I NUOVI PRINCIPI ATTIVI (HORIZON SCANNING)

CARATTERISTICHE GENETICHE-EPIGENETICHE DEL PAZIENTE

E RICERCA CLINICA

Maria Cecilia Giron, PharmD, PhD

Pharmacology Section

Department of Pharmaceutical and Pharmacological Sciences

School of Medicine

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OUTLINE

- ✓ Drug development and clinical research in oncology
- ✓ Traditional chemotherapy versus targeted cancer therapies
- ✓ Trial designs for testing efficacy of molecular profiling-assigned targeted agents
- ✓ US Precision Medicine Initiative
- ✓ The “omics” world

Of more than 16.000 compounds currently in development, over 80% are focused on degenerative diseases, cancer and other non-communicable diseases

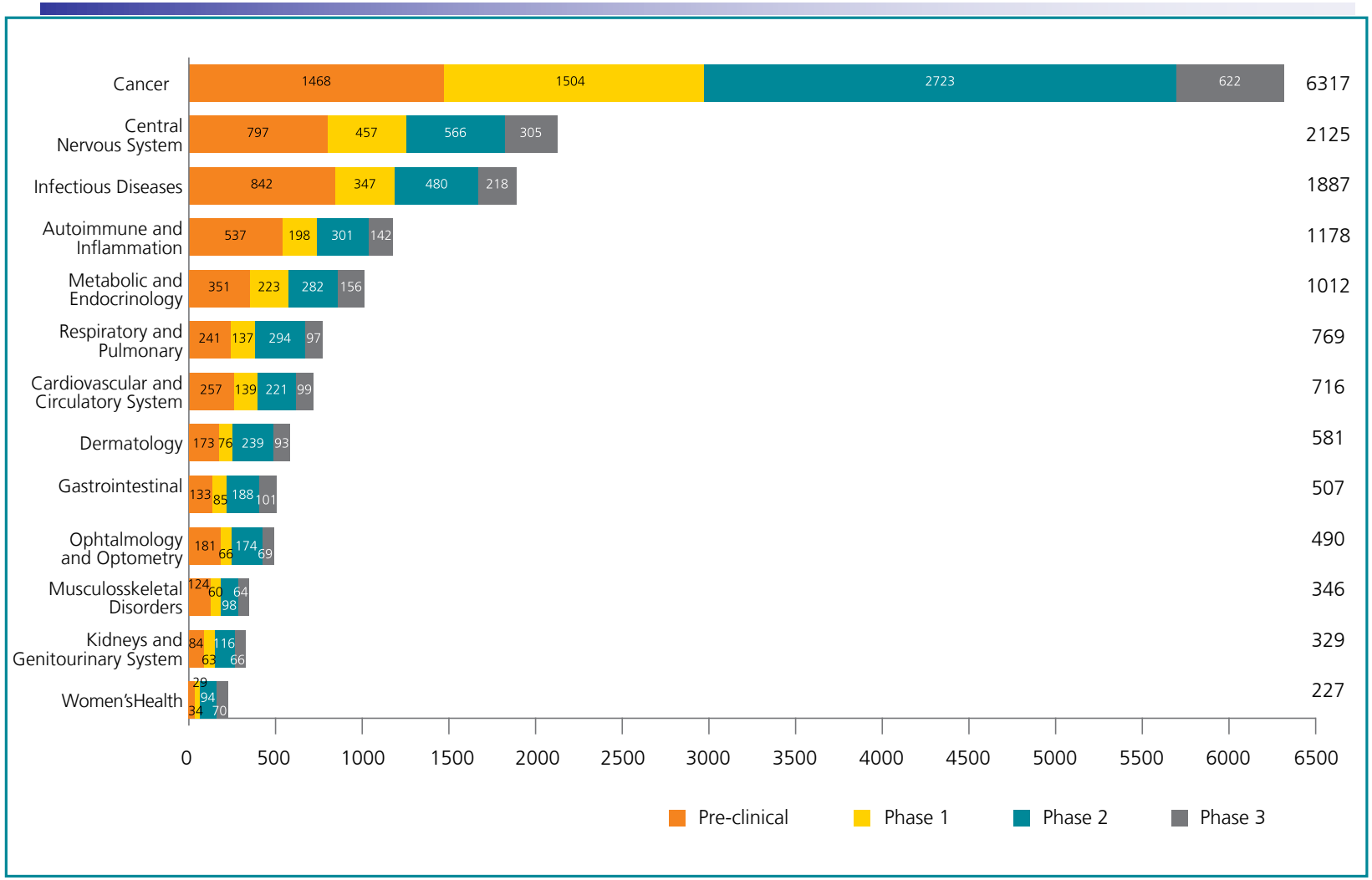
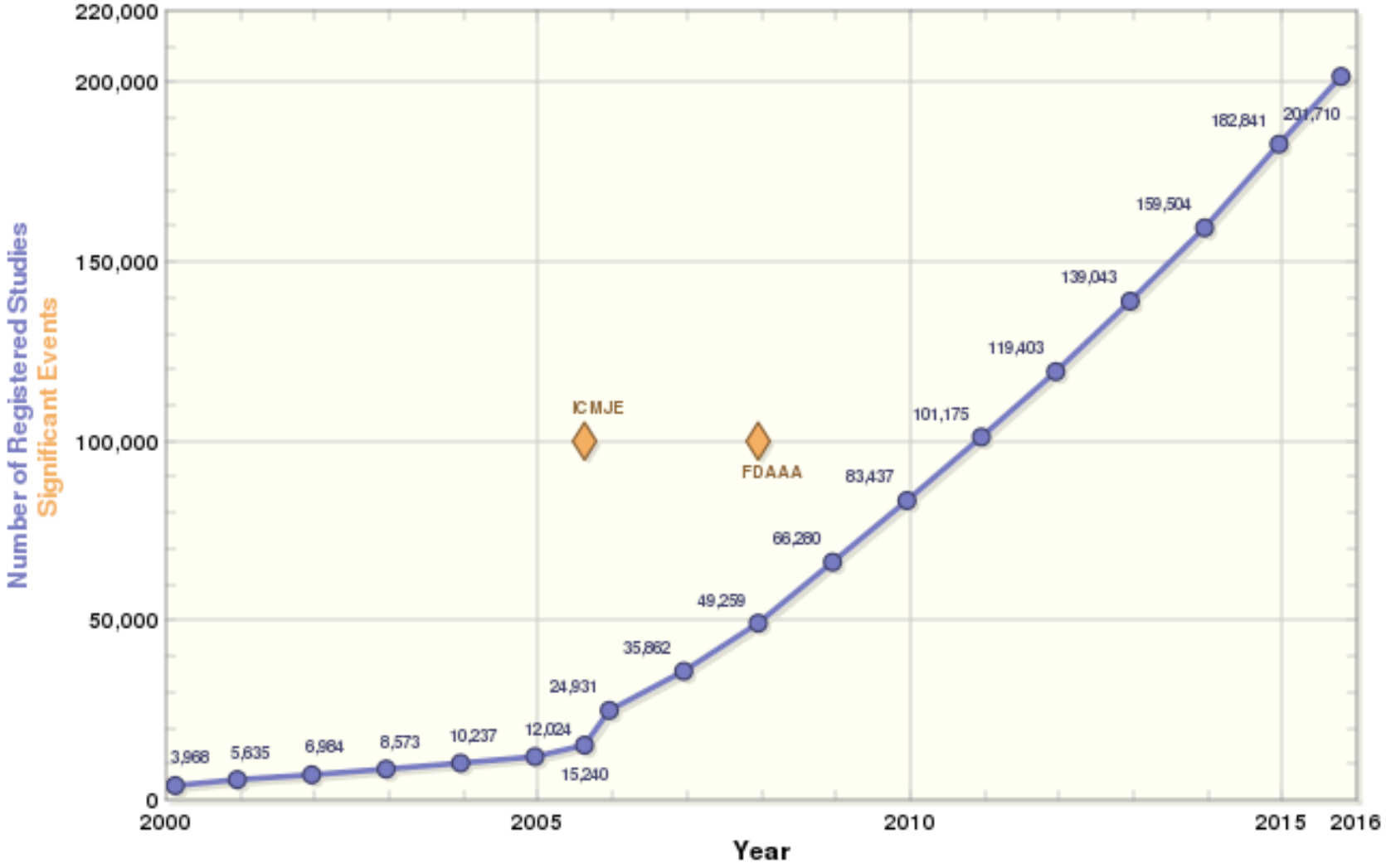


Figure 11: Registered Pipeline Compounds end of year 2011[60]

efpia
European Federation of Pharmaceutical Industries and Associations

NUMBER OF REGISTERED STUDIES OVER TIME AND SIGNIFICANT EVENTS (as of October 30, 2015)

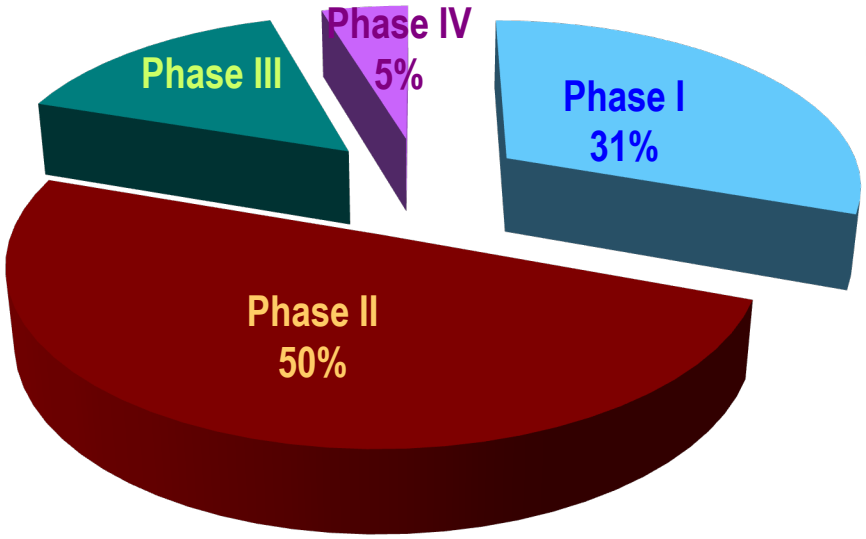


Source: https://ClinicalTrials.gov

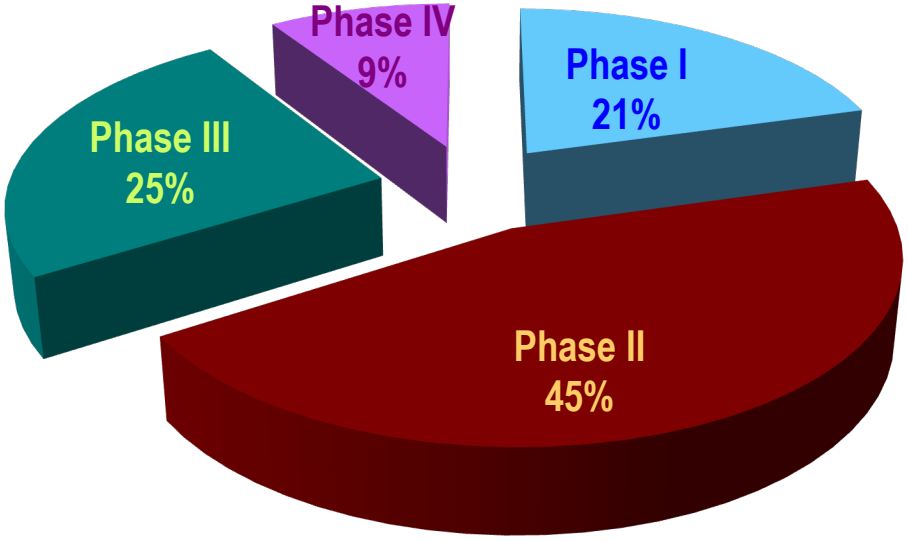
ICMJE: International Committee of Medical Journal Editors required trial registration as a condition of publication (September 2005)

FDAAA: Expanded registration requirements of FDAAA began and were implemented on ClinicalTrials.gov (December 2007)

CURRENT ON-GOING TRIALS IN ONCOLOGY



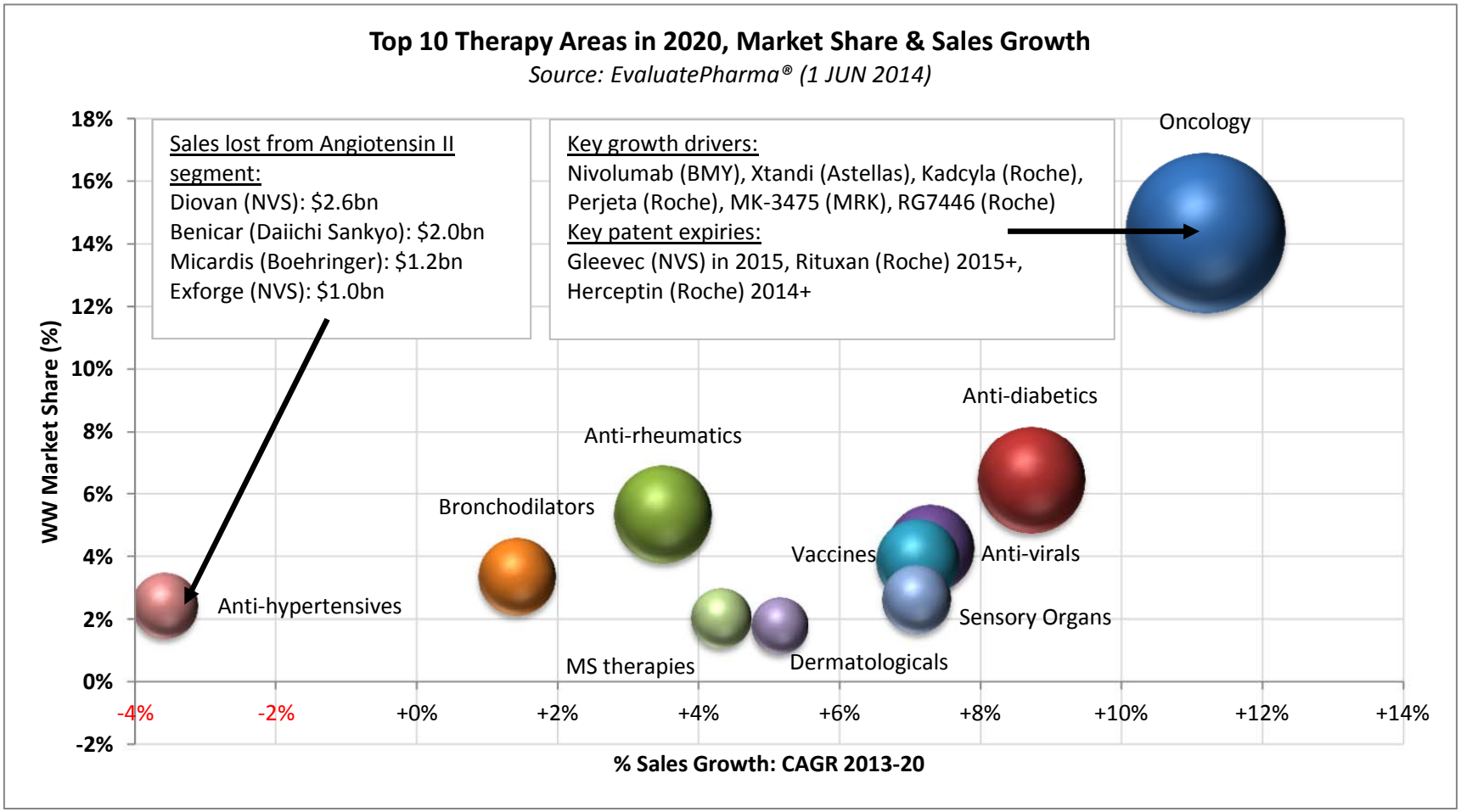
Total World: 2,377



Total EU: 577

Source: https://clinicaltrials.gov

SALES FORECAST BY THERAPEUTIC AREAS



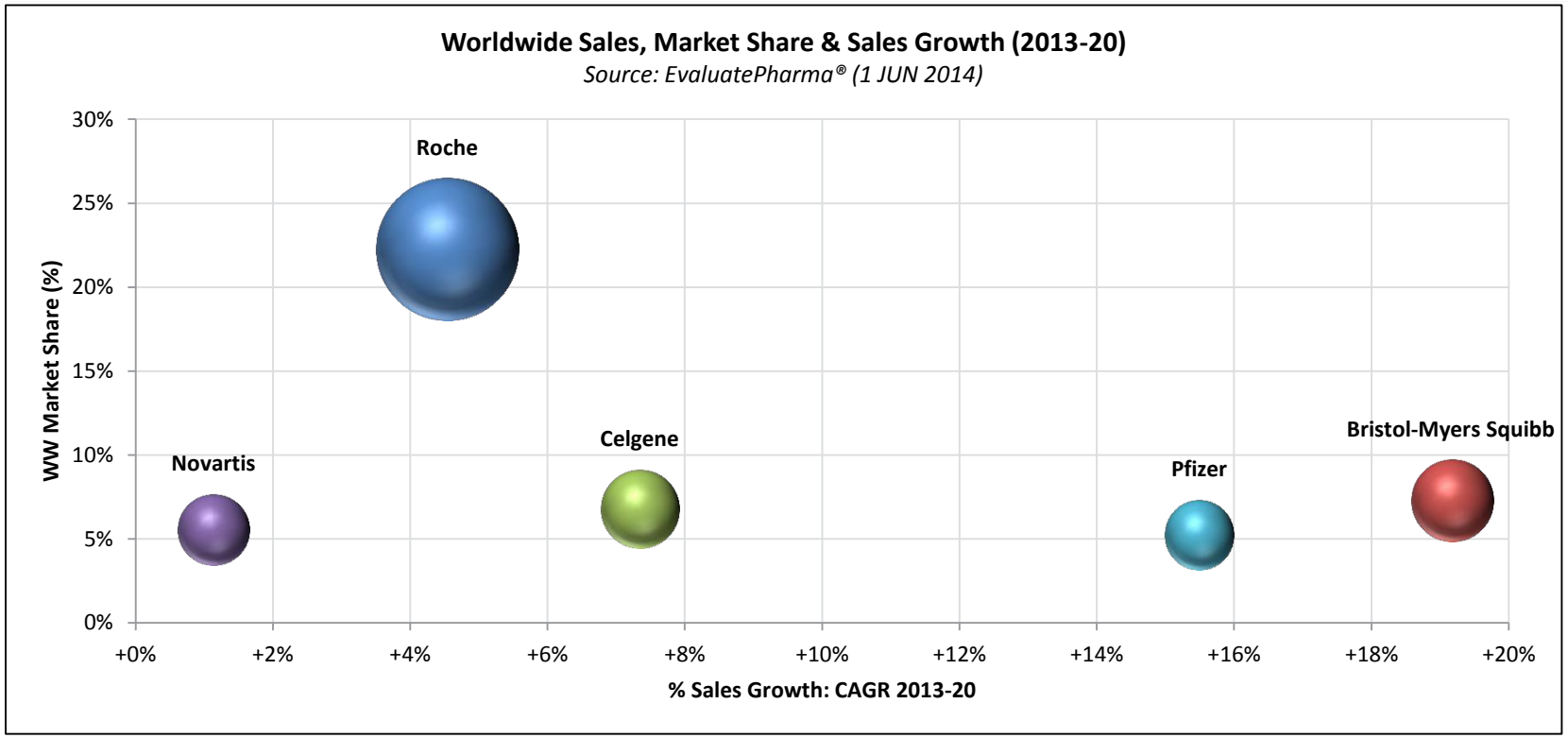
Worldwide Prescription Drug & OTC Sales by Therapy Area in 2020

EvaluatePharma®

SALES FORECAST BY PHARMACEUTICAL COMPANIES

Oncology the largest and fastest growing segment

EvaluatePharma® finds that oncology will remain the largest segment in 2020 with forecasts showing an annual growth of 11.2% and over $153bn sales in 2020. Growth from in-line products, and potential new entrants, is forecast to more than compensate for a number of major patent expiries over the period. Factor Xa inhibitors, Eliquis and Xarelto, are expected to drive a 10.4% annual growth in the anti-coagulant segment and collectively account for almost $9bn of new sales in 2020. Patent expiries on key products continue to erode sales from anti-hyperlipidaemics, with this segment falling seven places over the period to 2020.



Note: Bubble = WW Sales in 2020

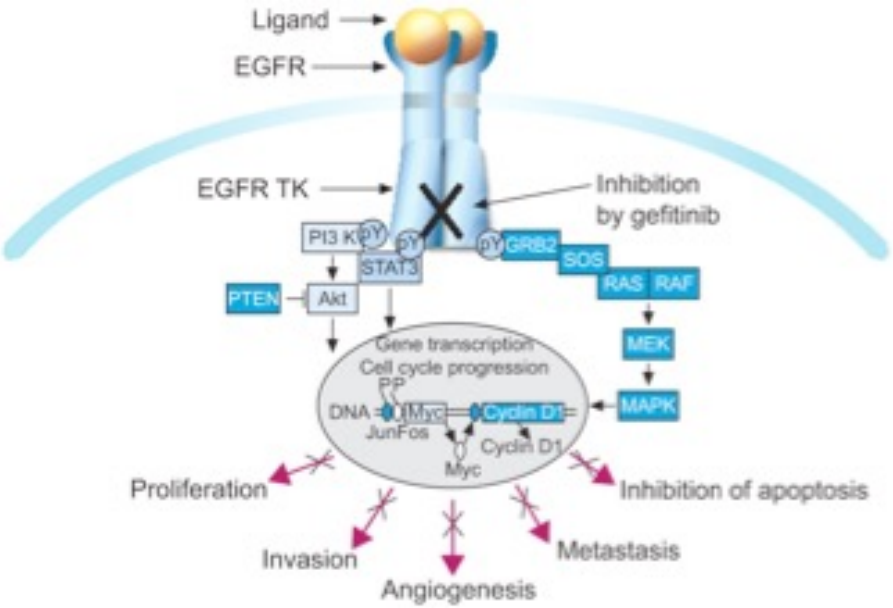
Worldwide Prescription Drug & OTC Sales by Therapy Area in 2020

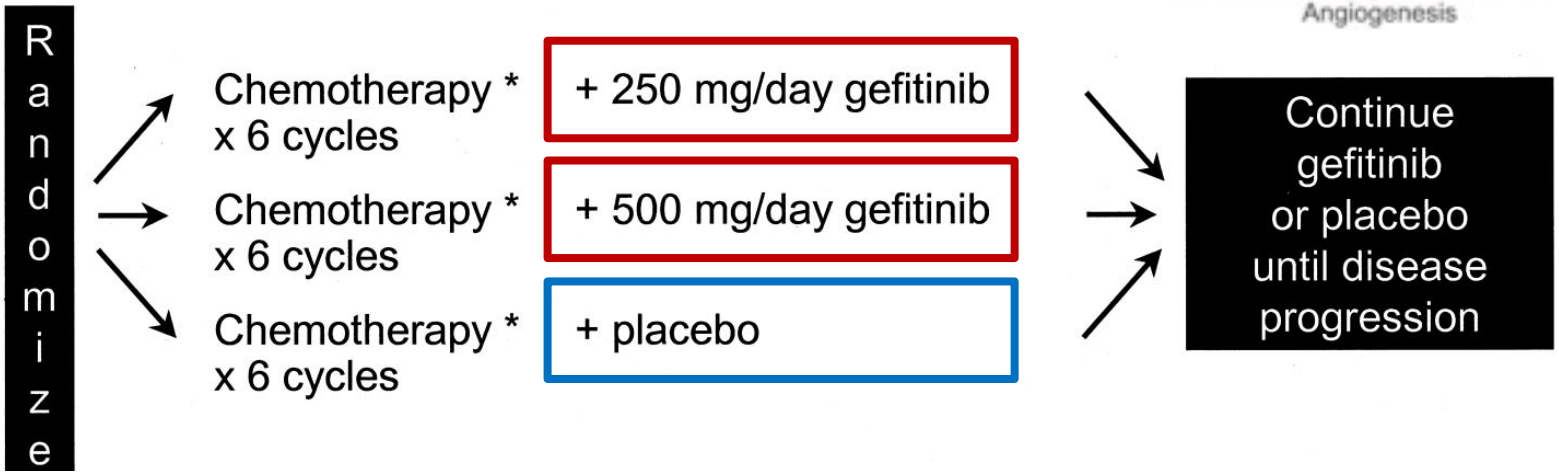
EvaluatePharma®

TRADITIONAL CHEMOTHERAPY AND TARGETED CANCER THERAPIES

GEFITINIB

the first selective inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain.





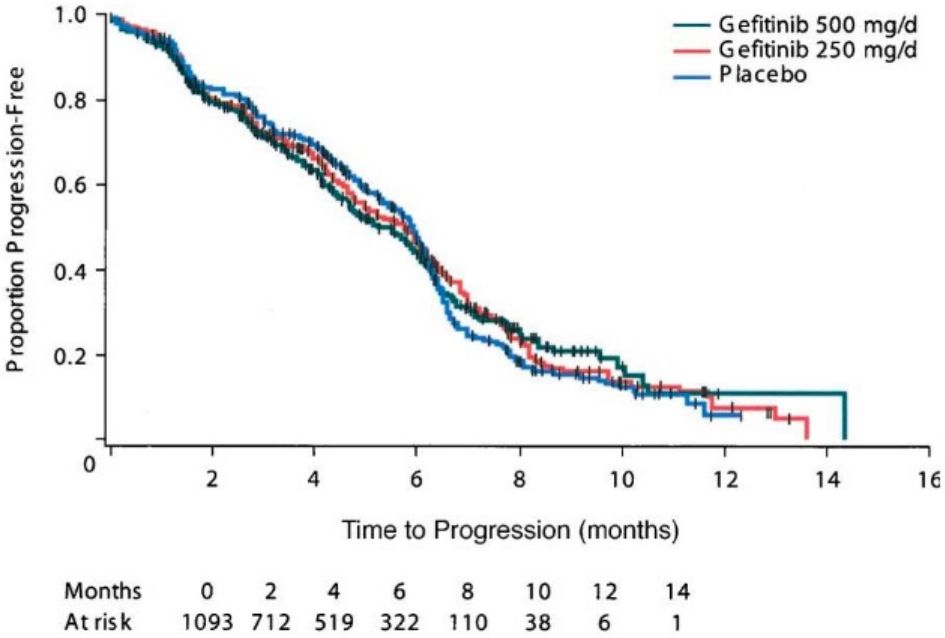
Giaccone G et al. J Clin Oncol. 2004;22:777-84.
Herbst RS et al. J Clin Oncol. 2004;22:785-94.

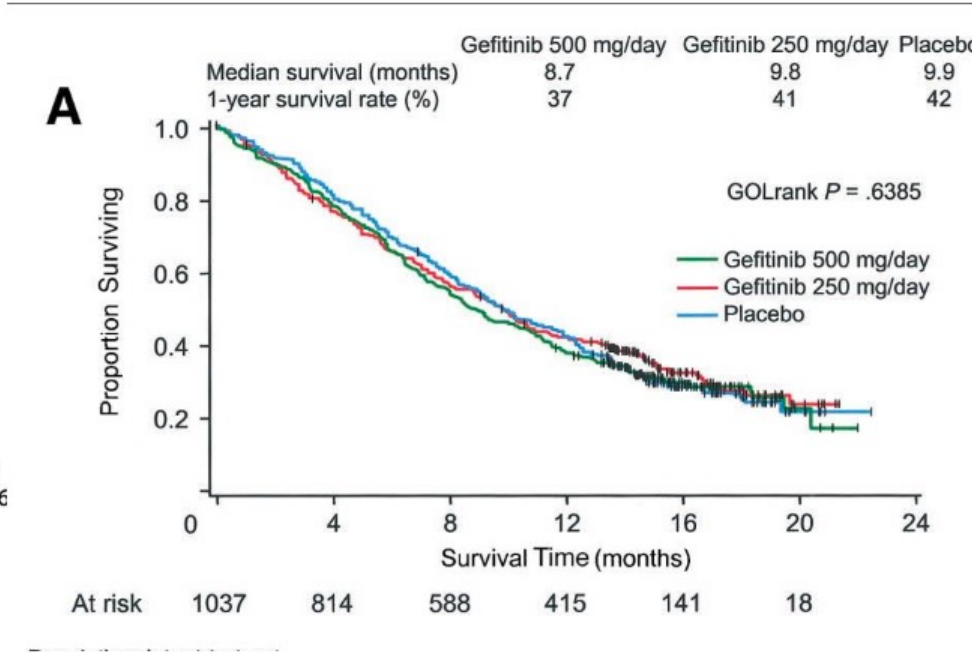
INTACT 1 - Chemotherapy: gemcitabine + cisplatin

INTACT 2 – Chemotherapy: paclitaxel + carboplatin

TRADITIONAL CHEMOTHERAPY AND TARGETED CANCER THERAPIES

The Phase III Trials INTACT 1 and INTACT 2





GEFITINIB + GEMCITABINE + CISPLATIN

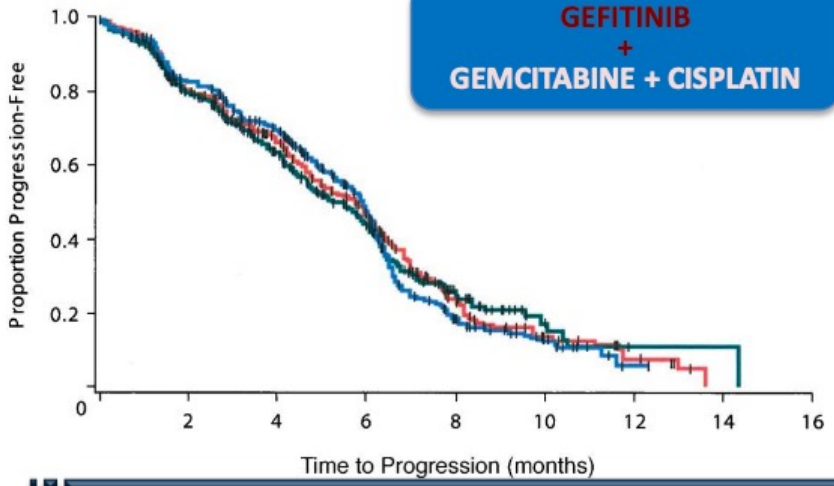
GEFITINIB + PACLITAXEL + CARBOPLATIN

Giaccone G et al. J Clin Oncol. 2004;22:777-84.

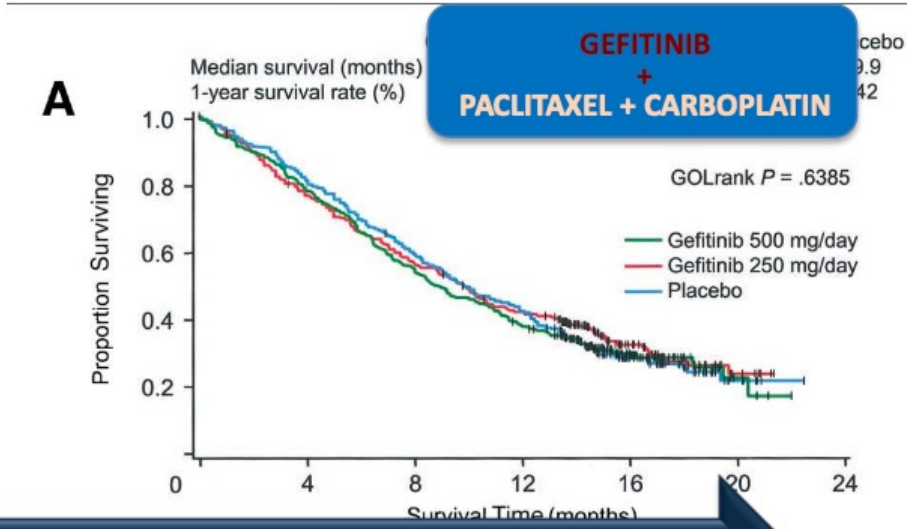
Herbst RS et al. J Clin Oncol. 2004;22:785-94.

TRADITIONAL CHEMOTHERAPY AND TARGETED CANCER THERAPIES

GEFITINIB + GEMCITABINE + CISPLATIN



GEFITINIB + PACLITAXEL + CARBOPLATIN



The traditional DRUG DEVELOPMENT MODEL

PRECLINICAL
- ❑ Target identification (serendipity)
- ❑ Leads synthesis and selection
- ❑ Preclinical activity assays

EARLY CLINICAL
- ❑ Dose and schedule
- ❑ Safety
- ❑ Feasibility

"DEFINITIVE" TRIALS
- ❑ Activity
- ❑ Efficacy
- ❑ Tolerability

In 2004 the SUCCESS RATE for ONCO DRUGS from FIRST-IN-MAN to REGISTRATION was 5%...

Can the pharmaceutical industry reduce attrition rates?

Ismail Kola and John Landis

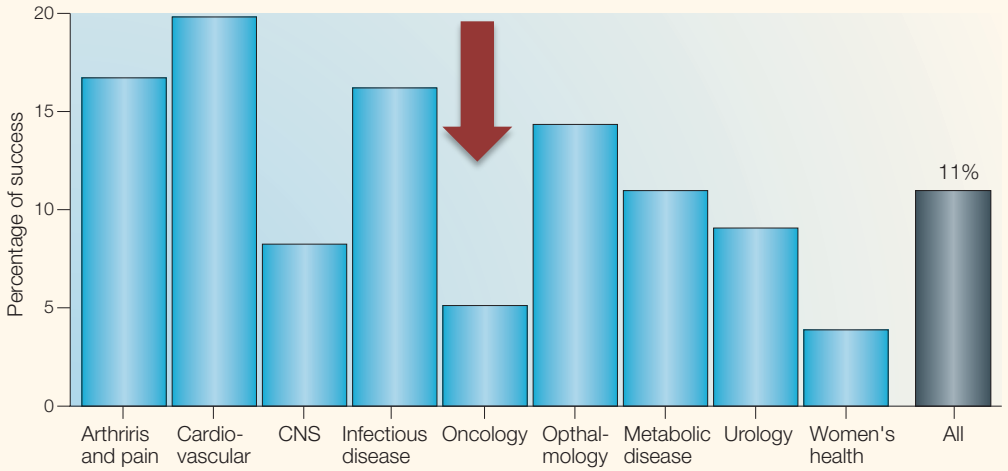
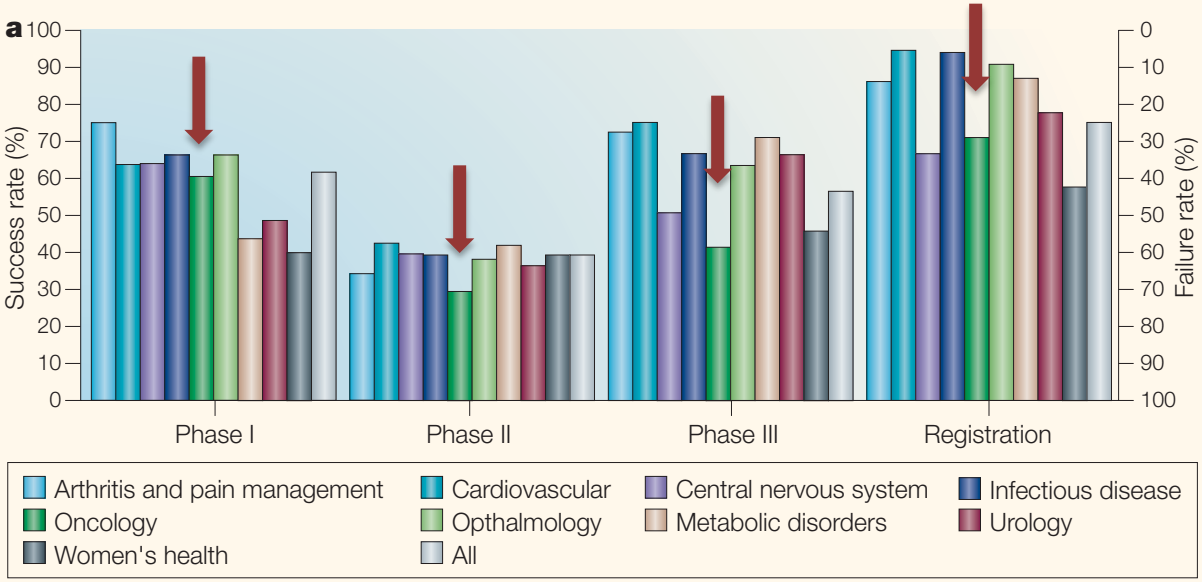


Figure 1 | **Success rates from first-in-man to registration.** The overall clinical success rate is 11%.



Drug Development in Oncology

Why does targeted therapy not cure all tumors?

The somatic activating mutations in the EGFR kinase domain explained the unique subset of drug-responsive cases

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Table 1. Characteristics of Nine Patients with Non–Small-Cell Lung Cancer and a Response to Gefitinib.

Patient No.	Sex	Age at Beginning of Gefitinib Therapy	Pathological Type*	No. of Prior Regimens	Smoking-Status†	Duration of Therapy	Overall Survival‡	*EGFR* Mutation§	Response¶
		yr				*mo*			
1	F	70	BAC	3	Never	15.6	18.8	Yes	Major; improved lung lesions
2	M	66	BAC	0	Never	>14.0	>14.0	Yes	Major; improved bilateral lung lesions
3	M	64	Adeno	2	Never	9.6	12.9	Yes	Partial; improved lung lesions and soft-tissue mass
4	F	81	Adeno	1	Former	>13.3	>21.4	Yes	Minor; improved pleural disease
5	F	45	Adeno	2	Never	>14.7	>14.7	Yes	Partial; improved liver lesions
6	M	32	BAC	3	Never	>7.8	>7.8	Yes	Major; improved lung lesions
7	F	62	Adeno	1	Former	>4.3	>4.3	Yes	Partial; improved liver and lung lesions
8	F	58	Adeno	1	Former	11.7	17.9	Yes	Partial; improved liver lesions
9	F	42	BAC	2	Never	>33.5	>33.5	No	Partial; improved lung nodules

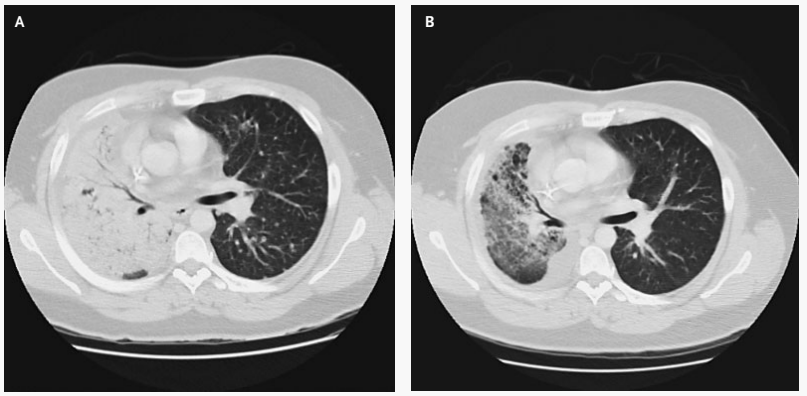


Figure 1. Example of the Response to Gefitinib in a Patient with Refractory Non–Small-Cell Lung Cancer.
A computed tomographic scan of the chest in Patient 6 shows a large mass in the right lung before treatment with gefitinib was begun (Panel A) and marked improvement six weeks after gefitinib was initiated (Panel B).

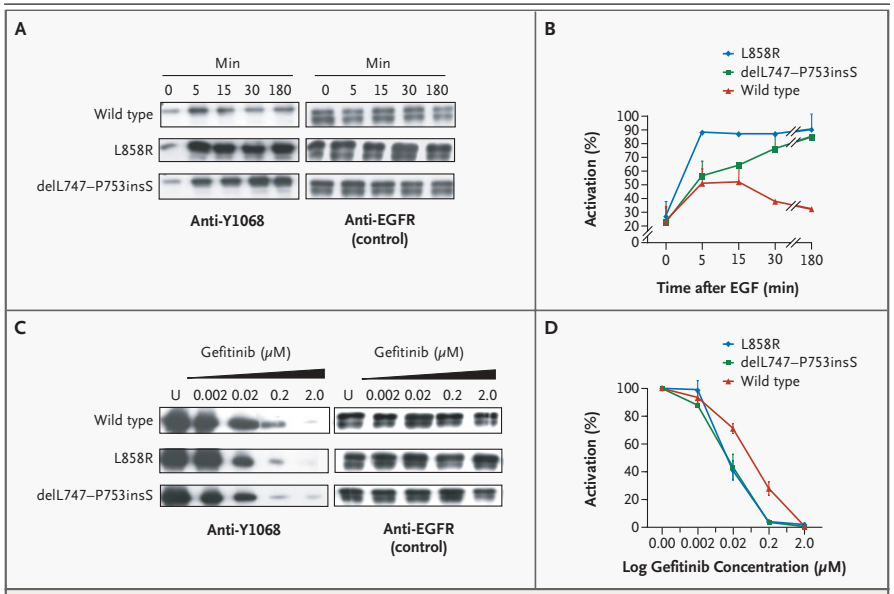
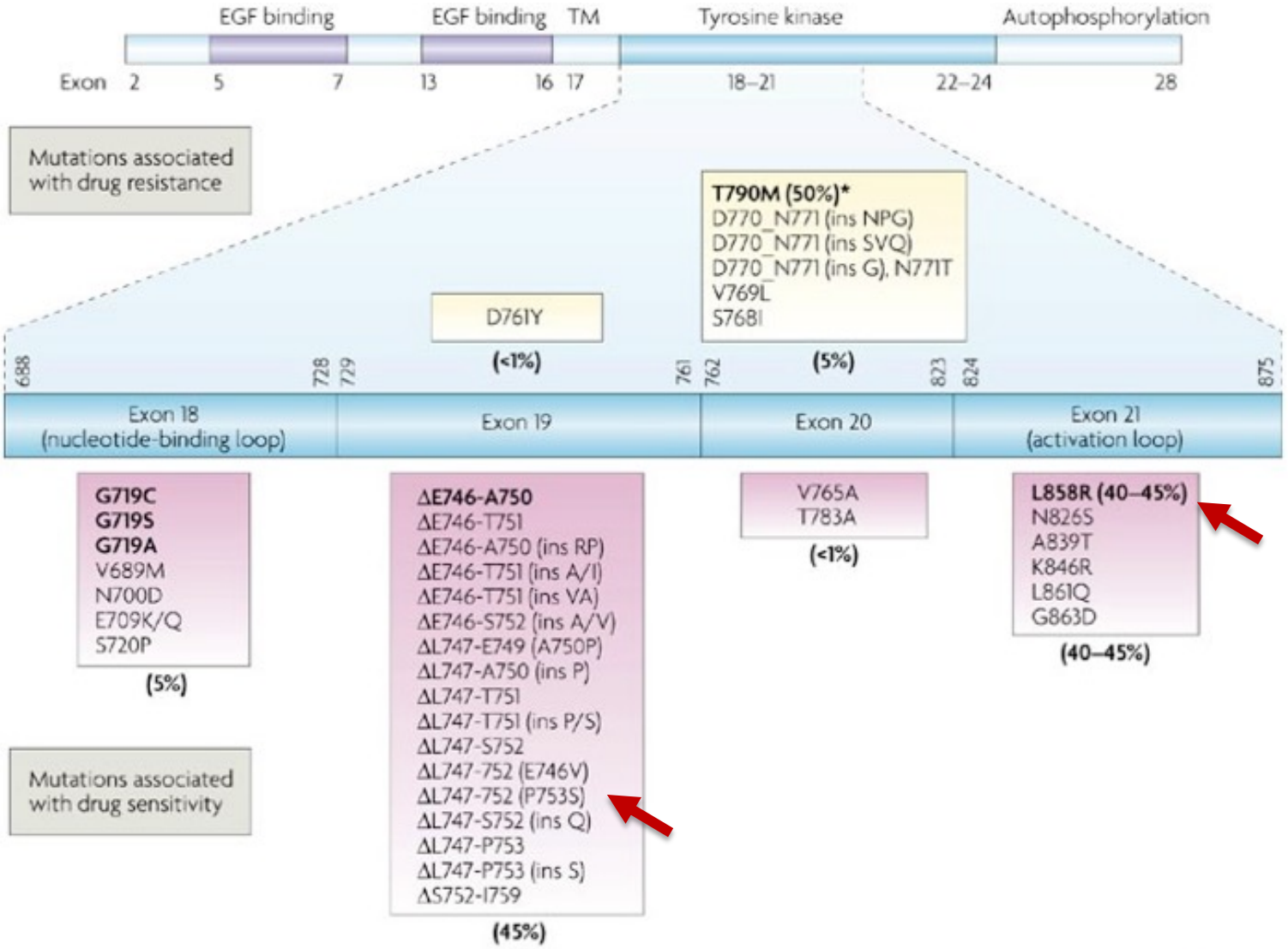
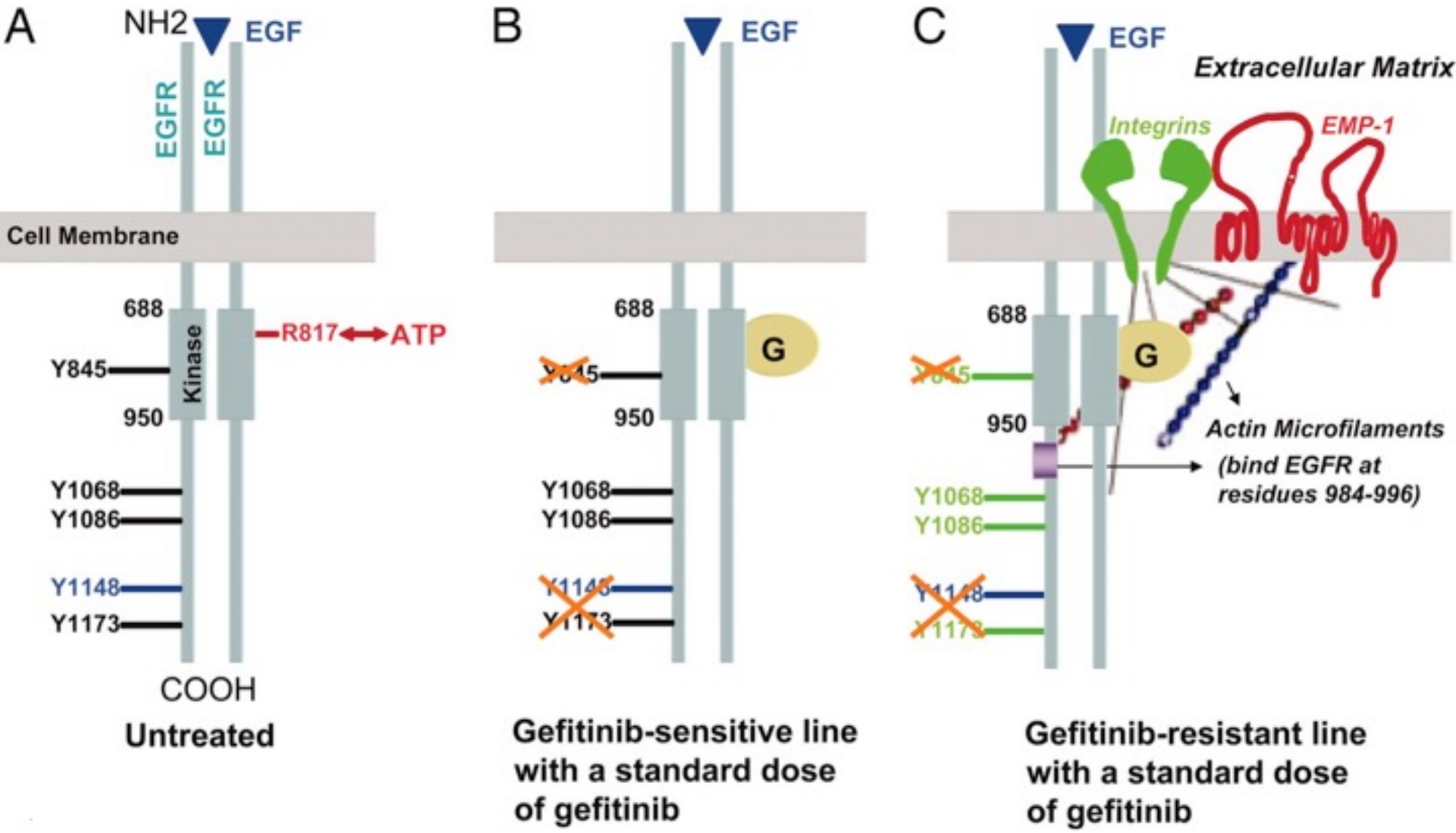


Figure 3. Enhanced EGF–Dependent Activation of Mutant EGFR and Increased Sensitivity of Mutant EGFR to Gefitinib.

The somatic activating mutations in the EGFR kinase domain explained the unique subset of drug-responsive cases

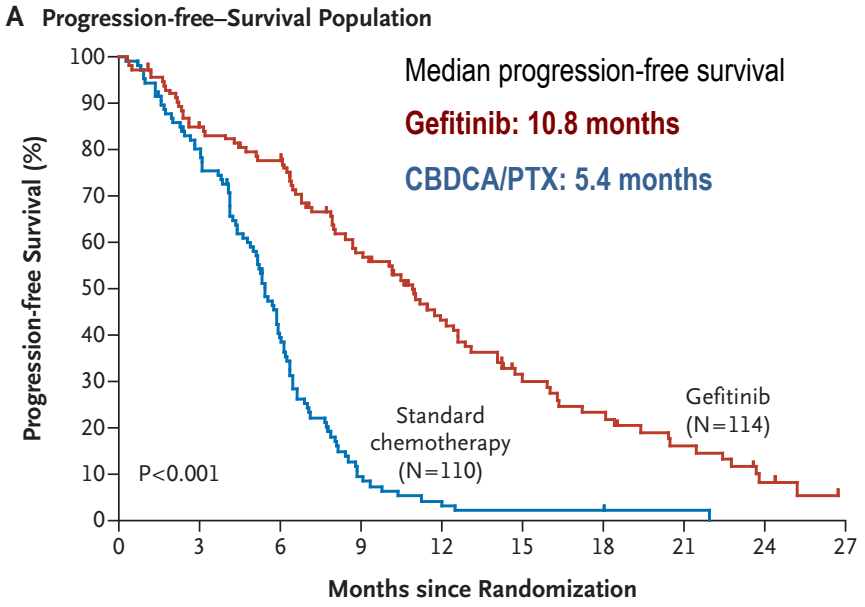


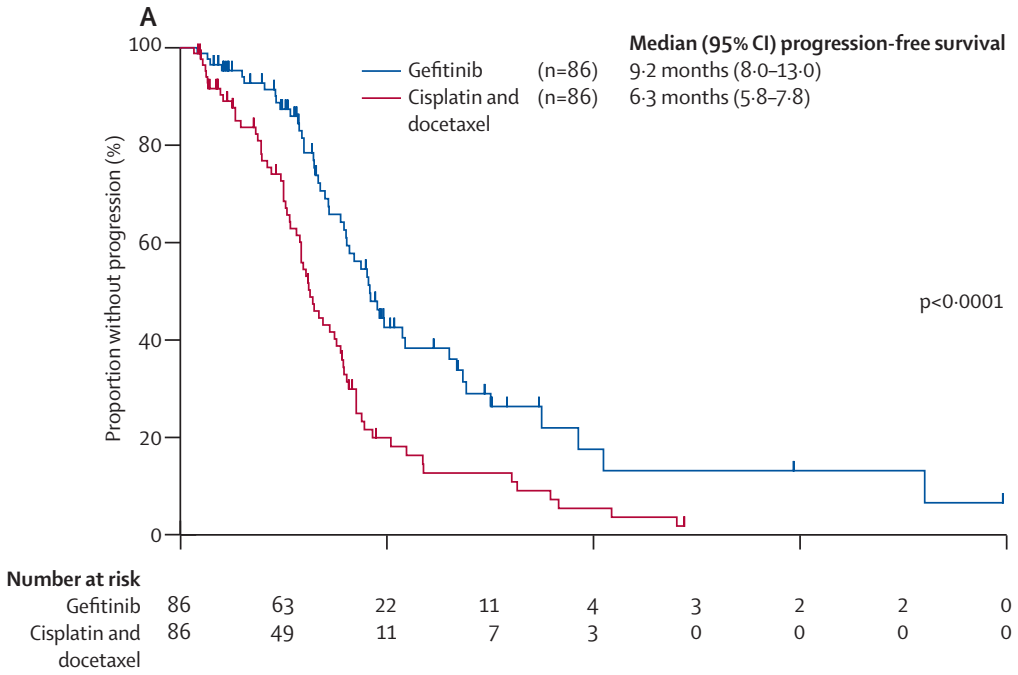
TRADITIONAL CHEMOTHERAPY OR TARGETED CANCER THERAPIES



TRADITIONAL CHEMOTHERAPY OR TARGETED CANCER THERAPIES

Gefitinib or Chemotherapy for Non–Small- Cell Lung Cancer with Mutated EGFR





Standard chemotherapy:

CARBOPLATIN + PACLITAXEL

Standard chemotherapy:

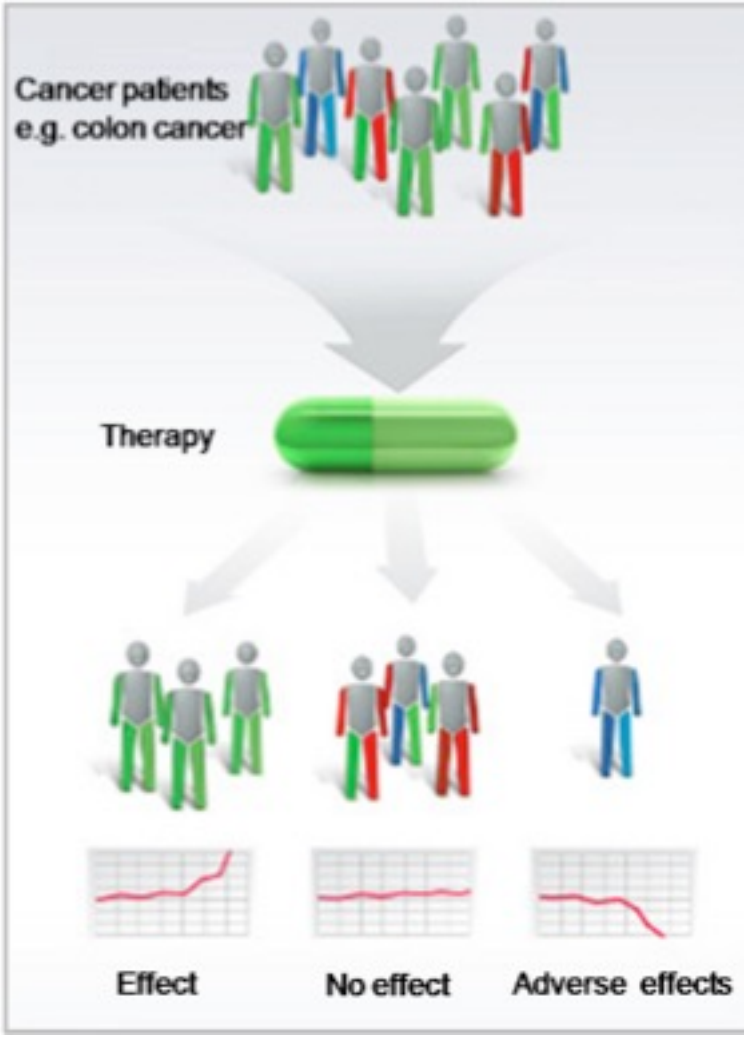
CISPLATIN + DOCETAXEL

Maemondo M et al. N Engl J Med 2010;362:2380 -8.

Mitsudomi T et al. Lancet Oncology 2010;11:121-128.

Drug Development in Oncology: the traditional model

- From the bench to bedside
- One size fits all …regardless of the drug intelligence



Drug Development in Oncology: the traditional model vs. precision medicine

Improving Clinical Trial Efficiency: Thinking outside the Box

Sumithra J. Mandrekar, PhD, Suzanne E. Dahlberg, PhD, and Richard Simon, DSc

The fundamental challenge for development of new cancer therapeutics is therefore to be able to identify and assess activity in molecularly defined patient subsets starting from early phase trials to predict which patients will respond to a new agent/regimen.

Drug Development in Oncology: the traditional model vs. precision medicine

Improving Clinical Trial Efficiency: Thinking outside the Box

Sumithra J. Mandrekar, PhD, Suzanne E. Dahlberg, PhD, and Richard Simon, DSc asco.org/edbook | 2015 ASCO EDUCATIONAL BOOK

The traditional drug development paradigm:

- ✓ **phase I** for establishing the safety profile,
- ✓ **phase II** for efficacy signal,
- ✓ **phase III** for establishing definitive clinical benefit

In **the personalized medicine**:

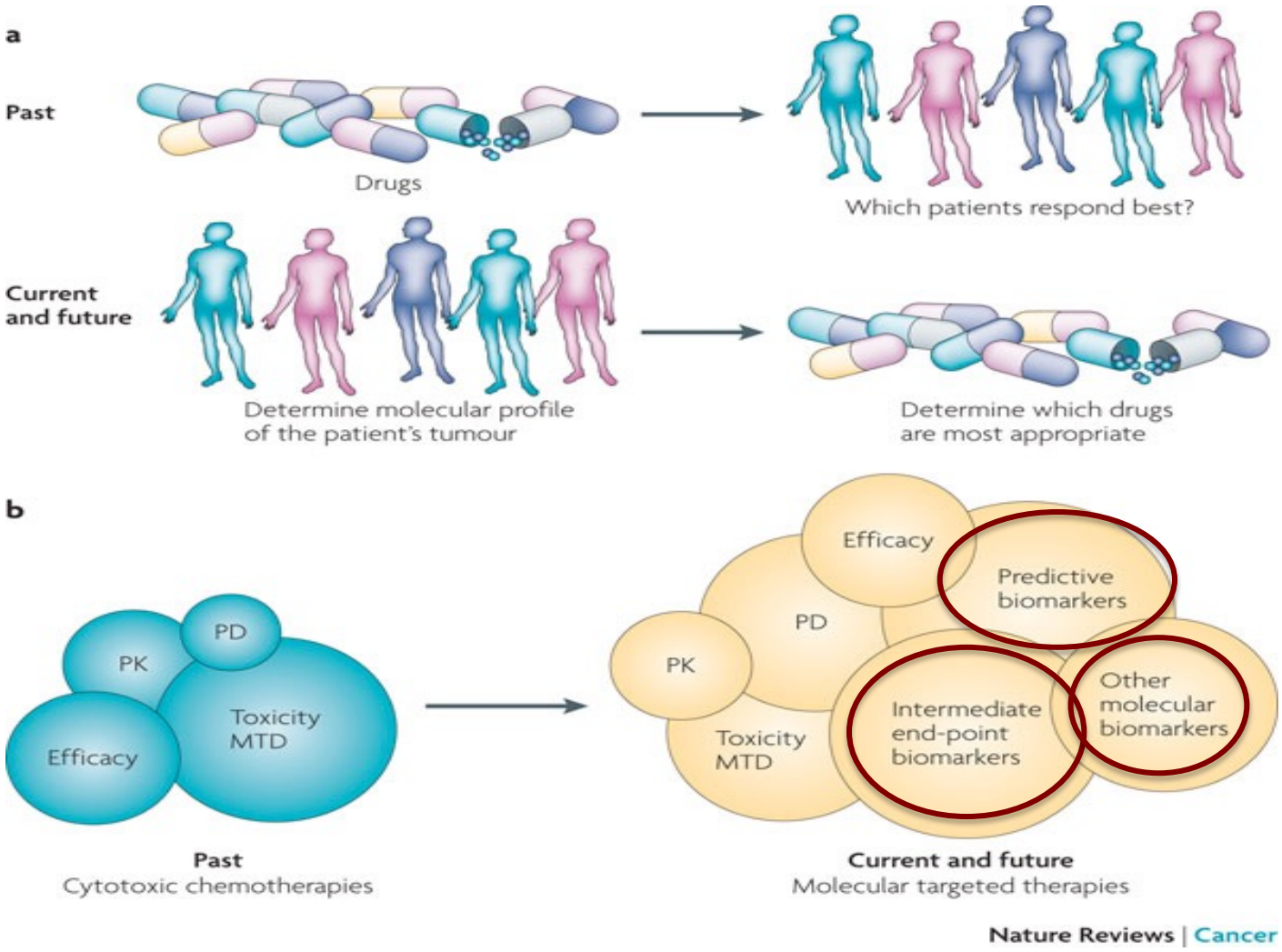
- ✓ a **phase I** study tests the methods of assessment of marker alteration in normal and tumor tissue samples and guides in the determination of cut points, and preliminary assessment of efficacy within molecularly defined subsets,
- ✓ a **phase II** study includes careful retrospective assessment of the marker to establish clinical value,
- ✓ **phase III** trials are confirmatory in nature that validate the marker (and companion diagnostic) through large prospective, randomized, controlled trials (RCT) in a multi-center setting.

Drug Development in Oncology: the traditional model vs. precision medicine

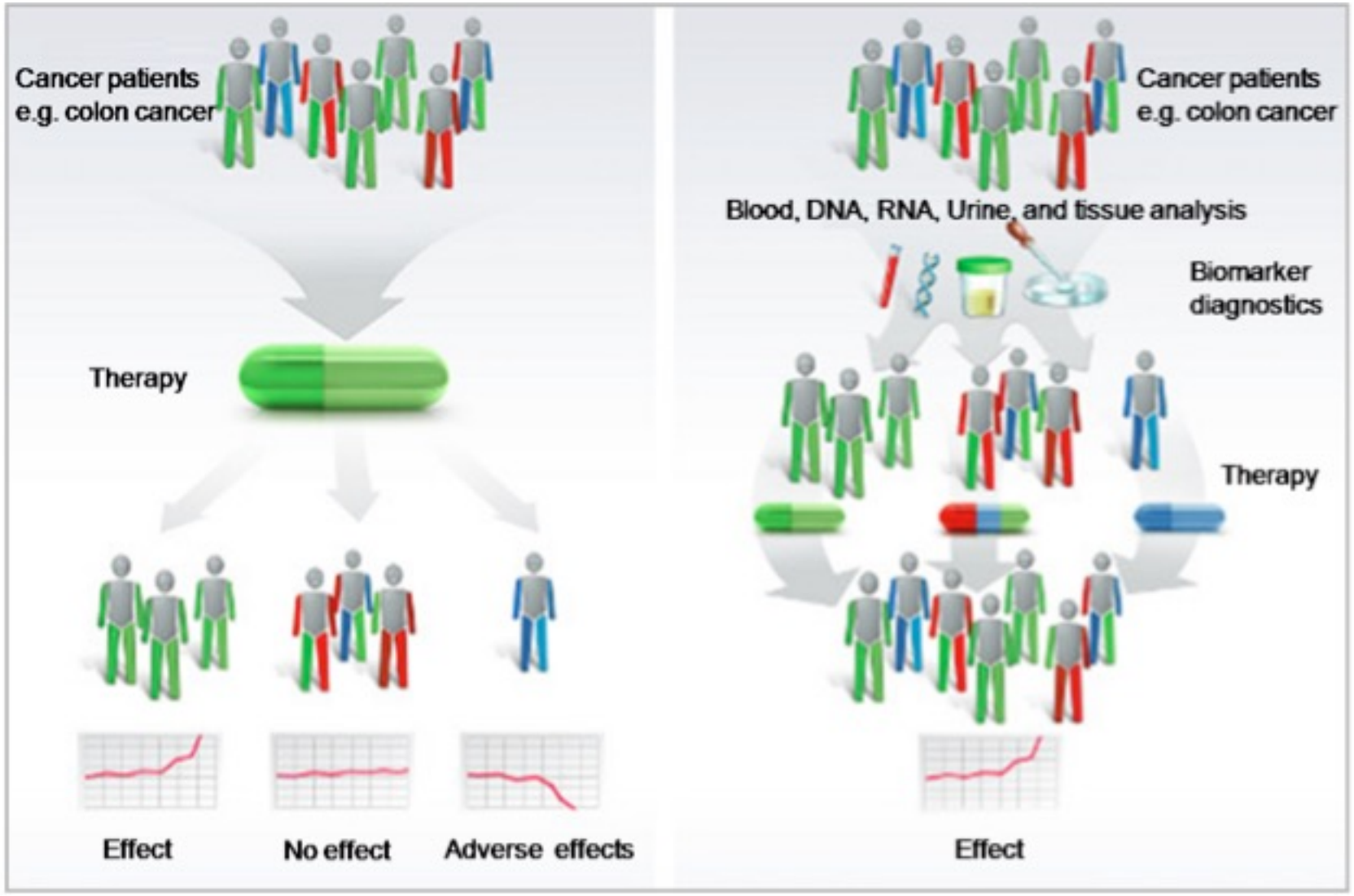
OPINION

Envisioning the future of early anticancer drug development

Timothy A. Yap, Shahneen K. Sandhu, Paul Workman and Johann S. de Bono



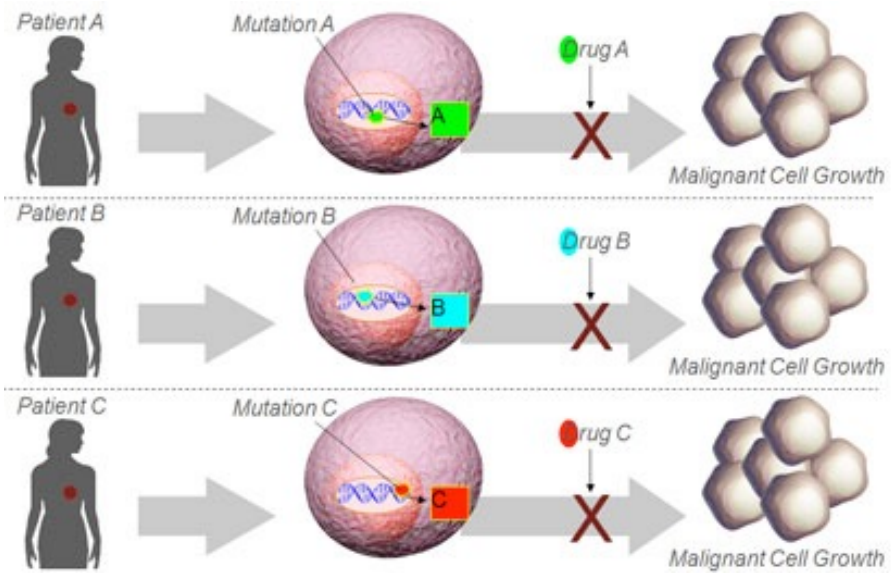
Drug Development in Oncology: the traditional model vs. precision medicine

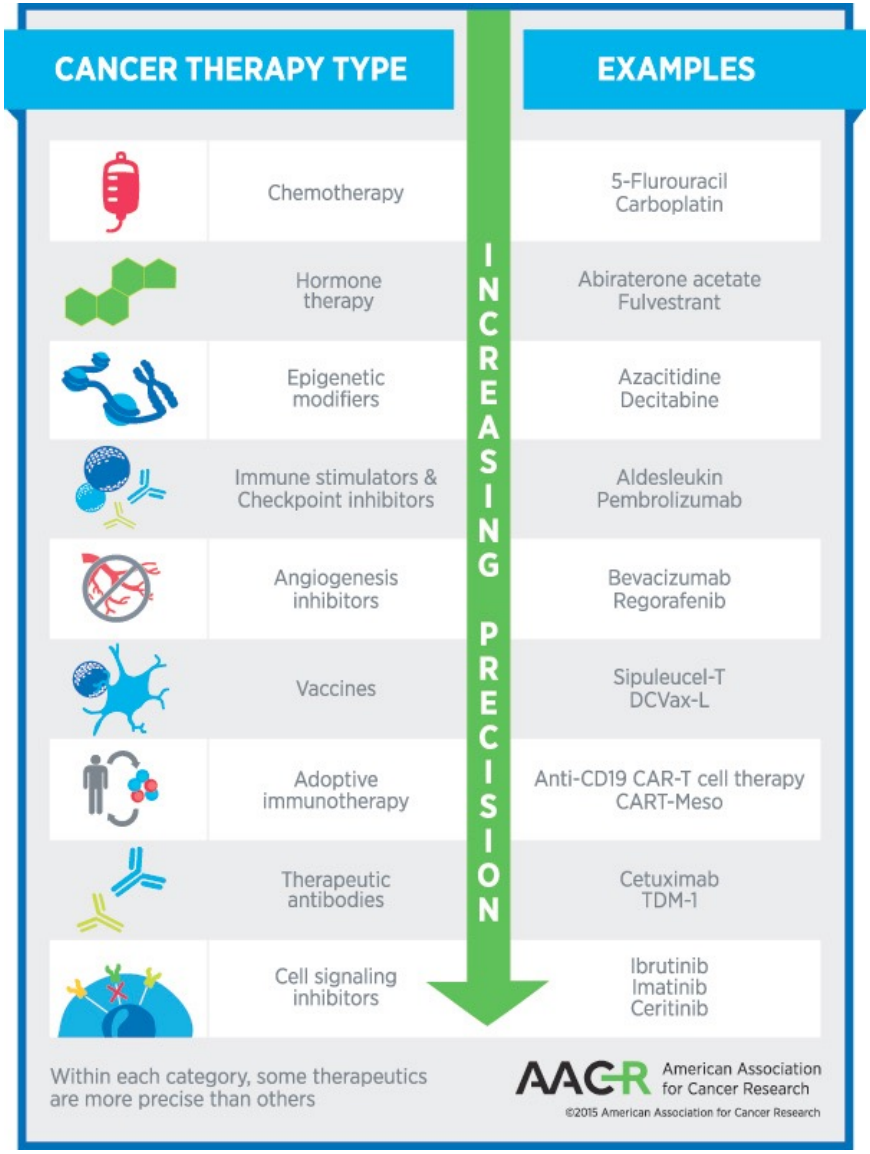


Drug Development in Oncology:
PRECISION MEDICINE

Each patient's cancer is driven by a unique combination of DNA changes, collectively termed its tumor "profile."

The goal of precision cancer medicine is to individualize treatments by tailoring them to the genetic characteristics of the patient's cancer – for example, selecting drugs matched to the tumor profile.





Opportunities and Challenges of Biomarker-Driven Targeted Therapies

INNOVATION

Implementing personalized cancer genomics in clinical trials

Richard Simon and Sameek Roychowdhury

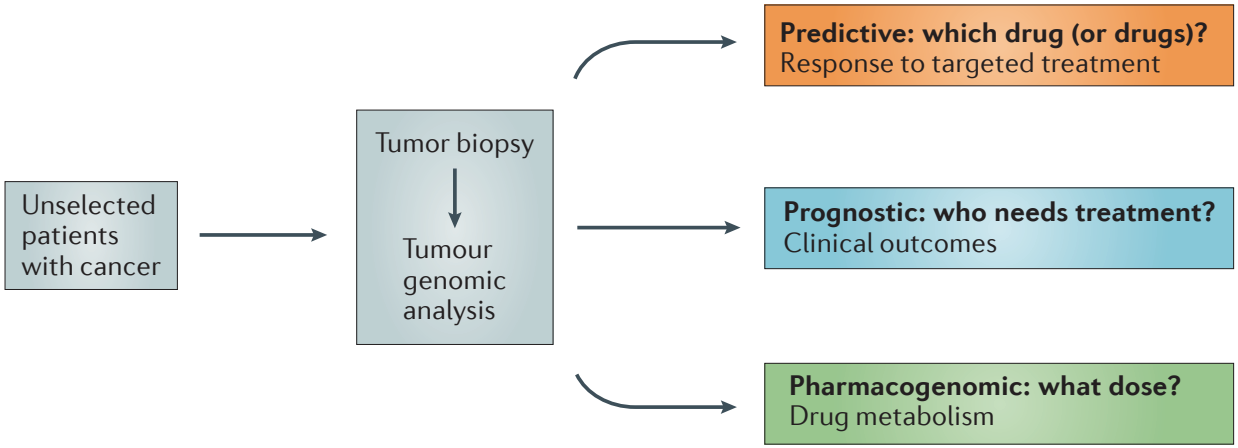
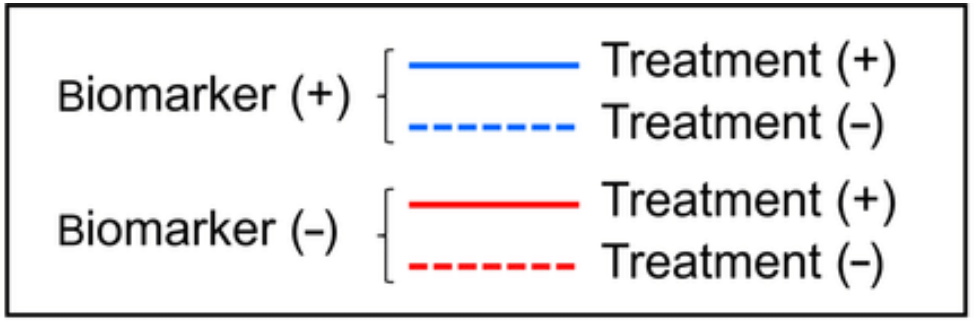


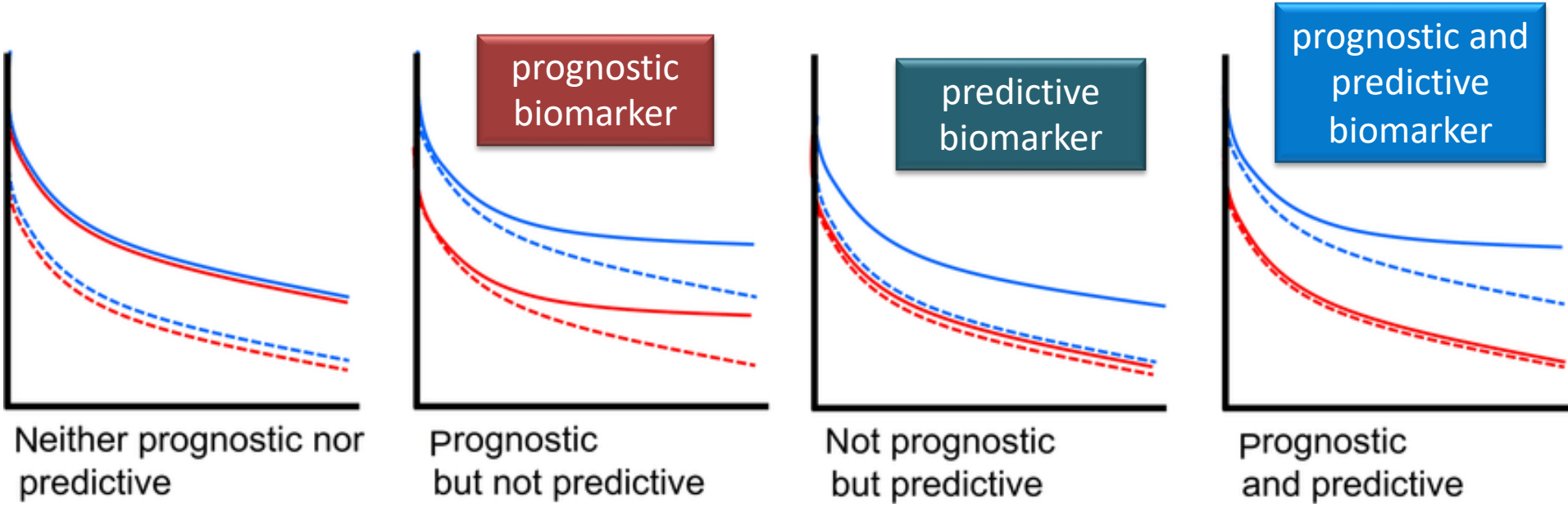
Figure 1 | **Development and application of biomarkers for oncology.** Genomic sequencing and other omics-based strategies have the potential to identify candidate biomarkers in clinical oncology. Clinical trial design is dictated by the type of biomarker being testing or developed. Predictive biomarkers inform the investigator of a potential clinical response to a given therapy. Prognostic biomarkers provide information on the risk of disease progression or relapse. Pharmacogenomic biomarkers relay data on how a patient may respond to a drug with respect to toxicity or efficacy.

Opportunities and Challenges of Biomarker-Driven Targeted Therapies

BIOMARKERS can be broadly classified into:

- ✓ **PROGNOSTIC**
- ✓ **PREDICTIVE**
- ✓ pharmacodynamic
- ✓ surrogate endpoints

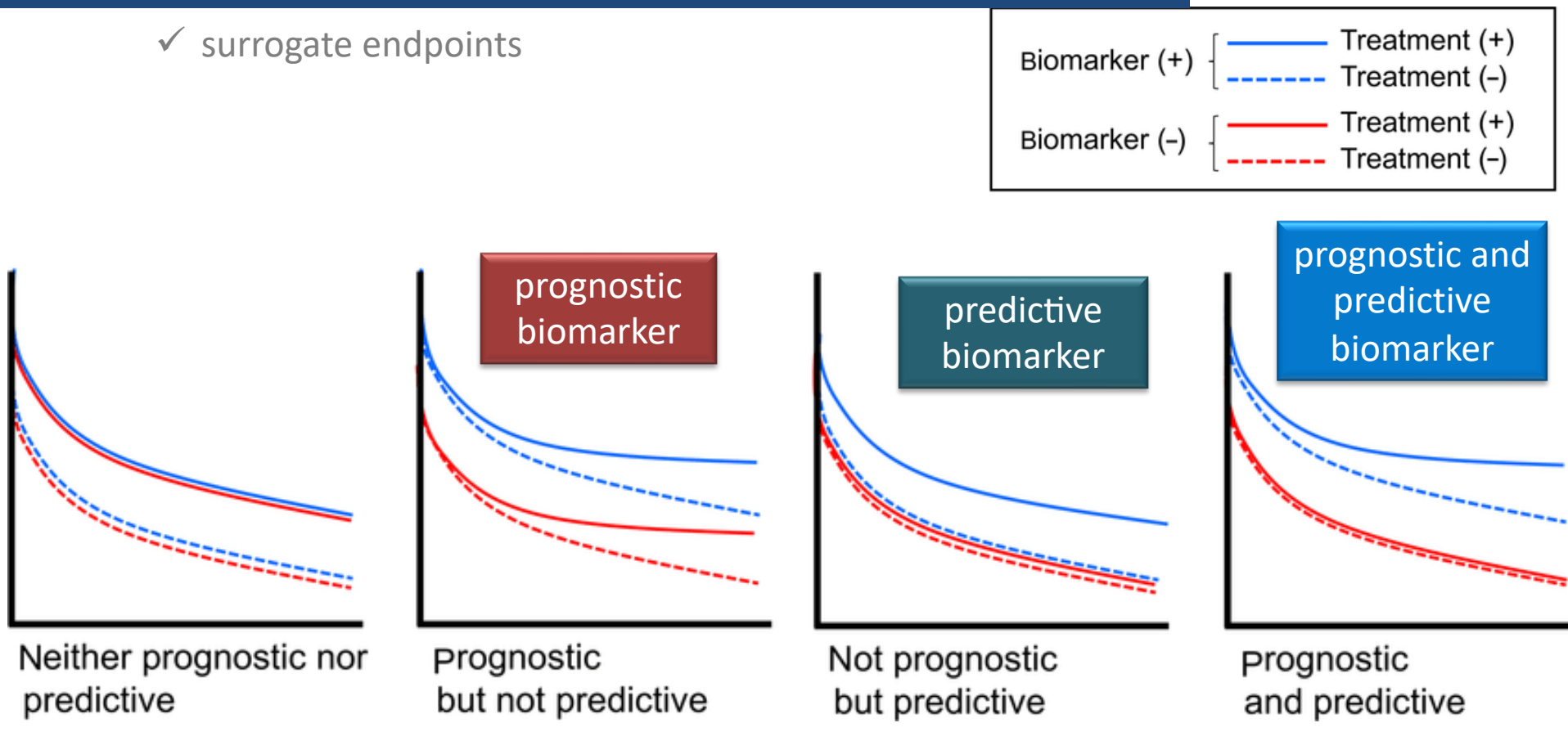




Opportunities and Challenges of Biomarker-Driven Targeted Therapies

A prognostic biomarker provides information about the patients overall cancer outcome, regardless of therapy, whilst a predictive biomarker gives information about the effect of a therapeutic intervention. A predictive biomarker can be a target for therapy

- ✓ surrogate endpoints



Opportunities and Challenges of Biomarker-Driven Targeted Therapies

Patient–centric trials for therapeutic development in precision oncology

Andrew V. Biankin[1,2,3,4], Steven Piantadosi[5] & Simon J. Hollingsworth[6]

362 | NATURE | VOL 526 | 15 OCTOBER 2015

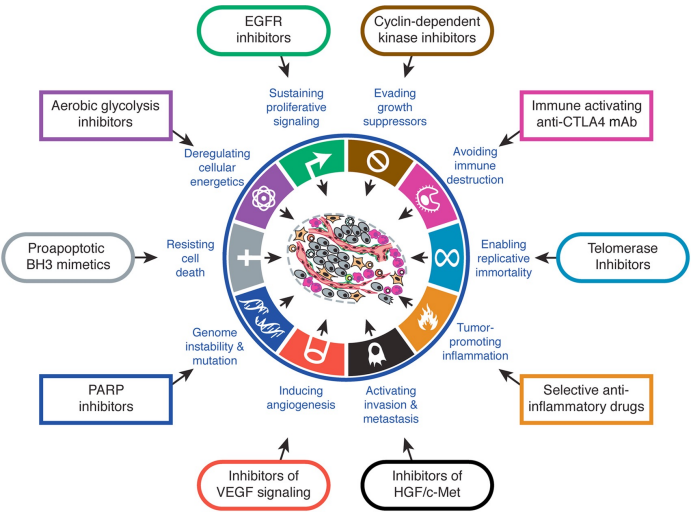
- ✓ Our appreciation of the molecular diversity of cancer and the ever-increasing number of molecular subtypes creates considerable complexity for the development of targeted drugs.
- ✓ When tested in trials of unselected participants, most targeted therapies reveal efficacy only if both the incidence of a responsive subpopulation and the effect size within the group is sufficiently high.
- ✓ Increasing the size of clinical trials to overcome this lack of enrichment yields minimal overall benefits at a cost that makes them unattractive and unaffordable to the community. **Designing trials that feasibly evaluate both patient selection and drug efficacy is crucial**, and it is essential to define the correct metrics to assess efficacy, particularly when the study needs to be small.

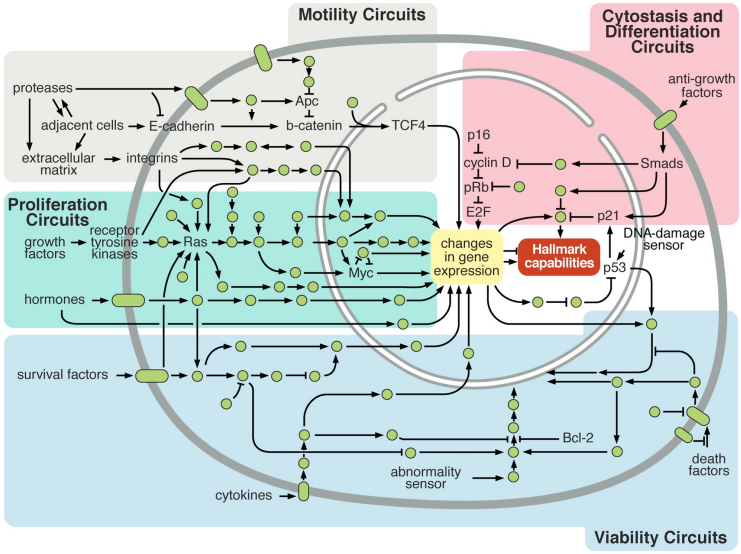
Opportunities and Challenges of Biomarker-Driven Targeted Therapies

Cell

Hallmarks of Cancer: The Next Generation

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





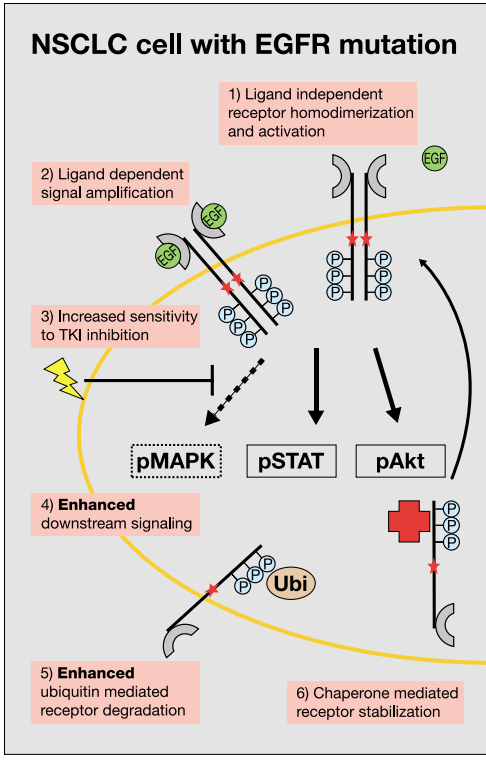


Table 1 | **Genomic alterations as putative predictive biomarkers for cancer therapy**

Genes	Pathways	Aberration type	Disease examples	Putative or proven drugs
PIK3CA[51,52], *PIK3R1* (REF. 53), *PIK3R2*, *AKT1*, *AKT2* and *AKT3* (REFS 54,55)	Phosphoinositide 3-kinase (PI3K)	Mutation or amplification	Breast, colorectal and endometrial cancer	• PI3K inhibitors • AKT inhibitors
PTEN[56]	PI3K	Deletion	Numerous cancers	• PI3K inhibitors
MTOR[57], *TSC1*[58] and *TSC2* (REF. 59)	mTOR	Mutation	Tuberous sclerosis and Bladder cancer	• mTOR inhibitors
RAS family (*HRAS*, *NRAS*, *KRAS*), *BRAF*[60] and *MEK1*	RAS–MEK	Mutation, rearrangement or amplification	Numerous cancers, including melanoma and prostate cancer	• RAF inhibitors • MEK inhibitors • PI3K inhibitors
Fibroblast growth factor receptor 1 (*FGFR1*), *FGFR2*, *FGFR3*, *FGFR4* (REF. 36)	FGFR	Mutation, amplification or rearrangement	Myeloma, sarcoma and bladder, breast, ovarian, lung, endometrial and myeloid cancers	• FGFR inhibitors • FGFR antibodies
Epidermal growth factor receptor (*EGFR*)	EGFR	Mutation, deletion or amplification	Lung and gastrointestinal cancer	• EGFR inhibitors • EGFR antibodies
ERBB2 (REF. 61)	ERBB2	Amplification or mutation	Breast, bladder, gastric and lung cancer	• ERBB2 inhibitors • ERBB2 antibodies
SMO[62,63] and *PTCH1* (REF. 64)	Hedgehog	Mutation	Basal cell carcinoma	• Hedgehog inhibitor
MET[65]	MET	Amplification or mutation	Bladder, gastric and renal cancer	• MET inhibitors • MET antibodies
JAK1, *JAK2*, *JAK3* (REF. 66), *STAT1*, *STAT3*	JAK–STAT	Mutation or rearrangement	Leukaemia and lymphoma	• JAK–STAT inhibitors • STAT decoys
Discoidin domain-containing receptor 2 (*DDR2*)	RTK	Mutation	Lung cancer	• Some tyrosine kinase inhibitors
Erythropoietin receptor (*EPOR*)	JAK–STAT	Rearrangement	Leukaemia	• JAK–STAT inhibitors
Interleukin-7 receptor (*IL7R*)	JAK–STAT	Mutation	Leukaemia	• JAK–STAT inhibitors
Cyclin-dependent kinases (*CDKs*;[67] *CDK4*, *CDK6*, *CDK8*), *CDKN2A* and cyclin D1 (*CCND1*)	CDK	Amplification, mutation, deletion or rearrangement	Sarcoma, colorectal cancer, melanoma and lymphoma	• CDK inhibitors
ABL1	ABL	Rearrangement	Leukaemia	• ABL inhibitors
Retinoic acid receptor-α (*RARA*)	RARα	Rearrangement	Leukaemia	• All-trans retinoic acid
Aurora kinase A (*AURKA*)[68]	Aurora kinases	Amplification	Prostate cancer and breast cancer	• Aurora kinase inhibitors
Androgen receptor (*AR*)[69]	Androgen	Mutation, amplification or splice variant	Prostate cancer	• Androgen synthesis inhibitors • Androgen receptor inhibitors
FLT3[70]	FLT3	Mutation or deletion	Leukaemia	• FLT3 inhibitors
MET	MET–HGF	Mutation or amplification	Lung cancer and gastric cancer	• MET inhibitors
Myeloproliferative leukaemia (*MPL*)	THPO, JAK–STAT	Mutation	Myeloproliferative neoplasms	• JAK–STAT inhibitors
MDM2 (REF. 71)	MDM2	Amplification	Sarcoma and adrenal carcinoma	• MDM2 antagonist
KIT[72]	KIT	Mutation	GIST, mastocytosis, leukaemia	• KIT inhibitors
PDGFRA and *PDGFRB*	PDGFR	Deletion, rearrangement or amplification	Haematological cancer, GIST, sarcoma and brain cancer	• PDGFR inhibitors
Anaplastic lymphoma kinase (*ALK*)[9,37,73,74]	ALK	Rearrangement or mutation	Lung cancer and neuroblastoma	• ALK inhibitors
RET	RET	Rearrangement or mutation	Lung cancer and thyroid cancer	• RET inhibitors
ROS1 (REF. 75)	ROS1	Rearrangement	Lung cancer and cholangiocarcinoma	• ROS1 inhibitors
NOTCH1 and *NOTCH2*	Notch	Rearrangement or mutation	Leukaemia and breast cancer	• Notch signalling pathway inhibitors

CDKN2A, cyclin-dependent kinase inhibitor 2A; ERBB2, also known as HER2; GIST, gastrointestinal stromal tumour; FLT3, FMS-like tyrosine kinase 3; HGF,

Table 1 | **Genomic alterations as putative predictive biomarkers for cancer therapy**

Genes	Pathways	Aberration type	Disease examples	Putative or proven drugs
PIK3CA[51,52], *PIK3R1* (REF. 53), *PIK3R2*, *AKT1*, *AKT2* and *AKT3* (REFS 54,55)	Phosphoinositide 3-kinase (PI3K)	Mutation or amplification	Breast, colorectal and endometrial cancer	• PI3K inhibitors • AKT inhibitors
PTEN[56]	PI3K	Deletion	Numerous cancers	• PI3K inhibitors
MTOR[57], *TSC1*[58] and *TSC2* (REF. 59)	mTOR	Mutation	Tuberous sclerosis and Bladder cancer	• mTOR inhibitors
RAS family (*HRAS*, *NRAS*, *KRAS*), *BRAF*[60] and *MEK1*	RAS–MEK	Mutation, rearrangement or amplification	Numerous cancers, including melanoma and prostate cancer	• RAF inhibitors • MEK inhibitors • PI3K inhibitors
Fibroblast growth factor receptor 1 (*FGFR1*), *FGFR2*, *FGFR3*, *FGFR4* (REF. 36)	FGFR	Mutation, amplification or rearrangement	Myeloma, sarcoma and bladder, breast, ovarian, lung, endometrial and myeloid cancers	• FGFR inhibitors • FGFR antibodies
Epidermal growth factor receptor (*EGFR*)	EGFR	Mutation, deletion or amplification	Lung and gastrointestinal cancer	• EGFR inhibitors • EGFR antibodies
ERBB2 (REF. 61)	ERBB2	Amplification or mutation	Breast, bladder, gastric and lung cancer	• ERBB2 inhibitors • ERBB2 antibodies
SMO[62,63] and *PTCH1* (REF. 64)	Hedgehog	Mutation	Basal cell carcinoma	• Hedgehog inhibitor
MET[65]	MET	Amplification or mutation	Bladder, gastric and renal cancer	• MET inhibitors • MET antibodies
JAK1, *JAK2*, *JAK3* (REF. 66), *STAT1*, *STAT3*	JAK–STAT	Mutation or rearrangement	Leukaemia and lymphoma	• JAK–STAT inhibitors • STAT decoys
Discoidin domain-containing receptor 2 (*DDR2*)	RTK	Mutation	Lung cancer	• Some tyrosine kinase inhibitors
Erythropoietin receptor (*EPOR*)	JAK–STAT	Rearrangement	Leukaemia	• JAK–STAT inhibitors
Interleukin-7 receptor (*IL7R*)	JAK–STAT	Mutation	Leukaemia	• JAK–STAT inhibitors
Cyclin-dependent kinases (*CDKs*;[67] *CDK4*, *CDK6*, *CDK8*), *CDKN2A* and cyclin D1 (*CCND1*)	CDK	Amplification, mutation, deletion or rearrangement	Sarcoma, colorectal cancer, melanoma and lymphoma	• CDK inhibitors

Trial designs for testing efficacy of molecular profiling-assigned targeted agents

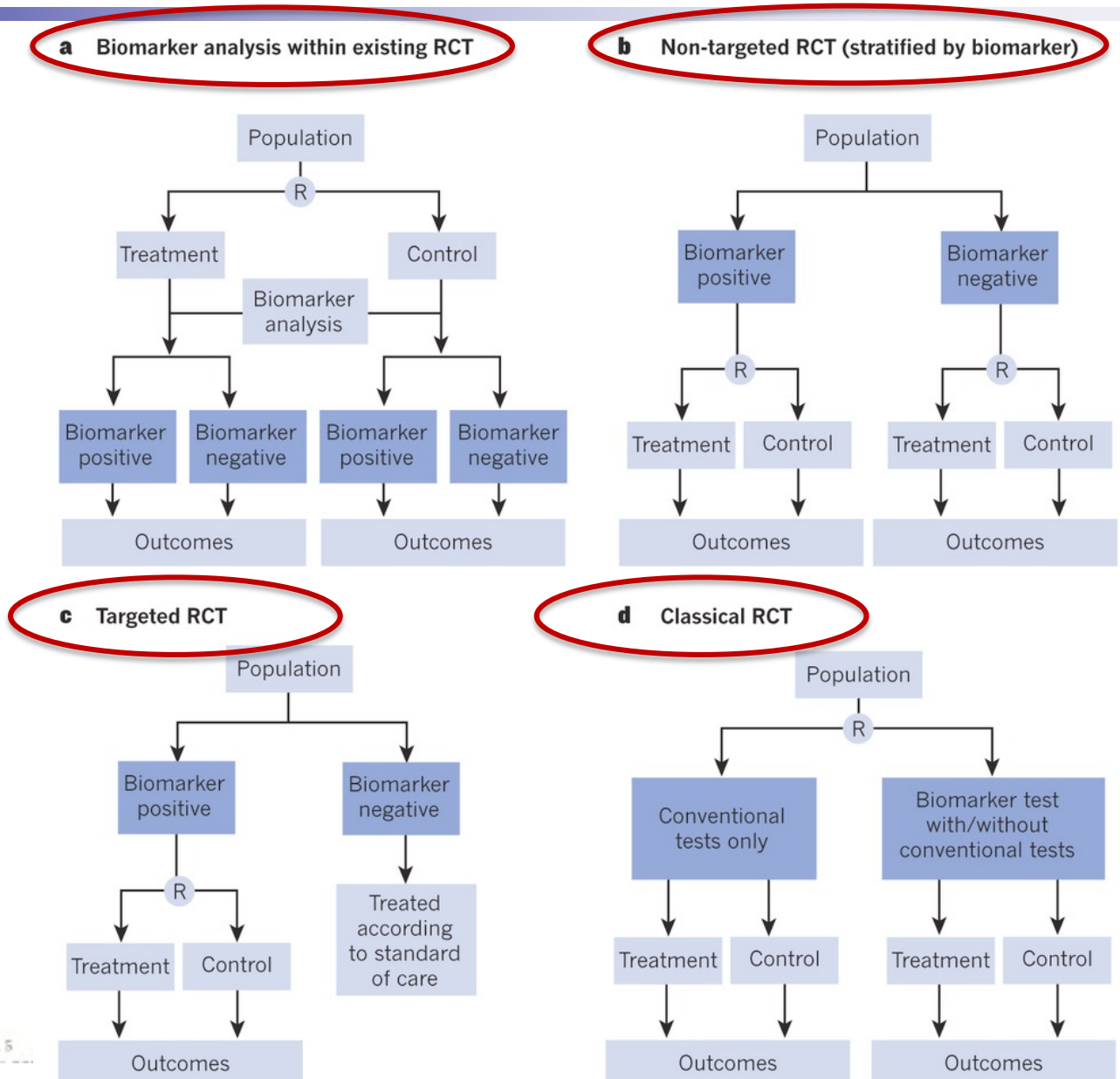
a. **Biomarker discovery in trials addressing a therapeutic question but no info on the marker status.**

b. **A non-targeted biomarker study designed and powered to address the biomarker hypothesis**

c. **Biomarker-targeted randomized controlled trial (RCT) in which the selection marker guides patient allocation.**

d. **RCT that compares biomarker-directed therapy with conventional therapy,**

R = randomization



Trial designs for testing efficacy of molecular profiling-assigned targeted agents

VOLUME 31 · NUMBER 15 · MAY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Designing Transformative Clinical Trials in the Cancer Genome Era

Stefan Sleijfer, Jan Bogaerts, and Lillian L. Siu

Table 2. Unselected Trial Designs Required for a Well-Powered Trial When a Very Strong Treatment Effect Is Restricted to Those Who Express the Unknown Marker

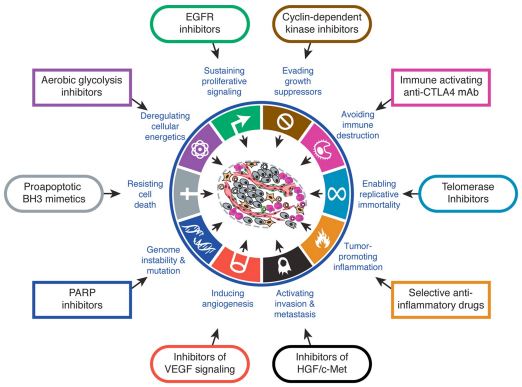
	Trial Targeting a True Hazard Ratio of 0.4 in the Selected Population			Trial Targeting a True Hazard Ratio of 0.6 in the Selected Population		
Prevalence of Marker	Unselected Hazard Ratio*	No. Events Needed	No. Patients Needed	Unselected Hazard Ratio*	No. Events Needed	No. Patients Needed
0.05	0.957	22,000	29,620	0.975	65,000	87,200
0.1	0.916	5,600	7,540	0.95	16,200	21,750
0.2	0.838	1,300	1,750	0.902	4,100	5,500
0.3	0.769	622	840	0.86	1,850	2,480
0.4	0.701	353	475	0.819	1,050	1,410
0.5	0.64	221	280	0.777	660	885
0.6	0.587	153	206	0.736	450	605
0.7	0.533	110	148	0.7	330	445
0.8	0.486	84	114	0.666	255	342
1†	0.4	52	70	0.6	164	220

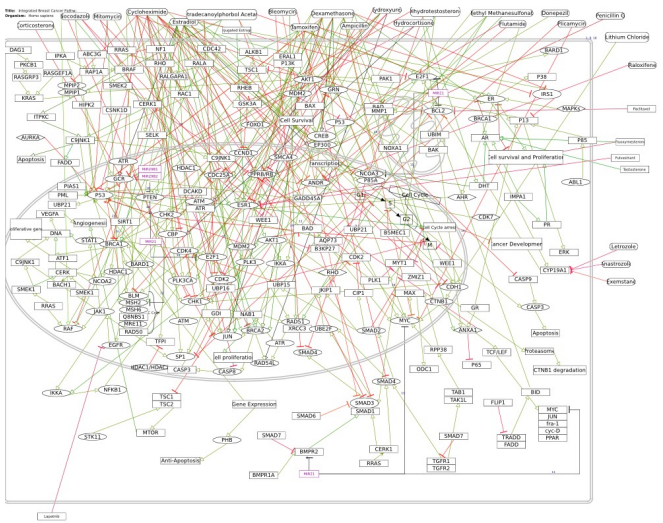
*The assumptions used lead to mixtures of exponential distributions, with an overall nonproportional hazards behavior. The tabulated ratios are averages depending on the settings of the trial. In the table, these are trials in which approximately 75% of patients are required to have an event before analysis.

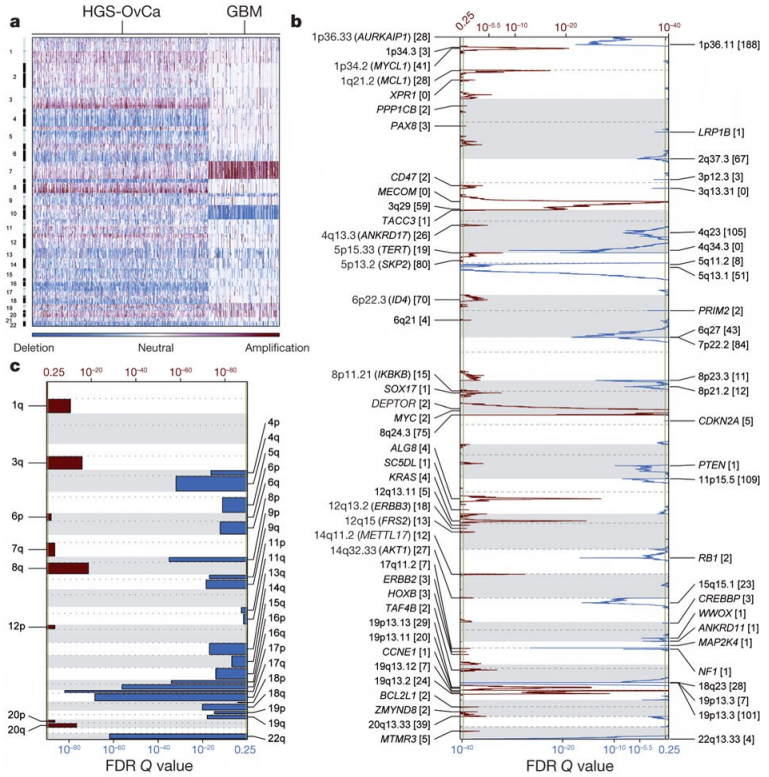
†This row represents the ideal situation where all patients belong in the sensitive class.

Trial designs for testing efficacy of molecular profiling-assigned targeted agents

In case of multiple cancer aberrant mutations





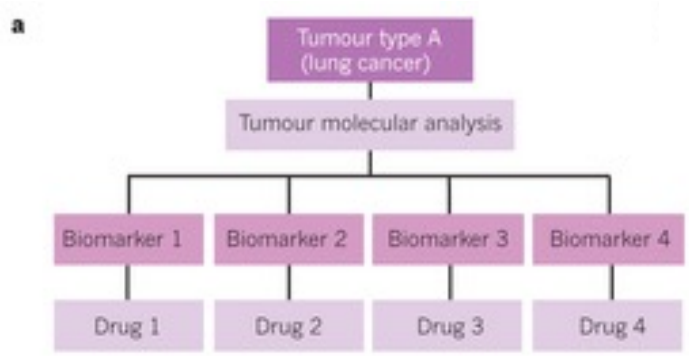


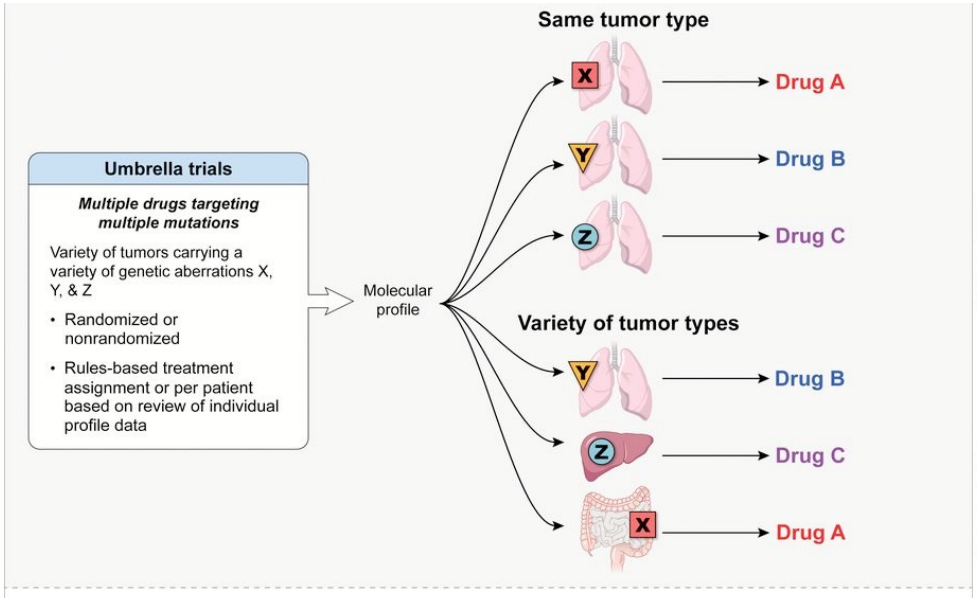
Many targets
= several (known) biomarkers
= many drugs

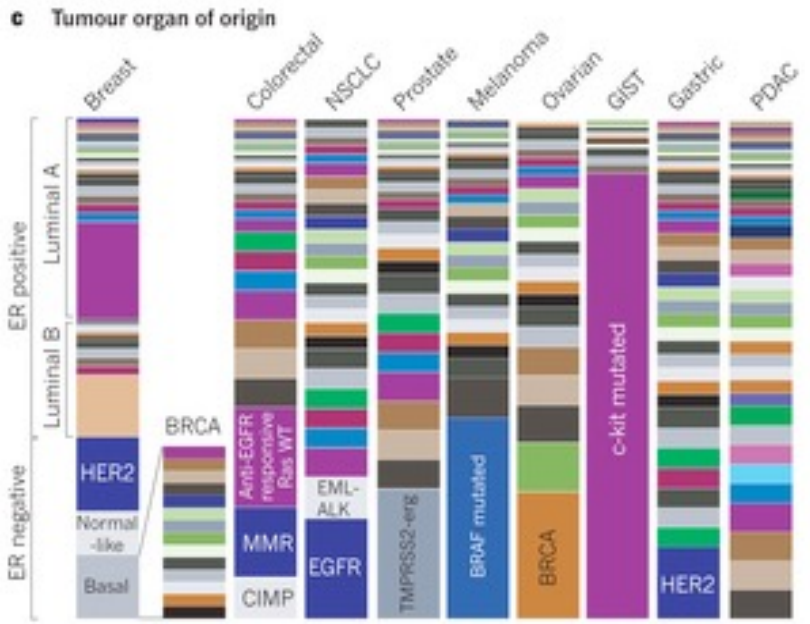
Trial designs for testing efficacy of molecular profiling-assigned targeted agents

UMBRELLA STUDIES

patients with the **same type** of cancer are screened for a series of hypothesized predictive biomarkers

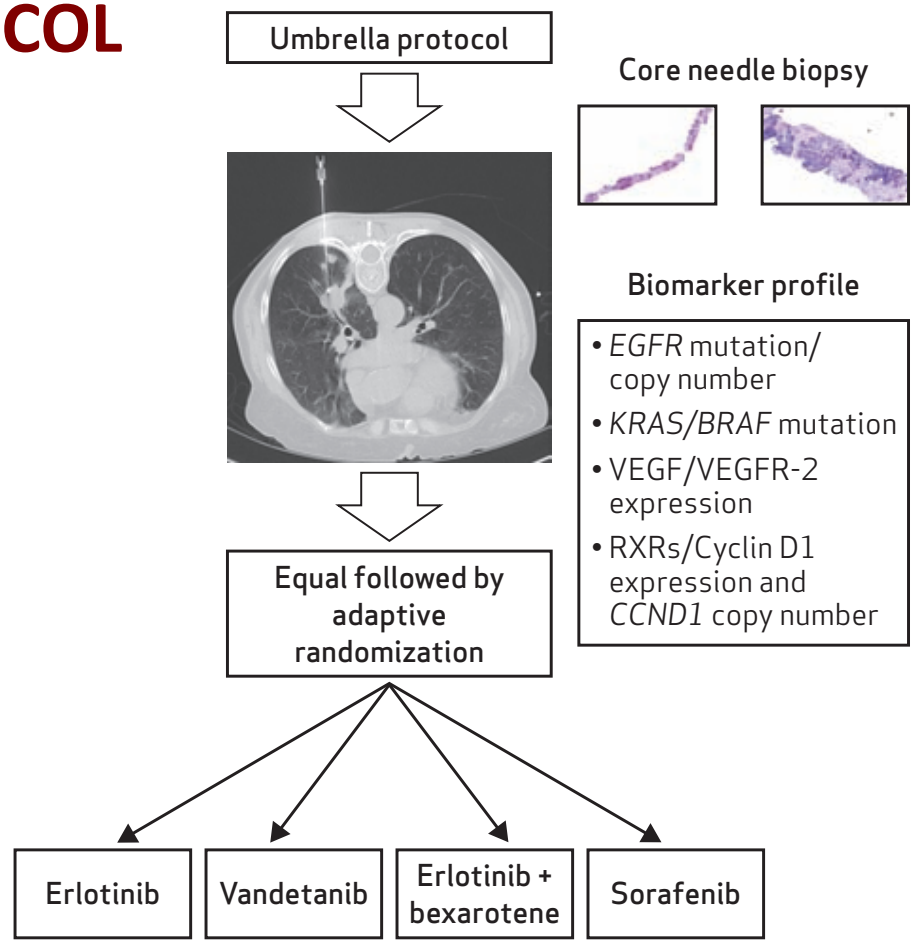






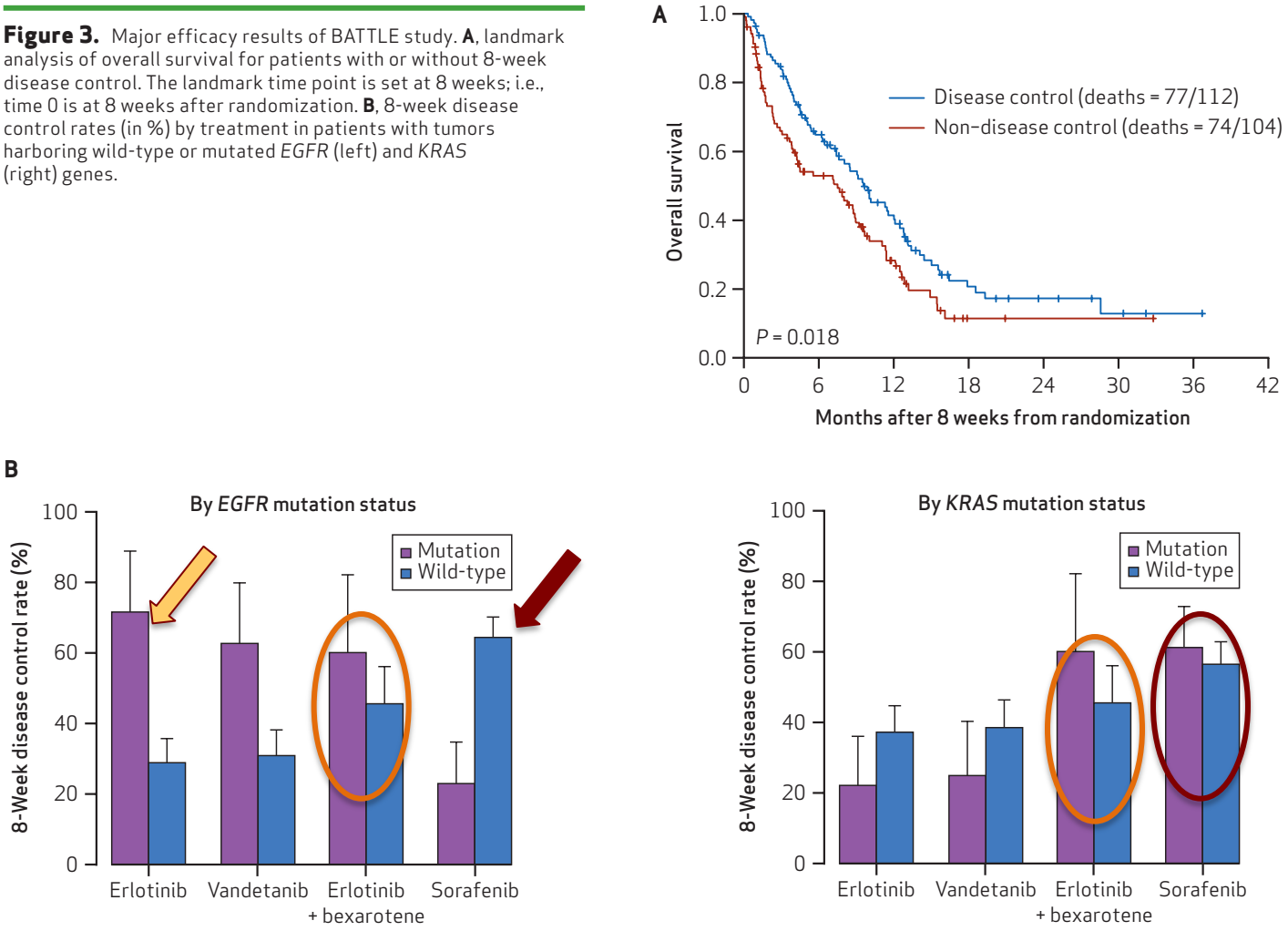
The BATTLE trial: personalizing therapy for lung cancer

UMBRELLA PROTOCOL



The BATTLE trial: personalizing therapy for lung cancer

Figure 3. Major efficacy results of BATTLE study. **A**, landmark analysis of overall survival for patients with or without 8-week disease control. The landmark time point is set at 8 weeks; i.e., time 0 is at 8 weeks after randomization. **B**, 8-week disease control rates (in %) by treatment in patients with tumors harboring wild-type or mutated *EGFR* (left) and *KRAS* (right) genes.



The NCI MPACT trial

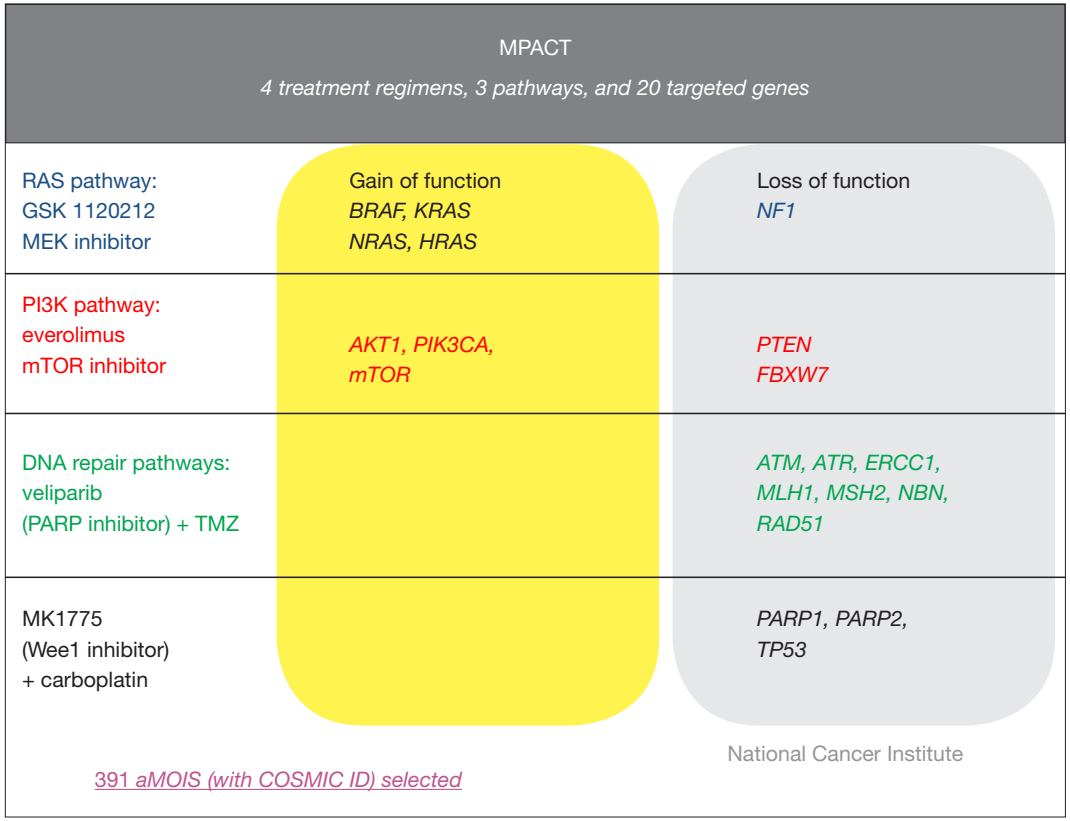
An overview of the NCI precision medicine trials—NCI MATCH and MPACT

Khanh Do[1], Geraldine O'Sullivan Coyne[2], Alice P. Chen[2]

www.thecco.net

Chin Clin Oncol 2015;4(3):31

Molecular Profiling-based Assignment of Cancer Therapy (MPACT) is a smaller, provocative trial designed to address whether targeting an oncogenic "driver" would be more efficacious than one not



aMOI = actionable mutation of interest

COSMIC = Catalogue of Somatic Mutations in Cancer

The NCI-MPACT trial

An overview of the NCI precision medicine trials—NCI MATCH and MPACT

Khanh Do[1], Geraldine O'Sullivan Coyne[2], Alice P. Chen[2]

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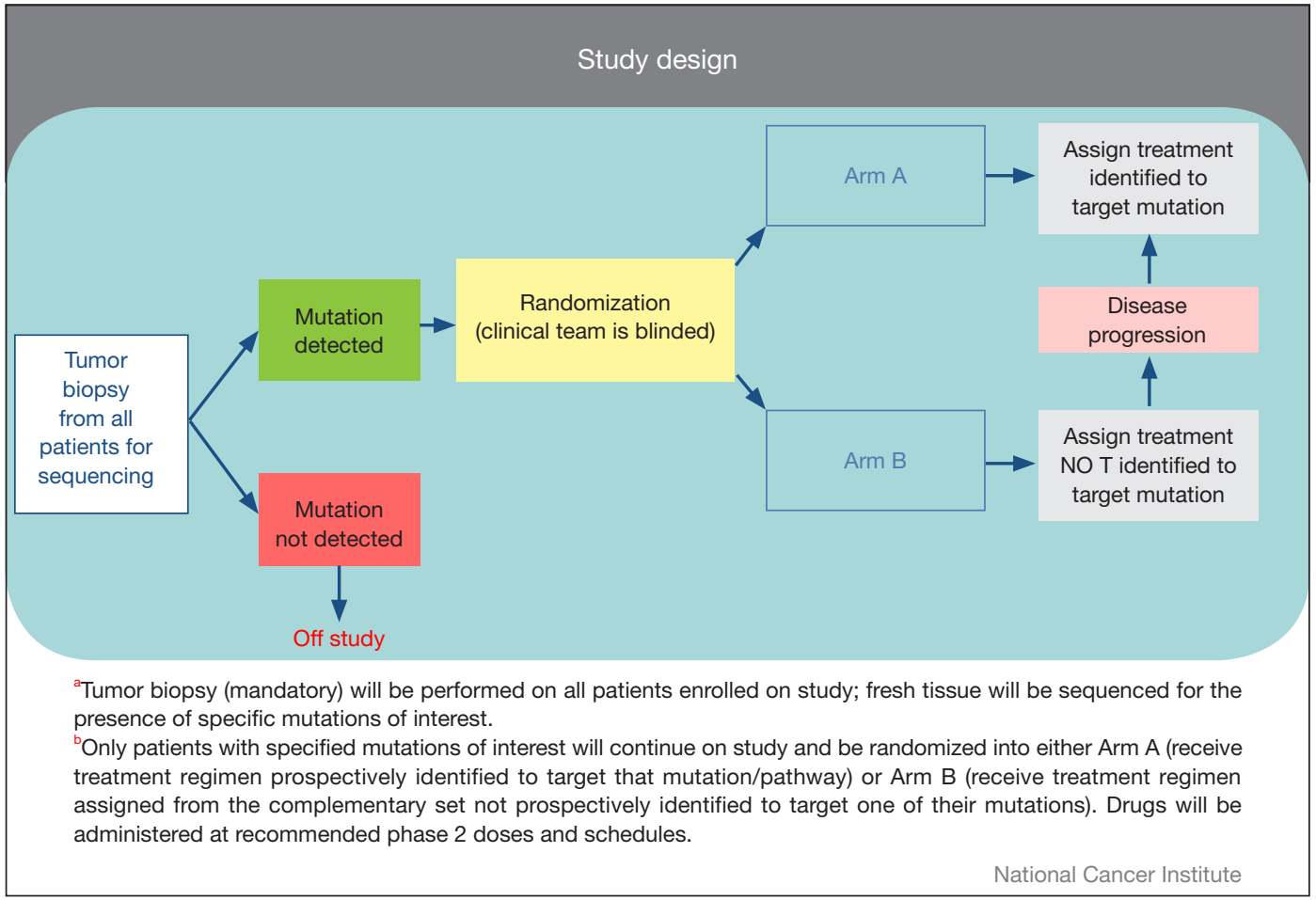
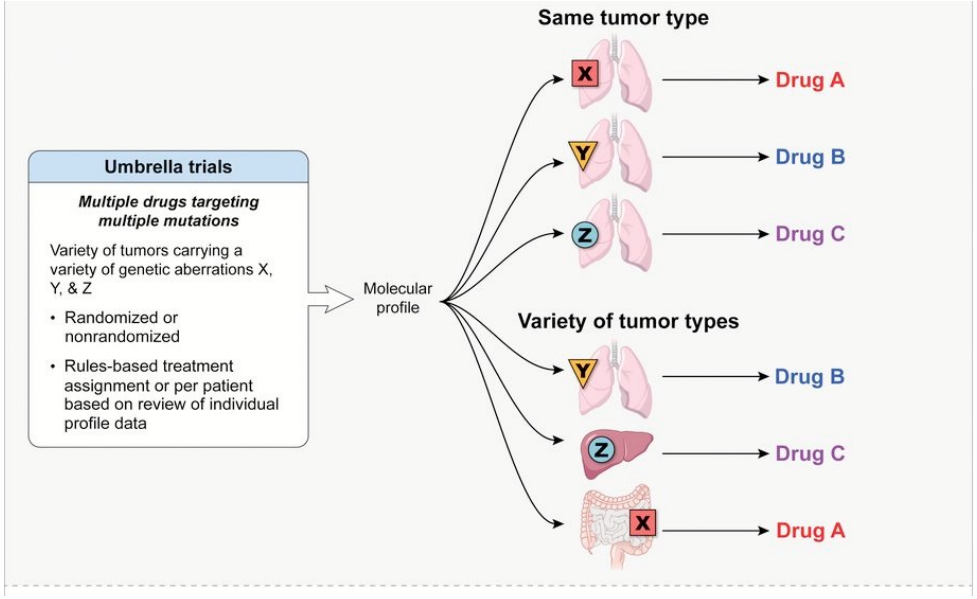


Trial designs for testing efficacy of molecular profiling-assigned targeted agents

UMBRELLA STUDIES

patients with the **same type of cancer** are screened for a series of hypothesized predictive biomarkers

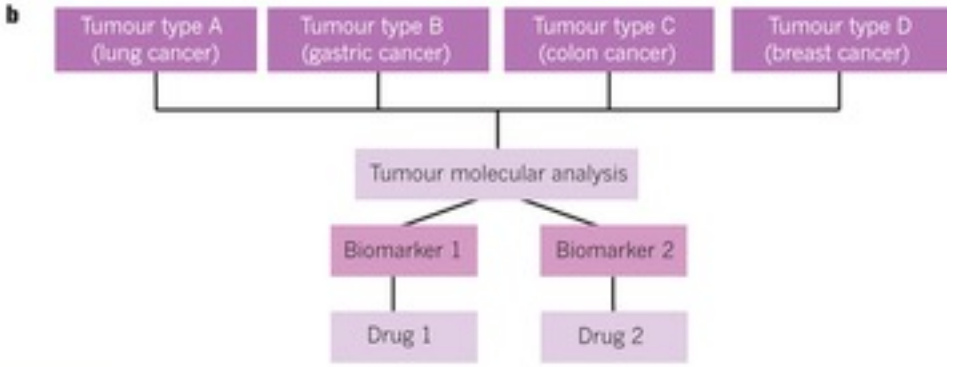


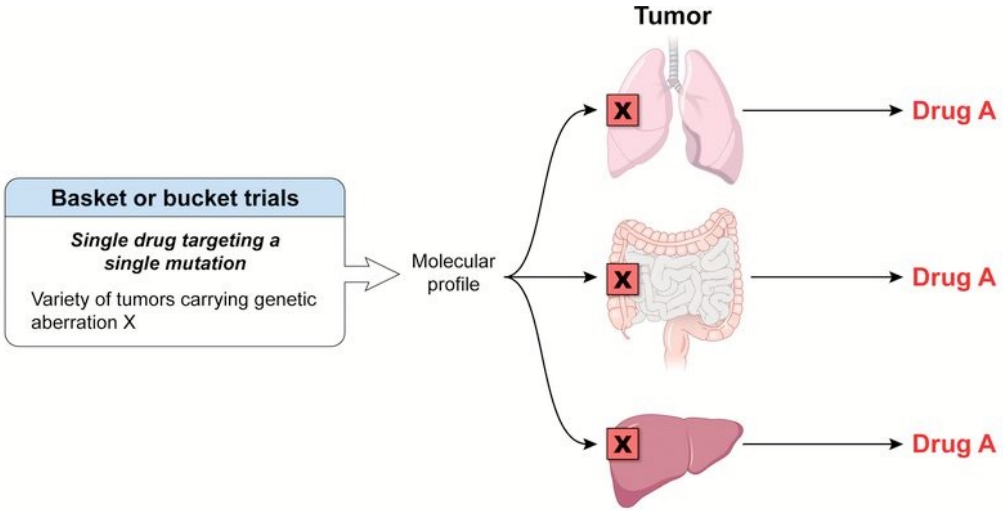
Pros & Cons

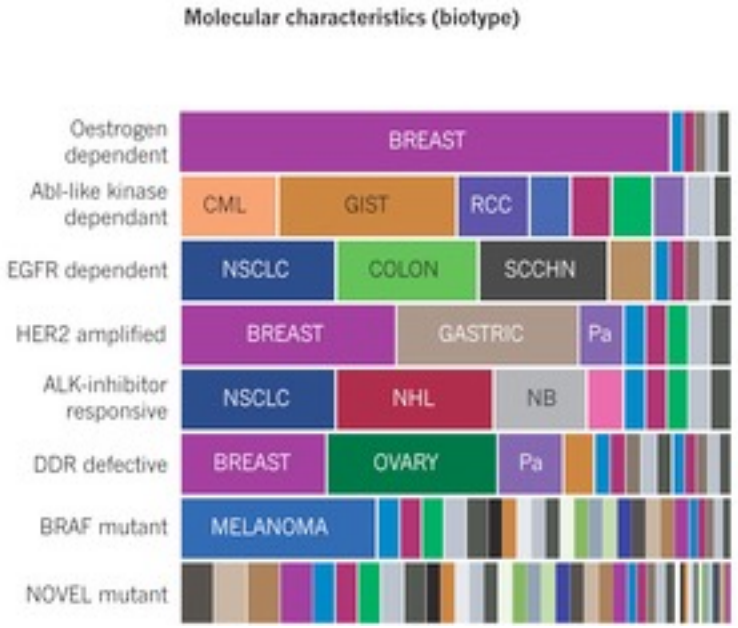
- ✓ Can be very efficient
- ✓ If randomized definitive conclusion about drug efficacy in selected patients
- ✓ Large amount of work
- ✓ Rules (of enrollment) has to be reviewed periodically by multidisciplinary team.

Trial designs for testing efficacy of molecular profiling-assigned targeted agents

BASKET STUDIES
recruit patients on the basis of **their molecular characteristics** irrespective of the organ in which their tumour originated

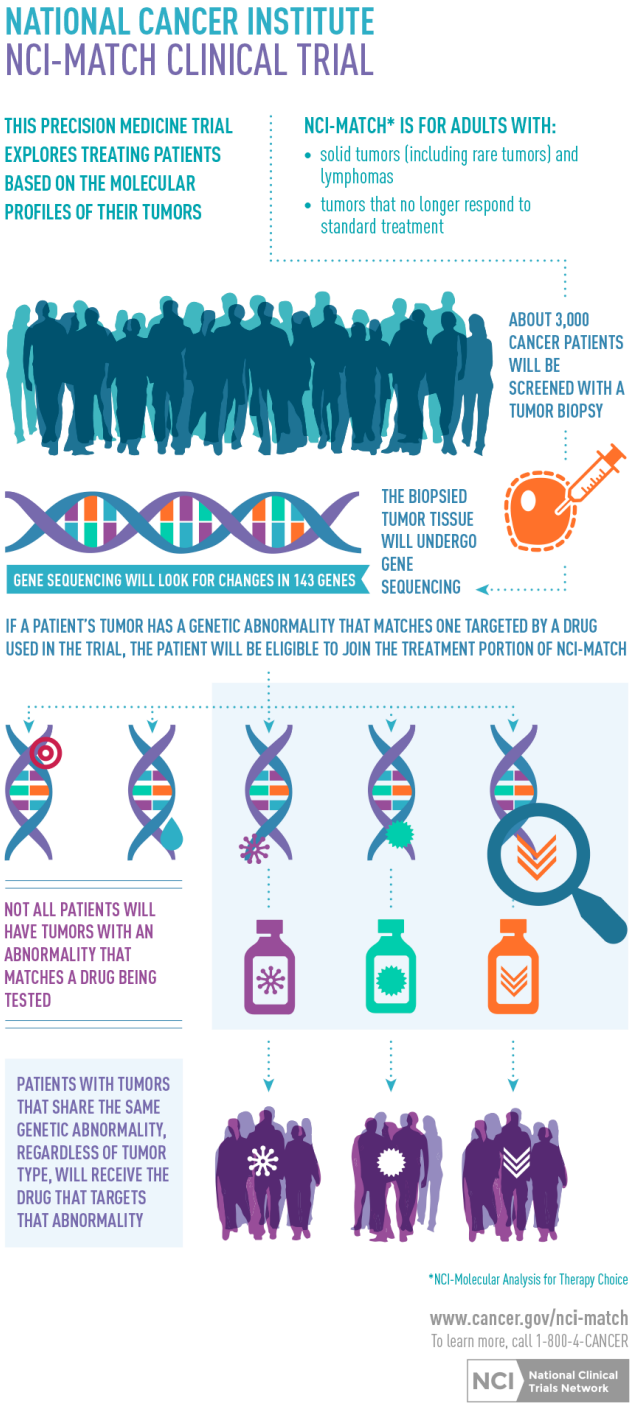


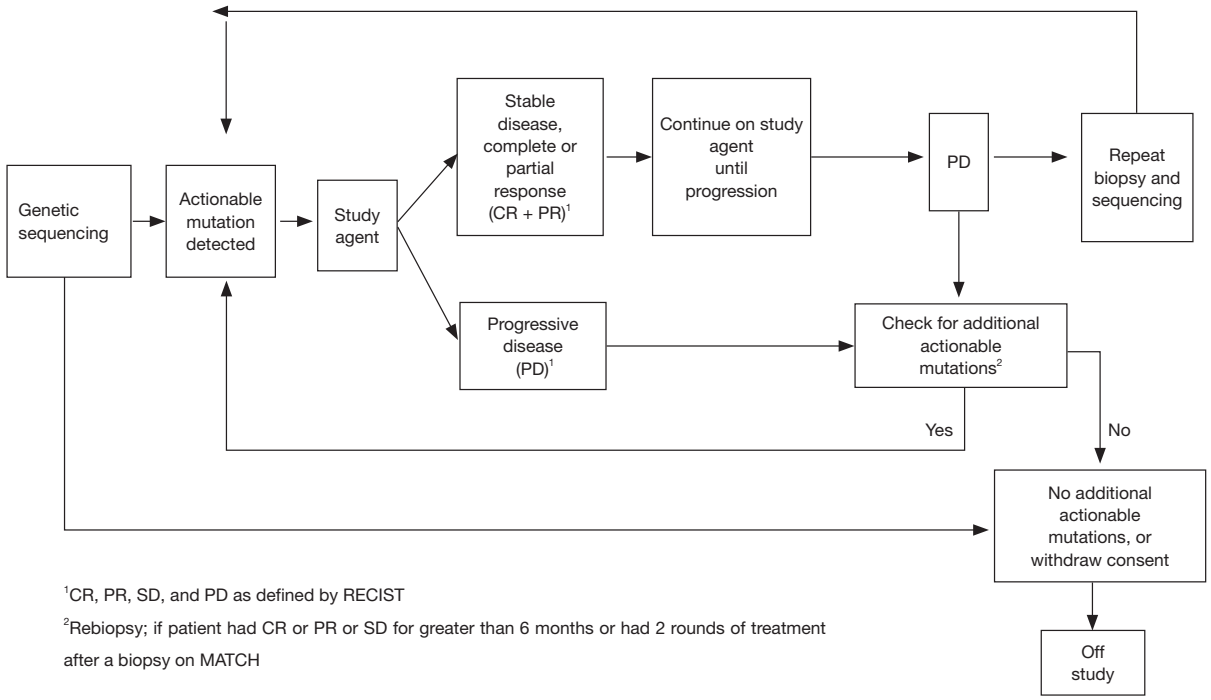




Many different type of tumours with a single biomarker = single drug

The NCI-MATCH trial





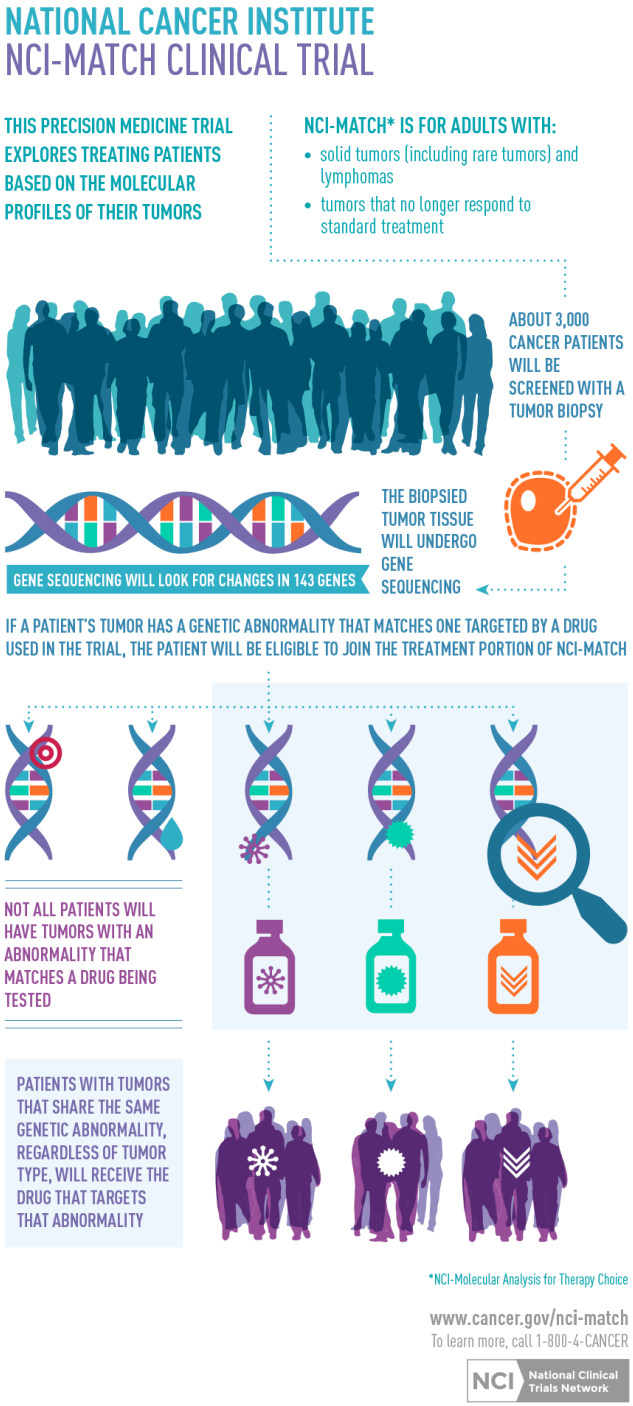
[1]CR, PR, SD, and PD as defined by RECIST

[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

An overview of the NCI precision medicine trials—NCI MATCH and MPACT

Khanh Do[1], Geraldine O'Sullivan Coyne[2], Alice P. Chen[2]

The NCI MATCH trial



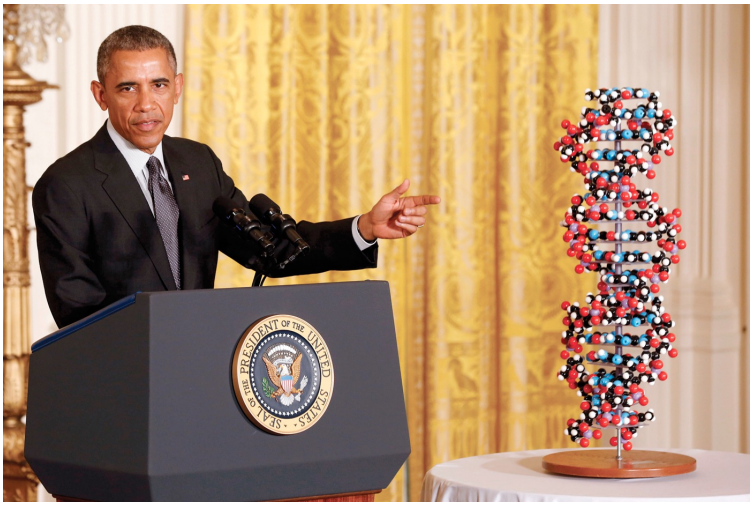
PROs & CONs

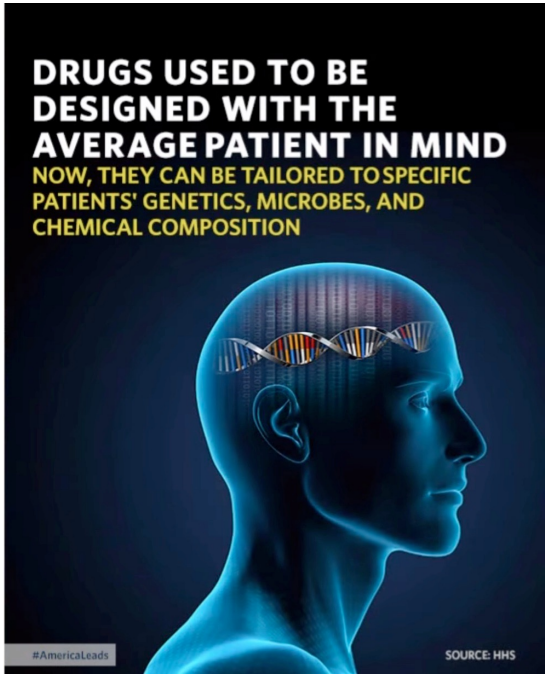
- ✓ Address the problems of rare subtypes (molecularly defined) of more frequent tumours
- ✓ Easy to implement in a early phase within a cooperative group
- ✓ Genome centered: outcomes may depends on clinical particularities of tumours (HCC)

Fifty years of cancer drug development: which lesson?

- ✓ The one-size-fits-all model is not effective with targeted therapy
- ✓ Companion diagnostic/biomarker and drug co-development is needed
- ✓ …just the very beginning of the tale

US Precision Medicine Initiative

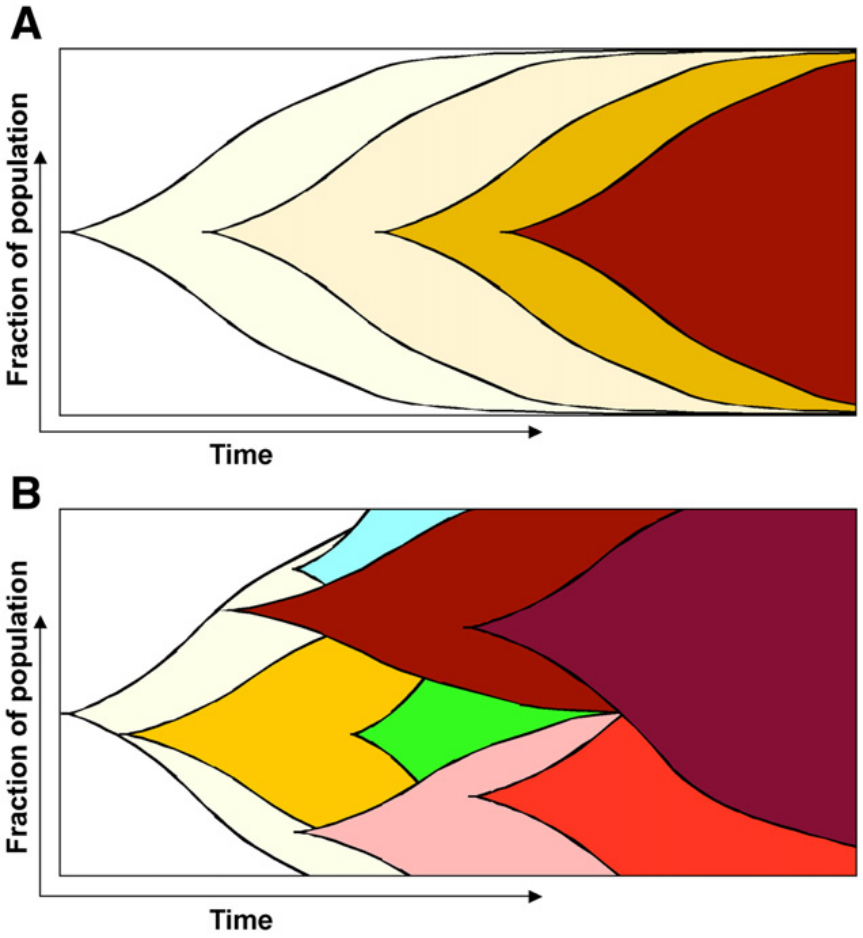




"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine — one that delivers the right treatment at the right time. In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable. Tonight, I'm launching a new ***Precision Medicine Initiative*** *to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."*

President Barack Obama, State of the Union Address, January 20, 2015

Is tumor heterogeneity in cancer a problem?



Traditional, linear model of clonal succession

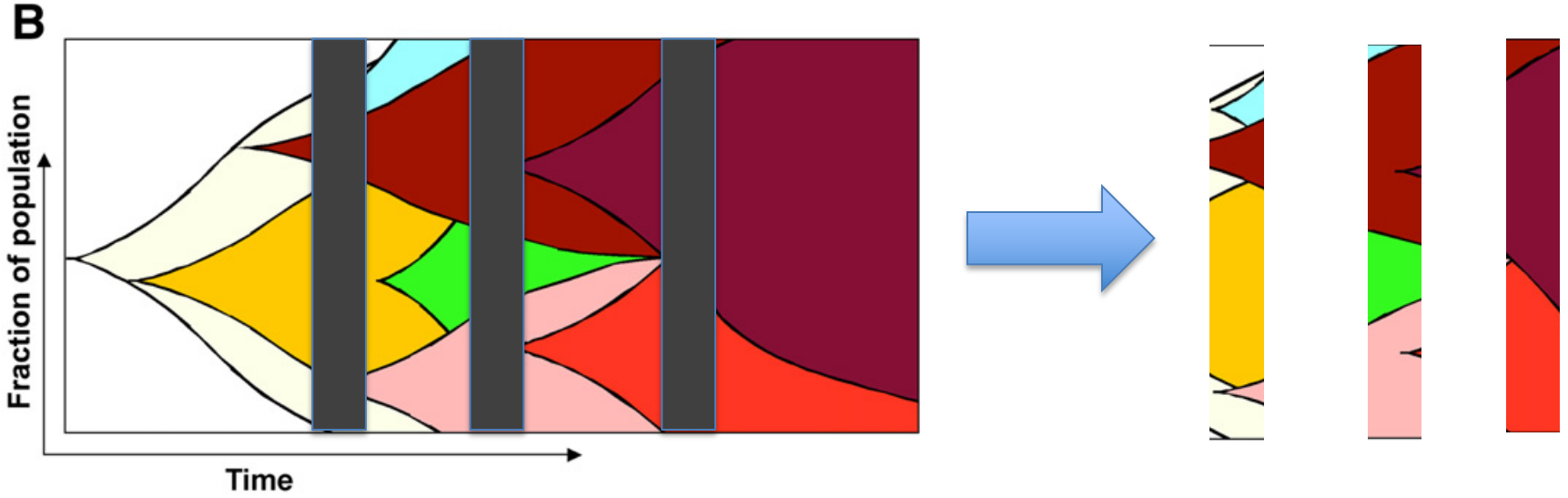
Multi-clonal model of tumor progression

Tumor heterogeneity: Causes and consequences

Andriy Marusyk, Kornelia Polyak *

Biochimica et Biophysica Acta 1805 (2010) 105–117

Is tumor heterogeneity in cancer a problem?



Different mutations for each sample!

Tumor heterogeneity: Causes and consequences

Andriy Marusyk, Kornelia Polyak *

Biochimica et Biophysica Acta 1805 (2010) 105–117

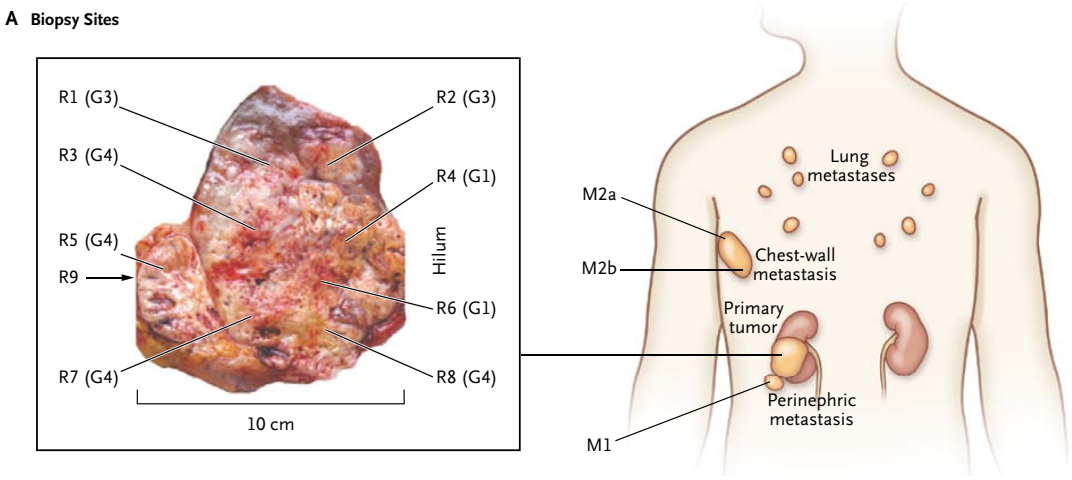
Intratumor heterogeneity fosters tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples

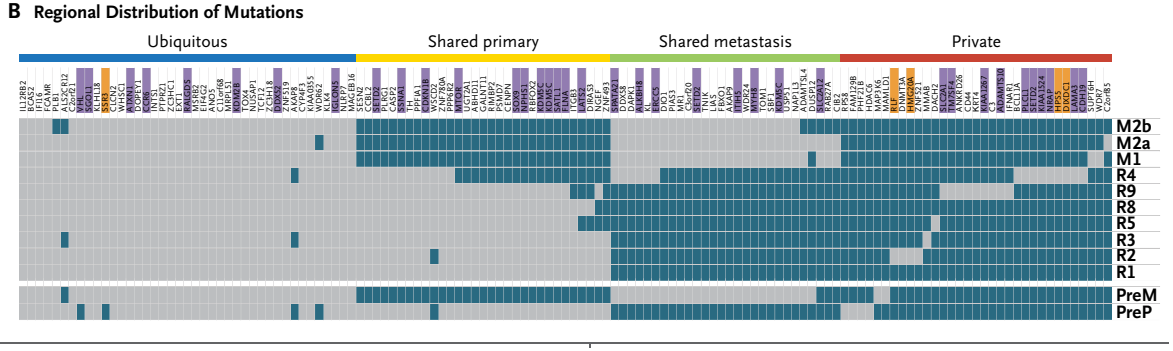
The NEW ENGLAND JOURNAL of MEDICINE

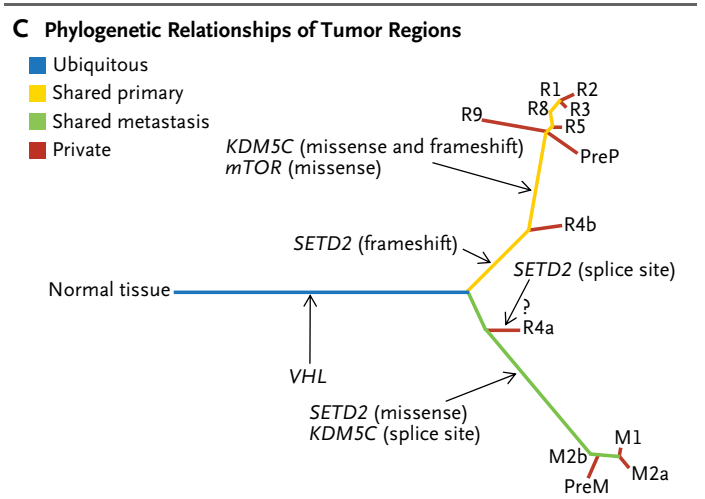
ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.







Problems in developing genetic-based therapies

- ✓ Intratumor heterogeneity
- ✓ Identify *Driver* versus *Passenger* mutations
- ✓ Resistance development to a targeted agent
- ✓ No info in the complete compendium of genetic alterations in cancer
- ✓ Most recognized genetic abberrations have not led to a candidate drug
- ✓ Essential is the identification of the core pathway rather than the single mutation
- ✓ One drug is never enough
- ✓ Need of strong and reliable preclinical infrastructures

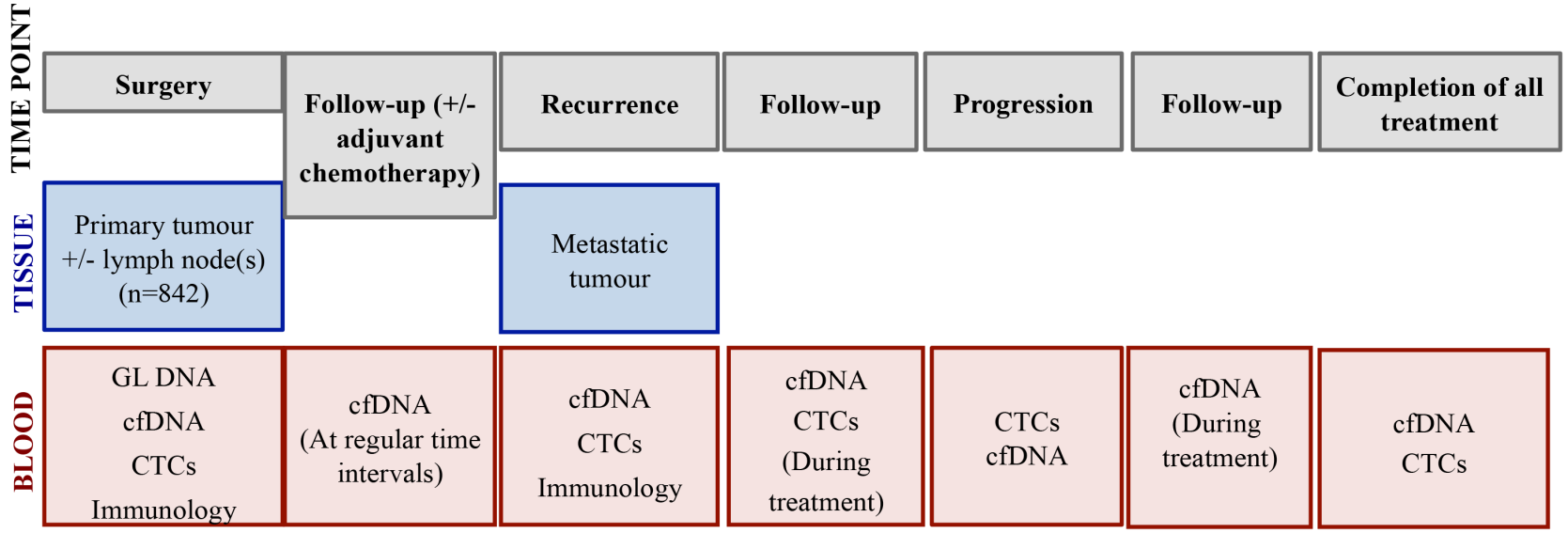
Is tumor heterogeneity in cancer a problem?

OPEN ACCESS Freely available online

PLOS BIOLOGY

Community Page

Tracking Genomic Cancer Evolution for Precision Medicine: The Lung TRACERx Study

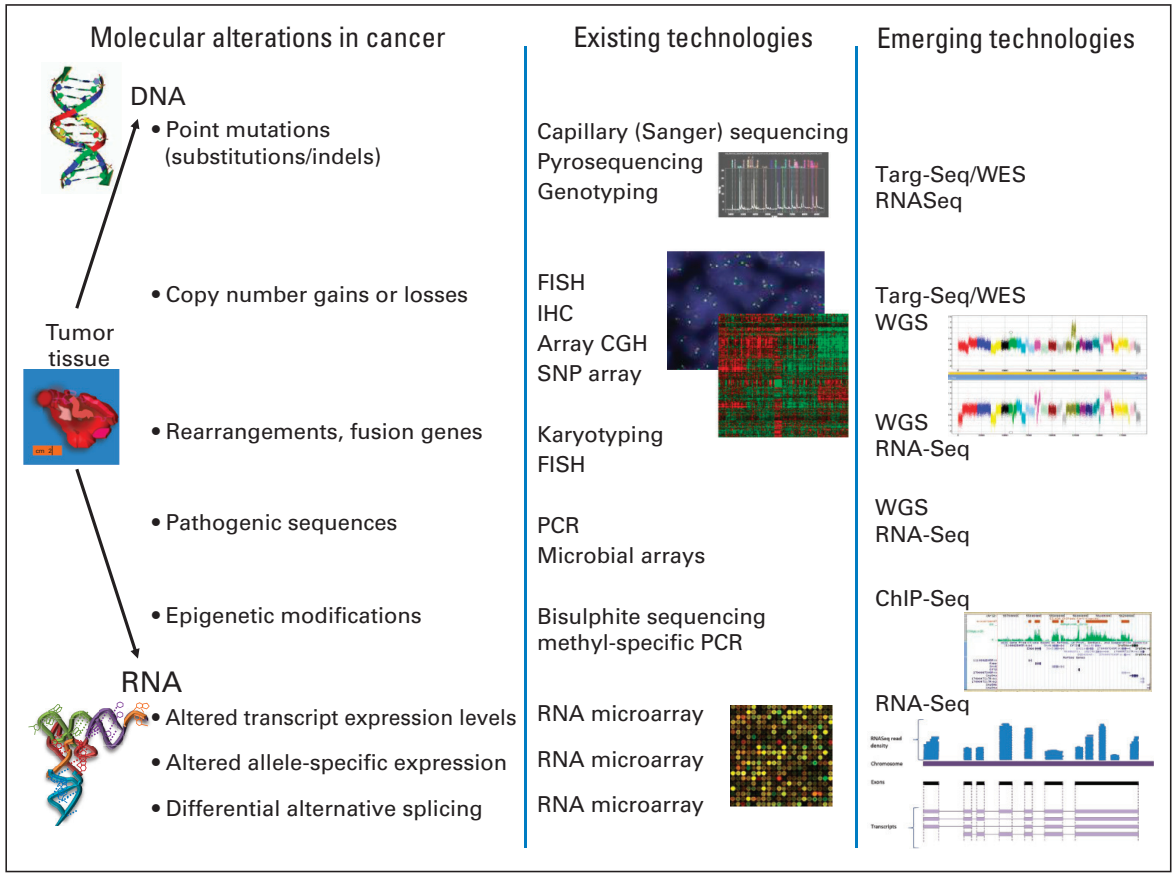


cfDNA, circulating-free tumour DNA;
CTC, circulating tumour cell;
GL DNA, germ line DNA;
TRACERx, TRAckingnon-small cell lung Cancer Evolution through therapy (Rx)

Genomic alterations and technologies for detection

Existing and Emerging Technologies for Tumor Genomic Profiling

Laura E. MacConaill



CGH, comparative genomic hybridization

ChIP-Seq, chromatin immunoprecipitation followed by massively parallel sequencing

FISH, fluorescent in situ hybridization

IHC, immunohistochemistry

PCR, polymerase chain reaction

RNA-Seq, RNA sequencing, also known as transcriptome sequencing

SNP, single nucleotide polymorphism

Targ-Seq, targeted sequencing

WES, whole-exome sequencing

WGS, whole-genome sequencing

VOLUME 31 · NUMBER 15 · MAY 20 2013

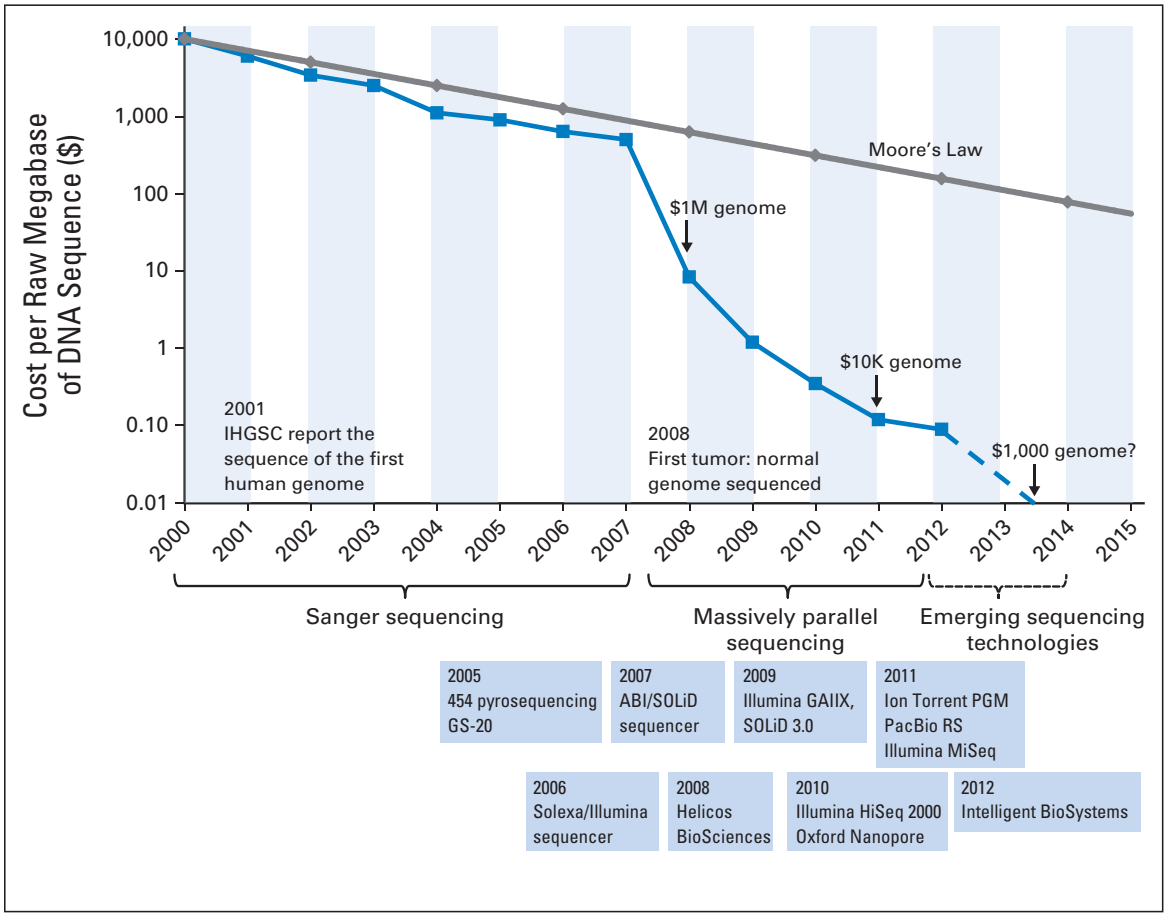
JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Cost of genome sequencing

Existing and Emerging Technologies for Tumor Genomic Profiling

Laura E. MacConaill



VOLUME 31 · NUMBER 15 · MAY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

2014 | Volume 12 | Issue 7 | e1001906

Opportunities and Challenges of Biomarker-Driven Targeted Therapies

Aligning incentives to fulfil the promise of personalised medicine

www.thelancet.com Vol 385 May 23, 2015

Victor J Dzau, Geoffrey S Ginsburg, Karen Van Nuys, David Agus, Dana Goldman

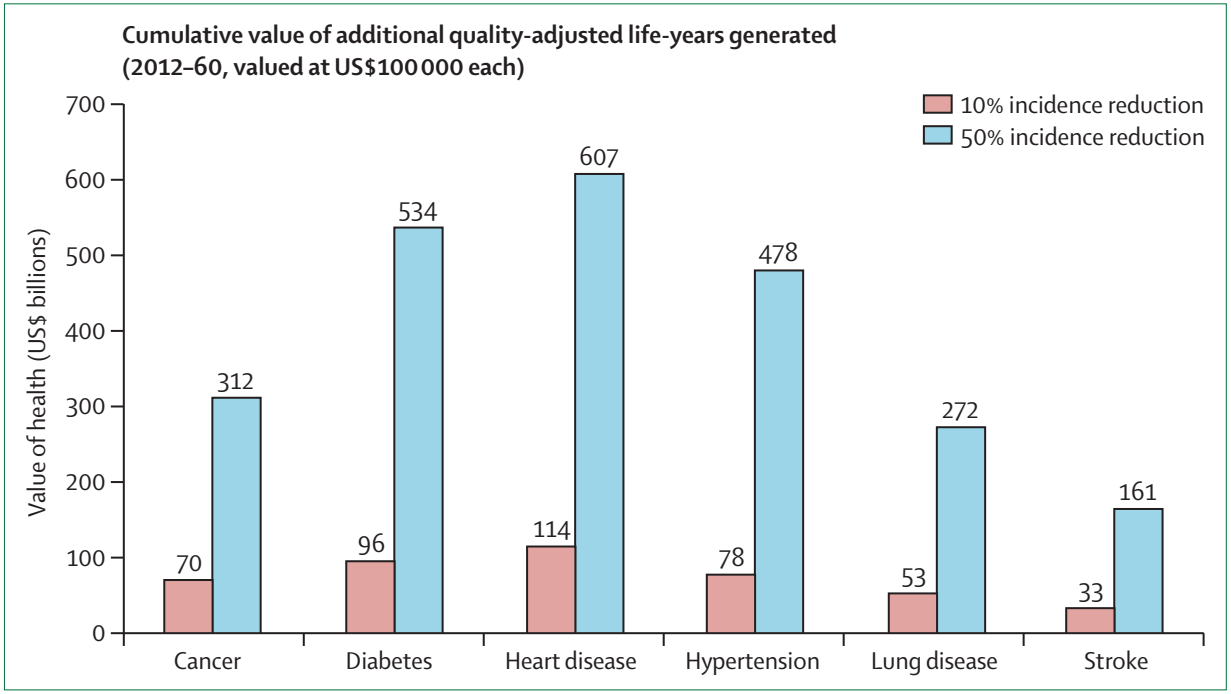


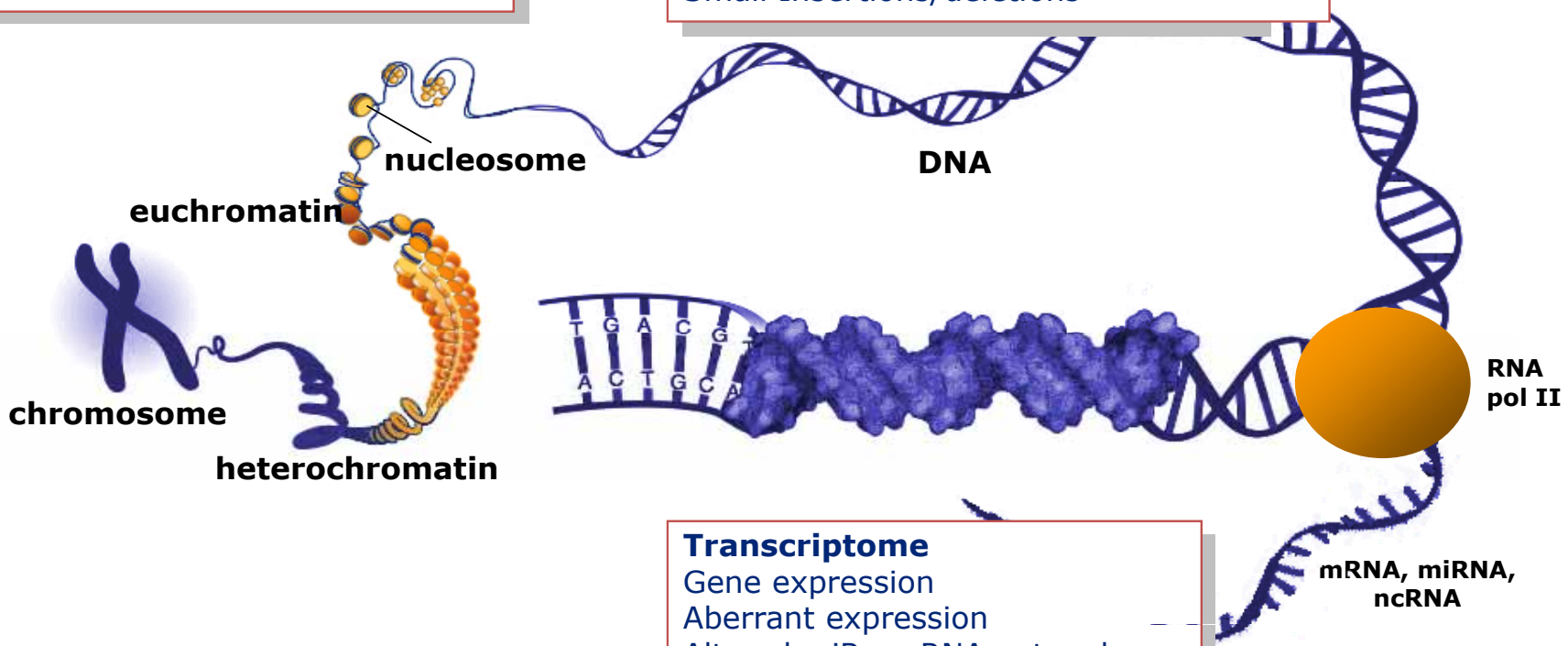
Figure: **Value of health from hypothetical personalised and precision medicine prevention innovation at two levels of incidence reduction in six diseases in the USA ($ billions)**

UCSF Initiative

Cancer is a genetic disease

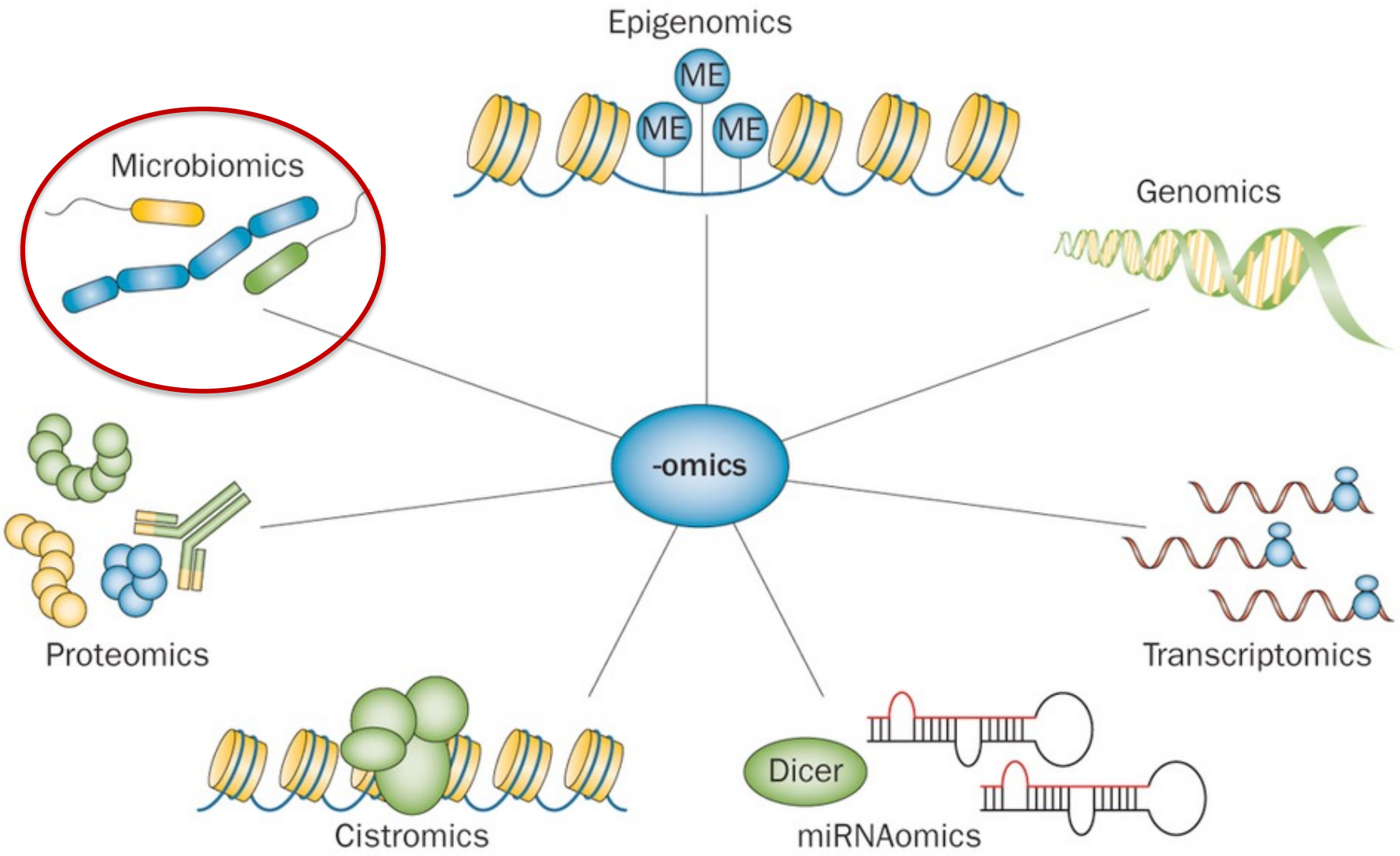
Epigenome
Changes in DNA methylation
Histone modifications
Chromosomal instability

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

The “omics” world



Tumour microenvironment: Gut bacterial balance affects cancer treatment

The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide

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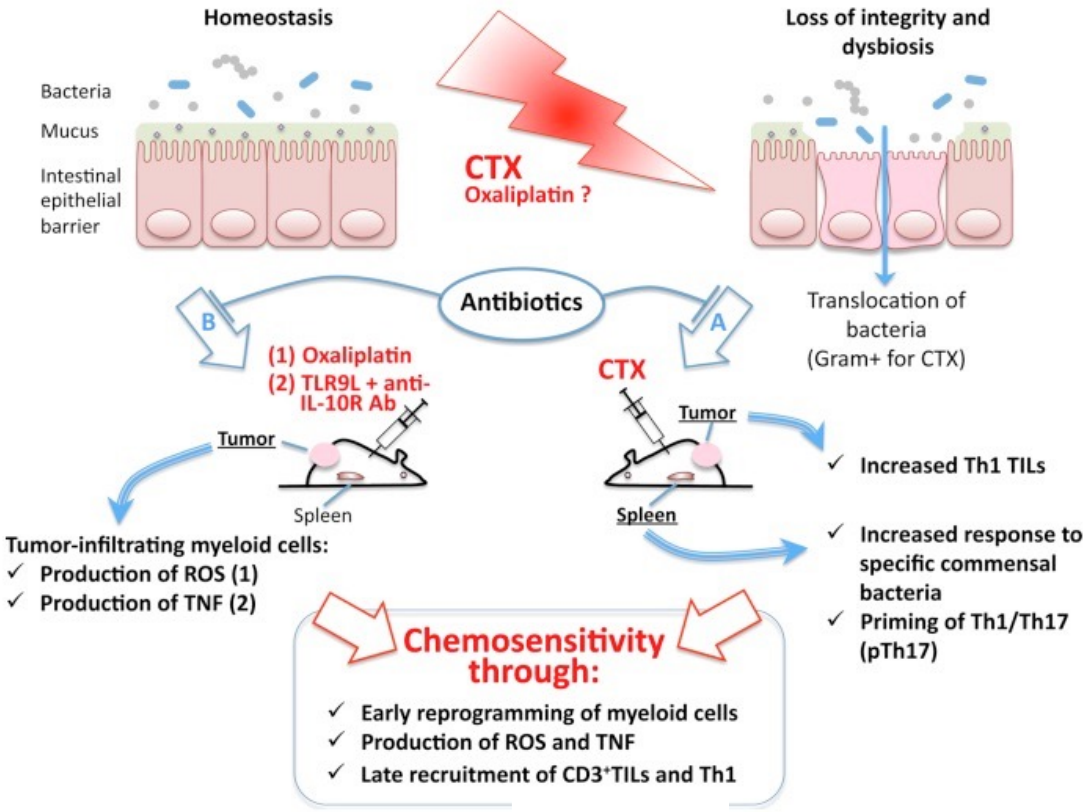

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Why should we need the gut microbiota to respond to cancer therapies?

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Thank you for your attention