



Facultad de Medicina  
Clínica Alemana - Universidad del Desarrollo



# Perspectivas en la Biología del Cáncer

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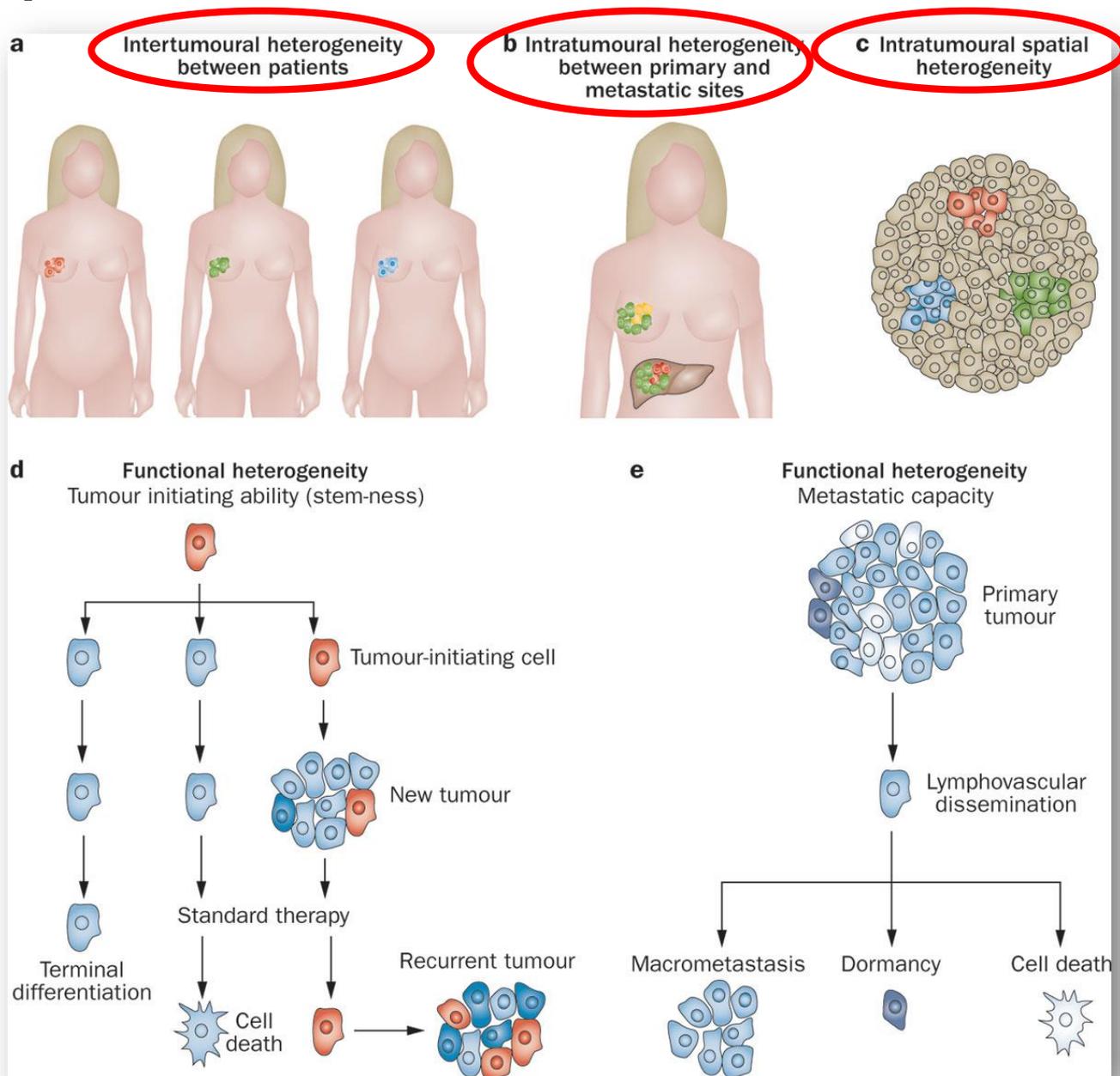
Oncología Molecular  
Agosto 2020

# Objetivos

- Comprender las limitaciones de terapias basadas en parámetros clínico-patológicos tradicionales
- Comprender las estrategias y potenciales beneficios de terapias de precisión, así como los desafíos que involucran
- Conocer ejemplos de programas de medicina de precisión y los resultados obtenidos en diferentes estudios

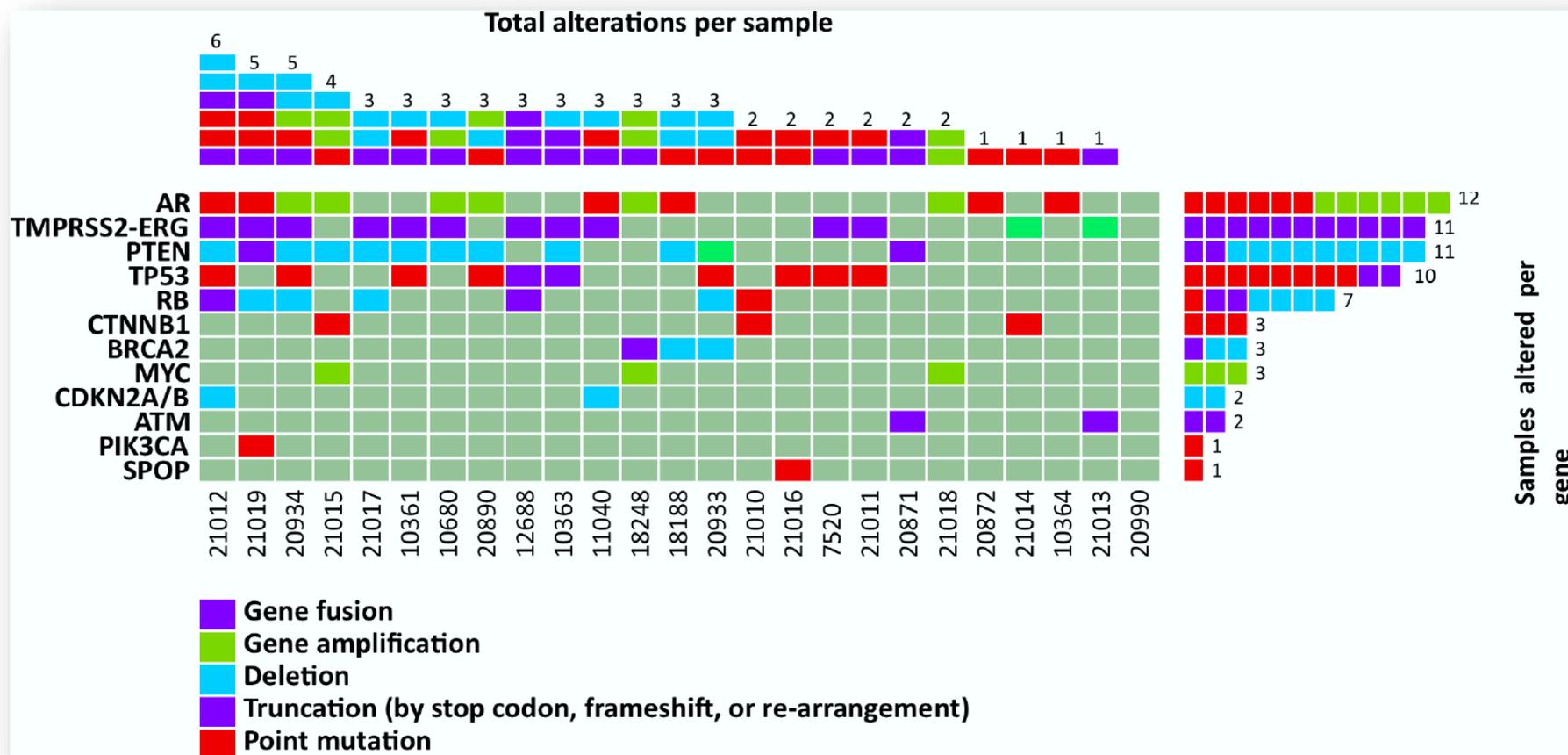
# Medicina de Precisión: Principios

# ¿Por qué Medicina de Precisión?



# Heterogeneidad Entre Pacientes

- Ej: tumores de próstata agresivos

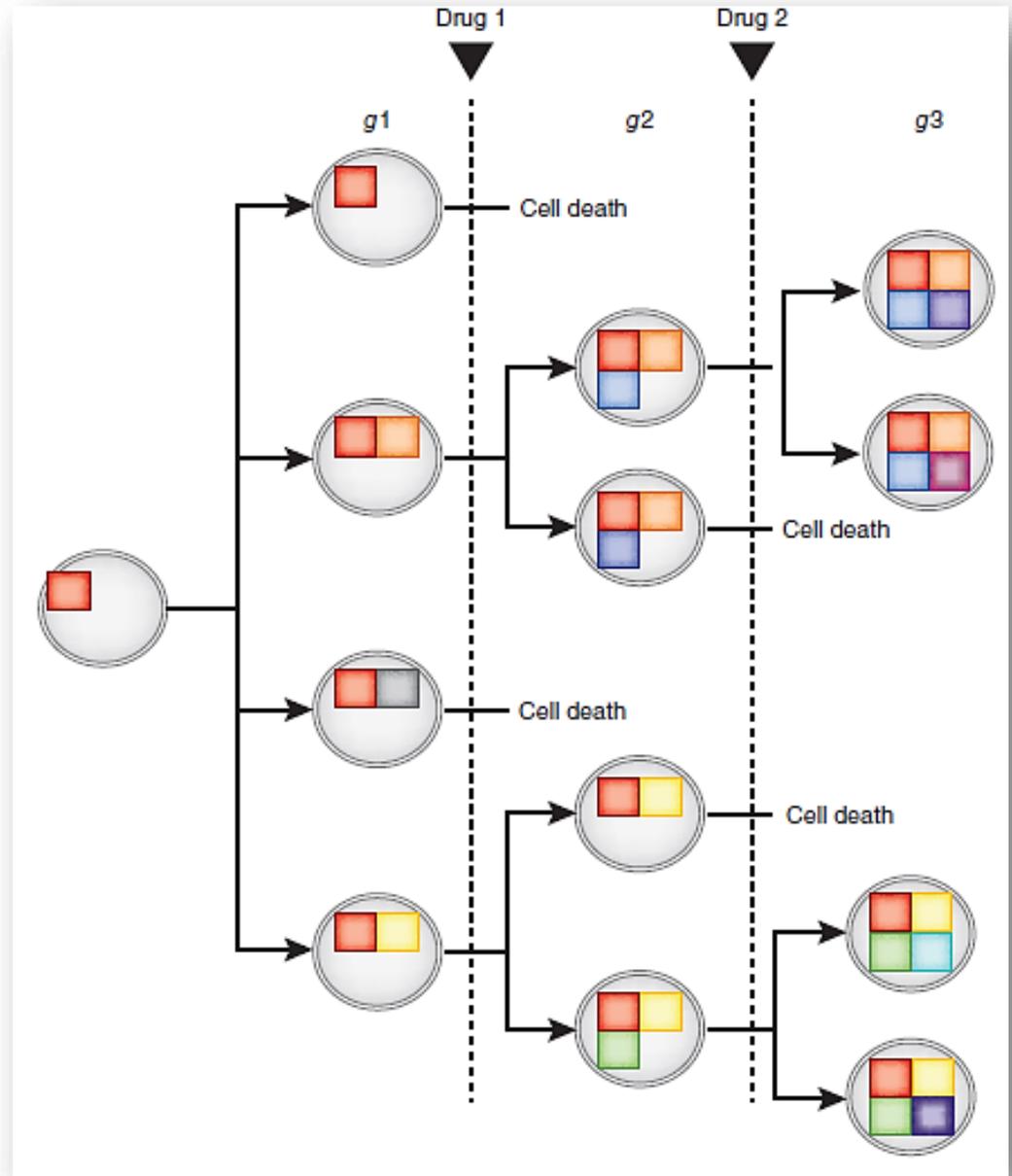


# Limitaciones de Terapias Tradicionales

Respuesta variable  
en el tiempo:

Evolución tumoral y  
selección mediada  
por tratamiento(s)

¿Predicción de  
drogas más  
efectivas?

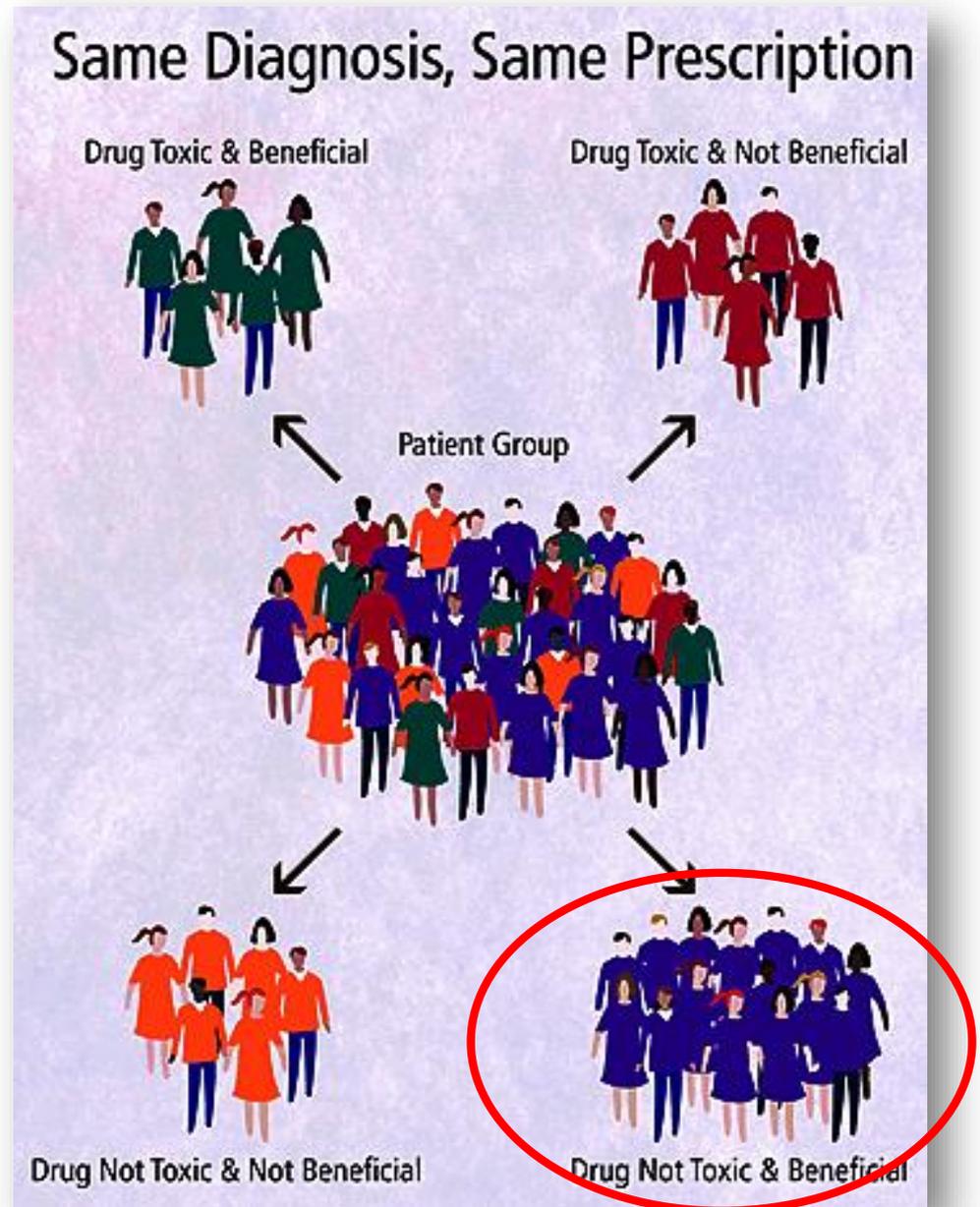


# Outcome de Terapias Tradicionales

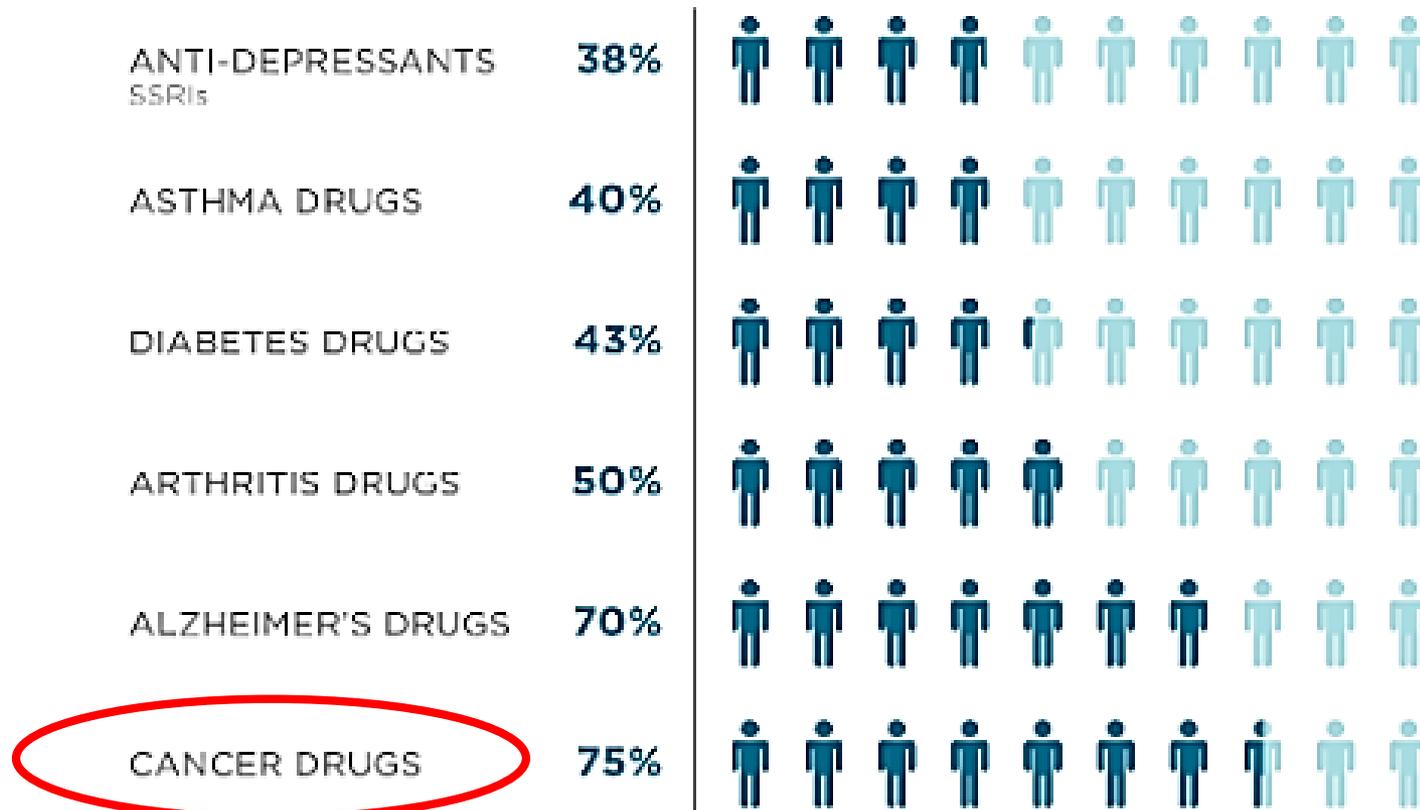
- Respuesta puede variar entre pacientes, aun con misma histología y parámetros clínicos equivalentes
- Respuesta puede variar a nivel celular: alta heterogeneidad celular predice respuestas diferenciadas
- Respuesta puede variar en el tiempo: emergencia de resistencia, metástasis
- Selección de tratamiento adecuado?

# Outcome de Terapias Tradicionales

Costos para el paciente,  
sistema de salud !



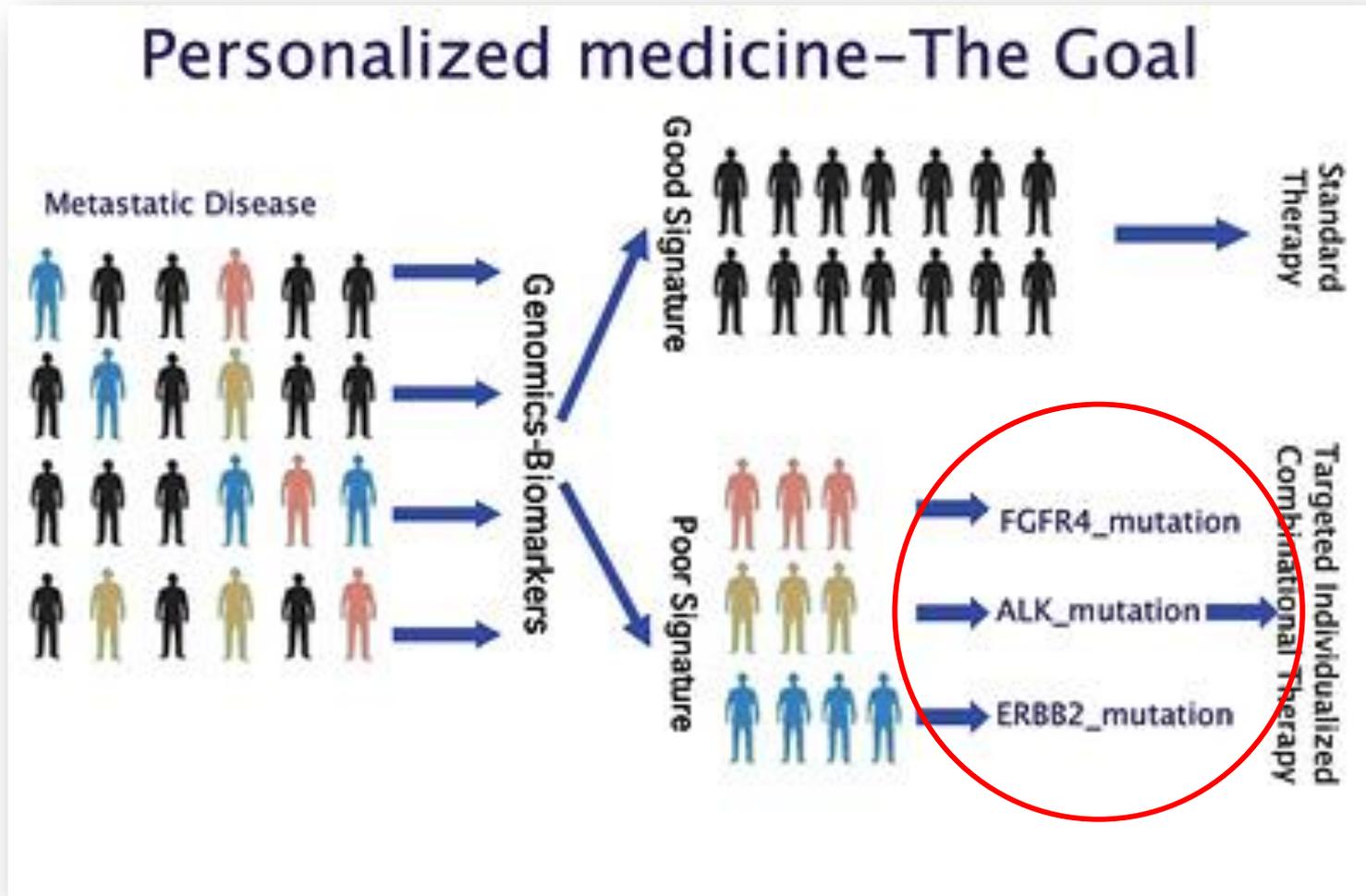
# Outcome de Terapias Tradicionales



% de pacientes sin  
respuesta efectiva/  
beneficiosa

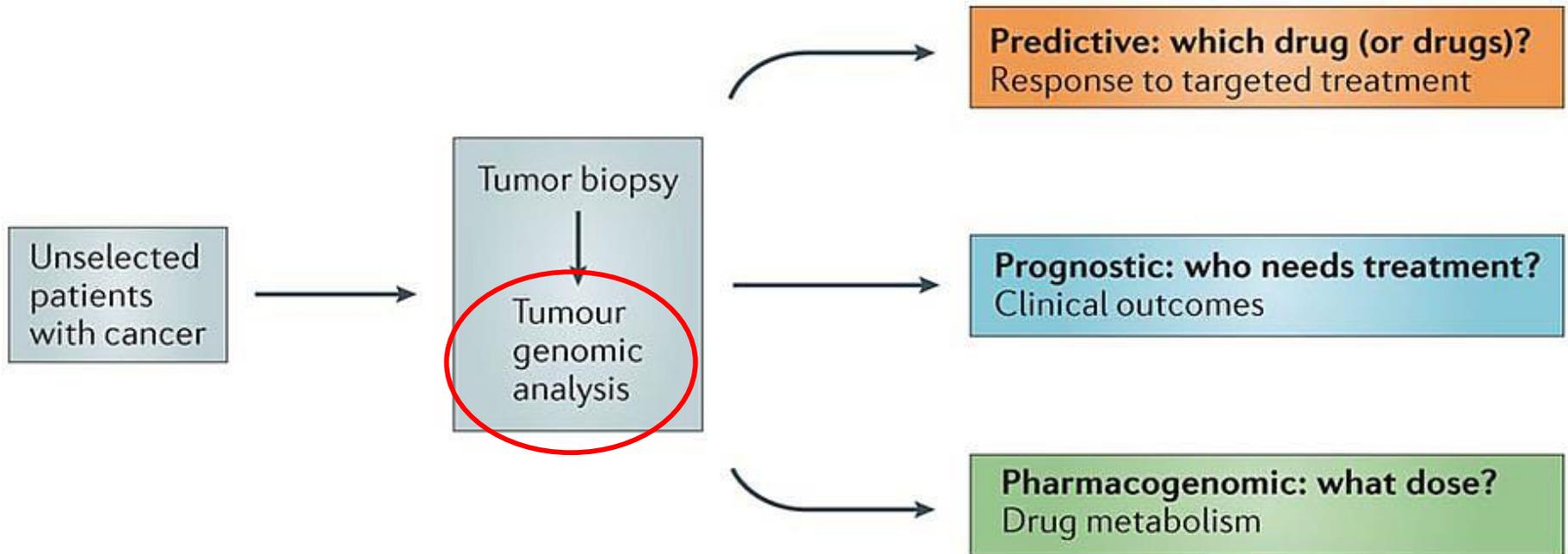
# Medicina de Precisión: la Alternativa

Principio: elección de terapia basada en hallazgos moleculares del tumor



# ¿Qué Predicen las Alteraciones?

- Selección de drogas
- Selección de pacientes que requieren tratamiento
- Ajuste de dosificación



# Alteraciones son Accionables

Genes	Pathways	Aberration type	Disease examples	Putative or proven drugs
<i>PIK3CA</i> <sup>51,52</sup> , <i>PIK3R1</i> (REF. 53), <i>PIK3R2</i> , <i>AKT1</i> , <i>AKT2</i> and <i>AKT3</i> (REFS 54,55)	Phosphoinositide 3-kinase (PI3K)	Mutation or amplification	Breast, colorectal and endometrial cancer	<ul style="list-style-type: none"> <li>• PI3K inhibitors</li> <li>• AKT inhibitors</li> </ul>
<i>PTEN</i> <sup>56</sup>	PI3K	Deletion	Numerous cancers	<ul style="list-style-type: none"> <li>• PI3K inhibitors</li> </ul>
<i>MTOR</i> <sup>57</sup> , <i>TSC1</i> <sup>58</sup> and <i>TSC2</i> (REF. 59)	mTOR	Mutation	Tuberous sclerosis and Bladder cancer	<ul style="list-style-type: none"> <li>• mTOR inhibitors</li> </ul>
RAS family ( <i>HRAS</i> , <i>NRAS</i> , <i>KRAS</i> ), <i>BRAF</i> <sup>60</sup> and <i>MEK1</i>	RAS–MEK	Mutation, rearrangement or amplification	Numerous cancers, including melanoma and prostate cancer	<ul style="list-style-type: none"> <li>• RAF inhibitors</li> <li>• MEK inhibitors</li> <li>• PI3K inhibitors</li> </ul>
Fibroblast growth factor receptor 1 ( <i>FGFR1</i> ), <i>FGFR2</i> , <i>FGFR3</i> , <i>FGFR4</i> (REF. 36)	FGFR	Mutation, amplification or rearrangement	Myeloma, sarcoma and bladder, breast, ovarian, lung, endometrial and myeloid cancers	<ul style="list-style-type: none"> <li>• FGFR inhibitors</li> <li>• FGFR antibodies</li> </ul>
Epidermal growth factor receptor ( <i>EGFR</i> )	EGFR	Mutation, deletion or amplification	Lung and gastrointestinal cancer	<ul style="list-style-type: none"> <li>• EGFR inhibitors</li> <li>• EGFR antibodies</li> </ul>
<i>ERBB2</i> (REF. 61)	ERBB2	Amplification or mutation	Breast, bladder, gastric and lung cancer	<ul style="list-style-type: none"> <li>• ERBB2 inhibitors</li> <li>• ERBB2 antibodies</li> </ul>
<i>SMO</i> <sup>62,63</sup> and <i>PTCH1</i> (REF. 64)	Hedgehog	Mutation	Basal cell carcinoma	<ul style="list-style-type: none"> <li>• Hedgehog inhibitor</li> </ul>
<i>MET</i> <sup>65</sup>	MET	Amplification or mutation	Bladder, gastric and renal cancer	<ul style="list-style-type: none"> <li>• MET inhibitors</li> <li>• MET antibodies</li> </ul>
<i>JAK1</i> , <i>JAK2</i> , <i>JAK3</i> (REF. 66), <i>STAT1</i> , <i>STAT3</i>	JAK–STAT	Mutation or rearrangement	Leukaemia and lymphoma	<ul style="list-style-type: none"> <li>• JAK–STAT inhibitors</li> <li>• STAT decoys</li> </ul>
Discoidin domain-containing receptor 2 ( <i>DDR2</i> )	RTK	Mutation	Lung cancer	<ul style="list-style-type: none"> <li>• Some tyrosine kinase inhibitors</li> </ul>
Erythropoietin receptor ( <i>EPOR</i> )	JAK–STAT	Rearrangement	Leukaemia	<ul style="list-style-type: none"> <li>• JAK–STAT inhibitors</li> </ul>
Interleukin-7 receptor ( <i>IL7R</i> )	JAK–STAT	Mutation	Leukaemia	<ul style="list-style-type: none"> <li>• JAK–STAT inhibitors</li> </ul>
Cyclin-dependent kinases ( <i>CDKs</i> ; <sup>67</sup> <i>CDK4</i> , <i>CDK6</i> , <i>CDK8</i> ), <i>CDKN2A</i> and cyclin D1 ( <i>CCND1</i> )	CDK	Amplification, mutation, deletion or rearrangement	Sarcoma, colorectal cancer, melanoma and lymphoma	<ul style="list-style-type: none"> <li>• CDK inhibitors</li> </ul>
<i>ABL1</i>	ABL	Rearrangement	Leukaemia	<ul style="list-style-type: none"> <li>• ABL inhibitors</li> </ul>
Retinoic acid receptor- $\alpha$ ( <i>RARA</i> )	<i>RAR<math>\alpha</math></i>	Rearrangement	Leukaemia	<ul style="list-style-type: none"> <li>• All-trans retinoic acid</li> </ul>
Aurora kinase A ( <i>AURKA</i> ) <sup>68</sup>	Aurora kinases	Amplification	Prostate cancer and breast cancer	<ul style="list-style-type: none"> <li>• Aurora kinase inhibitors</li> </ul>

# Medicina de Precisión: Epigenoma

**Table 1** Hypermethylated genes as predictors of chemosensitivity.

Gene name	Gene function	Tumor type application	Chemosensitivity prediction	Ref.
<i>MGMT</i>	DNA repair	Glioma, colon, lung, lymphoma	Sensitive to temozolomide, BCNU, ACNU, procarbazine	[20]
<i>CHFR</i>	Ubiquitin protein ligase	esophageal, gastric, cervical, lung, endometrial cancer and oral squamous cell carcinoma	Sensitive to paclitaxel and docetaxel	[24,28]
<i>FANCF</i>	DNA damage response	Ovarian	Sensitivity to cisplatin	[25]
<i>BRCA1</i>	DNA damage response	Breast, ovary	Sensitive to PARP inhibitors and alkylating agents	[29]
<i>MLH1</i>	DNA repair	Colon, stomach, endometrium, ovary	Resistance to cisplatin	[30]
<i>GSTP1</i>	Detoxification	Prostate, breast, kidney	Sensitivity to doxorubicin	[31]
<i>PRKCDBP</i>	Signal transduction	Colon	Resistance to TNF- $\alpha$	[32]
<i>SFN</i>	Signal transduction	Lung	Sensitive to cisplatin and gemcitabine	[33]
<i>TFAP2E</i>	Transcriptional regulator	Colon	Sensitivity to fluorouracil	[34]
<i>ABCB1</i>	Protein transport	Breast	Sensitivity to doxorubicin	[35]
<i>APAF1</i>	Apoptotic activator	Melanoma	Resistance to adriamycin	[36]
<i>CDK10</i>	Cell cycle control	Breast	Resistance to anti-estrogens	[37]
<i>IGFBP3</i>	Signal transduction	Lung	Resistance to cisplatin	[38]
<i>MT1E</i>	Antioxidant	Melanoma	Sensitivity to cisplatin	[39]
<i>TGM2</i>	Apoptosis	Lung, breast, ovary	Resistance to doxorubicin and cisplatin	[40]
<i>TP73</i>	Stress response	Renal, melanoma	Sensitivity to cisplatin	[41]

# Medicina de Precisión: Fármacos

Drug Name (Brand Name)	Biomarker(s)	Indication
Ado-trastuzumab emtansine (Kadcyla®)	ERBB2	Breast cancer
Afatinib (Gilotrif®)	EGFR	Metastatic non-small cell lung cancer
Anastrozole (Arimidex®)	ESR1; PGR	Breast cancer
Arsenic trioxide (Trisenox®)	PML-RARA	Acute promyelocytic leukemia
Busulfan (Busulfex® & Myleran®)	BCR-ABL1	Leukemia
Bosutinib (Bosulif®)	BCR-ABL1	Leukemia
Brentuximab Vedotin (Adcetris™)	CD30	Hodgkin's lymphoma, anaplastic large cell lymphoma
Capecitabine (Xeloda®)	DPYD	Multiple cancers
Cetuximab (Erbix®)	EGFR, KRAS	Colon cancer
Crizotinib (Xalkori®)	ALK	Lung cancer
Dabrafenib (Tafinlar®)	BRAF; G6PD	Melanoma
Dasatinib (Sprycel®)	BCR-ABL	Leukemia
Denileukin diftitox (Ontak®)	IL2RA	Lymphoma
Erlotinib (Tarceva®)	EGFR	Non-small cell lung cancer
Everolimus (Afinitor®)	ERBB2; ESR1	Breast cancer
Exemestane (Aromasin®)	ESR1; PGR	Breast cancer
5-Fluorouracil (5-FU) (Efudex®)	DPYD	Multiple cancers
Fulvestrant (Faslodex®)	ESR1; PGR	Breast cancer
Gefitinib (Iressa®)	EGFR	Non-small cell lung cancer
Imatinib (Gleevec®)	BCR-ABL; PDGFRB; KIT; FIP1L1-PDGFR	Multiple cancers, myelodysplastic syndrome
Irinotecan (Camptosar®)	UGT1A1	Colon cancer, small cell lung cancer
Lapatinib (Tykerb®)	ERBB2; HLA-DQA1; HLA-DRB1	Breast cancer
Lenalidomide (Revlimid®)	Del (5q)	Multiple myeloma, mantle cell lymphoma, and myelodysplastic syndrome
Letrozole (Femara®)	ESR1; PGR	Breast cancer
Mercaptopurine (Purinethol®)	TPMT	Acute lymphocytic leukemia, chronic myeloid leukemia, Crohn's disease, ulcerative colitis
Nilotinib (Tasigna®)	UGT1A1; BCR-ABL1	Chronic myelogenous leukemia
Obinutuzumab (Gazyva®)	MS4A1	Chronic lymphocytic leukemia, follicular lymphoma
Omacetaxine mepesuccinate (Synribo®)	BCR-ABL1	Chronic myeloid leukemia
Panitumumab (Vectibix®)	EGFR; KRAS	Colon cancer
Pemetrexed (Alimta®)	TS	Lung cancer
Pertuzumab (Perjeta®)	ERBB2	Breast cancer

# Medicina de Precisión: Fármacos

Drug Name (Brand Name)	Biomarker(s)	Indication
<b>Platinum Therapies</b>		
Carboplatin	ERCC1	Ovarian cancer
Cisplatin	TPMT	Multiple cancers
Oxaliplatin	ERCC1	Colorectal cancer
Nedaplatin	ERCC1	Multiple cancers
Triplatin tetranitrate	ERCC1	Multiple cancers
Satraplatin	ERCC1	Multiple cancers
Ponatinib (Iclusig®)	BCR-ABL1	Chronic lymphocytic leukemia, acute lymphocytic leukemia
Rituximab (Rituxan®)	MS4A1	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and autoimmune diseases
Tamoxifen (Nolvadex®)	ESR1; ESR2; PGR; F5; F2; CYP2D6	Breast cancer
Thioguanine (Tabloid®)	TPMT	Acute myeloid leukemia, acute lymphocytic leukemia, and chronic myeloid leukemia
Tositumomab (Bexxar®)	MS4A1	Non-Hodgkin's lymphoma
Trametinib (Mekinist®)	BRAF	Melanoma
Trastuzumab (Herceptin®)	ERBB2	Breast cancer
Tretinoin (Vesanoid®)	PML/RARalpha	Acute promyelocytic leukemia
Vemurafenib (Zelboraf™)	BRAF; NRAS	Melanoma



<http://www.personalizedmedicinecoalition.org/Education/Therapies>

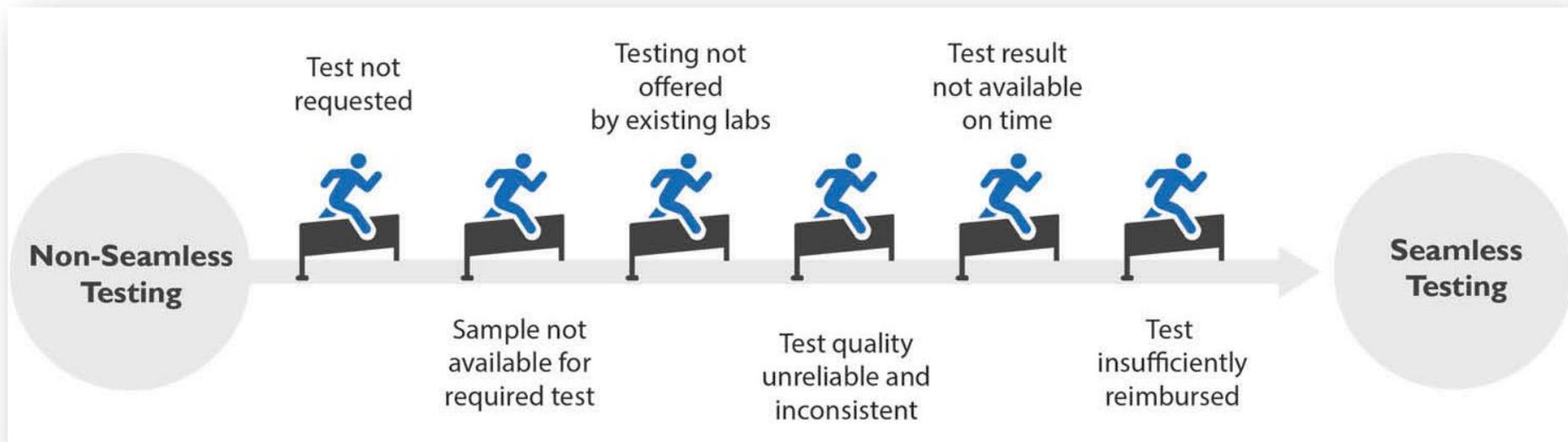
# Medicina de Precisión: Desafíos, Limitaciones

# Medicina de Precisión: Desafíos

- ¿Qué alteración molecular será más predictiva de una respuesta? ¿Modelos de testeo?
- ¿Esto será aplicable a todos los tumores que presenten dicha alteración?
- Porcentaje de células que presentan la alteración (visibilidad y método de detección)
- ¿Cuántas evaluaciones moleculares (tumor primario, recidiva, metástasis)?
- Costos!

# Medicina de Precisión: Desafíos

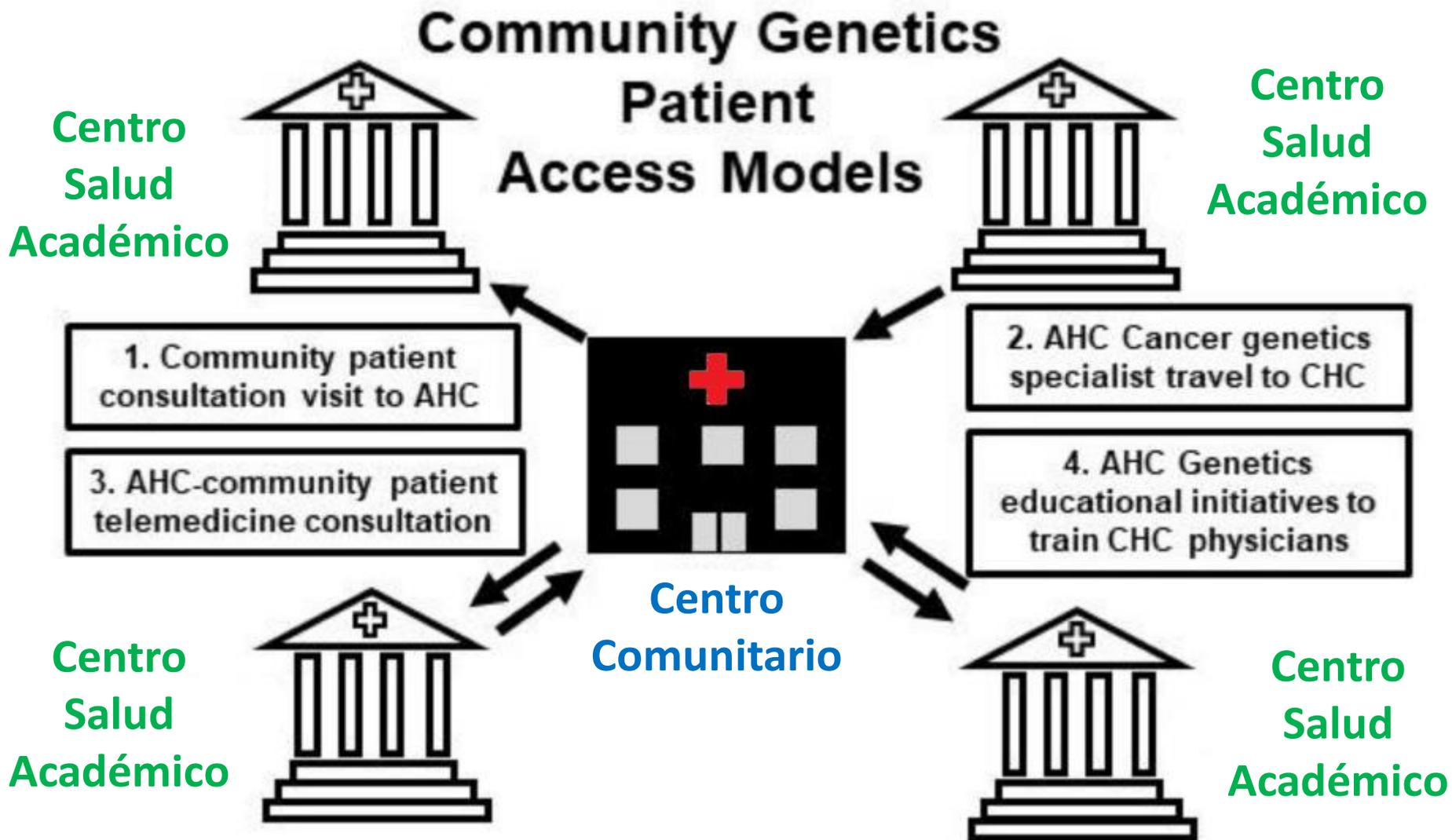
- ¿Quién realizará la toma de muestra?
- ¿Modelo de funcionamiento de análisis molecular: centralizado o institucional?
- Validación globalizada de datos



Keeling et al 2020. Expert Review of Molecular Diagnostics.

DOI: 10.1080/14737159.2020.1757436

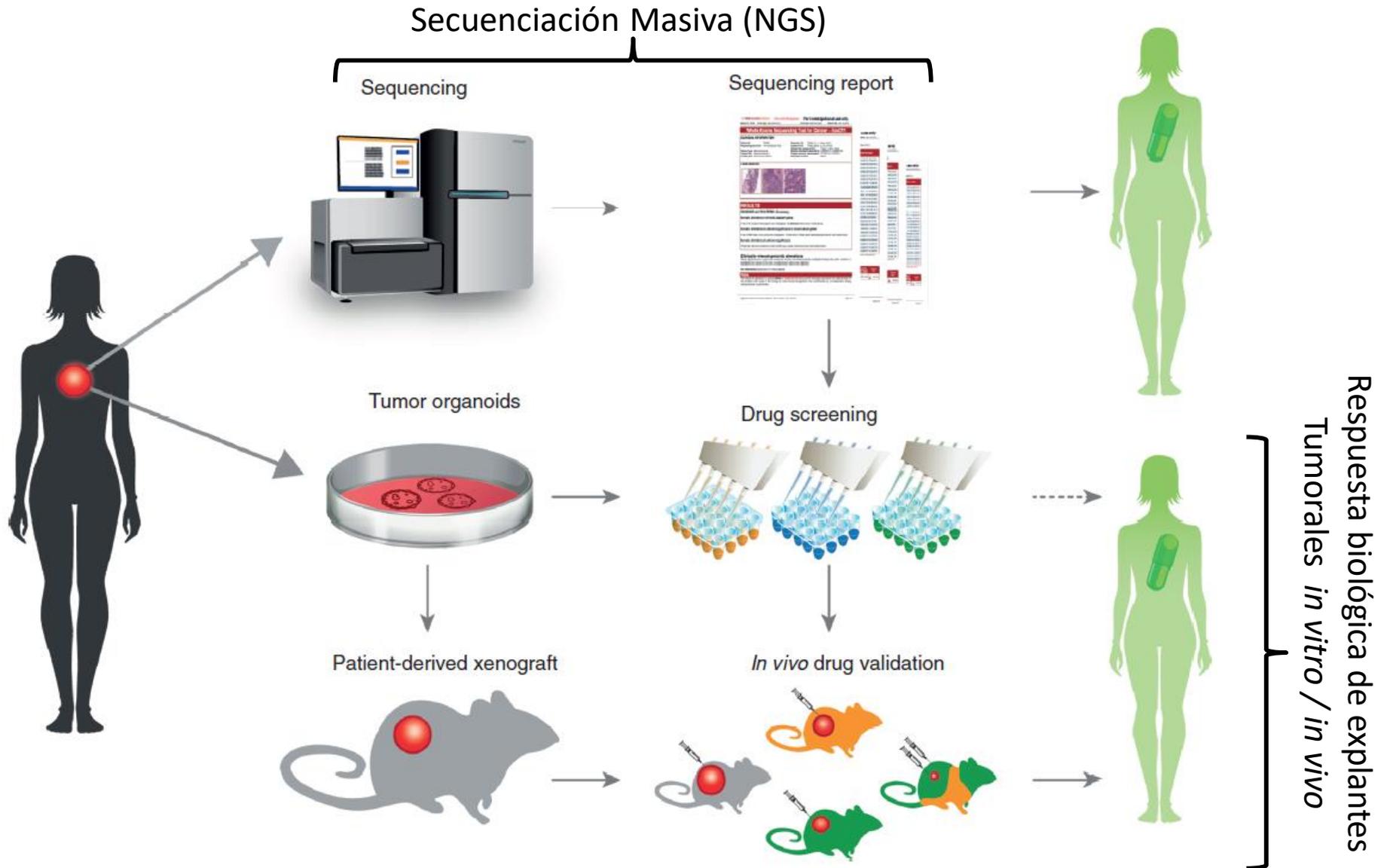
# Modelo: Accesibilidad de Pacientes



# Alteraciones: ¿Qué Técnica de Detección?

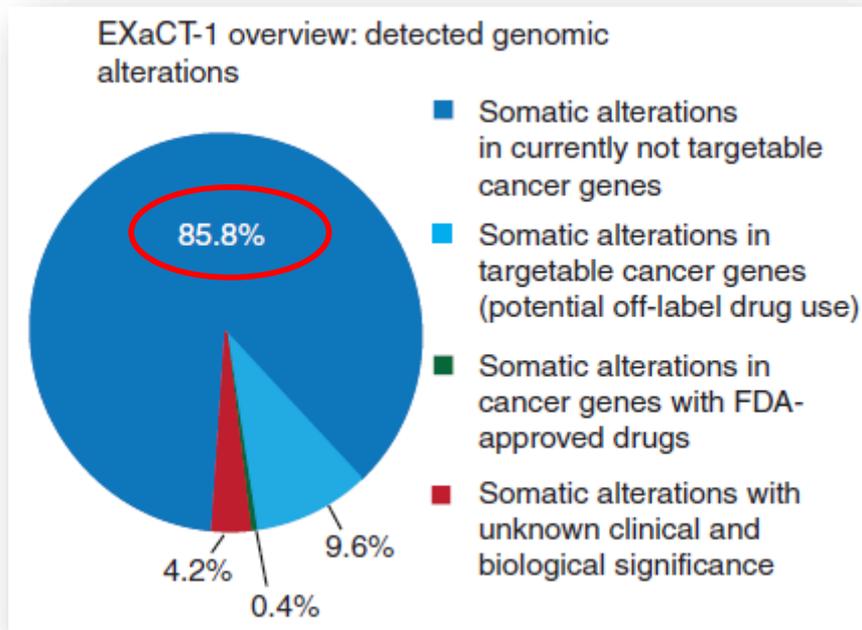
- Estudio comparó proteómica, genómica y epigenómica (Costello, Nature Biotechnol 2014, doi:10.1038/nbt.2877)
- Colaboración NCI y DREAM (Dialogue on Reverse Engineering Assessment and Methods) project
- Líneas celulares de cáncer de mama
- Mejor poder predictivo para respuesta a drogas: perfiles de expresión (microarrays)

# Estrategias Predictivas



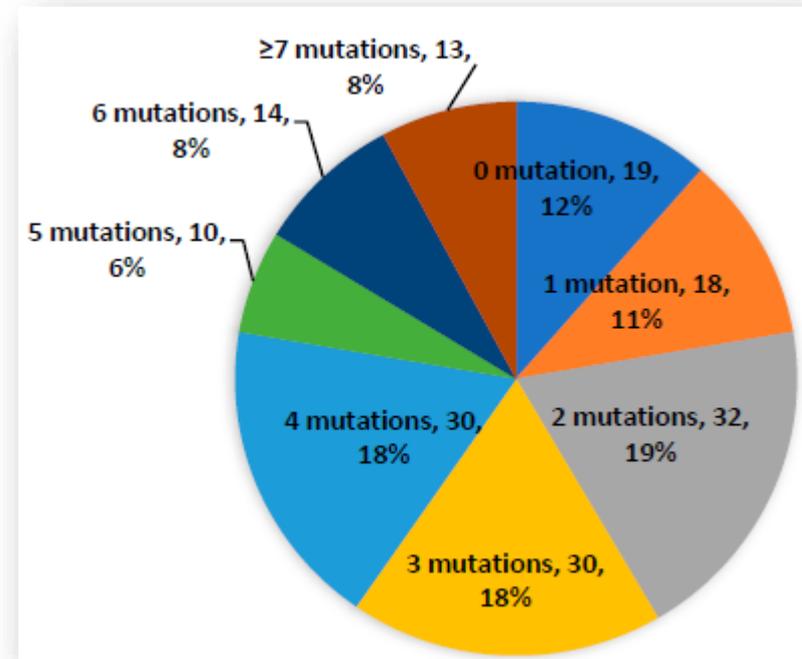
# Mutaciones Accionables: ¿Cuáles, cuántas?

- ¿Cuántos y cuáles genes analizar? (Panel)
- ¿Fármaco existente?



**2017**

Whole Exome Seq  
n = 769 advanced cancers

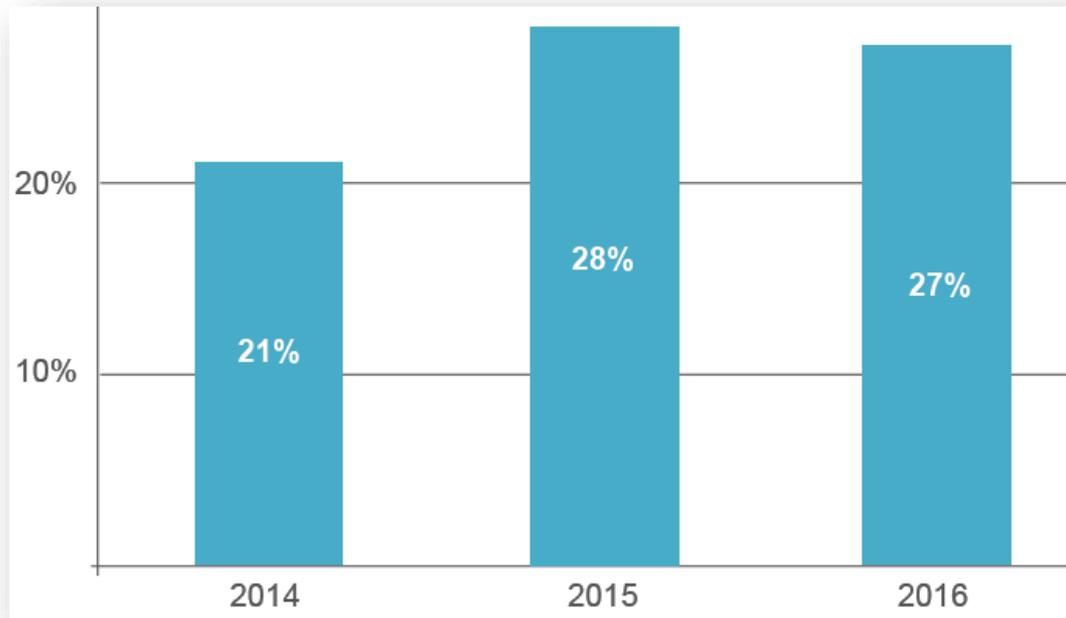


**2020**

NGS Panel 161 genes  
n = 166 advanced cancers

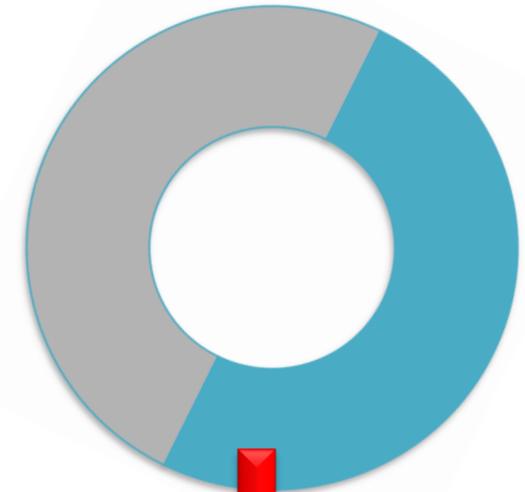
**54%** con terapia dirigida disponible

# Aprobaciones por la FDA



FDA: Aprobaciones correspondientes a terapias de aplicación personalizada (2014-2016)

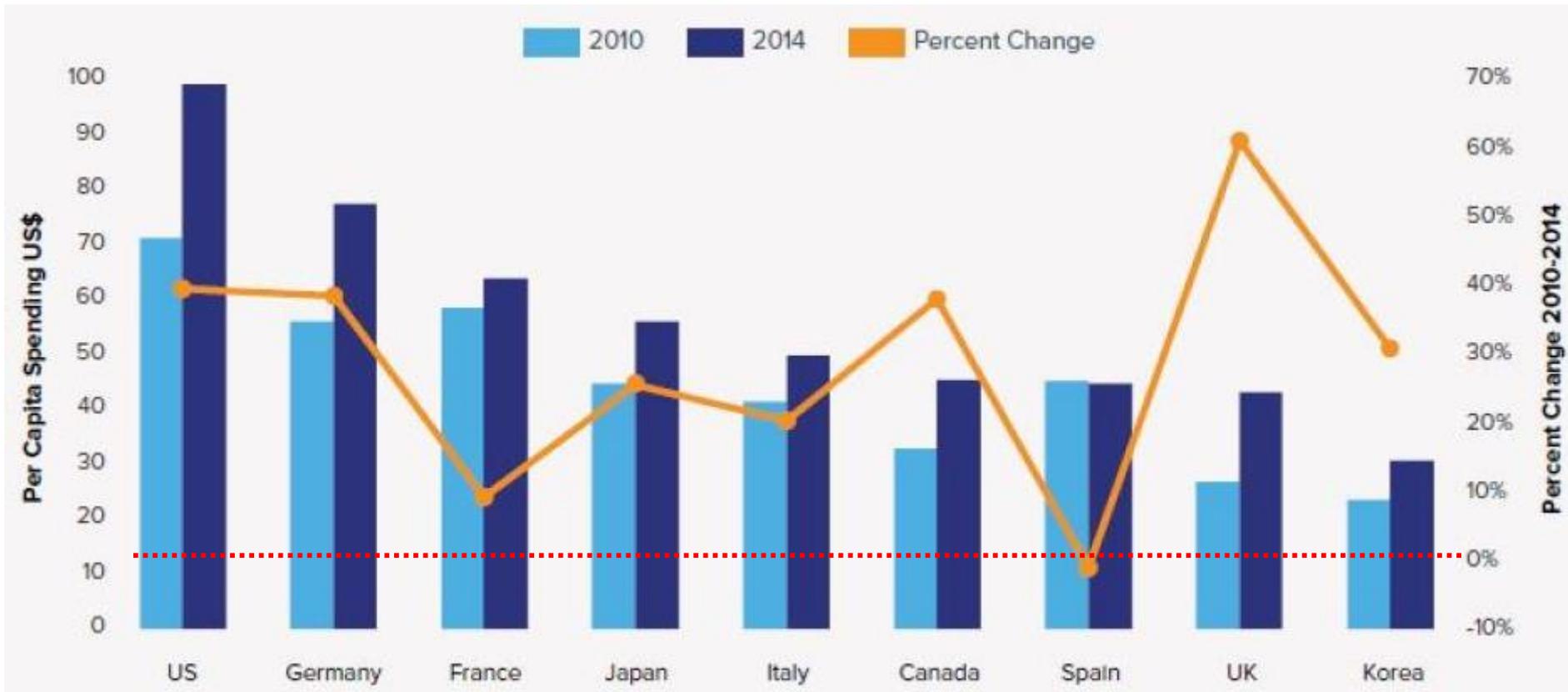
**2017: 34%**  
**2018: 42%**



**50%**  
Drogas antineoplásicas

# Costos Drogas Antineoplásicas

Período 2010-2014



(IMS HEALTH)

# ¿Costo Eficiencia de Testeo Genético?

## Beneficioso para sistema clínico

Some tests may be in line with physician economics

- Hypothetical colon cancer risk marker : risk marker increases the frequency of diagnostic colonoscopies
- Without test
  - Average patient sees physician first at age 50
  - Frequency of preventative colonoscopy is 7.5 years
- With test
  - Patients screened for risk marker at age 50
  - High-risk patients receive colonoscopy every 2 years



- Physicians receive ~\$2,500 per high-risk patient identified (through additional colonoscopies)\*

## **NO** Beneficioso para sistema clínico

Other tests can in theory hurt physician economics

- Oncotype Dx example: predicts the recurrence of breast cancer
- Without test
  - ~90% of patients would receive follow-on chemotherapy
- With test
  - Only ~50% of patients will receive chemotherapy



- Physicians will administer significantly less chemotherapy, thus diminishing billing fees per patient

# Costo Eficiencia: Consideraciones

Necesidad de considerar varios factores al evaluar la costo-eficiencia de la Medicina de Precisión

## Factores que encarecen:



- Tecnología
- Infraestructura
- Requisito de board multidisciplinario

## Factores favorables:

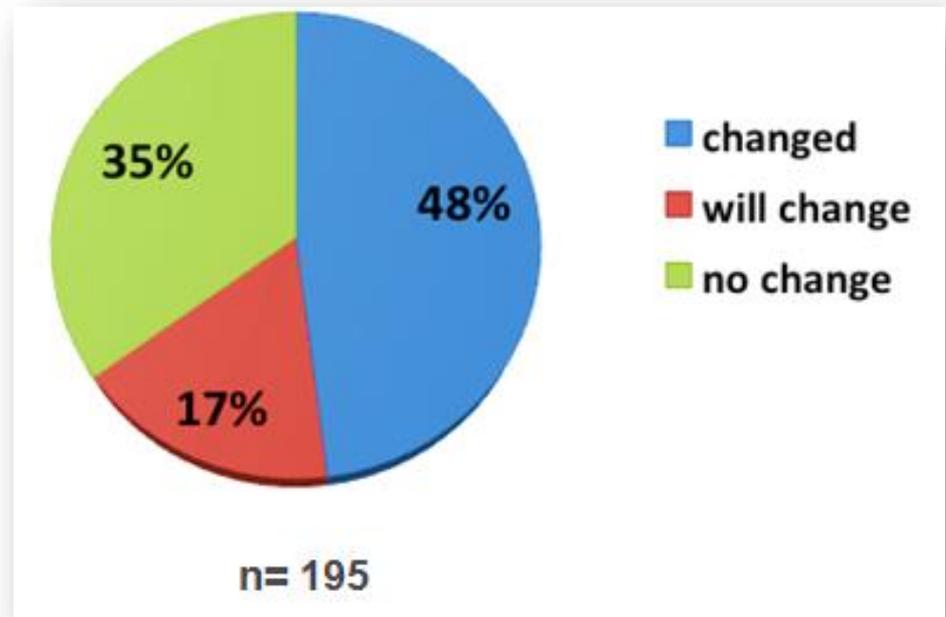


- Mayor sobrevida (ganancia de años-vida)
- Menor número de efectos adversos (costos, muertes)
- Ahorro en terapias inefectivas

# Toma de Decisiones Terapéuticas

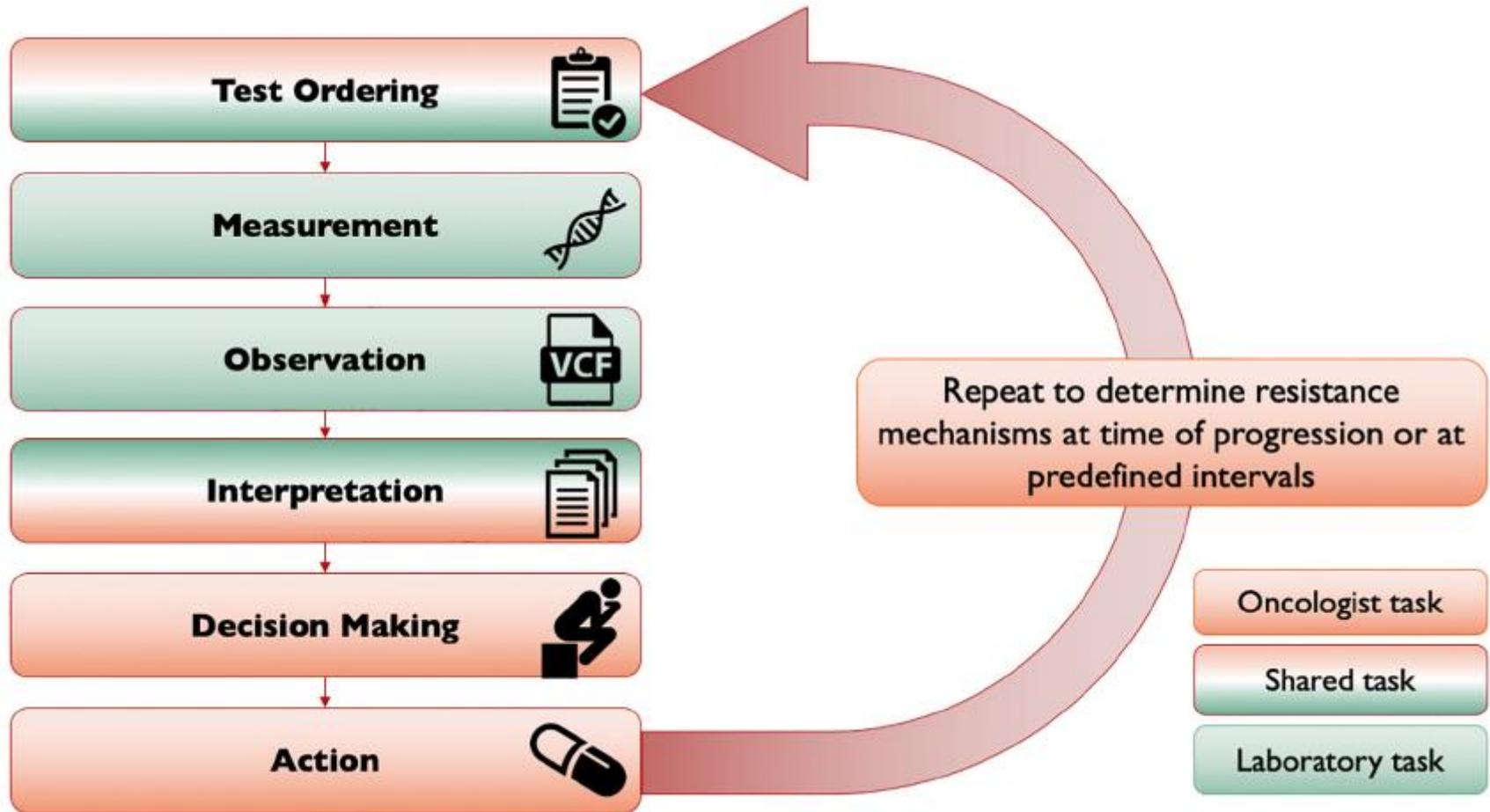
Requiere grupo interdisciplinario:

- Interpretación de datos moleculares
- Expertos en genómica del cáncer
- Oncólogos tratantes
  
- Cambio de conducta clínica basada en datos moleculares (Intermountain Healthcare)



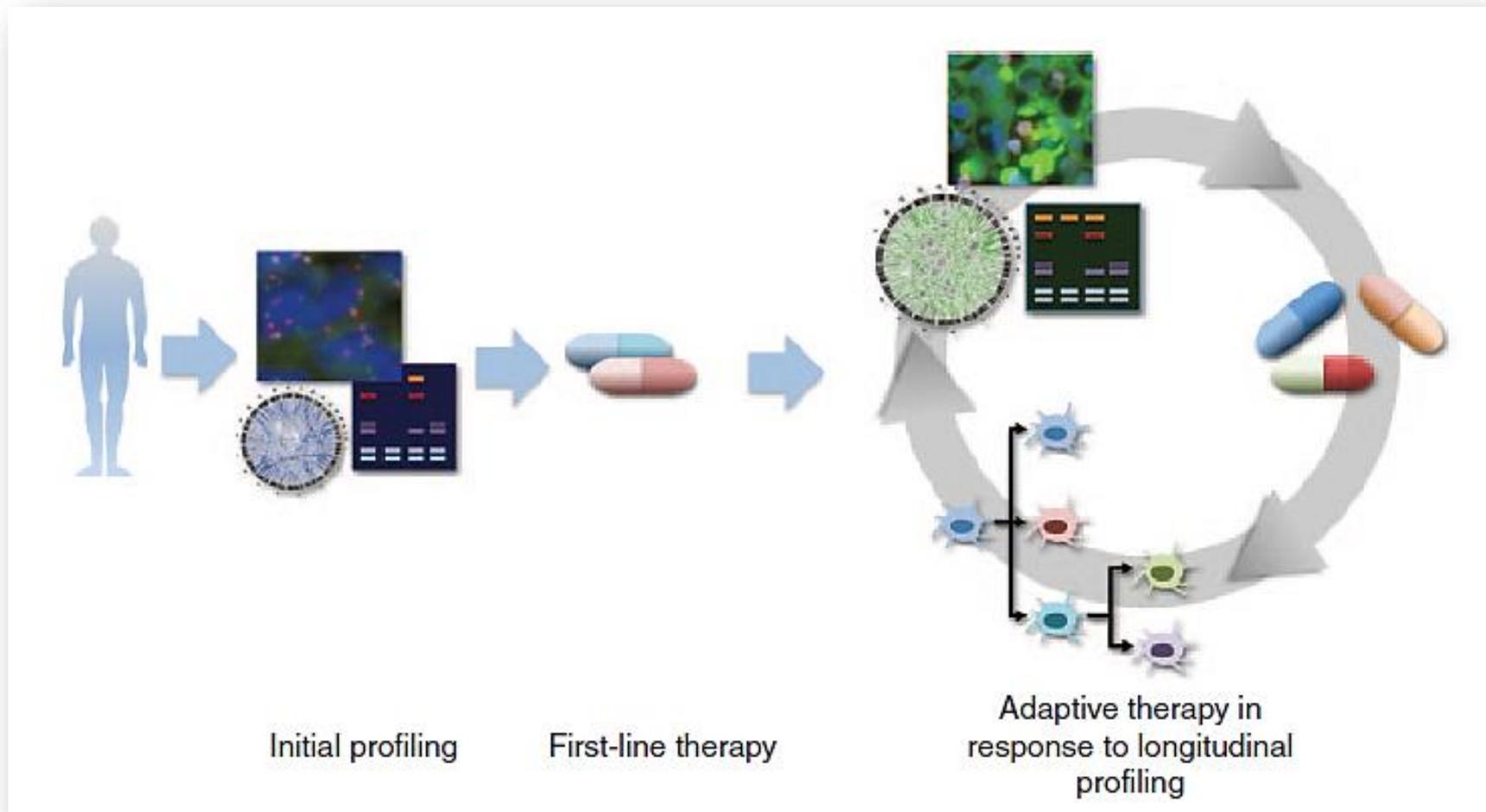
# Integración Interdisciplinaria (NGS)

- Oncólogos, bioinformáticos, investigadores, personal de laboratorio



# Situación Ideal: Reiterativa

Terapia adaptativa longitudinal, basada en mediciones moleculares reiteradas durante evolución de la enfermedad



# Implementación Progresiva

- Ej.: Personalised Medicine Consortium, Luxemburgo

## Think Big

- Strive to:
  - Prevent the preventable
  - Cure the curable
  - Manage chronic disease when necessary

## Act Small

- Small projects that can be easily replicated anywhere
- Partner with the most innovative companies and research institutes
- Use best practices from other countries and share our experiences

Big Dreams



Small Practical  
Projects

# Medicina de Precisión: Resultados

# Programas de Medicina de Precisión

Ej: Intermountain Healthcare (Stanford University;  
[www.precisioncancer.org](http://www.precisioncancer.org)): plazos factibles

**Personalized  
Medicine Clinic**



Day 1

**Molecular  
analysis  
(NGS)**



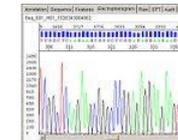
Day 8-9

**Tumor Biopsy  
or FFPE**



Day 2-3

**Analytics**



Day 10-12

**Pathology  
Review**



Day 4-5

**Molecular  
Tumor Board**



Day 13

**Sample  
Prep**



Day 6-7

**Results and  
Treatment**



**Day 14**

Adapted from L. Nadauld

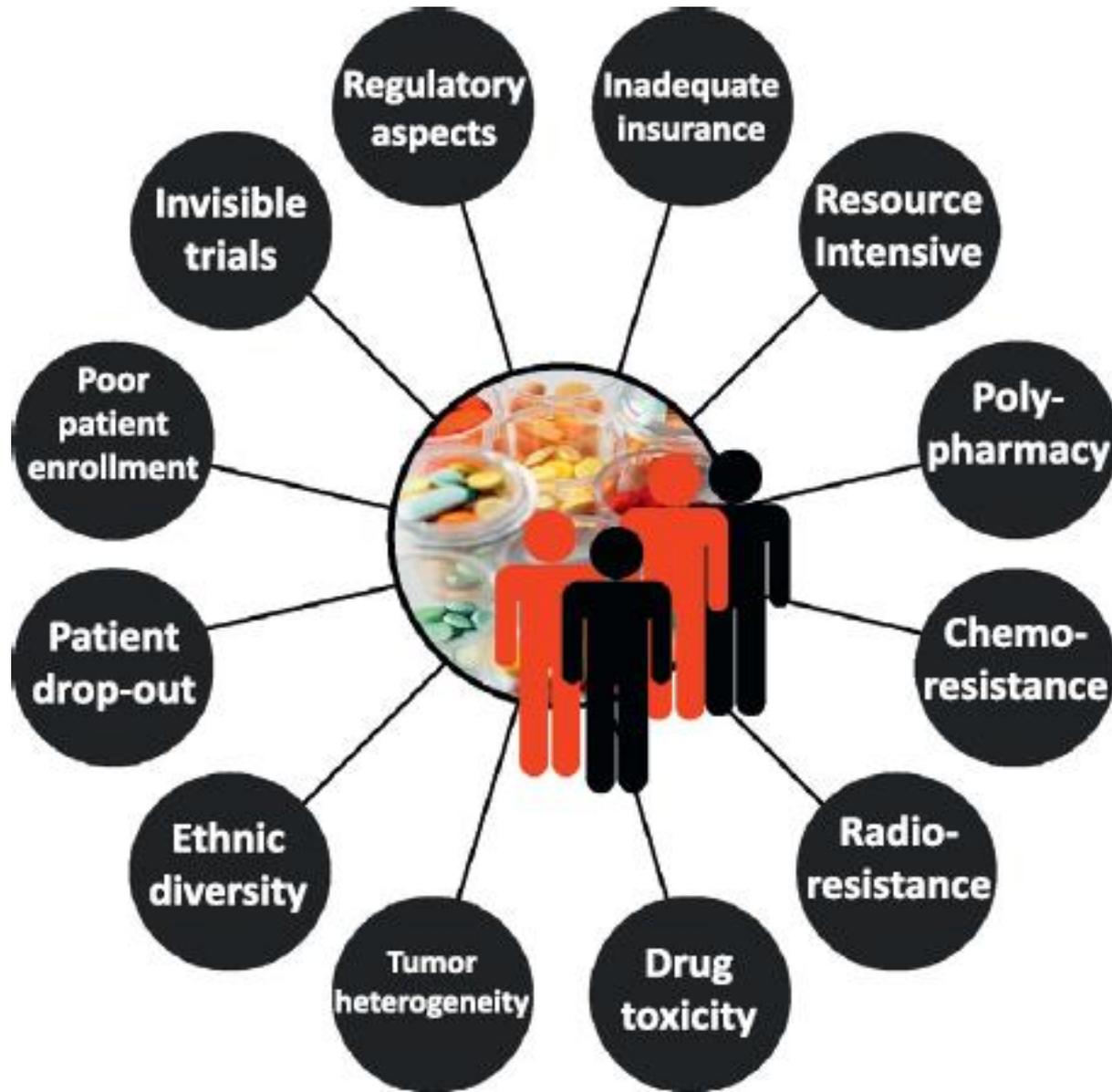
# Respuesta a Tratamiento: Ensayos Clínicos

- **MATCH:** Molecular Analysis for Therapy Choice (screening genómico y test de eficacia en diferentes tipos de tumores)
- **IMPACT:** Initiative for Molecular Profiling-based Assignment of Cancer Therapy (terapia dirigida a alteraciones "driver")
- Exceptional Responders' Initiative (análisis de pacientes con respuestas inesperadas duraderas)

# NCI-MATCH

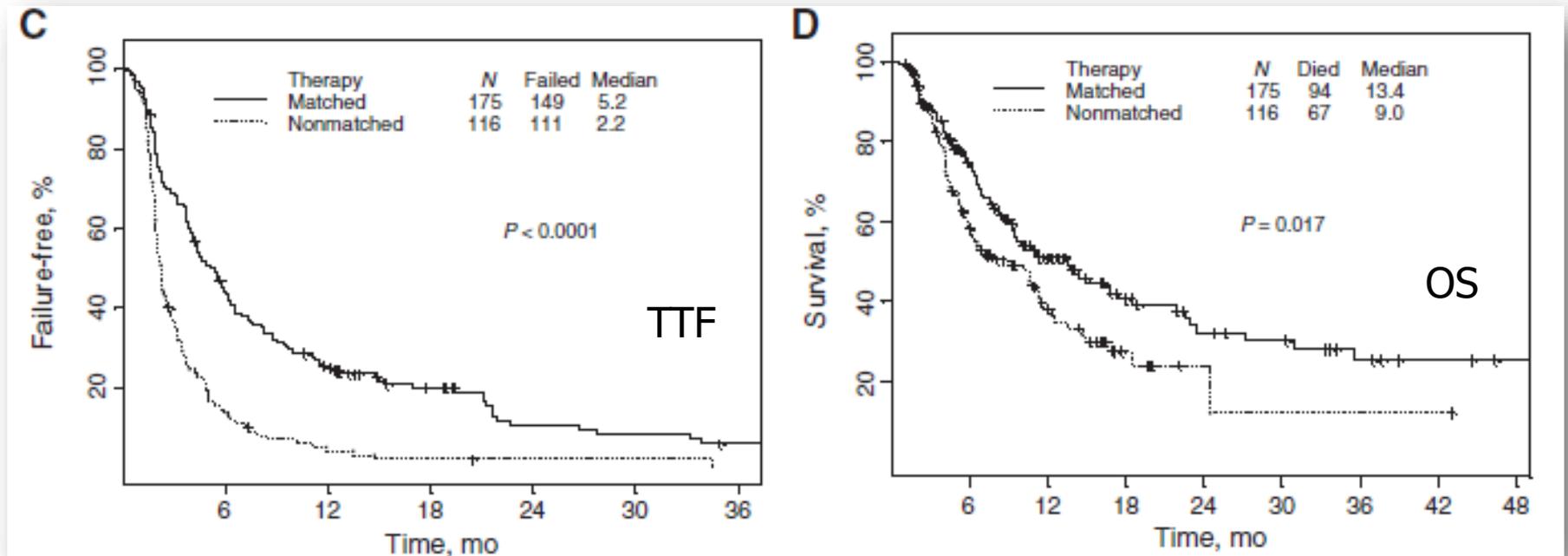
Identifier	Molecular eligibility variant	Treatment
EAY131-A	<i>EGFR</i> mutations	Afatinib (Gilotrif, Boehringer Ingelheim, Germany)
EAY131-B	<i>ERBB2</i> mutations	Afatinib (Gilotrif, Boehringer Ingelheim, Germany)
EAY131-C1	<i>MET</i> amplification	Crizotinib (Xalkori, Pfizer, CT)
EAY131-C2	<i>MET</i> exon 14 skipping	Crizotinib (Xalkori, Pfizer, CT)
EAY131-E	<i>T790M</i> , rare <i>EGFR</i> mutations	Osimertinib (Tagrisso, AstraZeneca, London, UK)
EAY131-F	<i>ALK</i> translocation	Crizotinib (Xalkori, Pfizer, CT)
EAY131-G	<i>ROS</i> translocation	Crizotinib (Xalkori, Pfizer, CT)
EAY131-H	<i>BRAF</i> V600E/K mutations	Dabrafenib (Tafinlar, GlaxoSmithKline, UK) + trametinib (see below)
EAY131-I	<i>PI3KCA</i> mutation	Taselisib (GDC-0032, RG7604, Roche, Basel, Switzerland)
EAY131-N	<i>PTEN</i> mutation/deletion	GSK2636771 (GlaxoSmithKline, UK)
EAY131-P	<i>PTEN</i> loss of expression	GSK2636771 (GlaxoSmithKline, UK)
EAY131-Q	<i>ERBB2</i> amplification	Ado-trastuzumab emtastine (Kadcyla, Genentech, SF)
EAY131-R	<i>BRAF</i> nonV600E/K mutations	Trametinib (Mekinist, GlaxoSmithKline, UK)
EAY131-S1	<i>NF1</i> mutation	Trametinib (Mekinist, GlaxoSmithKline, UK)
EAY131-S2	<i>GNAQ/GNA11</i> mutation	Trametinib (Mekinist, GlaxoSmithKline, UK)
EAY131-T	<i>SMO</i> or <i>PTCH</i> mutation	Vismodegib (Erivedge, Genentech, SF)
EAY131-U	<i>NF2</i> mutation	Defactinib (VS-6063, Verastem, MA)
EAY131-V	<i>KIT</i> mutation	Sunitinib (Sutent, Pfizer, CT)
EAY131-W	<i>FGFR1,2,3</i> abnormalities	AZD4547 (AstraZeneca, London, UK)
EAY131-X	<i>DDR2</i> mutation	Dasatinib (Sprycel, Bristol-Myers Squibb, NY)
EAY131-Y	<i>AKT</i> mutations	AZD5363 (AstraZeneca, London, UK)
EAY131-Z1A	<i>NRAS</i> mutation	Binimetinib (MEK162, ARRY-162, Array BioPharma, CO)
EAY131-ZIB	<i>CCND1</i> , 2, 3 AB	Palbociclib (Ibrance, Pfizer, CT)
EAY131-ZID	Loss of <i>MLH1</i> or <i>MSH2</i> expression	Nivolumab (Opdivo, Bristol-Myers Squibb, NY)

# Estudios Clínicos: Limitaciones

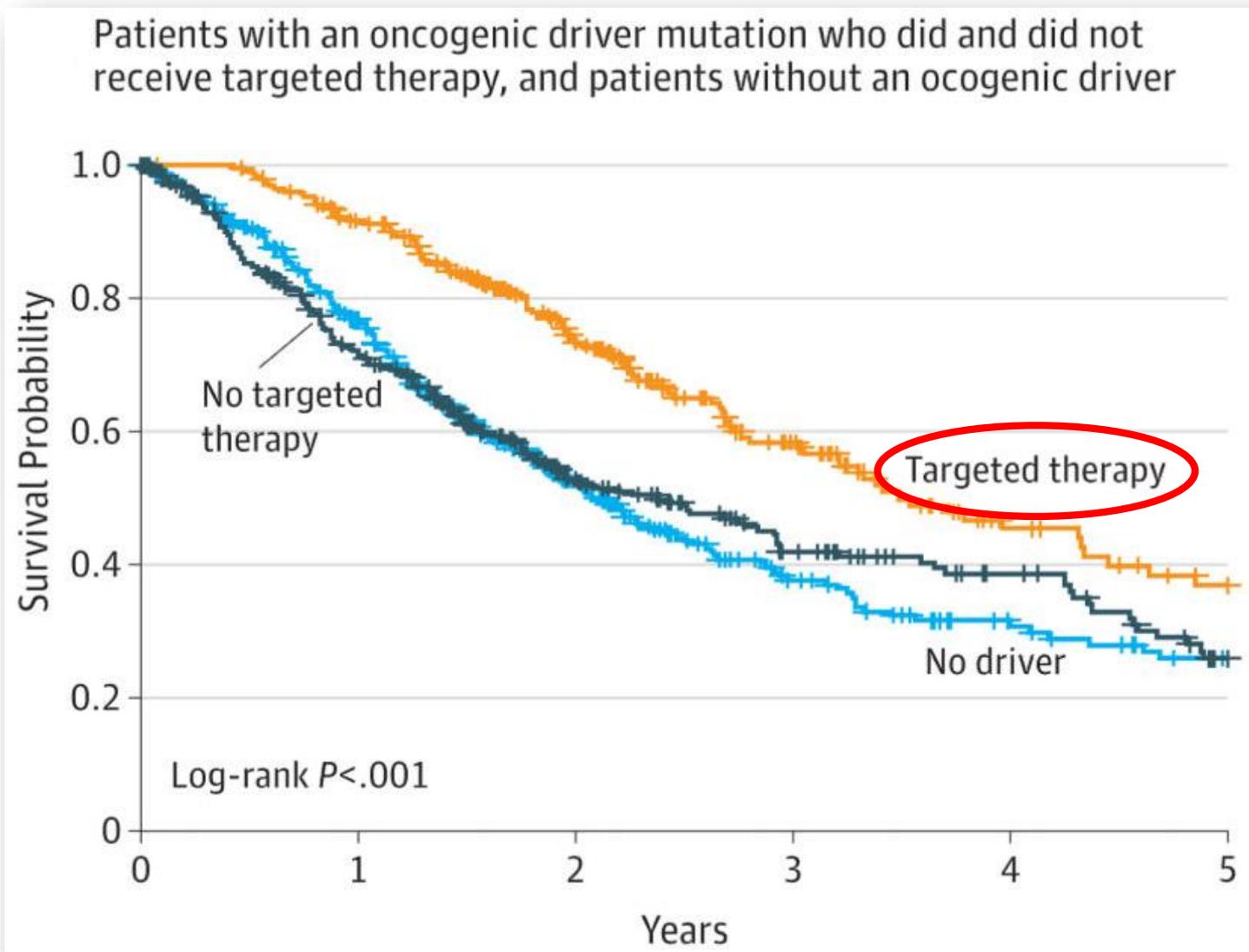


# Ensayos Clínicos M.D. Anderson

- Clinical Center for Targeted Therapy
- Pacientes con cáncer avanzado
- Estudio Fase I



# Adenocarcinoma Pulmonar



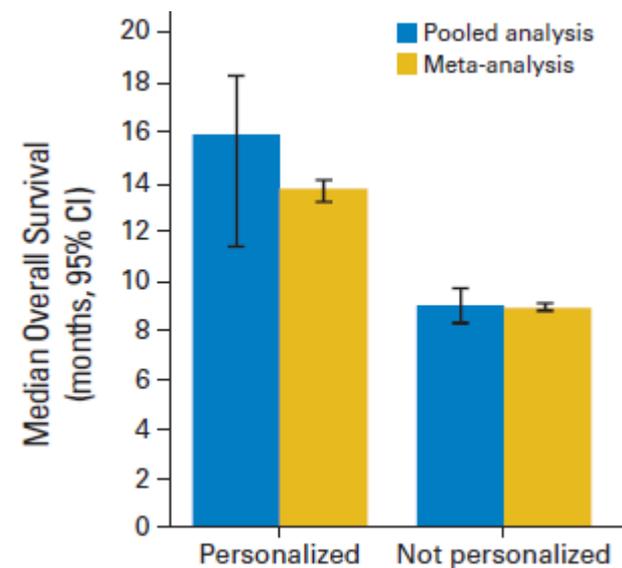
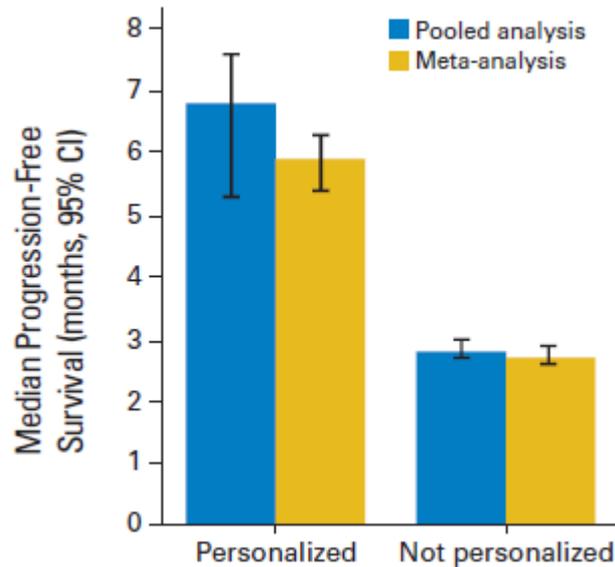
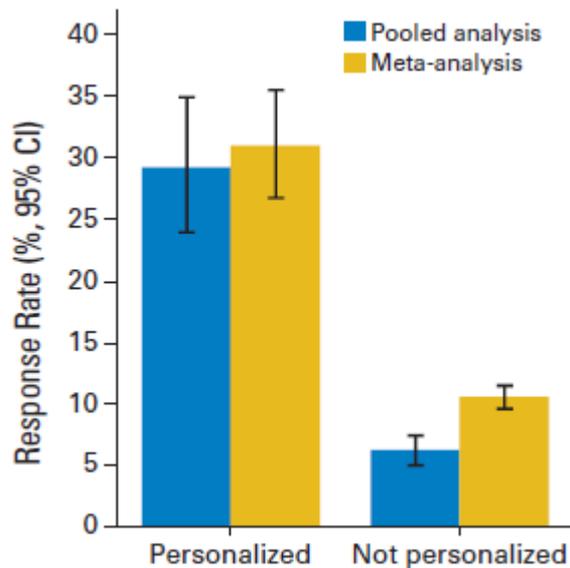
Panel: 10 genes

Mutación accionable en 466/733 casos (64%)

260 recibieron terapia personalizada

# ¿Impacto Clínico?

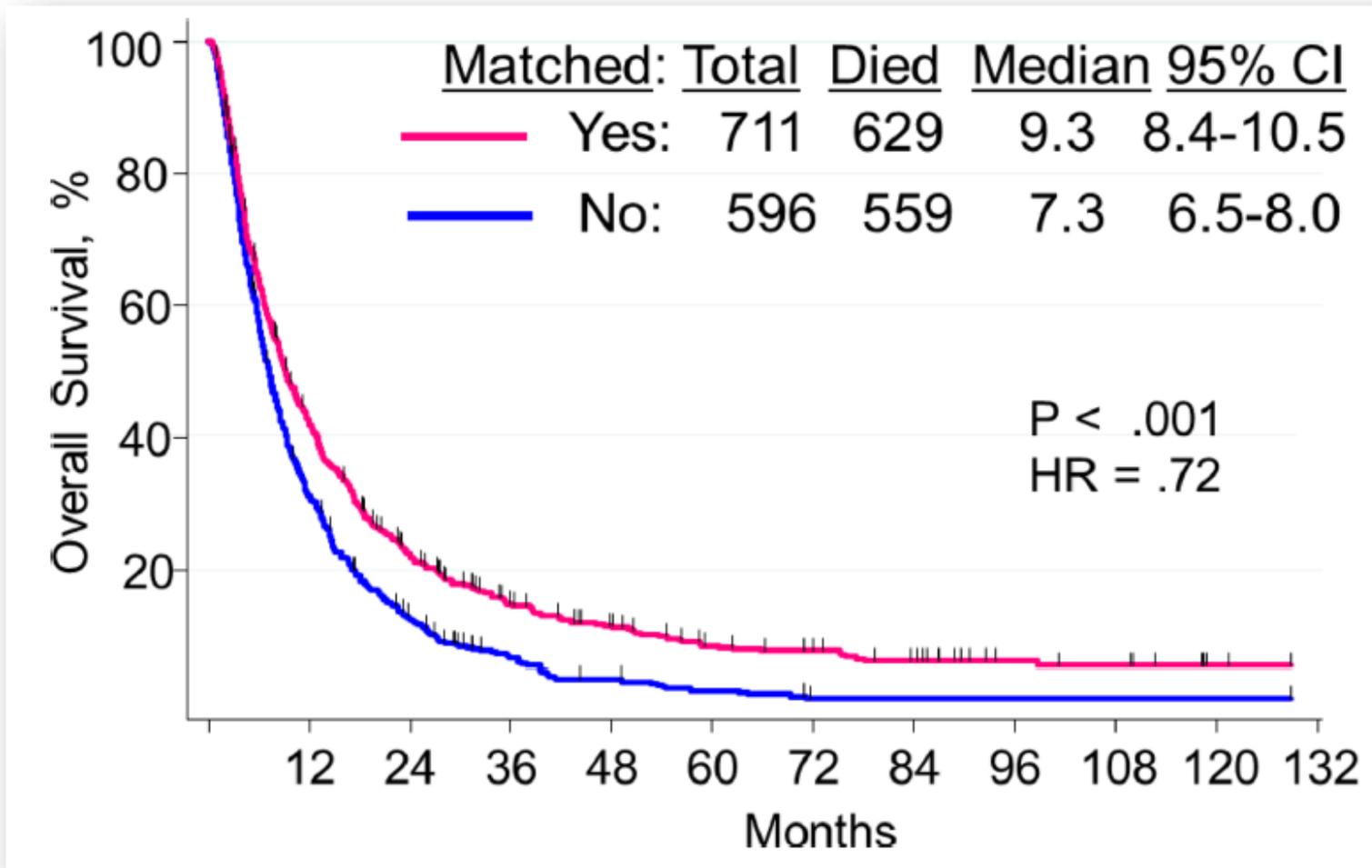
- Análisis de 570 estudios, >32.000 pacientes



Estrategia personalizada: predictor de mejor outcome y menos muertes asociadas a toxicidad

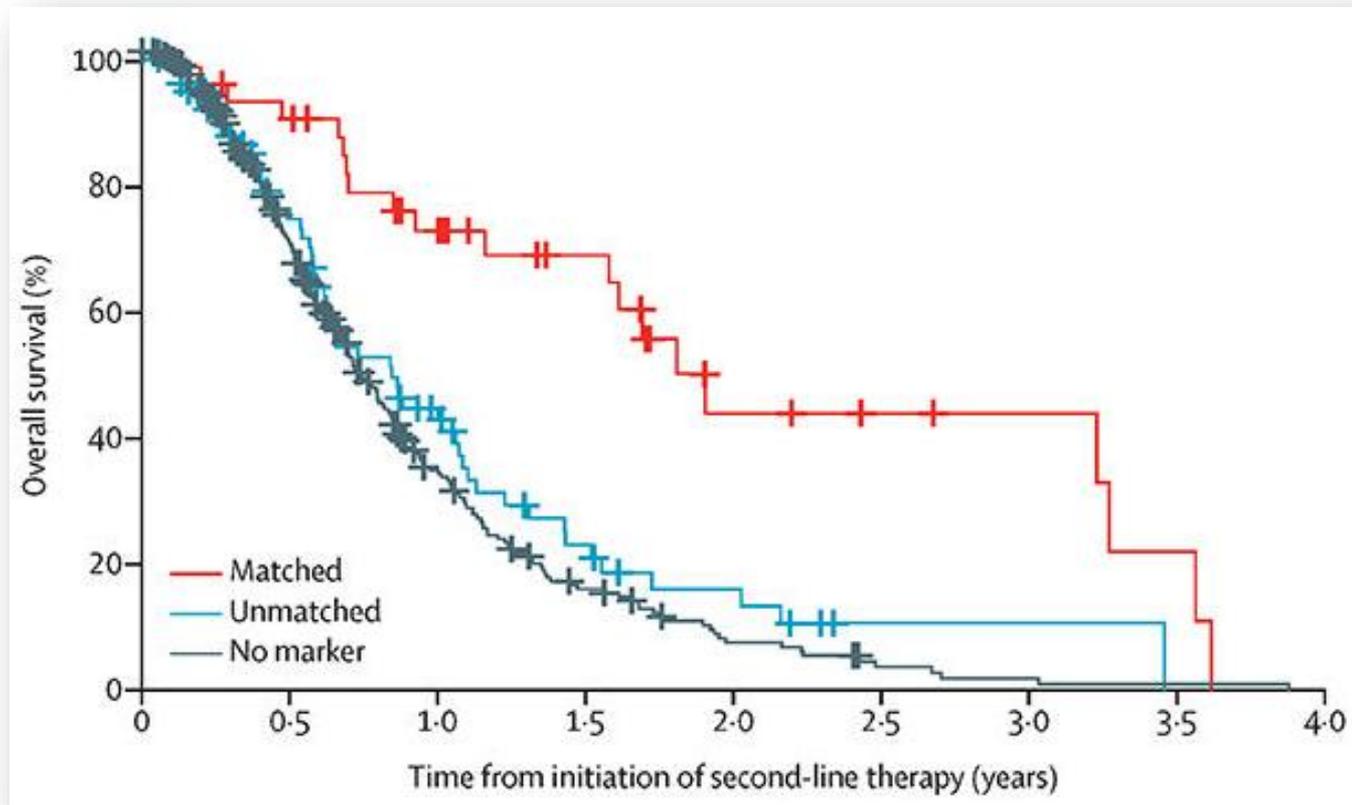
# Resultados IMPACT (2019)

- Alteración accionable en 37% de 3487 pacientes, cáncer avanzado o refractario



# Estudio "Know Your Tumor" (KYT)

- Análisis de 1.000 pacientes, cáncer de páncreas
- Mutaciones accionables en 26%



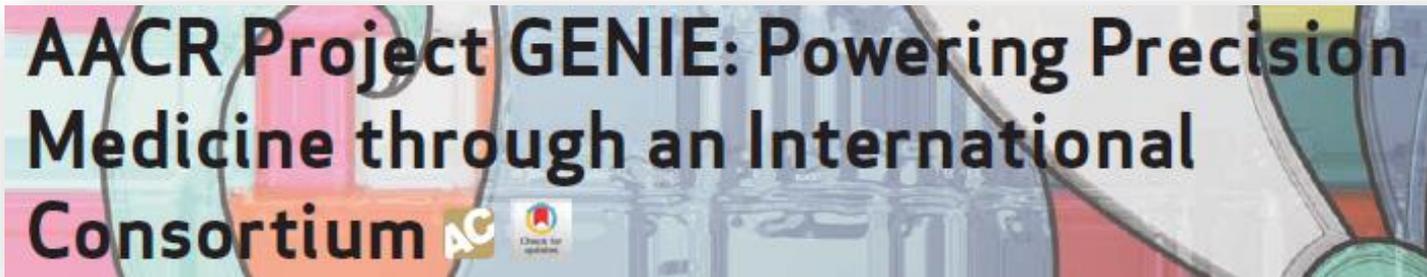
# Estudios Multicéntricos

**Effect of expanded genomic testing in lung adenocarcinoma (LUCA) on survival benefit: The Lung Cancer Mutation Consortium II (LCMC II) experience.**

- 16 Instituciones, 900 pacientes estadio IV
- Mutaciones en 8 genes, más amplificación y expresión génica en 5 genes

“Expanded tumor mutational analysis combined with targeted therapy in LUCA provides potential for patient benefit”

# Formación de Consorcio

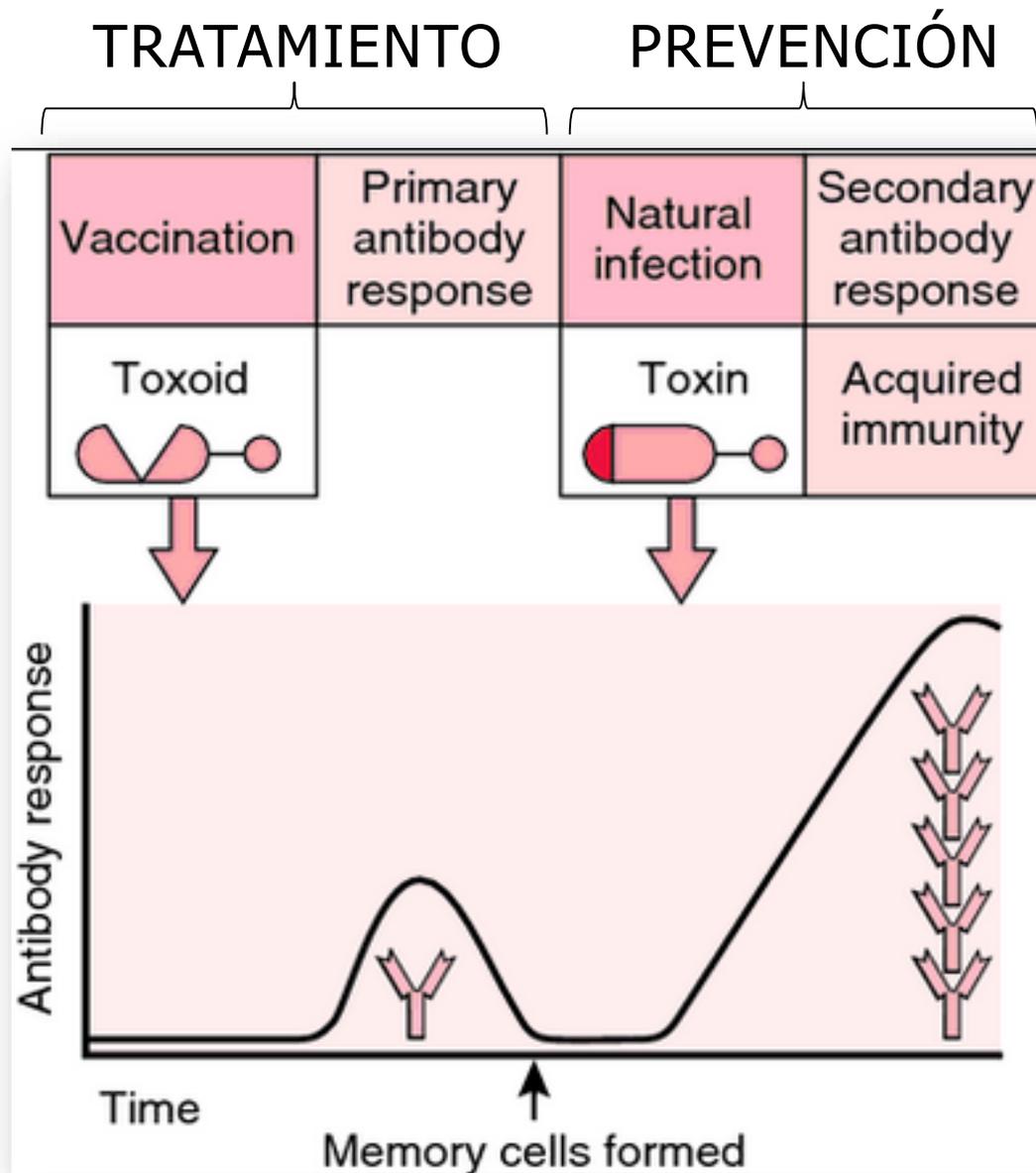


- Integración de datos (genómicos, clínicos)
- Acceso abierto, resultados de >39.000 pacientes (<https://www.aacr.org/professionals/research/aacr-project-genie/>)
- >100.000 pacientes en próximos 5 años

Center abbreviation	Center name
DFCI	Dana-Farber Cancer Institute, USA
GRCC	Institut Gustave Roussy, France
JHU	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, USA
MDA	The University of Texas MD Anderson Cancer Center, USA
MSK	Memorial Sloan Kettering Cancer Center, USA
NKI	Netherlands Cancer Institute, on behalf of the Center for Personalized Cancer Treatment, the Netherlands
UHN	Princess Margaret Cancer Centre, University Health Network, Canada
VICC	Vanderbilt-Ingram Cancer Center, USA

# Tratamientos Emergentes

# Vacunas



# Vacunas Aprobadas (FDA)

- 1 **Preventivas** (profilácticas): vacunación masiva, población sana
  - HPV (Gardasil, Gardasil 9: uso en mujeres y hombres; Cervarix: mujeres)
  - HBV (varias)
- 2 **Terapéuticas** (tratamiento): como parte del tratamiento contra el cáncer
  - Cáncer de próstata metastásico (Provenge)
- 3 **Vacunas en ensayos clínicos**  
(<https://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet>)

# También en Europa

## ORYX completes Phase I/IIa trial of MicOryx vaccine in MSH-H colorectal cancer patients

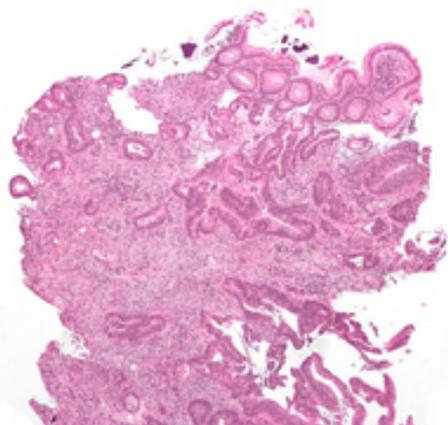
5 March 2015



Print



Email



German biotech firm ORYX has completed a Phase I/IIa trial of the therapeutic vaccine, MicOryx, to treat patients with advanced microsatellite instable (MSI-H-) colorectal cancer.

The open label, single centre trial included 22 patients (UICC stage III or IV), who had received standard chemotherapy.

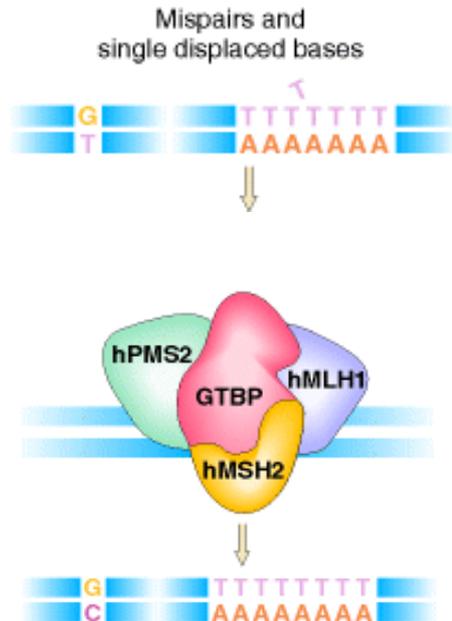
The trial's Phase I part evaluated safety and toxicity as the primary endpoint in six patients, while Phase IIa assessed the induction of cellular and humoral immune responses against MicOryx in 16 patients evaluated by CT or MRI scans according to RECIST.

- Total: 22 pacientes
- Bien tolerada, inducción de respuesta inmune humoral y celular

# Inestabilidad de Microsatélites (MSI)

- Fenotipo de hipermutabilidad genética
- Fallas en reparación de ADN: mismatch repair, MMR

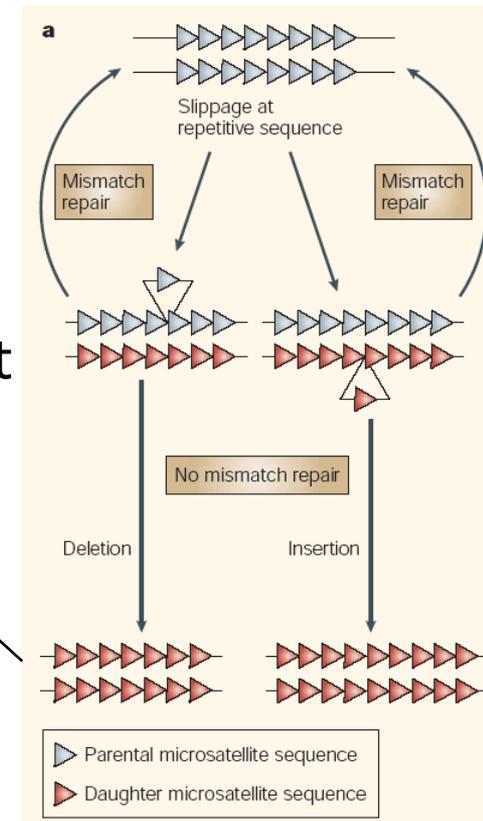
## Mismatch repair



(Frameshift peptides)

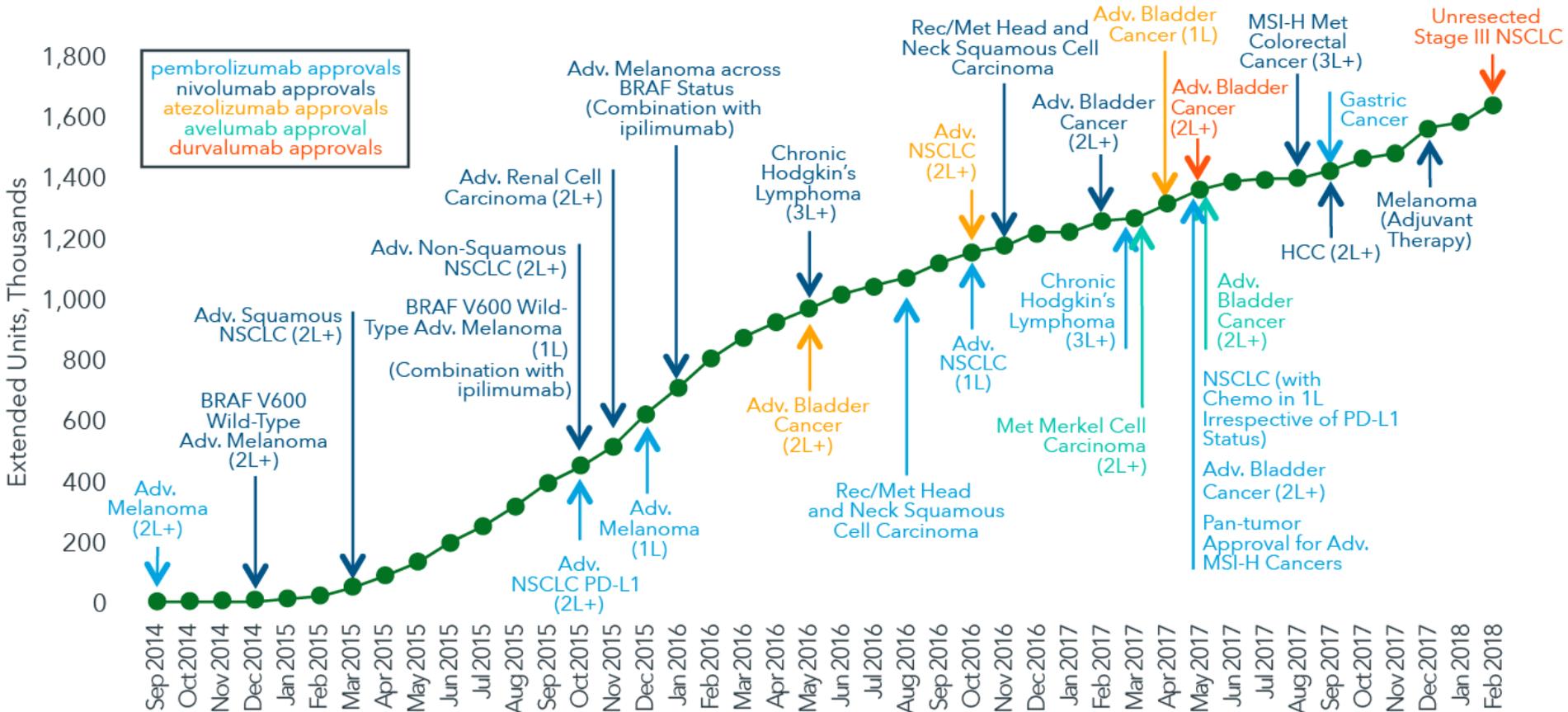
**FSP**

## MSI



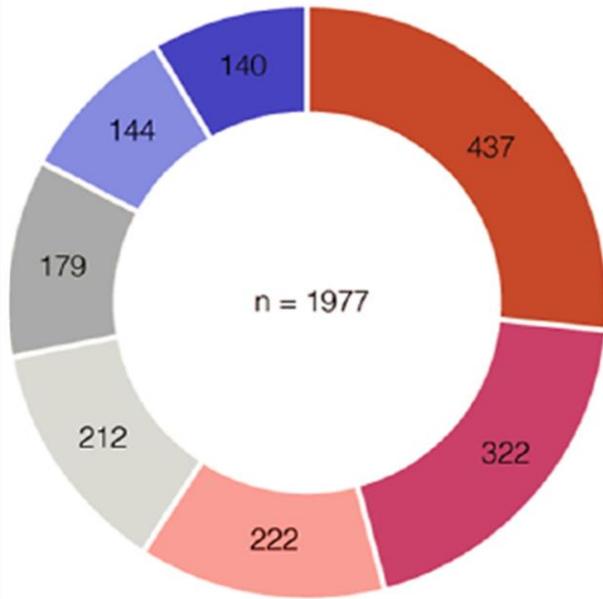
# Inmunoterapia: Aprobaciones

Immuno-Oncology PD-1 and PD-L1 Inhibitor Uptake in the United States



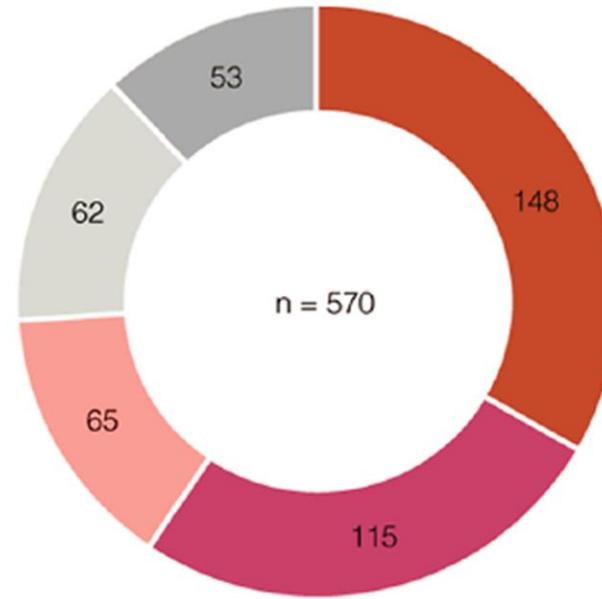
# Inmunoterapia: Estudios Clínicos 2019

Anti-PD-1-PD-L1 trials by cancer type



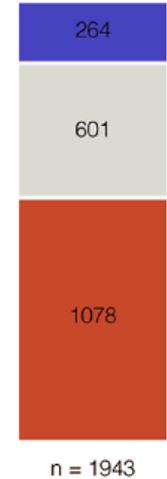
- Lung cancers
- GI cancers
- Melanoma
- HN cancers
- Urological cancers
- Breast cancers
- Lymphomas

CAR T cell trials by cancer type

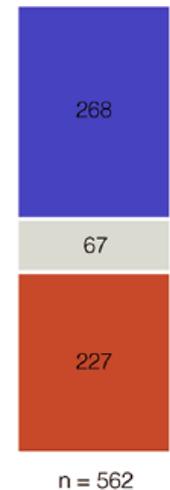


- B Cell lymphoma
- ALL
- CLL
- Multiple Myeloma
- GI cancers

Anti-PD-1-PD-L1 trials by region



CAR T cell trials by region

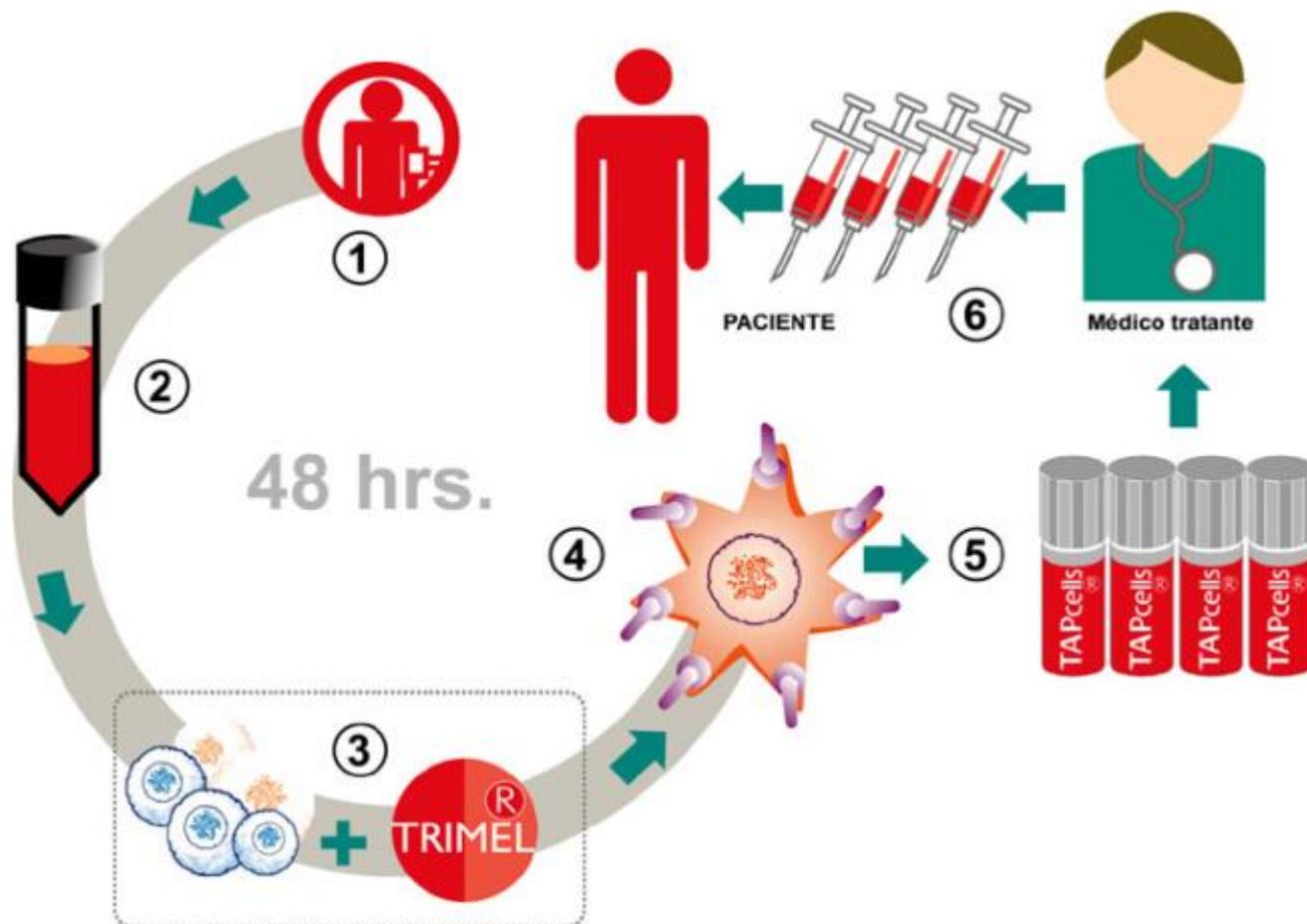


- USA
- Europe
- China

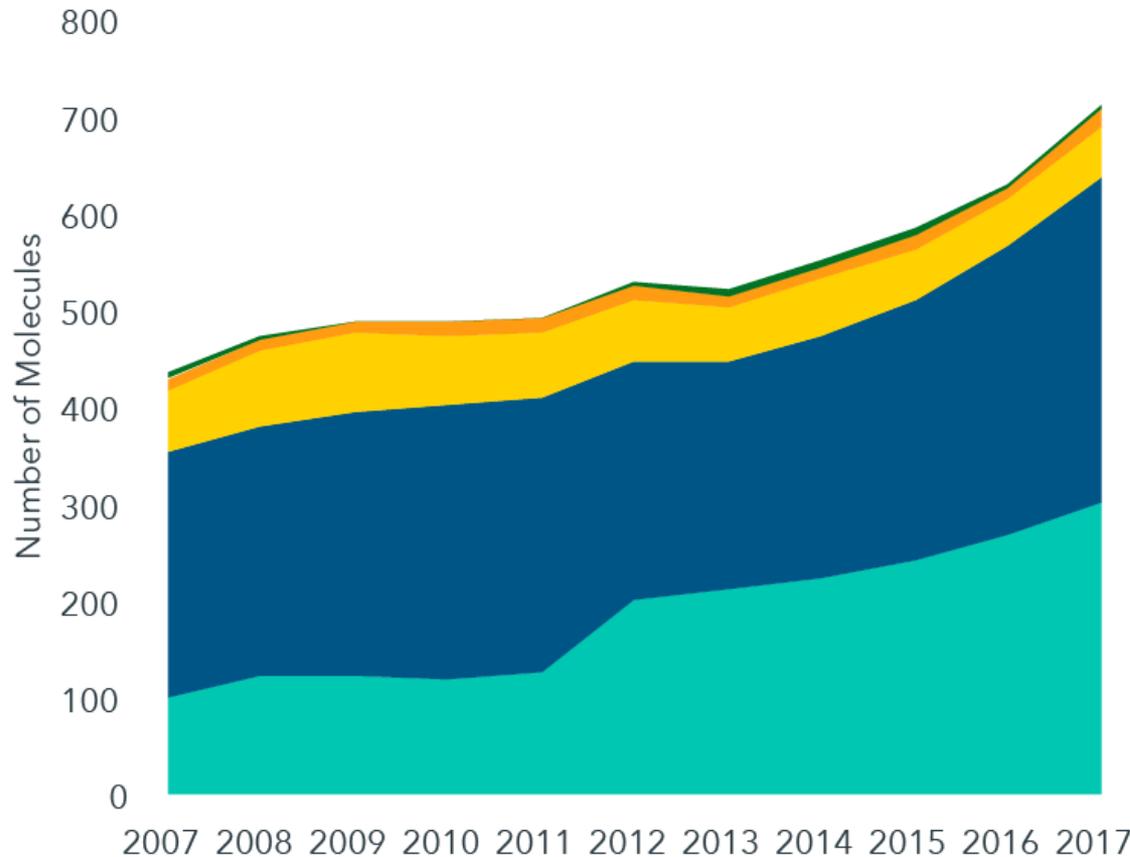
ClinicalTrials.gov

# Y en Chile

- TRIMEL (melanoma, cáncer de próstata): Extracto estandarizado de antígenos para inmunoterapia



# Nuevos tratamientos por categoría

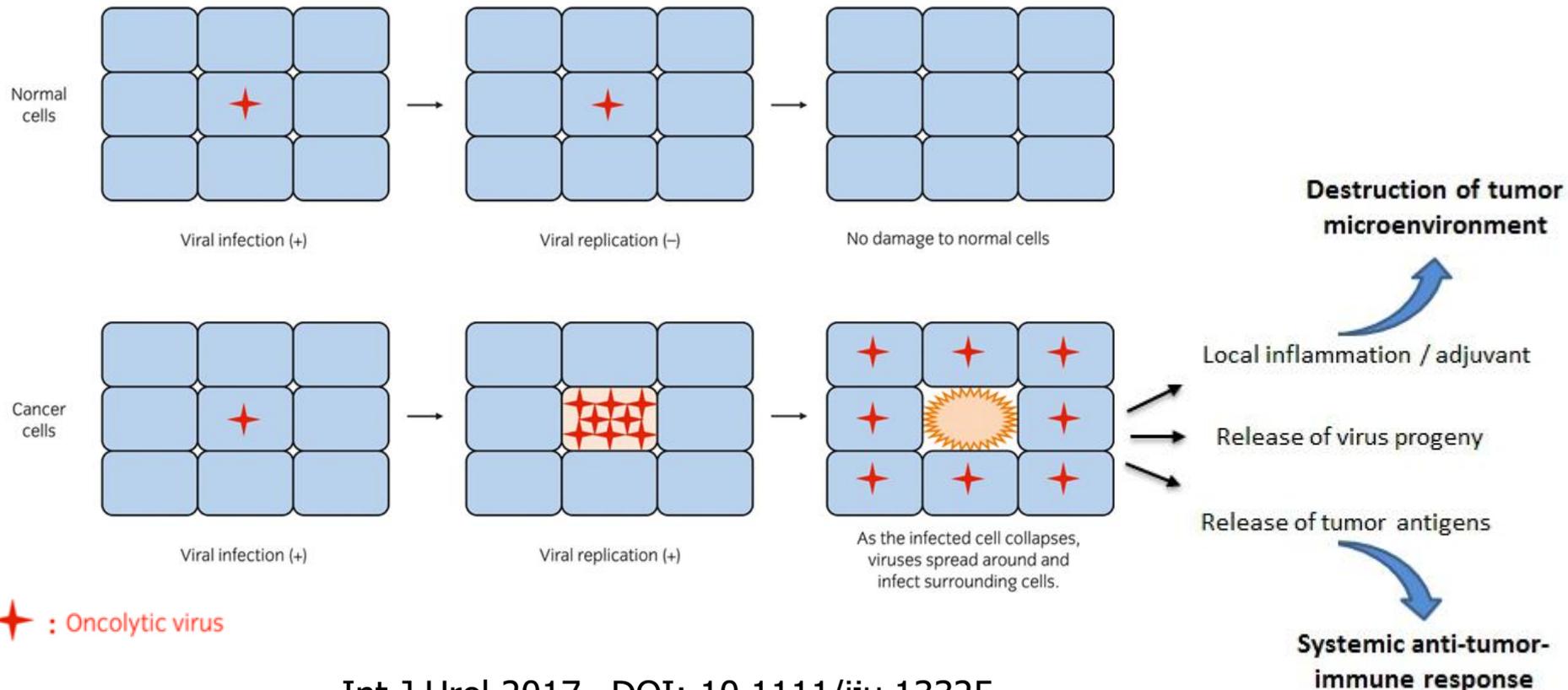


Year	2007 (434)	2017 (710)
Radiotherapies	0.9% (4)	0.4% (3)
Hormonals	3% (14)	2% (17)
Cytotoxics	15% (63)	8% (54)
Targeted Small Molecule	59% (254)	47% (335)
Targeted Biologics	23% (99)	42% (301)

Drogas en estado avanzado de desarrollo, período 2007 al 2017

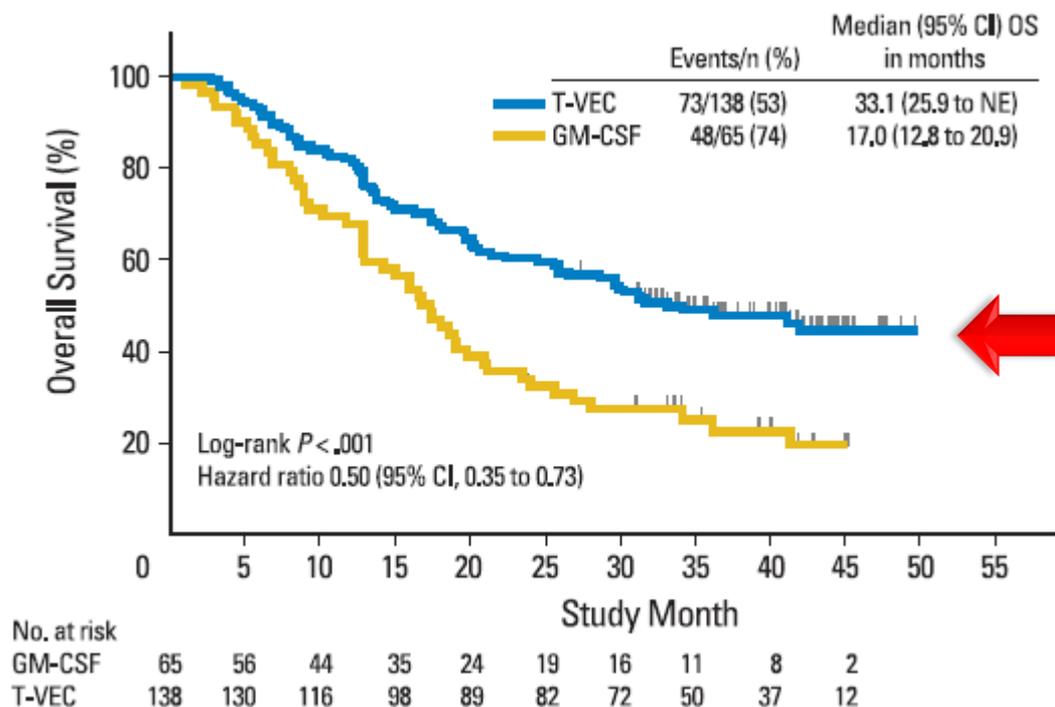
# Virus Oncolíticos

- Virus (naturales o modificados genéticamente)
- Replicación y lisis selectiva en células tumorales, sin efecto sobre las células normales



# T-Vec

- Derivado de herpes simplex tipo 1
- Produce GM-CSF: aumento de respuesta inmune sistémica anti-tumoral
- Estudio Fase III; Aprobada FDA 2015



T-Vec como terapia de primera línea (melanoma)

# Virus Oncolíticos en Desarrollo

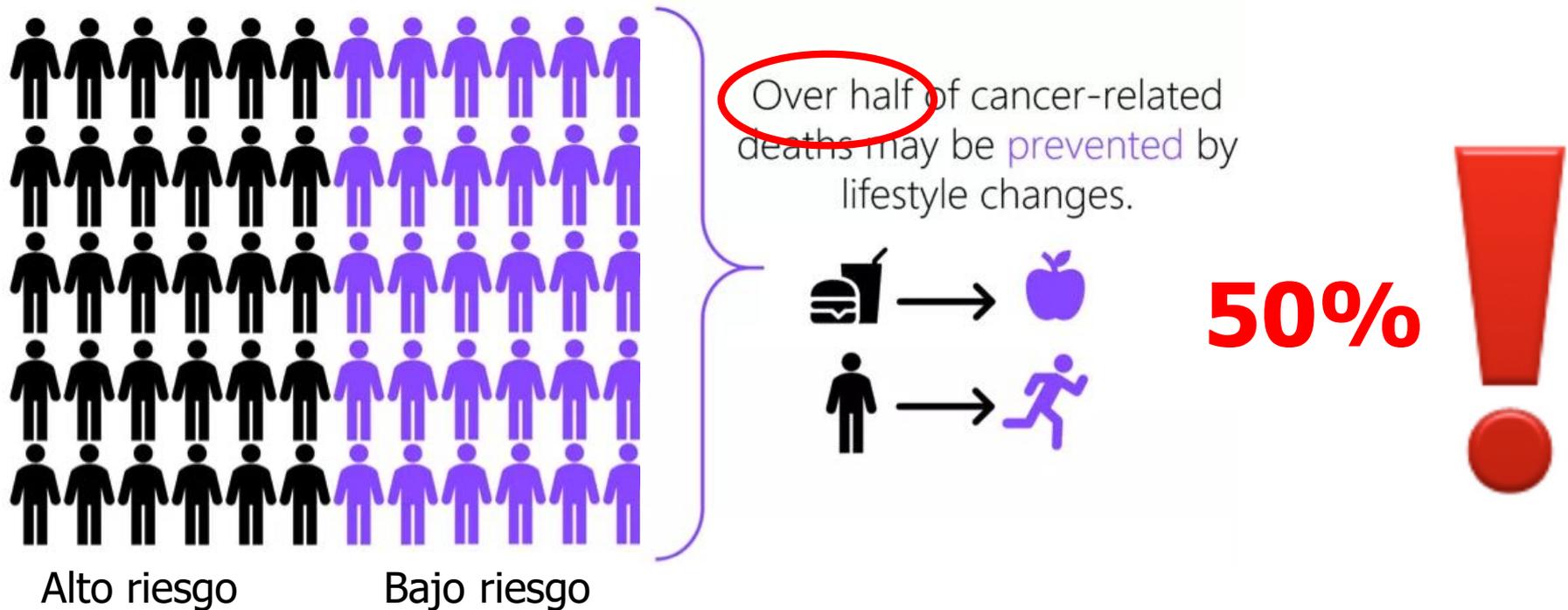
	Virus	Gene insertion	Target disease	Company	Status
T-Vec (Imlygic, talimogene laherparepvec)	HSV-1	Human GM-CSF	Unresected stage IIIB to IV melanoma	Amgen	The drug is approved in the USA in 2015 and in Europe in 2016
G47Δ	HSV-1	lacZ	Glioblastoma	Investigator-initiated	A phase II study started in 2015. It was designated as Sakigake breakthrough therapy by MHLW of Japan
JX-594 (Pexa-vec, pexastimogene devacirepvec)	Vaccinia virus	Human GM-CSF, lacZ	Advanced stage hepatocellular carcinoma	Sillajen	A phase III started in 2015
CG0070	Adenovirus	Human GM-CSF	Non-muscle invasive bladder cancer after BCG failure	Cold Genesys	A phase II/III randomized controlled trial is ongoing in patients with bladder cancer
Reolysin (pelareorep)	Reovirus		Metastatic and/or recurrent head and neck cancer	Oncolytics Biotech	A phase III is completed. It received an orphan drug designation from FDA

- Estudios Fase I o II en melanoma, glioma, páncreas, mama

# Prevención: Estrategias de Precisión

# Prevención

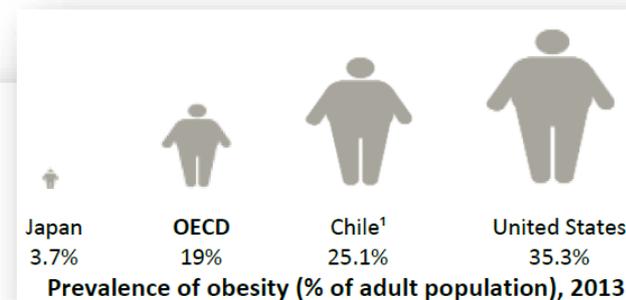
- Impacto de Prevención Primaria (población sana):  
Estudio prospectivo, 100.000 personas
- Hábitos, BMI (Índice Masa Corporal)



## Menores chilenos entre los cinco del planeta con más sobrepeso y obesidad

12/06/2017 - Cecilia Yáñez

Uno de cada tres niños y jóvenes tiene exceso de peso y el 10% de los menores de 20 años es obeso.



## Chile, entre los cinco países que más fuman en el mundo y el más bebedor de América



Según informe de la OMS, país lidera ranking de hábitos que provocan enfermedades no transmisibles como cáncer y diabetes.

Agosto 2015  Red de Salud UC • CHRISTUS 

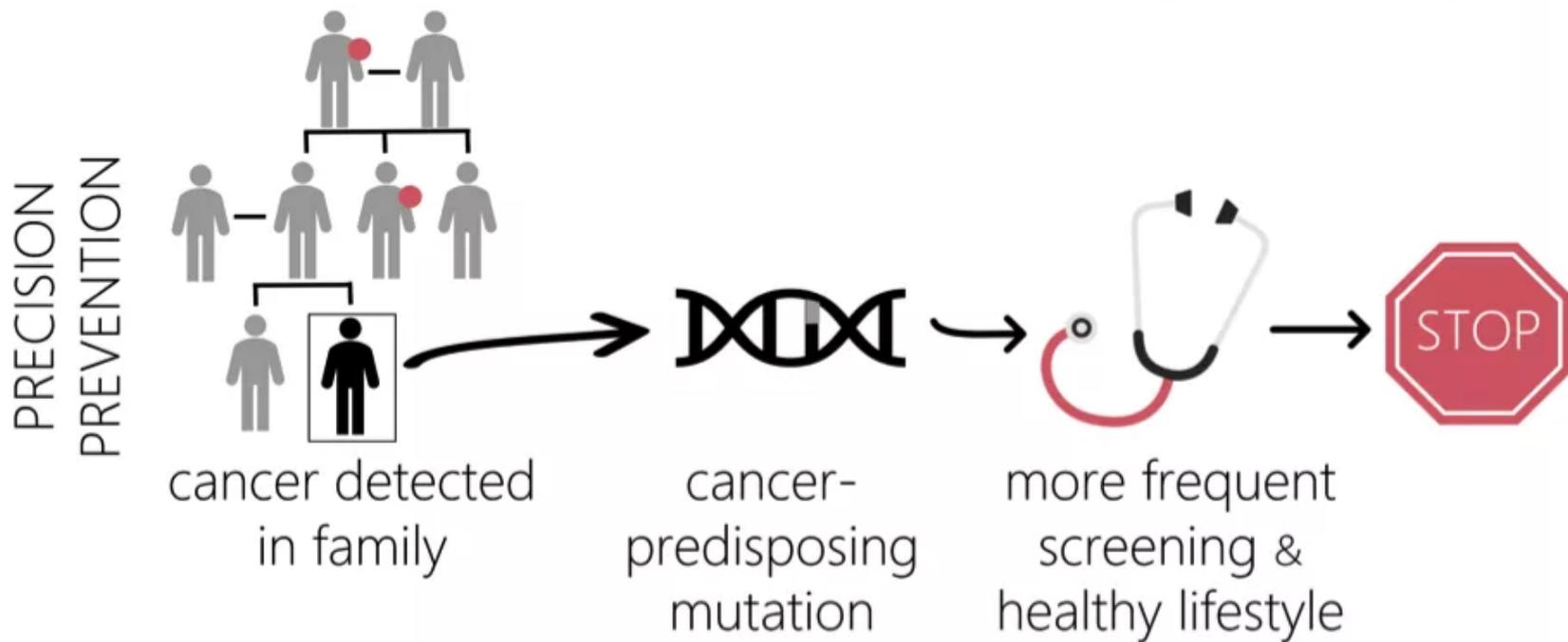
“Las adolescentes chilenas entre 13 y 15 años son actualmente las más fumadoras del mundo (según Tabaco Word Atlas, 2012) y las mujeres adultas chilenas son las más fumadoras de toda la región de las Américas.”

# Prevención de Precisión

Integrar:

- Estrategias de tamizaje («screening»)
- Minería de datos masivos (Big Data mining)
- Educación pública
- Creación de base de datos genómicos de pre-cáncer (Pre-Cancer Genome Atlas, **PCGA**): tumores y lesiones en estadíos tempranos
- Investigación, nuevas aplicaciones del conocimiento molecular
- Grupo de trabajo en Precision Prevention (iniciativa “Cancer Moonshot”)

# Prevencción de Precisión



# Generación y Manejo Masivo de Datos



# Tradicionalmente...

- Muchos estudios de investigación con pocos pacientes
- Heterogeneidad en la metodología y adquisición de datos, variables demográficas
- Datos poco comparables, meta-análisis en algunos casos
- Largos períodos para validación de los descubrimientos, aplicación clínica

# Actualmente...

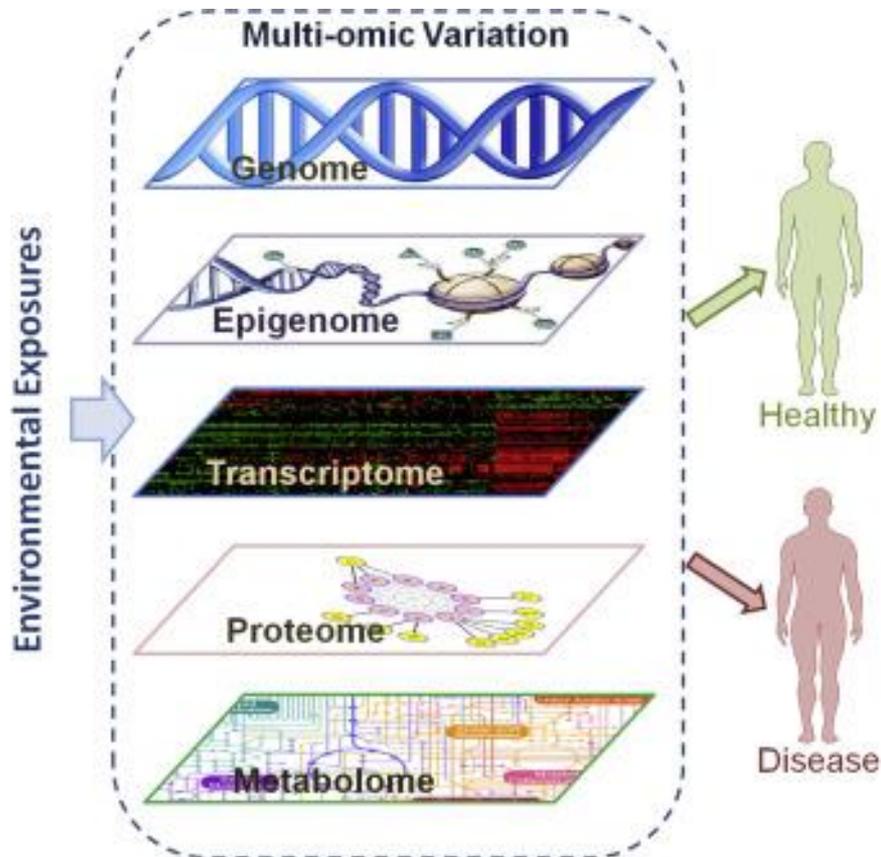
- Formación de consorcios, estudios con grandes poblaciones de pacientes (>5.000)
- Avance tecnológico: generación de gran cantidad de datos (p.ej. genoma completo) a precios cada vez más accesibles

## Desafíos:

- Requisito de especialistas para análisis de datos (bioinformáticos)
- Integración de datos (multi-omics)
- Espacio de almacenaje
- Temas éticos

# Multi-Omics

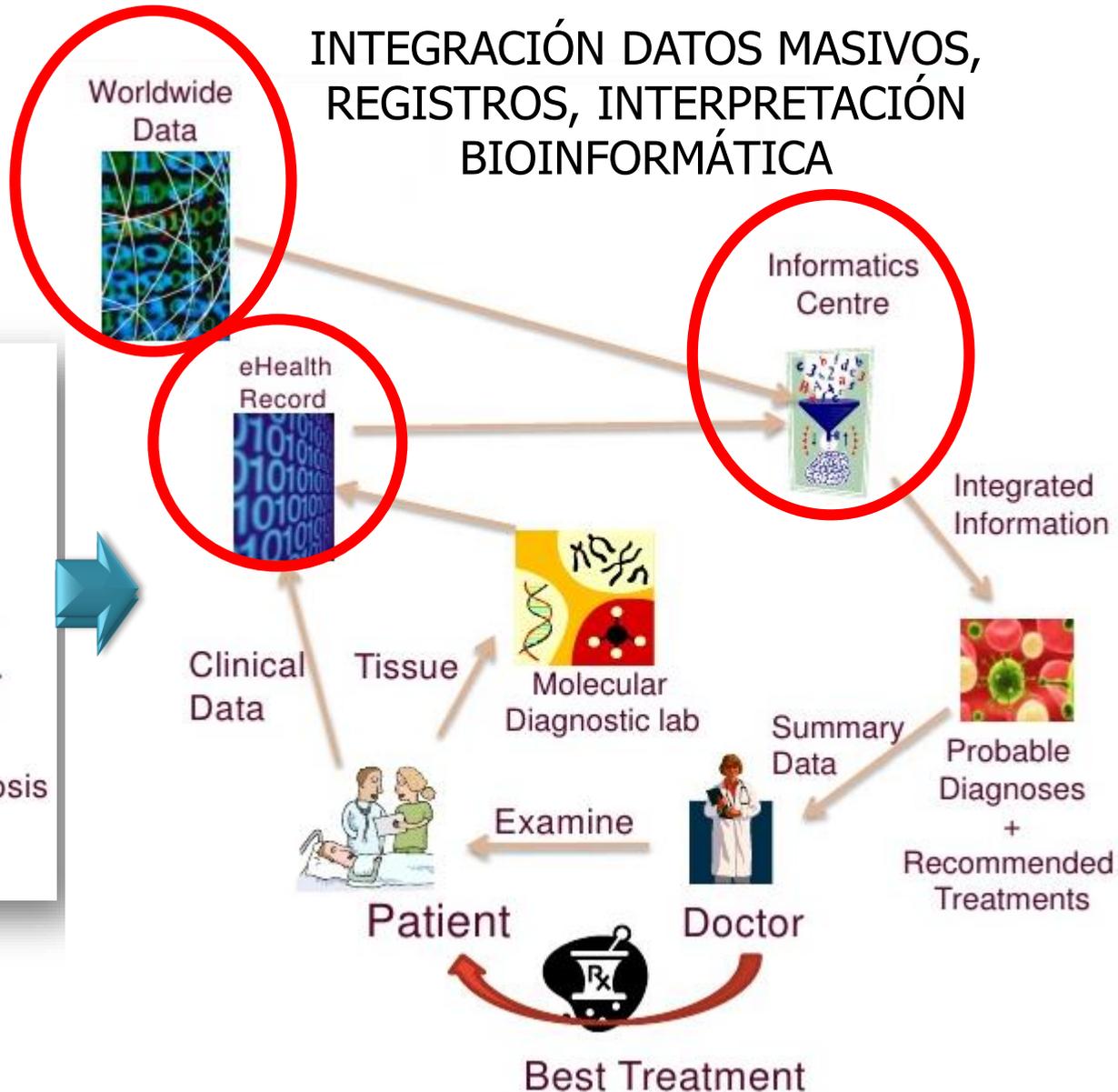
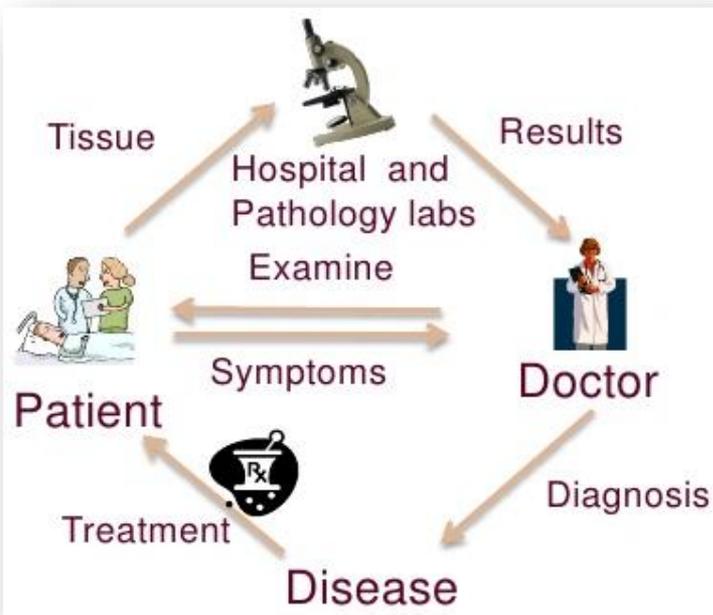
- Datos masivos obtenidos a través de diferentes tecnologías
- Integración de datos asociados a enfermedad



# Integración de Datos

INTEGRACIÓN DATOS MASIVOS,  
REGISTROS, INTERPRETACIÓN  
BIOINFORMÁTICA

TRADICIONAL



# Muchos Datos son Accesibles

- Repositorios virtuales («data cloud»)
- En 2014: **>1500** Bases de datos biológicas de acceso público
- The Cancer Genome Atlas (**TCGA**): datos moleculares de >11.000 pacientes, se han utilizado en >1000 estudios publicados
- International Cancer Genome Consortium (**ICGC**)
- **ONCOMINE**: datos de expresión génica (microarrays)



# Recursos “Big Data”

Project name	Lead institution(s)	Project URL
The Cancer Genome Atlas (TCGA)	National Cancer Institute National Human Genome Research Institute	<a href="http://cancergenome.nih.gov">cancergenome.nih.gov</a>
Therapeutically Applicable Research to Generate Effective Treatments (TARGET)	NCI Office of Cancer Genomics	<a href="http://ocg.cancer.gov/programs/target">ocg.cancer.gov/programs/target</a>
Clinical Proteomic Tumor Analysis Consortium (CPTAC)	NCI Office of Cancer Clinical Proteomics Research	<a href="http://proteomics.cancer.gov/programs/cptac">proteomics.cancer.gov/programs/cptac</a>
Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) Network	Department of Defense Department of Veterans Affairs National Cancer Institute	<a href="http://proteomics.cancer.gov/programs/apollo-network">proteomics.cancer.gov/programs/apollo-network</a>
The Cancer Imaging Archive (TCIA)	University of Arkansas for Medical Sciences NCI Division of Cancer Treatment and Diagnosis	<a href="http://www.cancerimagingarchive.net">www.cancerimagingarchive.net</a>
Genomic Data Commons (GDC)	NCI Center for Cancer Genomics	<a href="http://gdc.cancer.gov">gdc.cancer.gov</a>
Database of Genotypes and Phenotypes (dbGaP)	National Center for Biotechnology Information	<a href="http://www.ncbi.nlm.nih.gov/gap">www.ncbi.nlm.nih.gov/gap</a>
NCI Cloud Resources	National Cancer Institute	<a href="http://cbiit.cancer.gov/cloudresources">cbiit.cancer.gov/cloudresources</a>
Broad FireCloud	Broad Institute	<a href="http://firecloud.org">firecloud.org</a>
Institute for Systems Biology Cancer Genomics Cloud (ISB-CGC)	Institute for Systems Biology	<a href="http://isb-cgc.org">isb-cgc.org</a>
Seven Bridges Cancer Genomics Cloud (SB-CGC)	Seven Bridges	<a href="http://www.cancergenomicscloud.org">www.cancergenomicscloud.org</a>
NCI Cancer Research Data Commons	National Cancer Institute	<a href="http://cbiit.cancer.gov/cancerdatacommons">cbiit.cancer.gov/cancerdatacommons</a>

*NCI-supported projects annotated with lead institutions and URLs.*

# Recursos en la Web

- También hay aplicaciones de acceso público, para análisis de datos

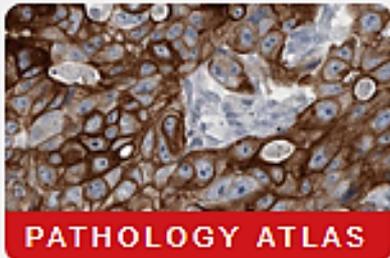
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Name	Main features
CGHub	Comprehensive data repository; huge data size
EGA	Comprehensive data repository; huge data size
COSMIC	Largest somatic mutation database; genome sequencing paper curation
CPRG	Interface for cancer program resources
GDAC	Data analysis; automatic pipelines; user-friendly reports
SNP500Cancer	Sequence and genotype verification of SNPs
canEvolve	Comprehensive analysis of tumor profile; Data from 90 studies involving more than 10,000 patients
MethyCancer	Relationship among DNA methylation, gene expression and cancer
SomamiR	Correlation between somatic mutation and microRNA; genome-wide displaying
cBioPortal	Graphical summaries; gene alteration; processed data; visualization
UCSC Cancer Genomics Browser	Clinical information; gene expression; copy number variation; visualization
CGWB	Visualization; gene mutation and variation; automated analysis pipeline
GDSC	Drug sensitivity information; drug response information
canSAR	Multidisciplinary information; drug discovery
NONCODE	ncRNAs; lncRNAs; up-to-date and comprehensive resource

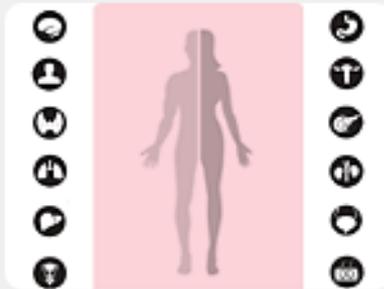
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# Datos + Análisis

## THE HUMAN PROTEIN ATLAS



The **Pathology Atlas** contains mRNA and protein expression data for the most common forms of human cancer. Correlation analyses based on mRNA expression levels of human genes in cancer tissue and the clinical outcome for almost 8000 corresponding cancer patients is presented in a gene-centric manner, and includes more than 18000 Kaplan-Meier plots with high significance ( $p < 0.001$ ). In addition, immunohistochemistry (IHC) analysis using a tissue microarray (TMA)-based analysis of the corresponding proteins in patients with the respective cancer types is presented for a majority of the protein-coding genes. More than 5 million IHC cancer tissue images are included in the atlas, showing protein expression levels for individual tumors of each cancer type.



To explore the Pathology Atlas and the prognostic genes in the 17 different cancer types, go to the [cancer-specific knowledge-based chapters](#).

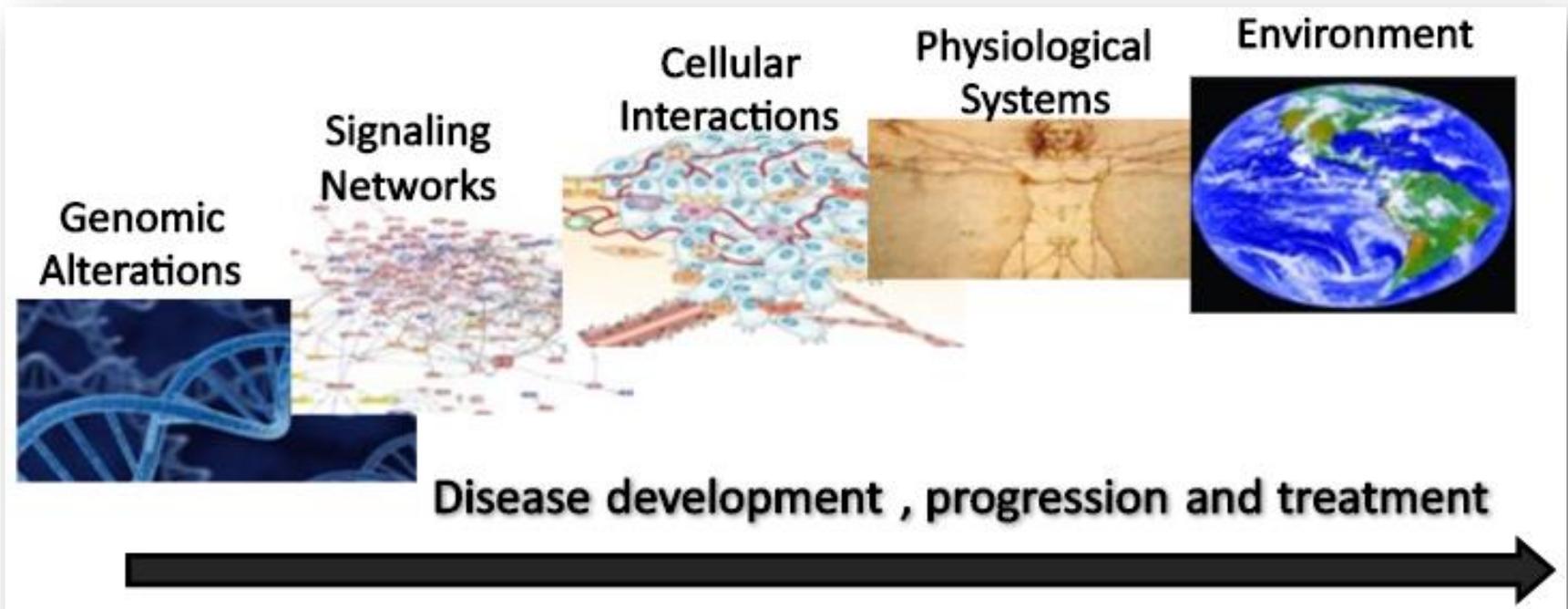
More information is available in the [Assays and annotation](#) section and on the [Cancer Proteome](#) pages.

The data in the Pathology Atlas is based on the integration of publicly available data from The Cancer Genome Atlas (TCGA) and data generated within the framework of the Human Protein Atlas (HPA).

<https://www.proteinatlas.org/pathology>

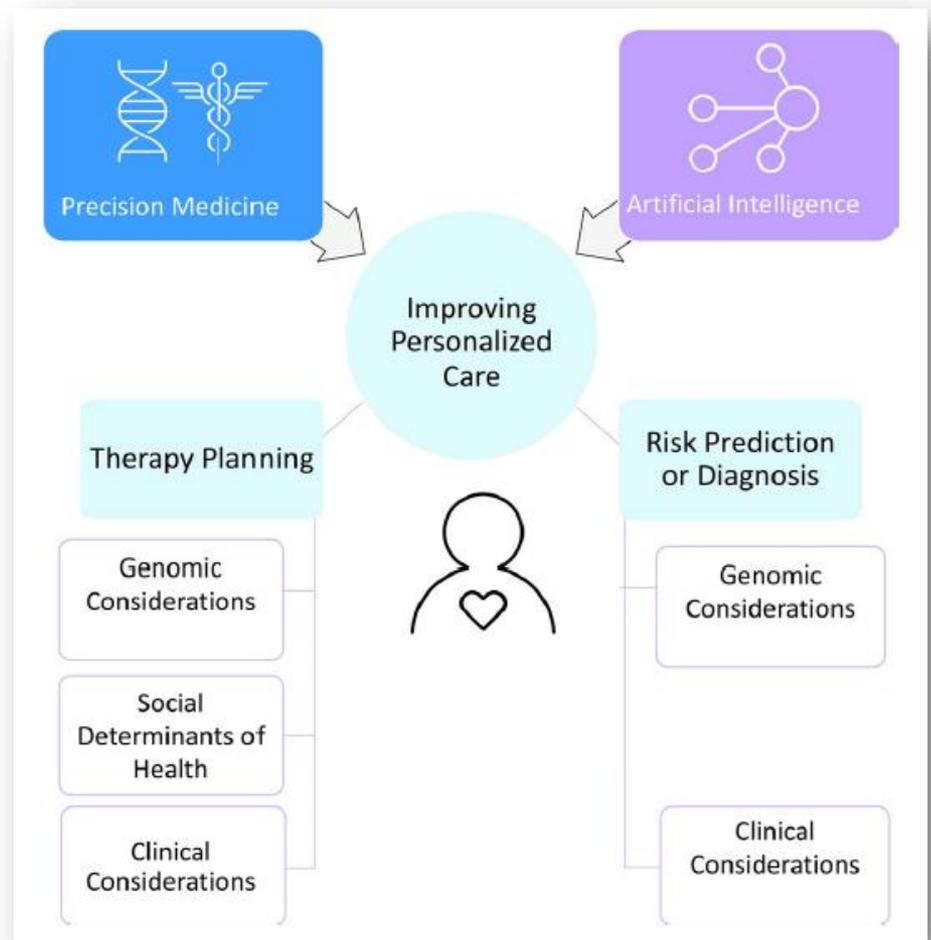
# NCI Cancer Systems Biology Consortium

- Integración de datos para generar modelos computacionales predictivos
- Aplicación de modelos de biología de sistemas: estrategia multidisciplinaria (físicos, matemáticos, ingenieros, bioinformáticos)



# Y en un Futuro Cercano...

- Alta complejidad y potencial de interacciones biológicas se abordarán con estrategias de inteligencia artificial
- Medicina de precisión
- Prevención



# Herramientas Bioinformáticas: Clínica

## **Cancer Genome Interpreter**

- Interpretación automatizada de variantes génicas (secuenciación genómica de tumores), relación con respuesta a terapia  
(<http://www.cancergenomeinterpreter.org>)

Tamborero et al 2018. <https://doi.org/10.1186/s13073-018-0531-8>

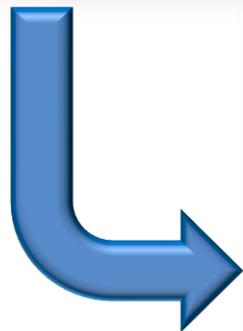
## **MTB Report**

- Método automatizado para selección de terapias en base a alteraciones genéticas de un tumor

Perera-Bel et al, 2018. <https://doi.org/10.1186/s13073-018-0529-2>

# Variantes/mutaciones ⇒ Terapia

Resource	Variant Type	URL
dbSNP <sup>a</sup>	Germline and somatic	<a href="https://www.ncbi.nlm.nih.gov/projects/SNP/">https://www.ncbi.nlm.nih.gov/projects/SNP/</a>
COSMIC <sup>a</sup>	Somatic	<a href="http://cancer.sanger.ac.uk/cosmic">http://cancer.sanger.ac.uk/cosmic</a>
ClinVar <sup>a</sup>	Germline predisposition and somatic	<a href="https://www.ncbi.nlm.nih.gov/clinvar/intro/">https://www.ncbi.nlm.nih.gov/clinvar/intro/</a>
gnomAD <sup>b</sup>	Germline	<a href="http://gnomad.broadinstitute.org/">http://gnomad.broadinstitute.org/</a>
69 genomes from CGI <sup>c</sup>	Germline	<a href="http://www.completegenomics.com/public-data/69-genomes/">http://www.completegenomics.com/public-data/69-genomes/</a>
Personalized Genome Project	Germline	<a href="http://www.personalgenomes.org/">http://www.personalgenomes.org/</a>
NCI Genomic Data Commons	Germline and somatic	<a href="https://portal.gdc.cancer.gov/">https://portal.gdc.cancer.gov/</a>
cBioPortal	Somatic	<a href="http://www.cbioportal.org">http://www.cbioportal.org</a>
Intogen (Partial TCGA dataset)	Somatic	<a href="https://www.intogen.org/search">https://www.intogen.org/search</a>
Pediatric Cancer Genome Project	Somatic	<a href="http://explorepcgp.org">http://explorepcgp.org</a>



Resource	URL
myvariant.info <sup>a</sup>	<a href="http://myvariant.info/">http://myvariant.info/</a>
CIViC <sup>a</sup>	<a href="https://civic.genome.wustl.edu/home">https://civic.genome.wustl.edu/home</a>
DGIdb <sup>a</sup>	<a href="http://dgidb.genome.wustl.edu/">http://dgidb.genome.wustl.edu/</a>
Cancer Genome Interpreter <sup>a</sup>	<a href="https://www.cancergenomeinterpreter.org/home">https://www.cancergenomeinterpreter.org/home</a>
Oncokb <sup>a</sup>	<a href="http://oncokb.org/">http://oncokb.org/</a>
Cancer Driver Log	<a href="https://candl.osu.edu/">https://candl.osu.edu/</a>
Clinical Knowledge Base	<a href="https://www.jax.org/clinical-genomics/clinical-offerings/ckb">https://www.jax.org/clinical-genomics/clinical-offerings/ckb</a>
My Cancer Genome	<a href="http://www.mycancergenome.org">http://www.mycancergenome.org</a>
Personalized Cancer Therapy	<a href="https://pct.mdanderson.org">https://pct.mdanderson.org</a>
PharmGKB	<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>
Precision Medicine Knowledge Base (Beta)	<a href="https://pmkb.weill.cornell.edu/">https://pmkb.weill.cornell.edu/</a>

# Accesibilidad de Datos

- Apoyo para interpretación de datos, selección de terapias de precisión
- Plataformas abiertas, o para miembros (costo!)
- Convergencia hacia standards comunes

**TABLE 1** | Summary of publicly available precision oncology knowledgebases.

Knowledgebase	Variant annotation	Drug availability	Trial matching	Literature citation	Website
CGI	Yes	Yes	No	Yes	<a href="http://www.cancergenomeinterpreter.org/">www.cancergenomeinterpreter.org/</a>
CIVIC	Yes	Yes	No	Yes	<a href="https://civicdb.org">https://civicdb.org</a>
DEPO	Yes	Yes	No	Yes	<a href="http://depo-dinglab.ddns.net/">http://depo-dinglab.ddns.net/</a>
HemOnc.org	Yes	Yes	No	Yes	<a href="http://www.hemonc.org/">www.hemonc.org/</a>
JAX CKB <sup>+</sup>	Yes	Yes	Yes*	Yes	<a href="https://ckb.jax.org/">https://ckb.jax.org/</a>
MCG	Yes	Yes	Yes	No	<a href="https://www.mycancergenome.org/">https://www.mycancergenome.org/</a>
OncokB	Yes	Yes	No	Yes	<a href="https://oncokb.org/">https://oncokb.org/</a>
PCT	Yes	Yes	Yes	Yes	<a href="https://pct.mdanderson.org/">https://pct.mdanderson.org/</a>
PMKB	Yes	Yes	No	Yes	<a href="https://pmkb.weill.cornell.edu/">https://pmkb.weill.cornell.edu/</a>
<b>Drug-associated knowledgebases</b>					
Genomics of drug sensitivity in cancer	Yes	Yes	No	No	<a href="https://www.cancerrxgene.org/">https://www.cancerrxgene.org/</a>
PharmGKB	Yes	Yes	No	No	<a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a>
Therapeutic target database	Yes	Yes	No	Yes	<a href="http://db.idrblab.net/ttd/">http://db.idrblab.net/ttd/</a>

\*Available only with subscription to CKB BOOST. <sup>+</sup>Partially publicly available databases.

# Chile: Iniciativas

- Laboratorio Diagnóstico Molecular Clínica Alemana  
(<https://portal.alemana.cl/wps/wcm/connect/Internet/Home/innovacion-y-avances/2018/05/clinica-alemana-inauguro-nuevo-laboratorio-de-diagnostico-molecular>)
- FALP: Laboratorio Diagnóstico Molecular (2018)  
(<https://falp.emol.com/pdfs/103.pdf>)
- Programa Chile Genómico  
(<http://www.chilegenomico.cl/proyecto-chilegenomico-2/>)
- Convenio Roche y Univ. de Concepción  
(<https://cienciasbiologicasudec.cl/farmaceutica-roche-y-universidad-de-concepcion-firman-convenio-para-promover-el-desarrollo-de-investigacion/>)

# Resumen

- La medicina de precisión podría mejorar respuestas y sobrevida de pacientes con cáncer
- Necesidad de validar modelos, terapias
- Evaluación masiva de datos, manejo bioinformático
- Aplicación requiere estrategia interdisciplinaria, infraestructura y tecnología, personal calificado
- Costos de implementación?
- Masificación?

**Think Big**

**Act Small**