



Memorial Sloan Kettering
Cancer Center™

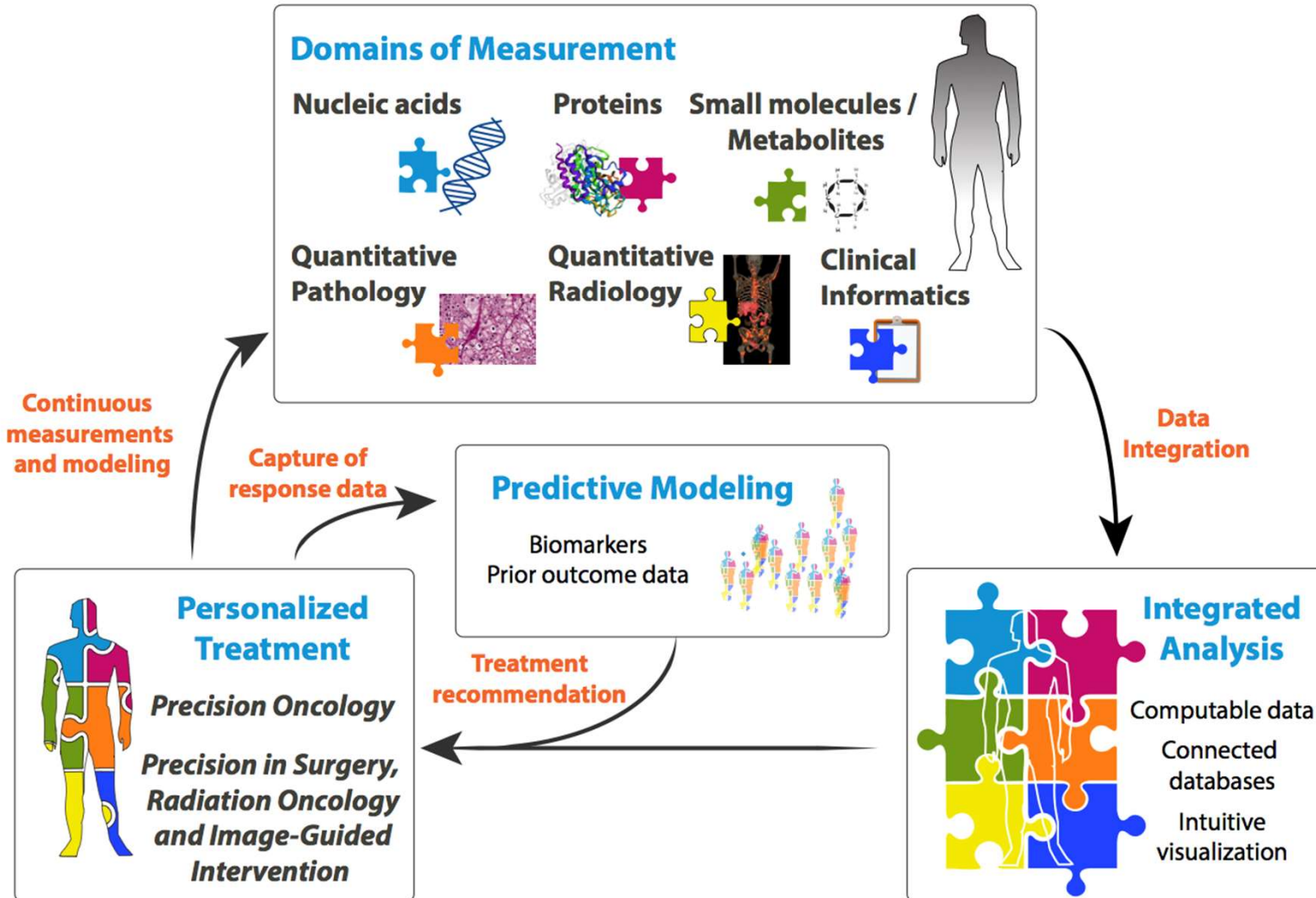
Towards Clinical Decision Support in Oncology: Identifying Driver Alterations and Therapeutic Options

Nikolaus Schultz, Ph.D.

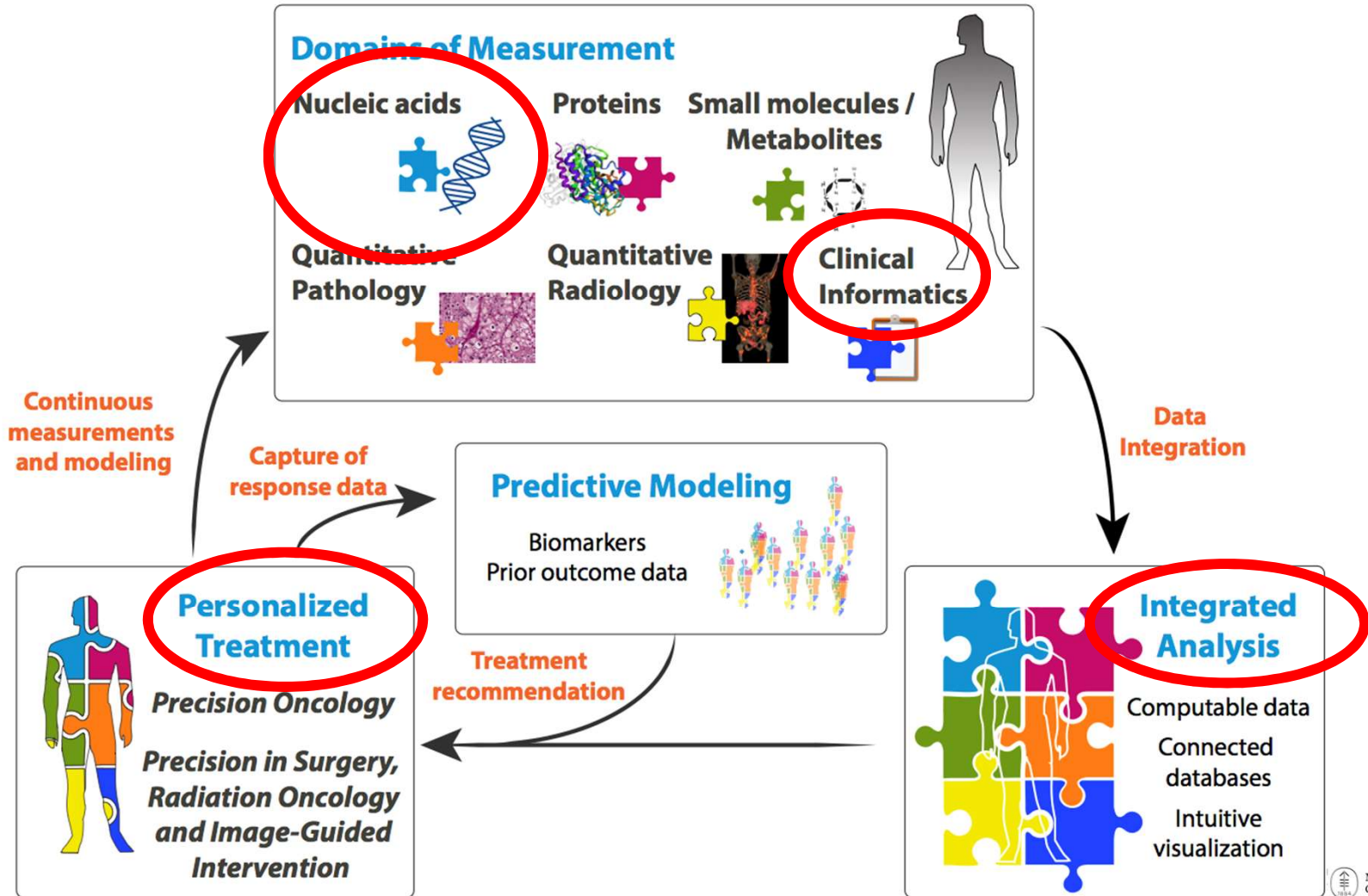
Associate Member, Computational Oncology
Head, Knowledge Systems
Kravis Center for Molecular Oncology

August 10, 2019

Precision Oncology



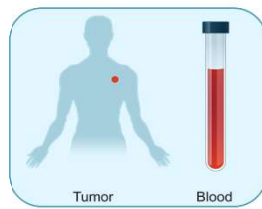
Precision Oncology



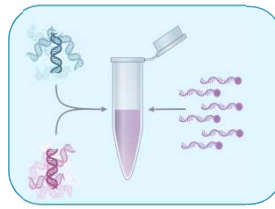
MSK-IMPACT Integrated Mutation Profilng of Actionable Cancer Targets



**Patient
Consent**



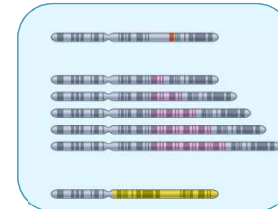
**Sample
Accessioning**



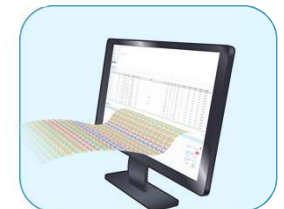
**Sample
Preparation**



Sequencing



Bioinformatics



**Case Review &
Sign Out**

Tumor / normal
468 genes
600x coverage
>40,000 samples to date

MSK-IMPACT Gene Panel

ABL1	BRCA2	CUL3	FANCC	IDH1	MAPK1	NOTCH4	PRDM1	SDHAF2	TNFAIP3	H3F3A	RHEB	MSI1
AKT1	BRD4	DAXX	FAT1	IDH2	MAX	NPM1	PRKAR1A	SDHB	TNFRSF14	H3F3B	SH2B3	MSI2
AKT2	BRIP1	DCUN1D1	FBXW7	IFNGR1	MCL1	NRAS	PTCH1	SDHC	TOP1	HIST1H3A	SRSF2	NTHL1
AKT3	BTK	DDR2	FGF19	IGF1	MDC1	NSD1	PTEN	SDHD	TP53	HIST1H3C	STAT3	NUF2
ALK	CARD11	DICER1	FGF3	IGF1R	MDM2	NTRK1	PTPN11	SETD2	TP63	HIST1H3D	STAT5A	PDCD1LG2
ALOX12B	CASP8	DIS3	FGF4	IGF2	MDM4	NTRK2	PTPRD	SF3B1	TRAF7	HIST1H3E	STAT5B	PPARG
APC	CBFB	DNMT1	FGFR1	IKBKE	MED12	NTRK3	PTPRS	SH2D1A	TSC1	HIST1H3F	TCEB1	PPP4R2
AR	CBL	DNMT3A	FGFR2	IKZF1	MEF2B	PAK1	PTPRT	SHQ1	TSC2	HIST1H3G	TCF3	PRDM14
ARAF	CCND1	DNMT3B	FGFR3	IL10	MEN1	PAK7	RAC1	SMAD2	TSHR	HIST1H3H	TCF7L2	PREX2
ARID1A	CCND2	DOT1L	FGFR4	IL7R	MET	PALB2	RAD50	SMAD3	U2AF1	HIST1H3I	TRAF2	PRKCI
ARID1B	CCND3	E2F3	FH	INPP4A	MITF	PARK2	RAD51	SMAD4	VHL	HIST1H3J	VEGFA	PRKD1
ARID2	CCNE1	EED	FLCN	INPP4B	MLH1	PARP1	RAD51C	SMARCA4	VTCN1	HIST2H3C	XRCC2	PTP4A1
ARID5B	CD274	EGFL7	FLT1	INSR	MLL	PAX5	RAD51L1	SMARCB1	WT1	HIST2H3D	ZFXH3	RAC2
ASXL1	CD276	EGFR	FLT3	IRF4	MLL2	PBRM1	RAD51L3	SMARCD1	XIAP	HIST3H3	ZRSR2	RECQL
ASXL2	CD79B	EIF1AX	FLT4	IRS1	MLL3	PDCD1	RAD52	SMO	XPO1	HLA-A	AGO2	RRAGC
ATM	CDC73	EP300	FOXA1	IRS2	MPL	PDGFRA	RAD54L	SOC1	YAP1	HOXB13	BABAM1	RRAS
ATR	CDH1	EPCAM	FOXL2	JAK1	MRE11A	PDGFRB	RAF1	SOX17	YES1	ID3	CARM1	RRAS2
ATRX	CDK12	EPHA3	FOXP1	JAK2	MSH2	PDPK1	RARA	SOX2	ACVR1	INHA	CDC42	RTEL1
AURKA	CDK4	EPHA5	FUBP1	JAK3	MSH6	PHOX2B	RASA1	SOX9	ANKRD11	INHBA	CSDE1	RXRA
AURKB	CDK6	EPHB1	GATA1	JUN	MTOR	PIK3C2G	RB1	SPEN	BCL10	MALT1	CYLD	SESN1
AXIN1	CDK8	ERBB2	GATA2	KDM5A	MUTYH	PIK3C3	RBM10	SPOP	BIRC3	MAP3K14	CYSLTR2	SESN2
AXIN2	CDKN1A	ERBB3	GATA3	KDM5C	MYC	PIK3CA	RECQL4	SRC	CALR	MAPK3	DROSHA	SESN3
AXL	CDKN1B	ERBB4	GNA11	KDM6A	MYCL1	PIK3CB	REL	STAG2	CD79A	MGA	DUSP4	SHOC2
B2M	CDKN2A	ERCC2	GNAQ	KDR	MYCN	PIK3CD	RET	STK11	CEBPA	MST1	ELF3	SLX4
BAP1	CDKN2B	ERCC3	GNAS	KEAP1	MYD88	PIK3CG	RFWD2	STK40	CENPA	MST1R	EPAS1	SMYD3
BARD1	CDKN2C	ERCC4	GREM1	KIT	MYOD1	PIK3R1	RHOA	SUFU	CSF3R	NCOA3	ERF	SOS1
BBC3	CHEK1	ERCC5	GRIN2A	KLF4	NBN	PIK3R2	RICTOR	SUZ12	CXCR4	NEGR1	EZH1	SPRED1
BCL2	CHEK2	ERG	GSK3B	KRAS	NCOR1	PIK3R3	RIT1	SYK	DNAJB1	NFKBIA	FAM58A	STK19
BCL2L1	CIC	ESR1	H3F3C	LATS1	NF1	PIM1	RNF43	TBX3	EIF4A2	NUP93	HLA-B	TAP1
BCL2L11	CREBBP	ETV1	HGF	LATS2	NF2	PLK2	ROS1	TERT	EIF4E	PGR	INPPL1	TAP2
BCL6	CRKL	ETV6	HIST1H1C	LMO1	NFE2L2	PMAIP1	RPS6KA4	TET1	EPHA7	PLCG2	KMT2B	TEK
BCOR	CRLF2	EZH2	HIST1H2BD	MAP2K1	NKX2-1	PMS1	RPS6KB2	TET2	ERRF1	POLD1	KMT5A	TP53BP1
BLM	CSF1R	FAM123B	HIST1H3B	MAP2K2	NKX3-1	PMS2	RPTOR	TGFBR1	FOXO1	PPM1D	KNSTRN	UPF1
BMPR1A	CTCF	FAM175A	HNF1A	MAP2K4	NOTCH1	PNRC1	RUNX1	TGFBR2	FYN	PPP6C	LYN	WHSC1
BRAF	CTLA4	FAM46C	HRAS	MAP3K1	NOTCH2	POLE	RYBP	TMEM127	GLI1	RAB35	MAPKAP1	WHSC1L1
BRCA1	CTNNB1	FANCA	ICOSLG	MAP3K13	NOTCH3	PPP2R1A	SDHA	TMPRSS2	GPS2	RAD21	MSH3	WWR1

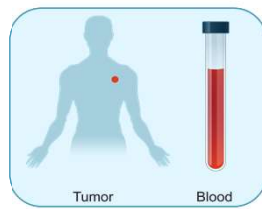
>40,000 cases: 341 genes (n=2,894), 410 genes (n=9,880), 468 genes (n>27,000)



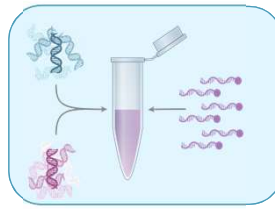
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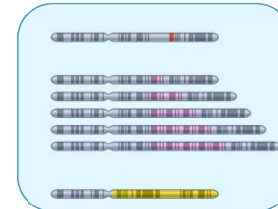
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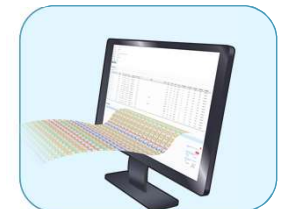
**Sample
Preparation**



Sequencing



Bioinformatics

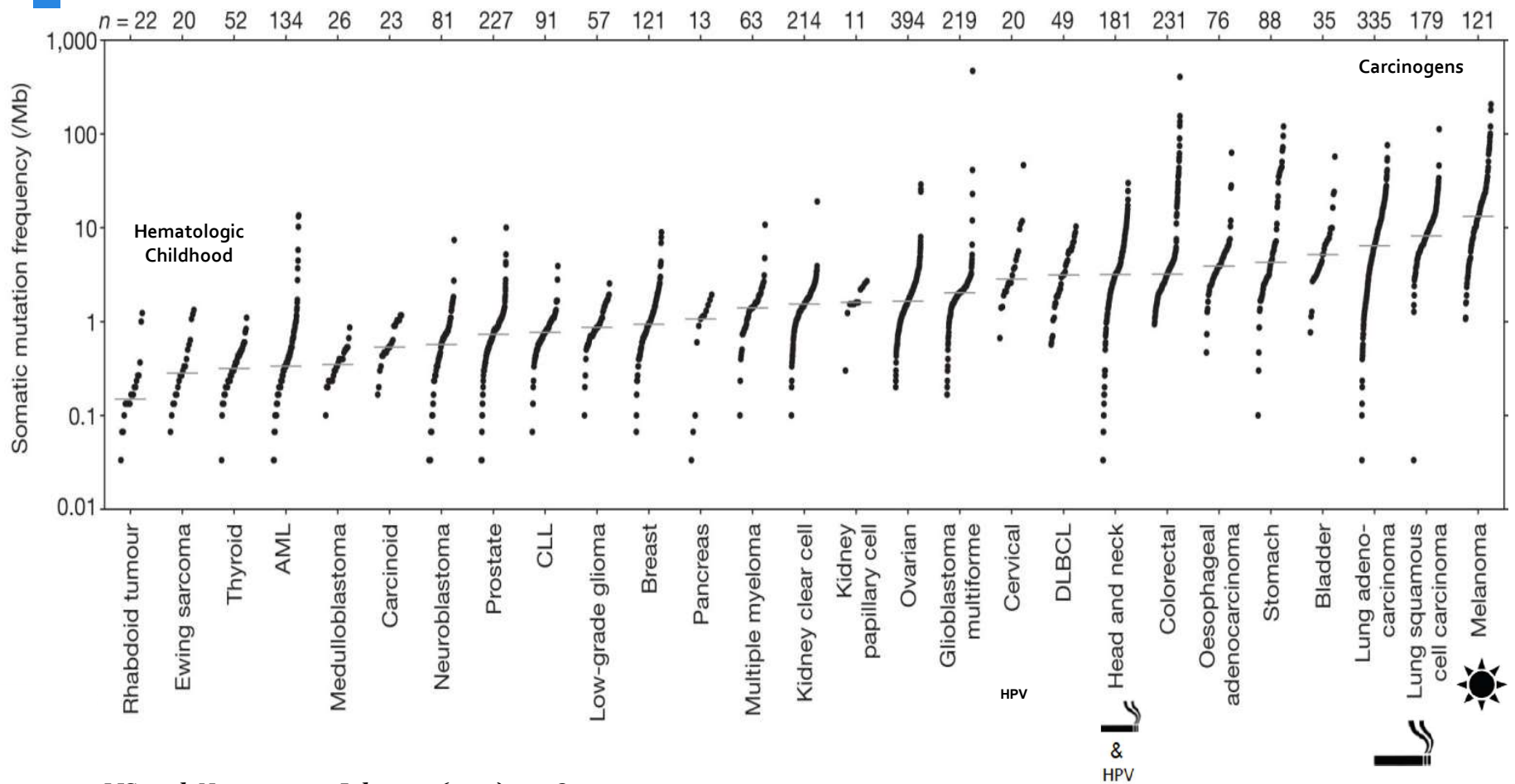


**Case Review &
Sign Out**

Somatic Alterations (tumor/normal pairs):
Sequence Mutations
Copy Number Gains and Losses (gene and arm-level)
Select Rearrangements / Fusions
Germline Mutations (with additional consent)

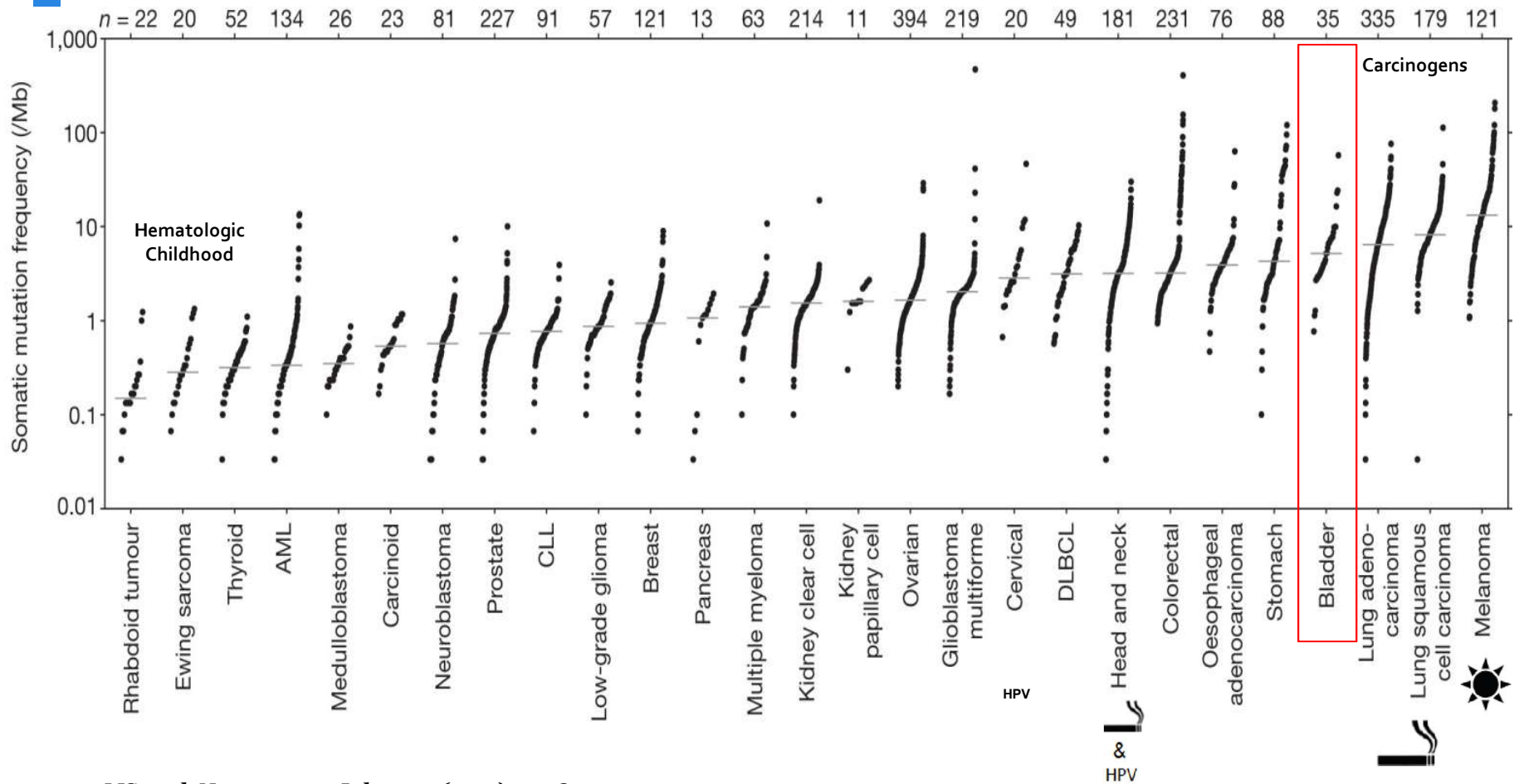


Most mutations in cancer are “passengers”



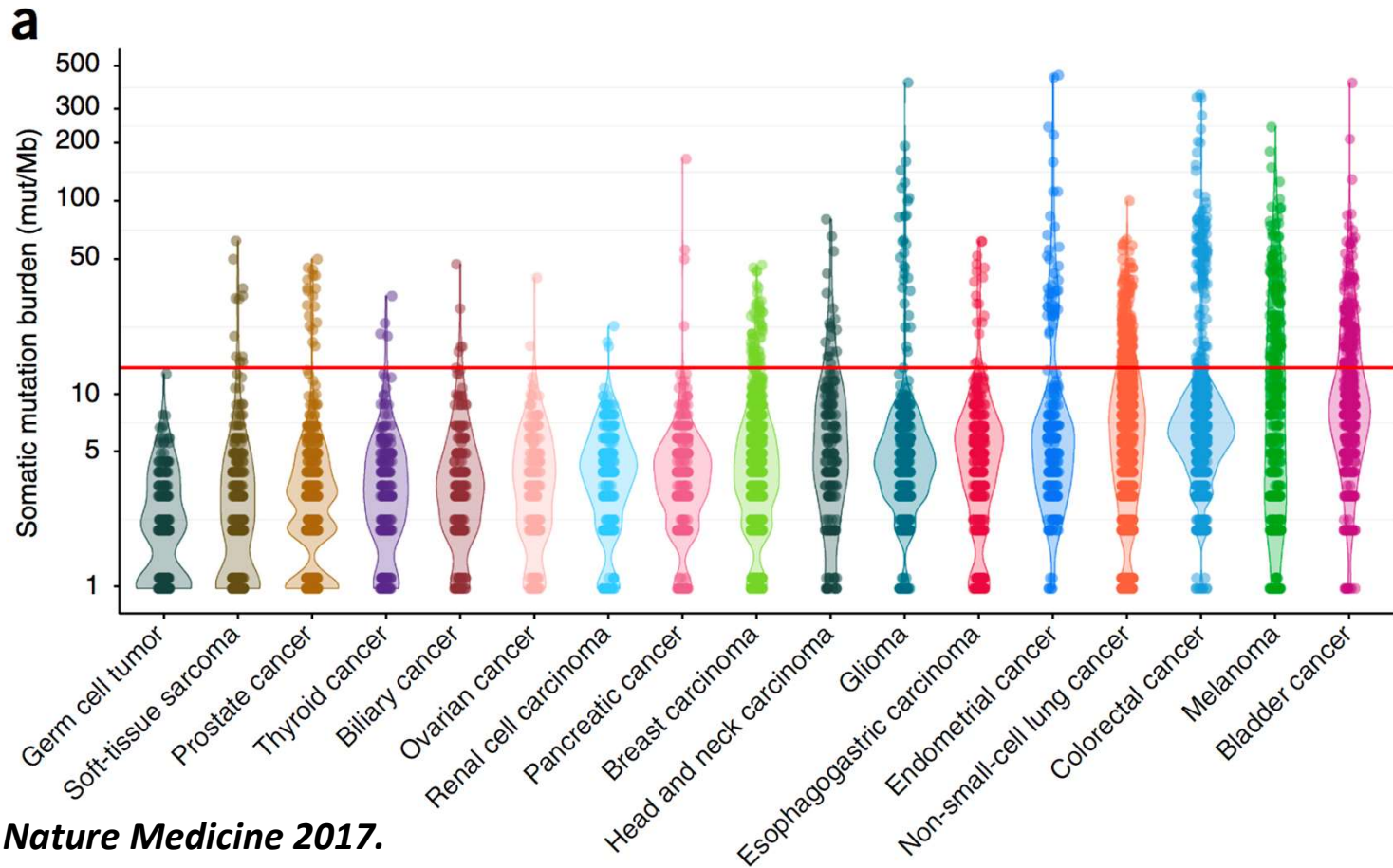
Lawrence, MS et al. Nature. 2013 Jul 11;499(7457):214-8

Most mutations in cancer are “passengers”



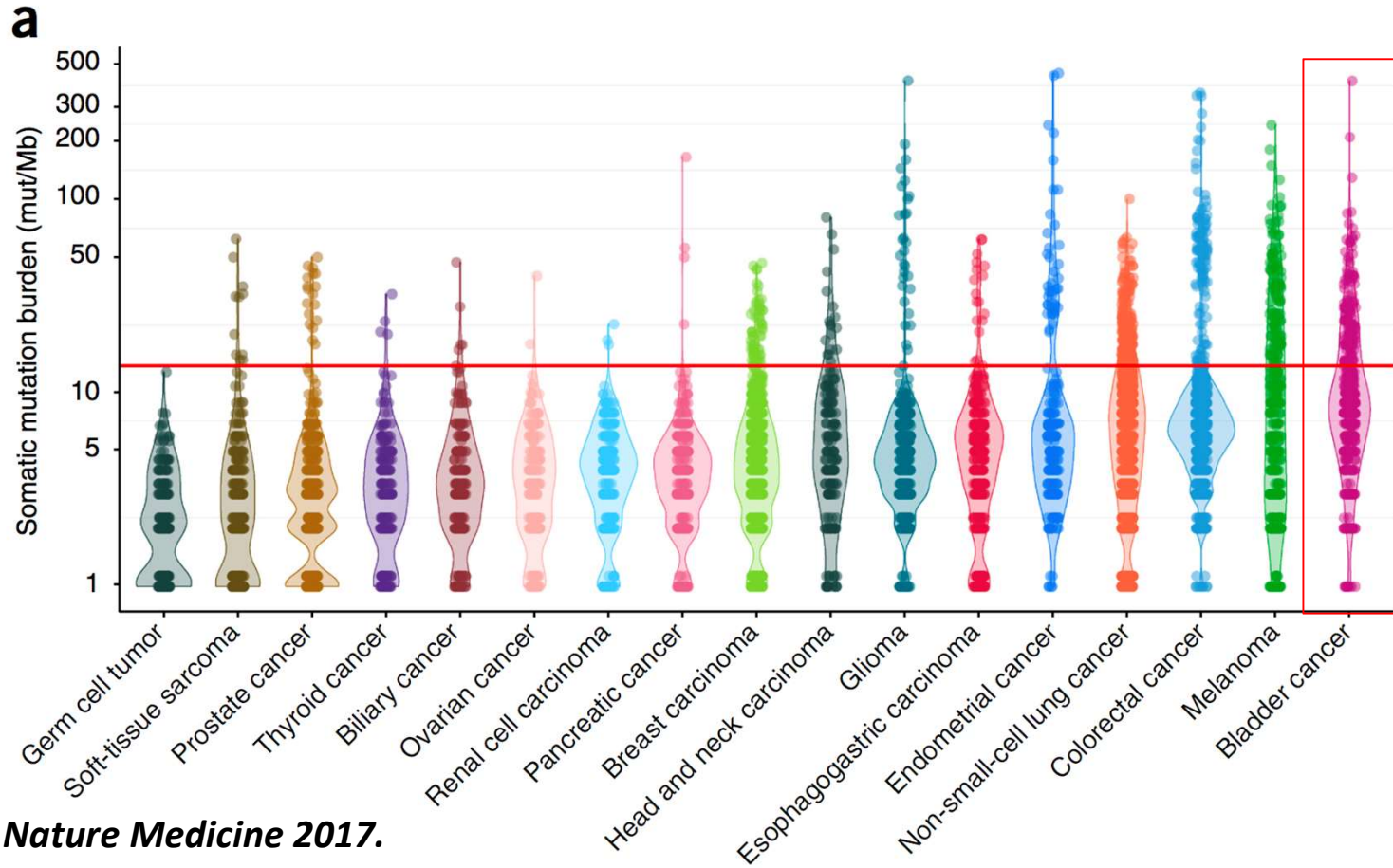
Lawrence, MS et al. Nature. 2013 Jul 11;499(7457):214-8

MSK-IMPACT can infer TMB



Zehir et al. Nature Medicine 2017.

MSK-IMPACT can infer TMB



Zehir et al. Nature Medicine 2017.



How can we identify driver & actionable variants?

- 1 Recurrence
- 2 Prior Knowledge
- 3 Intuitive visualization



How can we identify driver & actionable variants?

1

Recurrence

Frequently mutated amino acids



Cancer Hotspots

2

Prior Knowledge

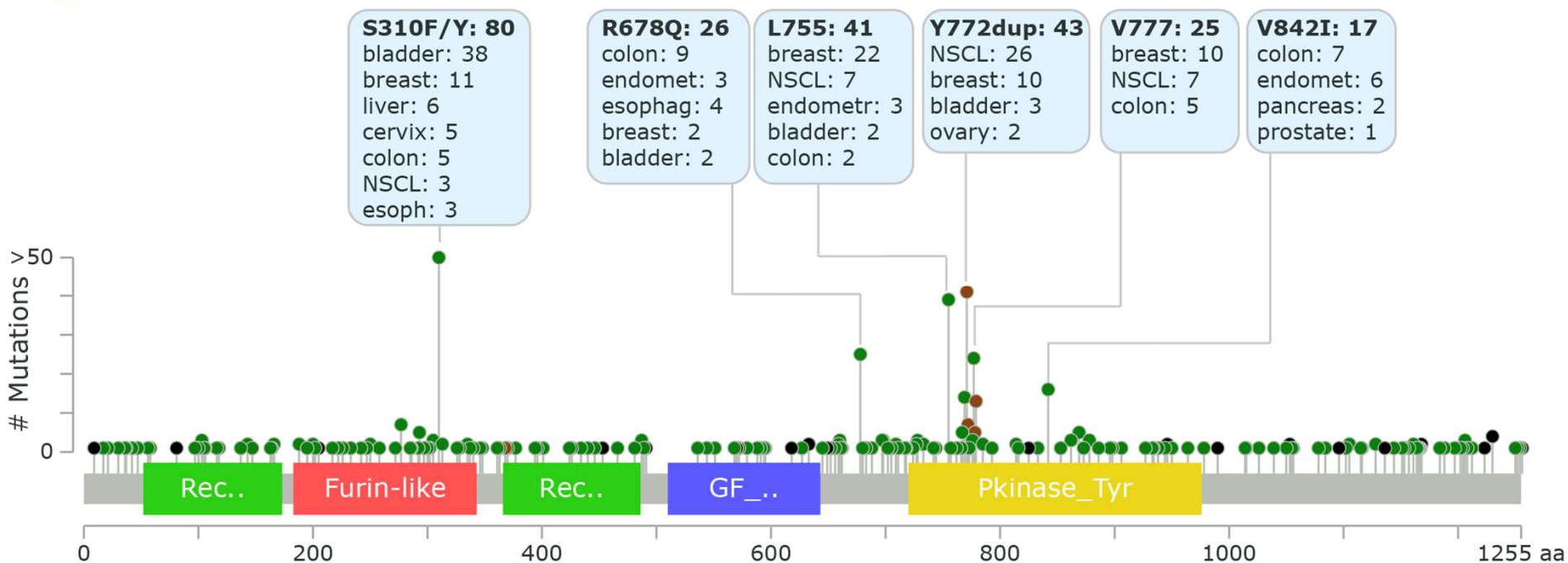
3

Intuitive visualization

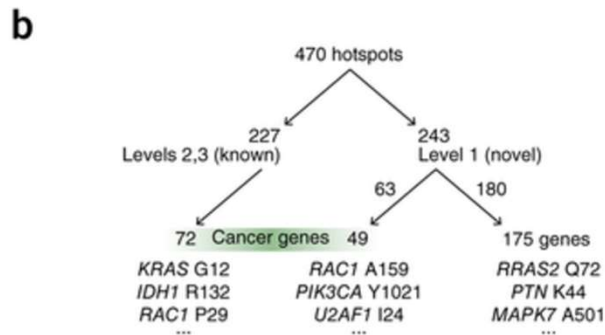
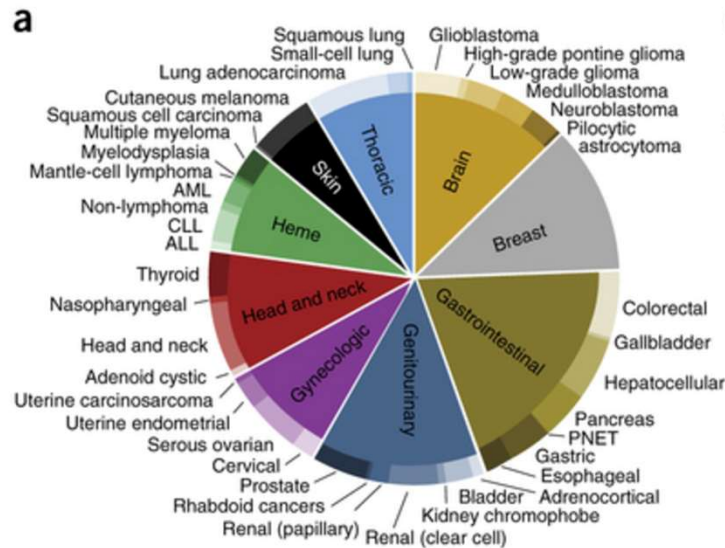


Memorial Sloan Kettering
Cancer Center

ERBB2 mutation pattern



Algorithmic detection of mutational hotspots

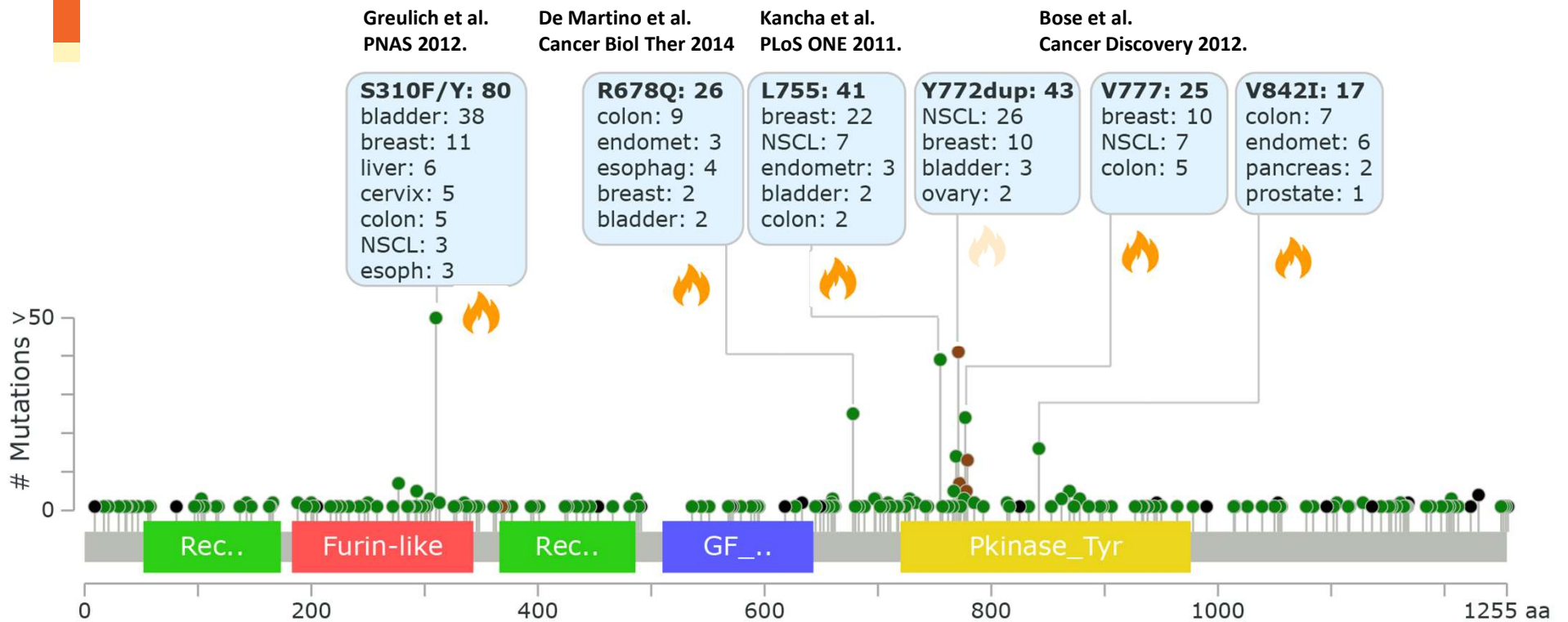


- Mutability of nucleotides in tri-nucleotide context
- Codon mutability

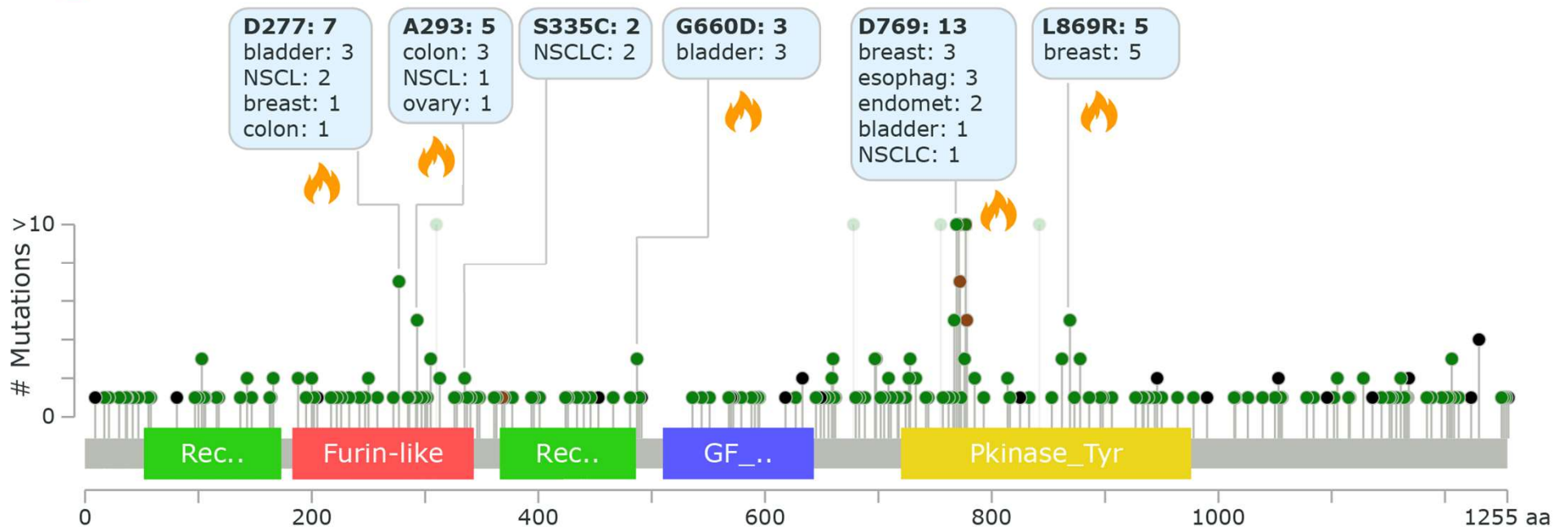
11,119 human tumors in 41 cancer types

470 somatic hotspots in 275 genes

ERBB2 hotspots in 10,000 tumor samples



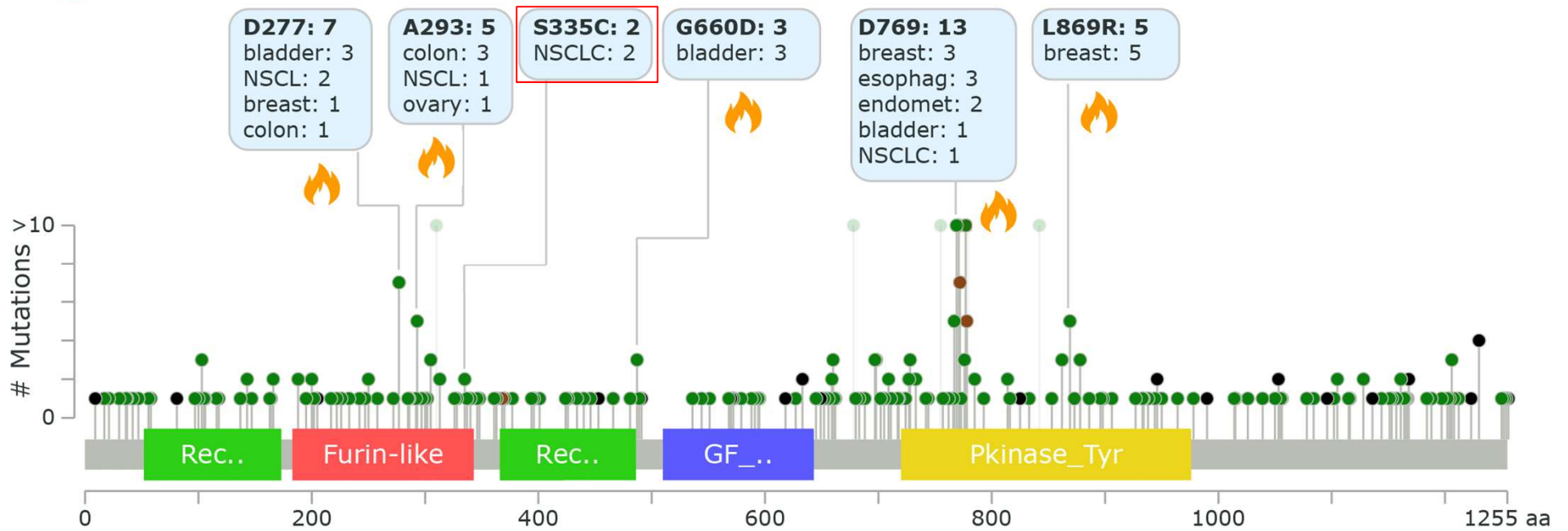
ERBB2 hotspots in 24,500 tumor samples



20 ERBB2 hotspot in analysis of 24,500 tumors

1165 hotspots in 247 genes

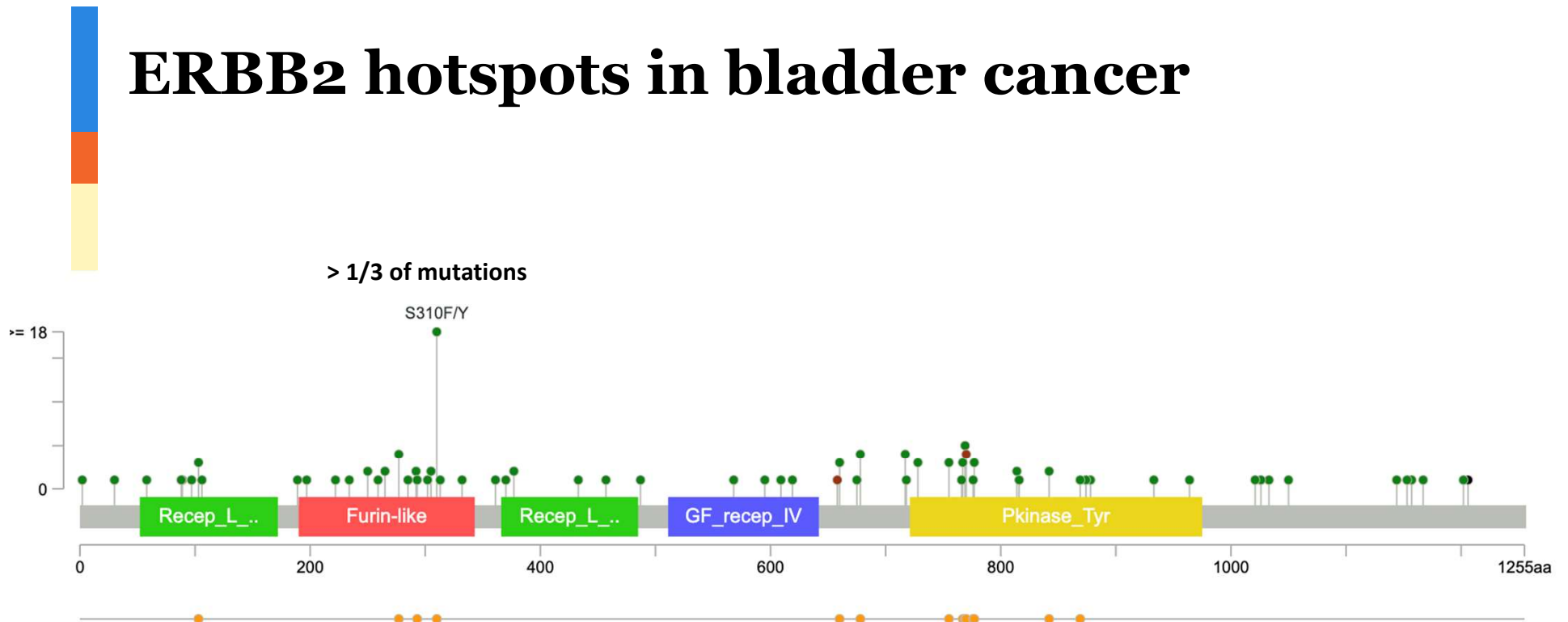
ERBB2 hotspots in 24,500 tumor samples



20 ERBB2 hotspot in analysis of 24,500 tumors

1165 hotspots in 247 genes

ERBB2 hotspots in bladder cancer





A RESOURCE FOR STATISTICALLY SIGNIFICANT MUTATIONS IN CANCER

[Show/Hide](#)† Mouse over **Variants** and **Samples** values for more informationSearch:

Gene	↕	Residue	↕	Variants [†]	↕	Q-value	↕	Samples [†]	↕
BRAF		V600				0		558	
KRAS		G12				0		736	
PIK3CA		H1047				0		283	
IDH1		R132				0		324	
NRAS		Q61				0		235	
PIK3CA		E545				0		277	
PIK3CA		E542				1.07e-215		145	
TP53		R273				9.66e-139		253	
TP53		R248				7.57e-120		216	
KRAS		G13				3.74e-119		92	
KRAS		Q61				1.23e-105		75	






<http://cancerhotspots.org/>Chang, MT et al. *Nat Biotechnol.* 2016 Feb;34(2):155-63

A RESOURCE FOR STATISTICALLY SIGNIFICANT MUTATIONS IN CANCER

Show/Hide

† Mouse over **Variants** and **Samples** values for more information

Search:

Gene	Residue	Variants †	Q-value	Samples †
ERBB2	S310	 F	4.27e-34	26
ERBB2	L755	 S M PW	1.74e-24	14
ERBB2	V842	 I	1.31e-10	14
ERBB2	R678	 Q	0.0000220	9
ERBB2	D769	 Y H N	0.0000269	8
ERBB2	V777	 L M	0.0001	5

Showing 1 to 6 of 6 mutations (filtered from 470 total mutations)

Previous **1** Next

Show mutations per page

Download

<http://cancerhotspots.org/>

Chang, MT et al. *Nat Biotechnol.* 2016 Feb;34(2):155-63

A RESOURCE FOR STATISTICALLY SIGNIFICANT MUTATIONS IN CANCER

Show/Hide

 † Mouse over **Variants** and **Samples** values for more information

 Search:

Gene	Residue	Variants †	Q-value	Samples †
ERBB2	S310		4.27e-34	26
ERBB2	L755			14
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ERBB2	R678			9
ERBB2	D769		0.0000269	8
ERBB2	V777		0.0001	5

Variant ↓ Count ↓

							25
							1

Showing 1 to 6 of 6 mutations (filtered from 470 total mutations)

 Previous **1** Next

 Show mutations per page

Download

<http://cancerhotspots.org/>

 Chang, MT et al. *Nat Biotechnol.* 2016 Feb;34(2):155-63



A RESOURCE FOR STATISTICALLY SIGNIFICANT MUTATIONS IN CANCER

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Gene	Residue	Variants †	Q-value	Samples †
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ERBB2	L755	S M PW		
ERBB2	V842	I		
ERBB2	R678	Q		
ERBB2	D769	Y H N		
ERBB2	V777	L M		

Showing 1 to 6 of 6 mutations (filtered from 470 total mutations)

Show mutations per page

26 total sample(s) with 9 distinct cancer type(s)

Search:

Cancer Type	Count
Bladder Urothelial Carcinoma	7
Stomach Adenocarcinoma	5
Cervical Squamous Cell Carcinoma	4
Invasive Breast Carcinoma	3
Cutaneous Squamous Cell Carcinoma	2
High-Grade Serous Ovarian Cancer	2
Colorectal Adenocarcinoma	1
Head and Neck Carcinoma	1

[1](#) [Next](#)[Download](#)<http://cancerhotspots.org/>Chang, MT et al. *Nat Biotechnol.* 2016 Feb;34(2):155-63



How can we identify driver & actionable variants?

- 1 **Recurrence**
Frequently mutated amino acids



- 2 **Prior Knowledge**
Driver & actionable variants



- 3 **Intuitive visualization**

Currently available Knowledgebases (for somatic mutations)

MY CANCER GENOME
GENETIC TESTING FOR CANCER MEDICINE

Search My Cancer Genome

Home DIRECT About Us

What is EGFR? EGFR in Lung Cancer EGFR c.2573T>G (L858R) Clinical Trials

EGFR c.2573T>G (L858R) Mutation in Non-Small Cell Lung Cancer

Properties

Location of mutation	Kinase domain (exon 2)
Frequency of EGFR mutations in NSCLC	>10% in the USA >10% in Asia Lynch et al., 2005; Park et al., 2009
Frequency of EGFR L858R mutations in EGFR-mutated NSCLC	41% (Stawiski and Skapek, 2012)

Implications for Targeted Therapeutics

Response to first generation EGFR Tyk inhibitors, gefitinib	Confers increased sensitivity*
Response to second generation EGFR Tyk inhibitors, dacomitinib, neratinib	Confers increased sensitivity*
Response to third generation EGFR Tyk (mutant specific)	Confers increased sensitivity*
Response to anti-EGFR antibodies	Currently no data for EGFR mutation in predicting response to NSCLC

My Cancer Genome
Vanderbilt

Personalized Cancer Medicine
MD Anderson Cancer Center

Search Gene Select Gene

Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy. In addition, patient genetic factors can be associated with drug metabolism, drug response and drug toxicity. Personalized tumor molecular profiles, tumor disease site and other patient characteristics are then potentially used for determining optimum individualized therapy options. Tumor biomarkers can be DNA, RNA, protein and metabolomic profiles that predict therapy response. However, the most recent approach is the

Personalized Cancer Therapy

Molecular Profiling → Predicts Markers → Makes prediction of drug sensitivity/resistance

Personalized Cancer Medicine
MD Anderson

Targeted Cancer Care
Massachusetts General Hospital Cancer Center

Targeted cancer trials and treatments an unique as your cancer experience.

Home > My Trial Guide

My Trial Guide

The Mass General Cancer Center's world class targeted therapy programs are constantly expanding, so there may be clinical trials here specifically suited to you.

Search Diseases, Genes & Mutations

To find trials and more information, use the tabs below to select a disease, gene, and mutation. If you don't know this information, please enter any information that you do have.

...or Search by Drug

If you are interested in learning about certain drugs or their associated trials, please use the "Drug" menu to search the drug you are interested in.

Disease: Select Disease 1 Drug: Select Drug 1

Targeted Cancer Care
Mass General

JAX-Clinical Knowledgebase (CKB)

JAX-CKB is a powerful tool for interpreting complex genomic profiles and represents a valuable resource for clinicians and translational and clinical researchers. JAX-CKB advances JAX's mission to discover genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

Recent News

- Current news updated daily
- New case report: First Sequencing in Cancer Patient Plasma DNA (Pilot) (7/20/17)

Basic Search

Filter by Gene
Filter by Variant
Filter by Drug/line
Filter by Drug

CKB
Jackson Labs

Knowledgebase

Welcome to the Precision Medicine Knowledgebase. The Precision Medicine Knowledgebase is organized to provide information about variants and interpretations in a structured way.

All Articles

Genes	140
Variants	262
Interpretations	251

Download Information
Download All Interpretations (Excel)

Most Recent Entries

Browse by Gene

EGFR	PTEN	PRKCA	KIT
BRCA1	TRPS1	CTNNA1	ERBB2
KRAS	MET	APC	ATM
NRAS	CDKN1B	EDNRA	ESRRA1

Browse by Tumor

Melanocytic/Melanoma	Melanoma
Adenocarcinoma	Glioblastoma
Glucagonoma	Transitional Cell Carcinoma
Papillary Carcinoma	Clear Cell Renal Cell Carcinoma

Precision Medicine Knowledgebase
Cornell

CanDL
Cancer Driver Log

Type gene, mutation or both here

Want to submit a mutation? Show Advanced Options

Cancer Driver Log
Ohio State University

CIViC
CLINICAL INTERPRETATIONS OF VARIANTS IN CANCER

Discover supported clinical interpretations of mutations related to cancer.

Participate with colleagues to add variants and support for cancer-related mutations.

The Precision Medicine Revolution

Precision medicine relies on the use of genomics and treatment strategies that are tailored to the unique features of each individual and their disease. In the context of cancer this might translate to the identification of specific mutations whose presence predicts response to a targeted therapy. The biomedical research community has been successful in large and growing number of cases. Currently these interpretations are largely in private or uncurated databases resulting in extensive repetition of effort.

CIViC's Role in Precision Medicine

Enabling precision medicine will require that information to be centralized, defined and interpreted for application in the clinic. CIViC is an open access, open source, community-driven web Resource for Clinical Interpretation of Variants in Cancer. Our goal is to enable precision medicine by providing an international forum for dissemination of knowledge and active discussion of the clinical significance of cancer genome alterations.

CIViC
Wash U

CANCER GENOME INTERPRETER

Alterations

View CGI example results

Search

Cancer type

- (CANCER) Any cancer type
- (HEMATO) Hematologic malignancies
- (COLO) Solid tumors

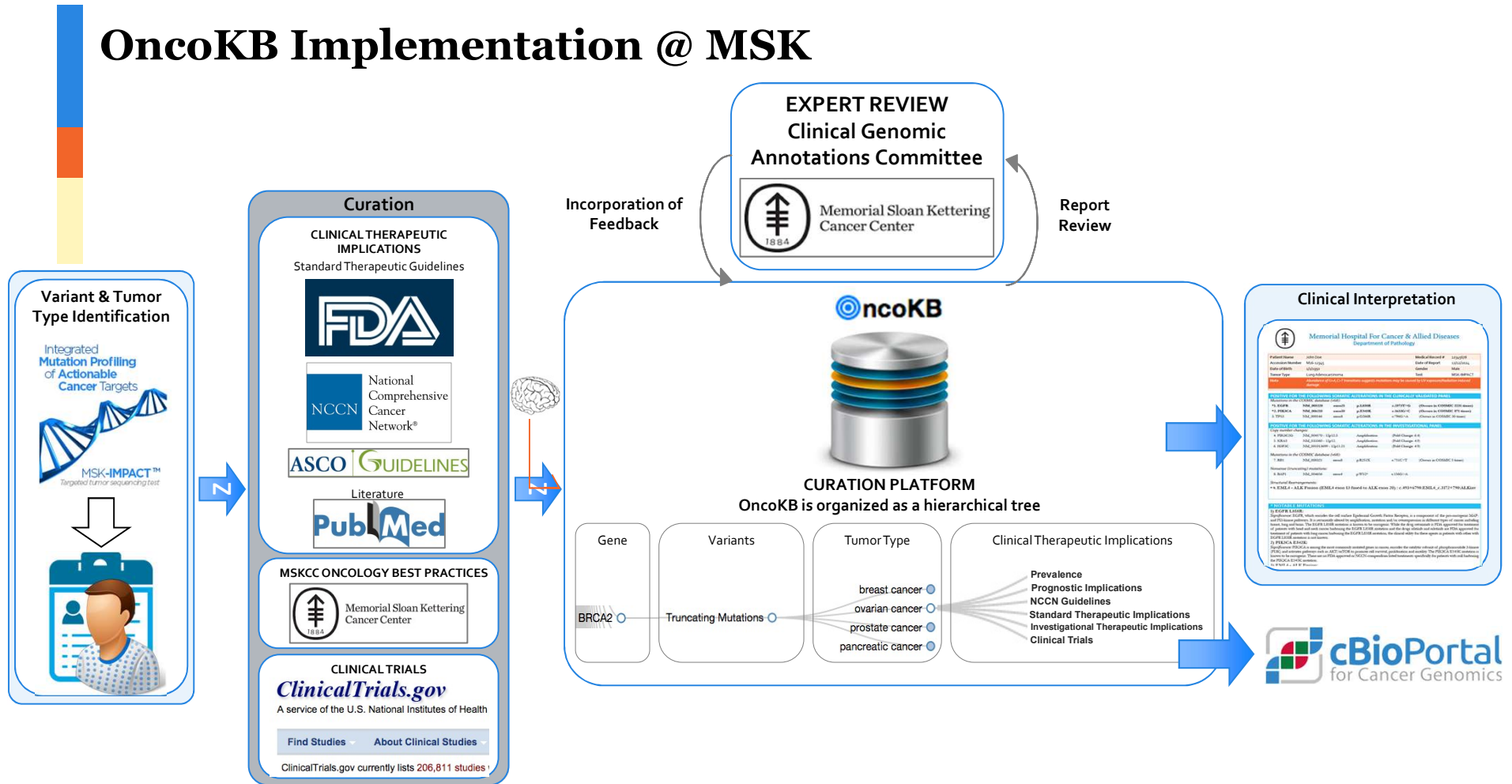
Cancer Genome Interpreter
UPF Barcelona



Key pieces of information about individual variants

- **Is the variant a known or likely driver?**
- **Is the variant therapeutically actionable?**
- Is the variant prognostic?
- Can the variant be used for diagnostic purposes?

OncoKB Implementation @ MSK



<http://oncokb.org/>

Onc@KB

Precision Oncology Knowledge Base

632

Genes

4737

Alterations

43

Tumor Types

89

Drugs

Search Gene / Alteration / Drug

Level 1
FDA-approved
25 Genes

Level 2
Standard care
13 Genes

Level 3
Clinical evidence
26 Genes

Level 4
Biological evidence
20 Genes

Level R1
Standard care
5 Genes

Level R2
Clinical evidence
6 Genes

When using OncoKB, please cite: [Chakravarty et al., JCO PO 2017](#).

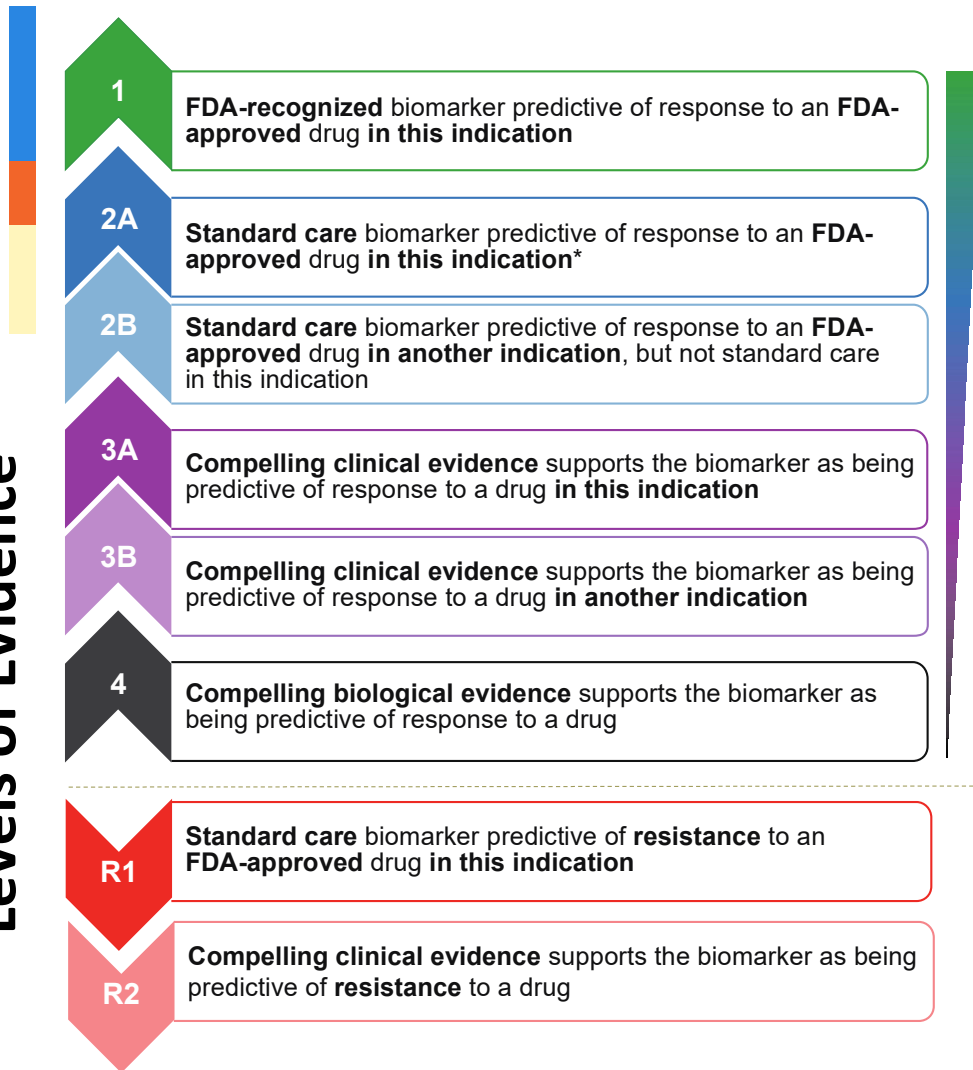
OncoKB is intended for research purposes only. Please review the [usage terms](#) before continuing.

When using OncoKB, please cite: [Chakravarty et al., JCO PO 2017](#).

[MSK](#) | [CMO](#) | [Quest Diagnostics](#) | [cBioPortal](#) | [OncoTree](#)



Levels of Evidence



Standard Therapeutic Implications
 *Includes biomarkers that are recommended as standard care by the NCCN or other expert panels but not necessarily FDA-recognized for a particular indication

Investigational Therapeutic Implications
 possibly directed to clinical trials

Hypothetical Therapeutic Implications
 based on preliminary, non-clinical data

Standard Therapeutic Implications

Investigational Resistance Implications
 based on clinical data

BRAF V600E in melanoma
EGFR in lung cancer
ERBB2 amp in breast/gastric

MET amp & splice in lung cancer
RET fusions in lung cancer

BRCA2 in prostate
ERBB2 amp in lung cancer

ERBB2, AKT1 mut in breast
IDH1 in several tumor types

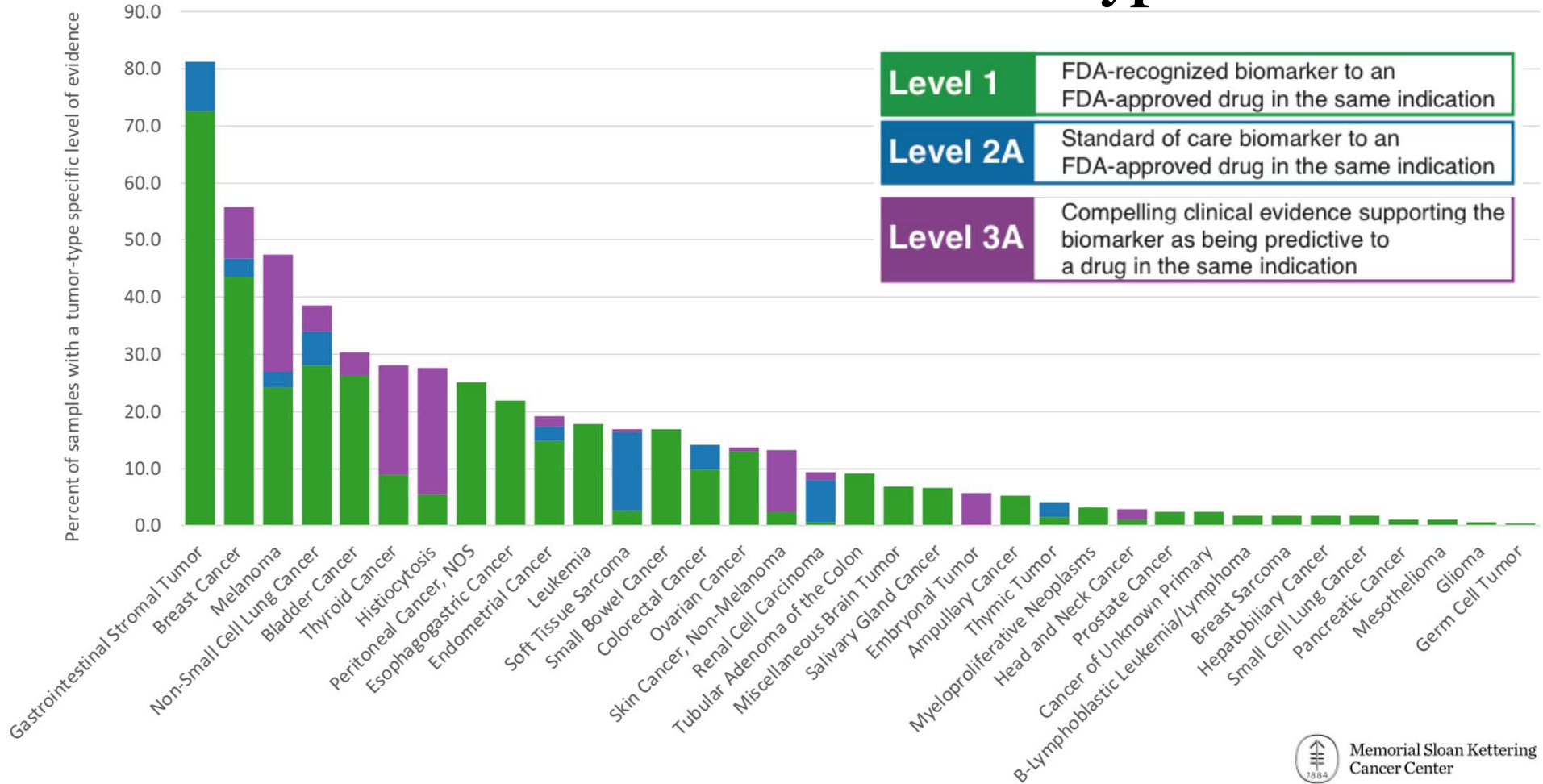
ERBB2 mutation in bladder cancer

KRAS mutations in lung

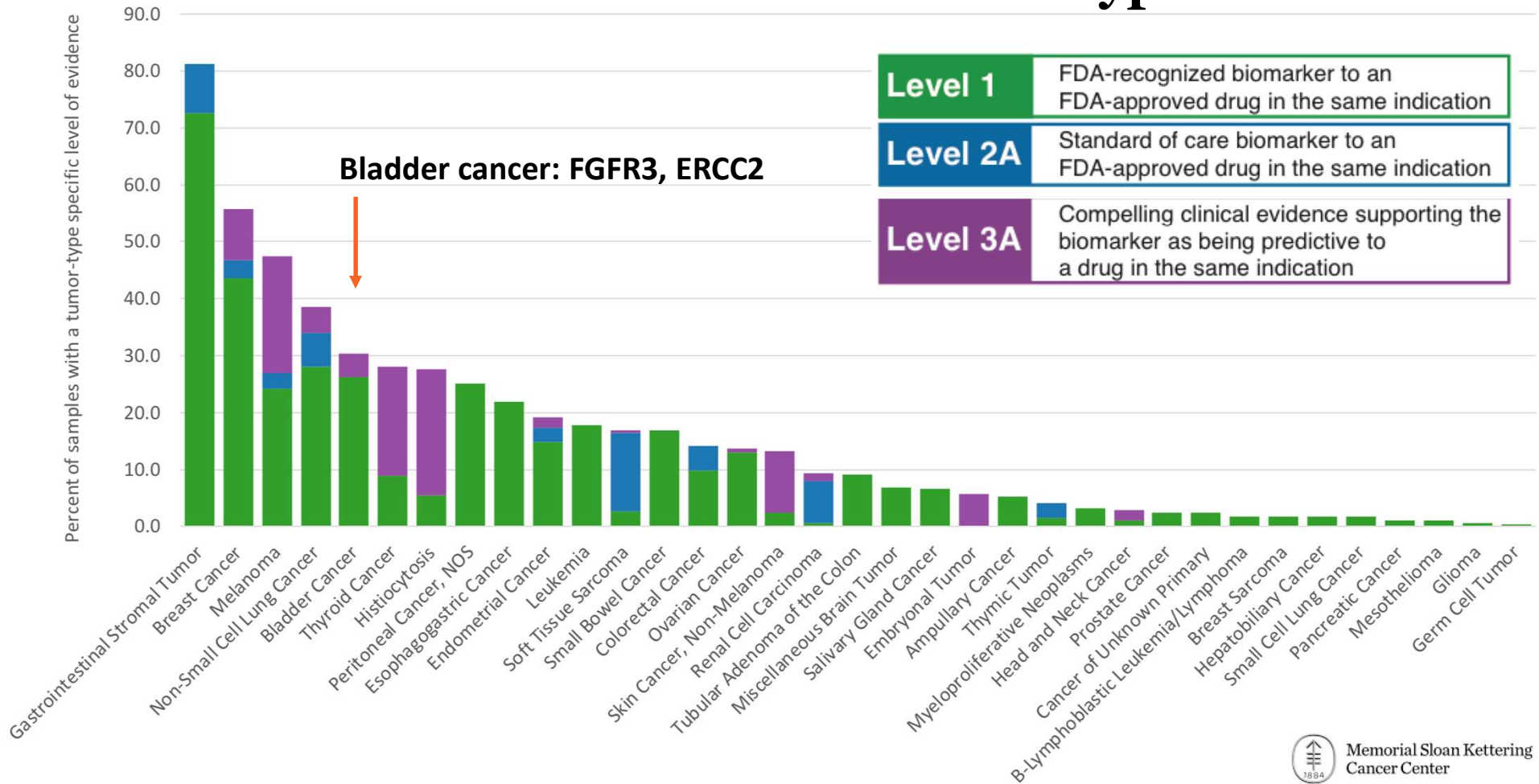
KRAS mutations in colorectal
PDGFRA D842V in GIST

ESR1 D538V in breast

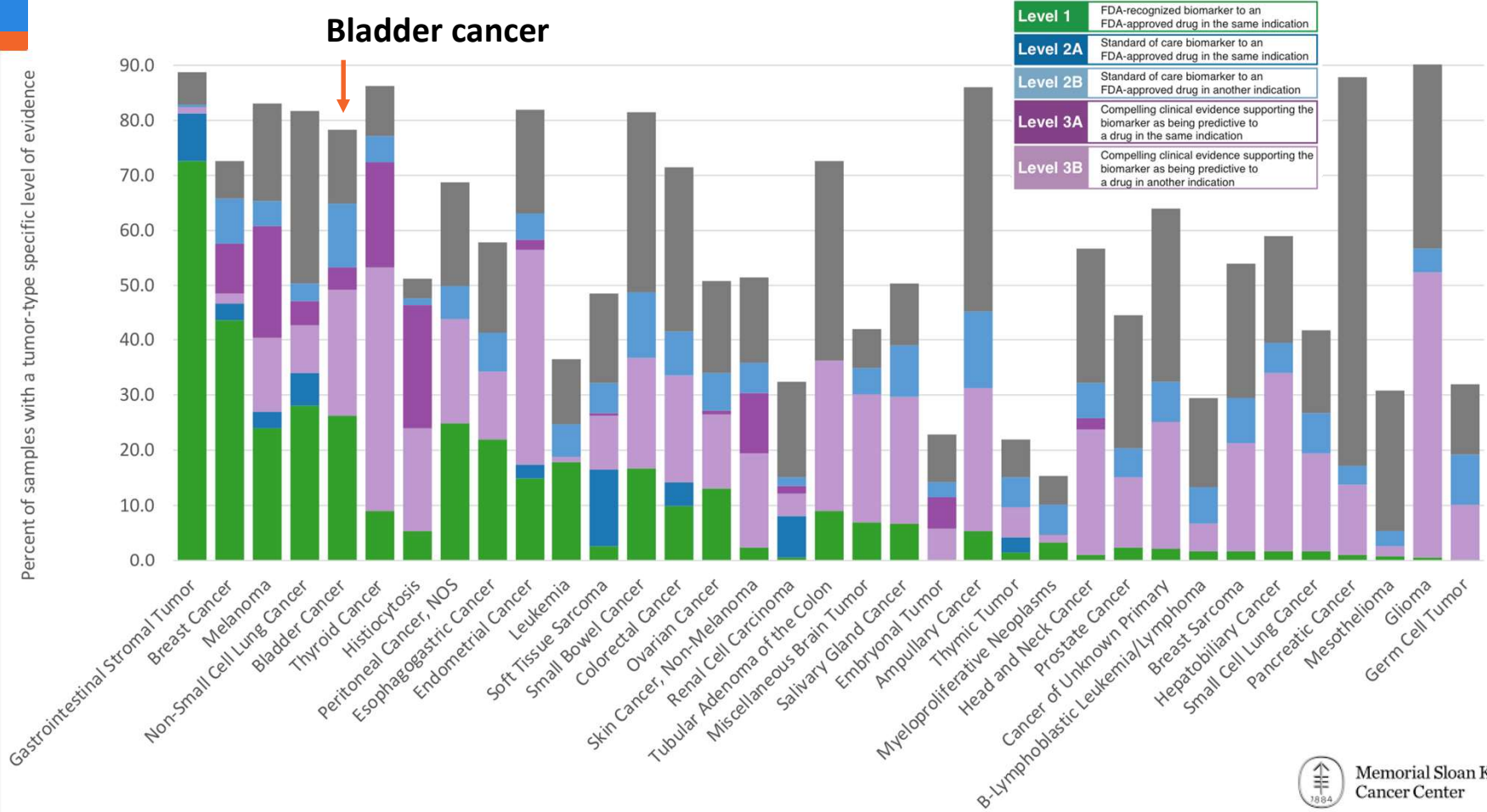
Actionable alterations across tumor types



Actionable alterations across tumor types



Actionable alterations across tumor types



Onc^oKB

Precision Oncology Knowledge Base

636

Genes

4780

Alterations

44

Tumor Types

89

Drugs

Search Gene / Alteration / Drug

Level 1
FDA-approved
25 Genes

Level 2
Standard care
13 Genes

Level 3
Clinical evidence
29 Genes

Level 4
Biological evidence
20 Genes

Level R1
Standard care
5 Genes

Level R2
Clinical evidence
6 Genes

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When using OncoKB, please cite: [Chakravarty et al., JCO PO 2017](#).

[MSK](#) | [CMO](#) | [Quest Diagnostics](#) | [cBioPortal](#) | [OncoTree](#)





Memorial Sloan Kettering
Cancer Center.

Memorial Hospital For Cancer & Allied Diseases
Molecular Diagnostics Service, Department of Pathology

1275 York Avenue New York, NY, 10065
Tel: (212) 639-8280 | Fax: (212) 717-3515

MSK-IMPACT Testing Report

Patient Name	Redacted	Medical Record #	Redacted
Date of Birth	Redacted	Accession #	Redacted
Gender	Redacted	Specimen Submitted	Bladder tissue
Tumor Type	Small Cell Bladder Cancer	Surgical Path. #	Redacted
Ref. Physician	Redacted	Account #	Redacted
Date of Receipt	Redacted	Date of Report	Redacted
Date of Procedure	Redacted		

Summary	28 mutations, no copy number alterations, 1 structural variant detected. 3 alterations have OncoKB treatment interpretations.
MSI Status	MICROSATELLITE STABLE (MSS). See MSI note below. ⁶
Tumor Mutation Burden	The estimated tumor mutation burden (TMB) for this sample is 24.6 mutations per megabase (mt/Mb). The median TMB assessed by MSK-IMPACT for all patients is 3.9 mt/Mb and for patients with Bladder Cancer is 8.8 mt/Mb as of the date this report was issued. ⁷

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
<i>Mutations</i>				
ERCC2	Missense Mutation	N238S (c.713A>G)	exon 8	MAF: 51.9%
AKT1	Missense Mutation	E17K (c.49G>A)	exon 3	MAF: 64.4%
ERBB2	Missense Mutation	E265K (c.793G>A)	exon 7	MAF: 47.7%
FBXW7	Missense Mutation	R505G (c.1513C>G)	exon 10	MAF: 48.6%
TERT	Non-coding	g.1295228C>T	Promoter	MAF: 50.1%
ELF3	Frameshift Deletion	c.1105_11del	exon 9	MAF: 37.7%
CREBBP	Nonsense Mutation	Q1073* (c.3217C>T)	exon 16	MAF: 43.0%
FBXW7	Nonsense Mutation	G517* (c.1549G>T)	exon 10	MAF: 47.0%
KMT2D	Nonsense Mutation	E1990* (c.5968G>T)	exon 28	MAF: 47.3%
TP53	Nonsense Mutation	Q331* (c.991C>T)	exon 9	MAF: 92.3%
RB1	Splicing Mutation	X405_splice (c.1215+1G>C)	exon 12	MAF: 85.7%
BRD4	Frameshift Deletion	M905Wfs*44 (c.2712del)	exon 14	MAF: 43.4%
UPF1	In-frame Deletion	K576_Q579del (c.1726_1737del)	exon 13	MAF: 47.4%
BCOR	Missense Mutation	Q793E (c.2377C>G)	exon 4	MAF: 94.9%
CREBBP	Missense Mutation	E1550K (c.4648G>A)	exon 28	MAF: 48.0%
DNMT3A	Missense Mutation	E774K (c.2320G>A)	exon 19	MAF: 60.6%
KMT2D	Missense Mutation	E2081Q (c.6241G>C)	exon 31	MAF: 45.3%
MST1	Missense Mutation	M722I (c.2166G>C)	exon 18	MAF: 24.9%

DMP ID: P-0034252-T01-IM6 (Bladder Cancer)

Gene	Type	Alteration	Location	MAF
MUTYH	Missense Mutation	R126W (c.376C>T)	exon 4	MAF: 52.2%
MYCL1	Missense Mutation	S329L (c.986C>T)	exon 3	MAF: 58.9%
REL	Missense Mutation	D327N (c.979G>A)	exon 9	MAF: 25.5%
ROS1	Missense Mutation	G430S (c.1288G>A)	exon 12	MAF: 43.8%
SETD8	Missense Mutation	E136K (c.406G>A)	exon 4	MAF: 20.3%
SUZ12	Missense Mutation	L529F (c.1585C>T)	exon 13	MAF: 43.8%
TEK	Missense Mutation	S201L (c.602C>T)	exon 4	MAF: 30.0%
WHSC1L1	Missense Mutation	Q705E (c.2113C>G)	exon 11	MAF: 24.2%
INSR	Nonsense Mutation	S634* (c.1901C>A)	exon 9	MAF: 21.8%
MET	Nonsense Mutation	O558* (c.1672C>T)	exon 5	MAF: 45.4%

Structural Variants

ID3	Deletion	c.-3112_c.1662del	exons 1-2		d
-----	----------	-------------------	-----------	--	---

^a: A glossary of terms and icons used in this report can be found after the "Test and Methodology" section.

^b: Denotes clinically/analytically validated variants.

^c: Note: Allele specific copy number analysis by FACETS suggests loss of heterozygosity of TP53. FACETS results are for investigational use only.

^d: Note: The FBXW7 exon10 mutations occur on different alleles.

^e: Note: Allele specific copy number analysis by FACETS suggests loss of heterozygosity of RB1. FACETS results are for investigational use only.

^f: The ID3 rearrangement is a deletion that includes ID3 exons 1-2. The functional significance is undetermined.

^g: MSI Note: The MSIsensor score is 0.06.

^h: TMB is reported for investigational use only.

RefSeq IDs for the genes with reported variants along with a list of all 468 genes can be found on the last page

Investigational biomarker:

Alteration(s)	Drugs(s)	Annotation
Level 3A ERCC2 N238S MAF: 51.9%	Cisplatin	ERCC2, a DNA helicase involved in the nucleotide excision repair (NER) pathway, is frequently mutated in bladder cancer. Germline mutations of ERCC2 are associated with xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome, and predispose to certain cancers. The ERCC2 N238S mutation is likely oncogenic. There is promising clinical data in patients with bladder cancer harboring oncogenic ERCC2 alterations treated with platinum-based chemotherapies such as cisplatin. Last updated in OncoKB: 01/31/2018.
Level 3B AKT1 E17K MAF: 64.4%	AZD5363	AKT1, an intracellular kinase, is mutated at low frequencies in a diverse range of cancers. The AKT1 E17K mutation is known to be oncogenic. While promising clinical data support the use of pan-AKT targeted inhibitors such as AZD5363 in patients with AKT1 E17K mutant ER+ breast and gynecologic cancers, their clinical utility in patients with AKT1 E17K mutant small cell bladder cancer is unknown. Last updated in OncoKB: 01/31/2018.
Level 3B ERBB2 E265K MAF: 47.7%	Neratinib	ERBB2, a receptor tyrosine kinase, is altered by amplification and/or overexpression in various cancers, most frequently in breast, esophagogastric and endometrial cancers. The ERBB2 E265K mutation is likely oncogenic. While there is promising clinical data in patients with breast and non-small cell lung cancers with known oncogenic ERBB2 alterations treated with the ERBB-targeted inhibitor neratinib, its clinical utility in patients with ERBB2 E265K mutant small cell bladder cancer is unknown. Last updated in OncoKB: 08/23/2018.

Technical Assessments

Tumor Coverage	620X	Test Version	468 genes
Status	Matched Sample	Run Number	2018-505

Coverage assessment: Unless specified, all exons tested had minimum depth of coverage of 100X.

Mutation assessment: Mutations are called against the patient's matched normal sample. This assay reports somatic variants confirmed to be absent in the matched normal.

Microsatellite instability (MSI) assessment by MSIsensor: MSIsensor Methodology: Microsatellite instability (MSI) status is assessed using the MSIsensor program (Niu B et al, 2014) that interrogates the length distribution of all genomic microsatellite loci included in the MSK-IMPACT capture region across tumor and matched normal. Evidence of microsatellite instability at 10% or greater of analyzable loci

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
<i>Mutations</i>				
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MUTYH	Missense Mutation	R126W (c.378C>T)	exon 4	MAF: 52.2%
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Investigational biomarker:

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How can we identify driver & actionable variants?

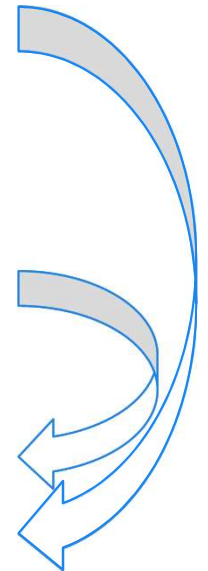
1 **Recurrence**
Frequently mutated amino acids



2 **Prior Knowledge**
Driver & actionable variants



3 **Intuitive visualization**





cBioPortal for Cancer Genomics: Data to knowledge / the last mile



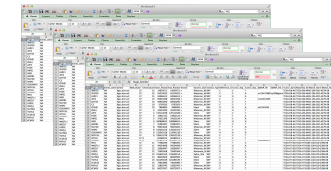
Tumor DNA, RNA



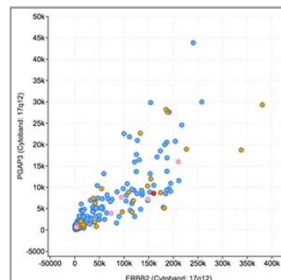
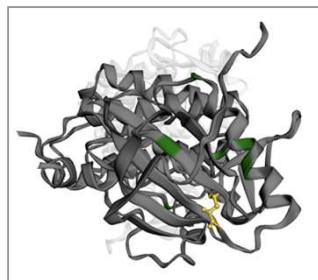
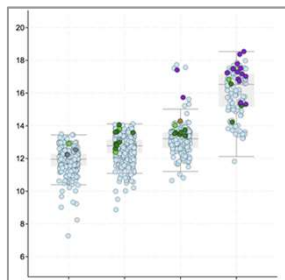
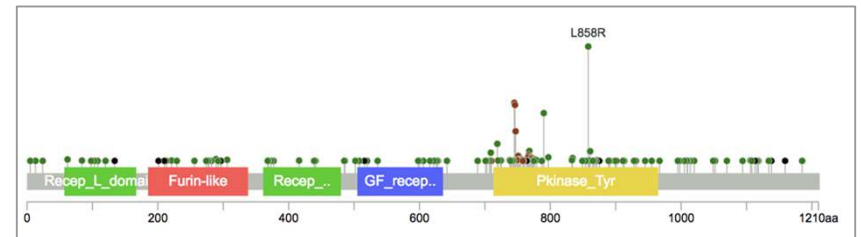
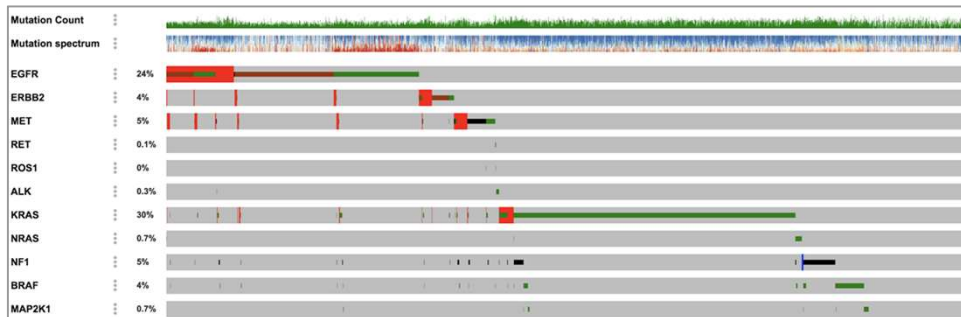
DNA sequencer,
Microarrays, etc.



Tumor and normal
sequences



Data



Patient: P-000580, Female, Non-Small Cell Lung Cancer (Lung Adenocarcinoma), DECEASED (79 months) darwin
Samples: P000080-T01-S01, Primary Lung, EGFR Show all samples MSK Clinical Sequencing Cohort (MSKCC)

Summary

10 Mutations (page 1 of 1)

Gene	Protein Change	Annotation	Mutation Type	Allele Freq	Copy #	Cohort	COSMIC
EGFR	T790M		Missense	0.13	De novo	MSKCC 3.7%	355
EGFR	L858R		Missense	0.48	De novo	MSKCC 8.7%	2247
TP53	N131I		Missense	0.81	De novo	MSKCC 45.6%	25
SMARCA4	E512*		Nonsense	0.31	De novo	MSKCC 3.9%	
TERT	Promoter		5'Flank	0.17	De novo	MSKCC 11.9%	
HGF	S166R		Missense	0.41	De novo	MSKCC 1.9%	1
NF1	V1364L		Missense	0.22	De novo	MSKCC 5.4%	
PDCD1	A129S		Missense	0.62	De novo	MSKCC 5.7%	
PITPR	Q402K		Missense	0.14	De novo	MSKCC 4.4%	
RNF43	R246S		Missense	0.27	De novo	MSKCC 2.3%	

Intuitive interface, quick response time, reduction of complexity

cBioPortal is open source software

<https://github.com/cBioPortal/cbioportal>

Licensed under the AGPL license

Free to download and use

Modifications welcome



open source



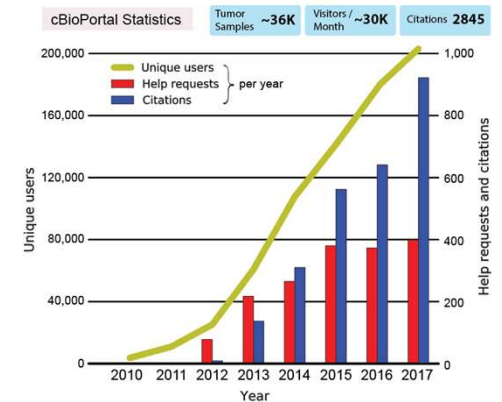
Software is now developed and maintained by multiple institutions

MSK, DFCI, Princess Margaret, CHOP, Cornell, The Hyve

Thousands of users at cbioportal.org

cBioPortal is installed at dozens of institutions and companies

Commercial support is available from The Hyve



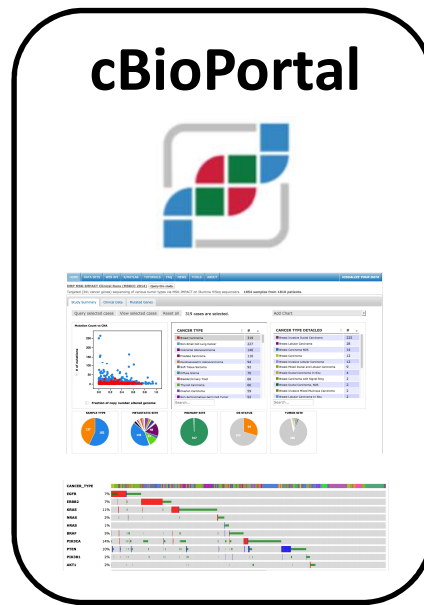
Memorial Sloan Kettering
Cancer Center

Public cBioPortal at <https://cbioportal.org>

Genomic data

TCGA, ICGC
Other public data

~10k
~40k



cBioPortal at MSK

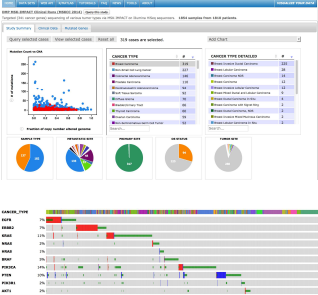
MSK clinical data
darwin CRDB CAISIS

Genomic data

- Clinical Sequencing
- CMO Research
- Foundation Medicine
- TCGA, ICGC
- Other public data

- ~40k
- ~15k
- ~2.5k
- ~10k
- ~40k

cBioPortal



OncoKB
Precision Oncology Knowledge Base
Annotation of Somatic Mutations in Cancer
Variant effect
Therapy Options

Recurrence
Cancer Hotspots
COSMIC
Catalogue of somatic mutations

Access controlled

Researchers & Clinicians

<http://cbioportal.org/>

Query Quick Search **Beta!** Download

Please cite: Cerami et al., 2012 & Gao et al., 2013

Select Studies for Visualization & Analysis:

0 studies selected (0 samples)

Search...

PanCancer Studies	3
Cell lines	2
Adrenal Gland	2
Ampulla of Vater	1
Biliary Tract	8
Bladder/Urinary Tract	13
Bone	2
Bowel	8
Breast	14
CNS/Brain	17
Cervix	2
Esophagus/Stomach	14
Eye	3
Head and Neck	13
Kidney	17

Quick select: TCGA PanCancer Atlas Studies Curated set of non-redundant studies

PanCancer Studies

- MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017) 10945 samples
- Pan-Lung Cancer (TCGA, Nat Genet 2016) 1144 samples
- Pediatric Pan-cancer (Columbia U, Genome Med 2016) 103 samples

Cell lines

- Cancer Cell Line Encyclopedia (Novartis/Broad, Nature 2012) 1020 samples
- NCI-60 Cell Lines (NCI, Cancer Res 2012) 67 samples

Adrenal Gland

Adrenocortical Carcinoma

- Adrenocortical Carcinoma (TCGA, PanCancer Atlas) 92 samples
- Adrenocortical Carcinoma (TCGA, Provisional) 92 samples

Ampulla of Vater

Ampullary Carcinoma

- Ampullary Carcinoma (Baylor College of Medicine, Cell Reports 2016) 160 samples

Biliary Tract

Cholangiocarcinoma

- Cholangiocarcinoma (MSK, Clin Cancer Res 2018) 195 samples

0 studies selected (0 samples)

Query By Gene

OR

Explore Selected Studies

What's New

@cbioportal



We are trying to get a better sense of local instances of cBioPortal around the world, how they are used, and whether there were any challenges during the installation. If you have a local instance (or tried to install one), please complete this survey: bit.ly/2XW3wNG

Sign up for low-volume email news alerts

Subscribe

Cancer Studies

The portal contains 260 cancer studies (details)

Cases by Top 20 Primary Sites



Lettering

<http://cbioportal.org/>

cBioPortal FOR CANCER GENOMICS

Data Sets Web API R/MATLAB Tutorials FAQ News Visualize Your Data About Login

Bladder Cancer (TCGA, Cell 2017)
All samples (412 patients / 413 samples) - EGFR, ERBB2 & 8 other genes

Queried genes are altered in
• 253 (61%) of queried patients
• 253 (61%) of queried samples

OncoPrint Cancer Types Summary Mutual Exclusivity Plots Mutations Co-expression Enrichments Survival Network Download

✓ The results below reflect the OQL specification from your query.

Add Clinical Tracks Heatmap Sort Mutations View Download 49 %

Gene	Alteration Type	Percentage
EGFR	AMP MUT	6%
ERBB2	AMP MUT	17%
ERBB3	AMP MUT	12%
FGFR1	AMP MUT	10%
FGFR3	AMP MUT	17%
KRAS	AMP MUT	7%
HRAS	MUT	4%
NRAS	MUT	1.9%
NF1	HOMDEL MUT	8%
BRAF	MUT	2.7%

Genetic Alteration

- Inframe Mutation (unknown significance)
- Missense Mutation (putative driver)
- Missense Mutation (unknown significance)
- Truncating Mutation (putative driver)
- Truncating Mutation (unknown significance)
- Amplification
- Deep Deletion
- No alterations

https://www.cbioportal.org/results/oncoprint?Action=Submit&RPPA_SCORE_THRESHOLD=2.0&Z_SCORE_THRESHOLD=2.0&cancer_study_list=blca_tcga_pub_2017&case_set_id=blca_tcga_pub_2017_all&data_priority=0&gene_list=EGFR%253A%252...

Lettering

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Knowledge Systems

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Schultz lab

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Henry Walch
Walid Chatila

HPC

Joanne Edington
Juan Perin

cBioPortal network

Ethan Cerami
Chris Sander
Pichai Raman
Trevor Pugh
Alex Sigaras
The Hyve



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