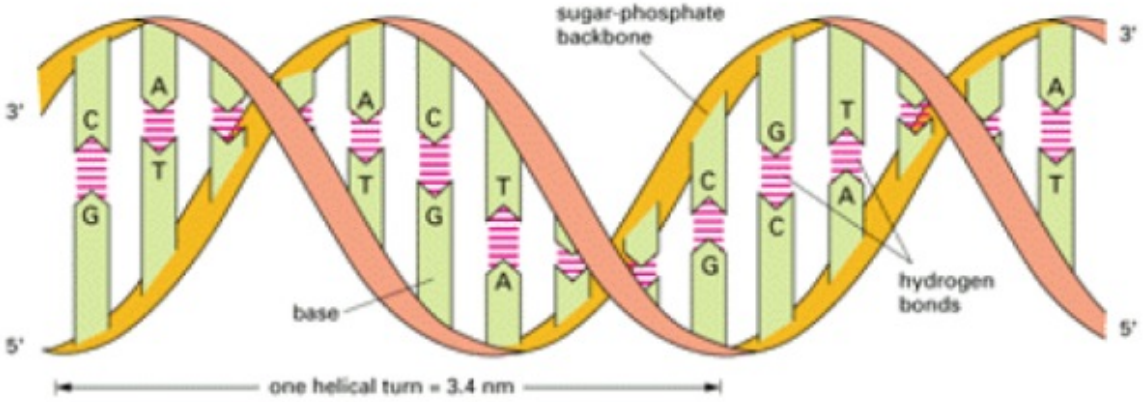
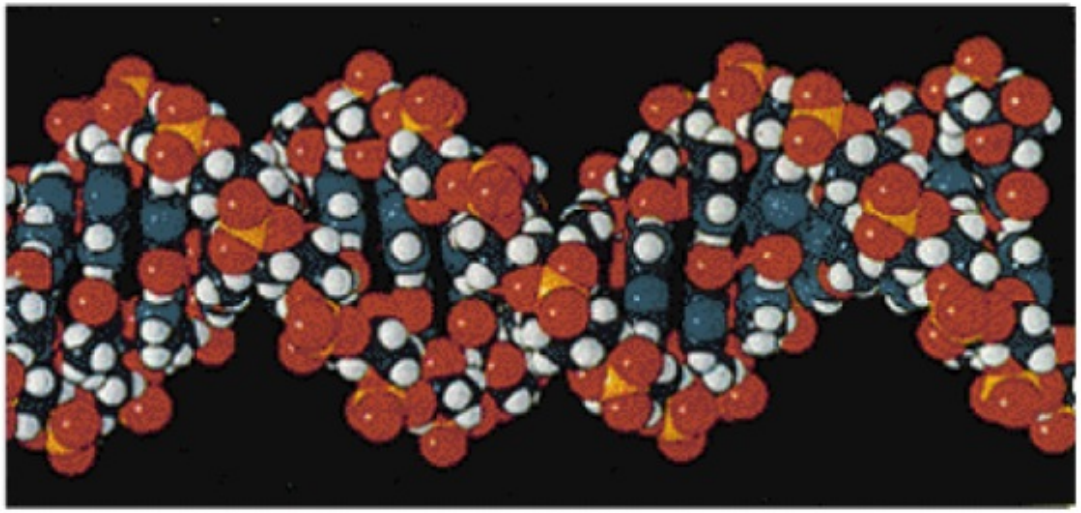
DNA DOUBLE HELIX

In a DNA molecule two antiparallel strands that are complementary in their nucleotide sequence are paired in a right-handed double helix with about 10 nucleotide pairs per helical turn. A schematic representation (*top*) and a space-filling model (*bottom*) are illustrated here.





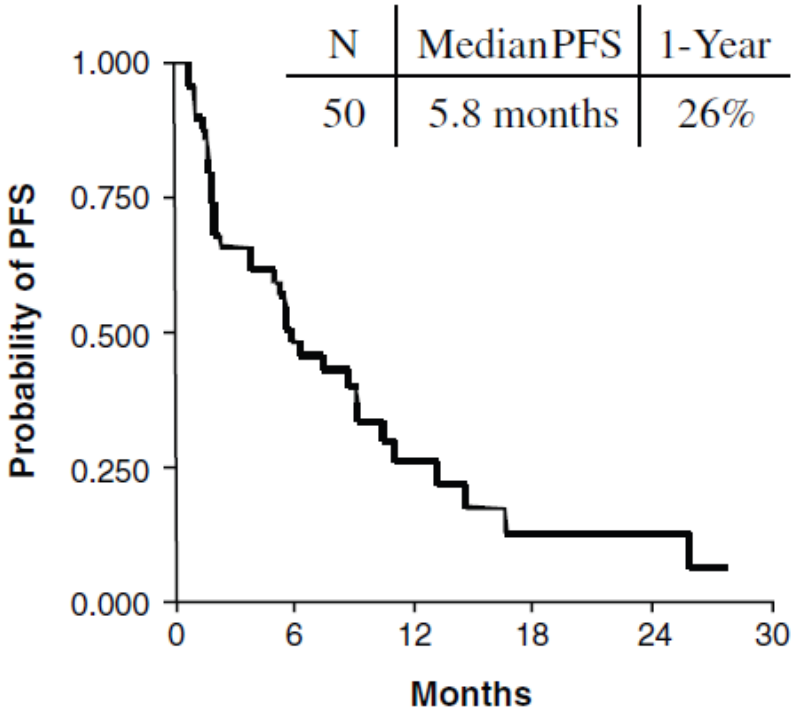
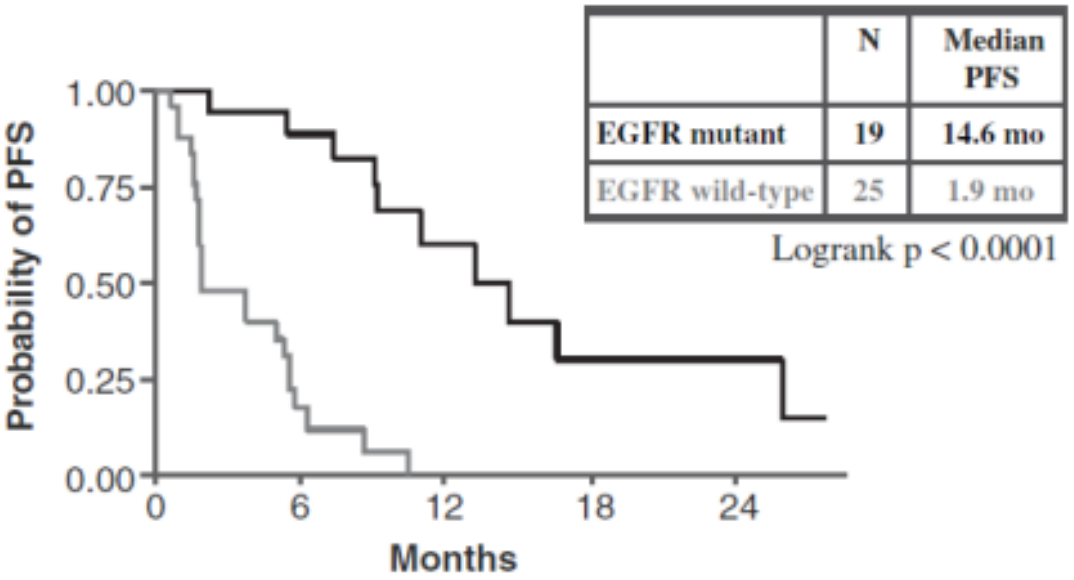


FIGURE 1a Clinically enriched patients. Non-smoking women with a particular type of lung cancer are more likely to respond to erlotinib or gefitinib than other patients with lung cancer. Patients meeting these clinical characteristics have a median progression-free survival (PFS) of about 6 months.
SOURCES: Johnson presentation (June 8, 2009); Bruce Johnson and David Jackman, Dana-Farber Cancer Institute.



	N	Median PFS
EGFR mutant	**19**	**14.6 mo**
EGFR wild-type	25	1.9 mo

Logrank $p < 0.0001$

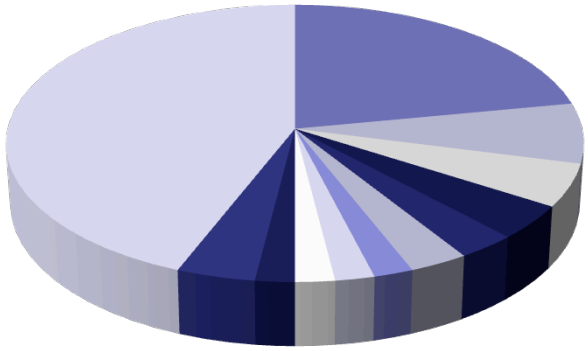
FIGURE 1b Genomically defined patients. Median progression-free survival (PFS) was nearly 15 months in individuals with lung cancer and epidermal growth factor receptor (EGFR) mutations that predict response to erlotinib, versus only about 2 months in individuals without these mutations.
SOURCES: Johnson presentation (June 8, 2009); Bruce Johnson and David Jackman, Dana-Farber Cancer Institute.

Category of genomic alteration	Exemplary cancer gene	Cancer	Targeted therapeutic agent
Translocation/fusion	*BCR-ABL*	CML	Imatinib, dasatinib, nilotinib
	PML-RARα	Acute promyelocytic leukemia	All-trans retinoic acid (ATRA)
	EML4-ALK	Breast, colorectal, lung	Crizotinib (phase III), foretinib (phase II)
	FIP1L1-PDGFR	Chronic eosinophilic leukemia	Imatinib
Amplification	*EGFR*	Lung, colorectal, glioblastoma, pancreatic	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	ErbB2	Breast, ovarian	Trastuzumab, lapatinib
	KIT	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	SRC	Sarcoma, CML, ALL	Dasatinib
	PIK3CA	Breast, ovarian, colorectal, endometrial...	PI3-kinase inhibitors, none approved; experimental: LY294002
Point mutation	*EGFR*	Lung, glioblastoma	Cetuximab, gefitinib, erlotinib, panitumumab, lapatinib
	KIT	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	PDGFR	GISTs, glioma, HCC, RCC, CML	Imatinib, nilotinib, sunitinib, sorafenib
	BRAF	Melanoma, pediatric astrocytoma	PLX4032 (phase III)
	MET	Lung	Cresatinib (phase III), foretinib (phase II)
	KRAS	Colorectal, pancreatic, GI tract, lung...	Resistance to erlotinib, cetuximab (colorectal)
	RAS/RAF	CTCL	Selumetinib (phase II)
	PTEN (mTOR)	Endometrial, prostate, NSCLC, renal	Ridaforolimus, temsirolimus, everolimus
	PI3K/Akt (mTOR)	Endometrial, prostate, NSCLC, renal	Ridaforolimus, temsirolimus, everolimus
	PTCH1, SMO (Hedgehog)	Basal cell carcinoma	GDC-0449 (vismodegib) (phase II)
Genotype	*VEGF-2578*	Breast	Bevacizumab
	VEGF-1154	Breast	Bevacizumab

The Cancer Gene Census is a catalogue of genes for which mutations have been causally implicated in cancer. Currently, more than 1% of all human genes are implicated via mutation in cancer. Approximately 90% have somatic mutations in cancer, 20% bear germline mutations that predispose to cancer and 10% show both somatic and germline mutations.

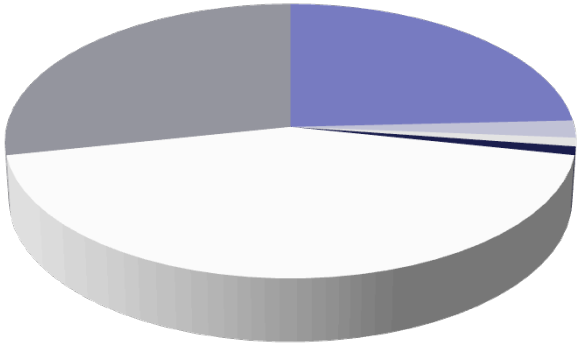
Symbol	Name	GeneID	Chr	Chr Band	Cancer Somatic Mut	Cancer Germline Mut
ABL1	v-abl Abelson murine leukemia viral oncogene homolog 1	25	9	9q34.1	yes	
ABL2	v-abl Abelson murine leukemia viral oncogene homolog 2	27	1	1q24-q25	yes	
ACSL3	acyl-CoA synthetase long-chain family member 3	2181	2	2q36	yes	
AF15Q14	AF15q14 protein	57082	15	15q14	yes	
AF1Q	ALL1-fused gene from chromosome 1q	10962	1	1q21	yes	
AF3p21	SH3 protein interacting with Nck, 90 kDa (ALL1 fused gene from 3	51517	3	3p21	yes	
AF5q31	ALL1 fused gene from 5q31	27125	5	5q31	yes	
AKAP9	A kinase (PRKA) anchor protein (yotiao) 9	10142	7	7q21-q22	yes	
AKT1	v-akt murine thymoma viral oncogene homolog 1	207	14	14q32.32	yes	
AKT2	v-akt murine thymoma viral oncogene homolog 2	208	19	19q13.1-q13.2	yes	
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	217	12	12q24.2	yes	
ALK	anaplastic lymphoma kinase (Ki-1)	238	2	2p23	yes	yes
ALO17	KIAA1618 protein	57714	17	17q25.3	yes	
APC	adenomatous polyposis of the colon gene	324	5	5q21	yes	yes
ARHGEF12	RHO guanine nucleotide exchange factor (GEF) 12 (LARG)	23365	11	11q23.3	yes	
ARHH	RAS homolog gene family, member H (TTF)	399	4	4p13	yes	
ARID1A	AT rich interactive domain 1A (SWI-like)	8289	1	1p35.3	yes	
ARID2	AT rich interactive domain 2	196528	12	12q12	yes	
ARNT	aryl hydrocarbon receptor nuclear translocator	405	1	1q21	yes	
ASPSCR1	alveolar soft part sarcoma chromosome region, candidate 1	79058	17	17q25	yes	
ASXL1	additional sex combs like 1	171023	20	20q11.1	yes	
ATF1	activating transcription factor 1	466	12	12q13	yes	
ATIC	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/	471	2	2q35	yes	
ATM	ataxia telangiectasia mutated	472	11	11q22.3	yes	yes

PIK3CA



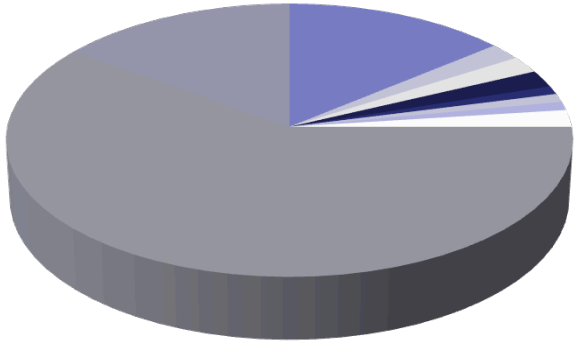
- large_intestine
- endometrium
- urinary_tract
- ovary
- skin
- stomach
- lung
- thyroid
- central_nervous_system
- upper_aerodigestive_tract
- others
- breast

BRAF



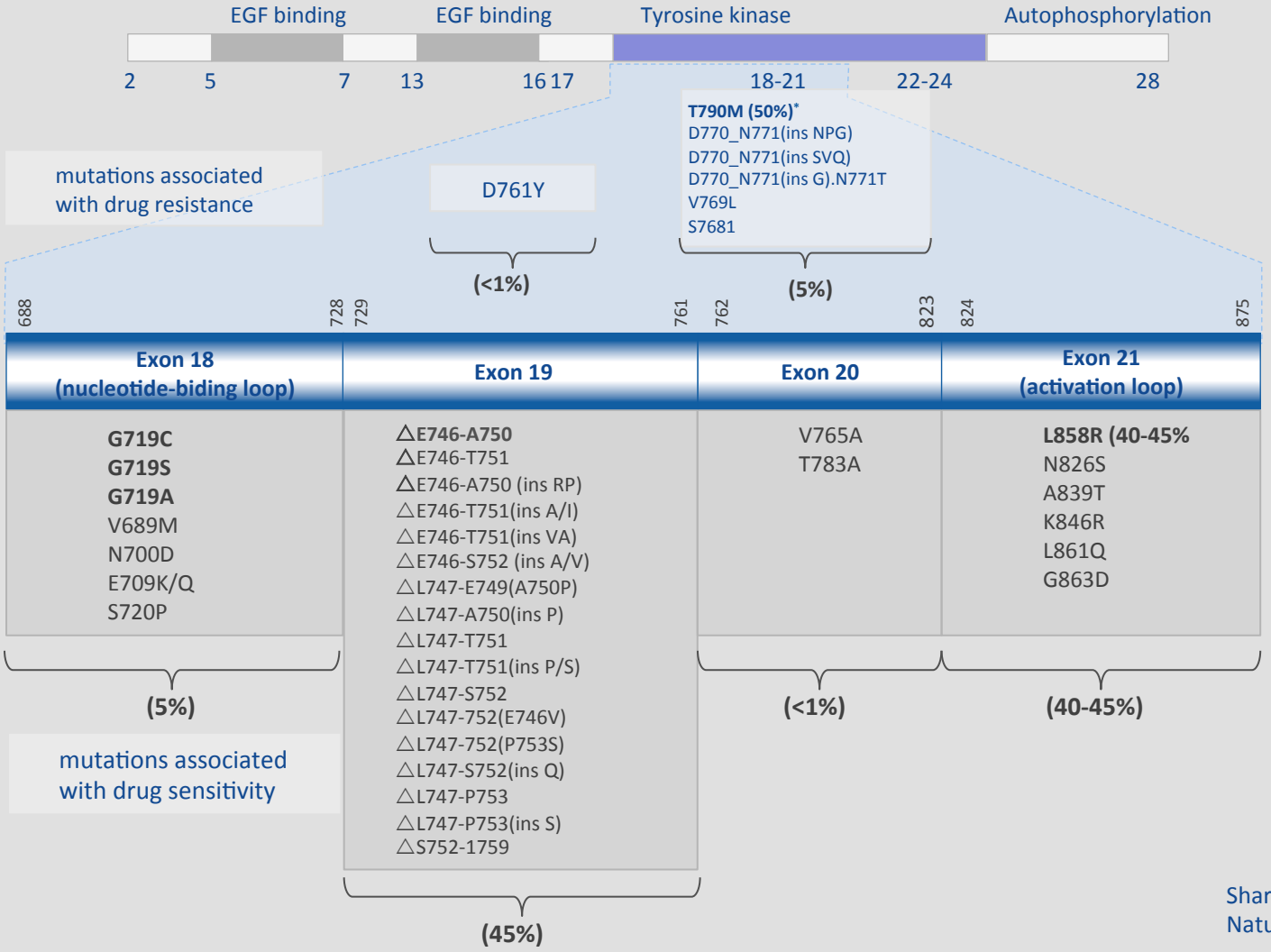
- skin
- NS
- ovary
- lung
- haematopoietic_and_lymphoid_tissue
- eye
- central_nervous_system
- others
- thyroid
- large_intestine

KRAS



- lung
- biliary_tract
- ovary
- endometrium
- haematopoietic_and_lymphoid_tissue
- stomach
- thyroid
- prostate
- others
- large_intestine
- pancreas

EGFR



Sharma, 2007
Nature Reviews Cancer

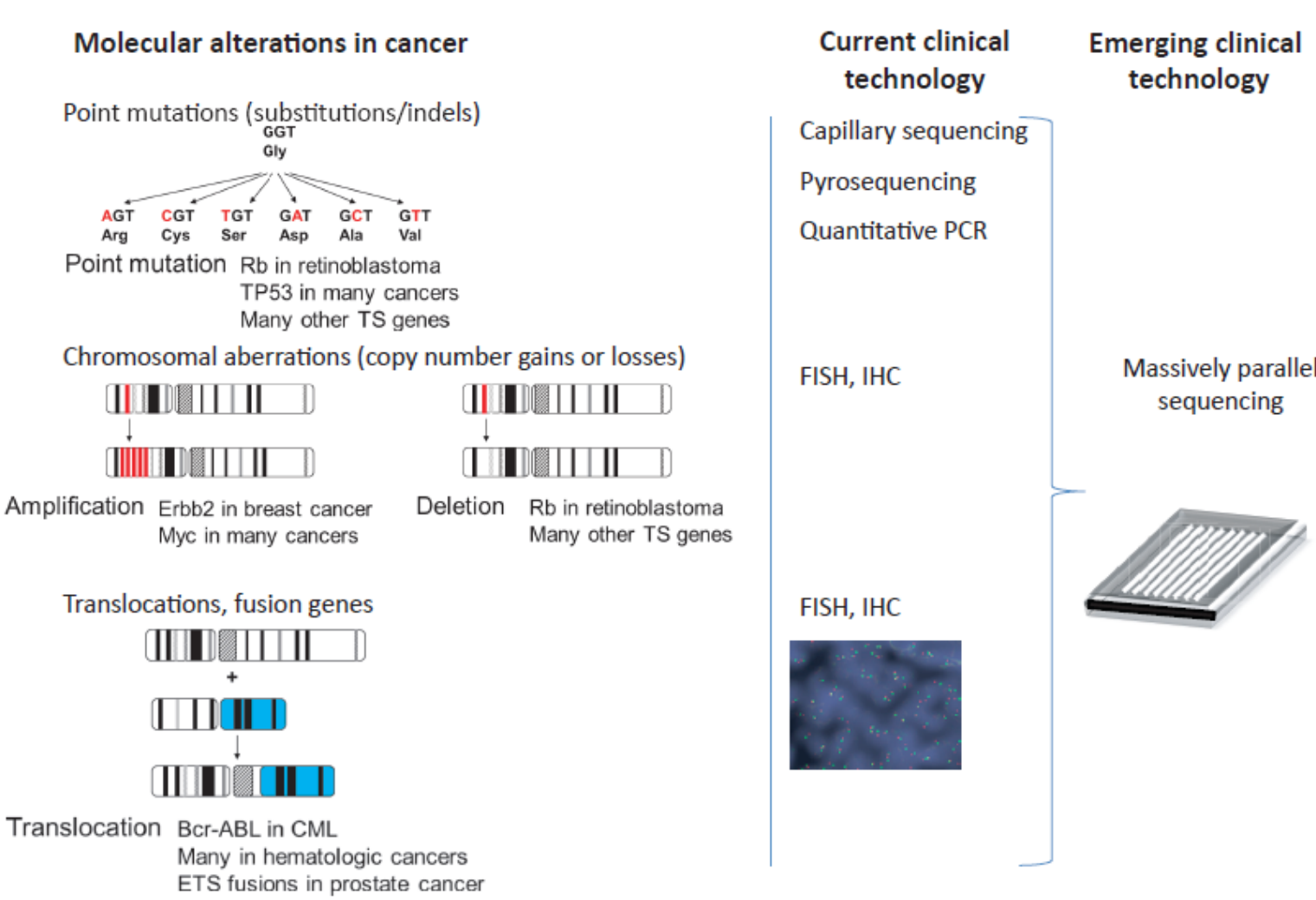
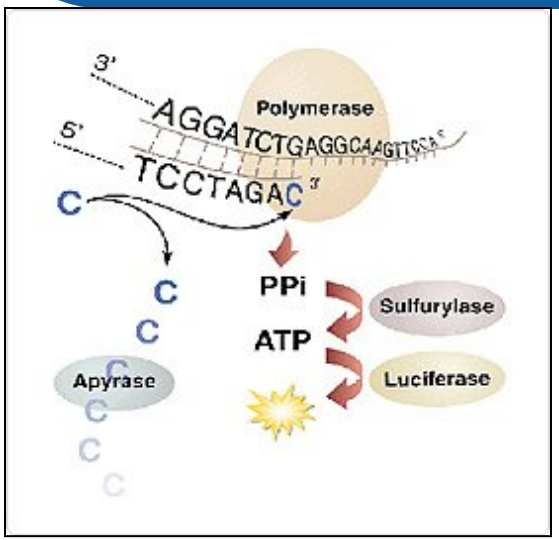


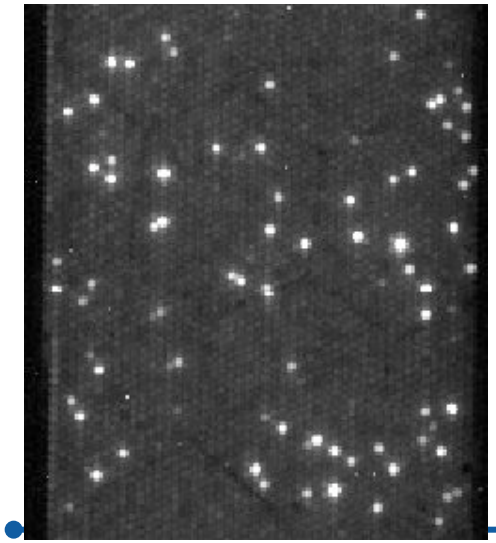
Figure 2. Genome alterations, current tests, and future technologies: the major classes of genomic alterations that give rise to cancer, exemplary cancer genes for each category, and the current and emerging clinical technologies for detecting these various types of alterations. TS, tumor suppressor; IHC, immunohistochemistry.

OUTLINE

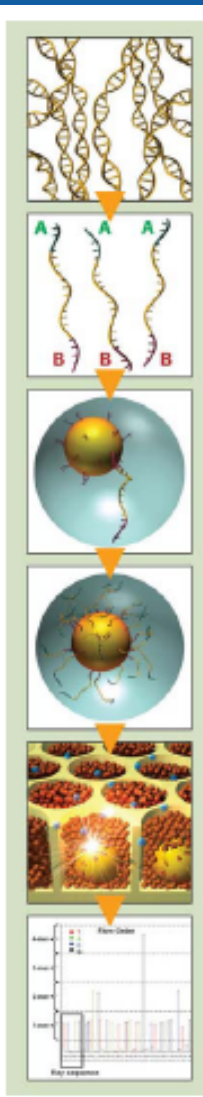
- Sequencing
- Targeting
- Analysis
  - Alignment
  - Refinement
  - Variant Calling
- Clinical Interpretation and Implementation

Roche 454 - PyroSequencing





- Genomic DNA is fractionated (300-800 bp)
- Short adaptors ligated onto fragment ends
  - Adaptors - priming sequences for amplification and sequencing
- Emulsion PCR
  - adaptor B contains 5'-biotin tag
  - streptavidin-coated beads
  - emulsified with amplification reagents
  - clonally amplified DNA fragments
- Pyrosequencing



454 LIFE SCIENCES

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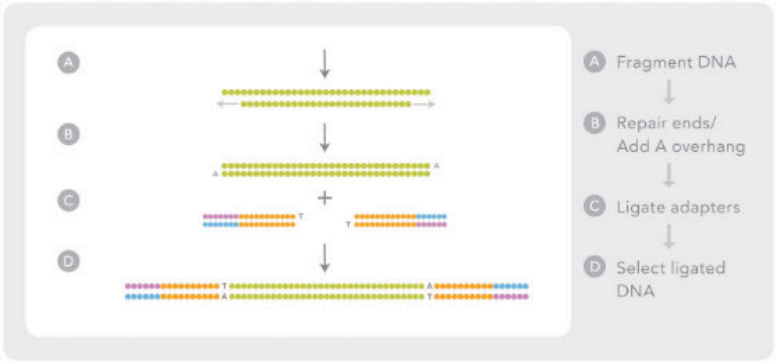
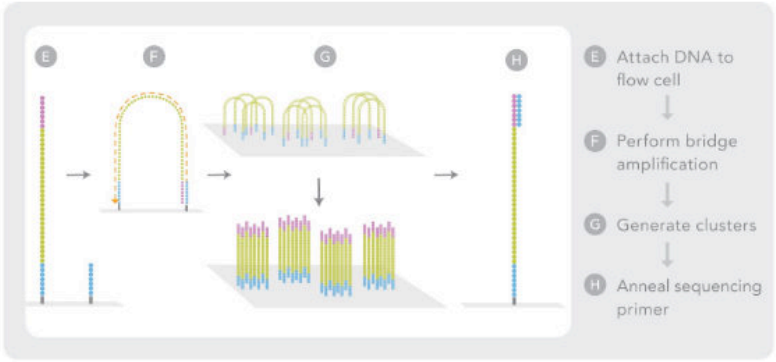
Illumina Technology

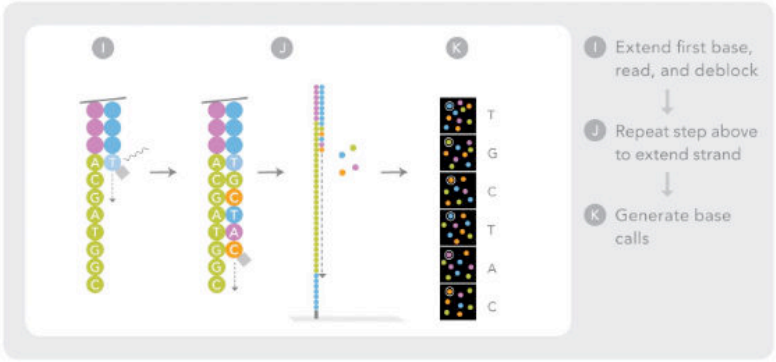
- Library Preparation



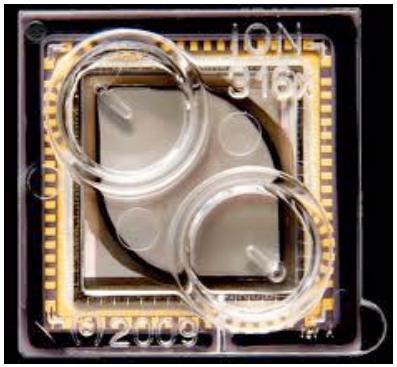
- Clonal amplification

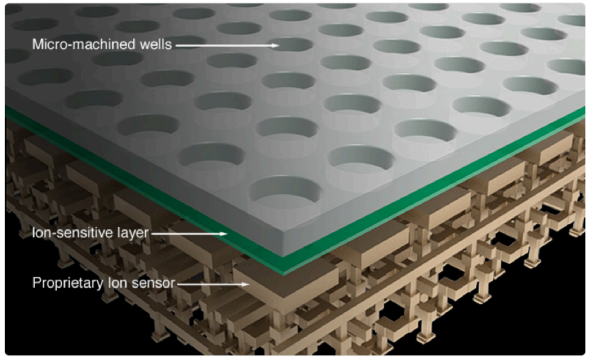


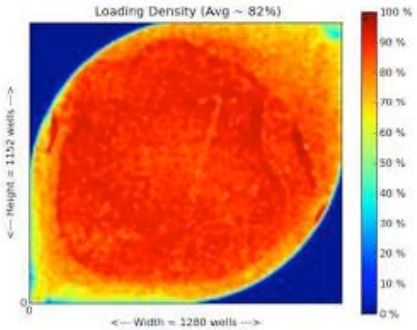
- Sequencing by synthesis

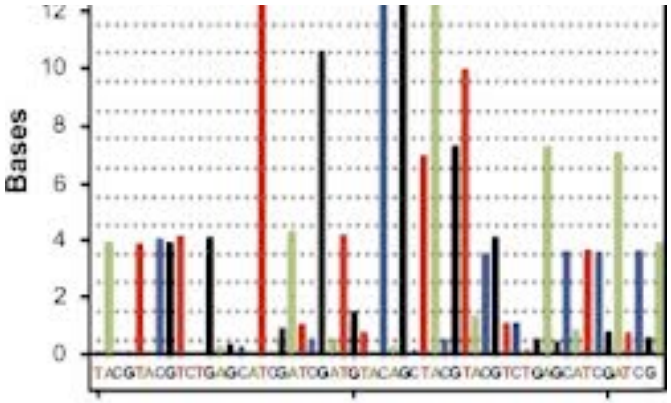


Ion Torrent – Semi conductor seq

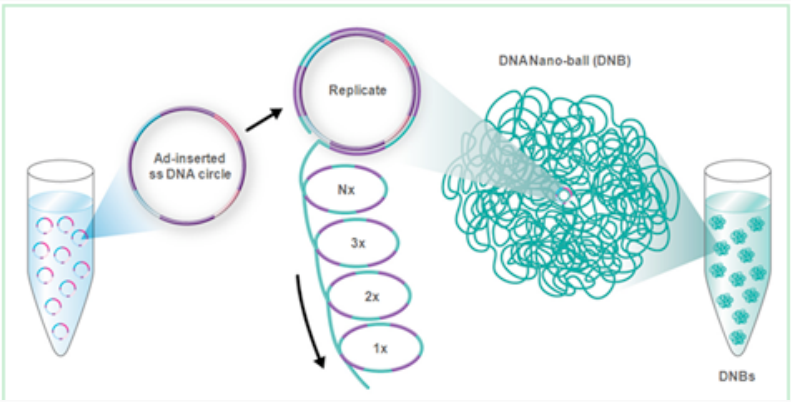


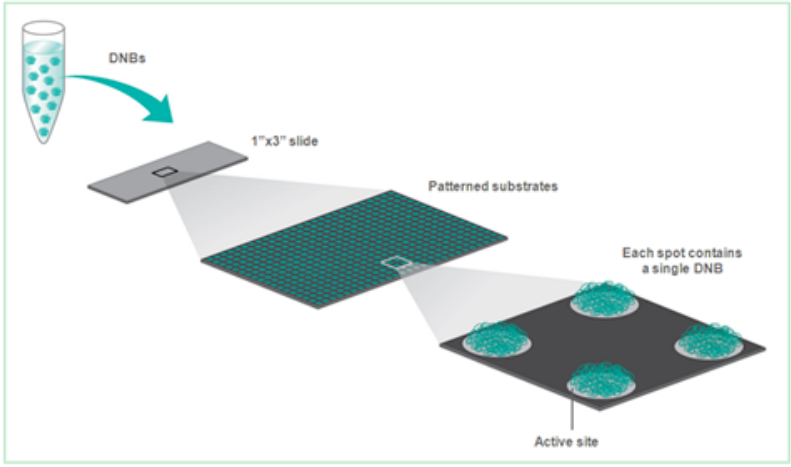


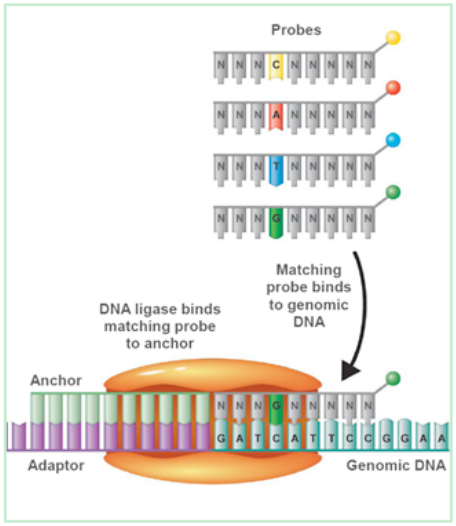


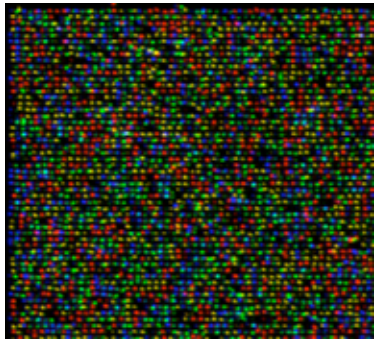


Complete Genomics





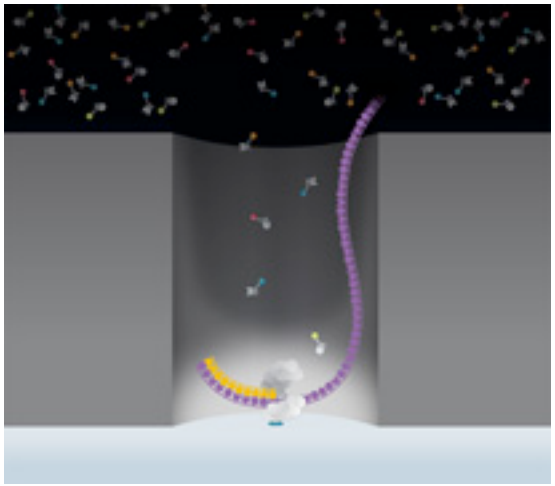


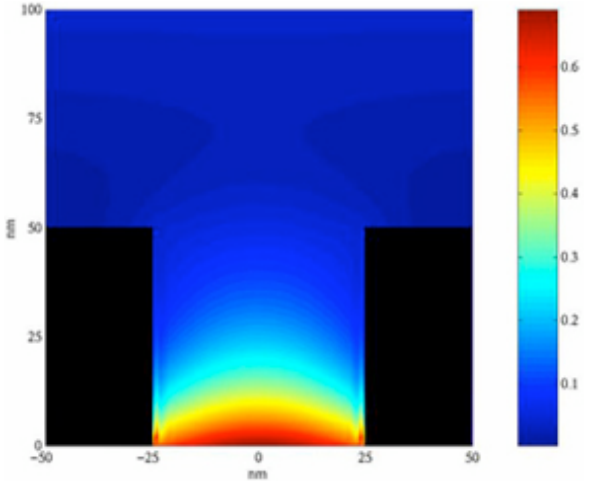


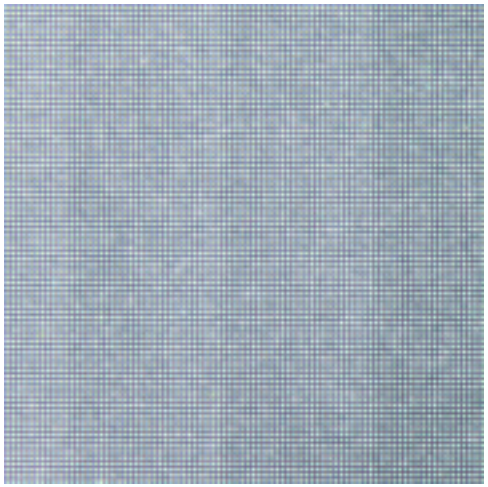
- DNA Nano-ball to amplify, place adapter inserts and generate self assembling arrays
- Sequencing by Ligation from multiple sites
- $20,000 per genome

Complete Genomics

Pacific BioSciences







- Single molecule sequencing suffers from poor signal/ noise
- The Zero Mode Wave (ZMW) guide acts like a filter to restrict the fluorescence measurement to the well bottom

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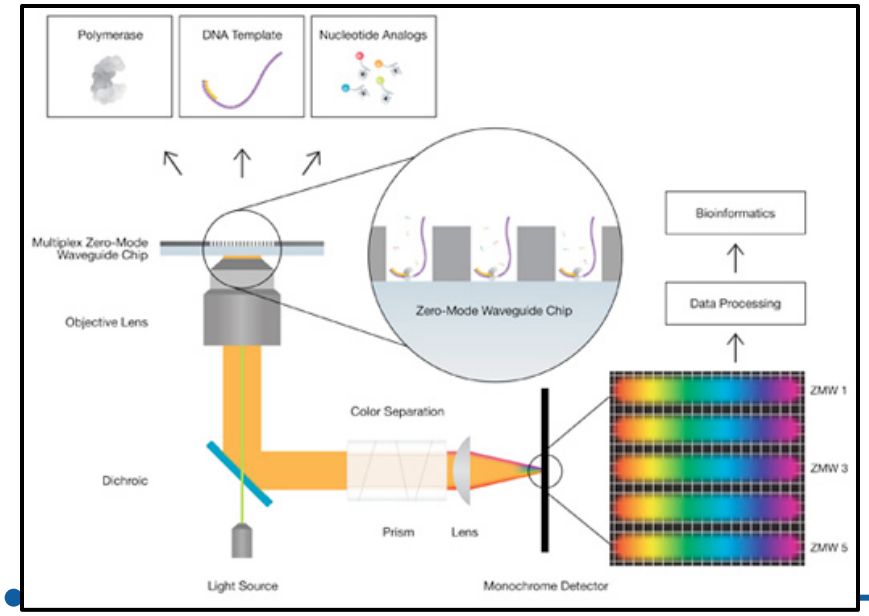

Real time sequencing thanks to engineered DNA polymerase and cleavable fluorophore.

- 80,000 to 300,000 wells.
- 1000 nt read length
- Strobe sequencing possible

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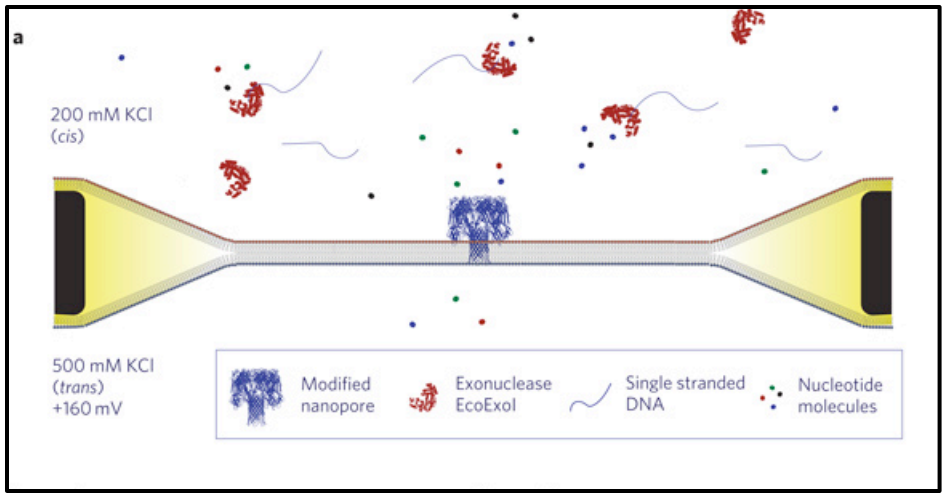
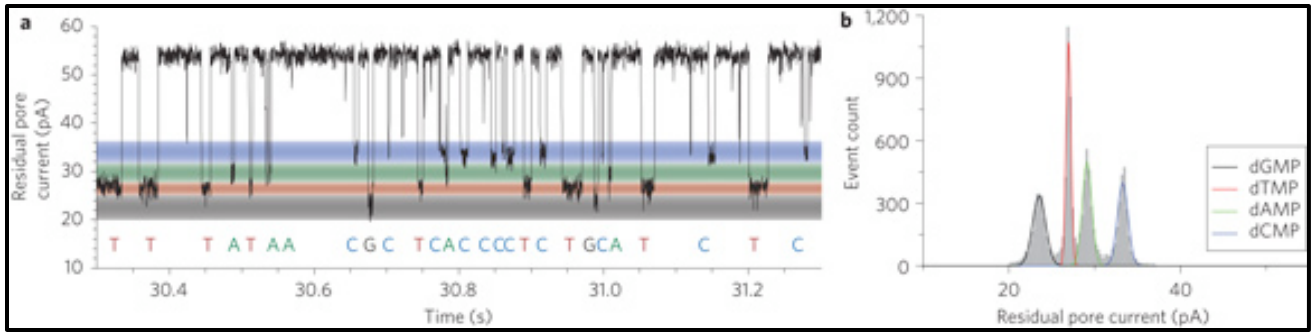
Oxford Nanopore



- Modifed αHemolysine with inserted Cyclodextrine
- Embedded in a lipid bilayer
- Flow of Nucleotide through the pore modifies the conductance
- Need to attach the Exonuclease to the pore



Oxford NANOPORE Technologies

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Overview of Technologies

	Roche 454	Illumina GA	ABI SOLiD	Complete Genomics	PacBio	Nanopore	Ion Torrent
Template	Emulsion PCR	Bridge Amplification	Emulsion PCR	DNA Nano-balls	True Single Molecule	True Single Molecule	Emulsion PCR
Chemistry	Pyrosequencing	Reversible Terminator	Degenerate Probes Ligation	Degenerate Probes Ligation	Cleavable Fluorophore	Exonulease	Polymerase
Processivity	Continuous	Sequential	Sequential	Sequential	Real Time	Real Time	Real Time
Parallelization	Micro-wells	Random Clusters (soon Self ordered arrays)	Random Beads deposition (soon Self ordered arrays)	Ordered active site array	Arrays of ZMW	Array of lipid bi-layers	nano-wells
Detection	Luminescence	Fluorescence	Fluorescence	Fluorescence	Fluorescence	Electronic	Electronic
Raw Output	Images	Images	Images	Images	Images	Traces	Traces

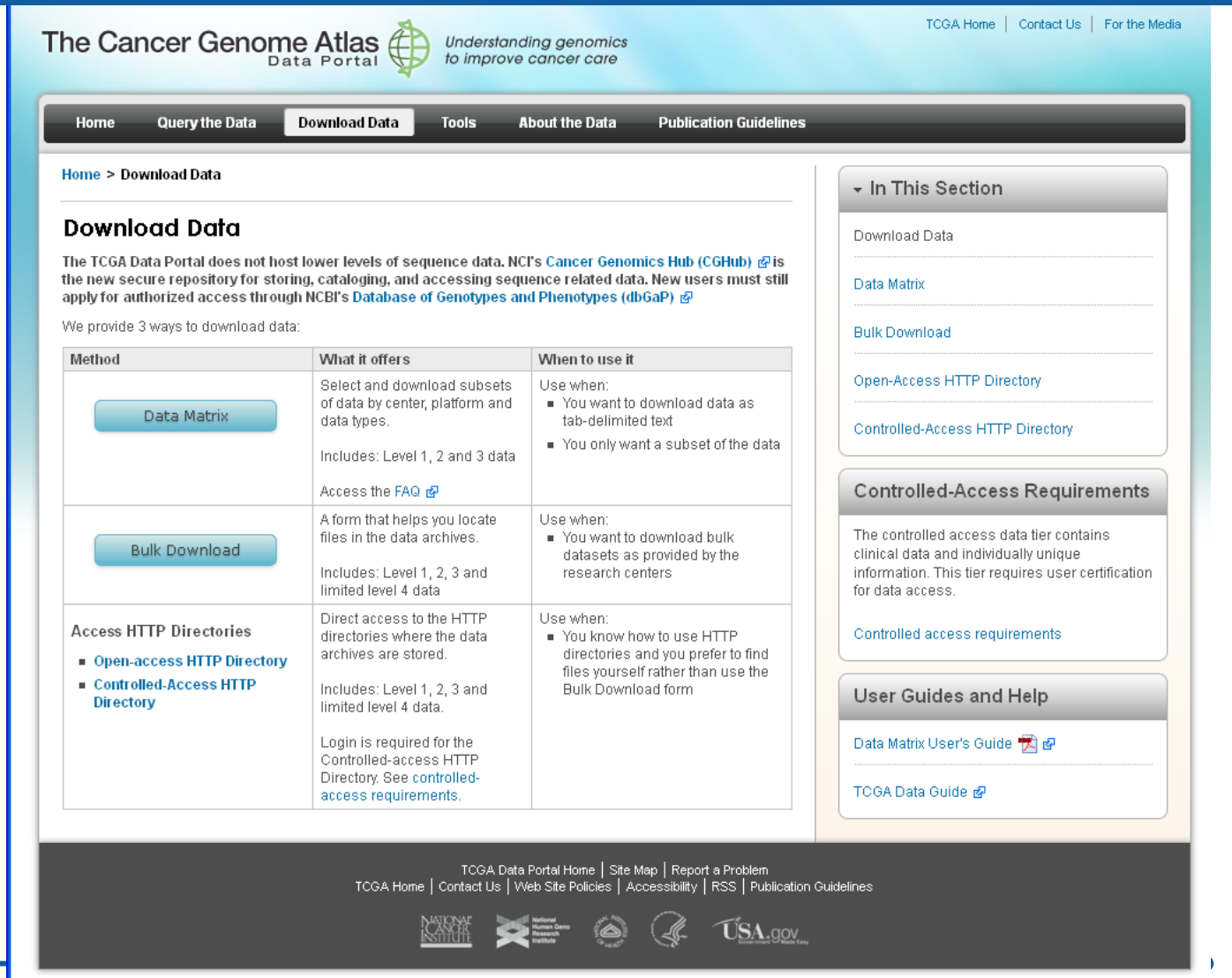
Current Instruments Comparison

Table 1 Price comparison of benchtop instruments and sequencing runs

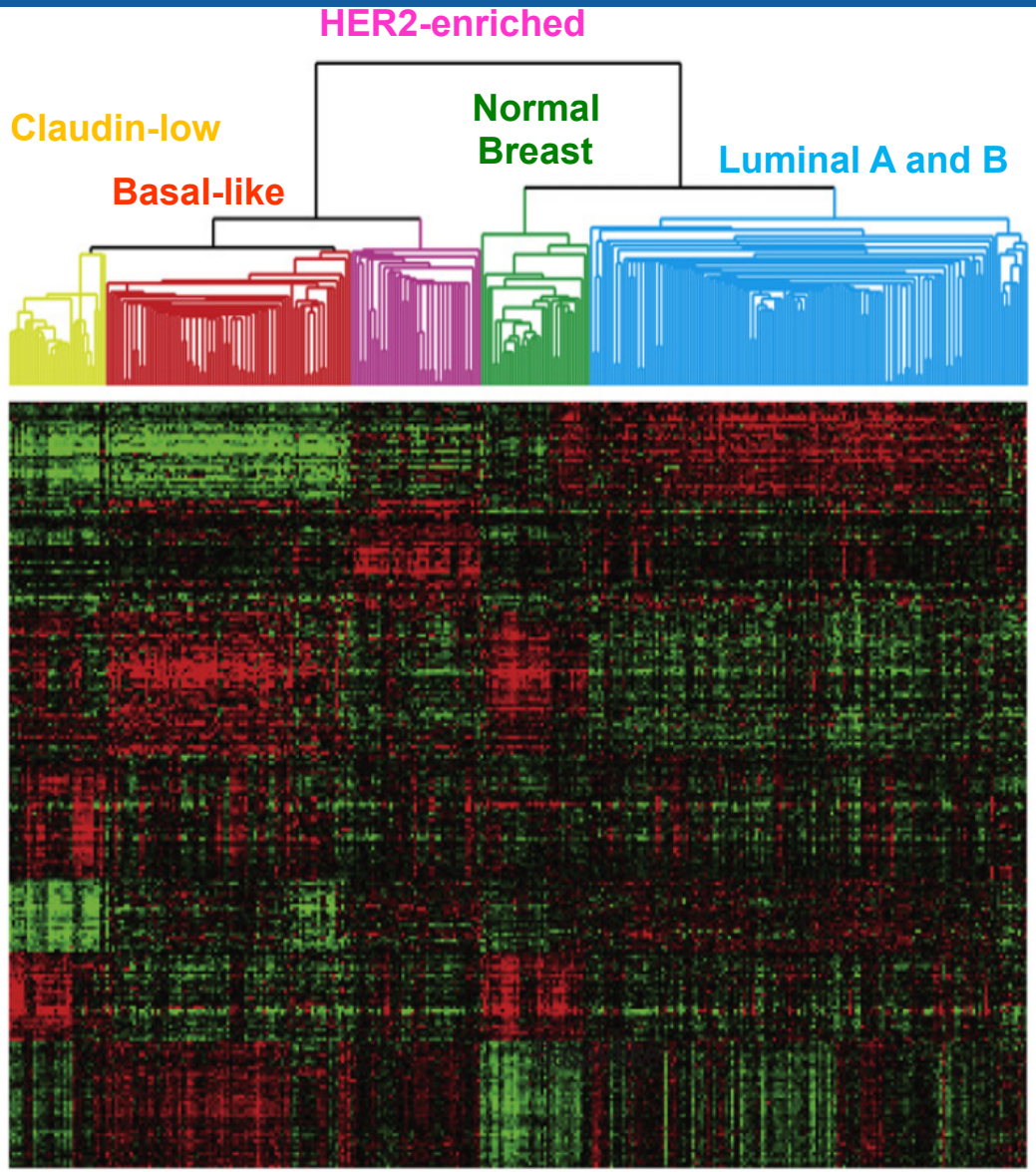
Platform	List price	Approximate cost per run	Minimum throughput (read length)	Run time	Cost/Mb	Mb/h
454 GS Junior	$108,000	$1,100	35 Mb (400 bases)	8 h	$31	4.4
Ion Torrent PGM						
(314 chip)	$80,490[a,b]	$225[c]	10 Mb (100 bases)	3 h	$22.5	3.3
(316 chip)		$425	100 Mb[d] (100 bases)	3 h	$4.25	33.3
(318 chip)		$625	1,000 Mb (100 bases)	3 h	$0.63	333.3
MiSeq	$125,000	$750	1,500 Mb (2 × 150 bases)	27 h	$0.5	55.5

Loman et al.

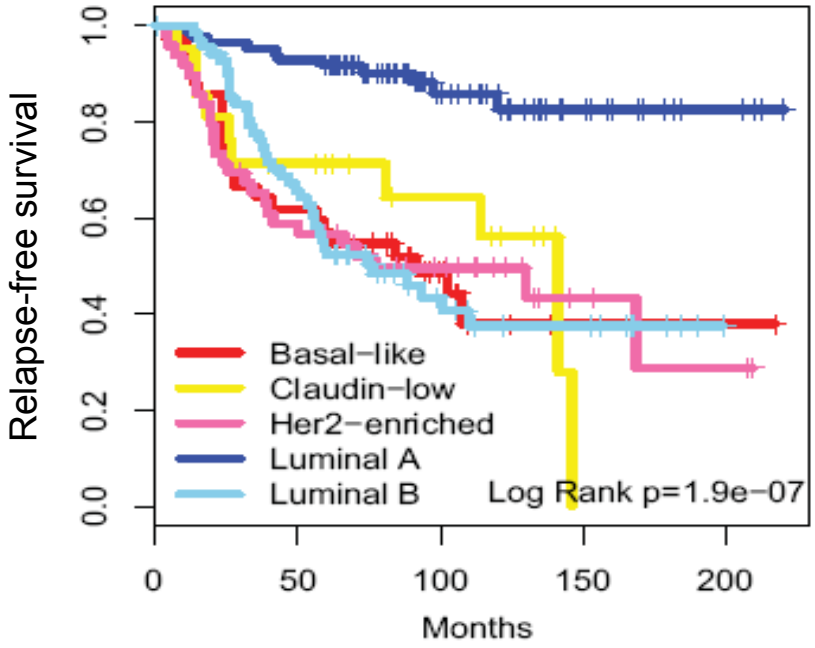
- Microarray data
- RNA sequencing
- Gene/isoform/exon level
- miRNA sequencing
- DNA Methylation
- Protein data
- CN segment data
- Most clinical data
- Pathology data



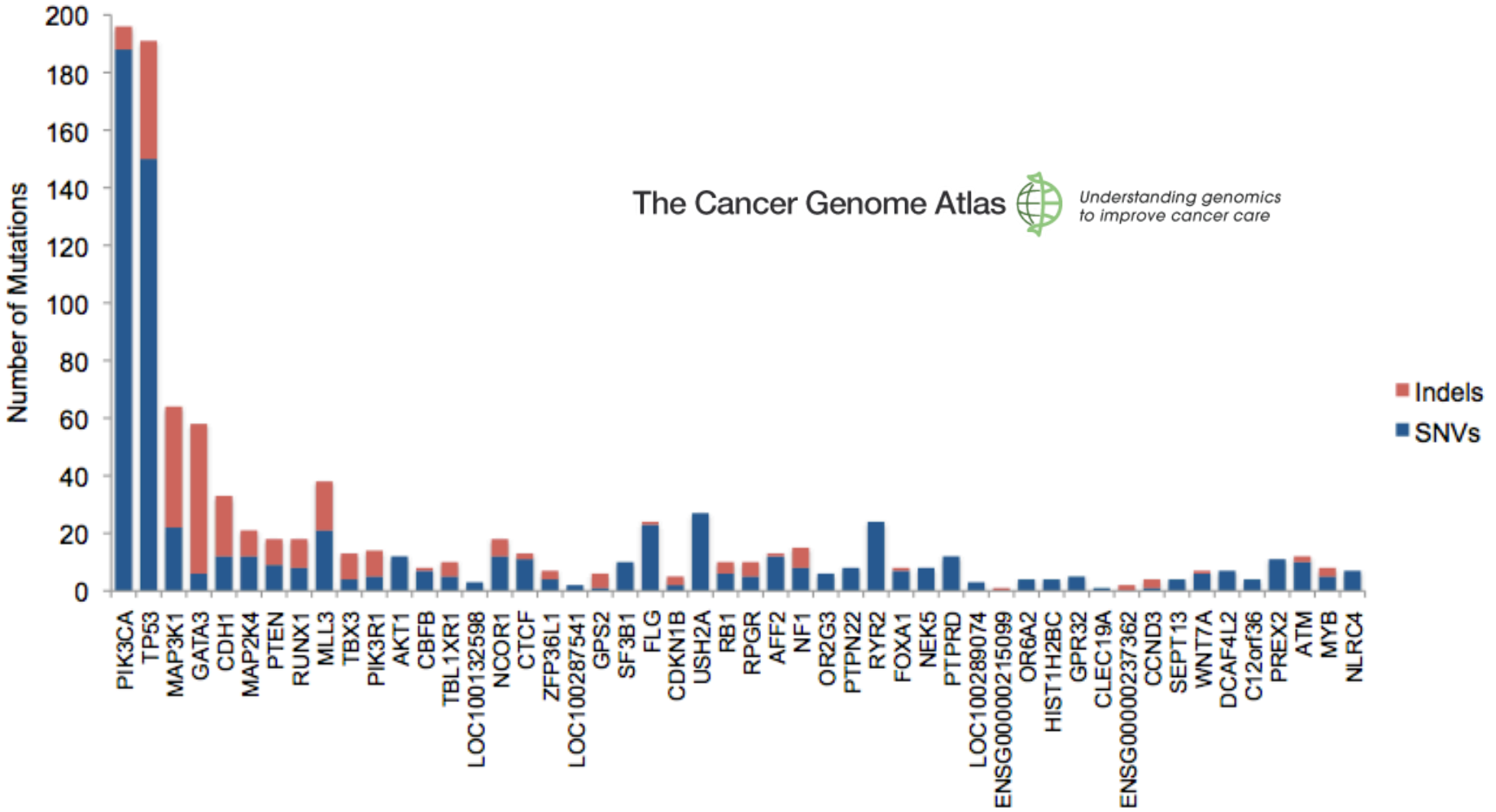
Gene Expression Subtypes



No da lo mismo…….



Significantly Mutated Genes



TCGA Significantly Mutated Genes By Subtype

Luminal A (n=225)

#Gene	SNVs	Indels	FDR CT
PIK3CA	112	5	0.00E+00
MAP3K1	19	34	0.00E+00
GATA3	3	29	0.00E+00
TP53	25	3	0.00E+00
CDH1	7	16	0.00E+00
MAP2K4	11	5	0.00E+00
RUNX1	6	7	0.00E+00
FAM157B	0	9	2.13E-16
PTEN	5	4	1.29E-11
MLL3	9	10	1.69E-11
AKT1	8	0	3.21E-09
NCOR1	7	6	6.79E-09
MICA	0	6	1.71E-07
CTCF	8	1	3.02E-06
TBX3	1	5	2.72E-05
CBFB	4	1	2.72E-05
AKAP3	0	6	3.78E-05
SF3B1	7	0	5.27E-05
CCND3	1	3	1.13E-03
TBL1XR1	5	1	1.18E-03
GPS2	1	3	6.05E-03
WNT7A	4	1	7.51E-03
ATN1	2	4	7.83E-03
NEK5	5	0	8.16E-03

Luminal B (n=126)

#Gene	SNVs	Indels	FDR CT
PIK3CA	39	3	0.00E+00
TP53	29	11	0.00E+00
GATA3	3	20	0.00E+00
PTEN	3	4	1.94E-07
MAP3K1	1	7	4.67E-07
TBX3	3	3	1.38E-04
KCNB2	5	2	3.53E-03
CDH1	3	3	6.64E-03
ZFP36L1	2	2	1.71E-02
OR2G3	3	0	4.95E-02
TRIM53	2	0	4.95E-02

Basal-like (n=93)

#Gene	SNVs	Indels	FDR CT
TP53	57	20	0.00E+00
PIK3CA	9	0	3.43E-07
PNPLA3	1	3	2.44E-02
TRIM6-TRIM34	2	3	4.85E-02
RB1	2	3	4.85E-02
ATP2B2	1	4	4.85E-02

HER2-enriched (n=57)

#Gene	SNVs	Indels	FDR CT
TP53	35	7	0.00E+00
PIK3CA	23	0	0.00E+00
SRPR	6	0	1.60E-03
PIK3R1	2	2	3.27E-02
ATP1A4	5	0	8.63E-02
ARMCX1	1	2	8.63E-02
ZNF266	3	0	1.95E-01

The Cancer Genome Atlas *Understanding genomics to improve cancer care*

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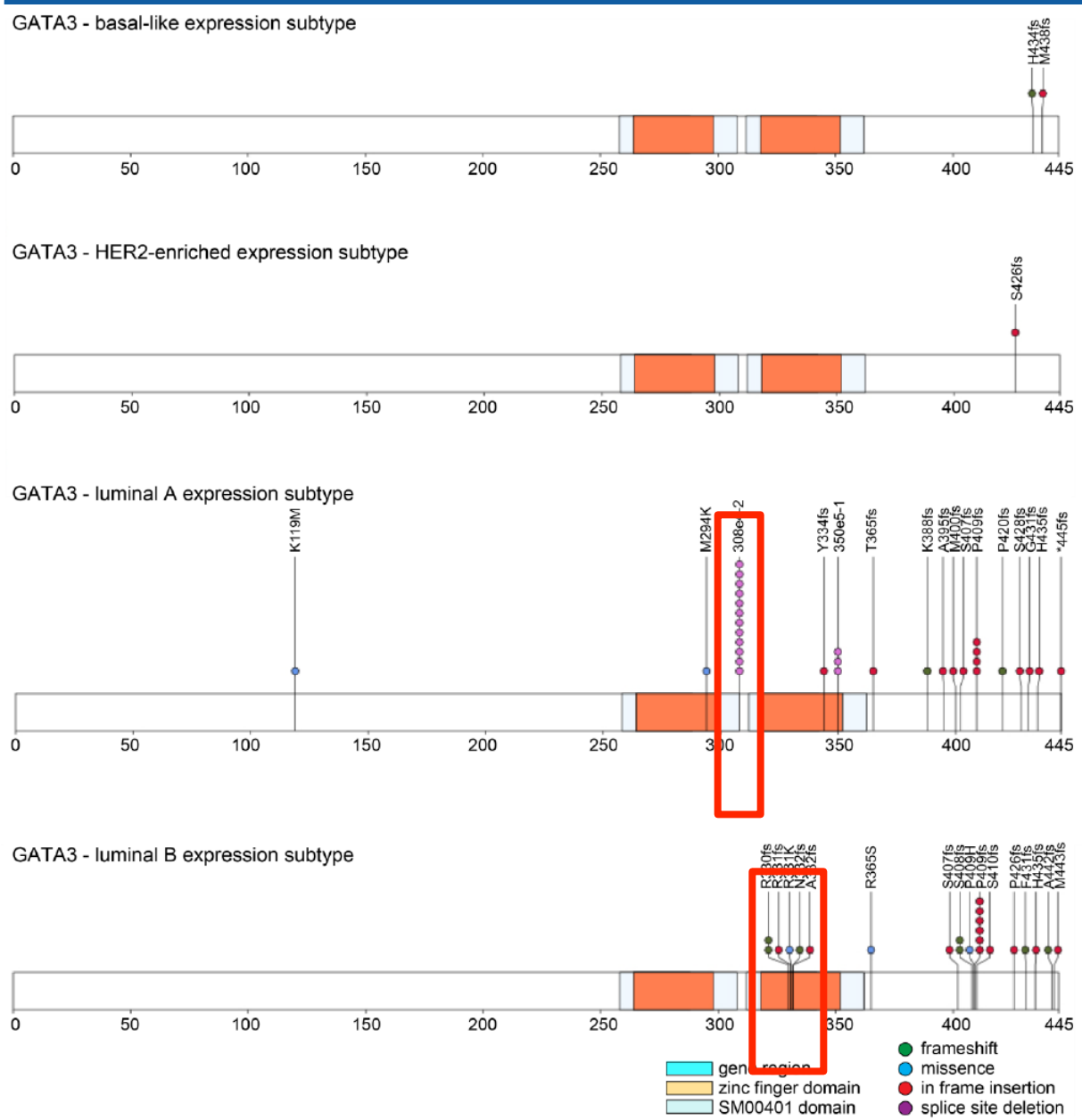

- 13/13 CA intron deletion variants were Luminal A.

- 8/9 mutations in exon 5 were in Luminal B.
- 7/9 were frame shifts.

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Whole-genome analysis informs breast cancer response to aromatase inhibition

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To correlate the variable clinical features of oestrogen-receptor-positive breast cancer with somatic alterations, we studied pretreatment tumour biopsies accrued from patients in two studies of neoadjuvant aromatase inhibitor therapy by massively parallel sequencing and analysis. Eighteen significantly mutated genes were identified, including five genes (*RUNX1*, *CBFB*, *MYH9*, *MLL3* and *SF3B1*) previously linked to haematopoietic disorders. Mutant MAP3K1 was associated with luminal A status, low-grade histology and low proliferation rates, whereas mutant TP53 was associated with the opposite pattern. Moreover, mutant *GATA3* correlated with suppression of proliferation upon aromatase inhibitor treatment. Pathway analysis demonstrated that mutations in *MAP2K4*, a MAP3K1 substrate, produced similar perturbations as MAP3K1 loss. Distinct phenotypes in oestrogen-receptor-positive breast cancer are associated with specific patterns of somatic mutations that map into cellular pathways linked to tumour biology, but most recurrent mutations are relatively infrequent. Prospective clinical trials based on these findings will require comprehensive genome sequencing.

Table 1 | Highlights of genomic, clinical and proteomic features of subtypes

Subtype	Luminal A	Luminal B	Basal-like	HER2E
$ER^+/HER2^-$ (%)	87	82	10	20
$HER2^+$ (%)	7	15	2	68
TNBCs (%)	2	1	80	9
TP53 pathway	*TP53* mut (12%); gain of *MDM2* (14%)	*TP53* mut (32%); gain of *MDM2* (31%)	*TP53* mut (84%); gain of *MDM2* (14%)	*TP53* mut (75%); gain of *MDM2* (30%)
PIK3CA/PTEN pathway	*PIK3CA* mut (49%); *PTEN* mut/loss (13%); *INPP4B* loss (9%)	PIK3CA mut (32%) PTEN mut/loss (24%) INPP4B loss (16%)	PIK3CA mut (7%); PTEN mut/loss (35%); INPP4B loss (30%)	PIK3CA mut (42%); PTEN mut/loss (19%); INPP4B loss (30%)
RB1 pathway	Cyclin D1 amp (29%); *CDK4* gain (14%); low expression of *CDKN2C*; high expression of *RB1*	Cyclin D1 amp (58%); *CDK4* gain (25%)	*RB1* mut/loss (20%); cyclin E1 amp (9%); high expression of *CDKN2A*; low expression of *RB1*	Cyclin D1 amp (38%); *CDK4* gain (24%)
mRNA expression	High ER cluster; low proliferation	Lower ER cluster; high proliferation	Basal signature; high proliferation	HER2 amplicon signature; high proliferation
Copy number	Most diploid; many with quiet genomes; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (24%)	Most aneuploid; many with focal amp; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (51%); 8p11.23 amp (28%)	Most aneuploid; high genomic instability; 1q, 10p gain; 8p, 5q loss; *MYC* focal gain (40%)	Most aneuploid; high genomic instability; 1q, 8q gain; 8p loss; 17q12 focal *ERRB2* amp (71%)
DNA mutations	*PIK3CA* (49%); *TP53* (12%); *GATA3* (14%); *MAP3K1* (14%)	*TP53* (32%); *PIK3CA* (32%); *MAP3K1* (5%)	*TP53* (84%); *PIK3CA* (7%)	*TP53* (75%); *PIK3CA* (42%); *PIK3R1* (8%)
DNA methylation	–	Hypermethylated phenotype for subset	Hypomethylated	–
Protein expression	High oestrogen signalling; high MYB; RPPA reactive subtypes	Less oestrogen signalling; high FOXM1 and MYC; RPPA reactive subtypes	High expression of DNA repair proteins, PTEN and INPP4B loss signature (pAKT)	High protein and phospho-protein expression of EGFR and HER2

Percentages are based on 466 tumour overlap list. Amp, amplification; mut, mutation.

Name	Method	Sensitivity	# loci/gene analyzed	Technical Validity
BEAMING	~Emulsion PCR	**0.01%**	**1/1**	partial
LiGAMP	LM-PCR	**0.01%**	**1/1**	partial
Pyrosequencing	454	5%	10,000/3	partial
Whole Genome	Shotgun sequencing	20%	3E9/20,000	in progress
Whole Exome	Shotgun sequencing	20%	30E6/20,000	in progress
OncoMAP	Mass Spec	**20%**	400/33	**CLIA**
SNaPShot	Single Base Extension	**5-10%**	40/13	**CLIA**
FoundationONE	Capture+NGS	10%	600kb/182	**CLIA**
UDT-Seq	HT Amplicon Sequencing	1%-5%	157,000/50	demonstrated

Solución propuesta: Ultra deep targeted sequencing (UDT-seq)

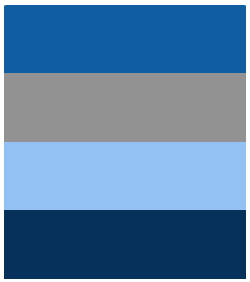
Ventajas

- Permite identificar simultáneamente mutaciones en todos los genes de interés en una misma muestra, en un solo análisis
- Alta sensibilidad (≈1%-0.2%)
- Menores costos
- Detecta mutaciones noveles
- Detectaría mutaciones propias de la población chilena

Panel de genes de interes

ABL2	CTNNA1	FGFR2	**PDGFRB**
AKT1	CTNNB1	GATA3	**PIK3CA**
ALK	CTNNB1	**JAK1**	PIK3R1
APC	**EGFR**	**JAK2**	**PTEN**
BRAF	**ERBB2**	JAK3	**RARA**
BRCA1	ERBB3	**KRAS**	RB1
BRCA2	ERBB4	MET	**RET**
CDH1	FGFR1	NOTCH1	TOP1
CDKN2A	FGFR1OP	PALB2	TP53

MLH1	CYP2C9
MSH2	CYP2D6
MSH6	DPD
PMS2	TPMT
CHK2	VKORC1
ATM	



Somatic

Germline and Somatic

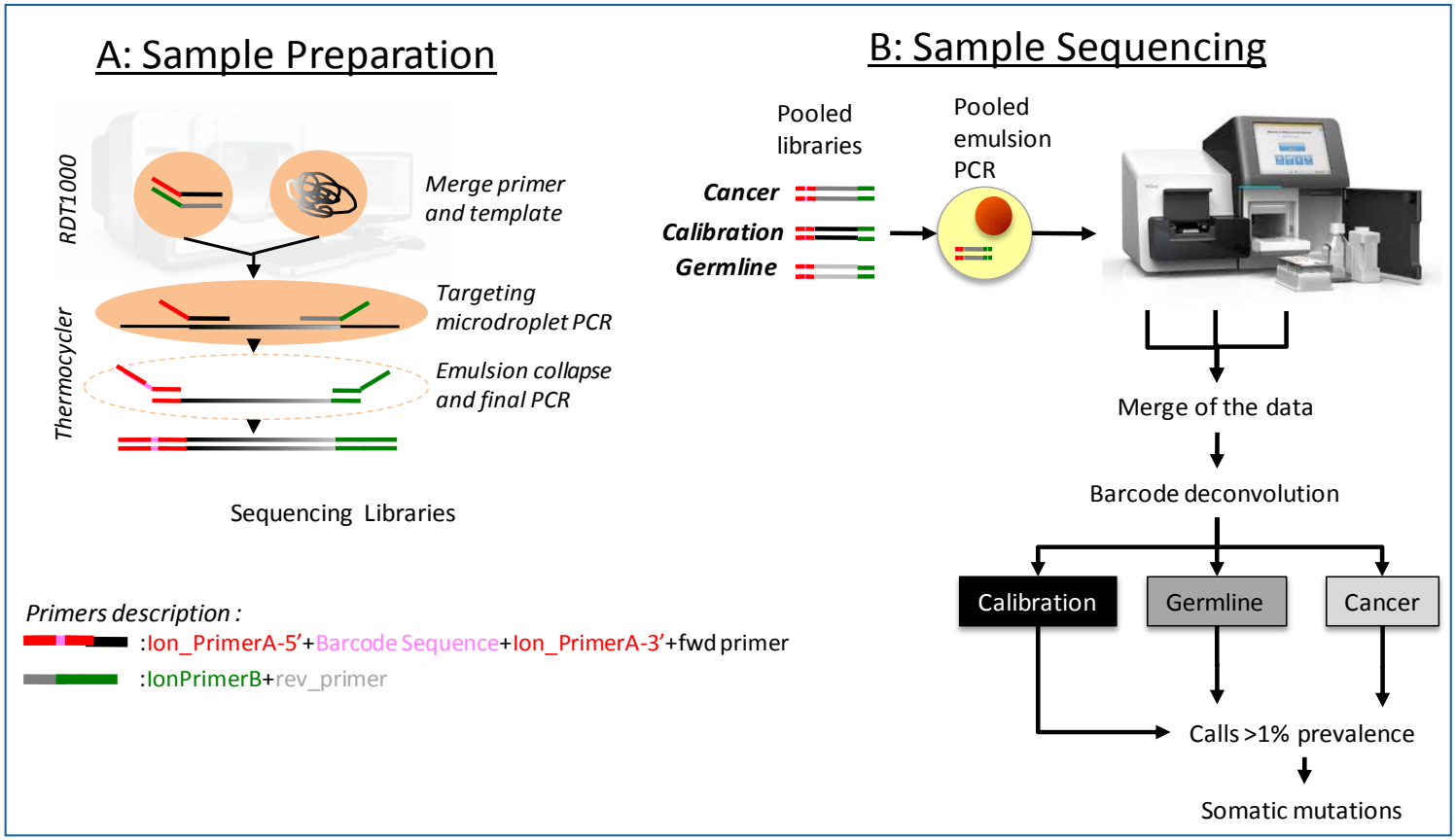
PKG signifiance

Reproductive significance

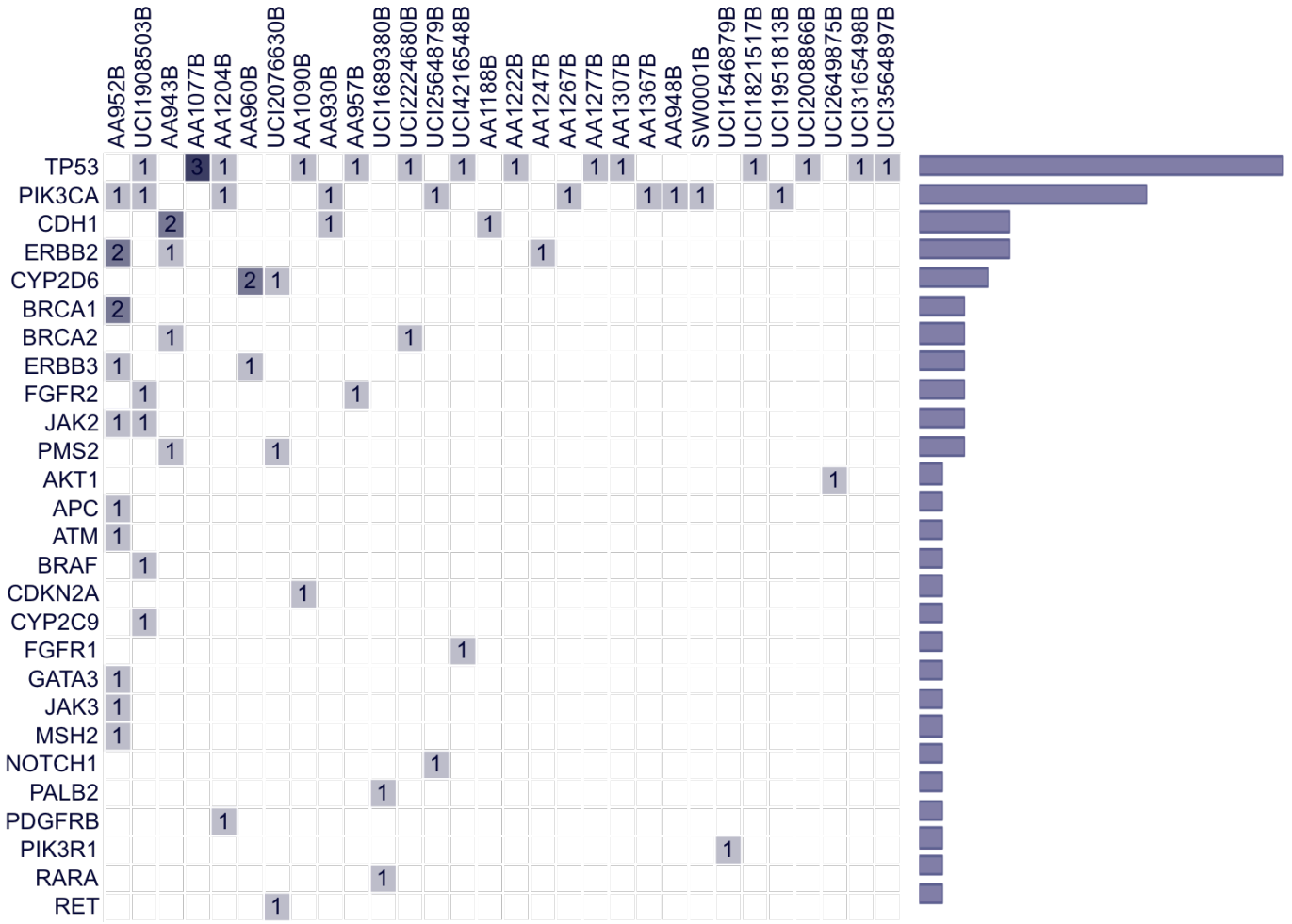
Eligibility for trial

With FDA inhibitor

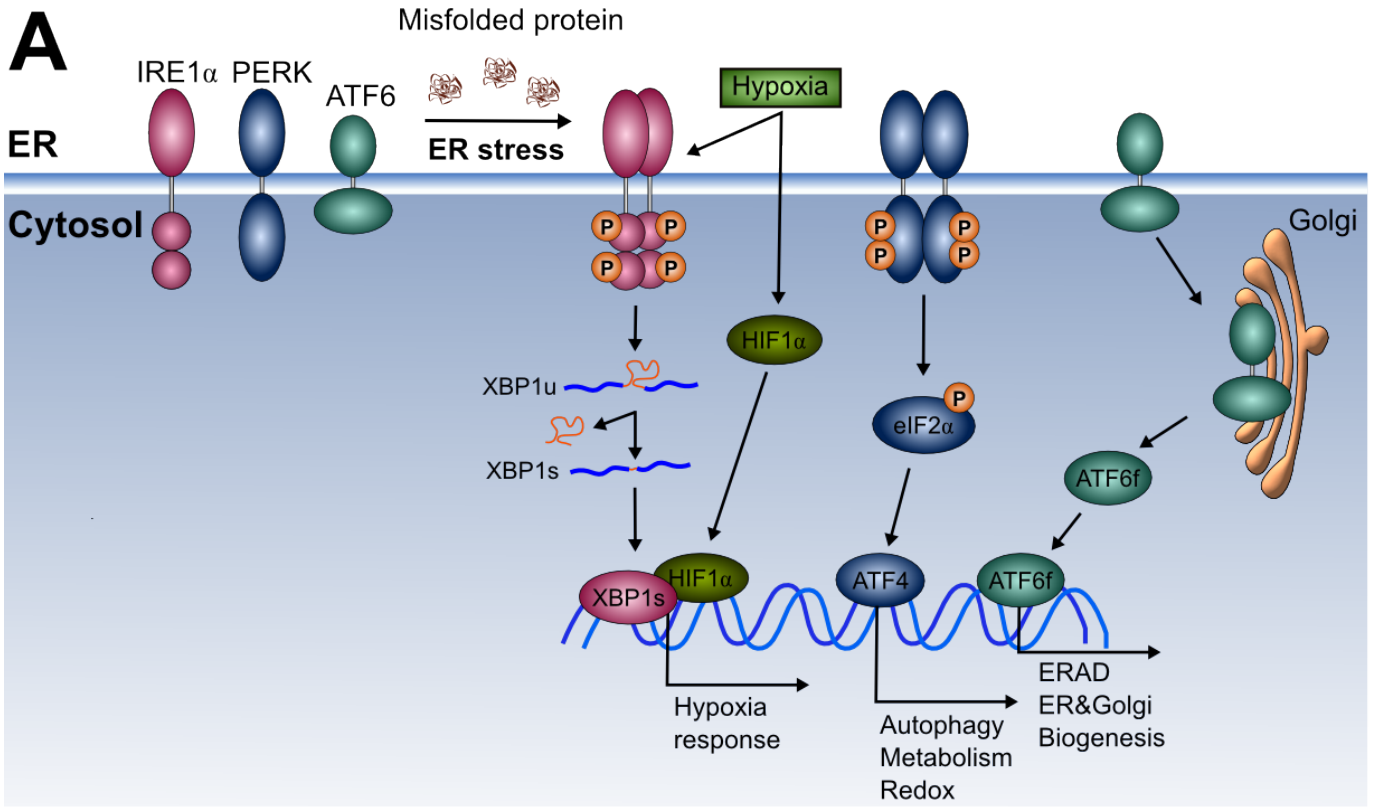
Solución propuesta: Ultra deep tageted sequencing (UDT-seq)



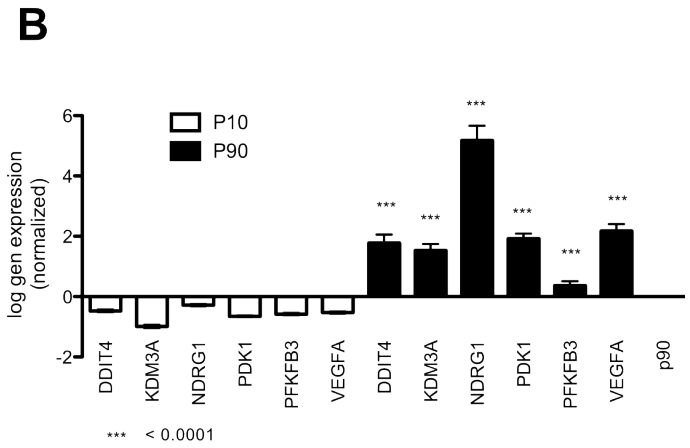
Mutaciones somáticas

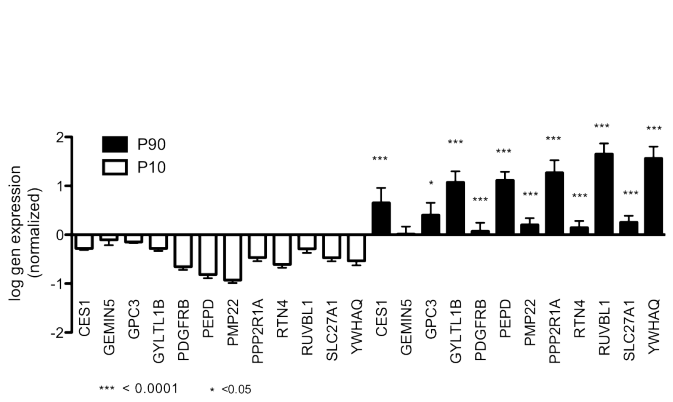


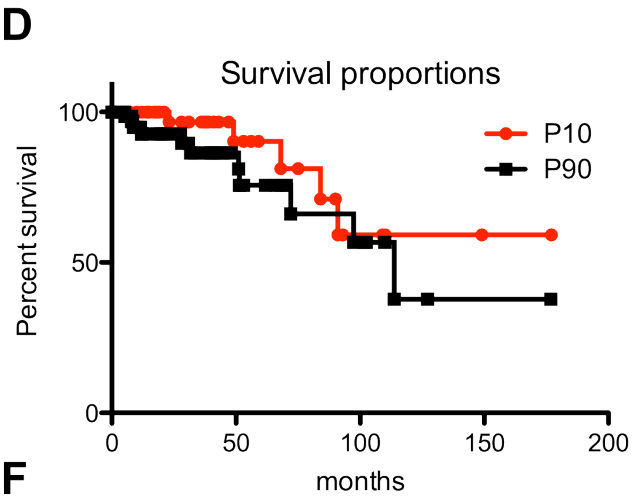
TCGA provisional data (955 patients)

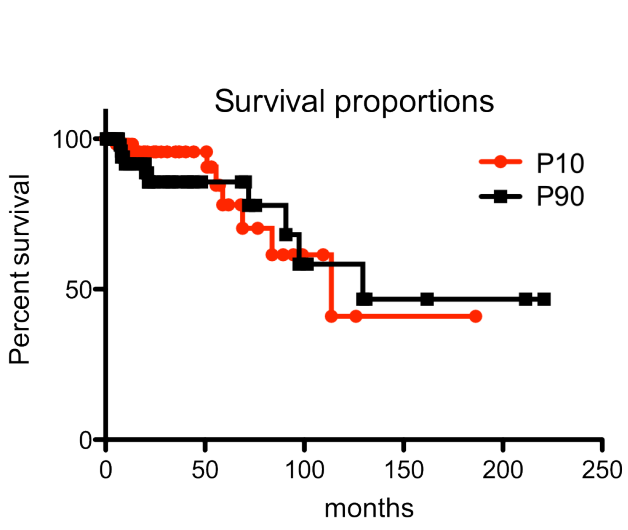


TCGA provisional data (955 patients)
(preliminary analysis)









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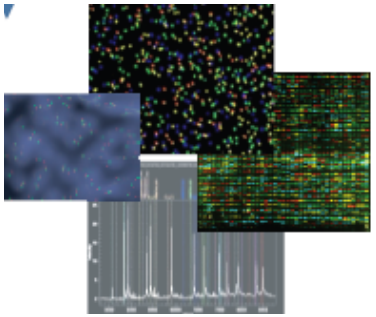
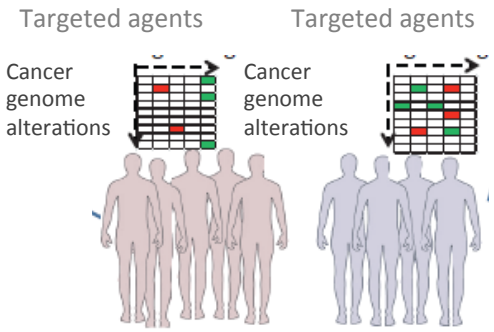
Genome technologies



"Individualized" profile of cancer alterations

Gene	Mut	Amp	Del	Trans
ABL				yes
AKT1				
BRAF				
CDK4				
EGFR	yes			
ERBB2				
FGFR				
FLT3				
JAK				
KIT				
KRAS				
MET				
PDGFRa				
PIK3CA				
PTEN				
RET				

Target therapy trials



Diagnosis and prognosis for individual patients

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- Katherine Marcelain (MV/PhD)
- Faustino Alonso (MD/Ms)
- Ricardo Verdugo (MV/PhD)
- Olga Barajas (MD)
- Mónica Ahumada (MD)
- Iván Gallegos (MD)
- Cristina Fernández (MD)
- Jessica Toro (Bq.)

Moores Cancer Center UC San Diego

- Kelly Frazer (PhD)
- Richard Schwab (MD)
- Olivier Harismendy (PhD)
- Anil Sadarangani (PhD)
- Catriona Jamieson (MD/PhD)

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Fondo de Fomento al Desarrollo Científico y Tecnológico

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