Associazione Giuseppe Dossetti
"La Terapia Personalizzata"

Terapia Personalizzata

Il Laboratorio applicato alla Clinica

Giampaolo Tortora

Cattedra di Oncologia Medica e
UOC di Oncologia Medica
Facoltà di Medicina e Chirurgia e
Azienda Ospedaliera Universitaria Integrata
Verona

Selected target therapeutics in the routine oncology practice		
Targeted therapeutics	**Target**	**Tumor**
Antibodies		
Trastuzumab	Her-2	Breast Ca
Rituximab	CD20	B-Cell Lymphoma
Cetuximab		& HN Ca
Bevacizu		C
Pa		
S		
Imat		
Gefitinib		
Erlotinib		NSCLC & Pancreatic Ca
Lapatinib	Her-2 & EGFR	Breast Ca
Sorafenib	VEGFRs/PDGFR/RAF	HCC & RCC
Sunitinib	VEGFRs/PDGFR/RET	RCC & GIST
Tensirulimus / Everolimus	mTOR	RCC
Bortezomib	Proteasome	MM & MCL
VorinostatBortezomib	HDAC	Cutaneous TCL

Drugs in the pipeline in 2010 = 850

Source – AACR 2010 internal statistics

From: Quek, Yan, Yong and Salto-Tellez. *Personalized Medicine* (2009) 6(5),465-468

Economic evaluation of new targeted therapie for the first-line treatment of patients with metastatic renal cell carcinoma

Ágnes Benedict, Robert A. Figlin*, Per Sandström†, Ulrika Harmenberg†, Anders Ullén†, Claudie Charbonneau†¶, Rickard Sandin§, Edit Remák, Subramanian Hariharan¶ and Sylvie Négrier**

Cost and effectiveness results for sunitinib, sorafenib and bevacizumab + IFN-α

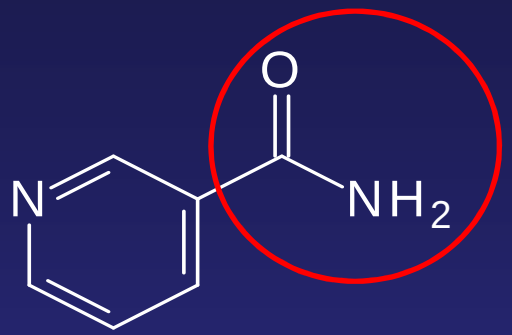
	Overall patient population			
US	**Total costs ($)**	**PFLY**	**LY**	**QALY**
Sunitinib	369 346.80	1.346	2.900	1.876
Sorafenib	382 922.67	0.826	2.743	1.706
Bevacizumab + IFN-α	437 144.46	1.152	2.670	1.714
Sweden	**Total costs ($)**	**PFLY**	**LY**	**QALY**
Sunitinib	167 950.66	1.346	2.900	1.862
Bevacizumab + IFN-α	215 214.66	1.152	2.670	1.703

PFLY, progression-free life years; LY, life years; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio (cost per QALY).

BJU Int 2011

Structures of PARP Inhibitors

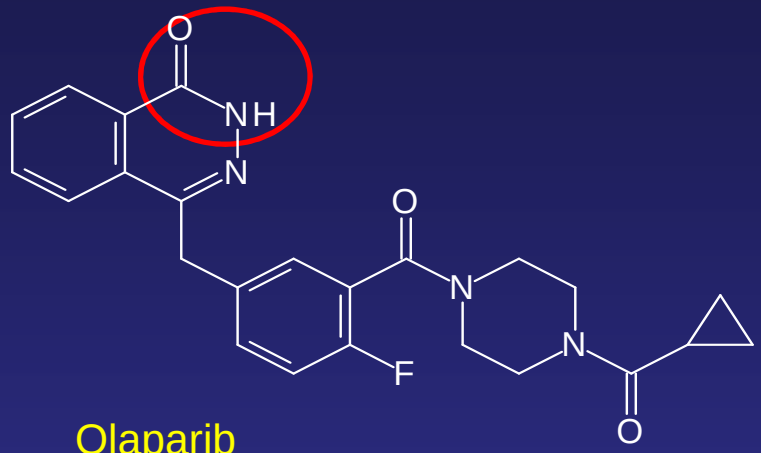
Courtesy of Hilary Calvert



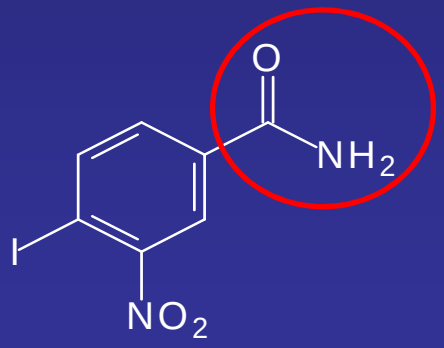
Nicotinamide
Component of NAD



AG014699
Agouron/Pfizer

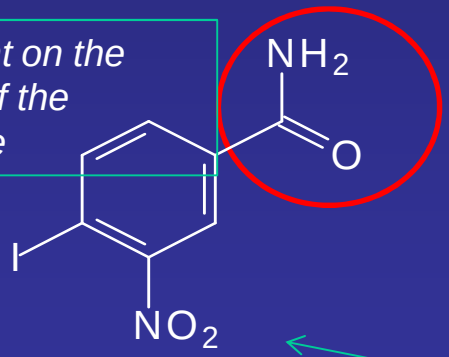


Olaparib
AstraZeneca



Iniparib
BSI 201
Bipar / Sanofi-Aventis

No constraint on the orientation of the carboxamide



Iniparib
BSI 201
Bipar / Sanofi-Aventis

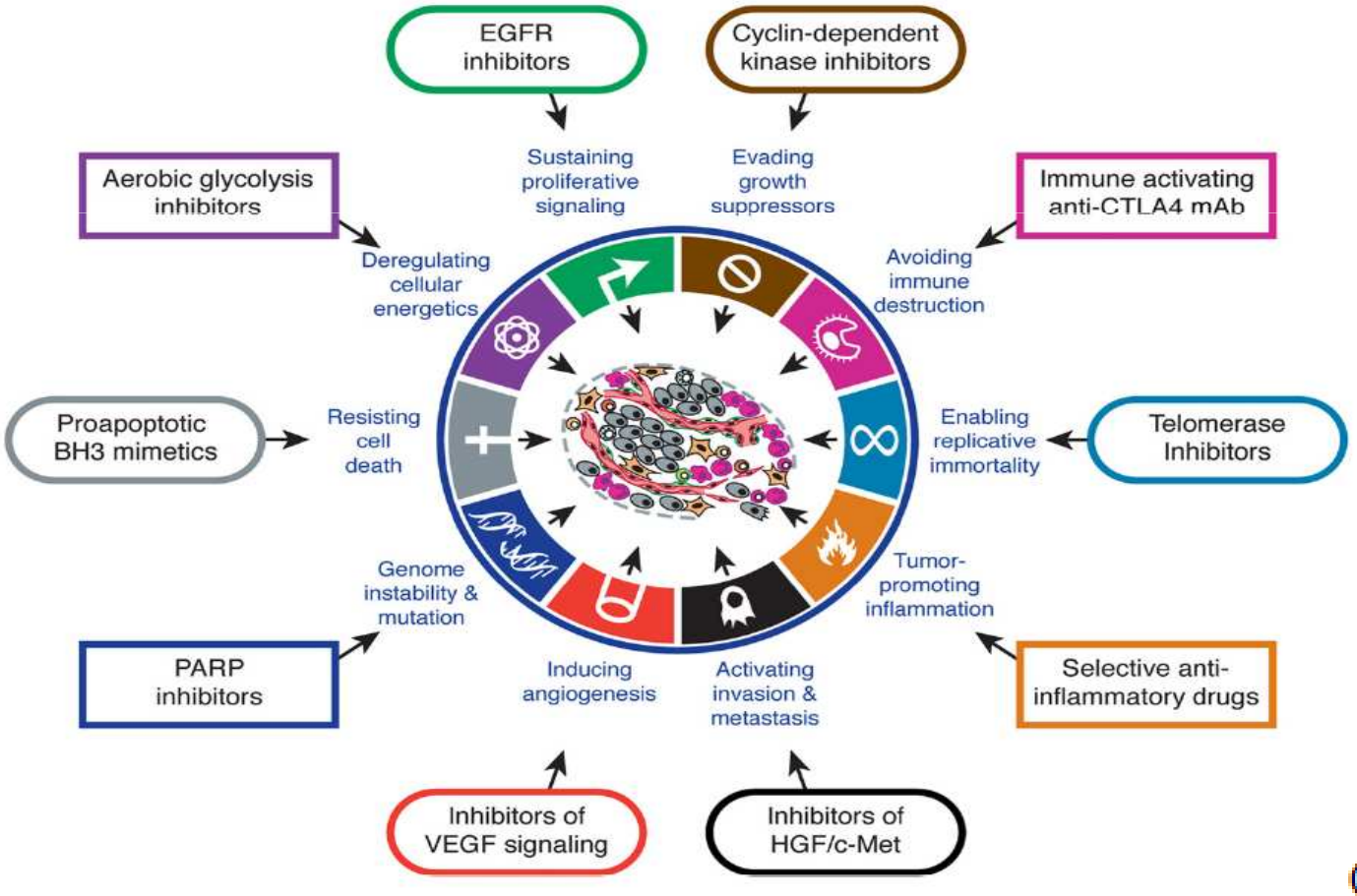
Iniparib is not a PARP Inhibitor

Site for metabolism to a reactive substituent

L’era post genomica e le terapie “targeted”

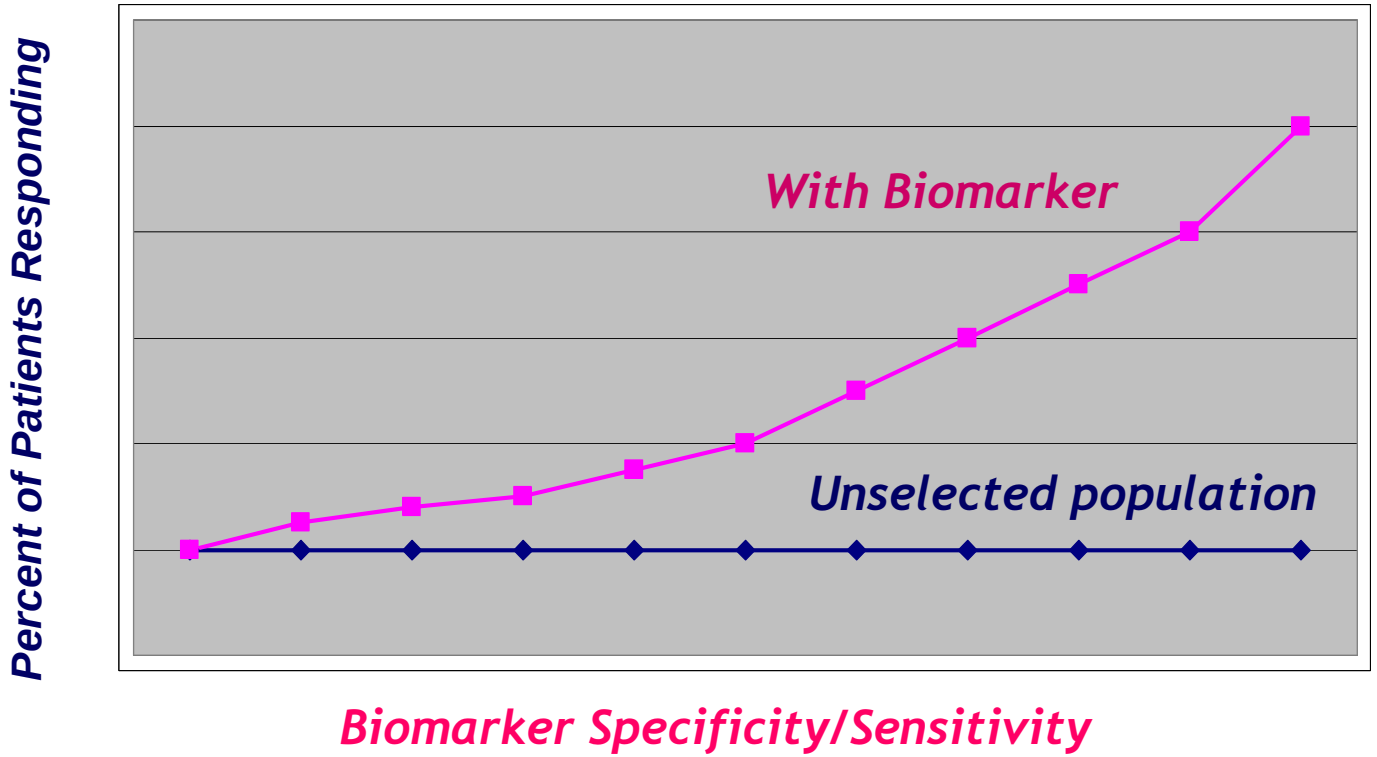
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]



Cell *144*, March 4, 2011

Patient Stratification & Biomarker Development

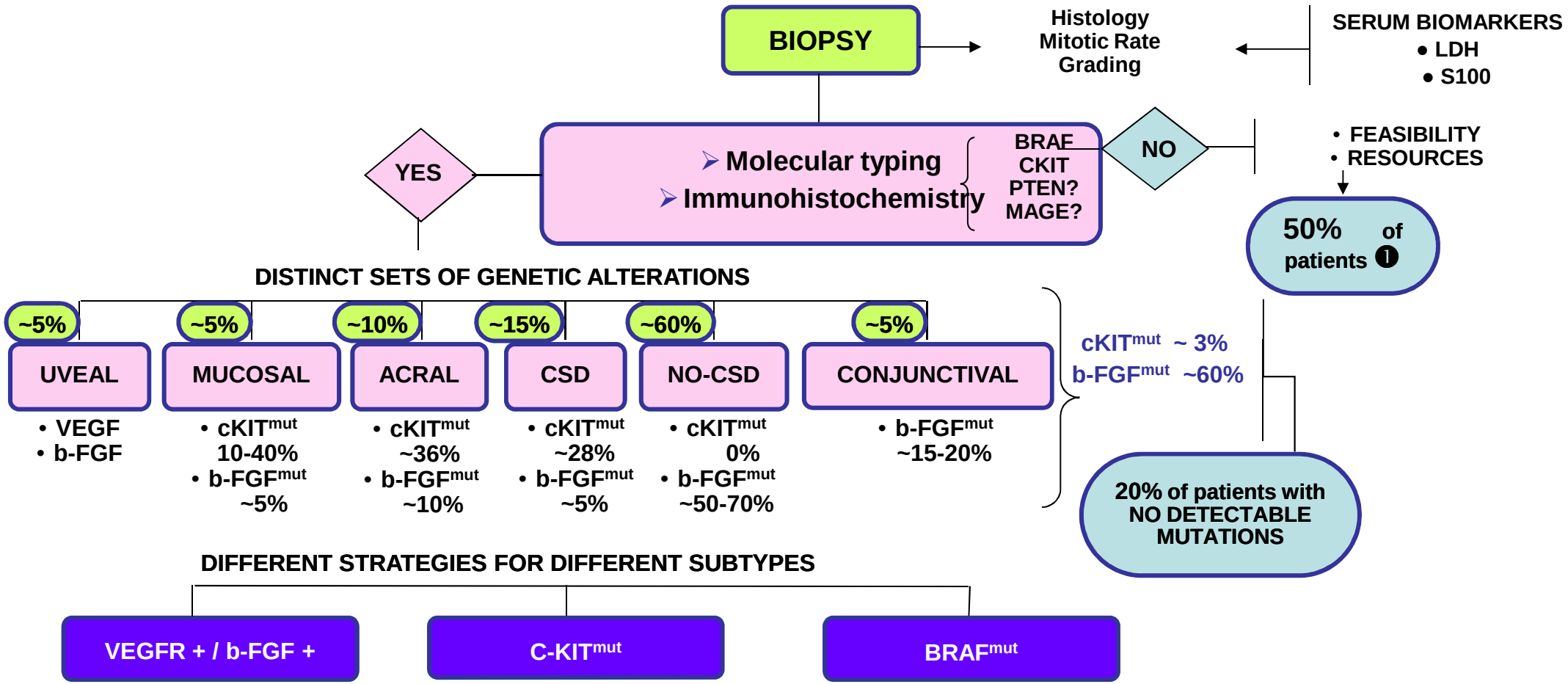


Stratification biomarkers used to enrich clinical trials

- **Increase responder population**
- **Reduce size, time & cost**
- **Improve overall results of clinical trials**

David Cunningham, Royal Marsden Hospital

Future Metastatic Melanoma Patient Flow

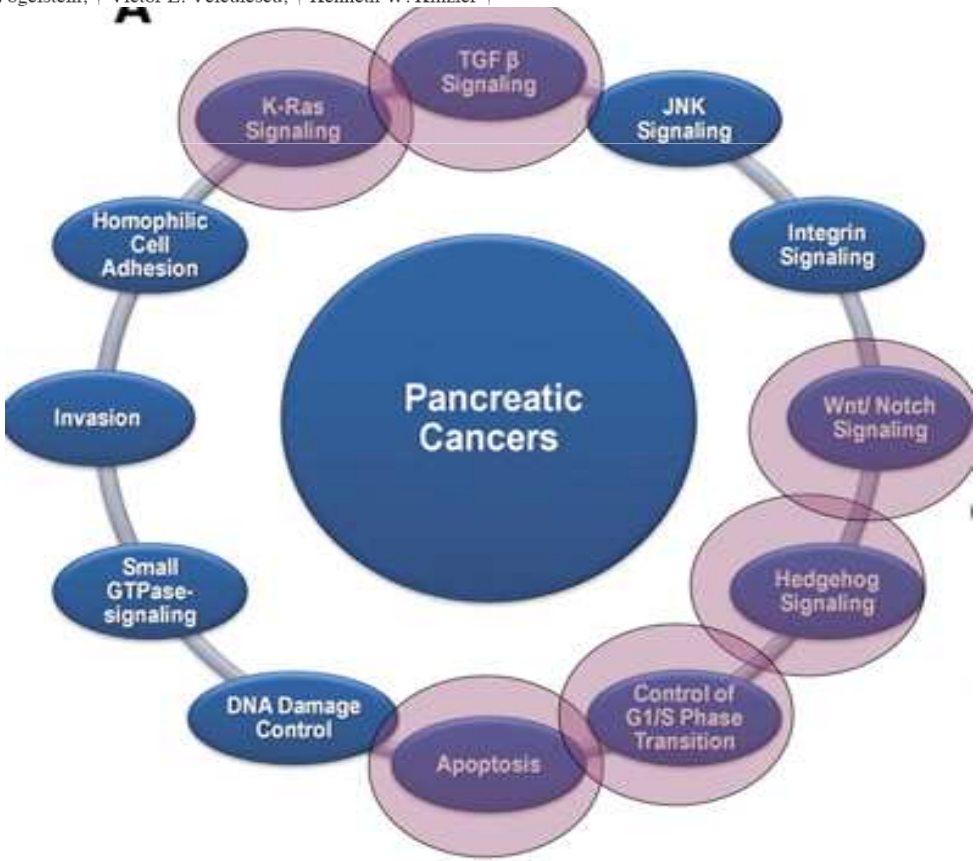


Alcune patologie neoplastiche però hanno meccanismi patogenetici diversi

Sciencexpress Research Article

Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses

Siân Jones,[1]* Xiaosong Zhang,[1]* D. Williams Parsons,[1,2]* Jimmy Cheng-Ho Lin,[1]* Rebecca J. Leary,[1]* Philipp Angenendt,[1]* Parminder Mankoo,[3] Hannah Carter,[3] Hirohiko Kamiyama,[4] Antonio Jimeno,[1] Seung-Mo Hong,[4] Baojin Fu,[4] Ming-Tseh Lin,[4] Eric S. Calhoun,[1] Mihoko Kamiyama,[4] Kimberly Walter,[4] Tatiana Nikolskaya,[5] Yuri Nikolsky,[6] James Hartigan,[7] Douglas R. Smith,[7] Manuel Hidalgo,[1] Steven D. Leach,[1,8] Alison P. Klein,[1,4] Elizabeth M. Jaffee,[1,4] Michael Goggins,[1,4] Anirban Maitra,[1,4] Christine Iacobuzio-Donahue,[1,4] James R. Eshleman,[1,4] Scott E.Kern,[1,4] Ralph H. Hruban,[1,4] Rachel Karchin,[3] Nickolas Papadopoulos,[1] Giovanni Parmigiani,[1,9] Bert Vogelstein,[1]† Victor E. Velculescu,[1]† Kenneth W. Kinzler[1]†



EGFR pathway and Biliary Tract Cancers

	Gallbladder	Cholangiocarcinoma	
		Extra-hepatic	Intra-hepatic
KRAS (%)	3-38	10-15	48-54
BRAF (%)	33	0	22
EGFR (%)	9-12	5-18	10-20
PI3KCA (%)	4	0	9
HER2 (%)	16	5	0

Hezel JCO 2010

Treatment	Target	No.	RR (%)	PFS
GEMOX		50	NA	44 % (4 months)
GEMOX-cetux	EGFR	51	NA	61% (4 months)
GEMOX-bev	VEGF	35	NA	7 months
AZD6244	MEK1/2	22	14	5.4 months
Erlotinib	EGFR	43	7	2.6 months
Lapatinib	EGFR/HER2	17	0	1.8 months
Sorafenib	BRAF/VEGFR	36	6	2 months
Sorafenib	BRAF/VEGFR	46	2	2.3 months



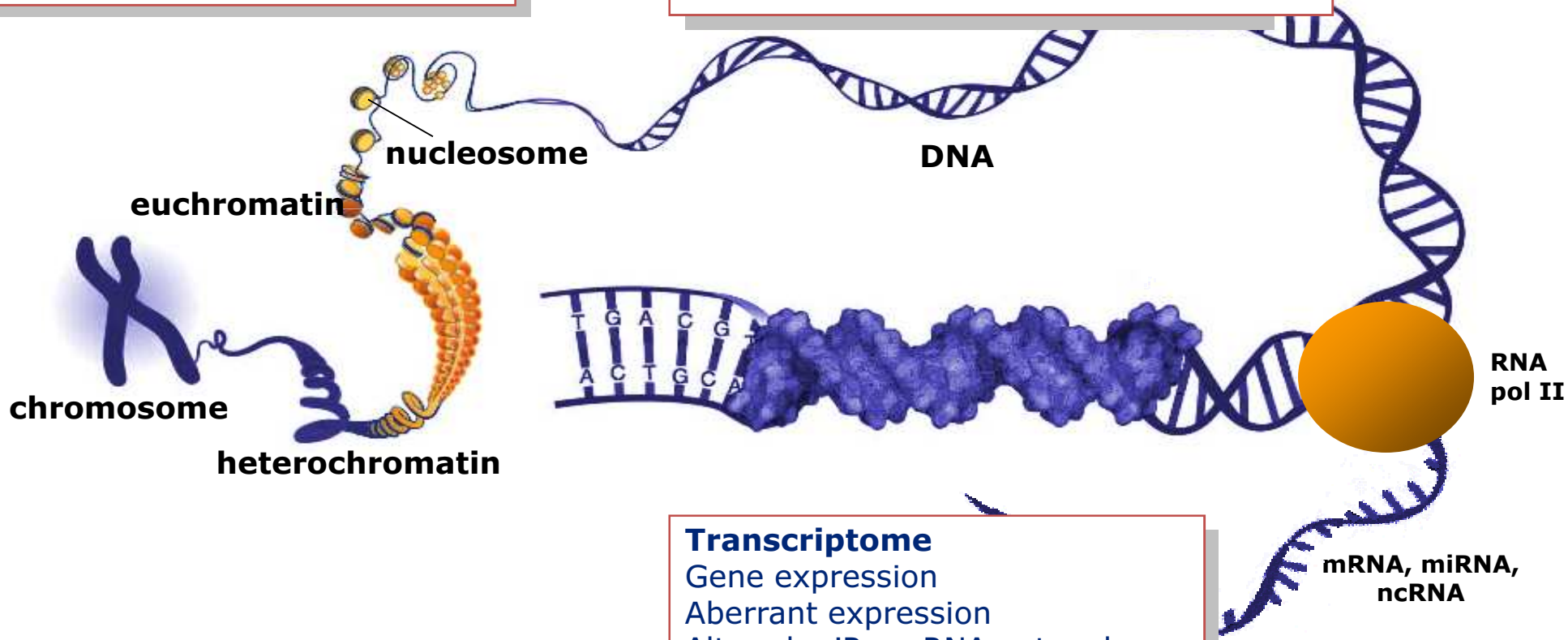
Obiettivi della Ricerca sul Genoma del Cancro

- **Identificare nel genoma dei tumori alterazioni responsabili della progressione tumorale**
- **Identificare nuovi bersagli terapeutici**
- **Selezionare farmaci basati sulle caratteristiche genomiche dei tumori**

Cancer is a genetic disease

Epigenome
Changes in DNA methylation
Histone modifications
Chromosomal instability

Genome
Chromosomal Organization
Copy Number Variation
Gene Fusion Event
Single Nucleotide Polymorphism
Small Insertions/deletions



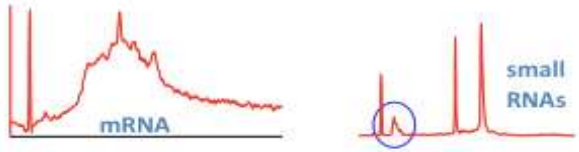
Transcriptome
Gene expression
Aberrant expression
Altered miR –mRNA networks
Gene fusions
Expressed SNPs and mutations



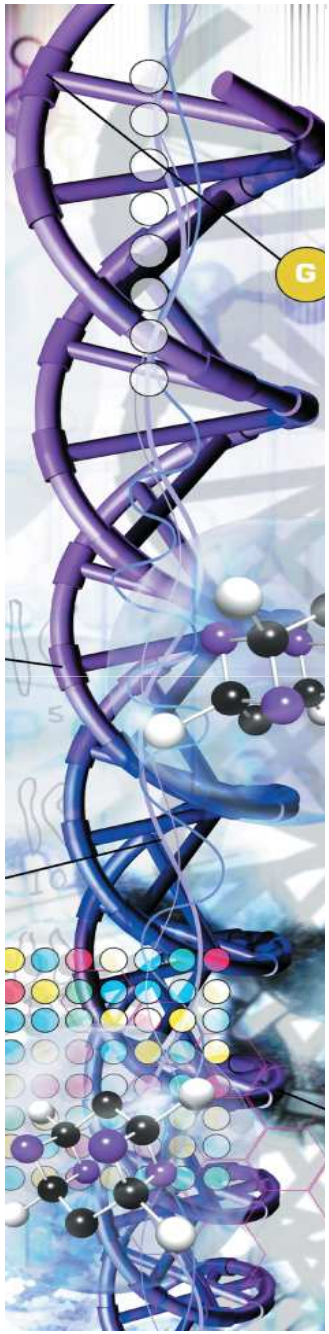
Sequencing Strategy







Genome	Exome	Transcriptome
		
SNP/CNV Chip analysis, gDNA sequencing	Agilent Sure select, exome sequencing	Expression array, mRNAseq, miRNAseq
Tumor tissue & normal 30 fold (75Gb)	Tumor tissue & normal >100 fold (5Gb)	Tumor tissue & adjacent normal ~100million reads (5Gb)



International Cancer Genome Consortium

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Cancer Genome Projects | Committees | Policies and Guidelines | Media | Contacts

International Cancer Genome Consortium

Brain Cancer
United States

Breast Cancer
European Union / United Kingdom

Breast Cancer
France

Breast Cancer
United Kingdom

Chronic Lymphocytic Leukemia
Spain

Colon Cancer
United States

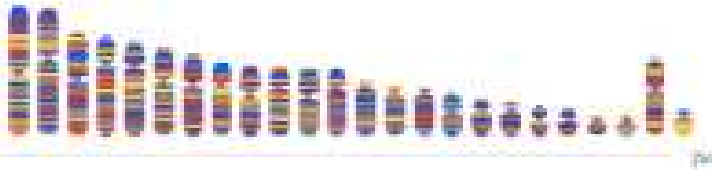
Gastric Cancer
China

Leukemia
United States

Liver Cancer
France

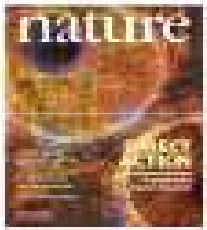
Liver Cancer
Japan

Lung Cancer
United States



[show]

ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.



International network of cancer genome projects. Nature 464: 993-998 (15 April 2010)

HTML

ICGC Public Presentation April 15, 2010 : PDF | PPT

International Cancer Genome Consortium (ICGC) Goals, Structure, Policies and Guidelines : HTML | PDF



Members of the ICGC

Committed Projects to date: 23

Lung Cancer
United States

Malignant Lymphoma
Germany

Oral Cancer
India

Ovarian Cancer
Australia

Ovarian Cancer
United States

Pancreatic Cancer
Australia

Pancreatic Cancer
Canada

Pediatric Brain Tumors
Germany

Prostate Cancer
Canada

Prostate Cancer
Germany

Rare Pancreatic Tumors
Italy

Renal Cancer
European Union / France

Policies and Guidelines
International Cancer Genome Consortium

Access to Data
Data Coordination Center

Apply for Access to Controlled Data
Data Access Compliance Office

Info@icgc.org | Contacts

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Last updated on: 12 May 2010

ICGC

International Cancer Genome Consortium

Sequenziamento del genoma di 12.000 tumori



Sequenziamento del genoma di 250 tumori del pancreas

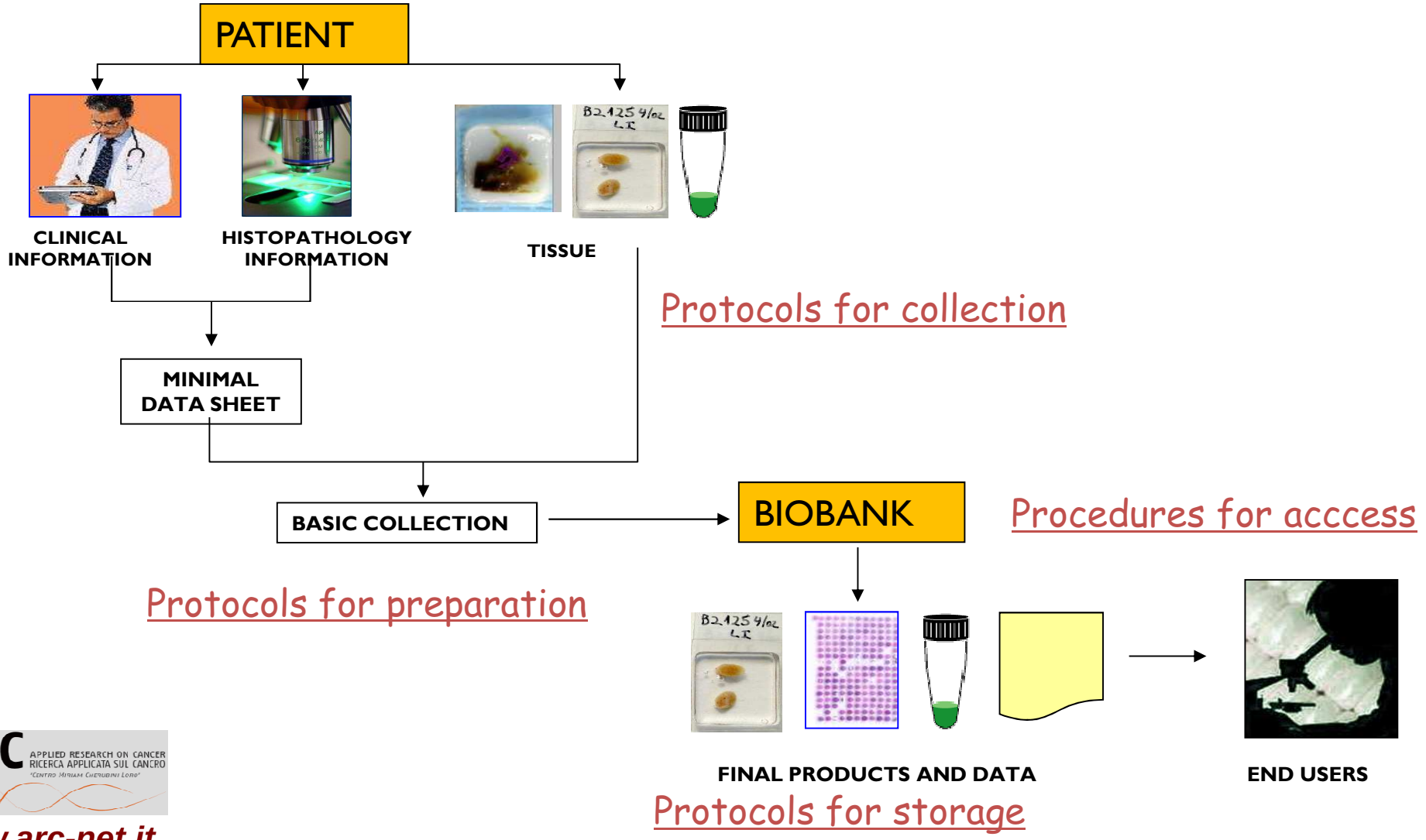
ARC NET APPLIED RESEARCH ON CANCER RICERCA APPLICATA SUL CANCRO 'CENTRO MIRIAM CHERUBINI LORO'

Il Centro di Ricerca ARC-NET e' il capofila dell'iniziativa Italiana

www.arc-net.it

Sample quality matters

Standard Operating Procedures



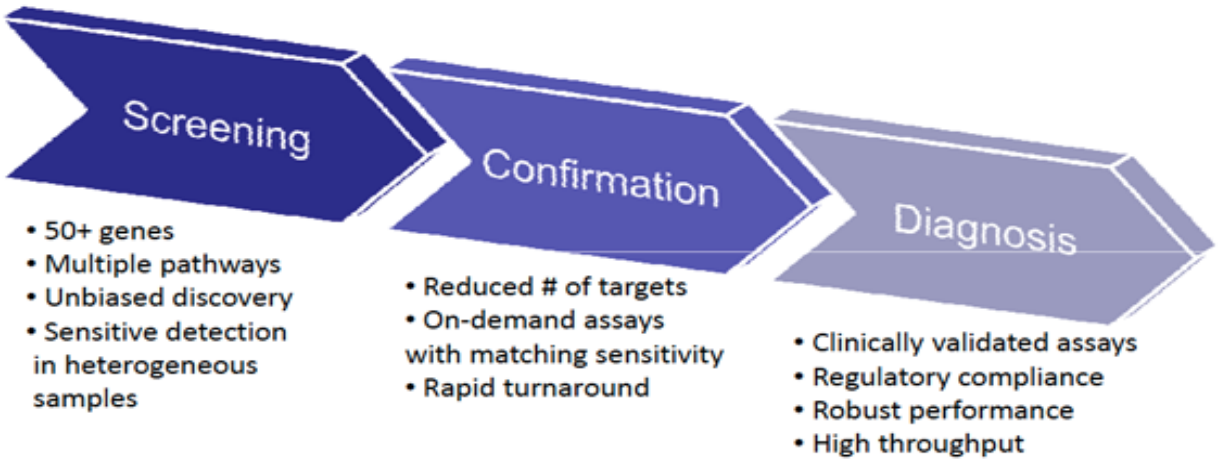
ARC NET APPLIED RESEARCH ON CANCER RICERCA APPLICATA SUL CANCRO 'CENTRO MIRIAM CHERUBINI LORO'

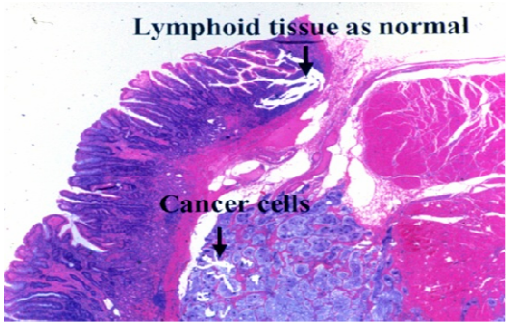
www.arc-net.it

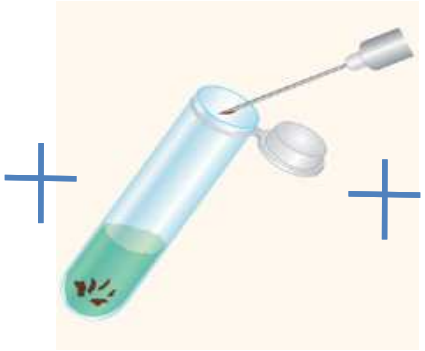
La diagnostica molecolare di domani

Abbiamo bisogno di nuovi strumenti capaci di :

- **ricavare tutte le informazioni genetiche dai tessuti in numeri elevati di casi**
- **avere tempi e costi adeguati**

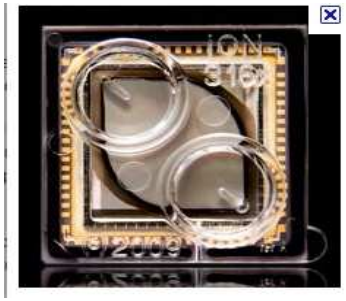








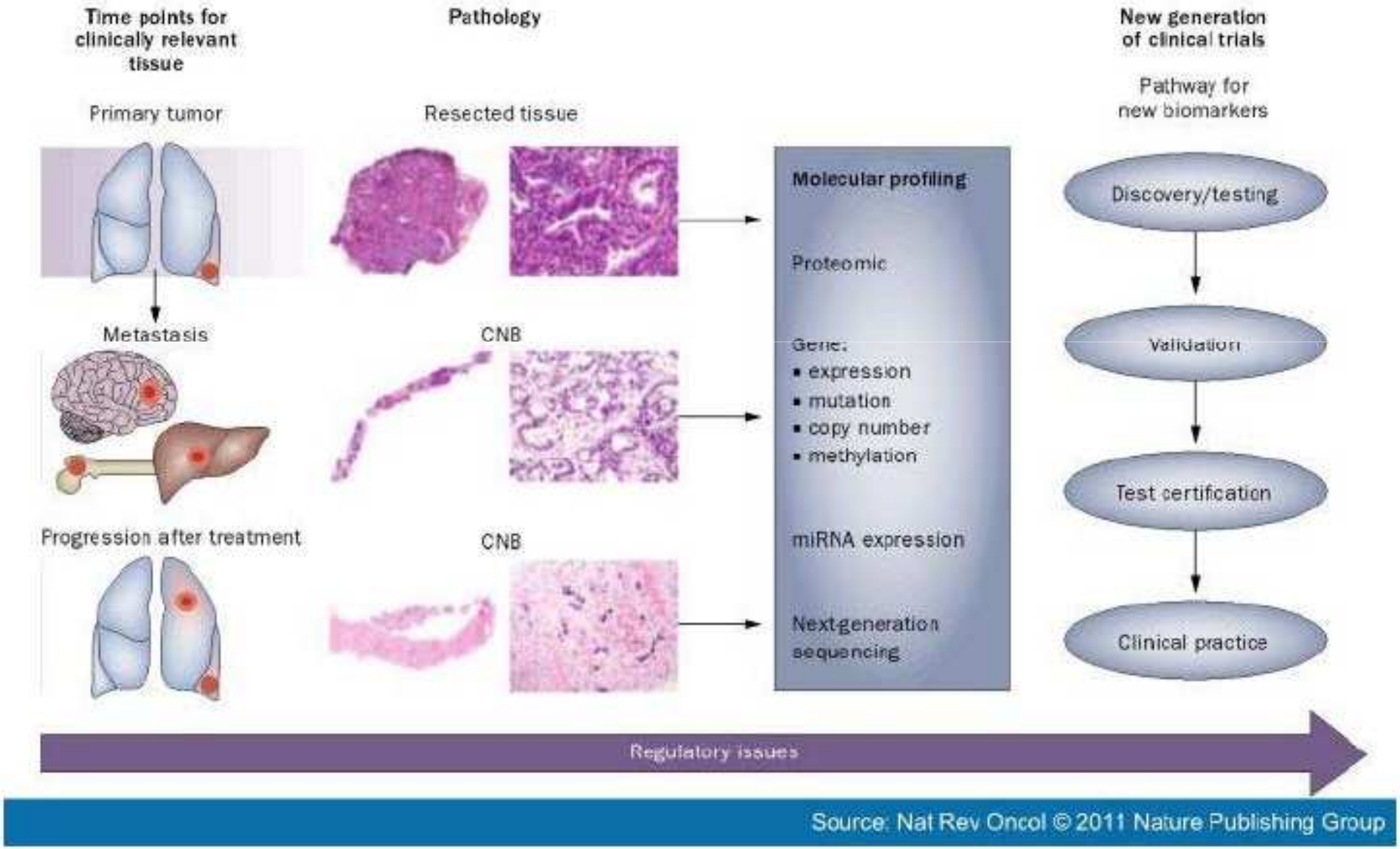
Next Generation Sequencing of Cancer-Associated Genes in FFPE DNA





Multigene panel
10 cases per week = 400 cases/year

New generation clinical trials



Source: Nat Rev Oncol © 2011 Nature Publishing Group

Problematiche e nuovi scenari

- **Piccole percentuali di pazienti ma con elevata possibilità di risposta.**
- **Estensione d'uso a patologie diverse da quelle in indicazione se sono presenti le alterazioni molecolari bersaglio per i farmaci.**
- **Durata dei trattamenti: tossicità, costi ecc.**
- **Utilizzo di nuove tecnologie e diagnostica per immagini per ridurre tossicità e costi**

LE SFIDE DELL'ERA DELLE TERAPIE TARGETED

Attualmente sono in fase di sviluppo circa 800 farmaci antitumorali

- **Molti (troppi ?) farmaci**
- **Sempre più malattie in cui utilizzarli**
- **Maggiore uso di controlli con placebo**
- **Maggiore impiego di trial clinici randomizzati**
- **Più tempo per raggiungere gli endpoints**
- **Più linee di terapia efficaci**
- **Documentazioni più costose**
- **Maggiore complessità delle norme "regolatorie"**

Modificata da Schilsky RL. Nature Rev. Drug Discovery 9, 363-366, 2010.