Plataforma de Mercados Biotecnológicos

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

NANOMED SPAIN

PLATAFORMA ESPAÑOLA INNOVACIÓN TECNOLOGÍA SANITARIA

IX Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica

Nuevos Retos en Investigación Biomédica

asebio

farmaindustria

federación española de empresas de TECNOLOGÍA SANITARIA

Las plataformas de Medicamentos Innovadores, Nanomedicina, Tecnología Sanitaria y Mercados Biotecnológicos cuentan con apoyo financiero del Ministerio de Economía y Competitividad

Nuevos retos en la Investigación en Oncología

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VHIO VALL D'HEBRON Institute of Oncology

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Where are we now?

Where are we now?

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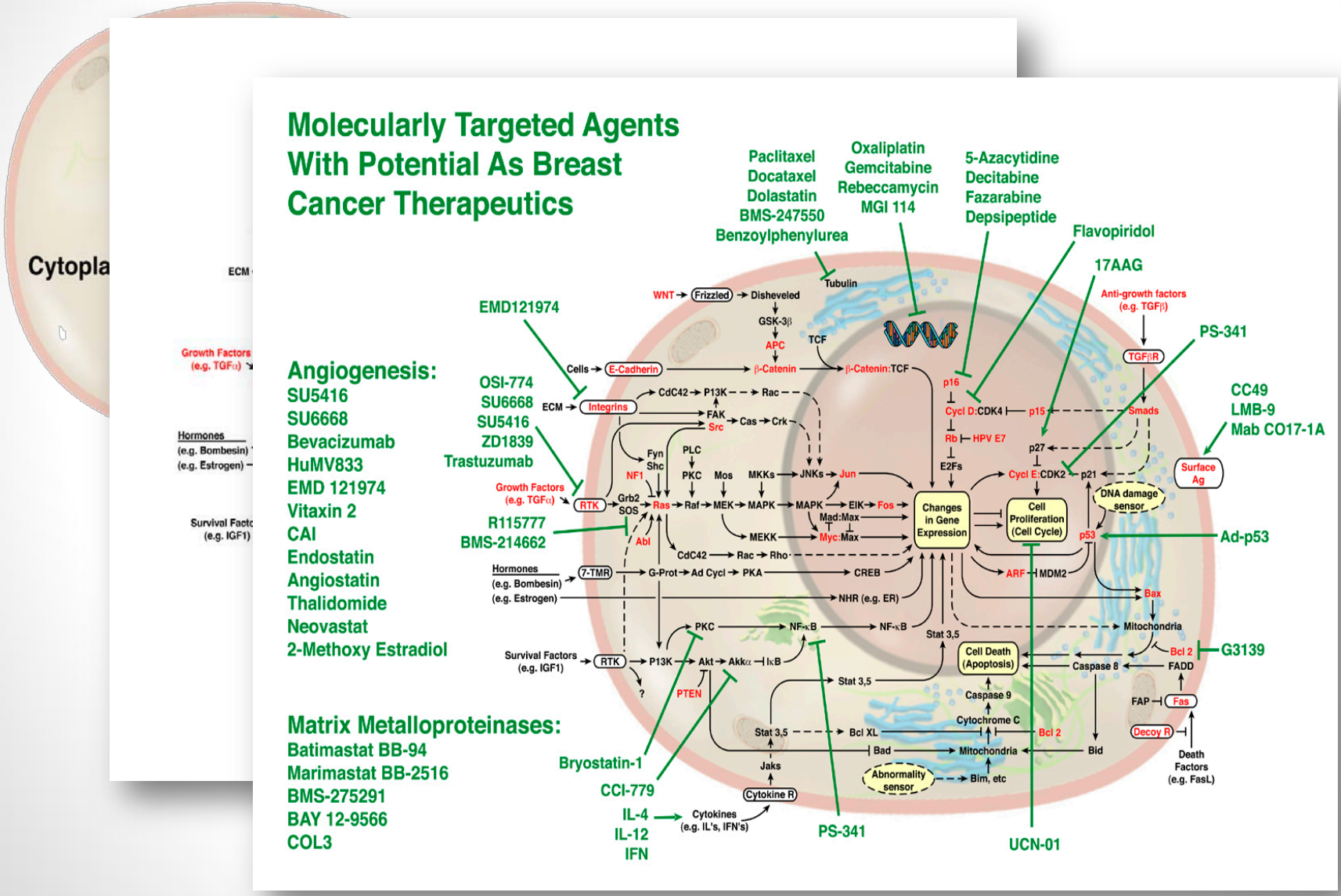
From biology to target and from target to drug



Where are we now?

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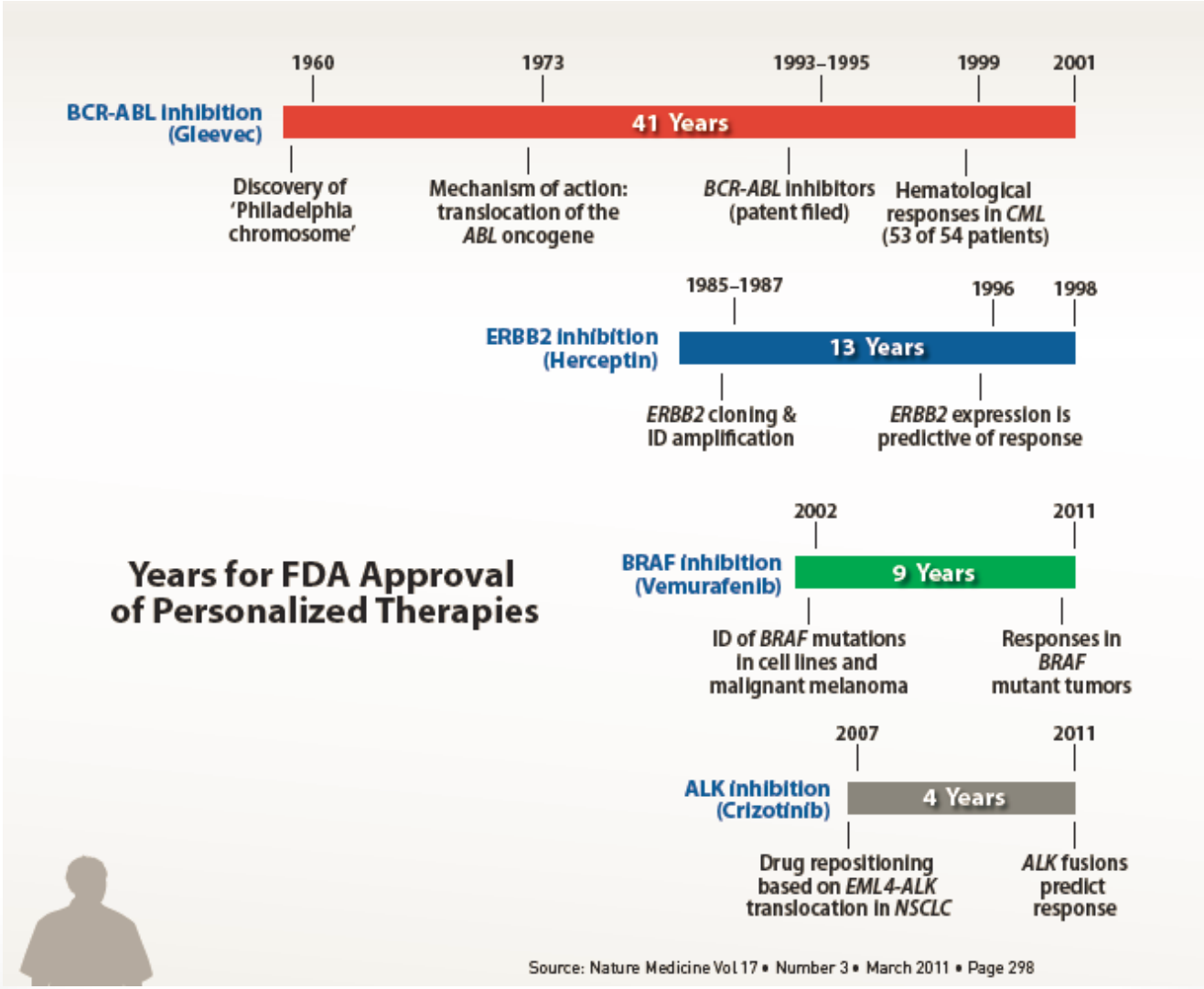
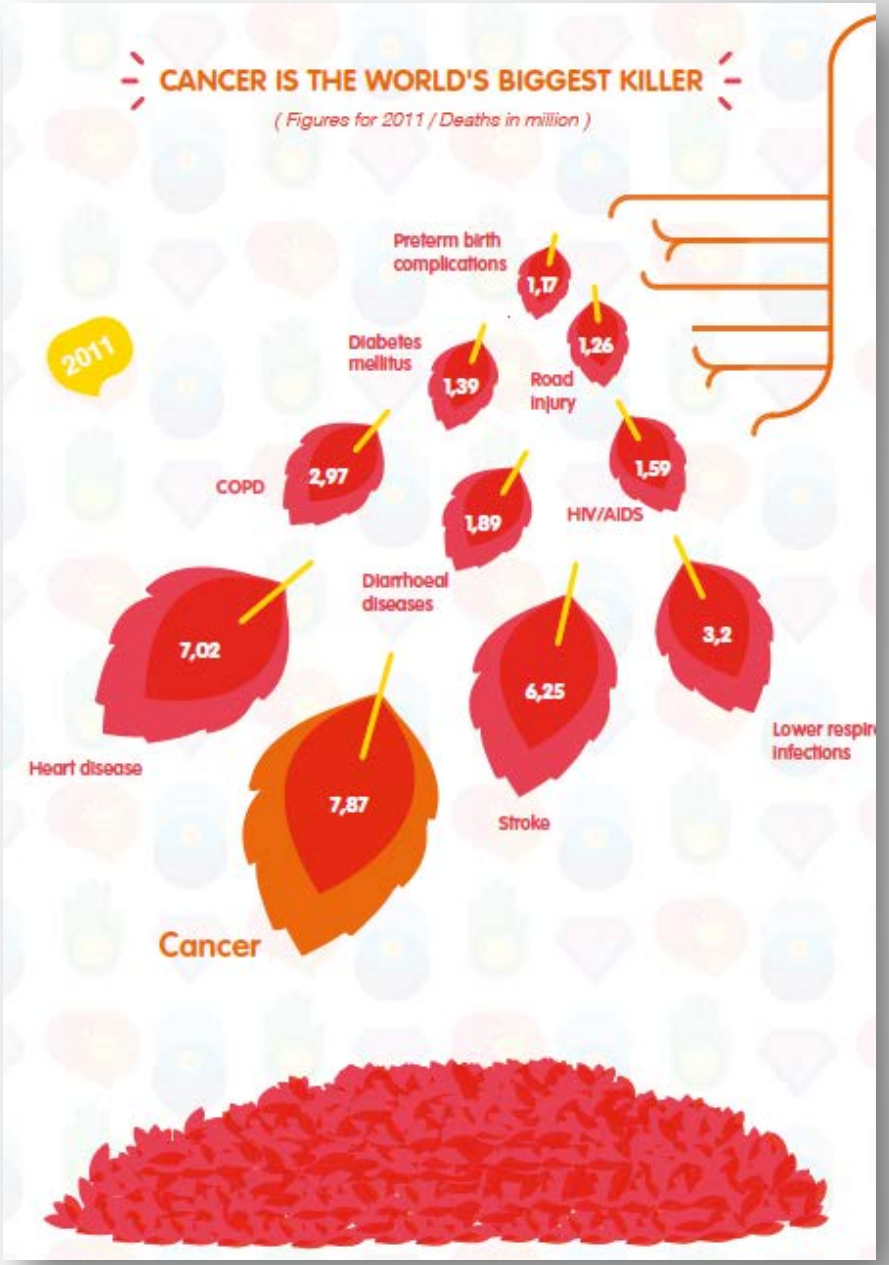
Target Discovery to Drug approval



ESTIMATED INCIDENCE AND MORTALITY FOR SELECT CANCERS

	ESTIMATED 2015 INCIDENCE			ESTIMATED 2015 DEATHS		
	Total	Male	Female	Total	Male	Female
ALL SITES	1,658,370	848,200	810,170	589,430	312,150	277,280
HEAD AND NECK REGION						
Brain & other nervous system	22,850	12,900	9,950	15,320	8,940	6,380
Oral cavity & pharynx	45,780	32,670	13,110	8,650	6,010	2,640
Tongue	14,320	10,310	4,010	2,190	1,500	690
Mouth	12,920	7,750	5,170	2,120	1,200	920
Pharynx	15,520	12,380	3,140	2,660	2,010	650
Larynx	13,560	10,720	2,840	3,640	2,890	750
Lung & bronchus	221,200	115,610	105,590	158,040	86,380	71,660
Breast	234,190	2,350	231,840	40,730	440	40,290
GASTROINTESTINAL SYSTEM						
Esophagus	16,980	13,570	3,410	15,590	12,600	2,990
Stomach	24,590	15,540	9,050	10,720	6,500	4,220
Liver & intrahepatic bile duct	35,660	25,510	10,150	24,550	17,030	7,520
Gallbladder & other biliary	10,910	4,990	5,920	3,700	1,660	2,040
Pancreas	48,960	24,840	24,120	40,560	20,710	19,850
Small intestine	9,410	4,960	4,450	1,260	670	590
Colon and rectum†	93,090	45,890	47,200	49,700	26,100	23,600
UROGENITAL SYSTEM						
Kidney & renal pelvis	61,560	38,270	23,290	14,080	9,070	5,010
Ovary	21,290		21,290	14,180		14,180
Uterine corpus	54,870		54,870	10,170		10,170
Uterine cervix	12,900		12,900	4,100		4,100
Urinary bladder	74,000	56,320	17,680	16,000	11,510	4,490
Prostate	220,800	220,800		27,540	27,540	
Testis	8,430	8,430		380	380	
SKIN						
Skin (excluding basal & squamous)	80,100	46,610	33,490	13,340	9,120	4,220
Melanoma	73,870	42,670	31,200	9,940	6,640	3,300
HEMATOLOGICAL SYSTEM						
Leukemia	54,270	30,900	23,370	24,450	14,210	10,240
Acute lymphocytic leukemia	6,250	3,100	3,150	1,450	800	650
Chronic lymphocytic leukemia	14,620	8,140	6,480	4,650	2,830	1,820
Acute myeloid leukemia	20,830	12,730	8,100	10,460	6,110	4,350
Chronic myeloid leukemia	6,660	3,530	3,130	1,140	590	550
Lymphoma	80,900	44,950	35,950	20,940	12,140	8,800
Hodgkin lymphoma	9,050	5,100	3,950	1,150	660	490
Non-Hodgkin lymphoma	71,850	39,850	32,000	19,790	11,480	8,310
Myeloma	26,850	14,090	12,760	11,240	6,240	5,000
OTHER CANCERS						
Bones & joints	2,970	1,640	1,330	1,490	850	640
Soft tissue (including heart)	11,930	6,610	5,320	4,870	2,600	2,270



And yet...

Where are we now?

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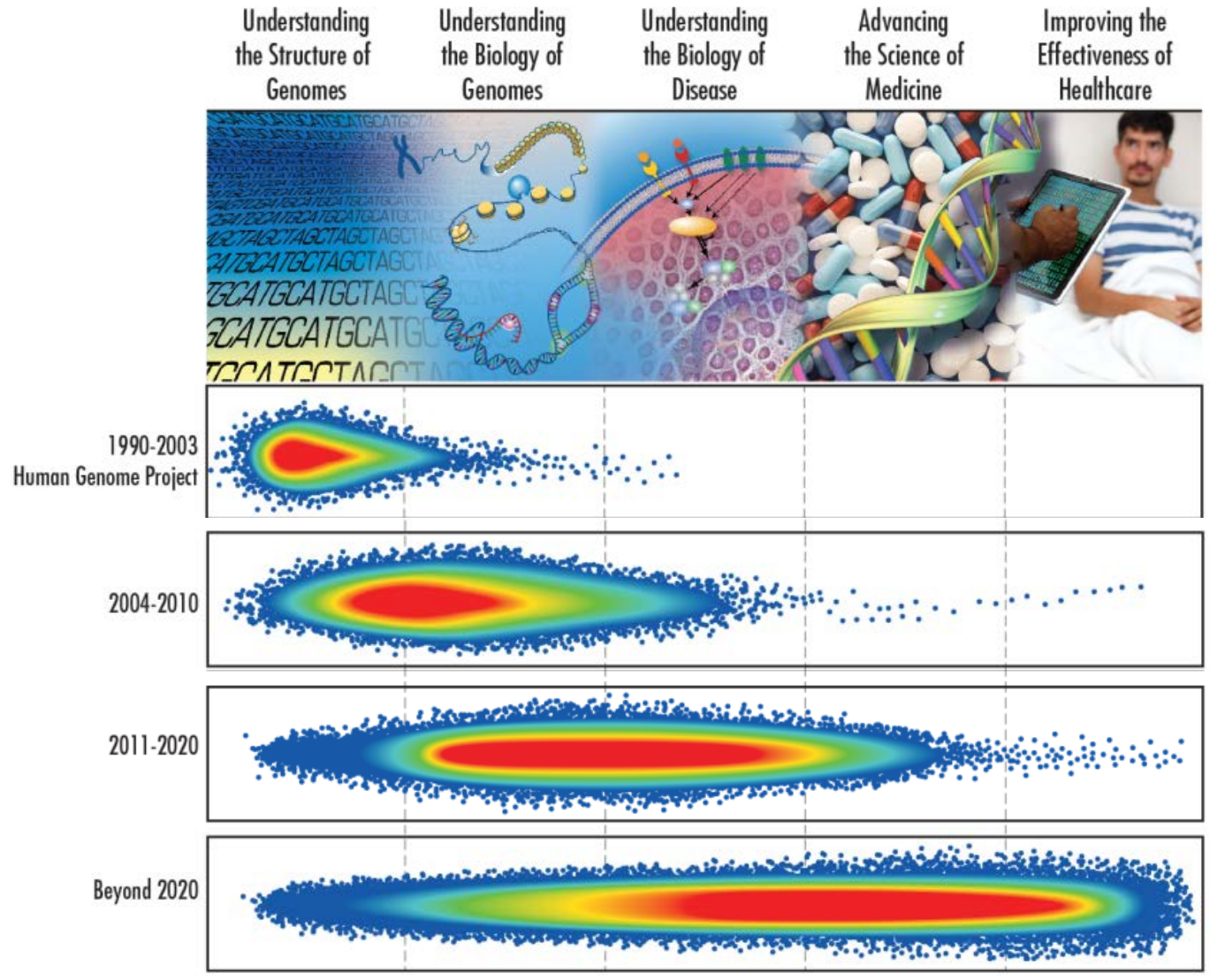

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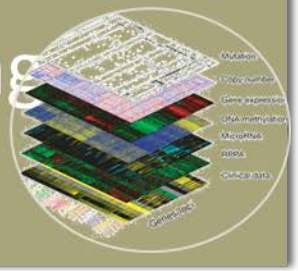
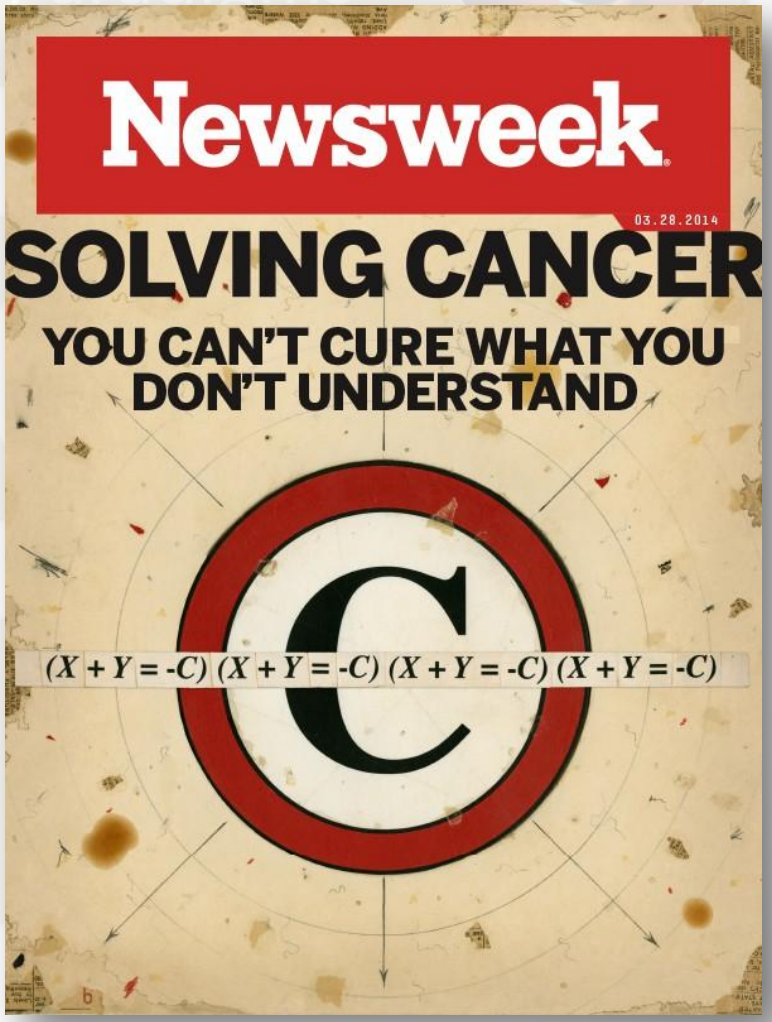
Understanding the disease



Therapeutic Paradigms

Cancer and society

New research models



The conundrum:

The biology is complex…

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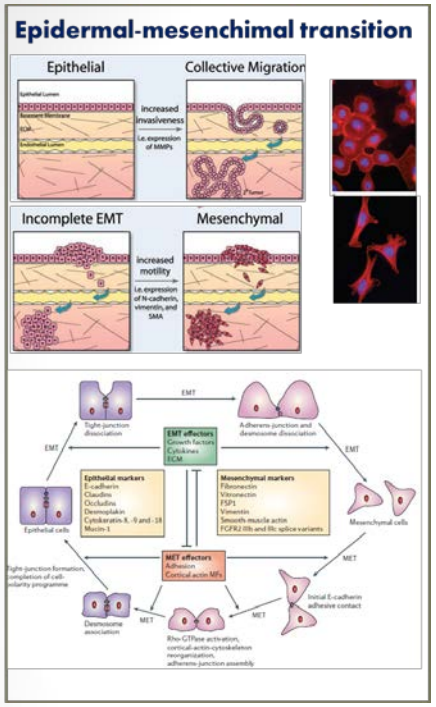

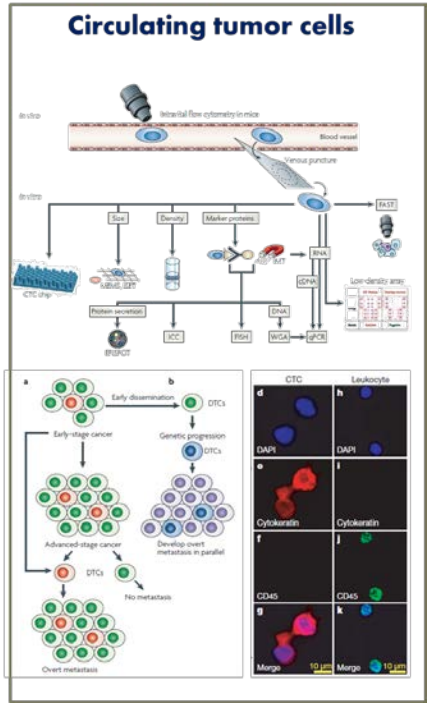

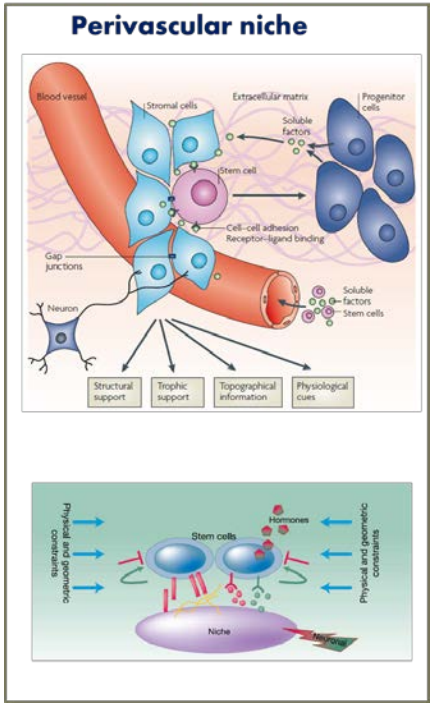

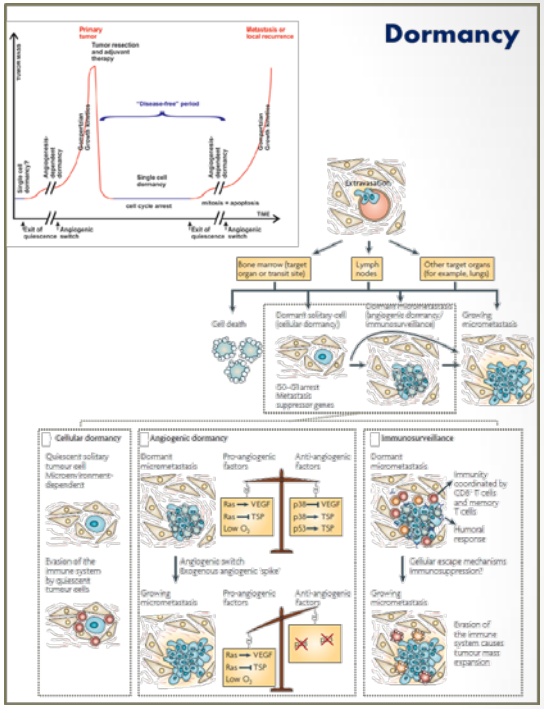

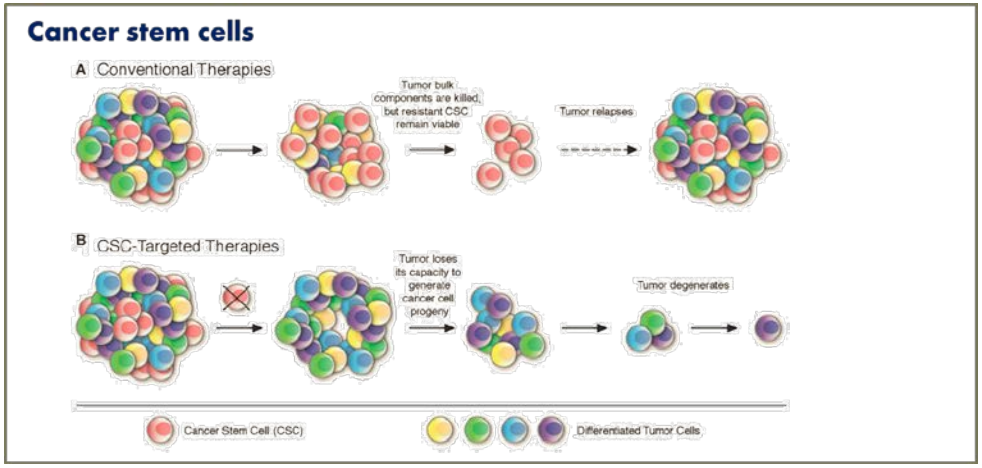

The conundrum:

The biology is complex…

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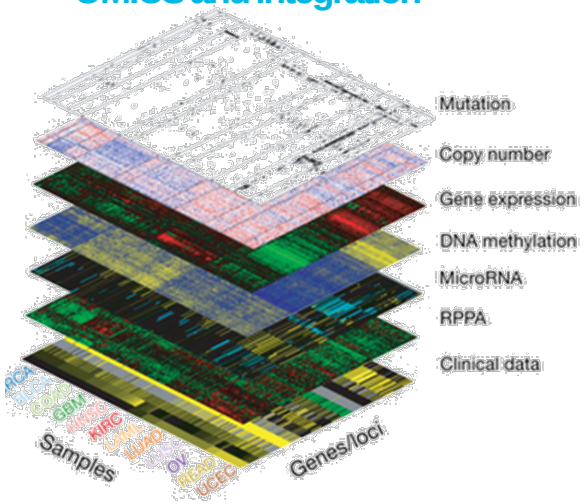
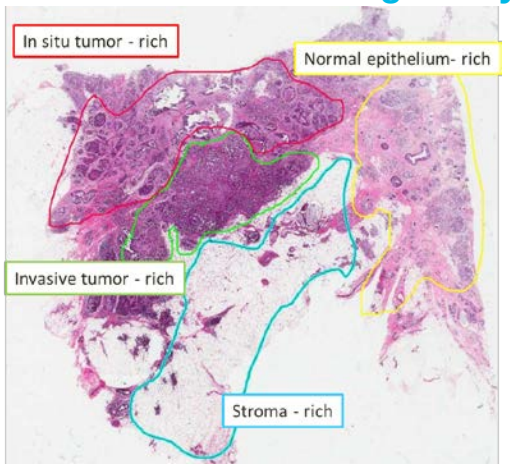
Driver vs passenger

OMICS and integration



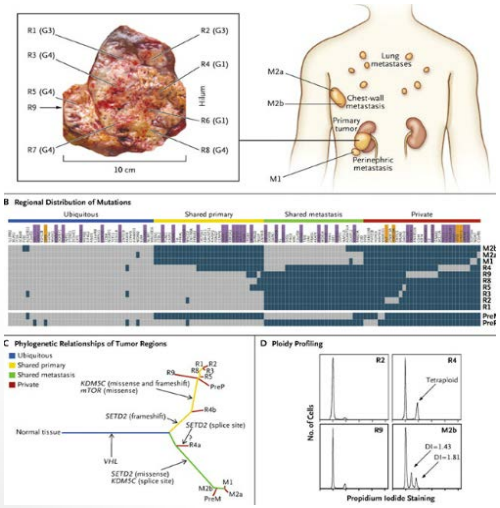
Intra-tumor cellular heterogeneicity



Allele frequency

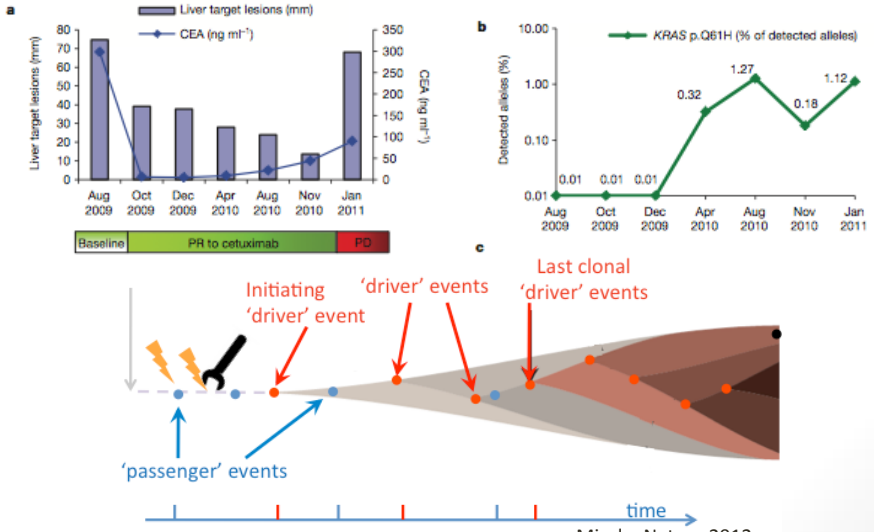
Functional relevance

Intra-patient tumor heterogeneity



Gerlinger, N Engl J Med 2012

Temporal tumor heterogeneity and Clonal evolution



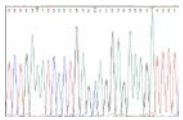
Misale, Nature 2012.
Campbell et al. Nature 2010

The conundrum:

The biology is complex…

Technology has improved…

SANGER sequencing



RT-PCR

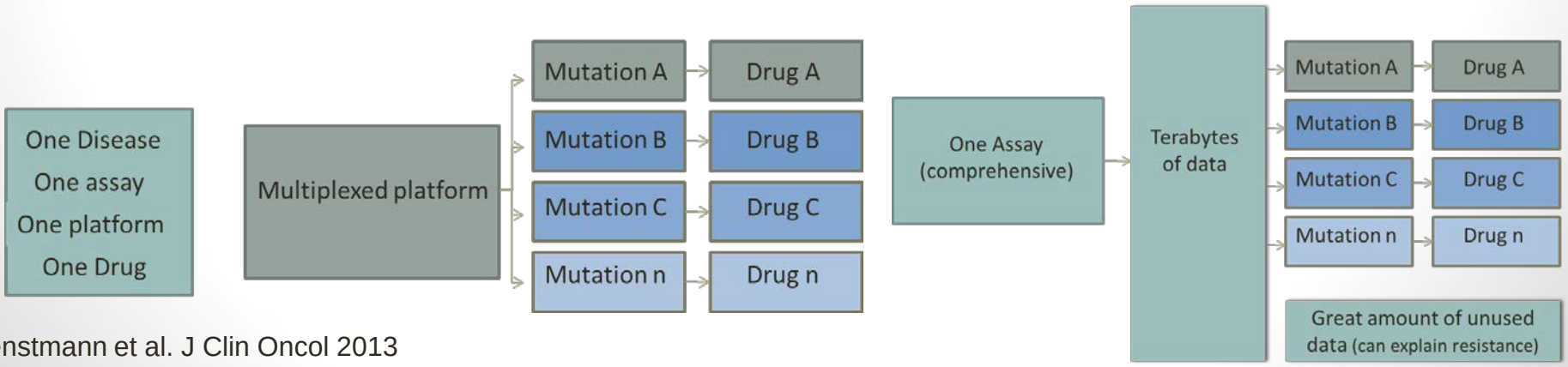
Sequenom/ SNAPshot

NGS

One test, one drug

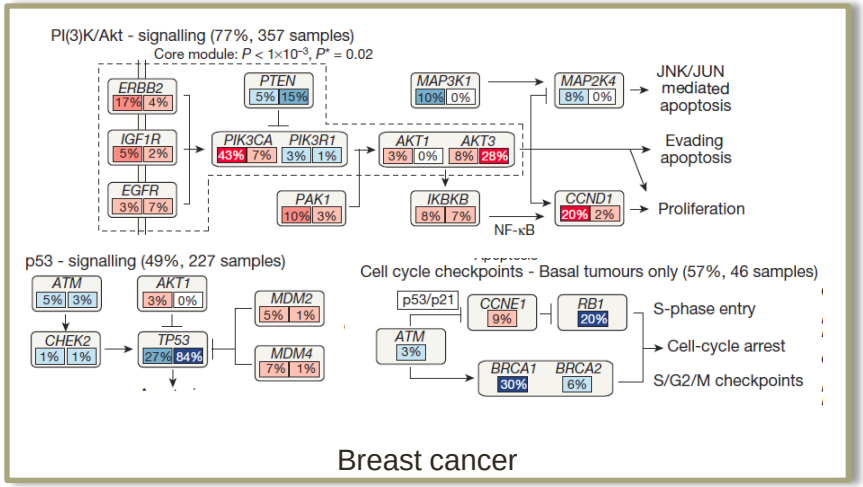
Multicategorical model

Omnisciencist–reduccionist model

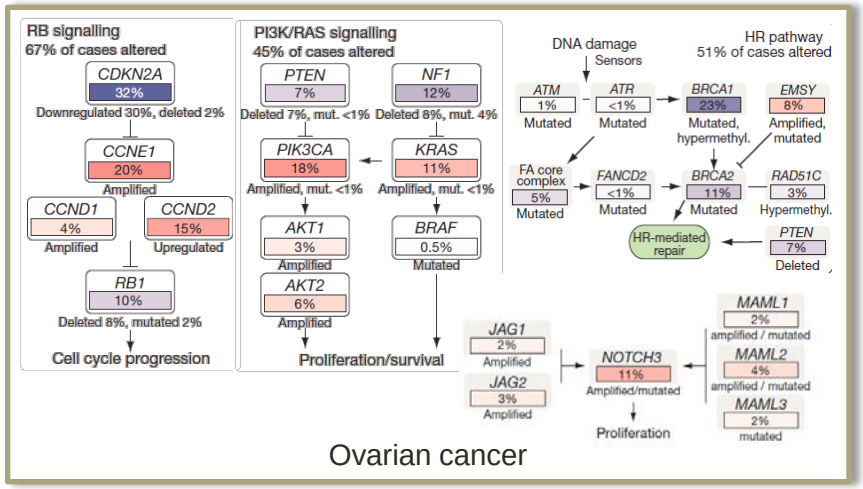


Dienstmann et al. J Clin Oncol 2013

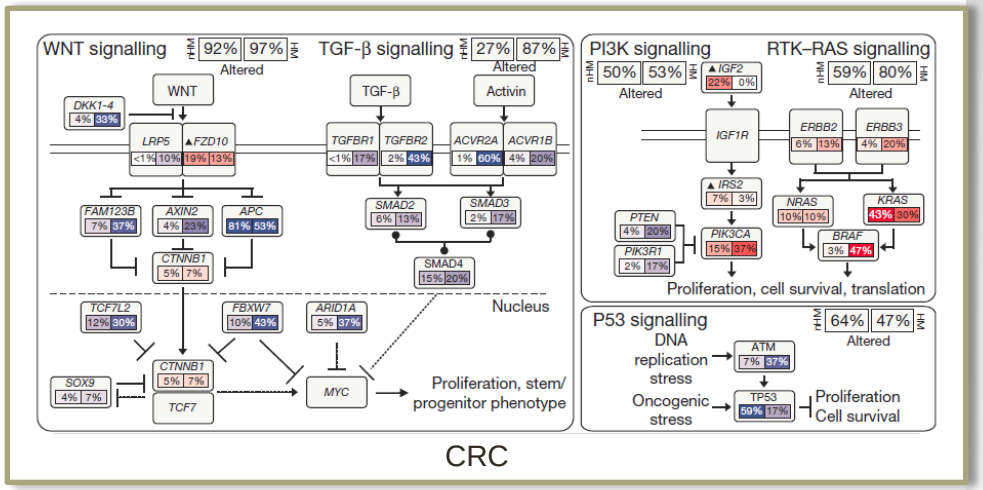
The Cancer Genome Atlas



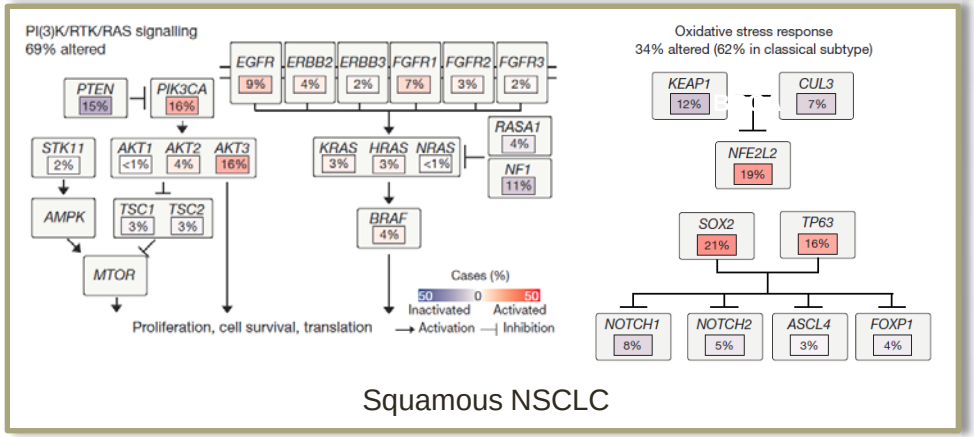
Breast cancer



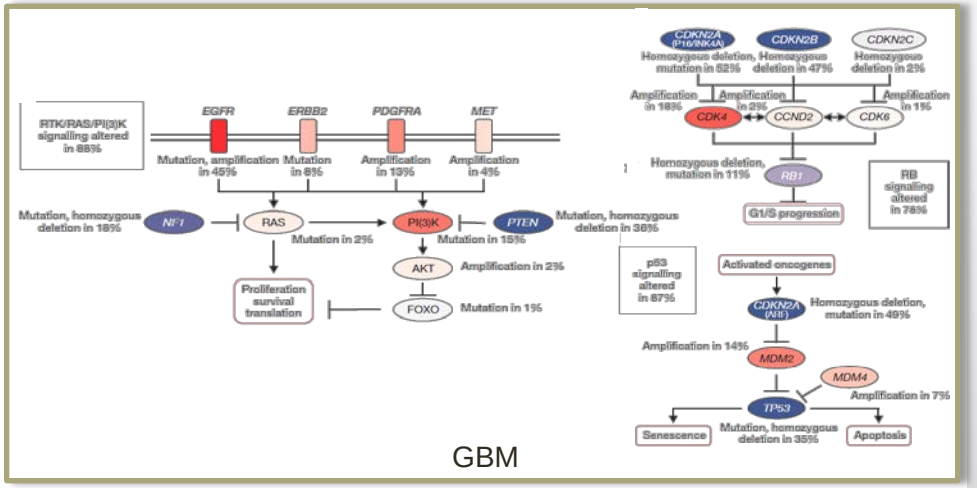
Ovarian cancer



CRC



Squamous NSCLC



GBM

Nature, October 2008
Nature, June 2011
Nature, July 2012

Nature, September 2012
Nature, October 2012

The revolution in cancer

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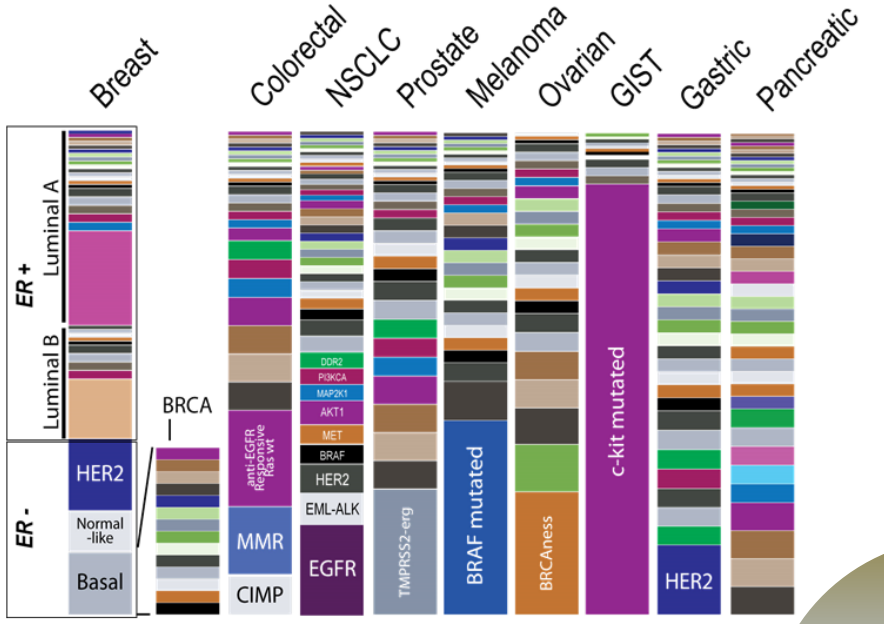
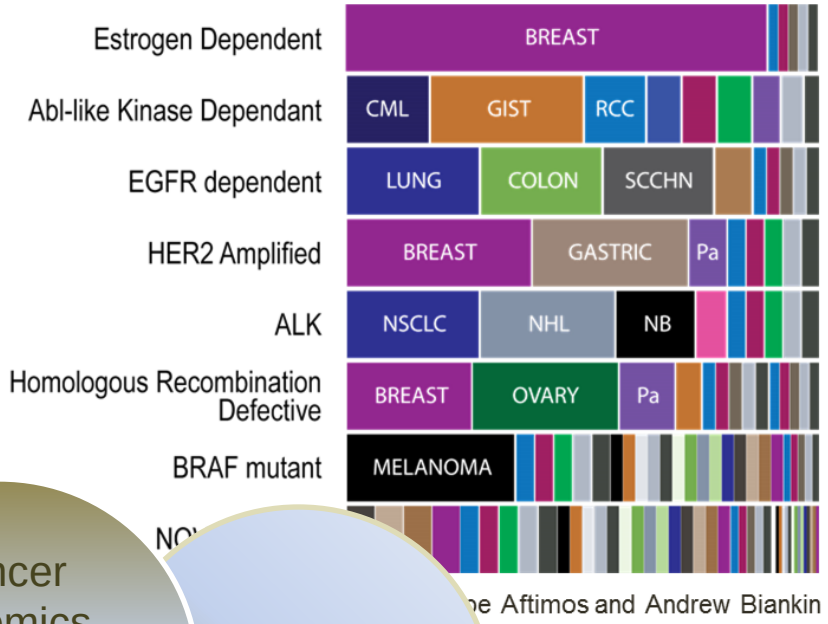
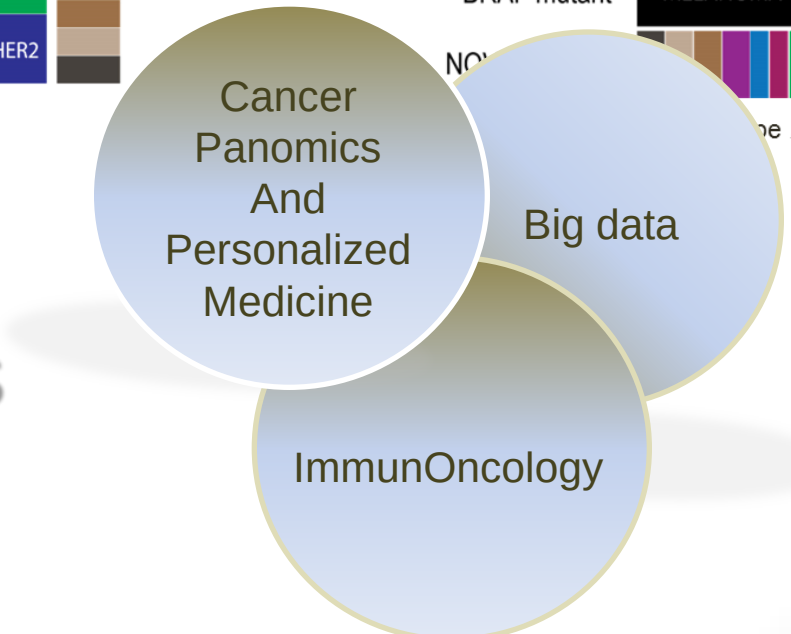
Disease reclassification?





Disruptive advancements



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Understanding the disease

Therapeutic Paradigms

Targeted therapies

Cytotoxics

Immune therapies

New mode

Integration of Research and Care

1940 2010

CYTOTOXICS

Classical Goals:

-Identify Dose Limiting toxicities (**CTCAE** v.1 to 4.03)
-**PK** and PD data
-**RECIST** v.1.1 criteria

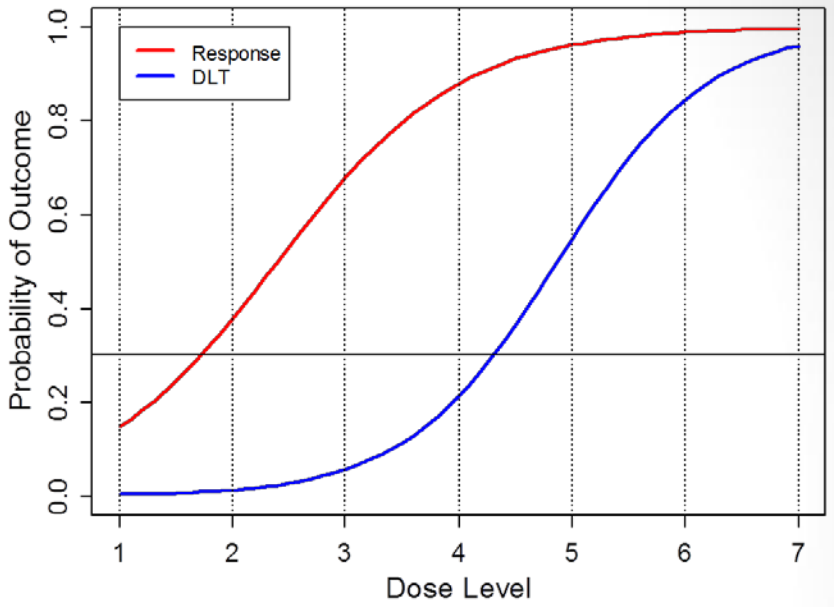
General Assumption

Monotone non decreasing dose-response curve

↑ Dose ⇒ ↑ tumor shrinkage

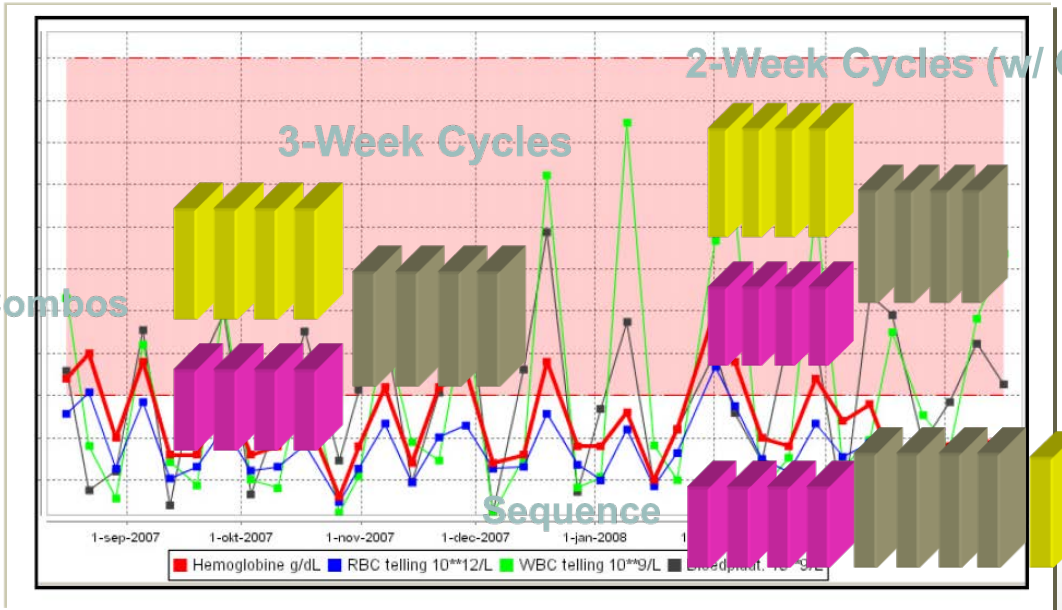
↑ tumor shrinkage ⇒ ↑ clinical benefit (and more toxicity)

Clinical benefit can be ↑ survival, ↑ QOL etc.



Intergroup/CALGB 9741

Node-Positive Stage II-IIIA



- Doxorubicin (A) 60 mg/m²
- Paclitaxel (T) 175 mg/m²
- Cyclophosphamide (C) 600 mg/m²

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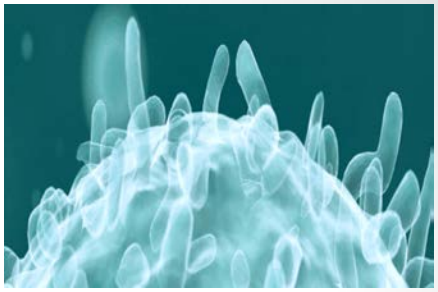
CYTOTOXICS

TARGETED AGENTS

IMMUNOTHERAPIES



Timeline in Early Drug Development — *1990* — *2010*

FIRST PARADIGM | **SECOND PARADIGM** | **THIRD PARADIGM**

OBJECTIVES	CLASSICAL APPROACH	MODIFICATIONS	NEW CHALLENGES
Dose recommendation	- DLT/MTD definition based on dose-response relationship - RP2D establishment	- No clear correlation between dose-response - Need for a BED correlation, proof-of-mechanism based on PK/PD data	- Less clear dose-response relationship, DLTs/MTD not always reached - Proof-of-mechanism measures not well defined yet
Pharmacokinetic & Pharmacodynamic data	- Helps in dosage and schedule definition - Exploratory	- PD biomarkers of efficacy - Mandatory for BED finding and dose recommendation	- Need for integrating validated measures of immune modulation (immune-biomarkers)
Response evaluation	- RECIST v.1.1 - WHO criteria	- mRECIST - Choi criteria	- irRC criteria (1D) - New irRECIST criteria (2D)
Toxicity assessment	- CTCAE v.4.03 - Relevant acute toxicities	- Need for a revised CTCAE version in light of new emergent toxicities - Incorporation of chronic toxicities	- Need for a new irAEs grading system - Relevant acute, subacute and chronic toxicities
Candidate populations	- Only heavily pre-treated patients with no standard treatment options	- New patient populations: molecularly selected populations, window-of-opportunity, phase 0 and healthy volunteer studies	- New subgroups of patients who could early benefit from immunotherapy: progressive melanoma after ipilimumab or BRAF inhibitor, progressive SqNSCLC after platinum

1990 2010

TARGETED AGENTS

General Assumption

Not all targeted therapies have toxicity

- Toxicity may not occur at all
- Toxicity may not increase with dose

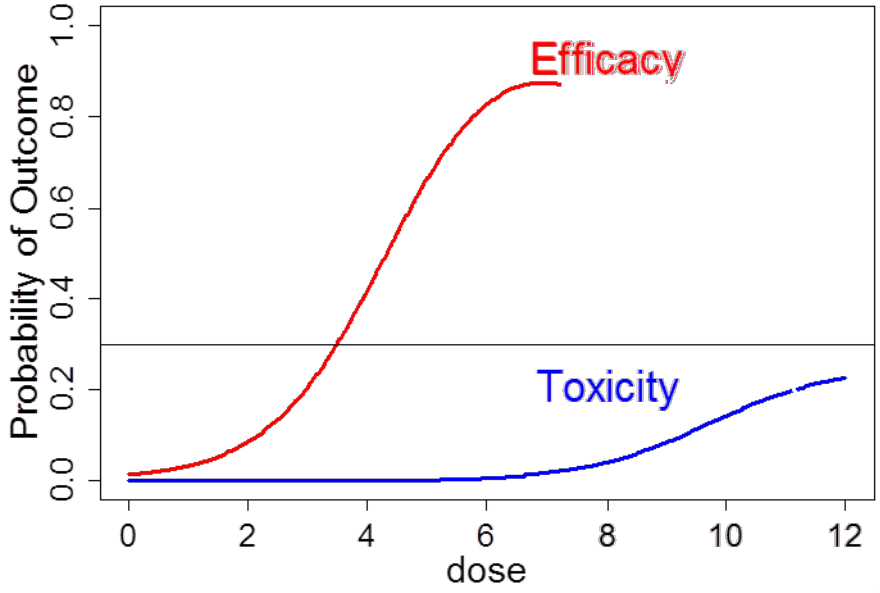
Previous assumption may not hold: does efficacy increase with dose?

MTD may not be the goal of Phase I since specificity of effect may be lost at MTD

Pharmacologic effect may not equal biologic effect

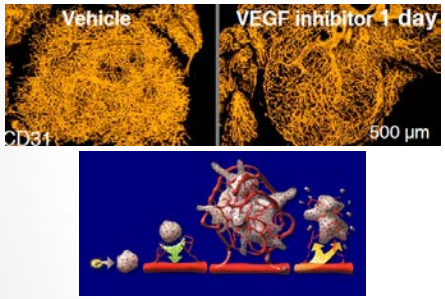
Goal: identify optimal biologically effective dose (OBED)

Rule of "No response in Phase I = inactive drug" shouldn't apply



1990 2010

TARGETED AGENTS



DRUG

↓

TARGET

Proof of Mechanism

pVEGFR

Does the drug hit the proposed target in patients?
Pharmacodynamics

BIOLOGICAL RESPONSE

Proof of Activity/Mechanism

MVD
Ktrans

Measure biological response in patients
Understand molecular mechanisms in patients
(biological activity, toxicity, resistance)

PREDICTIVE ENDPOINT

↓

CLINICAL ENDPOINT

Proof of Efficacy

PET-FDG
KI67
RECIST
PFS/OS

Surrogate biomarkers correlate with a proven clinical outcome

Enabling Stratified Medicine in NSCLC

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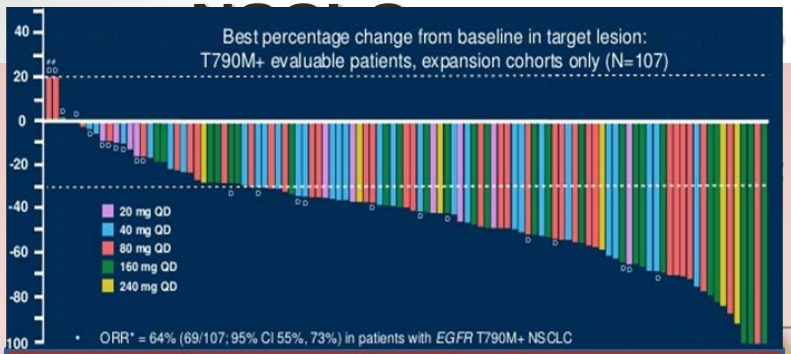
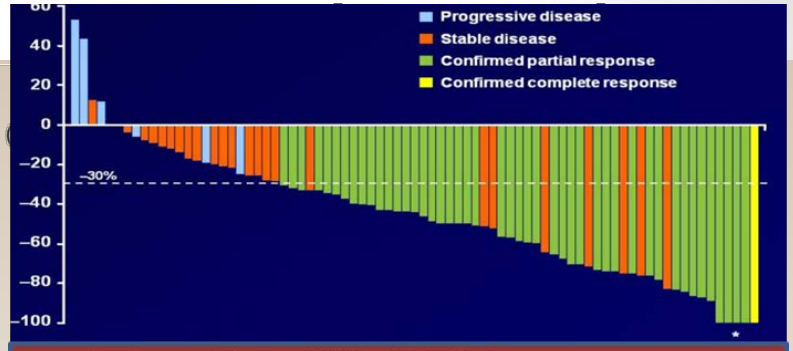
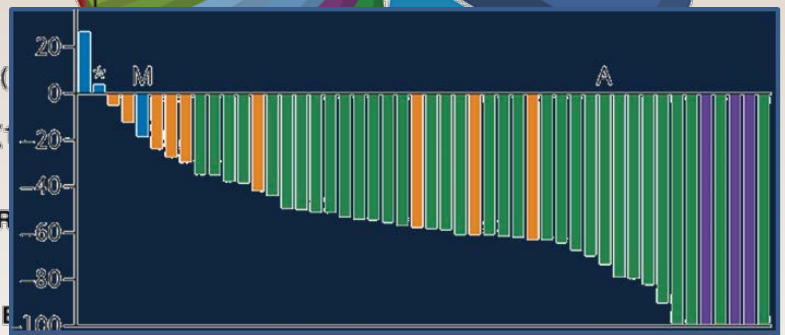


AZD9291 in T790M+ NSCLC. Jänne NEJM2015

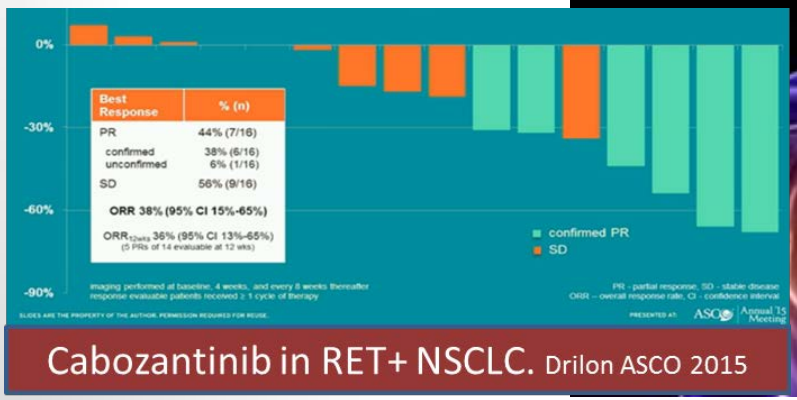


Crizotinib in ALK+ NSCLC. Shaw NEJM 2013

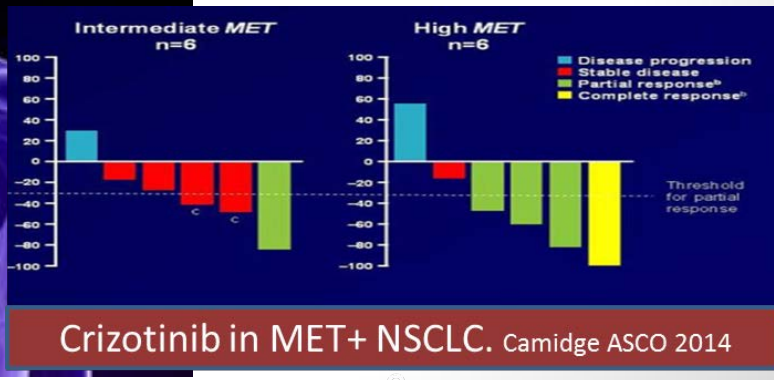
Dabrafenib in BRAF+ NSCLC. Planchard ESMO 2014



Crizotinib in ROS1+ NSCLC. Shaw NEJM 2014



Cabozantinib in RET+ NSCLC. Drilon ASCO 2015



Crizotinib in MET+ NSCLC. Camidge ASCO 2014

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1990 2010

Molecularly Informed clinical trials

Successful stories of targeted therapies

FDA guidance on co-development of diagnostics

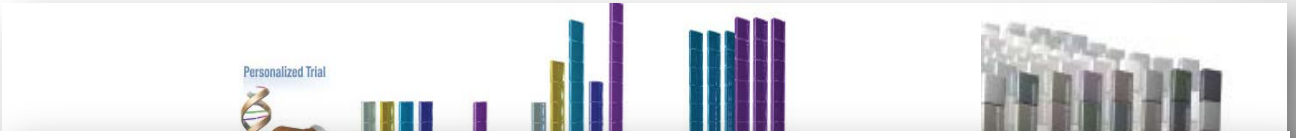


Table 1. Response rate of successful targeted therapies in molecularly-selected populations evaluated in early clinical trials

Marker/population	Agent	Mechanism of action	Response	Reference
HER2 overexpressed/amplified breast cancer	Trastuzumab	anti-HER2 antibody	12%	[6]
	Trastuzumab-DM1	anti-HER2 antibody + drug conjugate	44%	[12]
CD117 overexpressed GIST	Imatinib	c-KIT, PDGFR inhibitor	54%	[13]
BRCA 1/2 mutant breast, ovarian and prostate cancer	Olaparib	PARP inhibitor	47%	[7]
BRAF V600E mutant melanoma	Vemurafenib	BRAF inhibitor	75%	[8]
	Dabrafenib	BRAF inhibitor	60%	[14]
Basal cell carcinomas (majority have inactivating mutations in PTCH1 or activation of SMO)	Vismodegib	SMO inhibitor (Hh pathway)	58%	[15]
ALK rearranged NSCLC	Crizotinib	ALK, MET inhibitor	57%	[9]
Medullary thyroid cancer (known to have *RET* mutations, MET expression and VEGF activation)	Cabozantinib	MET, VEGFR2, RET inhibitor	29%	[16]
PIK3CA mutant breast cancer	BYL719	selective PI3K alpha inhibitor	44%[a]	[10]
FGFR1 or *FGF* amplified breast cancer	E-3810	FGFR, VEGFR inhibitor	70%	[11]

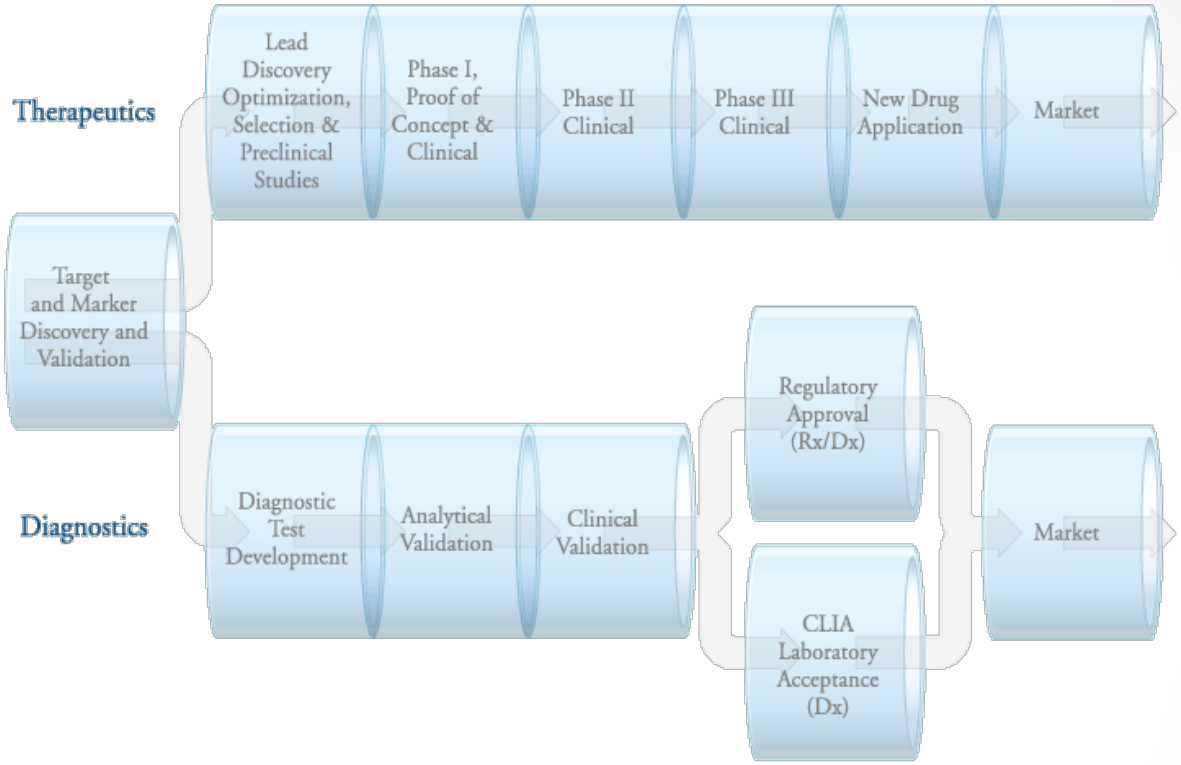
1990 2010

TARGETED AGENTS

Pharmacologic effect may not equal biologic effect

Goal: identify optimal biologically effective dose (OBED)

Rule of "No response in Phase I = inactive drug" shouldn't apply



- Safer drugs, role of **chronic toxicities**
- Proof-of-Mechanism (PD biomarkers)
- **mRECIST** and Choi criteria
- **New toxicities not graded in CTCAE**
- Changes in candidate **populations**

Ceritinib in *ALK*-Rearranged NSCLC

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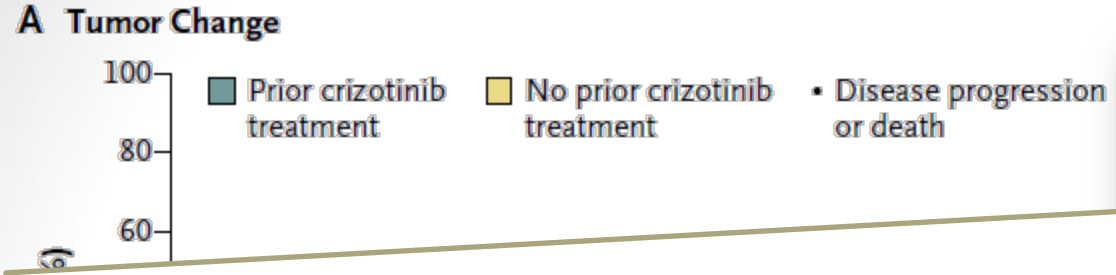

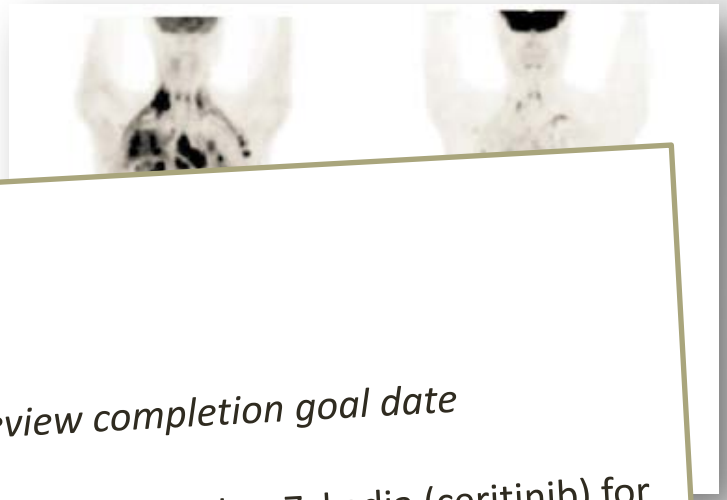

FDA NEWS RELEASE

For Immediate Release: April 29, 2014

FDA approves Zykadia for late-stage lung cancer

Breakthrough therapy drug approved four months ahead of review completion goal date

The U.S. Food and Drug Administration today granted accelerated approval to Zykadia (ceritinib) for patients with a certain type of late-stage (metastatic) non-small cell lung cancer (NSCLC).

Zykadia is the fourth drug with breakthrough therapy designation to receive FDA approval..

The FDA granted Zykadia breakthrough therapy designation, priority review and orphan product designation because the sponsor demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies; the drug had the potential, at the time of the application was submitted, to be a significant improvement in safety or effectiveness in the treatment of a serious condition; and the drug is intended to treat a rare disease, respectively.

AT. Shaw, et al. NEJM 3/27/14

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Institute of Oncology

1990 2010

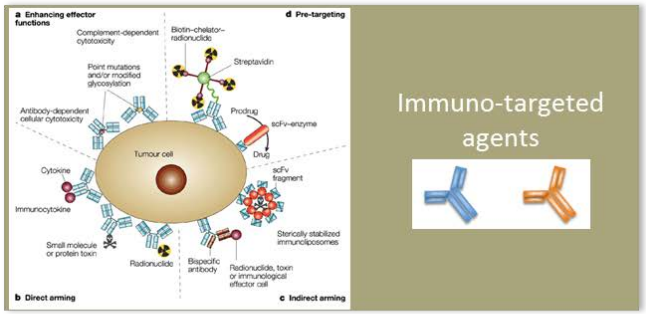
IMMUNOTHERAPIES

And now:

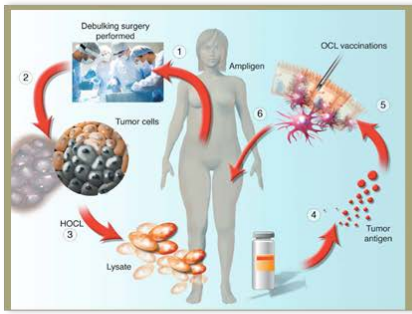
The Third Paradigm

The rationale:

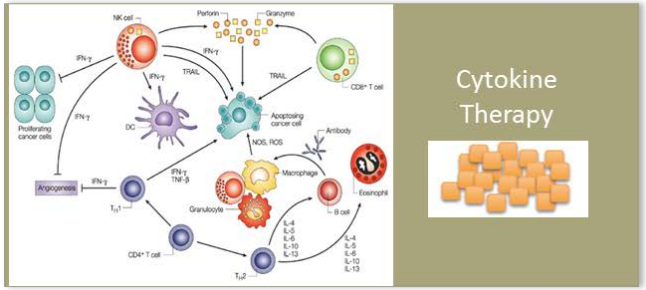
- ✓ Potentially Highly Tumor-Specific
- ✓ Can be Effective Against Disseminated Disease Including Unrecognized Micro-metastases
- ✓ Can Involve Severe, Sudden Onset Life-threatening Treatment-limiting Side-Reaction



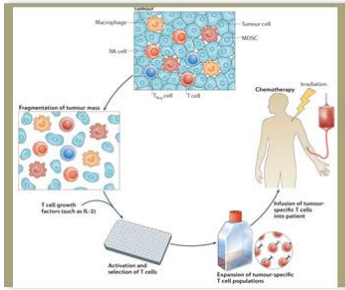
Immuno-targeted agents



Vaccines



Cytokine Therapy



Adoptive T cell Therapy

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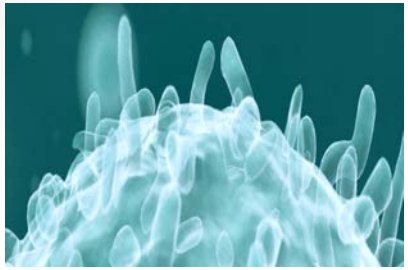
1990 2010

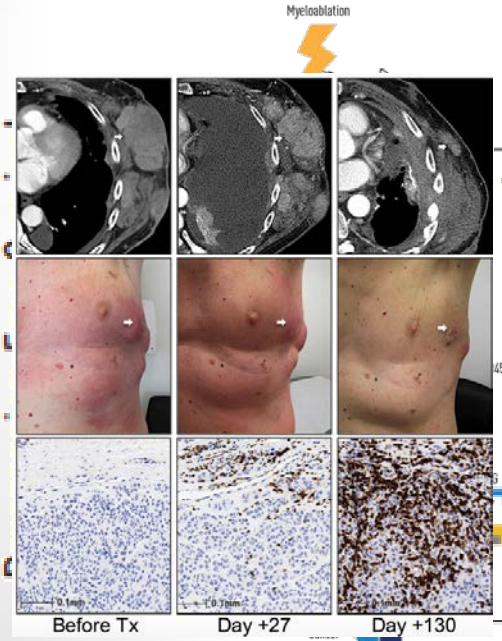
IMMUNOTHERAPIES

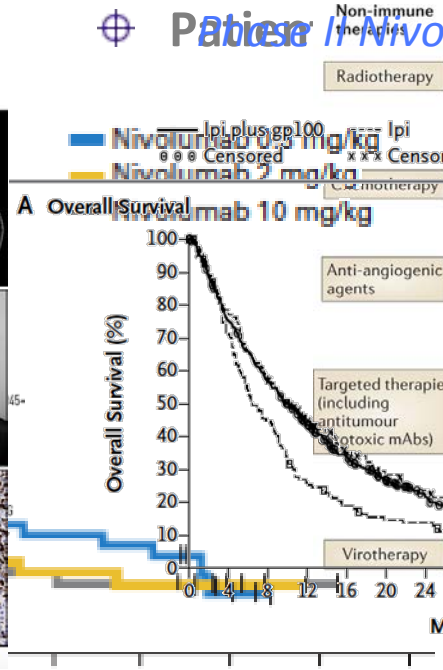


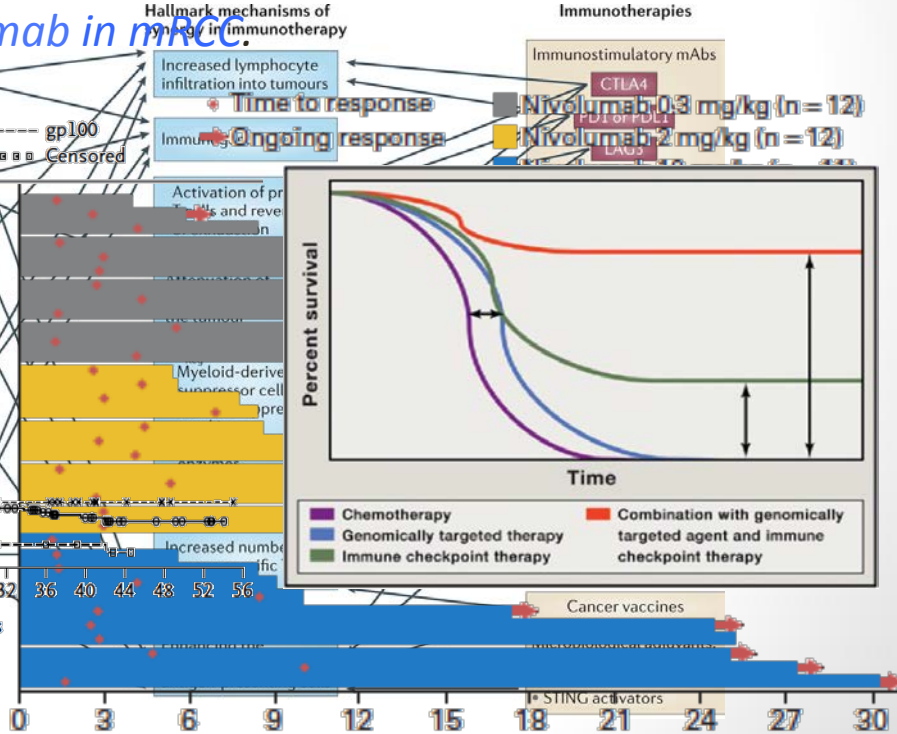
Challenges:

- Lack of good preclinical models
  - Prediction and Management of toxicities
  - Triage of relevant combinations
- Dose/response/toxicity relationship
- Relevant endpoints
- Patient selection

Phase II Nivolumab in mRCC







Teicher B. Cancer Drug Discovery and Development. Second edition.

Drake CG et al. Nature 2014;515(7528):496-7.

Topalian SL et al. Nat Rev Cancer 2012;12(1):61-6.

Motzer RJ. et al. J Clin Oncol 2014 Dec 1

Hodi FS. et al. N Engl J Med 2010;363(8):711-23.

Sharma P, Allison JP. Cell 2015

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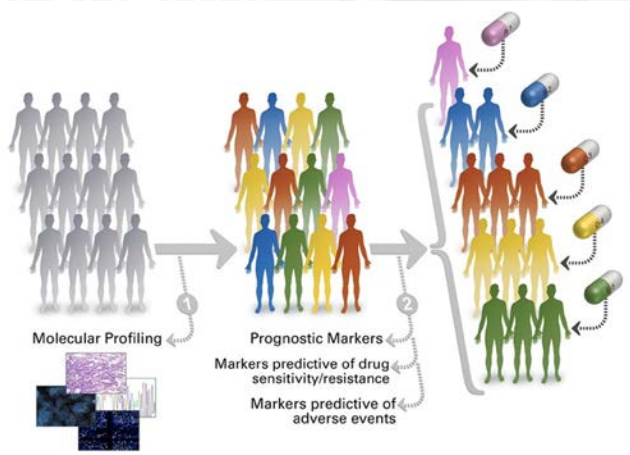
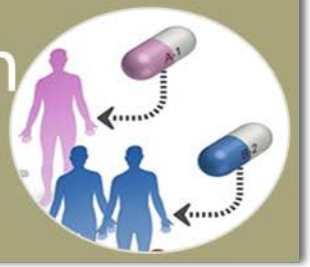
Understanding the disease

Therapeutic Par



Cancer and society

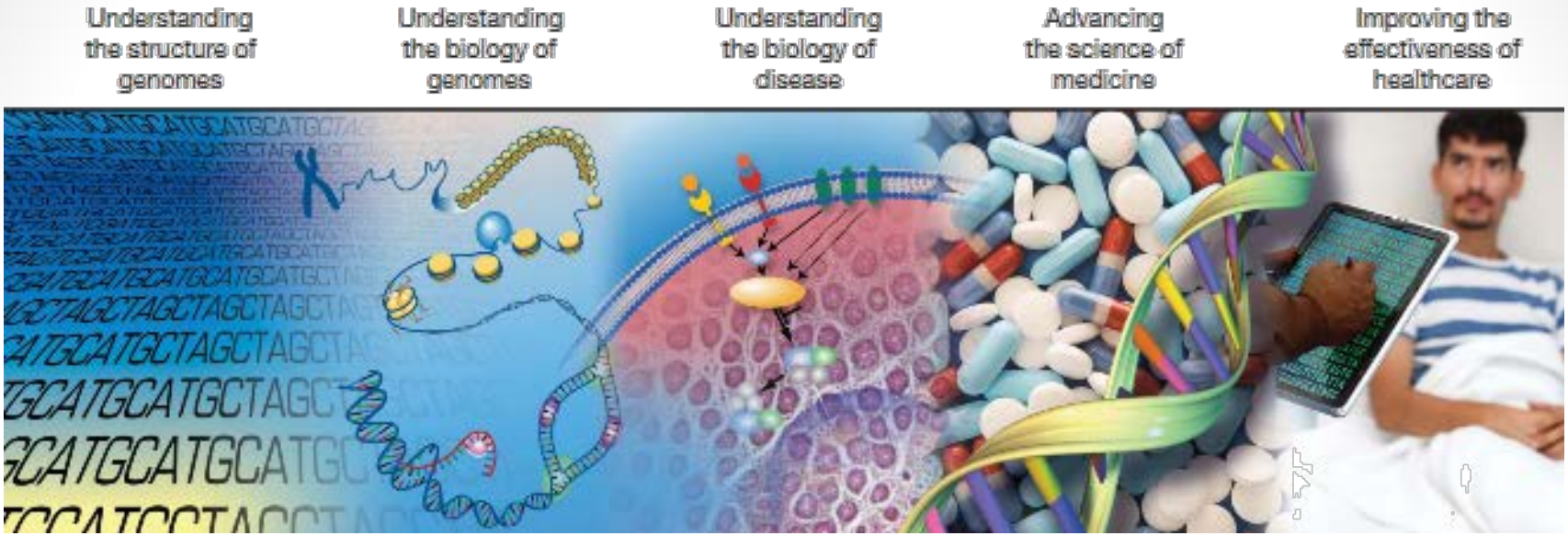
New research models



Integration of Research and Care

Path Toward Personalized Medicine

VHIO VALL D'HEBRON Institute of Oncology



Green, ED et al (2011). Charting a course for genomic medicine from base pairs to bedside. *Nature* 470: 204-213

Change in personalized healthcare investment from 2005 to 2010 [1]

↑ 75%

Biopharmaceutical companies investing in personalized healthcare research in 2010 [1]

94%

Prominent personalized medicine treatments & diagnostics available [2]

13 in 2006 ▶ **113** in 2014

[1] Tufts Center for the Study of Drug Development, 2010; [2] Personalized Medicine Coalition, 2014

Personalized Medicine: Winther trial

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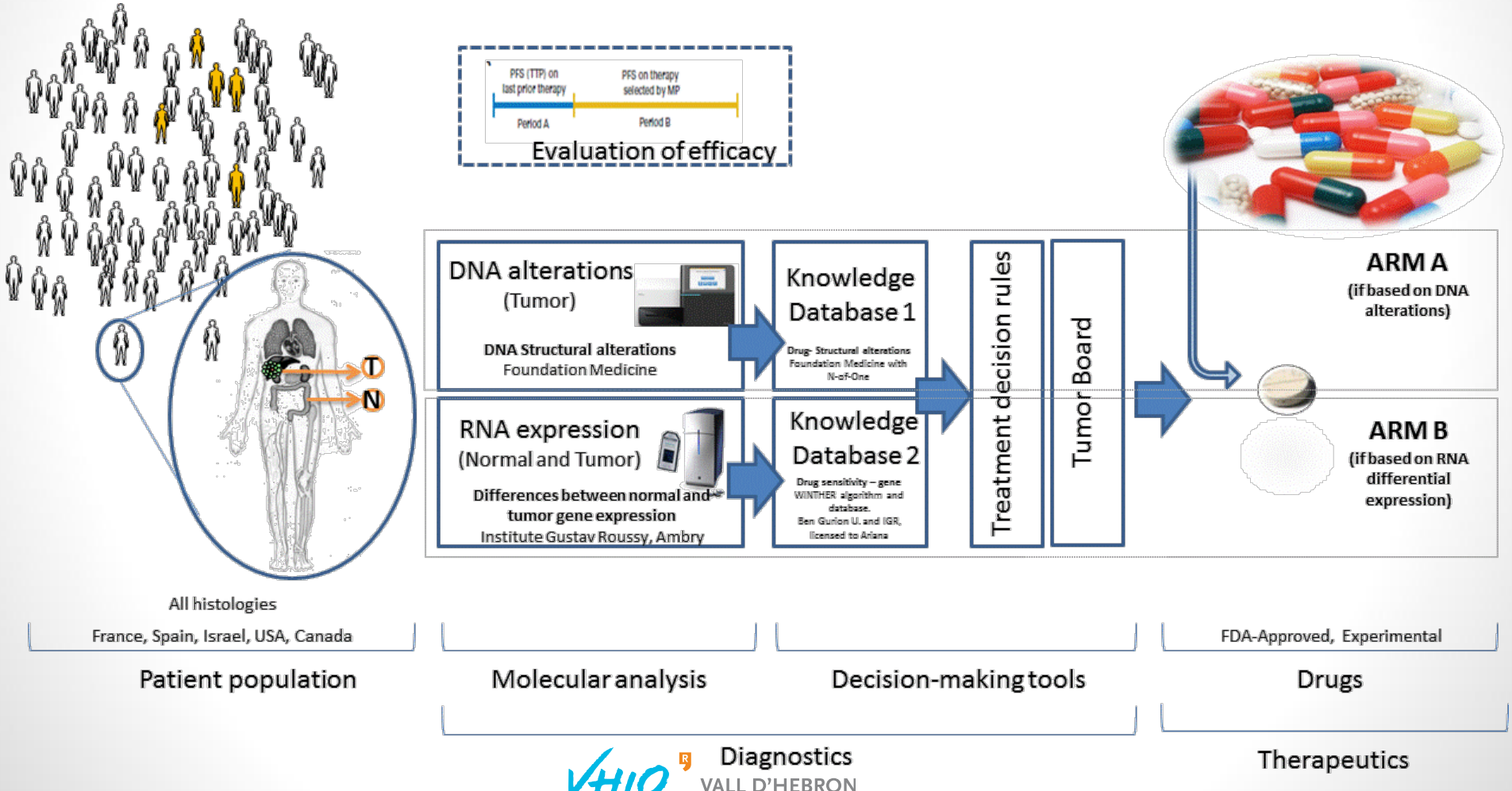
- **International, pilot study in Personalized therapy:** includes a variety of different technologies (Next Generation Sequencing, Copy Number Variations, gene expression). 5 Countries. Academia, Pharma, Dx Companies, and NGO and Charities. Supported by WIN consortium, ASCO and EU.



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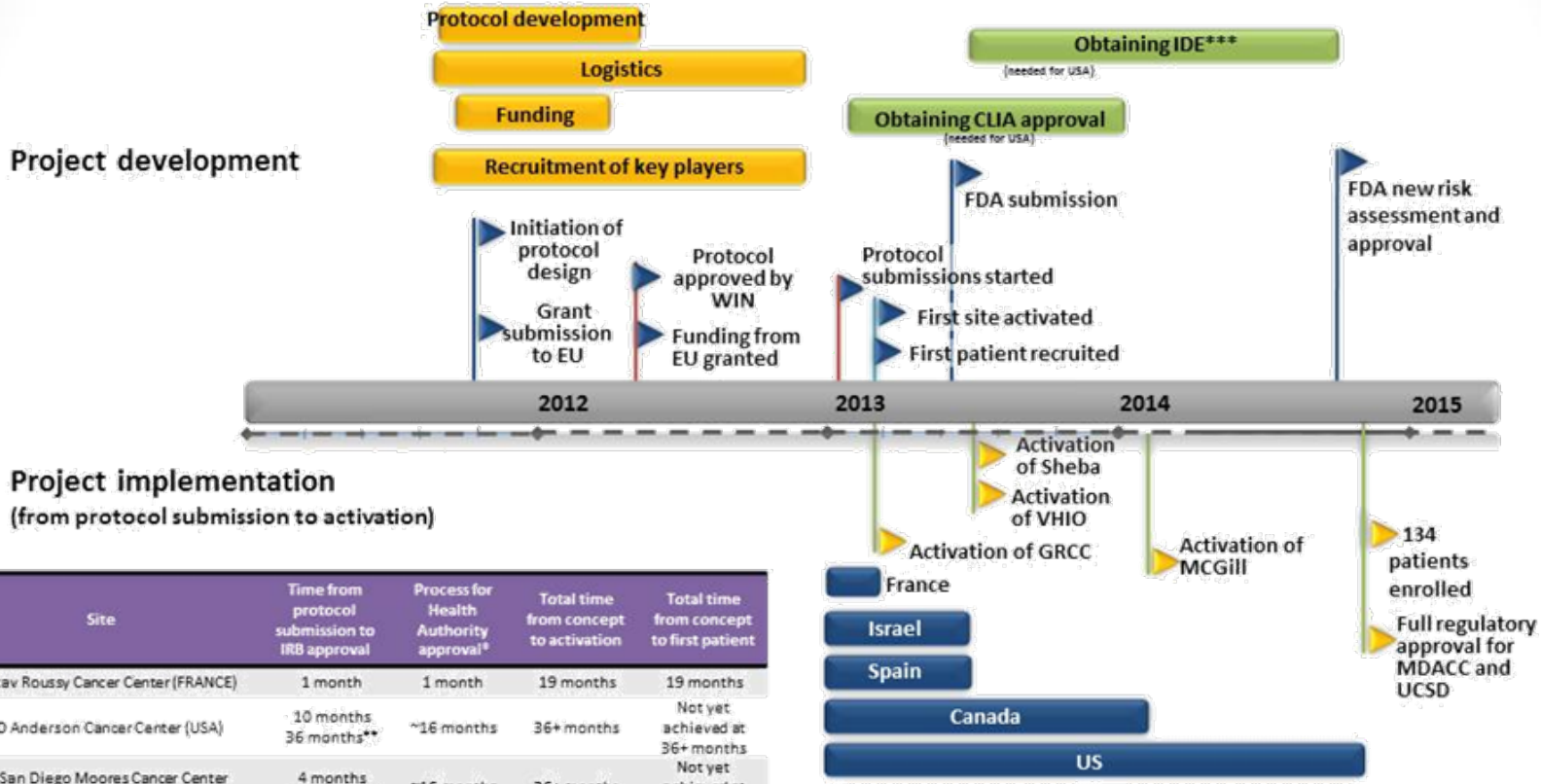
Site	Principal Investigator	Challenge	Solution
Gustave-Roussy Cancer Campus (FRANCE)	Prof. JC. Soria, Chair of the Drug Development Department (DITEP) (Study PI)	• Classified as triage trial. • Approved drugs could be used off label after multidisciplinary tumor board discussion, and with permission by the health authorities.	• Multiple clinical trials for patients. • Charities, pharmaceutical, and institutional funding. • Request coverage by health insurance on a case-by-case basis. • Encourage pharmaceutical industry to provide free drug if under IRB-approved protocol (perhaps similar to pharmacy assistance program)
UC San Diego Moores Cancer Center (USA)	Prof. Razelle Kurzrock, Senior Deputy Center Director, Clinical Science and Director, Center for Personalized Cancer Therapy	• Classified as triage trial • Approved drugs could to be used off label. Non-government (private) health insurance may cover, albeit unpredictably • Diagnostic "omics" tools need to be CLIA-approved and FDA initially ruled them a "significant risk" and requested an IDE; initial IDE package rejected by the FDA. Reassessment by FDA with protocol modification in the	• CLIA lab had to be included and results cross-validated with those from GRCC lab in France. • Need for IDE was an unexpected new requirement and a package had to be prepared for obtaining it. Timeline for package preparation was significant
MD Cen (USA)	Therapeutics,	• Classified as a therapeutic clinical trial per Health Authorities that includes the diagnostic and therapeutic part • Need to define drugs that will be used in clinical trial • Drugs need to be covered by the clinical trial	• Need to introduce pharmacovigilance (reporting adverse events). • Comprehensive list of drugs available • Depends on clinical trial funding for the cost of drugs.
Vall d'Hebron Institute of Oncology (SPAIN)	Jordi Rodon, MD, Director of the Molecular Therapies Research Unit	• Classified as a therapeutic clinical trial per Health Authorities that includes the diagnostic and therapeutic part • Need to define drugs that will be used in clinical trial • Drugs need to be covered by the clinical trial	• Need to introduce pharmacovigilance (reporting adverse events). • Comprehensive list of drugs available • Depends on clinical trial funding for the cost of drugs.
Oncology Institute at the Chaim Sheba Medical Center (ISRAEL)	Raanan Berger, MD, PhD, Director, Division of Medical Oncology	• Classified as a therapeutic clinical trial per Health Authorities • Drug costs need to be covered by the clinical trial • Cost of clinical research higher than what is covered	• Clinical trial includes the diagnostic and therapeutic part. • Depends on clinical trial funding for the cost of drugs. • Extra resources need to be allocated by the site
Segal Cancer Center, McGill University (CANADA)	Prof. Wilson Miller, Deputy Director of Segal Cancer Centre & director of the Clinical Research Units, McGill University	• IRB and Health Authorities had different views regarding the regulatory approach for the study. • Classified as a therapeutic trial. • Site needs to request Health Authority permission for off-label drug use in each case. • Site not included in the initial grant	• Coordination between Health Authorities and IRB by the site. • Local pharmaceutical affiliates may provide drug for patients. • Development of an ad-hoc fast-track review system by Health Authorities for this project. • Site added in the grant and resources reallocated

- Classified as a therapeutic clinical trial per Health Authorities that includes the diagnostic and therapeutic part
- Need to define drugs that will be used in clinical trial
- Drugs need to be covered by the clinical trial

- Need to introduce pharmacovigilance (reporting adverse events).
- Comprehensive list of drugs available
- Depends on clinical trial funding for the cost of drugs.

Personalized Medicine: Winther trial

VALL D'HEBRON Institute of Oncology



Site	Time from protocol submission to IRB approval	Process for Health Authority approval*	Total time from concept to activation	Total time from concept to first patient
Gustav Roussy Cancer Center (FRANCE)	1 month	1 month	19 months	19 months
MD Anderson Cancer Center (USA)	10 months 36 months**	~16 months	36+ months	Not yet achieved at 36+ months
UC San Diego Moores Cancer Center (USA)	4 months 36 months**	~16 months	36+ months	Not yet achieved at 36+ months
Vall d'Hebron Institute of Oncology (SPAIN)	1 month	2 months	22 months	22 months
Oncology Institute at the Chaim Sheba Medical Center (ISRAEL)	6 months	4 months	22 months	22 months
Segal Cancer Center, McGill University (Canada)	9 months	1 month	30 months	30months

Rodon et al. Annals Oncology 2014

Personalized Medicine:

How to measure clinical benefit"

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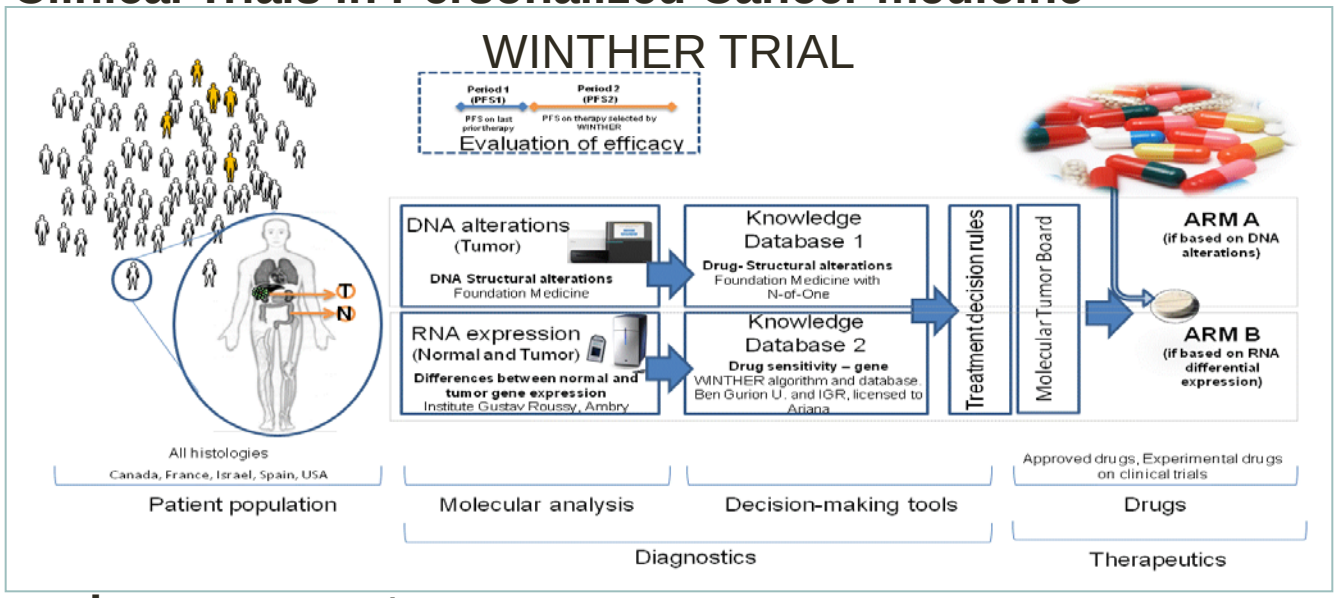
Clinical Trials in Personalized Cancer medicine



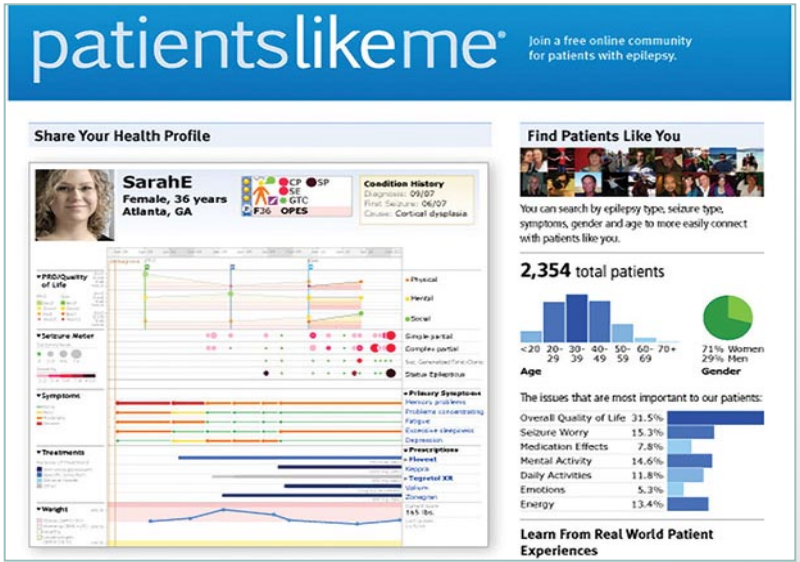
Genomic case reports

nature

Annals of Oncology

The NEW ENGLAND JOURNAL of MEDICINE

Case registries



Personalized Medicine:

Implementing Genomic-driven Medicine

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Right

Industry

Portfolio of
Clinical Trials

Personalized Medicine:

Understanding each other

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Sample **Trials**

Pharma

Physicians/Clinical Investigators

TRANSLATIONAL RESEARCH

FINANTIALS

CLINICAL RESEARCH

REGULATORY

Cost/ coverage

Turnaround time

Treatment

Multiplexing

Robustness

Research

Science

Cooperative groups

Translational scientists

“Big Data” in Oncology

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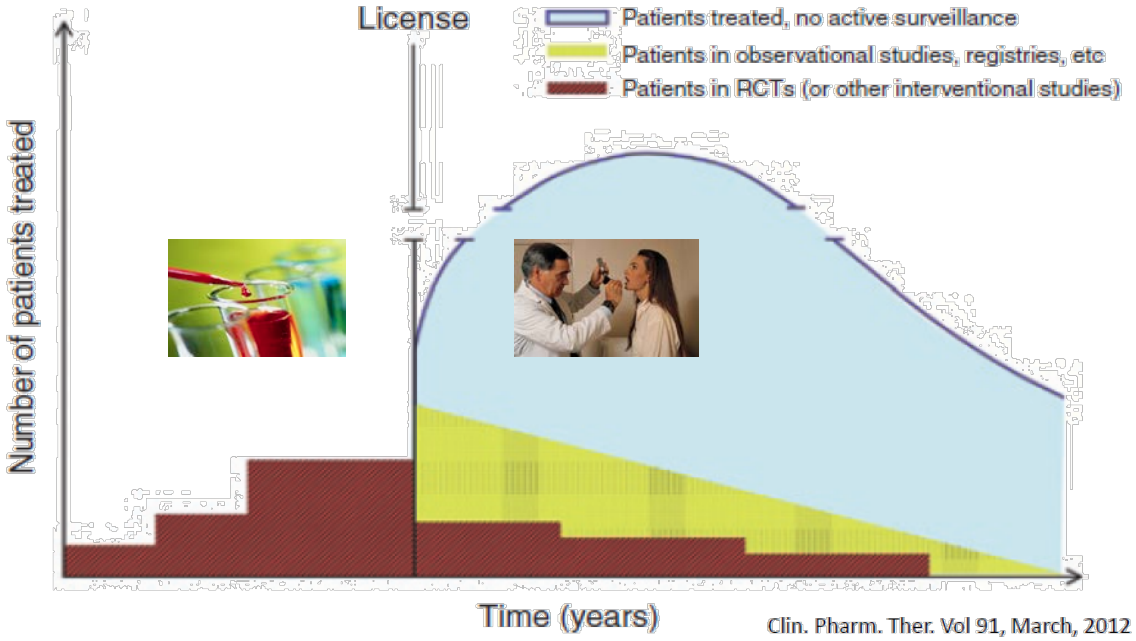
- We’ve lived in a world where research was in one side of the house and clinical care was on the other



Clin. Pharm. Ther. Vol 91, March, 2012

- But we can also aggregate data from our routine clinical care and gain valuable insights from massive numbers of patients
- In the future, most new knowledge creation in oncology will come from the analysis of “real world data”
- We will need to create a true “learning health system” for cancer care.

"Big Data" in Oncology

Cancer Workflow: Research and Patient-Care

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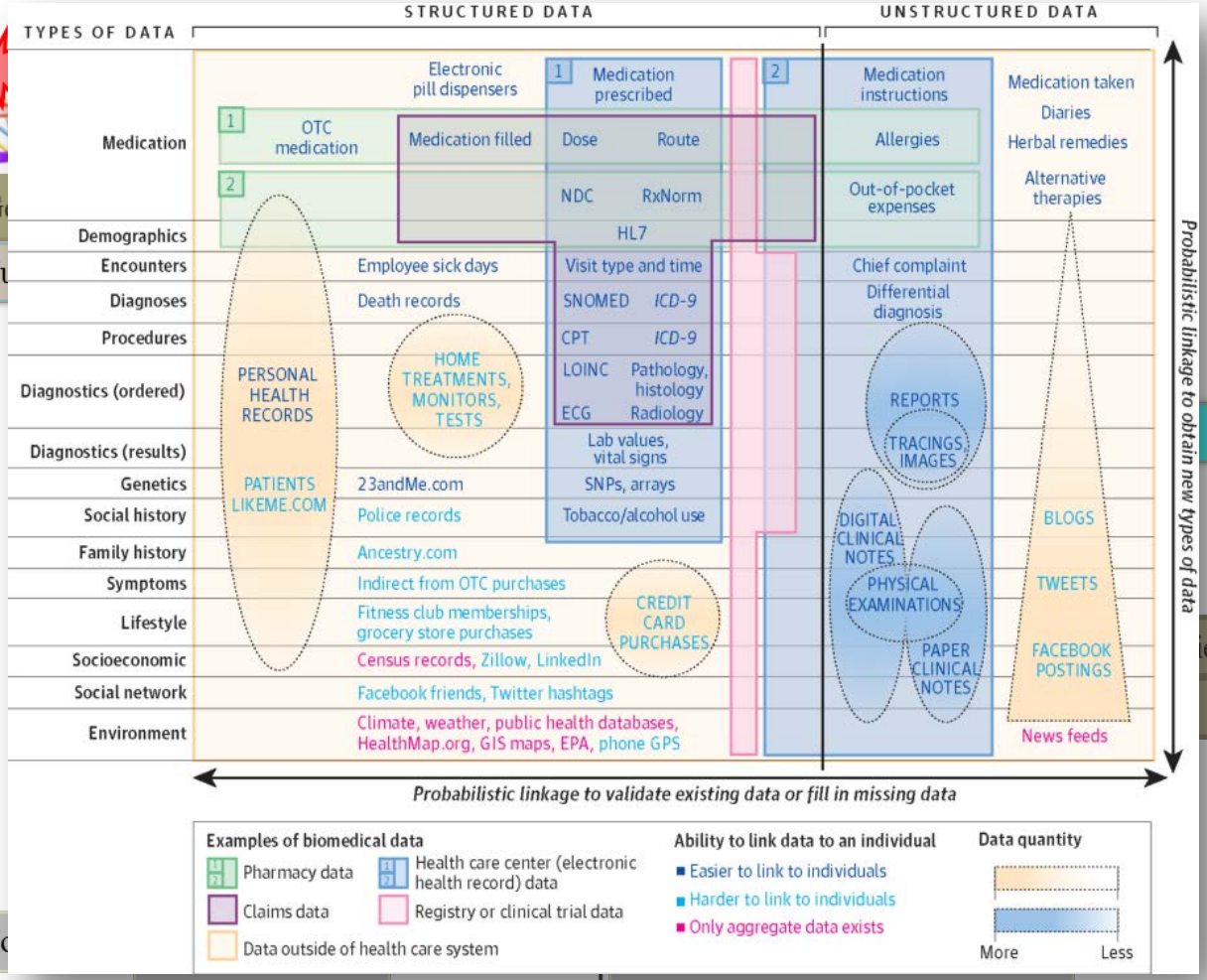


Basic Science

Primary Care

- Diagnosis
- Sub-type Analysis

Oncologist

- Personalize Therapy
- Apply Treatment Guidelines

Body

Symptom/Finding

Medical Hx

Family Hx

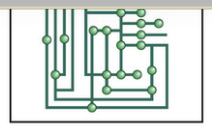
iew of Systems

Chemotherapy

Surgery

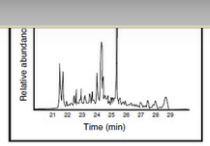
Radiation

Biologics



Metabolome

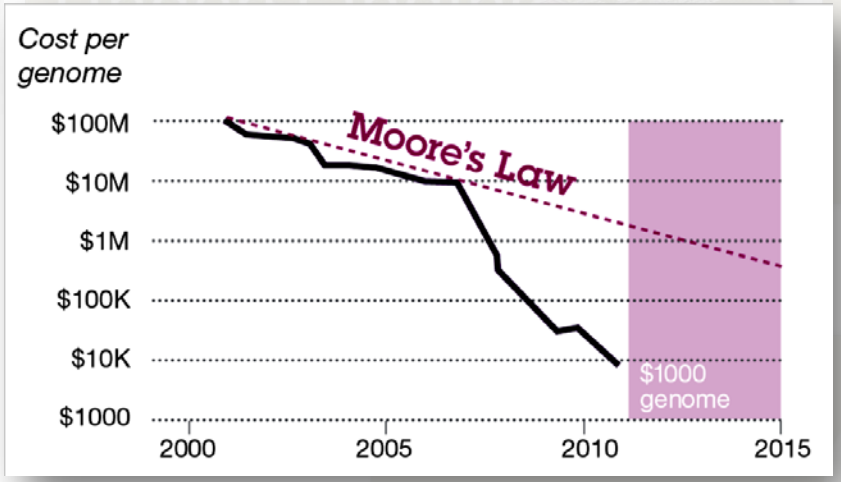
Lipidome



Proteome

Nature Immunology 2015;16,902–5.

Finding the Missing Link for Big Biomedical Data. JAMA. 2014;311(24):2479-2480.



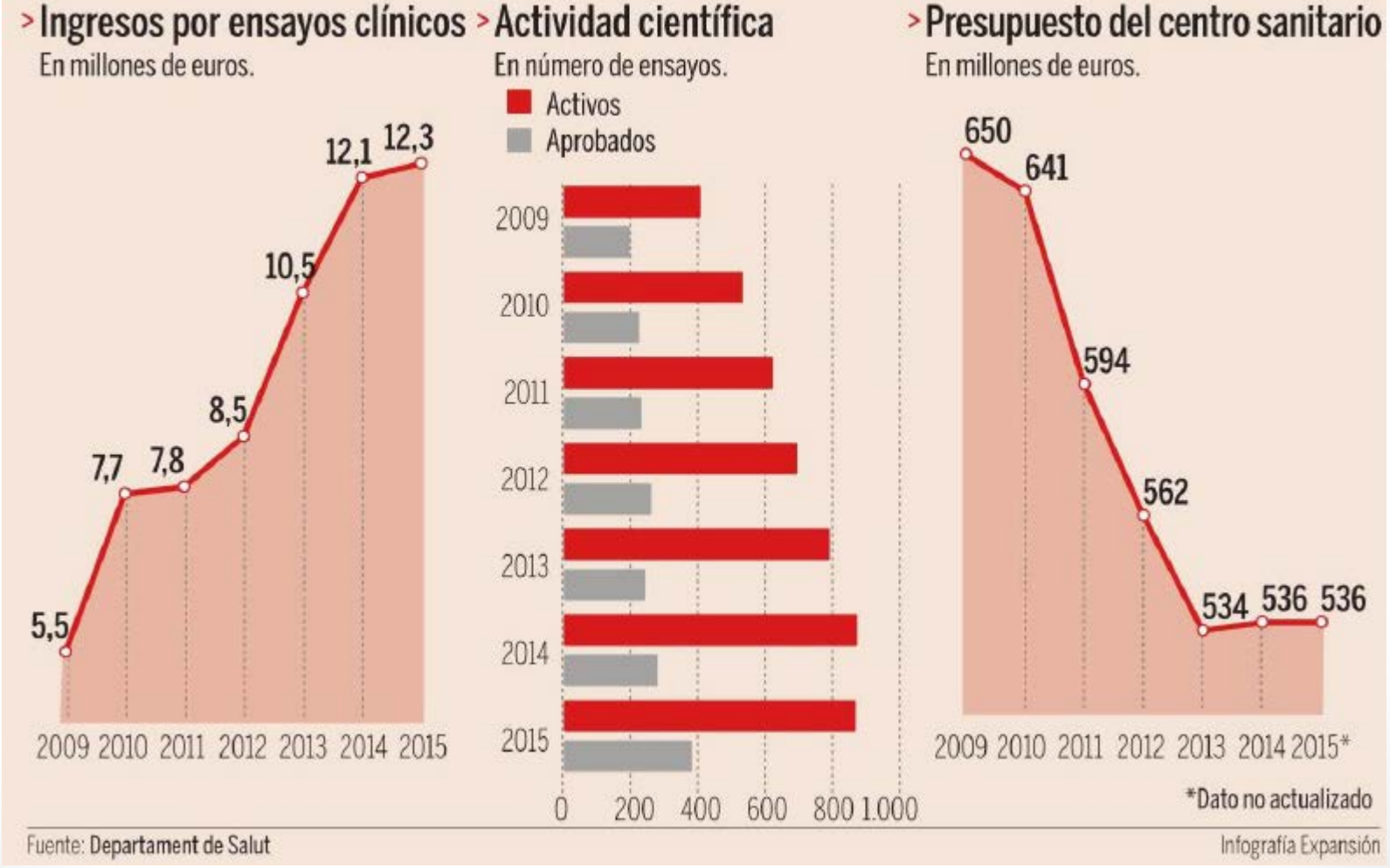
Therapeutic Paradigms

society

New research models

Integration of Research and Care

EVOLUCIÓN DE LOS ENSAYOS CLÍNICOS EN VALL D'HEBRON



Fuente: **Departament de Salut**

Infografía Expansión

The conundrum:

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The biology is complex…

Technology has improved…

…but the physician's brain is still dichotomic

The Dichotomic Brain

MUTANT or **WILD TYPE**
INCLUDED or **EXCLUDED**
RESPONDER or **NOT RESPONDER**
DRUG A or **DRUG B**

On-label treatments

Off-label treatments
Clinical trials

Healthcare

*HER2*ampl. HER2-inhibitors
EGFR mut.- EGFR inhibitors
ALK/ROS1 ampl. ALK-inhibitors
CKIT mut- inhibidores KIT
BRAF mut.- BRAF inhibitors
BRCA1/2 mut.- PARP inhibitors

Clinical Research

*FGFR1*ampl. FGFR inhibitors
*FGFR2*ampl. FGFR inhibitors
*FGFR1*mut. FGFR inhibitors
*FGFR2*mut. FGFR inhibitors
*FGFR3-TACC3*trans.- FGFR inhibitors
PTCH mut.- SMO inhibitors
SMO mut.- SMO inhibitors
KRAS mut.- MEK inhibitors
NRAS mut.- MEK inhibitors
*PIK3CA*mut. PI3K inhibitors
*PTEN*mut.- PI3K inhibitors
AKT1/2 mut.- AKT inhibitors
*NOTCH1*mut. NOTCH inhibitors
*HER2*mut. HER2-inhibitors
*MET*ampl. MET-inhibitors
*MET*mut. MET-inhibitors
…

Modern times: NGS as the high-density multiplexing platform

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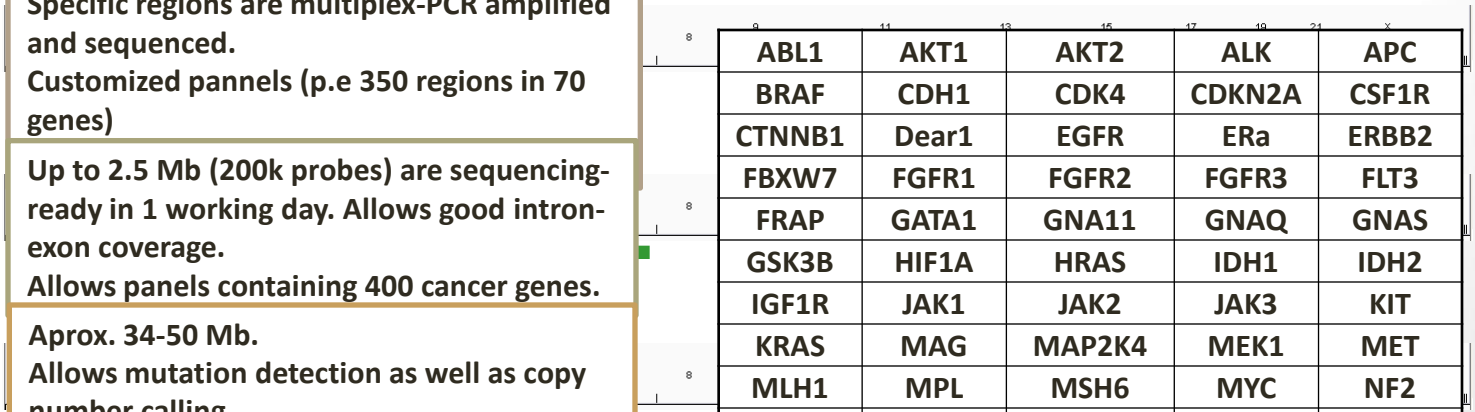
CLINICAL PRACTICE

- **Amplicon-seq**
- **Capture approaches**
- **Exome-seq**
- **Whole genome sequencing**

Specific regions are multiplex-PCR amplified and sequenced.
Customized pannels (p.e 350 regions in 70 genes)

Up to 2.5 Mb (200k probes) are sequencing-ready in 1 working day. Allows good intron-exon coverage.
Allows panels containing 400 cancer genes.

Aprox. 34-50 Mb.
Allows mutation detection as well as copy number calling.
Expensive, needs time for bioinformatics



ABL1	AKT1	AKT2	ALK	APC
BRAF	CDH1	CDK4	CDKN2A	CSF1R
CTNNB1	Dear1	EGFR	ERa	ERBB2
FBXW7	FGFR1	FGFR2	FGFR3	FLT3
FRAP	GATA1	GNA11	GNAQ	GNAS
GSK3B	HIF1A	HRAS	IDH1	IDH2
IGF1R	JAK1	JAK2	JAK3	KIT
KRAS	MAG	MAP2K4	MEK1	MET
MLH1	MPL	MSH6	MYC	NF2
NF3	NOTCH1	NOTCH4	NRAS	PDGFRA
PIK3CA	PIK3R1	PIK3R5	PRKAG1	PRKAG2
PTCH1	PTEN	RB1	RET	RICTOR
RUNX1	SMAD4	SMARCB1	SMO	SRC
STK11	TNK2	TP53	VHL	WT1

RESEARCH

Liquid biopsies: genotyping Circulating tumor DNA

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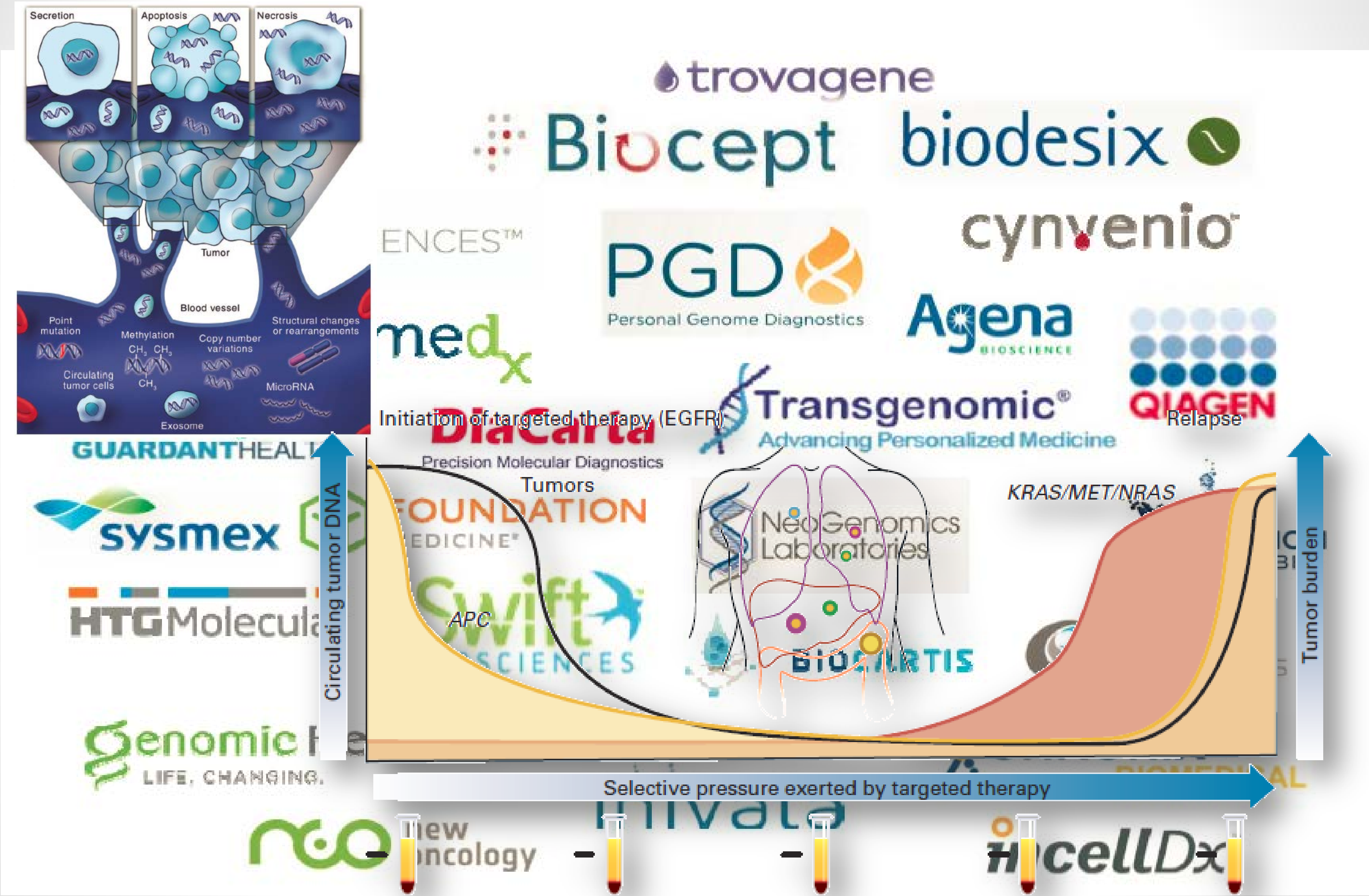

Molecular prescreening initiavies: matching alteration and drug

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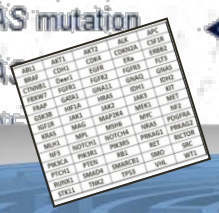
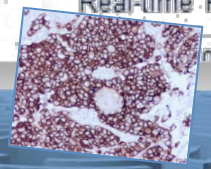
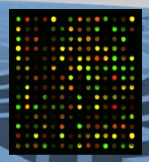
Breast cancer HER2 positive
Breast cancer HR positive
Breast cancer Triple negative
NSCLC EGFR mutant
NSCLC ALK rearranged
Squamous NSCLC
CRC KRAS wild-type
CRC KRAS mutant
Ovarian cancer
Endometrial cancer
Melanoma BRAF m
Melanoma BRAF wi
Papillary thyroid cancer
Medullary thyroid cance
Pancreatic cancer
Gastric cancer HER2 p
Gastric cancer HER2 n
Bladder cancer
Glioblastoma
Medulloblastoma
Basal cell carcinoma

PIK3CA mutation
PIK3CA amplification
PTEN mutation
PTEN loss of expression
KRAS mutation
NRAS mutation
HRA

IHC
FISH
CGH
Sanger Sequencing
Real-time PCR mutation kits
hout genotyping







PI3K inhibitor
BRAF inhibitor
MEK inhibitor
MEK inhibitor
nhibitor
hibitor
nhibitor
FR inhibitor
versible EGFR/HER2 inhibitor
cond-generation EGFR antibod
P90 inhibitor

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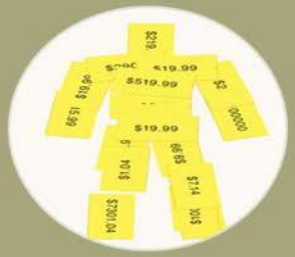
Understanding the disease

Therapeutic Paradigms

Cancer and society



New research models

Integration of Research and Care

Social expectations

Social expectations

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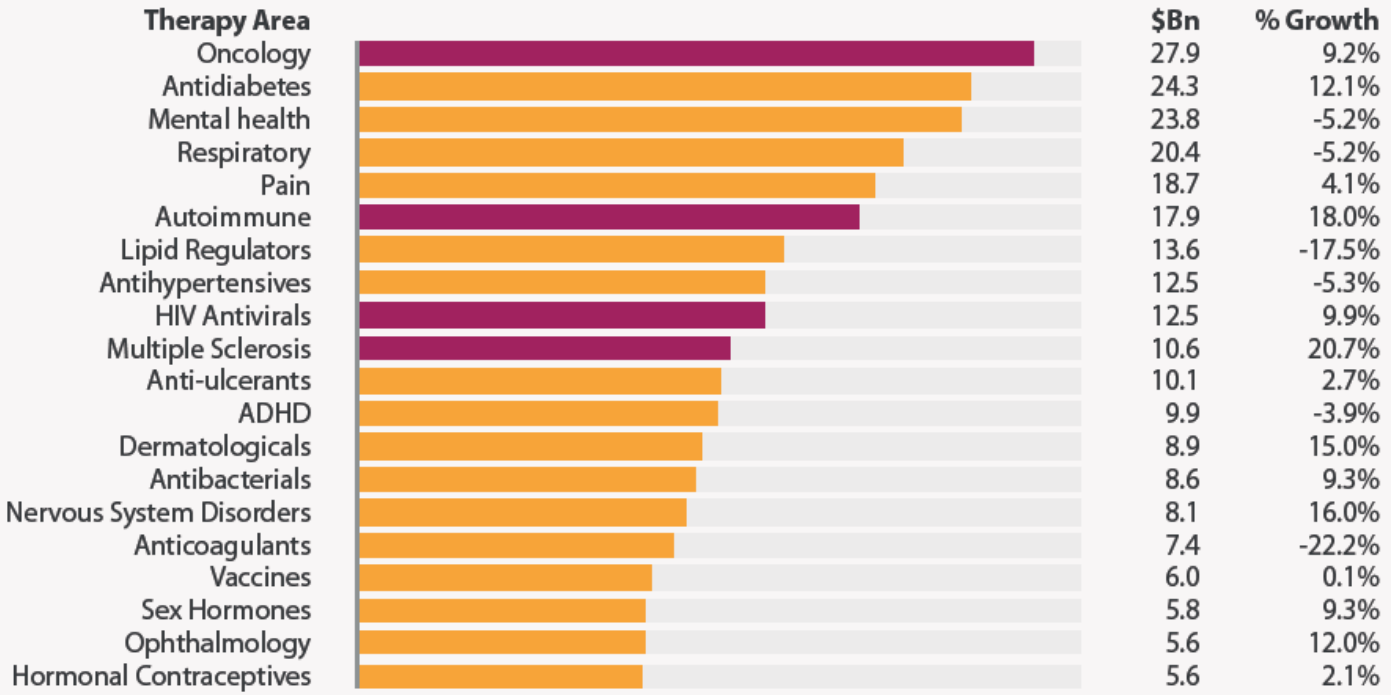
Spending on Medicines in Leading Therapy Areas

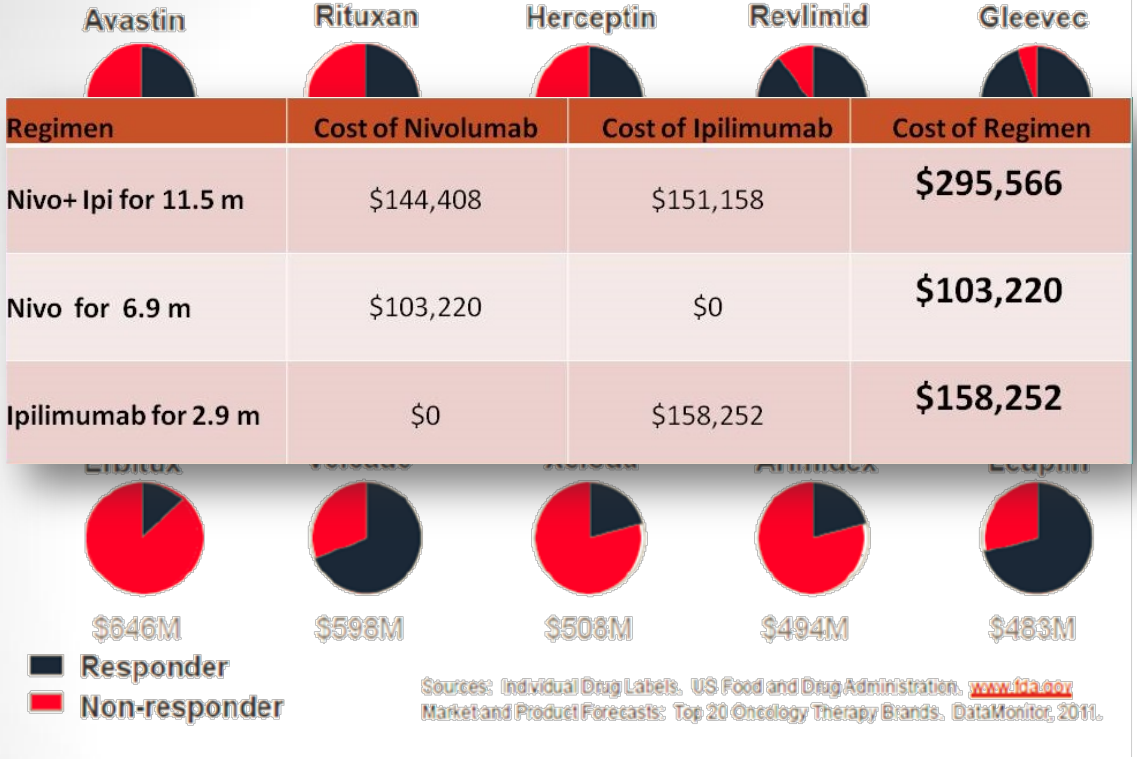
Over one-third of spending is concentrated in the top 5 therapies

Spending in leading therapy areas



http://www.imshealth.com/portal/site/imshealth. Accessed May 2014.

Cost and Value

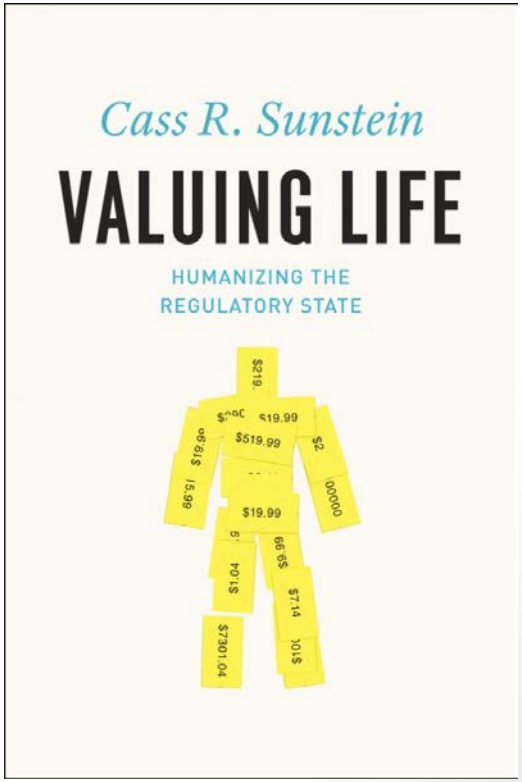


Regimen	Cost of Nivolumab	Cost of Ipilimumab	Cost of Regimen
Nivo+ Ipi for 11.5 m	$144,408	$151,158	**$295,566**
Nivo for 6.9 m	$103,220	$0	**$103,220**
Ipilimumab for 2.9 m	$0	$158,252	**$158,252**

Drug
Effectiveness
Statistically significant
Clinically relevant
Cost-Effective
Value ≠ Cost
QALYs

The QALY is just a well researched number.
The value of a life is far more complex question

Many people are cheering a new potential solution: paying for drugs according to how well they actually work.



Cost and Value

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Comparison of Major Value-Based Frameworks

Framework Comparison		ASCO Framework	Sloan Kettering "DrugAbacus"	NCCN* Value Tool	Quintiles Value Framework
Inputs	Clinical Benefit	X	X	X	X
	Toxicity / Safety	X	X	X	X
	Price	X	X	X	X
	Quality / Consistency of Data		X	X	X
	Novelty		X		X
	Rarity of Disease		X		X
	Population		X		X
	Treatment Duration		X		X
	Cost of Drug Development		X		
Outputs	Net Health Benefit	X			
	Cost vs. Benefit		X	X	X
	Recommended Price		X		X
Limitations	Not Comparable Across Landscape	X			
	Currently Available	Preliminary Draft	X		X
	Designed for Use by Singular Patient	X	X	X	
Methods	Adjustable Weighting		X		X
	Complex, Customized Formula		X		X

Vikas Chawla1, Craig White1,2, John Doyle1 (1Quintiles Advisory Services, New York, NY, USA; 2PhD Program in Health Policy, Harvard Graduate School of Arts and Sciences, Cambridge, MA

Financial turmoil

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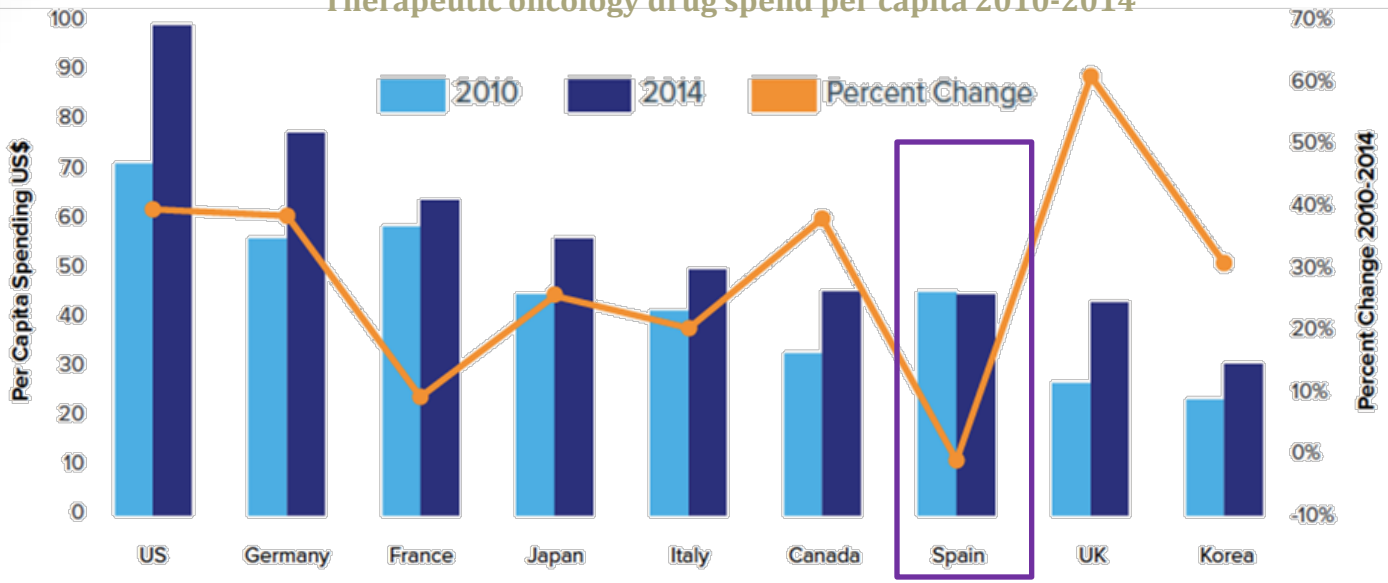
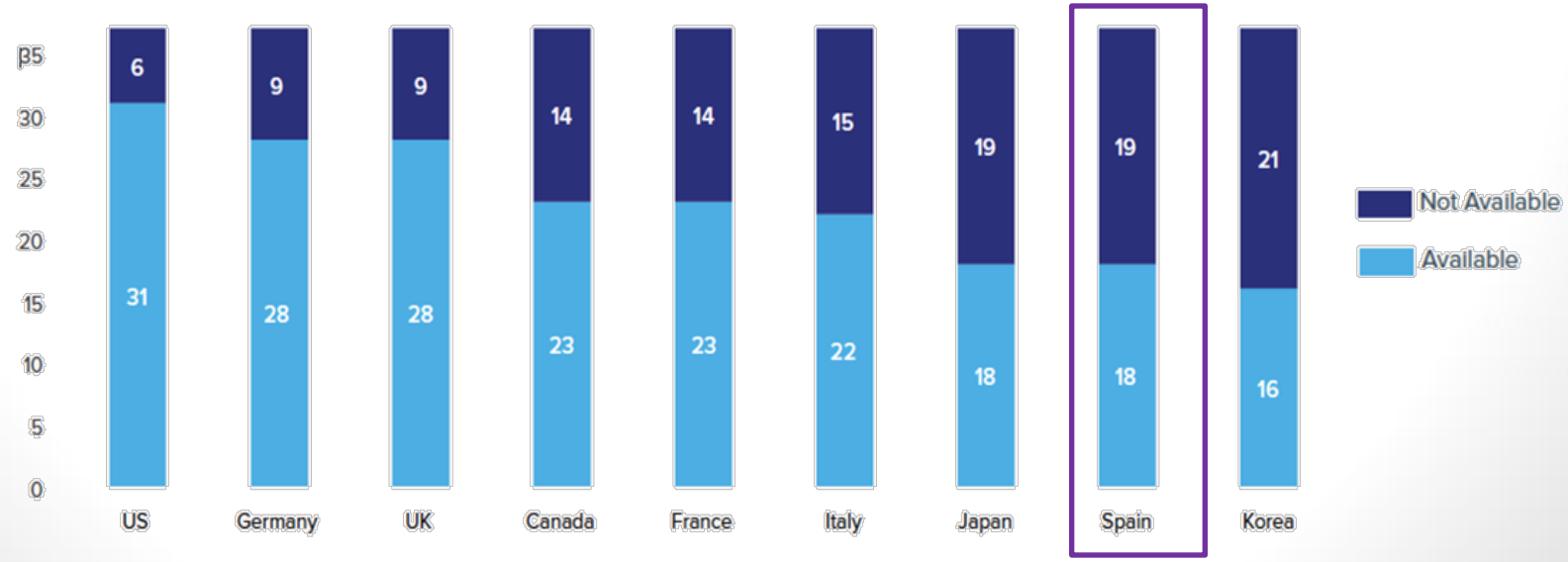
Therapeutic oncology drug spend per capita 2010-2014



Global New Molecular Entities 2009-2013 (Availability as of 2014)



Source: IMS Health MIDAS, Dec 2014; The World Bank, 2015

Political turmoil

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Una publicación de Sanitaria
Domingo, 13 de marzo de 2016 | Nº 2977

Redacción Médica
A la vanguardia de la información sanitaria

CATALUÑA

UNA INVERSIÓN DE 25 MILLONES DE EUROS

La investigación mundial dispondrá del 'big data' catalán

La ag
Lunes,

POR UNANIMIDAD

El 'big data' en centros de investigación, paralizado por el Parlamento

El G
Juev

≡ EL PAÍS

CATALUÑA

ANDALUCÍA CATALUÑA C. VALENCIANA GALICIA MADRID PAÍS VASCO MÁS COMUNIDADES TITULARES »

La CUP exige la "paralización inmediata" del VISC+

Los a
sin el

CON TODAS LAS GARANTÍAS POSIBLES

Los médicos de Barcelona reclaman aplicar el Visc+

Reclamar

PROGRAMA VISC+

Sábado, 30

Comín se estrena en el Parlamento garantizando que no venderá datos clínicos

El consejero cree que frenar el programa Visc+ significaría frenar la investigación

Miércoles, 03 de febrero de 2016, a las 13:39

Science	Molecular Oncology. Immunology.
Technology	Genomics, Big data
Trials	Acknowledge that all cancers will be rare diseases; New clinical trial models; New infrastructure and regulatory models
Teamwork	Public-Private, Biobanking, Regulators and Public opinion. Investment. Integration of Research in Health Care