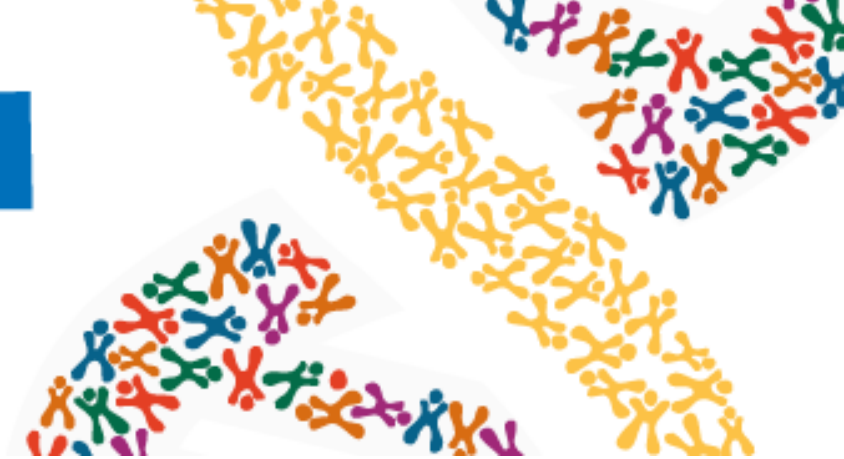
Curso

Medicina Personalizada de Precisión

De la teoría
a la práctica



Medicina de Precisión en Oncología

Presente y Futuro

Hospital Universitario de La Princesa
SaludMadrid

UAM
UNIVERSIDAD AUTONOMA DE MADRID

26 DE SEPTIEMBRE

16:00-20:30 **Módulo II: Presente y futuro de la Medicina Personalizada de Precisión**

Dr. Luis Paz-Ares
Jefe de Servicio de Oncología Médica
Hospital Doce de Octubre

Dr. Ramón Colomer
Jefe de Servicio de Oncología Médica
Hospital La Princesa

25 DE SEPTIEMBRE

15:30-16:00 **Inauguración**

D. José Luis Álvarez-Sala
Decano Facultad de Medicina UCM

Dª. Irene Navarro
Directora general Fundación Madrid Excelente

D. Federico Plaza
Vicepresidente Fundación Instituto Roche

16:00-20:30 **Módulo I: De la Biología Molecular a la Medicina: Fundamentos de la Medicina Personalizada de Precisión**

Dr. Miguel Urioste
Unidad Clínica de Cáncer Familiar
Centro Nacional de Investigaciones Oncológicas (CNIO)

Dra. Cristina Rodríguez
Grupo de Cáncer Endocrino Hereditario
Programa de Genética del Cáncer Humano
Centro Nacional de Investigaciones Oncológicas (CNIO)

26 DE SEPTIEMBRE

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Jefe de Servicio de Oncología Médica
Hospital La Princesa

27 DE SEPTIEMBRE

16:00-19:00 **Módulo III: Investigación clínica en Medicina Personalizada de Precisión**

Dra. Esther Vilas
Miembro del Patronato. Fundación Instituto Roche
Head of Medical Strategy. Roche Farma

Dr. Francisco Abad
Jefe de sección del Servicio de Farmacología Clínica
Hospital La Princesa

19:00 **Lección magistral**

"El ejercicio de la Medicina Personalizada de Precisión como modelo de humanización de la asistencia sanitaria"

Dr. Fernando Bandrés
Catedrático y profesor de la Facultad de Medicina de la UCM

20:00 **Clausura**

Dª. Irene Navarro
Directora general
Fundación Madrid Excelente

Dª. Consuelo Martín de Dios

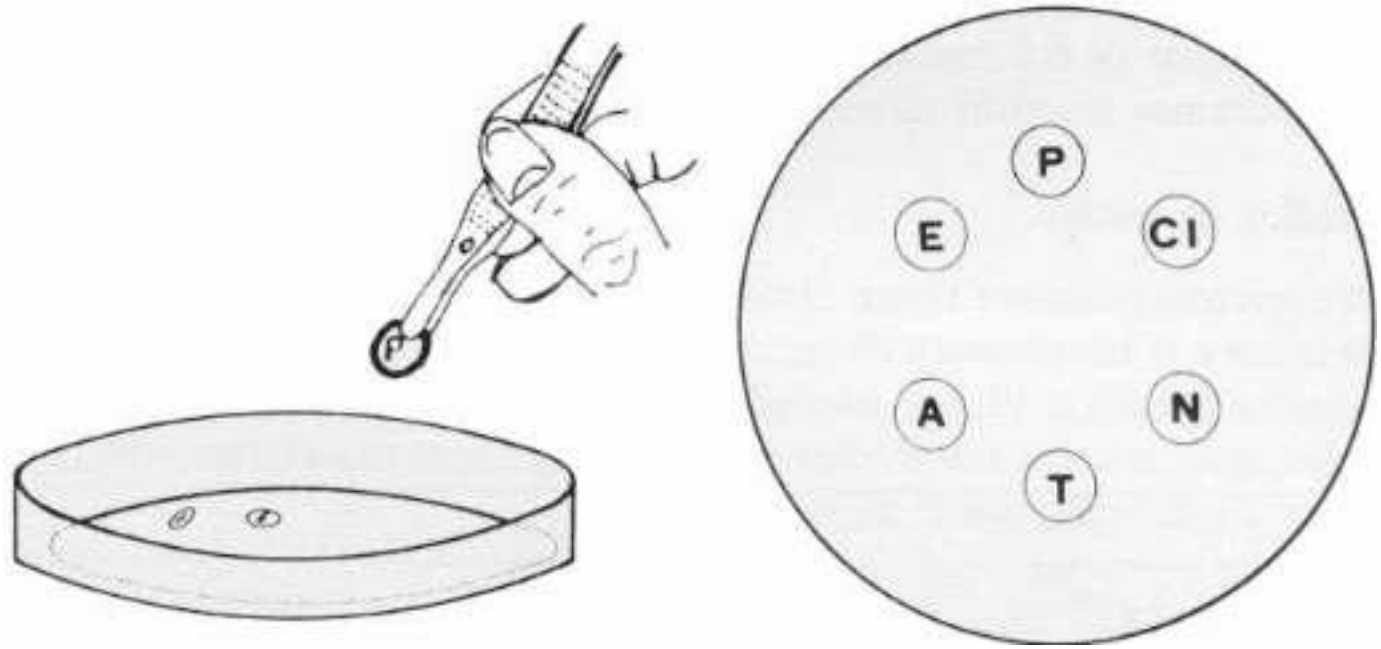
Why Precision Medicine?

Targets tumors with greater accuracy

Mitigates unnecessary treatments

Reduces prescription errors

Antibiograma



CIUDAD SANITARIA DE LA SEGURIDAD SOCIAL **- BARCELONA**

Apellidos	Nombre	PROCEDENCIA: RG-T y R CI-EM-AMB
N.° de Historia no consta	Análisis N.°	C.I.
Servicio solicitado Exudado herida (29-5-78)		

Por siembra en placas de agar-sangre, se desarrollan abundantes colonias de estreptococo, y de estafilococo plasmacoagulasa negativo.

Identificación, en curso.

ANTIBIOGRAMA:

	RESIST.	SENSIB.	MUY SEN.
Penicilina G.	☐	☐	☒
Cloxacilina	☐	☐	☒
Dicloxacilina	☐	☐	☐
Eritromicina	☐	☐	☒
Lincomicina	☐	☐	☒
Neomicina	☐	☐	☐
Cefalosporinas	☐	☐	☒
Estreptomicina	☐	☐	☐
Cloranfenicol	☐	☐	☒
Novobiocina	☐	☐	☐
Kanamicina	☐	☐	☒
Tetraciclinas	☐	☒	☐
Amikacina	☐	☐	☒

estafilococo	RESIST.	SENSIB.	MUY SEN.
Gentamicina	☐	☐	☒
Colistina	☐	☐	☐
Ampicilina	☐	☐	☐
Aminosidina	☐	☐	☐
Carbenicilina	☐	☐	☐
Rifampicina	☐	☐	☐
Rifamicina	☐	☐	☐
Cefazolina	☐	☐	☐
Fosfomicina	☒	☐	☐
Trimetoprim	☐	☐	☒
Furant. In.	☐	☐	☐
Ac. nalidíxico	☐	☐	☐
	☐	☐	☐

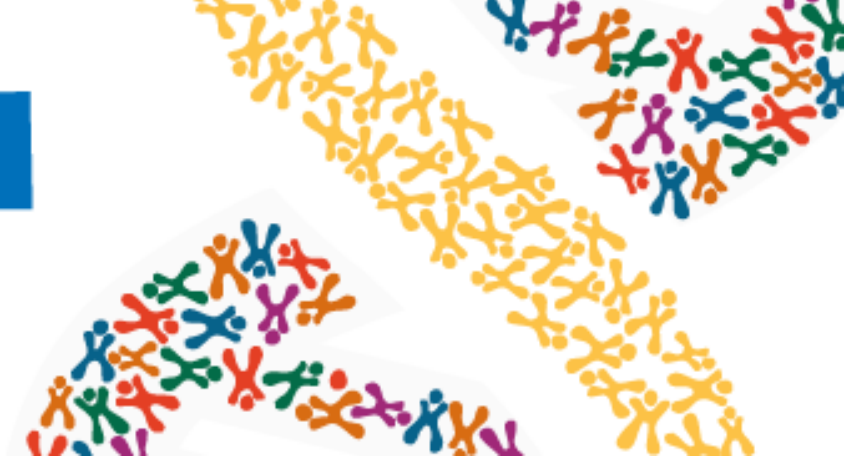
SERVICIO DE BACTERIOLOGIA-SEROLOGIA
C.R. 73

FECHA 1 JUN. 1978

Curso

Medicina Personalizada de Precisión

De la teoría
a la práctica



Medicina de Precisión en Oncología

Oncología personalizada

Dr Ramon Colomer

Servicio de Oncología Médica

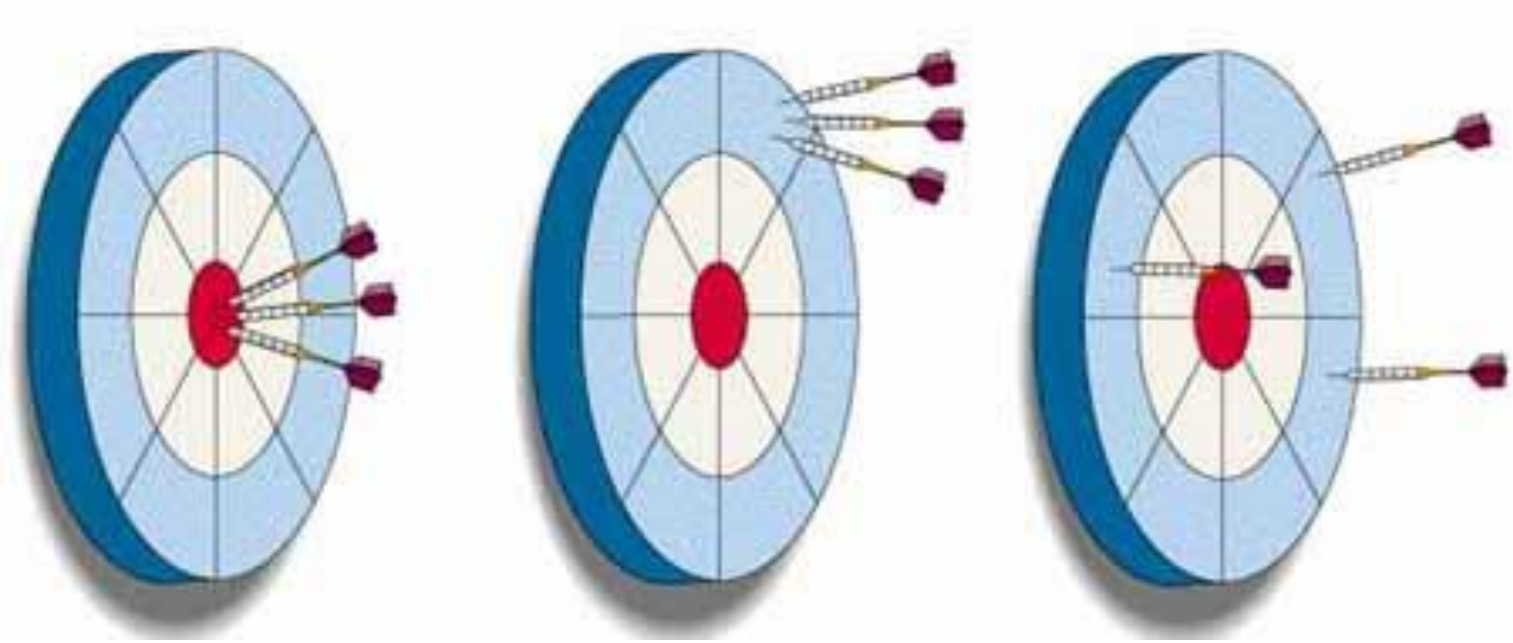
Hospital Universitario La Princesa, Madrid

Hospital Universitario de La Princesa
SaludMadrid

UAM
UNIVERSIDAD AUTONOMA DE MADRID

Dianas para el tratamiento del cáncer

Dianas terapéuticas: precision... y puntería

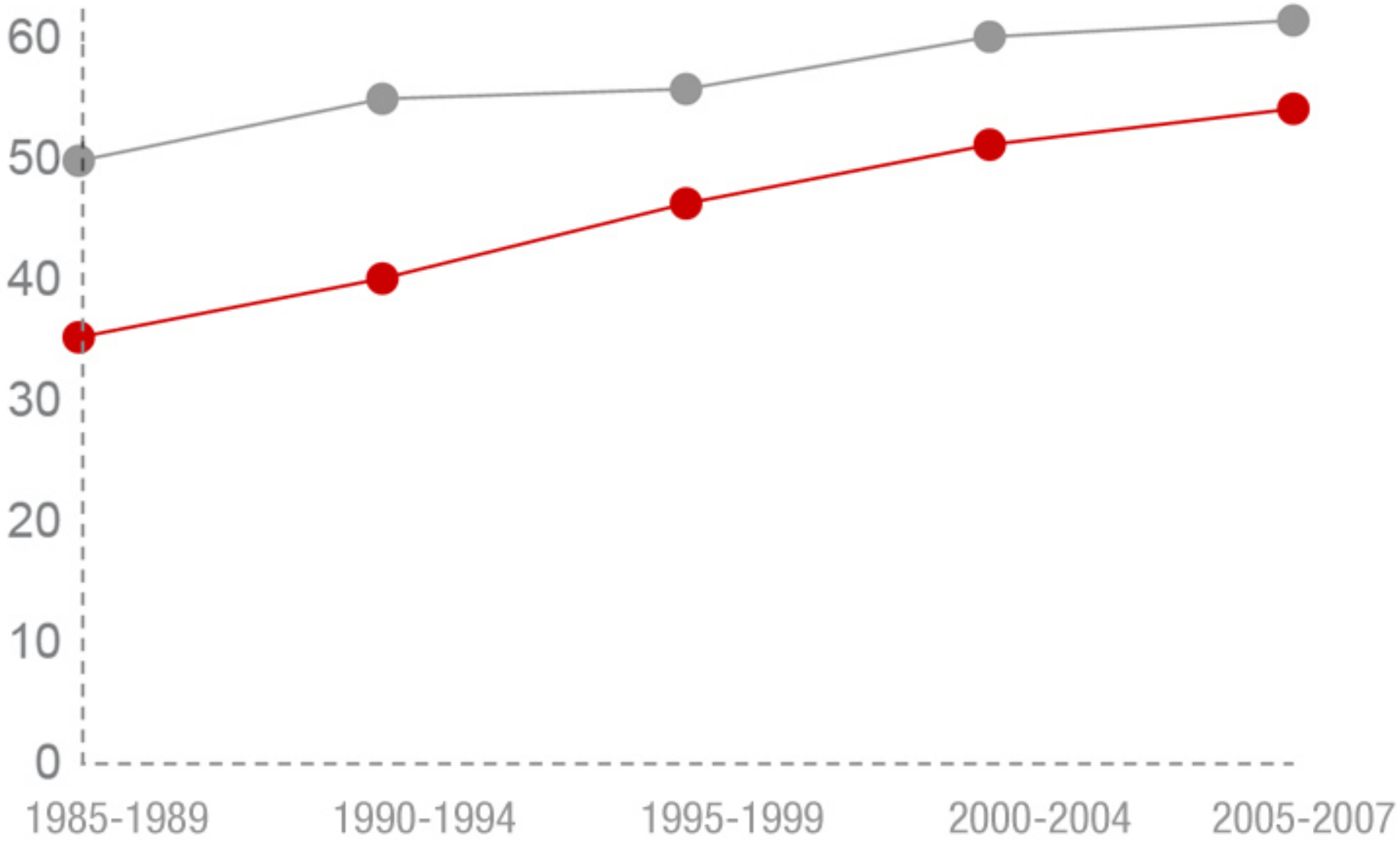


Buena Precision
Buena Puntería

Buena Precision
Mala puntería

Poca Precision
Mala puntería

Supervivencia del cáncer en hombres (rojo), y mujeres (gris), 2017



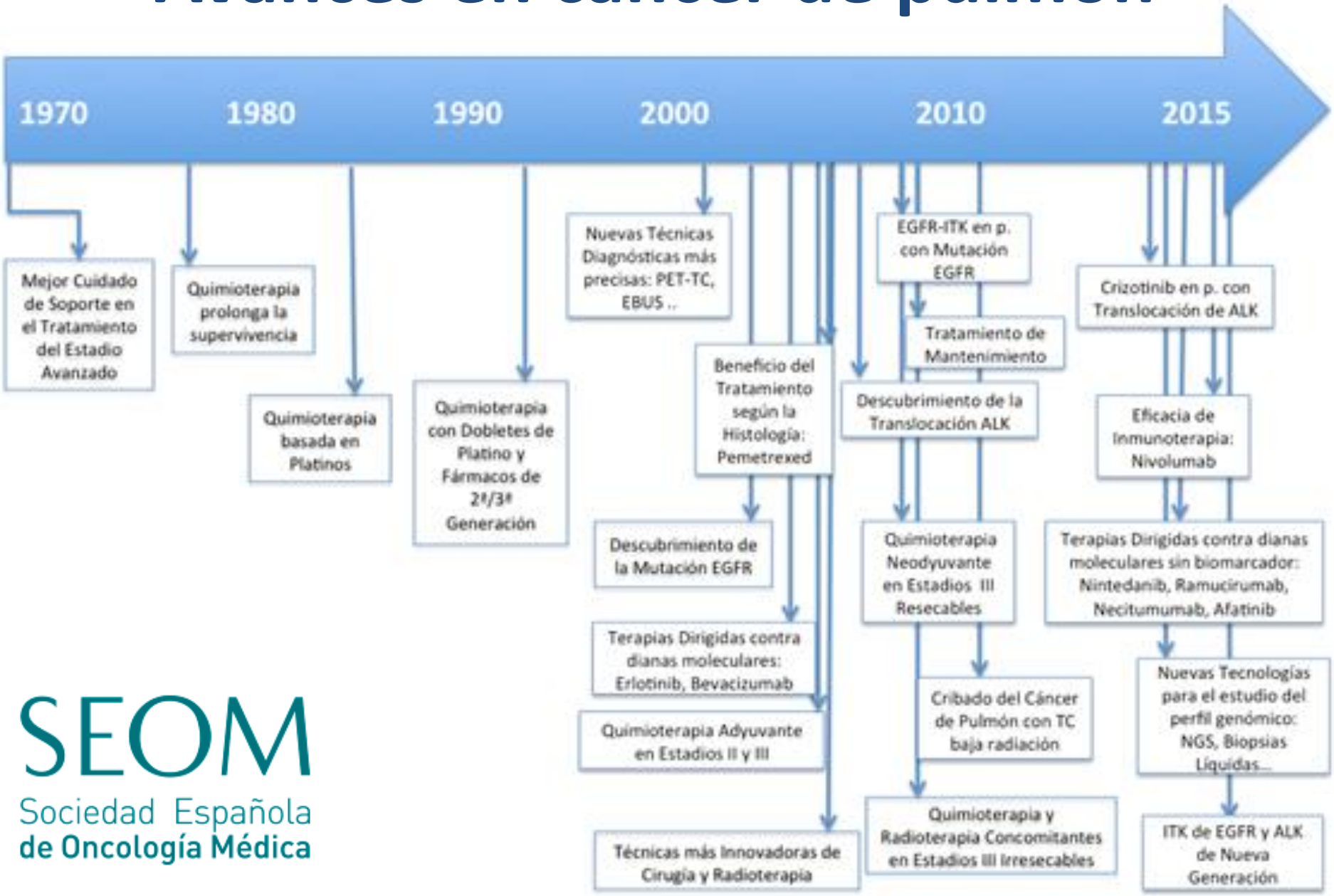
Por qué el cáncer tiene hoy más supervivencia?

- Evitar carcinógenos
- Diagnóstico precoz
- **Avances en los tratamientos**
    - **Ocurren igual en todos los tipos de cáncer?**

Avances en cáncer de páncreas

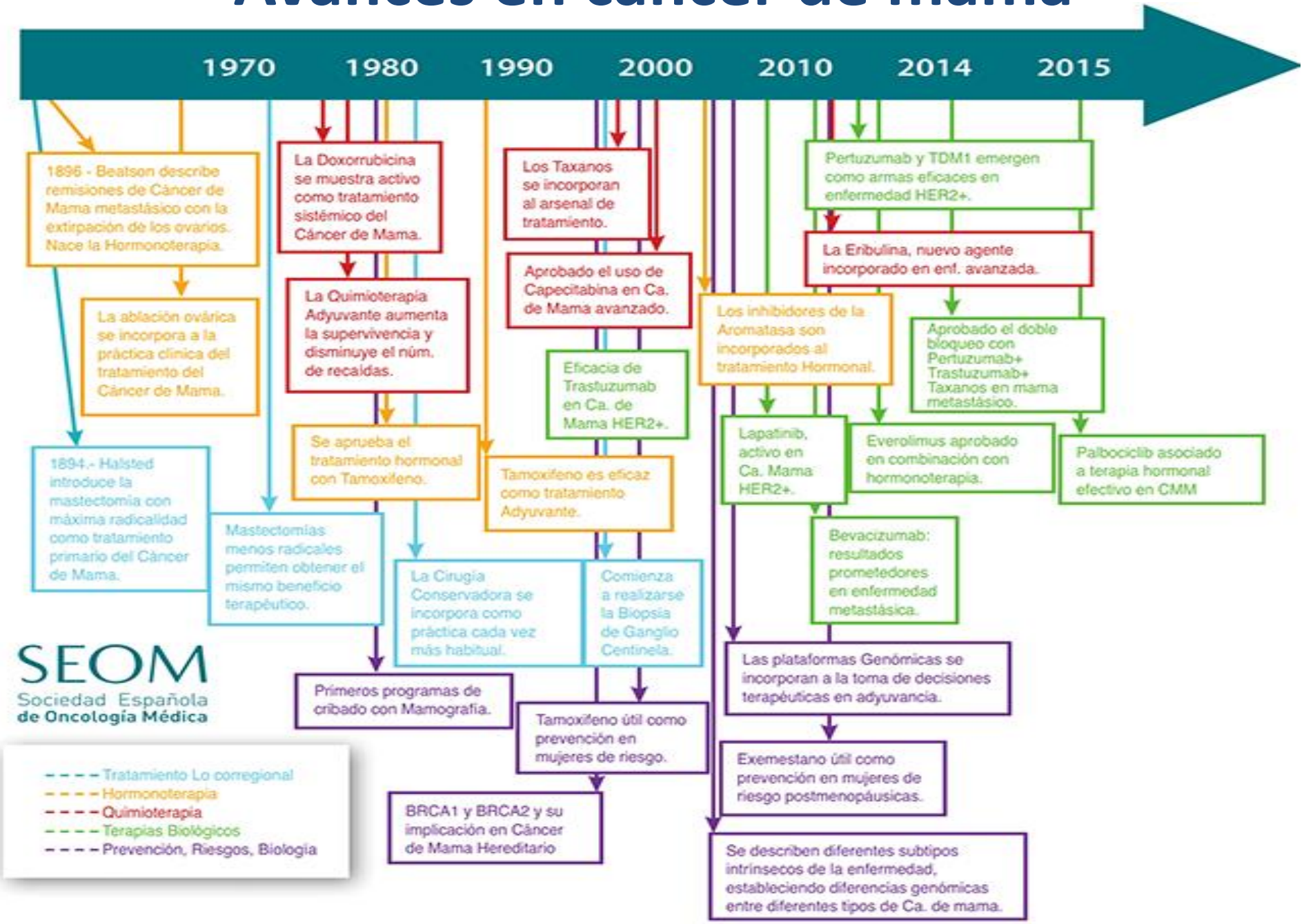
SEOM
Sociedad Española
de Oncología Médica

Avances en cáncer de pulmón

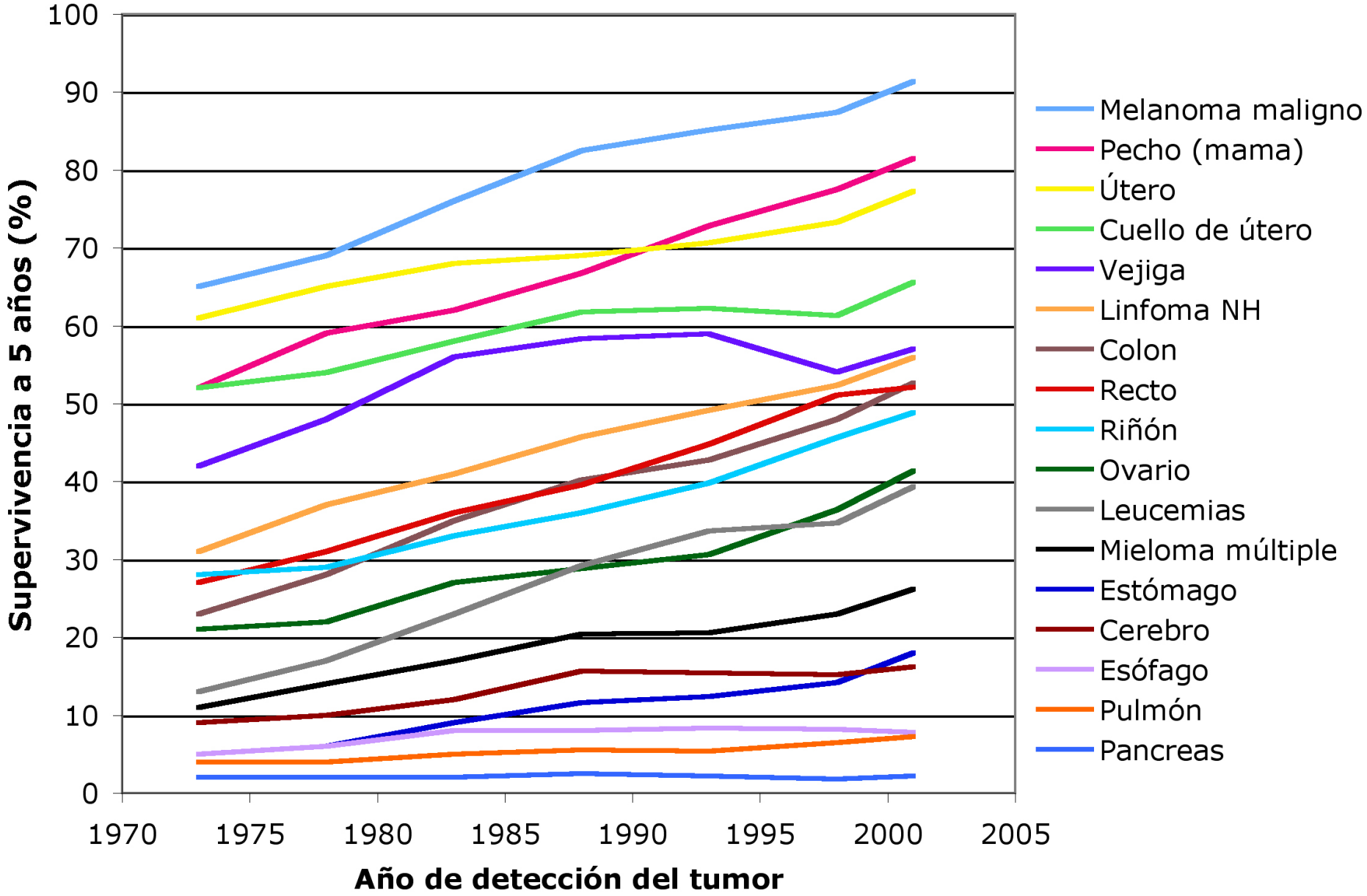


SEOM
Sociedad Española
de Oncología Médica

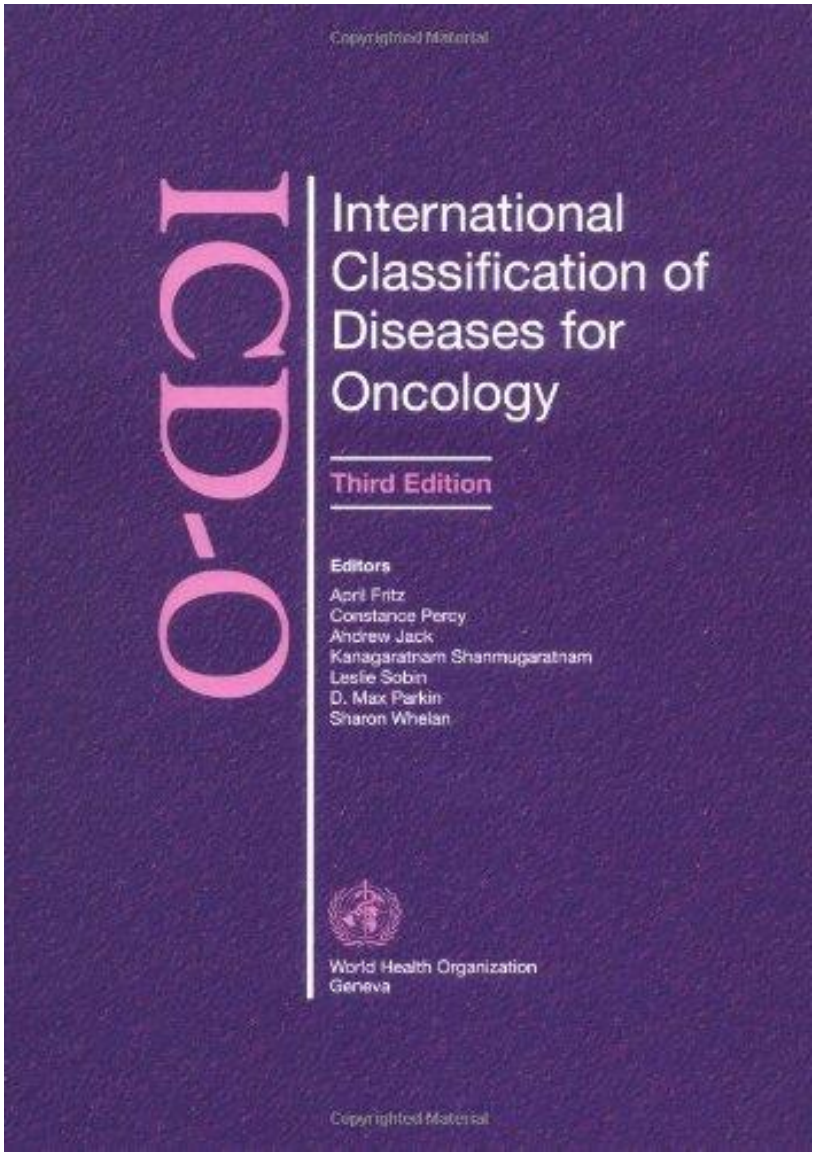
Avances en cáncer de mama



Supervivencia al cáncer en mujeres



2000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ICD-O
International Classification of Diseases for Oncology
Third Edition
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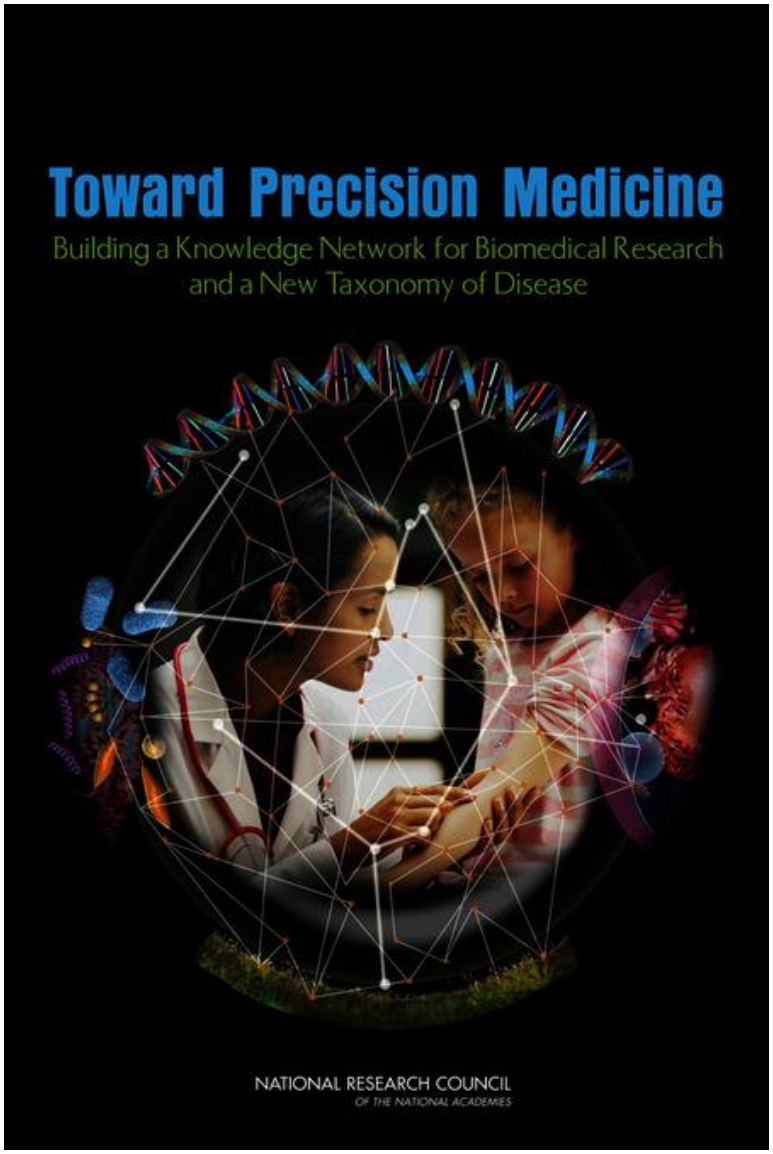
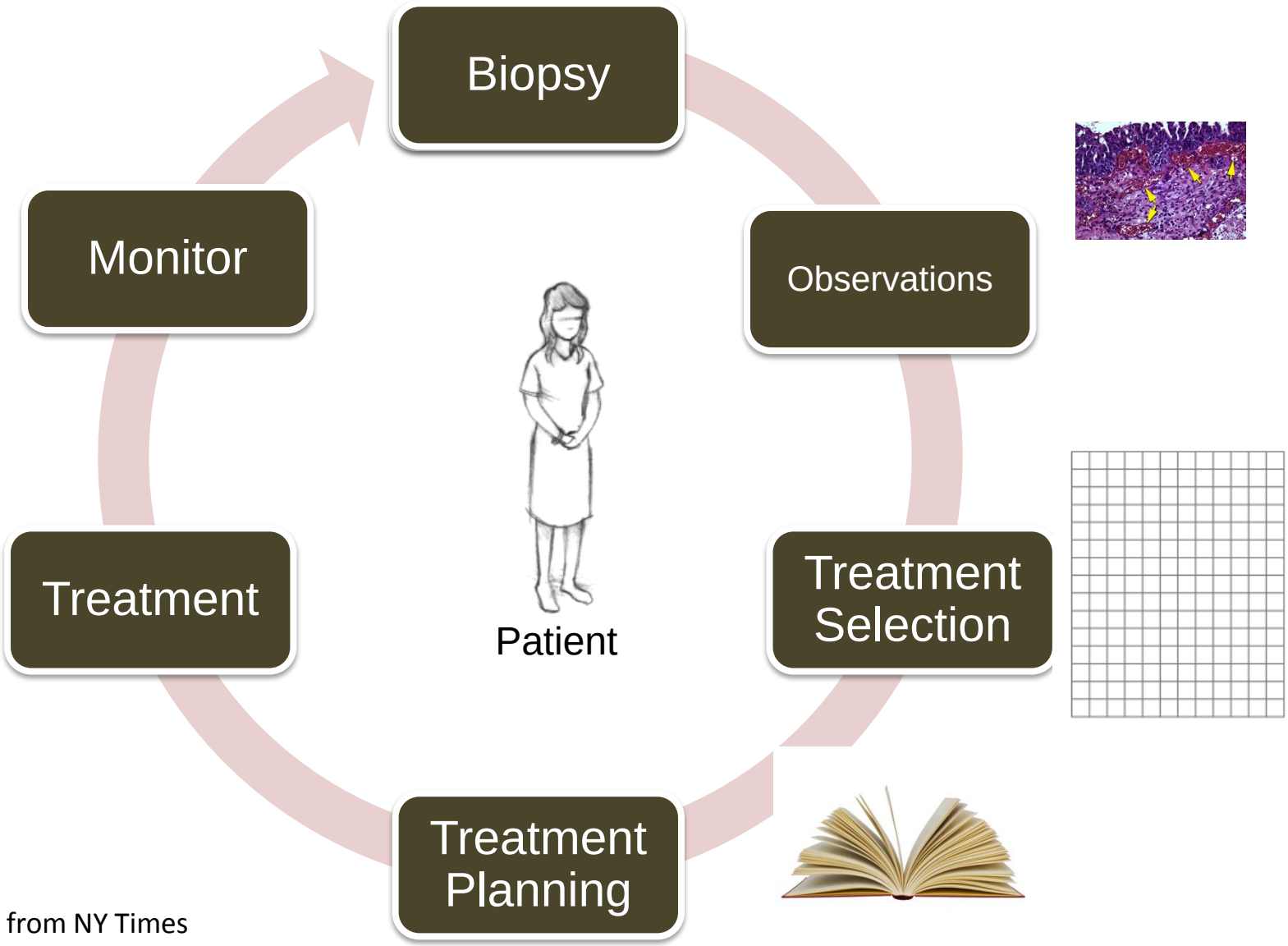

Toward Precision Medicine
Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease
NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

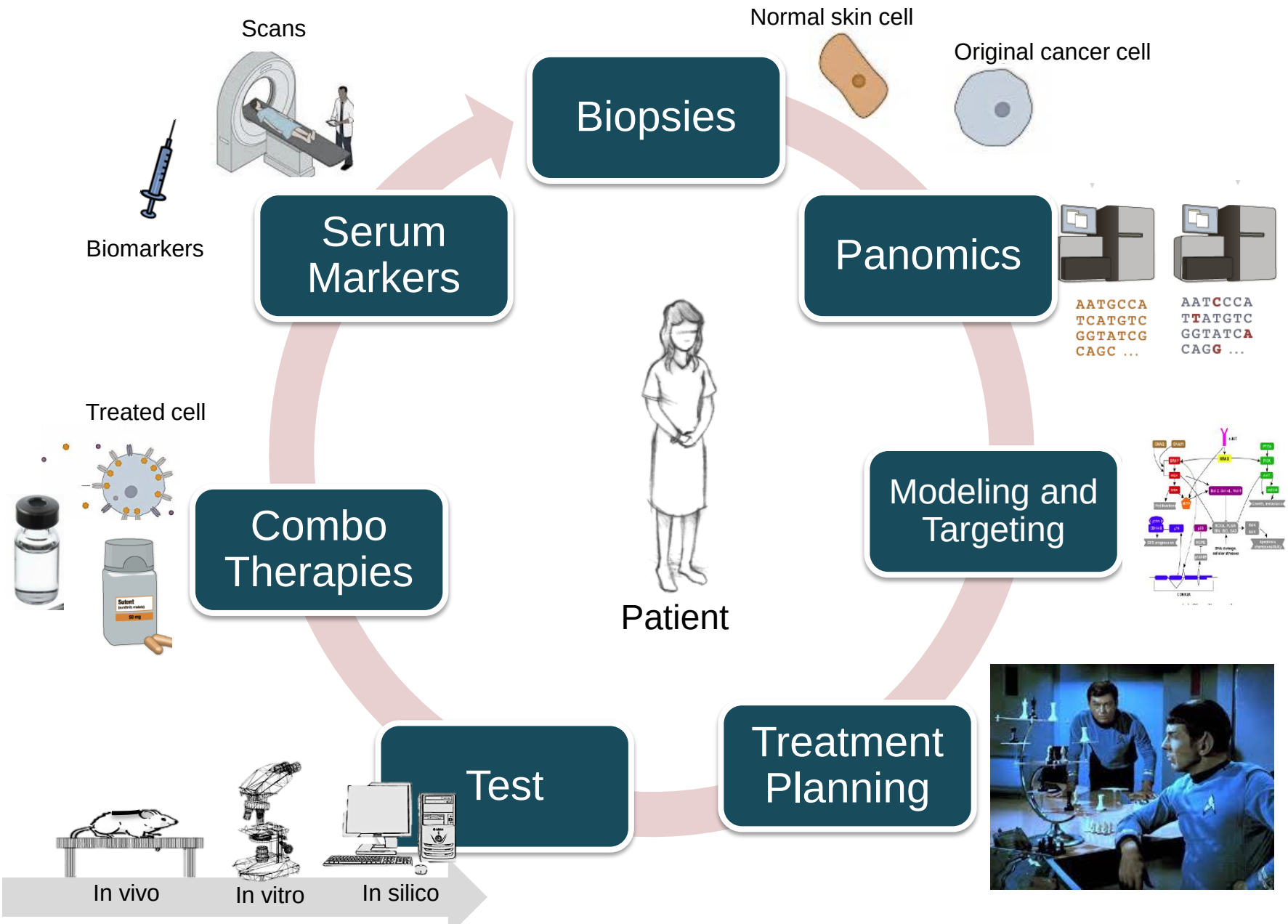
Oncología estándar	Oncología de Precisión
• Define los cánceres según el órgano donde se originan	• Define los cánceres según sus **causas moleculares**, además de los signos y síntomas tradicionales

Oncology Workflow

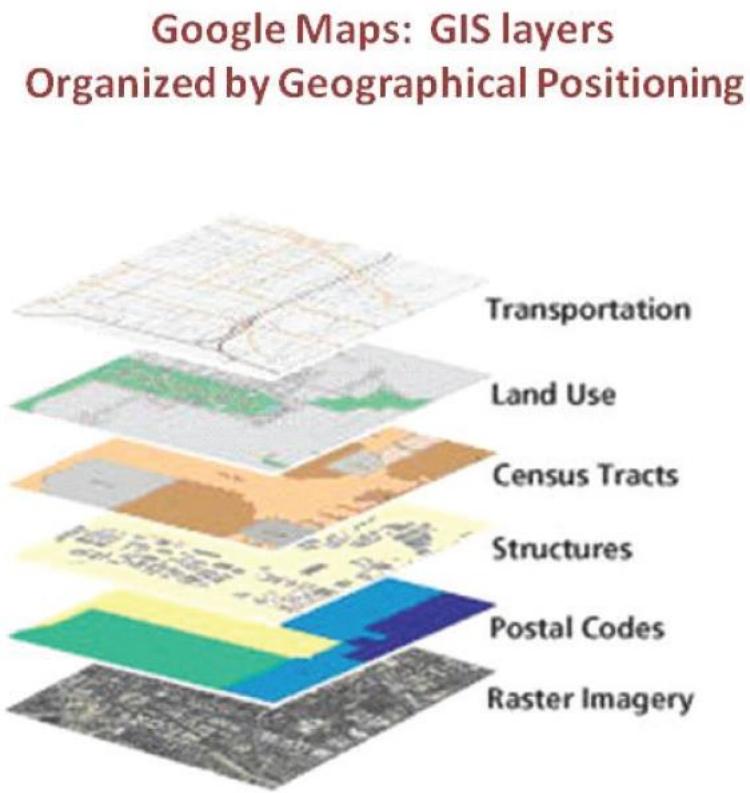


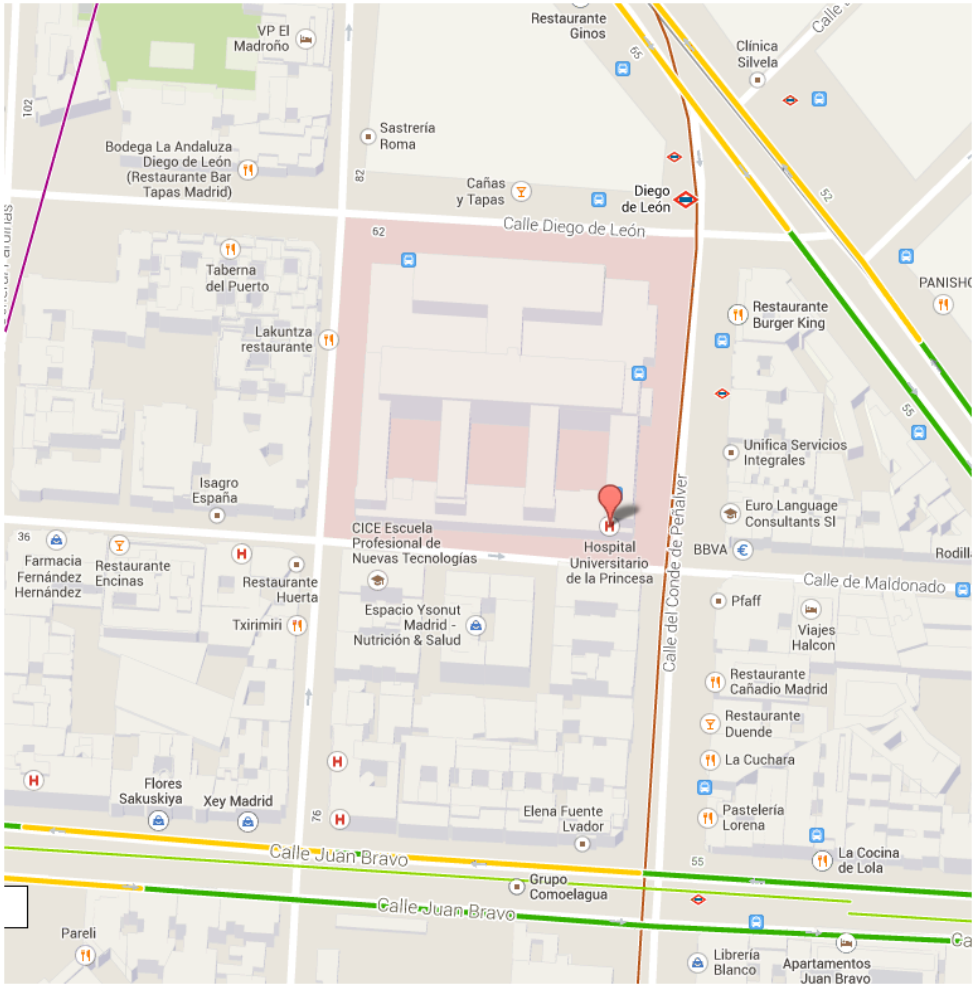
Adapted from NY Times

Precision Oncology Workflow



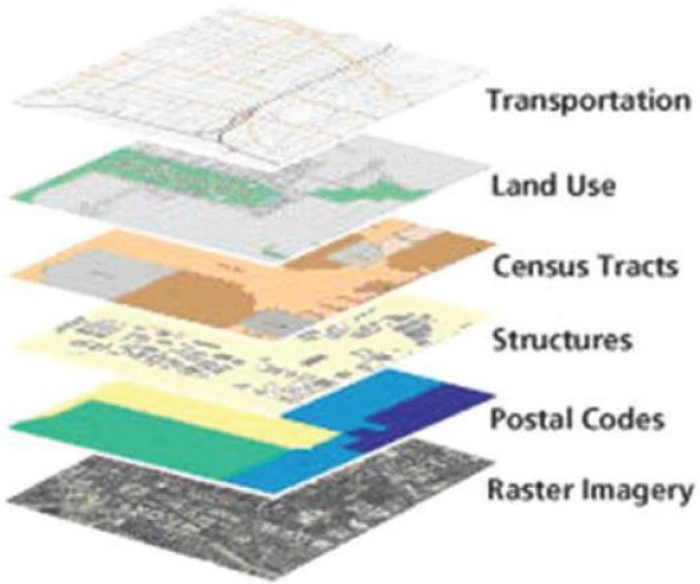
Capas de información



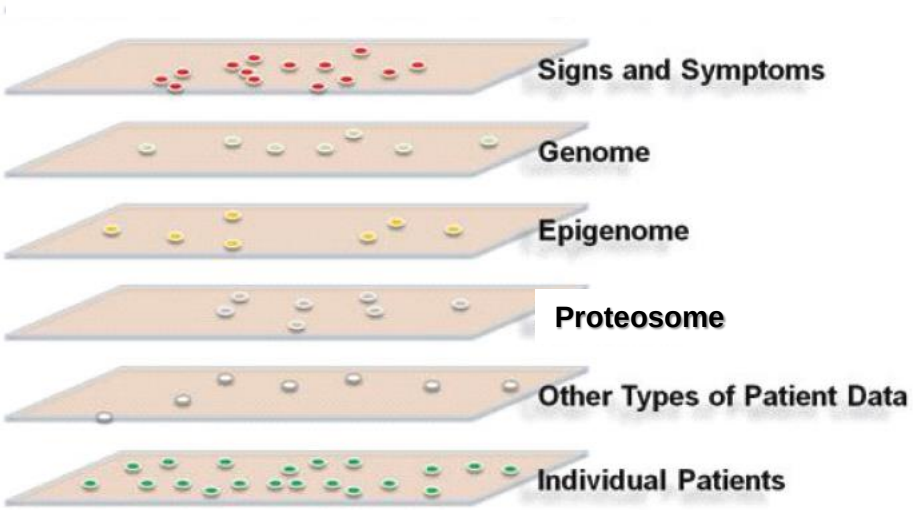


Capas de información

Google Maps: GIS layers
Organized by Geographical Positioning



Information Commons
Organized Around Individual Patients



Volume 31, Issue 15

May 20, 2013

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

VOLUME 31 · NUMBER 15 · MAY 20 2013

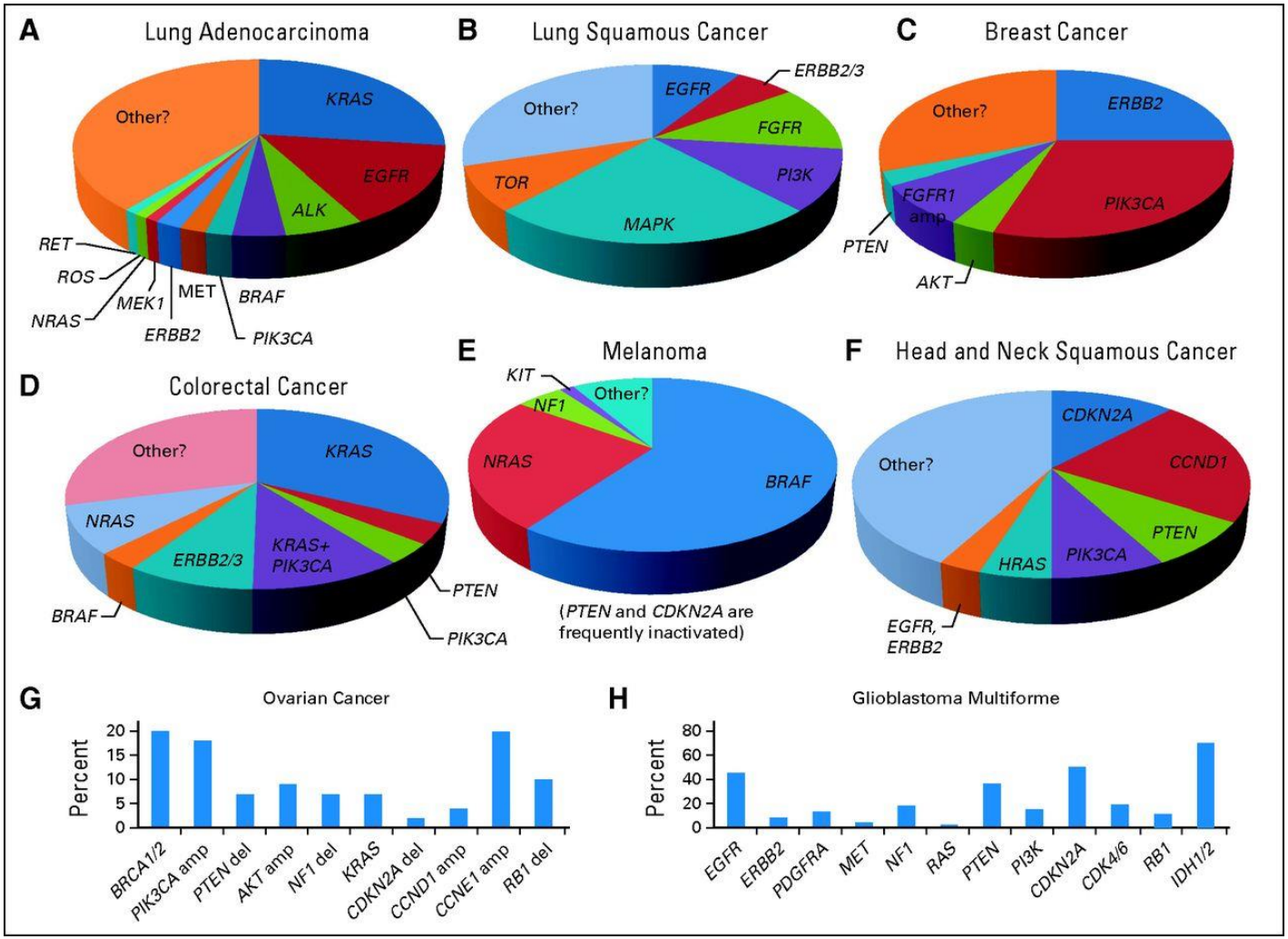
JOURNAL OF CLINICAL ONCOLOGY

SPECIAL SERIES OVERVIEW

Precision Oncology

Levi A. Garraway, *Dana-Farber Cancer Institute; Brigham and Women's Hospital, Harvard Medical School, Boston; The Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA*
Jaap Verweij, *Erasmus University Medical Center/Daniel den Hoed Cancer Center, Rotterdam, the Netherlands*
Karla V. Ballman, *Mayo Clinic, Rochester, MN*

Genomic alterations affecting actionable signaling pathways in common solid tumors



Garraway L A JCO 2013;31:1806-1814

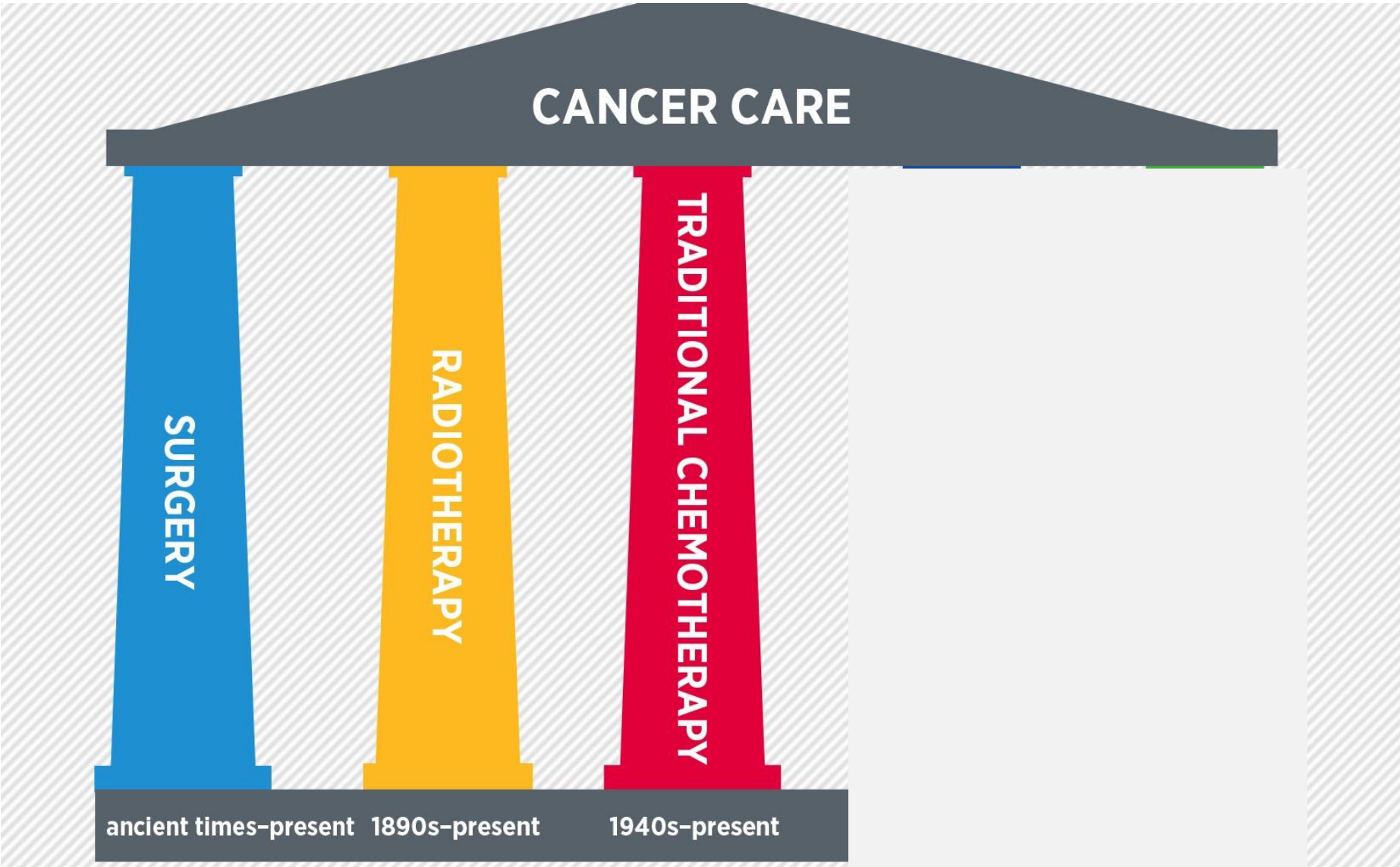
JOURNAL OF CLINICAL ONCOLOGY ASCO

ESMO 2014: Precision Medicine

Why precision medicine in cancer care? Because each patient's cancer is unique and may respond differently to the standard treatment approach.

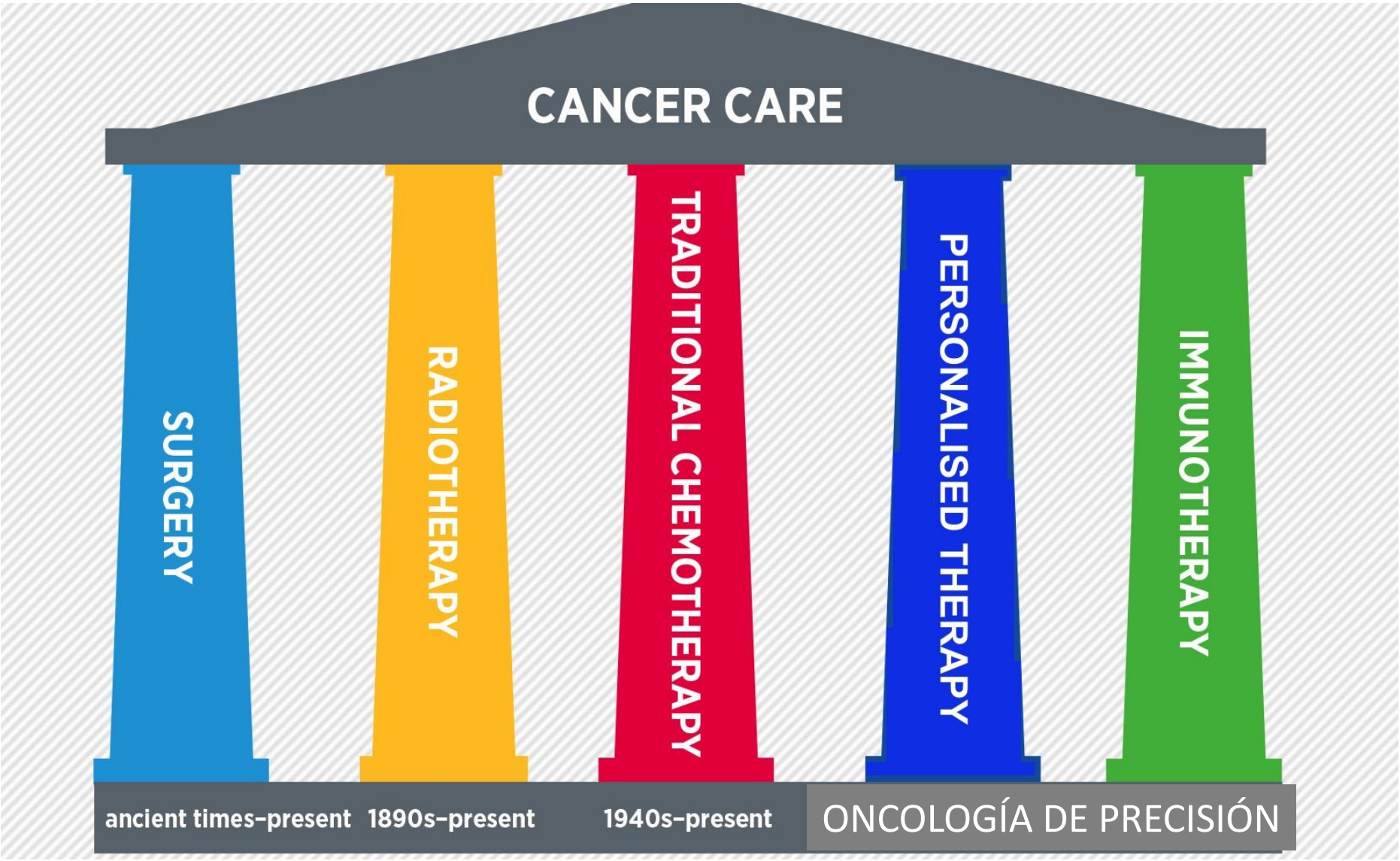

ESMO

PILARES DEL TRATAMIENTO DEL CÁNCER



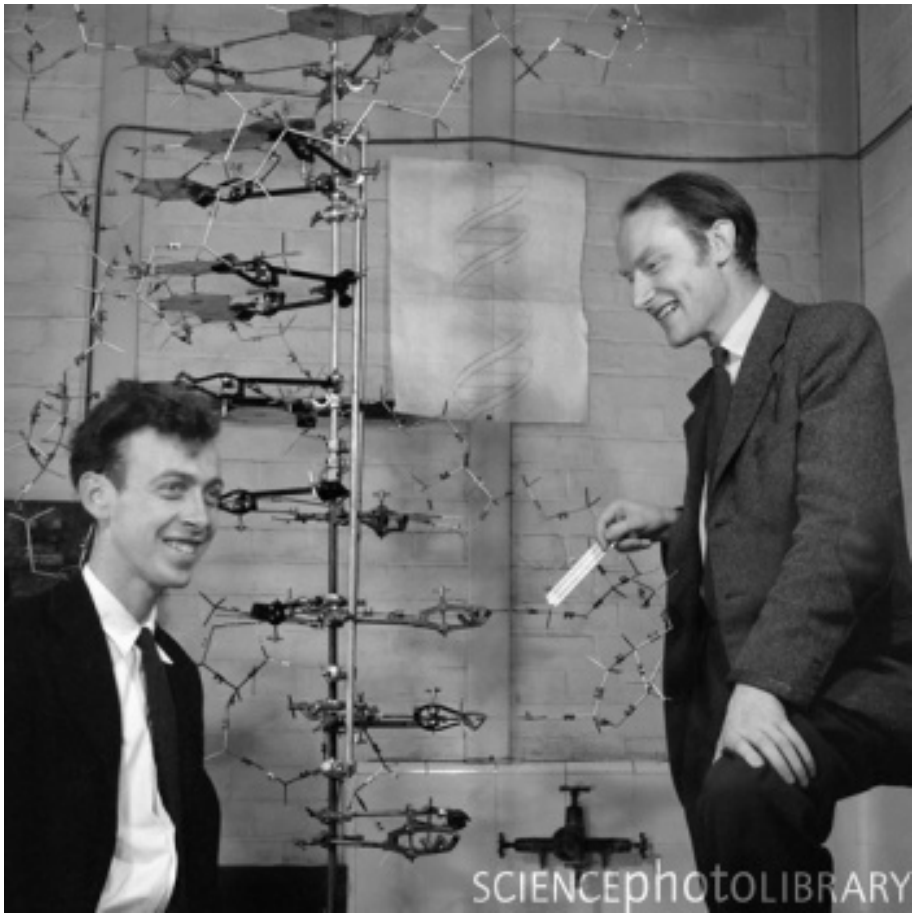
American Association for Cancer Research Cancer Progress Report 2025 (modificado)

MÁS OPCIONES PARA EL MANEJO DEL CÁNCER



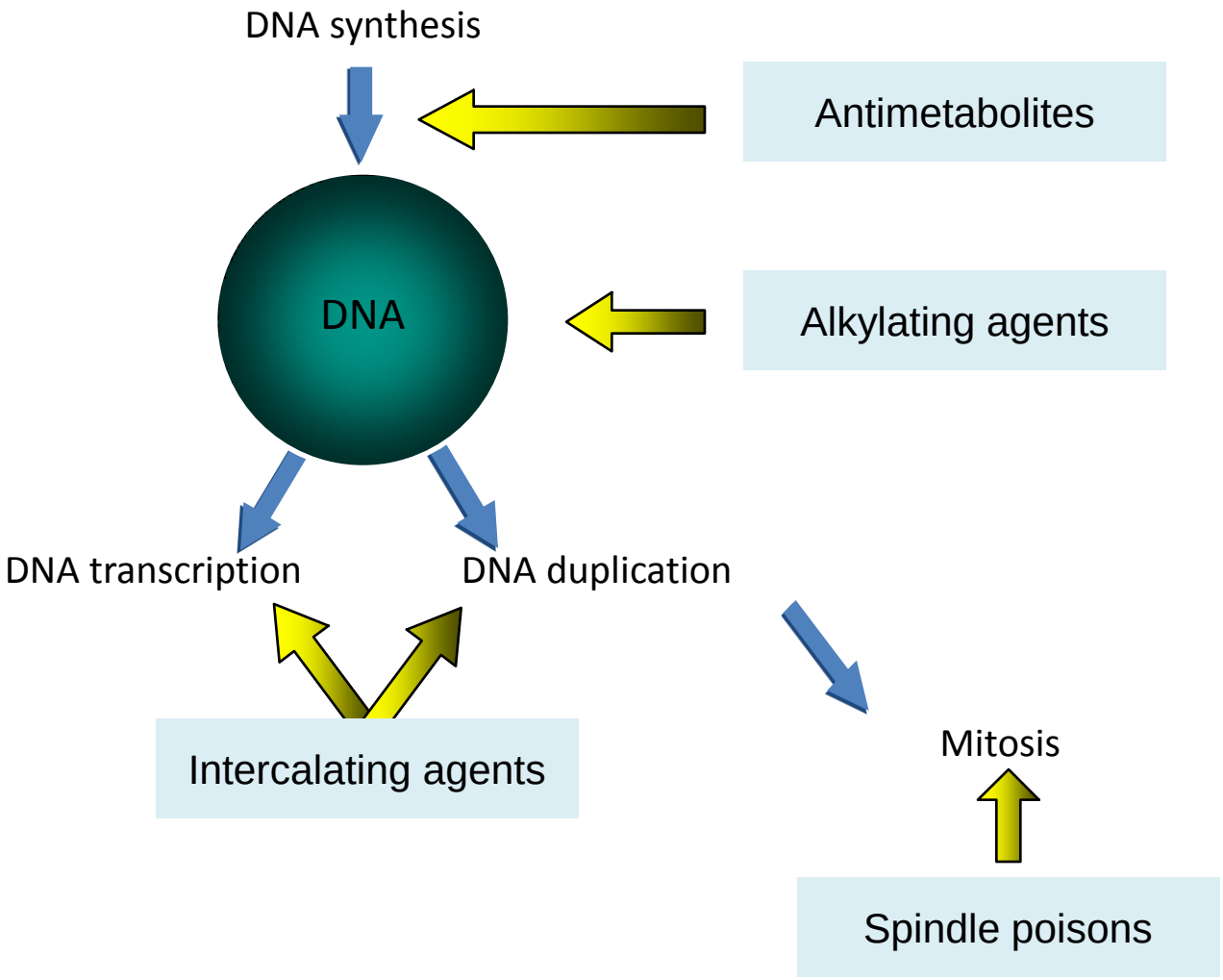
American Association for Cancer Research Cancer Progress Report 2025 (modificado)

El paradigma clásico: el cáncer es una enfermedad del ADN

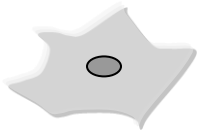


Nature, 1953

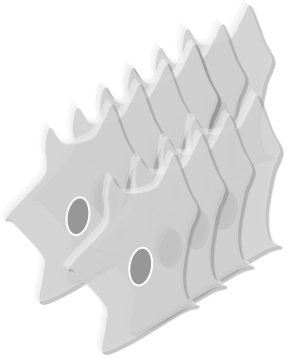
Lugares de acción de los fármacos citotóxicos



Aparición de la biologia molecular

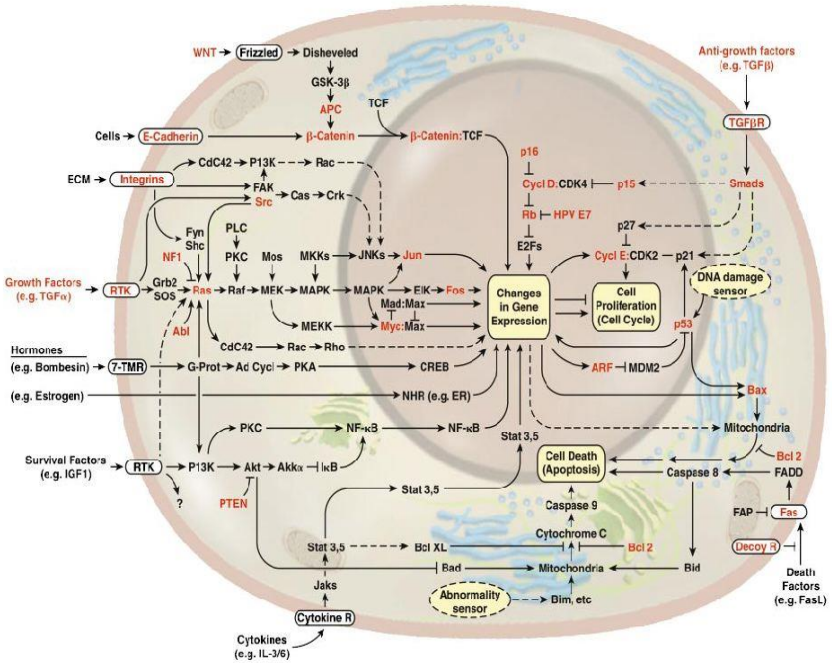


MYC+RAS



Normal cell

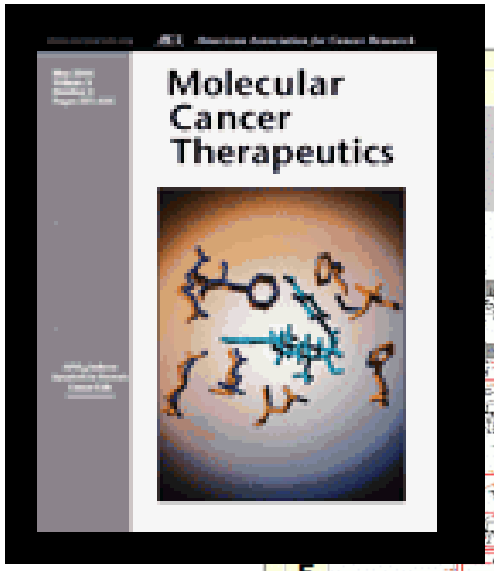
Cancer

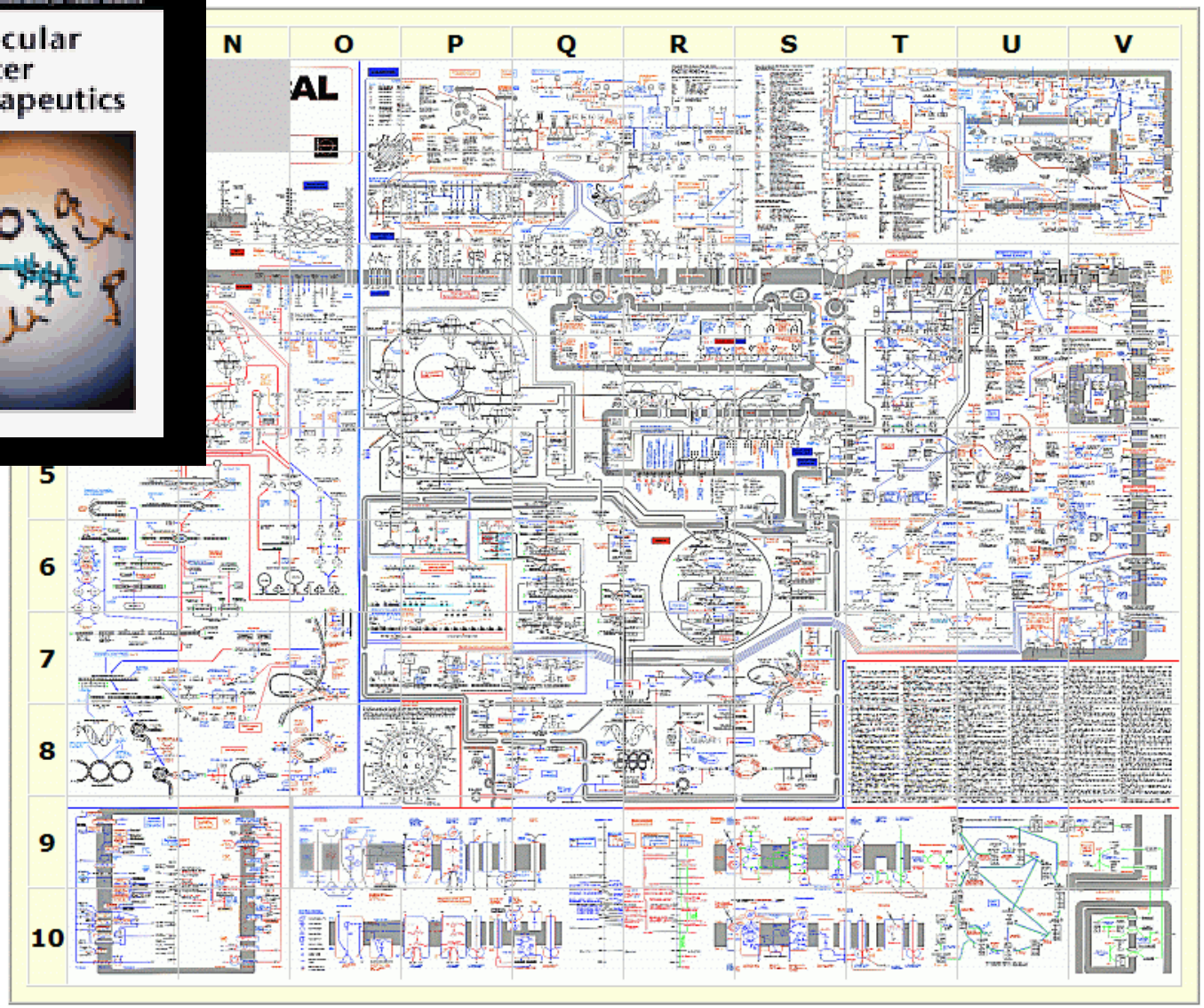


1980s

2000

Molecular targeting of cancer.... finding the right fit





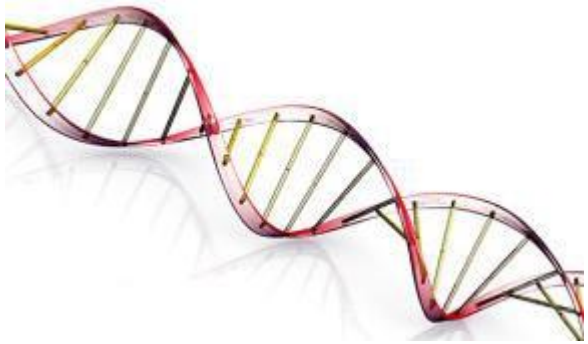
What is Targeted Therapy?

Fases de la Oncología de Precisión

Jeff Shrager and Jay M. Tenenbaum
NATURE REVIEWS | CLINICAL ONCOLOGY

Precision Oncology 1.0

- Precision Oncology 1.0
  - Testing for **small** numbers of molecular abnormalities
  - Is almost always constrained by the tissue-of-origin, and microscopic histology.



Utilización de biomarcadores en el desarrollo de estrategias de Medicina Personalizada en Cáncer

Los biomarcadores moleculares predictivos de respuesta a tratamientos específicos se están utilizando especialmente en el caso de pacientes con cáncer de mama, cáncer de pulmón, cáncer colorrectal y melanoma.

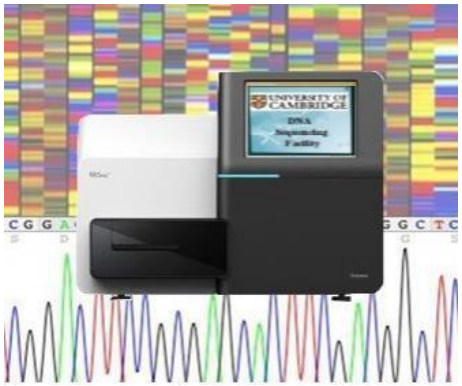
Determinaciones moleculares utilizadas con mayor frecuencia para la selección de

BIOMARCADOR	CÁNCER	FÁRMACO
HER2 (amplificación/sobrexpresión)	Mama	Trastuzumab Lapatinib
	Estómago	Trastuzumab
KIT y PDGFRA (mutación)	GIST	Imatinib
KRAS y NRAS (mutación)	Colo-rectal	Panitumumab Cetuximab
EGFR (mutación)	Pulmón (adenocarcinoma)	Gefitinib Erlotinib
ALK (traslocación)	Pulmón (adenocarcinoma)	Crizotinib
BRAF (mutación)	Melanoma	Vemurafenib

Ejemplos de asociaciones farmacogenéticas de marcador único con fármaco único

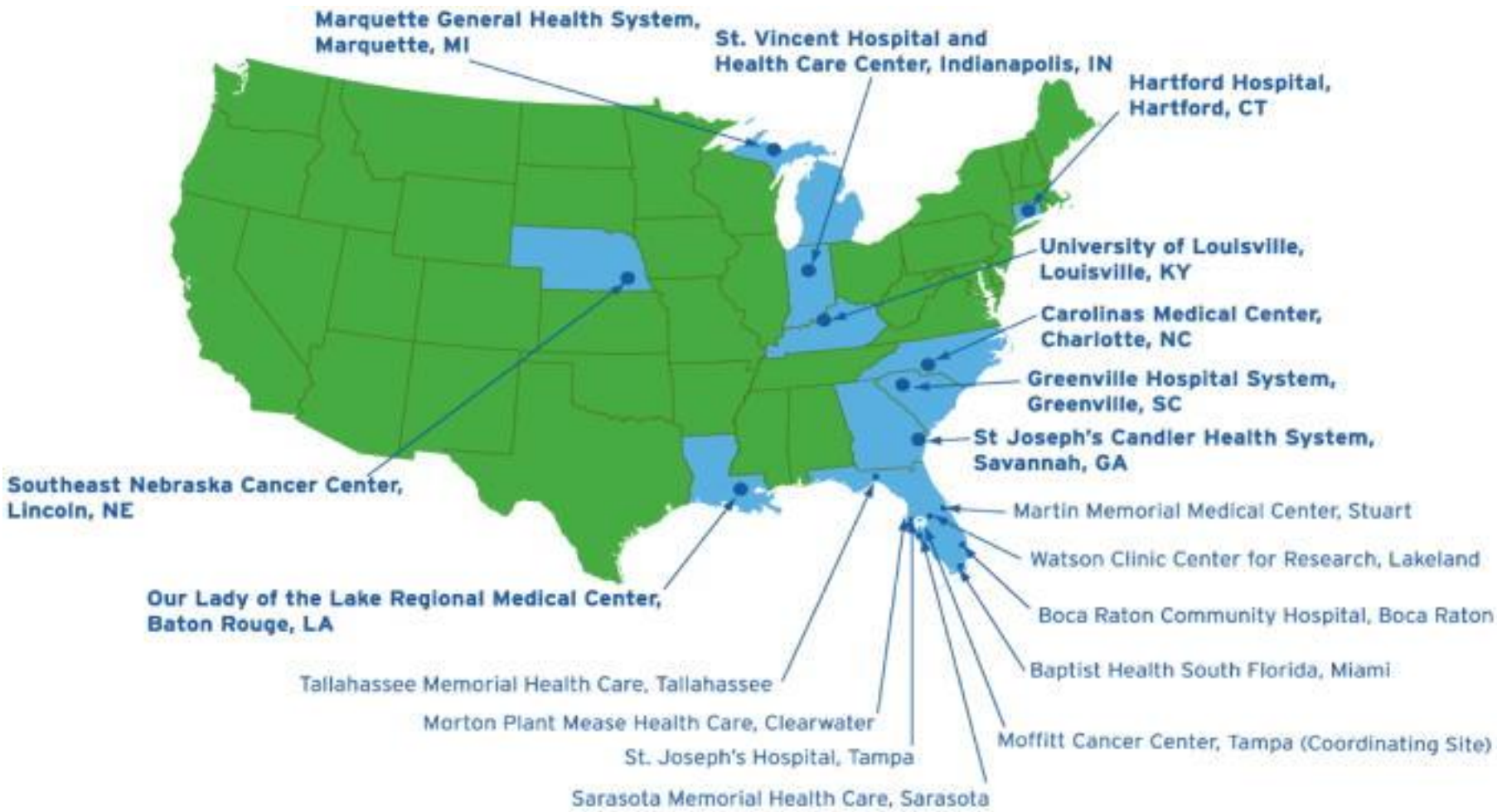
Molecular marker	*Drug*	*Tumor site*	*Guidelines and Recommendations*	*FDA label*
Estrogen and Progesterone receptors	Tamoxifen	Breast	NCCN, ASCO	Yes
HER2/ERBB2	Trastuzumab	Breast	NCCN, ASCO, NICE	Yes
KRAS	Cetuximab and Panitumumab	Colon	NCCN, ASCO, EGAPP	Yes
cKit	Imatinib	Gastrointestinal stroma	NA	Yes
ALK	Crizotinib	Lung	NCCN	Yes
EGFR	Erlotinib and Afatinib	Lung	NCCN	Yes
BRAF	Vemurafenib, Trametinib and Dabrafenib	Melanoma	NA	Yes

Precision Oncology 2.0



- Examining dozens or potentially **hundreds** of mutational hotspots simultaneously Requires specialized equipment
- Few patients have had the opportunity to take advantage of Precision Oncology 2.0, but with the broad availability of next-generation sequencing and molecular diagnostic service providers to aid in interpretation, it is rapidly becoming astandard of care at leading cancer centres worldwide

Moffitt's Total Cancer Care

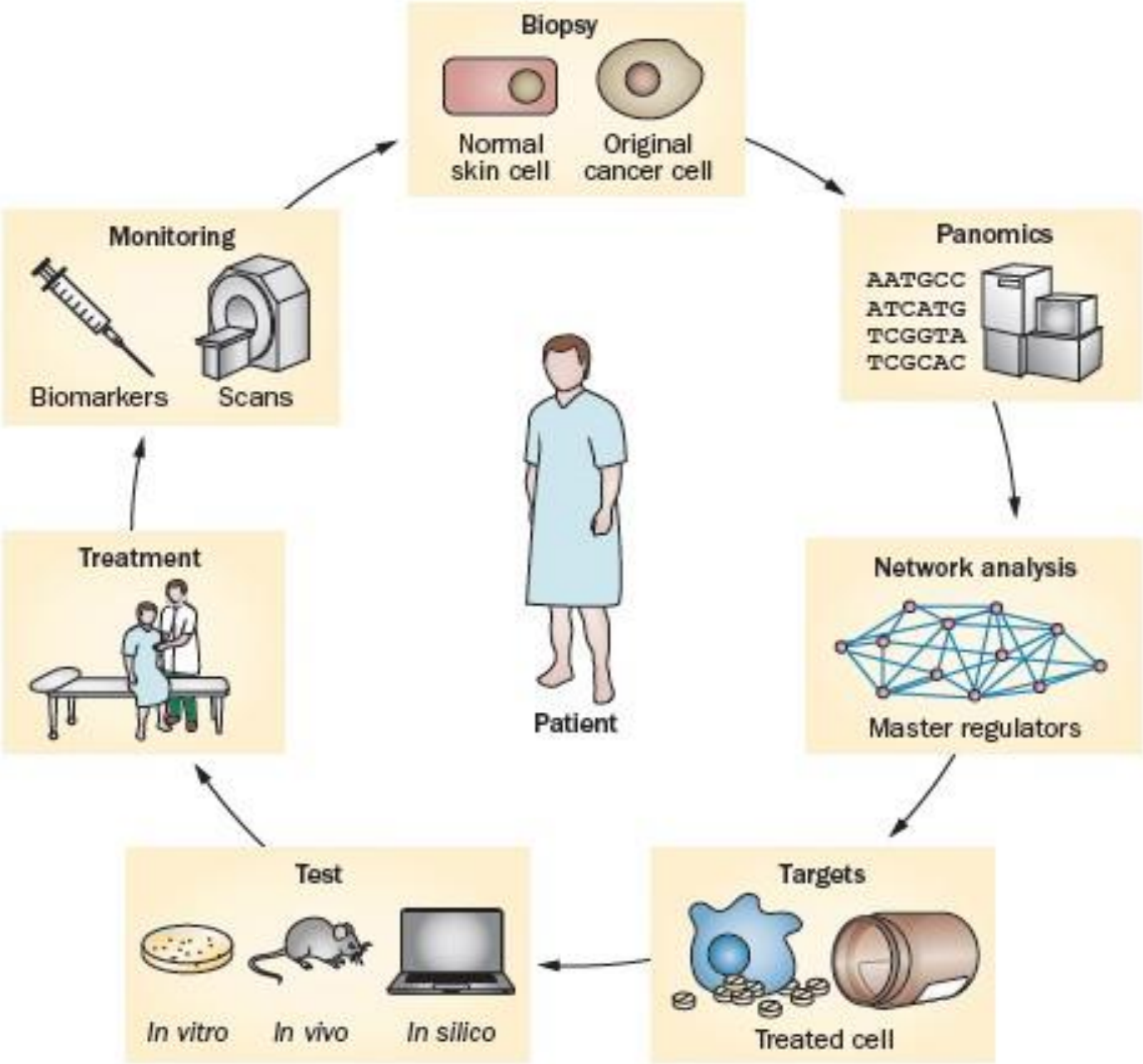


Ejemplos de Precision Oncology 2.0

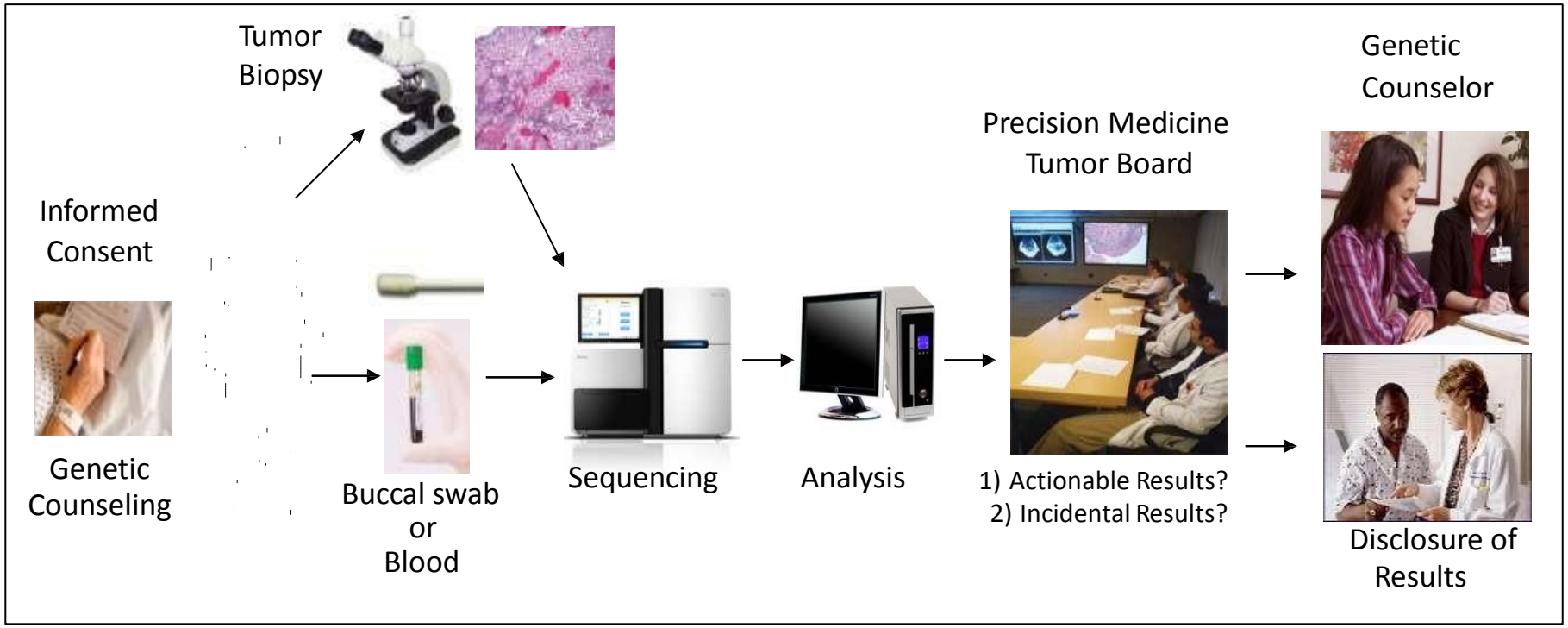
- Centre for Integrated Diagnostics. *Massachusetts General Hospital*
- UW-OncoPlex—Cancer Gene Panel. *University of Washington*

Precision Oncology 3.0

- Pan-omics and network-based statistical reverse engineering methods.
- Treatment decisions, monitoring, and subsequent treatment choices are all based on molecular analysis of the biochemical
- Every treatment is a probe in a small cohort of patients, and aggregating the results to achieve strong evidence. Developing computational and analytical tools
- Overcoming economic, social, and structural impediments
- Convincing payers to cover off-label use of approved drugs
- Many Medical Institutions involved
  - Duke Centre / Weill Cornell Medical College at New York–Presbyterian Hospital
  - MD Anderson Cancer Centre / University of Michigan, London, Cancer Research UK;
  - Dana-Farber Cancer Institute, INCa ;, Curie Institute, Gustave Roussy, Villejuif;
  - Massachussets General Hospital, Nationwide program, Norway; Princess Margaret Canc
  - John Hopkins, Baltimore, USA; Michigan


Biopsy
Normal skin cell
Original cancer cell
Panomics
AATGCC
ATCATG
TCGGTA
TCGCAC
Network analysis
Master regulators
Targets
Treated cell
Test
In vitro
In vivo
In silico
Treatment
Monitoring
Biomarkers
Scans
Patient

MI-ONCOSEQ:
The Michigan Oncology Sequencing Center



Michigan Center for Translational Pathology

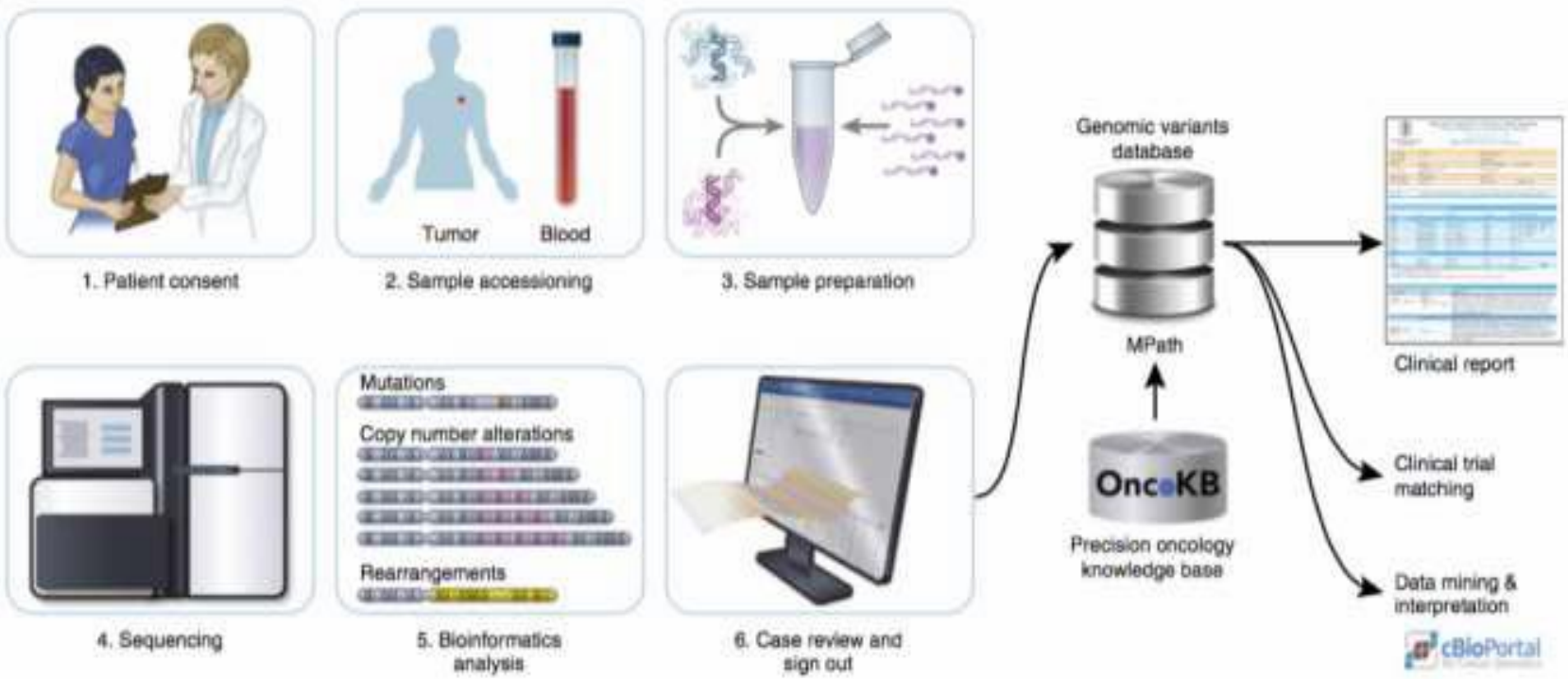
Prostate Cancer Foundation

University of Michigan Health System

MSK-IMPAKT

Panel of 410 genes

> 10000 advanced cancer patients



Zehir A *et al.*,
Nature Med 2017

DANA-FARBER
CANCER INSTITUTE

Discover. Care. Believe.

What You Need To Know About Precision Cancer Medicine

At Dana-Farber, **every cancer patient is offered precision cancer testing as part of its PROFILE research project,** created in partnership with Brigham and Women's Hospital and Boston Children's Hospital.

Precision medicine, **an evolving approach to cancer care,** aims to **individualize treatment** based on the genetic characteristics of a person's cancer.

1 Every patient is offered testing

As of Nov. 2016, Dana-Farber has received nearly 50,000 consents to test

2 Patients give informed consent and a test is ordered

3 A genomic test is performed on the tumor specimen
The data is analyzed and interpreted

4 An interpretation of the data is delivered to an oncologist

As of Nov. 2016, the PROFILE program has generated nearly 16,000 reports

5 Based on the data, patients can receive:

- Targeted therapies
- Enrollment in clinical trials
- A changed, more accurate diagnosis
- A change in therapy

73% of patients have clinically important results – meaning that the analysis of their tumor profile yields data that is related to their clinical care

GENOMICS

THE PROMISE OF PRECISION CANCER TREATMENT

Cancer Treatment Centers of America

An understanding of the genetic profile of a specific tumor helps physicians better understand what caused the tumor and tailor treatment based on these findings.

Cancer patients today are treated according to their cancer type, stage and prior therapies.

Research suggests that genetic changes in breast, colon and lung cancers link them to other cancers.

Cancer patients often try out a few different lines of chemotherapy before the right combination is found.

Clinicians now are starting to define what drives the cancer regardless of its location in the body.

WHAT IS DRIVING THE SHIFT?

A huge drop in the cost
of sequencing an individual's genome. Sequencing an individual's genome cost $10 million-$50 million in 2002 but now is available for $3,000-$5,000.

Increasing knowledge
about the genetics of cancer. For example, many mutational cancers have a gene mutation previously seen only in colon cancers.

Efforts by pharmaceutical companies
to target DNA defects that lead to cancer. More than 100 FDA-approved drugs are now packaged with genetic information that will further

Paneles de múltiples genes disponibles comercialmente en EEUU usando *next-generation sequencing* (NGS)

Organization	*Tumor panel*	*Markers*	*Licenses and accreditation*	*Sample requirements*	*NGS platform*	*Analytic sensitivity*	*Sequence alignment*	*Variant identification and molecular annotation*	*Turn-around time*
Arup Laboratories	Solid Tumor Mutation Panel	48 genes	CLIA and CAP	FFPE <10% tumor tissue not accepted	Not reported	Not reported	Not reported	Not reported	12 to 14 days
AsuraGen	SuraSeq™	17 genes and 500 annotated COSMIC mutations	CLIA and CAP	FFPE or FNA	Ion Torrent and multiple Illumina platforms	94% to 100%	Proprietary sequencing data analysis performed using SuraScore™	Proprietary variant caller: SuraSight™	Not reported
Foundation Medicine	FoundationOne™	236 genes; 47 introns from another 19 genes	CLIA and CAP	FFPE ≥ 40 μm and ≥ 20% tumor tissue	Illumina HiSeq2000	95% to 99%	Not reported	Online Interactive Cancer Explorer™	14 to 17 days

CAP – College of American pathologists
CLIA – Clinical Laboratory Improvement Amendments
FFPE – formalin-fixed paraffin embedded
FNA – fine needle aspirates

CURRENT GENE LIST

ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

SELECT REARRANGEMENTS

ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

FOUNDATIONONE

315 genes
Introns of 28 genes involved in rearrangement

34 genomic markers common to all three tests

ABL1	HRAS	PTEN
AKT1	IDH1	PTPN11
BRAF	IDH2	RB1
CDH1	KIT	RET
CDKN2A	KRAS	SMAD4
CTNNB1	MPL	SMARCB1
EGFR	NOTCH1	SMO
ERBB2	NPM1	SRC
FGFR1	NRAS	STK11
FGFR3	PDGFRA	TP53
GNA11	PIK3CA	VHL
GNAQ		

Foundation Medicine - FoundationOne

Additional 177 genes and 19 rearrangements unique to this test

AsuraGen - SuraSeq 7500

3 additional unique genes:
FES, HIF1A, IKBKB

Arup Laboratories - Solid Tumor Mutation Panel

1 additional unique gene:
HNF1A

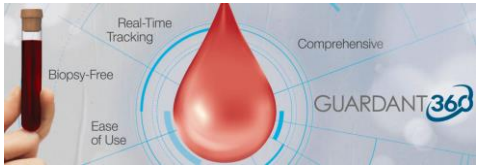
TABLE 1. Commercial Targeted DNA Pan-Cancer Next-Generation Sequencing Assays

VENDOR	ASSAY NAME	NO. OF GENES	RESULTS	ESTIMATED TURNAROUND TIME
Foundation Medicine (Cambridge, MA)	Foundation One	315	SNVs, CNVs, fusions	12-14 days
University of Washington (Seattle, WA)	UW-Oncoplex	234	SNVs, CNVs, fusions	6 weeks
Paradigm (Ann Arbor, MI)	PCDx	114	SNVs, CNVs, fusions	4-5 days
Genomics and Pathology Services, Washington University School of Medicine (St. Louis, MO)	Solid Tumor Gene Set	48	Hot-spot mutations, 6 fusions	3 weeks
ARUP Laboratories (Salt Lake City, UT)	Solid Tumor Mutation Panel	48	Hot-spot mutations	14 days
Caris Life Sciences (Irving, TX)	MI Profile	46	Hot-spot mutations	14 days
Knight Diagnostic Laboratories (Portland, OR)	GeneTrails Solid Tumor Panel	37	Hot-spot mutations	10-14 days

CNVs indicates copy number variations; SNVs, single nucleotide variations or point mutations. Gene content is subject to change with additional content added over time.

CA CANCER J CLIN 2016;66:75–88

73 genes point mutation
23 genes indels
18 genes amplification
6 genes fusions



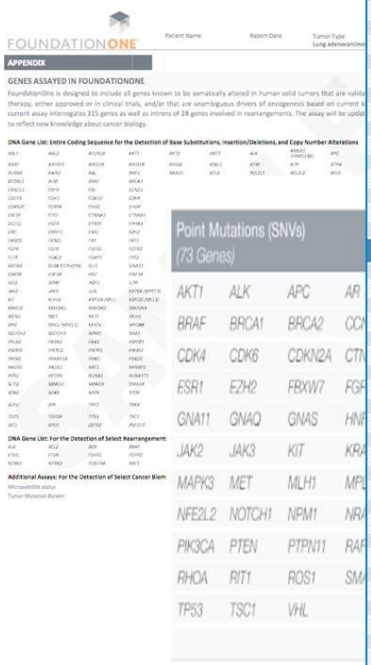
GUARDANT360®

Complete Sequencing of Covered Exons*

Point Mutations (SNVs) (73 Genes)							Indels (23 Genes)		Amplifications (18 Genes)		Fusions (6 Genes)
AKT1	ALK	APC	AR	ARAF	ARID1A	ATM	ATM	APC	AR	BRAF	ALK
BRAF	BRCA1	BRCA2	CCND1	CCND2	CCNE1	CDH1	ARID1A	BRCA1	CCND1	CCND2	FGFR2
CDK4	CDK6	CDKN2A	CTNNB1	DDR2	EGFR	ERBB2 (HER2)	BRCA2	CDH1	CCNE1	CDK4	FGFR3
ESR1	EZH2	FBXW7	FGFR1	FGFR2	FGFR3	GATA3	CDKN2A	EGFR	CDK6	EGFR	NTRK1
GNA11	GNAQ	GNAS	HNF1A	HRAS	IDH1	IDH2	ERBB2	GATA3	ERBB2	FGFR1	RET
JAK2	JAK3	KIT	KRAS	MAP2K1/MEK1	MAP2K2/MEK2	MAPK1/ERK2	KIT	MET	FGFR2	KIT	ROS1
MAPK3/ERK1	MET	MLH1	MPL	MTOR	MYC	NF1	MLH1	MTOR	KRAS	MET	
NFE2L2	NOTCH1	NPM1	NRAS	NTRK1	NTRK3	PDGFRA	NF1	PDGFRA	MYC	PDGFRA	
PIK3CA	PTEN	PTPN11	RAF1	RB1	RET	RHEB	PTEN	RB1	PIK3CA	RAF1	
RHOA	RIT1	ROS1	SMAD4	SMO	STK11	TERT**	SMAD4	STK11			
TP53	TSC1	VHL					TP53	TSC1			
							VHL				

Next-Generation Sequencing Expanded NGS Gene List

Genomic Stability Testing (DNA)									
Microsatellite Instability (MSI)					Tumor Mutational Load (TML)				
Mutations (DNA)									
ABI1	BRD4	CRLF2	FOXO4	HOXC11	KLF4	MUC1	PAK3	RHOH	TAL2
ABL1	BTG1	DDB2	FSTL3	HOXC13	KLK2	MUTYH	PATZ1	RNF213	TBL1XR1
ACKR3	BTK	DDIT3	GATA1	HOXD11	LASP1	MYCL (MYCL1)	PAX8	RPL10	TCEA1
AKT1	C15orf65	DNM2	GATA2	HOXD13	LMO1	NBN	PDE4DIP	SEPT5	TCL1A
AMER1 (FAM123B)	CBLC	DNMT3A	GNA11	HRAS	LMO2	NDRG1	PHF6	SEPT6	TERT
AR	CD79B	EIF4A2	GPC3	IKBKE	MAFB	NKX2-1	PHOX2B	SFPQ	TFE3
ARAF	CDH1	ELF4	HEY1	INHBA	MAX	NONO	PIK3CG	SLC45A3	TFPT
ATP2B3	CDK12	ELN	HIST1H3B	IRS2	MECOM	NOTCH1	PLAG1	SMARCA4	THRAP3
ATRX	CDKN2B	ERCC1	HIST1H4I	JUN	MED12	NRAS	PMS1	SOCS1	TLX3
BCL11B	CDKN2C	ETV4	HLF	KAT6A (MYST3)	MKL1	NUMA1	POU5F1	SOX2	TMPRSS2
BCL2	CEBPA	FAM46C	HMGN2P46	KAT6B	MLLT11	NUTM2B	PPP2R1A	SPOP	UBR5
BCL2L2	CHCHD7	FANCF	HNF1A	KCNJ5	MN1	OLIG2	PRF1	SRC	VHL
BCOR	CNOT3	FEV	HOXA11	KDM5C	MPL	OMD	PRKDC	SSX1	WAS
BCORL1	COL1A1	FOXL2	HOXA13	KDM6A	MSN	P2RY8	RAD21	STAG2	ZBTB16
BRD3	COX6C	FOXO3	HOXA9	KDSR	MTCP1	PAFAH1B2	RECQL4	TAL1	ZRSR2
Mutations and Copy Number Variations (DNA)									
ABL2	BRCA2	COPB1	ESR1	FUS	KIT	MYB	PER1	RUNX1	TFG
ACSL3	BRIP1	CREB1	ETV1	GAS7	KLHL6	MYC	PICALM	RUNX1T1	TFRC
ACSL6	BUB1B	CREB3L1	ETV5	GATA3	KMT2A (MLL)	MYCN	PIK3CA	SBDS	TGFBR2
AFF1	C11orf30 (EMSY)	CREB3L2	ETV6	GID4 (C17orf39)	KMT2C (MLL3)	MYD88	PIK3R1	SDC4	TLX1
AFF3	C2orf44	CREBBP	EWSR1	GMPS	KMT2D (MLL2)	MYH11	PIK3R2	SDHAF2	TNFAIP3
AFF4	CACNA1D	CRKL	EXT1	GNA13	KRAS	MYH9	PIM1	SDHB	TNFRSF14
AKAP9	CALR	CRTC1	EXT2	GNAQ	KTN1	NACA	PML	SDHC	TNFRSF17
AKT2	CAMTA1	CRTC3	EZH2	GNAS	LCK	NCKIPSD	PMS2	SDHD	TOP1
AKT3	CANT1	CSF1R	EZR	GOLGA5	LCP1	NCOA1	POLE	SEPT9	TP53
ALDH2	CARD11	CSF3R	FANCA	GOPC	LGR5	NCOA2	POT1	SET	TPM3
ALK	CARS	CTCF	FANCC	GPHN	LHFP	NCOA4	POU2AF1	SETBP1	TPM4
APC	CASC5	CTLA4	FANCD2	GPR124	LIFR	NF1	PPARG	SETD2	TPR
ARFRP1	CASP8	CTNNA1	FANCE	GRIN2A	LPP	NF2	PRCC	SF3B1	TRAF7
ARHGAP26	CBFA2T3	CTNNB1	FANCG	GSK3B	LRIG3	NFE2L2	PRDM1	SH2B3	TRIM26
ARHGEF12	CBFB	CYLD	FANCL	H3F3A	LRP1B	NFIB	PRDM16	SH3GL1	TRIM27
ARID1A	CBL	CYP2D6	FAS	H3F3B	LYL1	NFKB2	PRKAR1A	SLC34A2	TRIM33
ARID2	CBLB	DAXX	FBXO11	HERPUD1	MAF	NFKBIA	PRRX1	SMAD2	TRIP11
ARNT	CCDC6	DDR2	FBXW7	HGF	MALT1	NIN	PSIP1	SMAD4	TRRAP
ASPSCR1	CCNB1IP1	DDX10	FCRL4	HIP1	MAML2	NOTCH2	PTCH1	SMARCB1	TSC1
ASXL1	CCND1	DDX5	FGF10	HMGA1	MAP2K1	NPM1	PTEN	SMARCE1	TSC2
ATF1	CCND2	DDX6	FGF14	HMGA2	MAP2K2	NR4A3	PTPN11	SMO	TSHR
ATIC	CCND3	DEK	FGF19	HNRNPA2B1	MAP2K4	NSD1	PTPRC	SNX29	TTL
ATM	CCNE1	DICER1	FGF23	HOOK3	MAP3K1	NTS C2	RABEP1	SOX10	U2AF1
ATP1A1	CD274 (PDL1)	DOT1L	FGF3	HSP90AA1	MCL1	NTRK1	RAC1	SPECC1	USP6
ATR	CD74	EBF1	FGF4	HSP90AB1	MDM2	NTRK2	RADS0	SPEN	VEGFA
AURKA	CD79A	ECT2L	FGF6	IDH1	MDM4	NTRK3	RADS1	SRGAP3	VEGFB
AURKB	CDC73	EGFR	FGFR1	IDH2	MDS2	NUP214	RADS1B	SRSF2	VTI1A
AXIN1	CDH11	ELK4	FGFR1OP	IGF1R	MEF2B	NUP93	RAF1	SRSF3	WHSC1
AXL	CDK4	ELL	FGFR2	IKZF1	MEN1	NUP98	RALGDS	SS18	WHSC1L1
BAP1	CDK6	EML4	FGFR3	IL2	MET (cMET)	NUTM1	RANBP17	SS18L1	WIF1
BARD1	CDK8	EP300	FGFR4	IL21R	MITF	PALB2	RAP1GDS1	STAT3	WISP3
BCL10	CDKN1B	EPHA3	FH	IL6ST	MLF1	PAX3	RARA	STAT4	WRN
BCL11A	CDKN2A	EPHA5	FHIT	IL7R	MLH1	PAX5	RB1	STAT5B	WT1
BCL2L11	CDX2	EPHB1	FIP1L1	IRF4	MLLT1	PAX7	RBM15	STIL	WWTR1
BCL3	CHEK1	EPS15	FLCN	ITK	MLLT10	PBRM1	REL	STK11	XPA
BCL6	CHEK2	ERBB2 (HER2)	FLI1	JAK1	MLLT3	PBX1	RET	SUFU	XPC
BCL7A	CHIC2	ERBB3 (HER3)	FLT1	JAK2	MLLT4	PCM1	RICTOR	SUZ12	XPO1
BCL9	CHN1	ERBB4 (HER4)	FLT3	JAK3	MLLT6	PCSK7	RMI2	SYK	YWHAE
BCR	CIC	ERC1	FLT4	JAZF1	MNX1	PDCD1 (PD1)	RNF43	TAF15	ZMYM2
BIRC3	CIITA	ERCC2	FNBP1	KDM5A	MRE11A	PDCD1LG2 (PDL2)	ROS1	TCF12	ZNF217
BLM	CLP1	ERCC3	FOXA1	KDR (VEGFR2)	MSH2	PDGFB	RPL22	TCF3	ZNF331
BMPR1A	CLTC	ERCC4	FOXO1	KEAP1	MSH6	PDGFRA	RPL5	TCF7L2	ZNF384
BRAF	CLTCL1	ERCC5	FOXP1	KIAA1549	MSI2	PDGFRB	RPN1	TET1	ZNF521
BRCA1	CNBP	ERG	FUBP1	KIF5B	MTOR	PDK1	RPTOR	TET2	ZNF703
	CNTRL							TFEB	
Gene Fusions (RNA)								**Variant Transcripts (RNA)**	
ALK	BRAF	NTRK1	NTRK2	NTRK3	RET	ROS1	RSPO3	EGFR vIII	MET Exon 14 Skipping



SARAH CANNON Research Institute

Sample PDF, Caris Life Sciences website,Accessed May 2017

Presented By David Spigel at 2017 ASCO Annual Meeting

Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)


397-387

Illumina units

Cost of sequencing highly reduced

It is now possible for clinical sequencing all 22,000 genes for $1,000 or less

Oxford Nanopore sequencing unit

FDA Approved Targeted Drugs Are Rapidly Increasing

Zytiga
COMETRIQ (cabozantinib)
AROMASIN exemestane tablets
Portrazza
CYRAMZA
Fareston® 60mg (toremifene citrate) Tablets
Kadcyla
ZYKADIA ceritinib
FASLODEX fulvestrant
Tasigna
Stivarga
Herceptin trastuzumab
GILOTRIF afatinib tablets
ERBITUX
IRESSA gefitinib
Lynparza olaparib
Jakafi ruxolitinib tablets
Caprelsa (vandetanib) Tablets
ALECENSA alectinib
COTELLIC
imbruvica (ibrutinib)
TAGRISSO osimertinib
Odomzo (sonidegib)
Arimidex anastrozole
CRIZOTINIB
Arzerra
IBRANCE palbociclib
ZELBORAF | ACCESS SOLUTIONS
Inlyta
Tafinlar + Mekinist
gleevec
Votrient pazopanib tablets
Nexavar
Erivedge (vismodegib) capsule
Beleodaq
Xtandi
Xtandi (enzalutamide)
Tarceva erlotinib
Tykerb (lapatinib) 250 mg tablets
PERJETA pertuzumab
SUTENT sunitinib malate
Zolinza
Bosulif bosutinib
AFINITOR everolimus tablets
LENVIMA (lenvatinib) capsules
ICLUSIG (ponatinib) tablets 45 mg, 15 mg
TORISEL (temsirolimus) injection

70% of cancer drugs in development have a biomarker

CANCER THERAPY TYPE	EXAMPLES
Chemotherapy	5-Flurouracil Carboplatin
Hormone therapy	Abiraterone acetate Fulvestrant
Epigenetic modifiers	Azacitidine Decitabine
Immune stimulators & Checkpoint inhibitors	Aldesleukin Pembrolizumab
Angiogenesis inhibitors	Bevacizumab Regorafenib
Vaccines	Sipuleucel-T DCVax-L
Adoptive immunotherapy	Anti-CD19 CAR-T cell therapy CART-Meso
Therapeutic antibodies	Cetuximab TDM-1
Cell signaling inhibitors	Ibrutinib Imatinib Ceritinib

INCREASING PRECISION

Within each category, some therapeutics are more precise than others

AACR American Association for Cancer Research

PERSPECTIVE

The precision-oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

Precision oncology promises to pair individuals with cancer with drugs that target the specific mutations in their tumour, in the hope of producing long-lasting remission and extending their survival. The basic idea is to use genetic testing to link patients with the drugs that will work best for them, irrespective of the tissue of origin of their tumour. Enthusiasm has been fuelled by reports of exceptional or super responders — individuals for whom experimental therapies seem to work spectacularly well.

In one such example, an individual with metastatic bladder cancer showed a dramatic response to the drug everolimus[1]. Sequencing later revealed that the patient had a mutation that affects the mTOR pathway, which is the mechanism of action of everolimus. Yet despite the hype surrounding rare cases such as these, most people with cancer do not benefit from the precision strategy, nor has this approach been shown to improve outcomes in controlled studies. Precision oncology remains a hypothesis in need of verification.

Few patients benefit from precision oncology. Data from some 2,600 people enrolled in a sequencing programme at the MD Anderson Cancer Center in Houston, Texas, showed that just 6.4% were paired with a targeted drug for identified mutations[2]. Similarly, the Molecular Analysis for Therapy Choice (NCI-MATCH) trial at the US National Cancer Institute has enrolled 795 people who have relapsed solid tumours and lymphoma, but as of May 2016 it had only been able to pair 2% of patients with a targeted therapy[3].

NOT SO EXCEPTIONAL

But being assigned such a therapy is not proof of benefit. When patients with diverse, relapsed cancers are given drugs based on biological markers, only around 30% respond at all, and the median progression-free survival is just 5.7 months[4]. Multiplying the percentage of patients receiving targeted therapies by this response rate, I estimate that precision oncology will benefit around 1.5% of patients with relapsed and refractory solid tumours.

It is on this tiny proportion of patients that the hopes for precision oncology have been built. Although many patients have undergone sequencing in the past decade (Foundation Medicine, a commercial provider of tumour profiling, has sequenced at least 18,000 patients), the number of reported cases of exceptional and super responders over that time are few. In a search of the biomedical literature with a colleague, we identified only 32 cases[5].

Moreover, even when vignettes such as these are reported, they often have major gaps. The number and duration of responses to previous therapies, and the number of patients who were treated to identify the super responder[6], are often omitted. Because even the most serious malignancies, such as pancreatic cancer, exist along a continuum, some patients are already destined to outlive the average. Indeed, we found several cases in which the 'exceptional' responders had already experienced exceptional responses to conventional chemotherapy before their supposedly miraculous response to precision oncology[5]. It is hard to avoid the unsettling conclusion that such cases do not reflect the success of precision oncology, but rather the selective reporting of individuals who were always likely to do well.

When considered objectively, the prospects and potential of precision oncology are sobering. At best, we may expect short-lived responses in a tiny fraction of patients, with the inevitable toxicity of targeted therapies and inflated cost that this approach guarantees.

PRECISION ONCOLOGY ON TRIAL

In medical science, the ultimate judge of a therapeutic strategy is the randomized controlled trial. So far, precision oncology has been tested in only one such published study[6]. The SHIVA trial assigned 99 patients with cancer to therapies based on an identified mutation or mutations, and 96 patients to the treatment selected by their physicians. Median progression-free survival, the primary endpoint, was almost equally poor in both cases (2.3 and 2.0 months, respectively).

WHEN CONSIDERED OBJECTIVELY, THE PROSPECTS AND POTENTIAL OF PRECISION ONCOLOGY ARE SOBERING.

No single trial can prove that a therapy does not work in any circumstances, and SHIVA is no exception. It paired patients with drugs for 'pathway' mutations, not just for mutations that can be targeted with drugs, allowing those running the trial to enrol more than a quarter of screened patients. But further randomized controlled trials are needed to test alternative hypotheses, and the use of different medications and alternative pathways. These trials will have to balance applicability and generalizability (the percentage of screened patients that can be enrolled) against the strength of the biological rationale. Several more trials are needed before we can judge whether this strategy is viable.

Precision oncology is inspirational. What doctor or patient would not want to harness genetics to tailor a therapy to an individual? But travelling back in a time machine is also inspirational. Who would not want to wind back the clock to remove their cancer before it spreads? In both cases, however, as of 2016, the proposal is neither feasible, cost-effective nor assured of future success. Yet in only one of these cases does the rhetoric so far outpace the reality that we risk fooling even ourselves. ■

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SOUNDING BOARD

Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D., and John A. Hickman, D.Sc.

Rapid advances in the molecular characterization of tumors, including complete gene sequencing of multiple cancers in the Cancer Genome Project, have led to an increased understanding of the molecular pathways that underlie cancer. These genomic changes differentiate tumors from normal tissues, permitting targeted treatments for several types of tumor and thereby extending survival and improving patients' quality of life. Examples include trastuzumab for human epidermal growth factor receptor type 2 (HER2)–expressing breast cancer[1] and vemurafenib for melanomas that express mutated BRAF.[2] These drugs have become standards of

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encouraged investment by funding bodies and cancer centers in personalized (or precision) cancer medicine. The concept underlying this research is that molecular analysis of a tumor in an individual patient will allow the selection of effective drugs to control that tumor and thereby prolong survival. This concept is appealing to patients and to foundations that support cancer research, and the molecular characterization of tumors is being marketed directly to patients, despite a lack of evidence of benefit.[3] Here we critically review the problems that have been associated with personalized medicine in patients with cancer; we suggest that the clinical benefit of personalized medicine as it is currently practiced will be limited.

RESEARCH PROGRAMS

There is a strong focus on personalized medicine by large cancer centers and those who fund research. In his State of the Union address, President Barack Obama announced that he had allocated $215 million in the 2016 U.S. budget for precision medicine, of which $70 million is allocated to the National Cancer Institute (NCI) to support research and clinical trials of personalized cancer medicine as part of the Cancer Moonshot Initiative.[4] Almost all the 69 NCI-supported cancer centers have websites that emphasize programs in personalized medicine, although

Lung Cancer Mutation Consortium,[5,6] which consists of 16 sites in the United States that are testing for driver mutations in multiple genes in metastatic adenocarcinoma of the lung, and the Stratification in Colorectal Cancer program in the United Kingdom,[7] which has funding of £5 million (approximately $6.6 million U.S.) to provide genomic analysis for 2000 patients with colorectal cancer, but such collaborations are rare. The Cancer Moonshot Initiative from the U.S. government provides opportunities to boost collaboration.[4]

Ideally (and historically), different cancer institutions emphasize different avenues of research, so resources are applied to investigate multiple promising areas. Funding for research

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De la teoría
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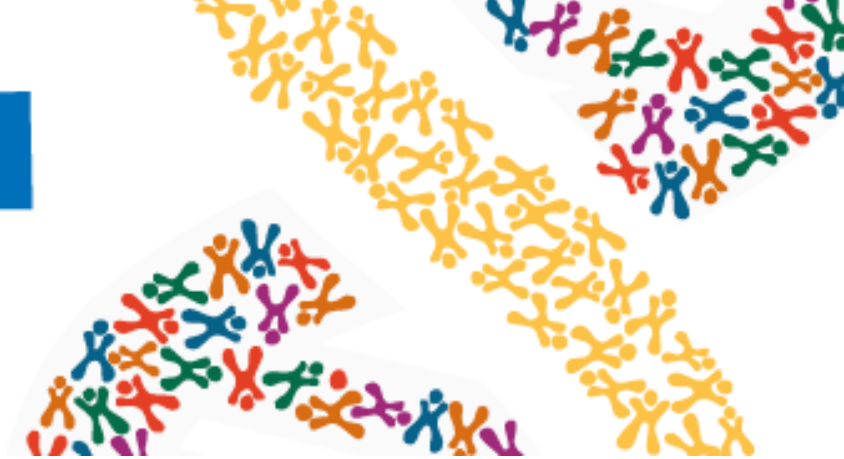

Medicina de Precisión en Oncología

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Un tema más

- Hay un papel para los tests genómicos para el diagnóstico precoz del cáncer?

Predicción genética: *fotografía del DNA*

Compañía	screening	muestra	Coste en $
Pathway Genomics	24 enfermedades	sangre	399
Genetic Testing Laboratories	25 enfermedades	sangre	285
23andMe	250 enfermedades	saliva	99

The New York Times

I Had My DNA Picture Taken, With Varying Results

Ozier Muhammad/The New York Times

Kira Peikoff, 28, had her DNA tested by three direct-to-consumer companies, and the results didn't agree.

By KIRA PEIKOFF

30 Diciembre, 2013

The New York Times

PSORIASIS

INCREASED RISK
ABOVE AVERAGE RISK
AVERAGE RISK

Genes Tested - HLA, IL12B, IL23R, Intergenic_1q21, SPATA2, STAT2, TNFAIP3, TNIP1

Description

This patient has typical genetic risk for psoriasis. This does not mean the patient will or will not develop the disease. This test outcome was determined using genetic laboratory results in conjunction with the patient's self-reported ethnicity. General preventive measures, such as smoking cessation or stress reduction, could be encouraged.

Elevated Risk

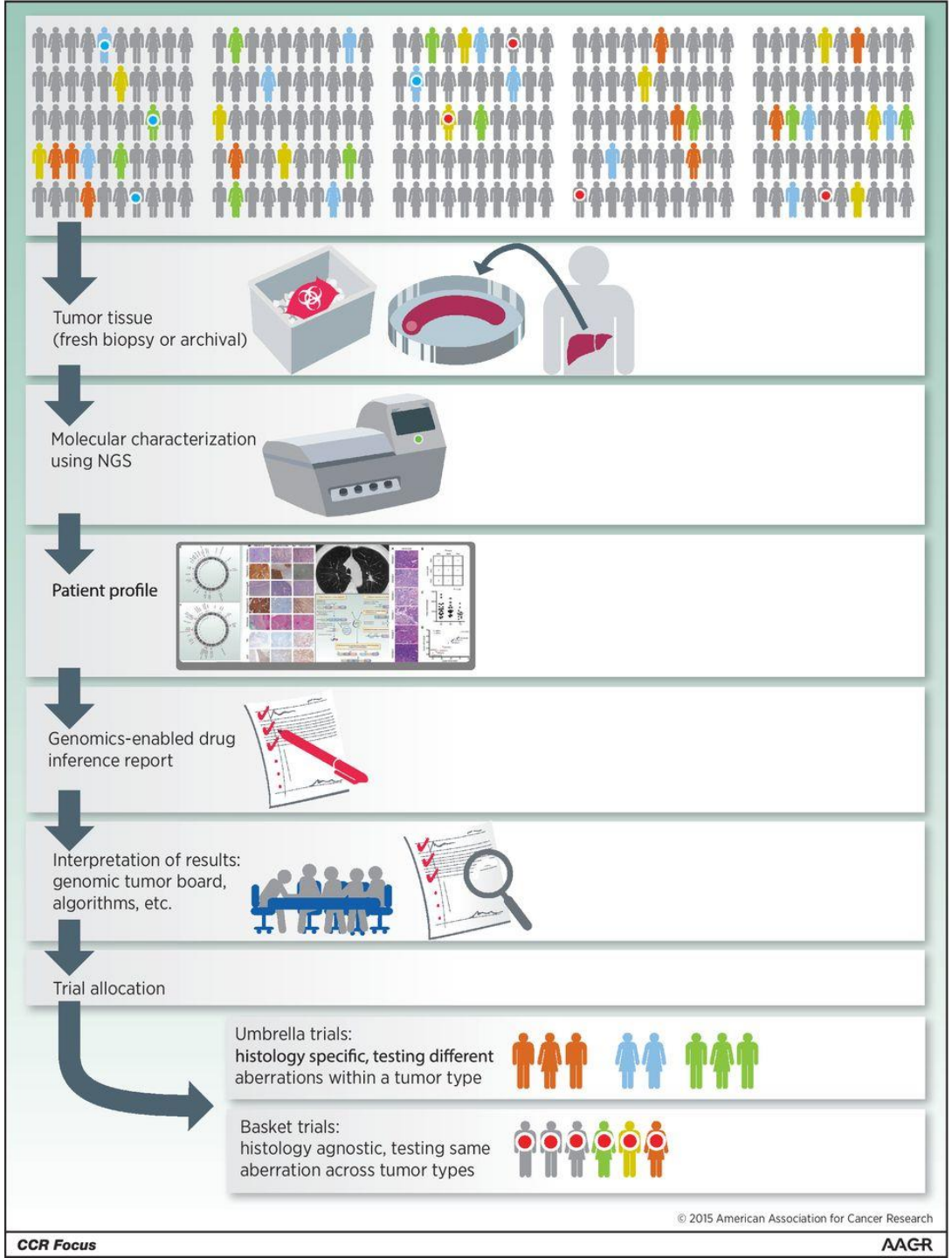
NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Psoriasis	★★★★★	20.2%	10.1%	1.99x

Name of the condition	Your lifetime risk	The normal risk	Your genetic risk level
	High genetic risk level Medium genetic risk level		
Psoriasis	2%	10.1%	low

Pathway found that Kira Peikoff had an average genetic risk of psoriasis, top, while 23andMe assessed it as higher than average, and Genetic Testing Laboratories as low.

«Es extraordinario explicar a los enfermos lo que hemos avanzado en 30 años»

RAMÓN COLOMER, jefe de Oncología y director médico del Hospital La Princesa de Madrid (Barcelona, 1959):
«Los conocimientos en biología molecular del cáncer han hecho posible el diseño de tratamientos específicos y su uso personalizado».



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