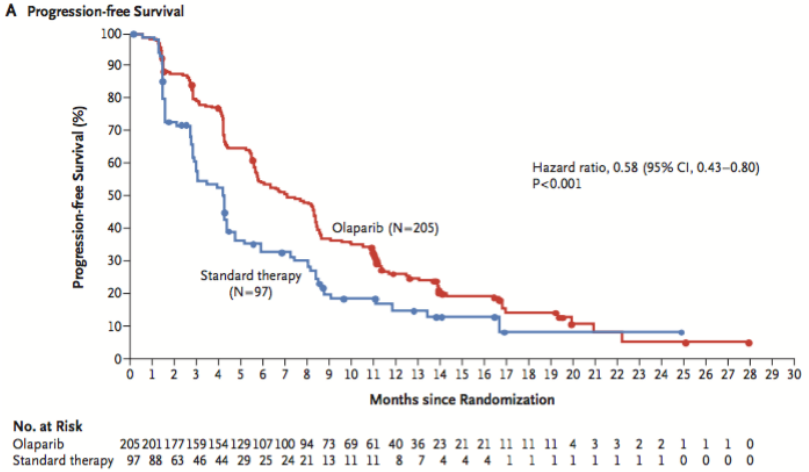
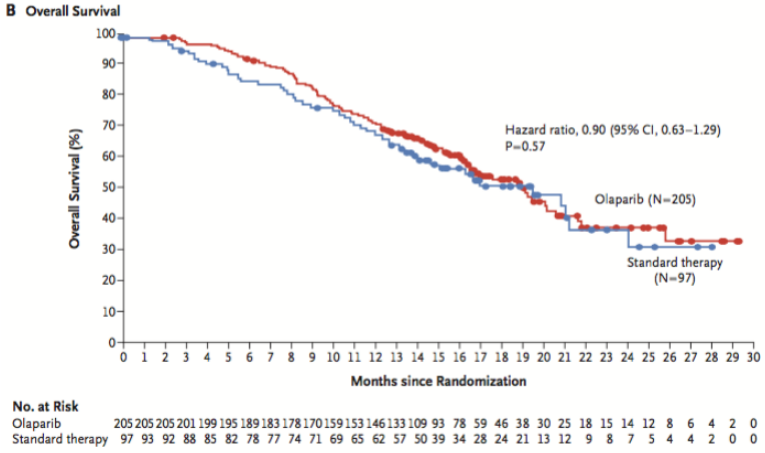
Olaparib in platinum-sensitive ovarian cancer





Olaparib in BRCAmut breast ca





Prescrizione test genetici: recenti modifiche

- La regione Lombardia: ha modificato la procedura di accesso al test genetico per le donne con ca ovarico sieroso metastatico:

per le donne con carcinoma ovarico/tubarico/primitivo peritoneale sieroso di alto grado con recidiva platino sensibile eleggibili alla consulenza secondo i criteri di cui al punto 2), la stessa dovrà essere eseguita tempestivamente e comunque garantendo la refertazione del test genetico in tempi coerenti con l'attivazione del trattamento. Nei casi in cui la donna non sia eleggibile alla consulenza secondo i criteri di cui al punto 2), si autorizza l'esecuzione dei test genetici con prescrizione da parte dello specialista oncologo/ginecologo oncologo, che ha in carico la paziente. La refertazione del test genetico dovrà essere assicurata in tempi coerenti con l'attivazione del trattamento e prevedere il successivo avvio della paziente stessa alla Unità di CGO in caso di test positivo o presenza di varianti a significato sconosciuto, ovvero con l'invio di notifica di test negativo all'unità CGO.

- Gene expression profiling
- Hereditary predisposition
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Background

28 French Centers —> 19386 patients enrolled and 17664 eligible

Primary objective: to describe the frequency of the molecular alterations in 6 genes

Secondary objectives:

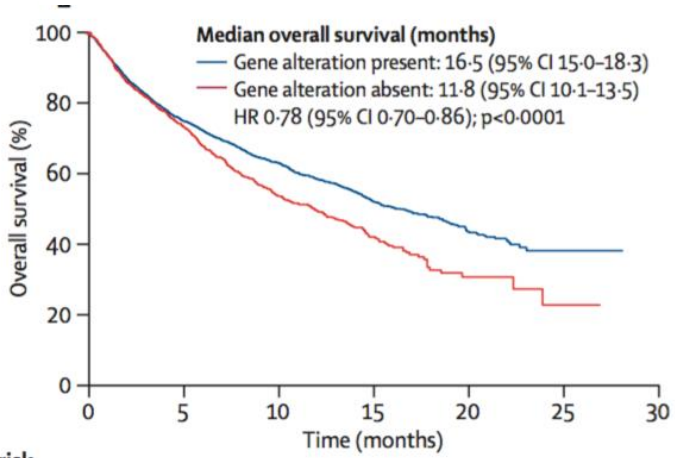
1. to combine the clinical and biological databases
2. to document the turnaround time in obtaining molecular results
3. to assess the ability of the physician to use these data to select therapy
4. to measure OS and PFS

Barlesi et al; Lancet; 2016

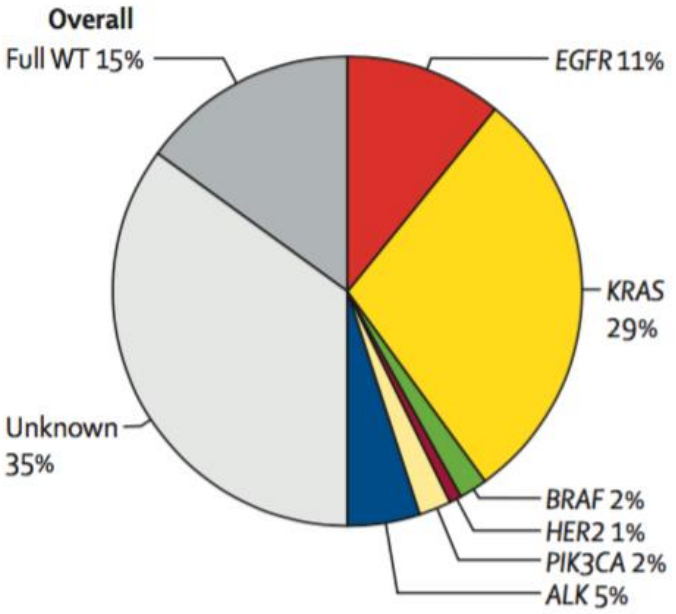
19386 results of routine molecular analysis

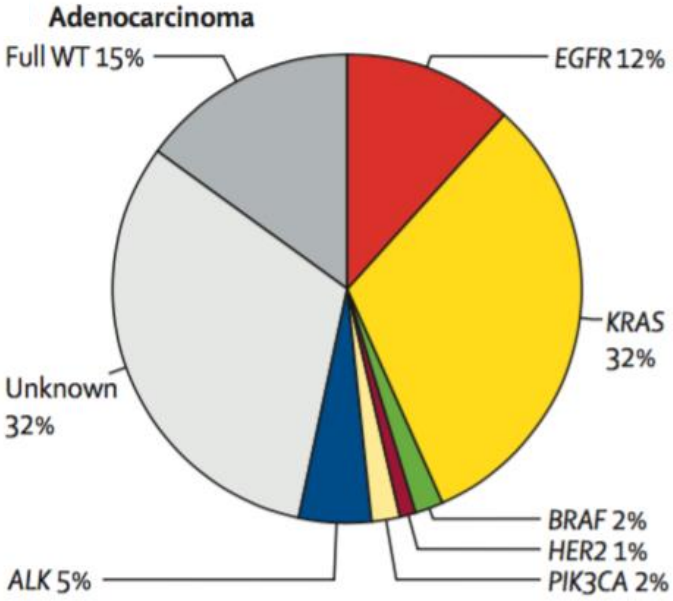
18679 molecular results (96%) from 17664 patients

A gene alteration observed in 50% of the analysis



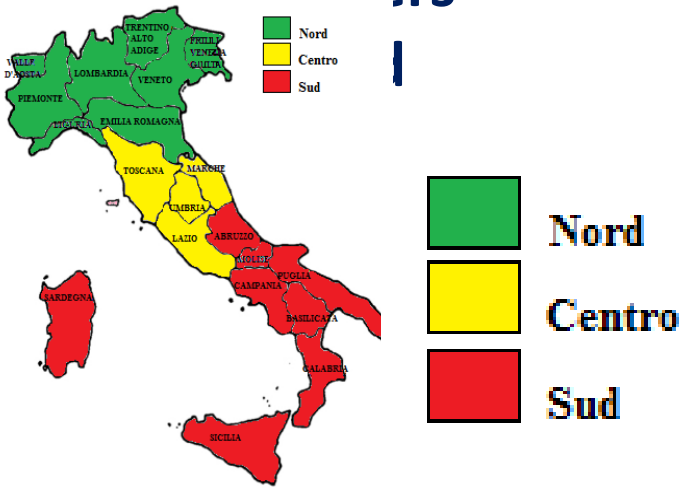
Number at risk							
Gene alteration present	3498	2141	1423	594	165	9	0
Gene alteration absent	1126	617	333	124	24	4	0





Background

38 centers



Nord

Centro

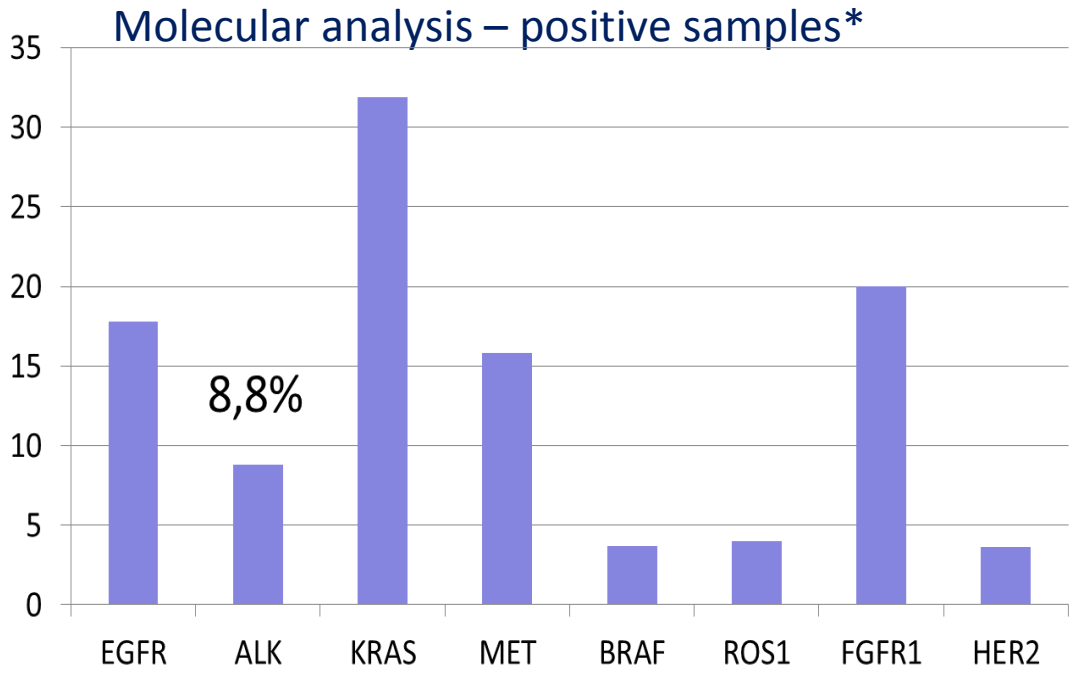
Sud

Inclusion criteria
Advanced NSCLC
1-year period: Nov 2014 – Dec 2015

Molecular evaluations and treatments choices according to the local clinical practice.

1787 patients with NSCLC enrolled

Gobbini et al; XVIII Congresso AIOM; 2016



	France	Italy
New diagnosis	39000/year	38000/year
N of centers involved	28	38
Patients molecularly classified	**17664** patients *screened* and **7680** *molecularly classified*	**1787**

Molecular screening should be organized, structured and pre-planned

Still limited number of patients molecularly classified

Gobbini et al; XVIII Congresso AIOM; 2016

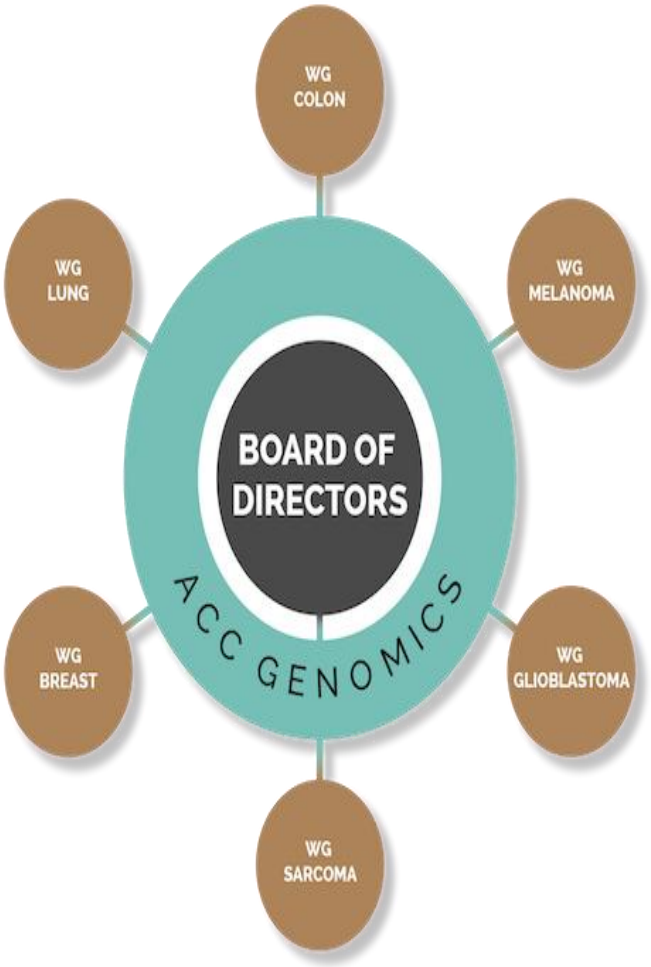
classified

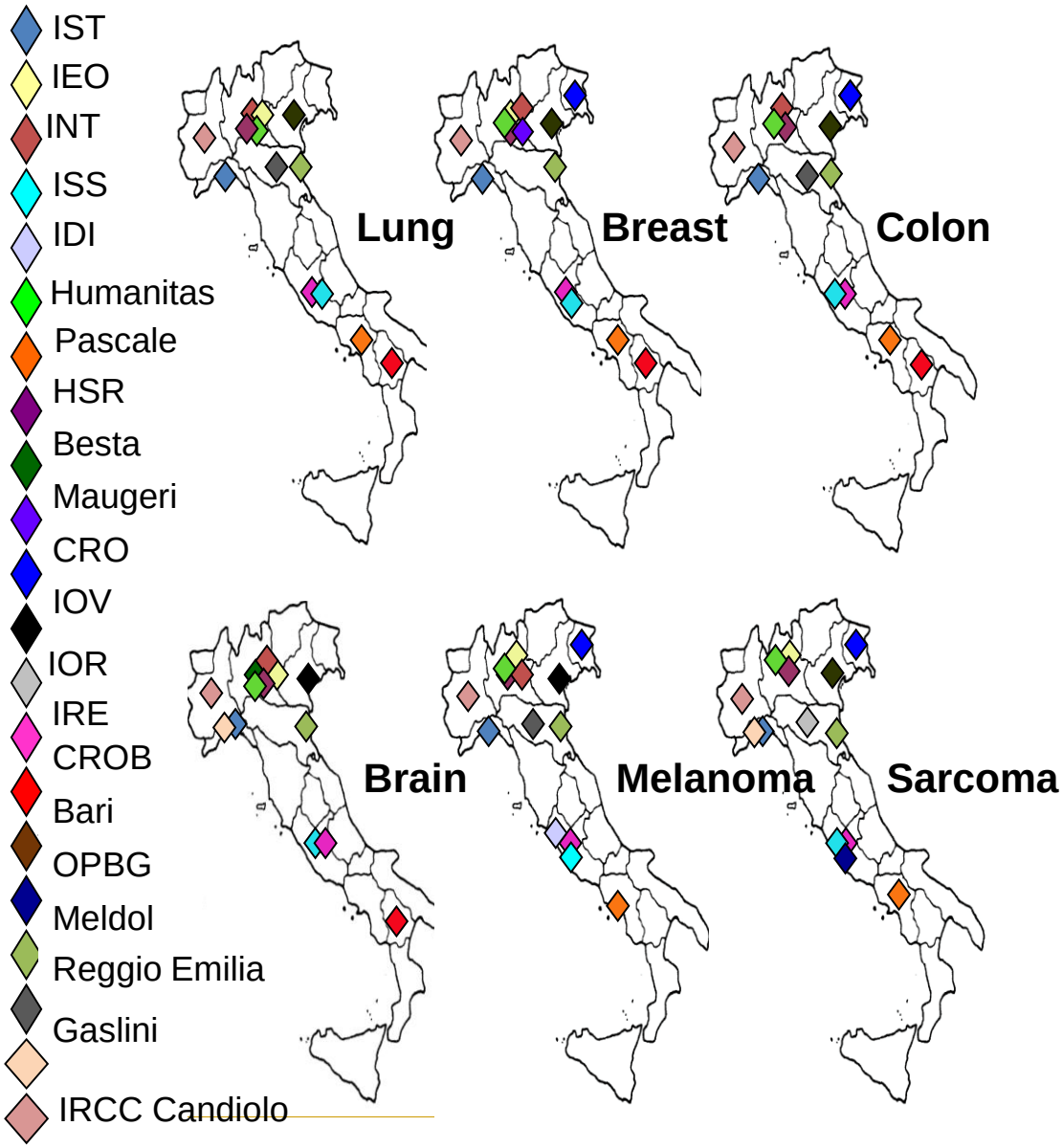
Alleanza Contro il Cancro (ACC)
21 IRCCS – Ministry of Health

Established by the Ministry of Health and ISS for

- **Promotion of active scientific collaborations among Italian cancer institutes/associations**
- **building of the Italian and European strategy in oncology, at the level of patient treatment and research**

Alleanza Contro il Cancro (ACC): struttura





IL PROGETTO ACC LUNG

The ACC Lung-Oncochip

1. Genes (all coding sequence)

Total: 182
Actionables: 164
Drivers: 33

2. Translocations (RNA)

- 139 Translocations
- 70 Actionables
- 69 Drivers

3. Amplifications/Deletions

- Known actionable/driver CNVs
- The 182 genes of the Chip

4. Germline Variants

- Identified in the pharmGKB data base
- 86 genes, 141 variants

Proposal

Primary Objective:

to validate the ACC - Lung Panel as a tool for molecular screening in patients with NSCLC

Comparison between the frequency of EGFR activating mutations and EML4-ALK translocation observed with NGS and routinary techniques (sensitivity and specificity)

Secondary Objectives:

1. To determine the percentage of enrolled NSCLC patients with an adequate amount of tissue to perform NGS —> (at least ≥ 70%)

   Evaluation of those critical issues that have determined an unsuccessful diagnosis for molecular testing

2. To investigate the **percentage of cases evaluated by NGS**—> (at least ≥ 90%)

3. To evaluate the frequency of the oncogenic alterations identified by NGS in **comparison with the data from literature**

Secondary Objectives:

4. To evaluate the proportion of patients carrying mutations, for which an **approved targeted therapy** is available, according to National and International Guidelines, that have received the recommend therapy —> (at least ≥ 90%)

5. To evaluate the performance of **each center** in terms of sensitivity, specificity and percentage of successful molecular characterization by NGS

6. To measure the **time interval** needed to obtain the molecular results (4 weeks from the first patient's visit to the biopsy, 10 working days from the initiation of molecular analysis to the final written report)

7. To measure **OS** and **PFS**

Proposal

Inclusion criteria:

- All consecutive patients with histological or cytological diagnosis of advanced (Stage IIIB/IV) NSCLC, seen at each center during the study period, will be included and considered in all analyses
- ECOG PS 0-2
- Written Informed Consent

Patients with inadequate amount of tissue or cytological specimen only should be screened at least for EGFR activating mutations and EML4-ALK

Patients with adequate amount of tissue for NGS remain eligible

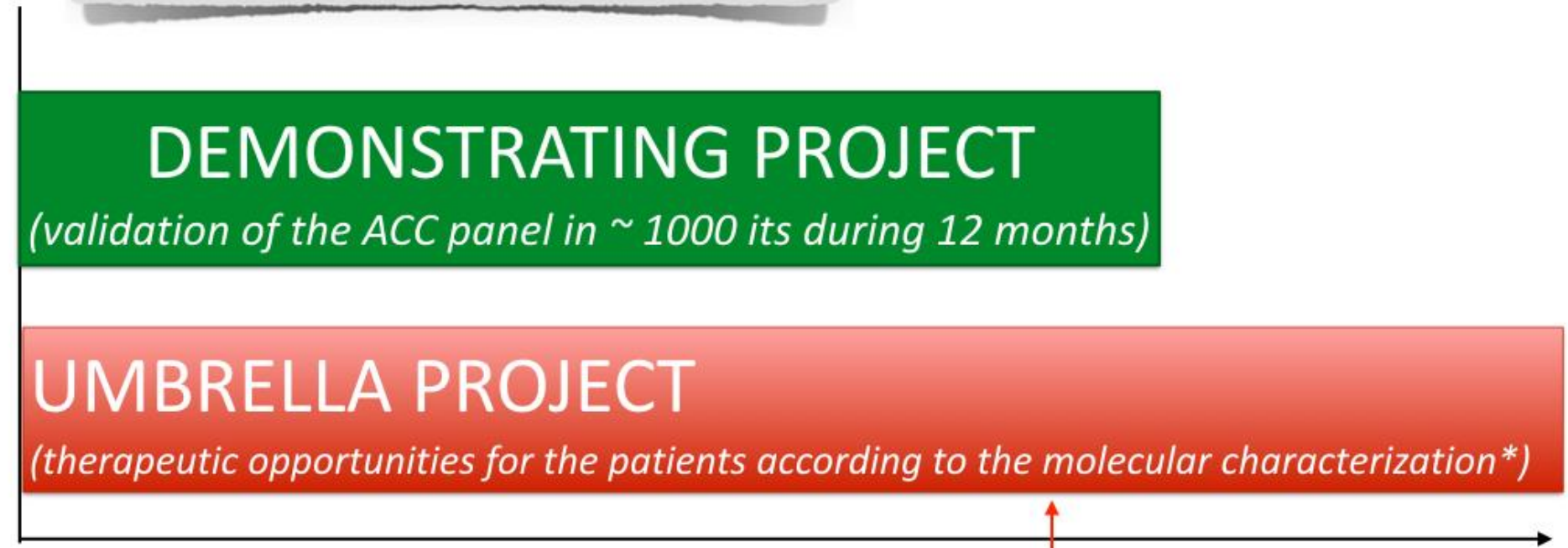
Proposal

DEMONSTRATING PROJECT

(validation of the ACC panel in ~ 1000 its during 12 months)

UMBRELLA PROJECT

(therapeutic opportunities for the patients according to the molecular characterization)*

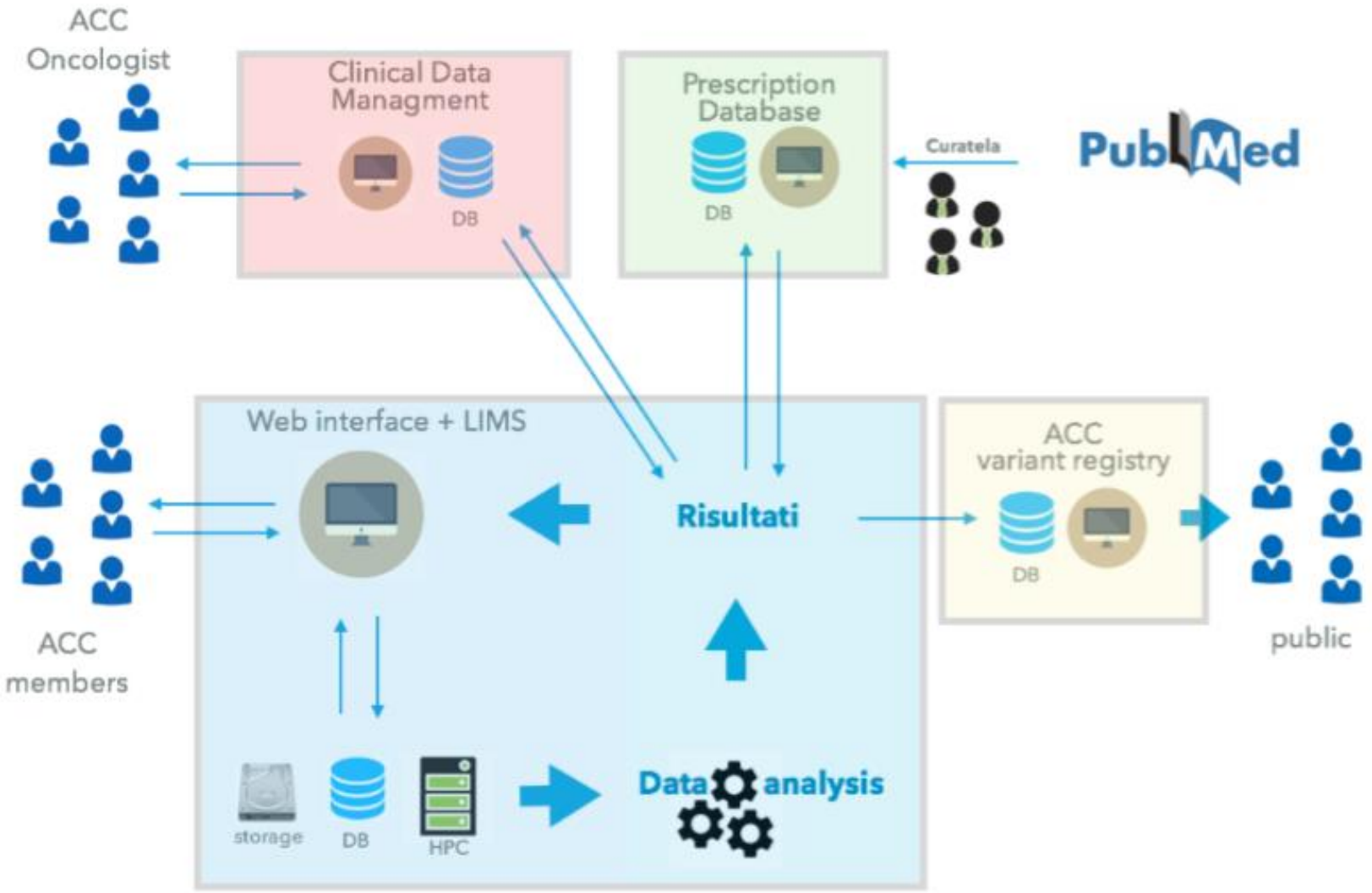


Collaboration with different partners:

- *Academy*
- *Research Hospital within the National System*
- *Pharma*
- *AIFA*

** treatment based on National Guidelines or study protocols, that will be objective of amendments*

La struttura bioinformatica di ACC



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GRAZIE DELL'ATTENZIONE