Memorial Sloan Kettering Cancer Center

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

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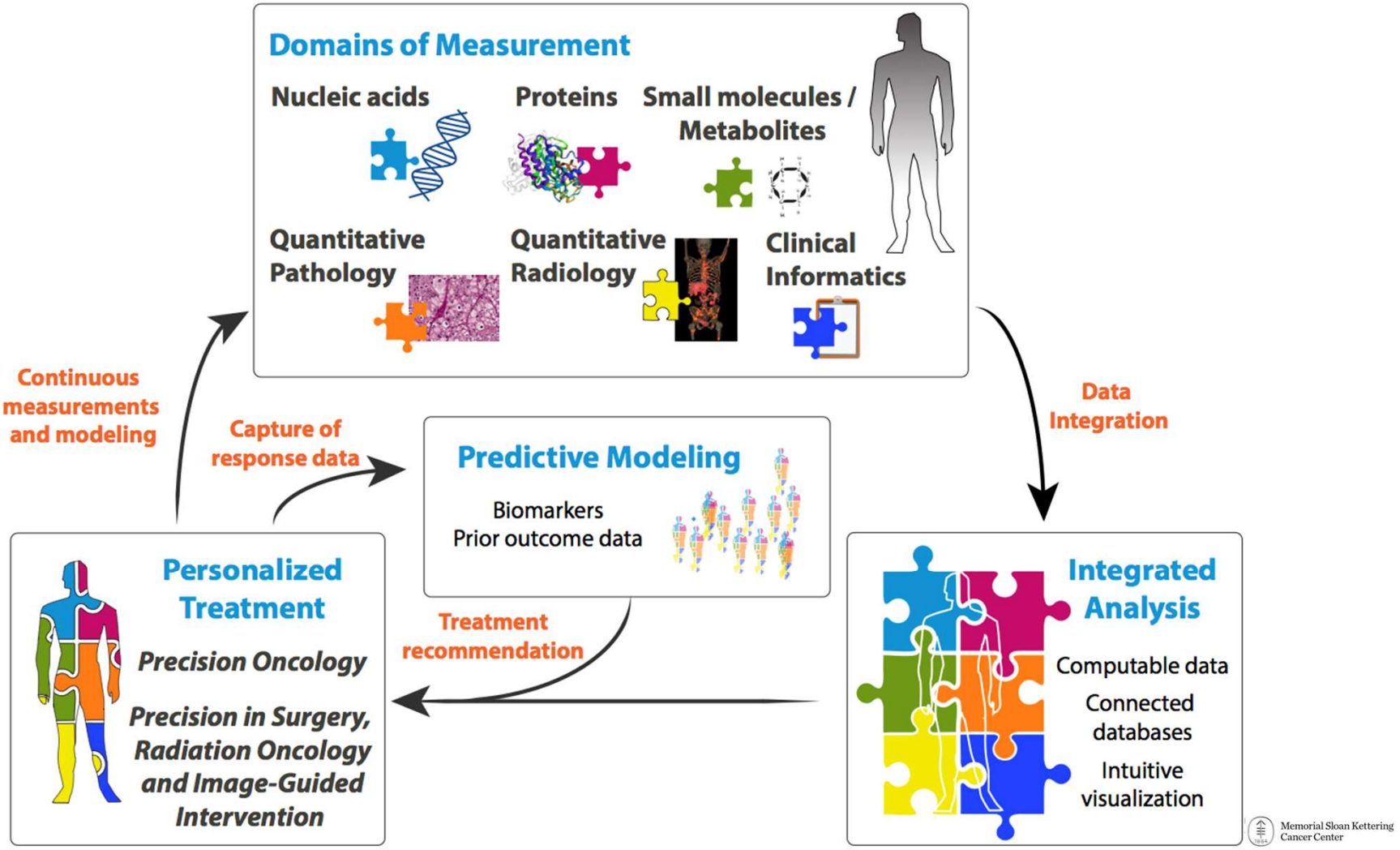
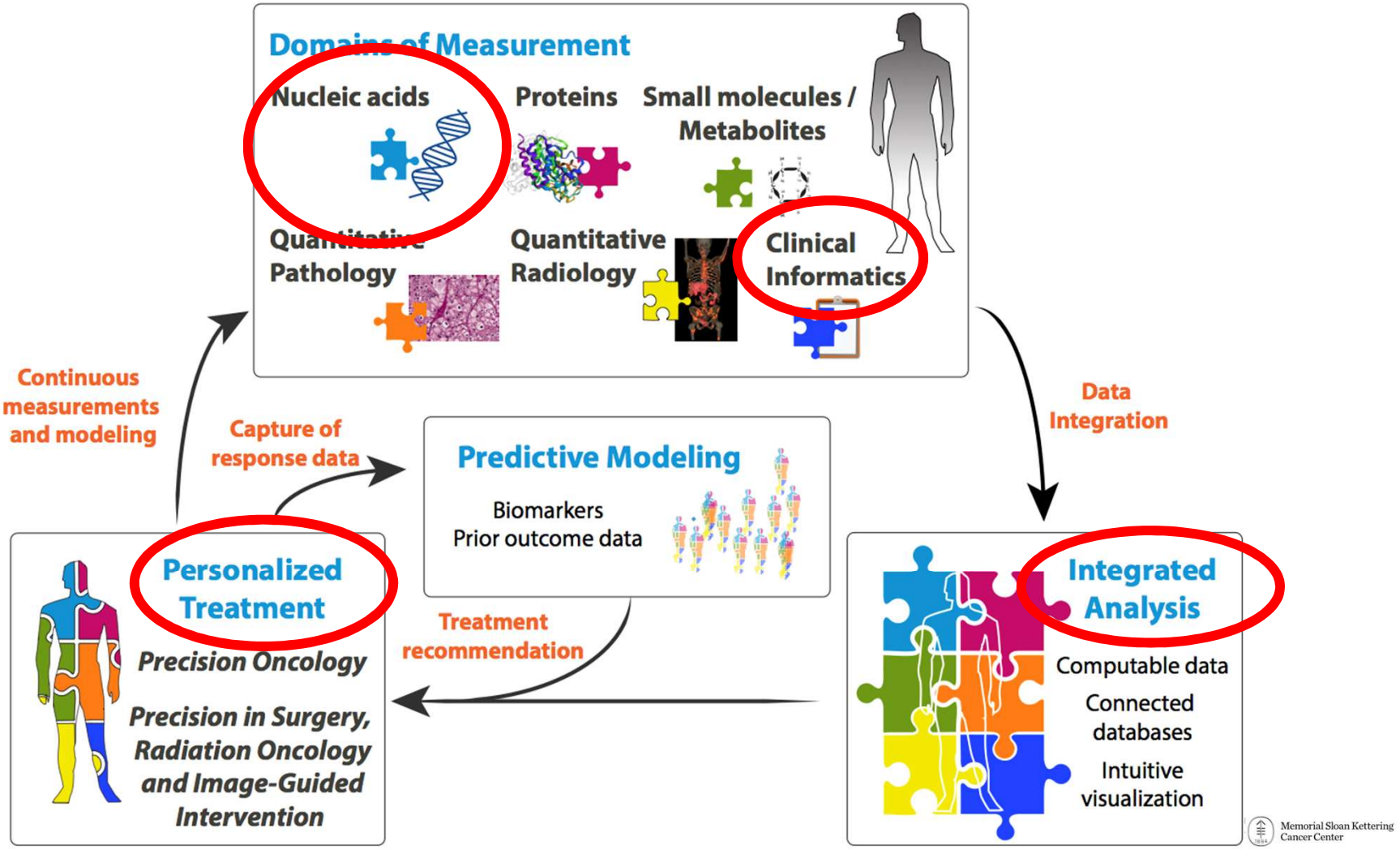
Head, Knowledge Systems
Kravis Center for Molecular Oncology

August 10, 2019

Precision Oncology

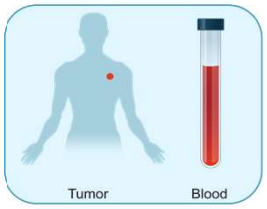


Precision Oncology

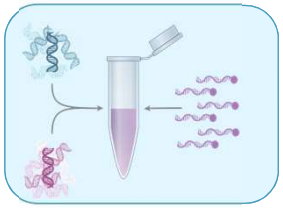


MSK-IMPACT Integrated Mutation Profiling of Actionable Cancer Targets

Patient Consent

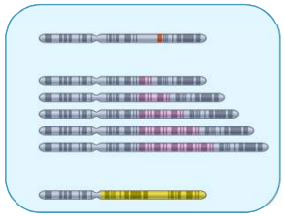


Sample Accessioning



Sample Preparation

Sequencing



Bioinformatics

Case Review & Sign Out

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

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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	ZFHX3	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	SOCS1	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	ERRFI1	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	WWTR1

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

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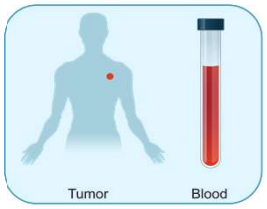
MSK-IMPACT Integrated Mutation Profiling of Actionable Cancer Targets

Patient Consent



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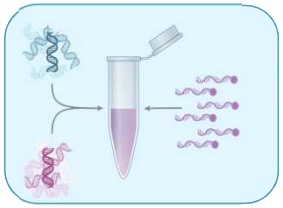

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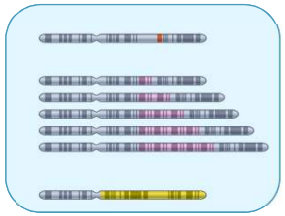

Bioinformatics

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)

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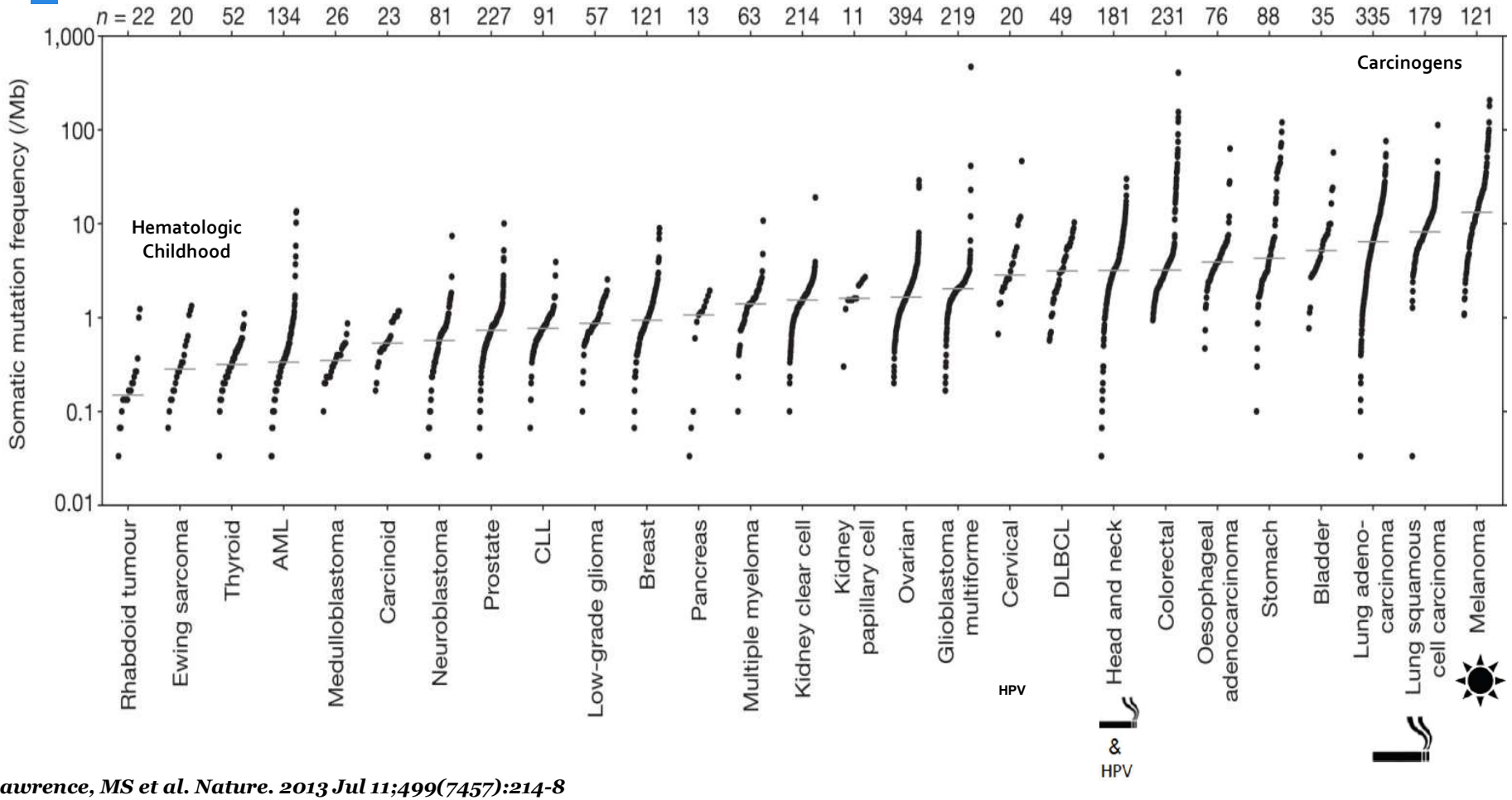
Most mutations in cancer are “passengers”



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

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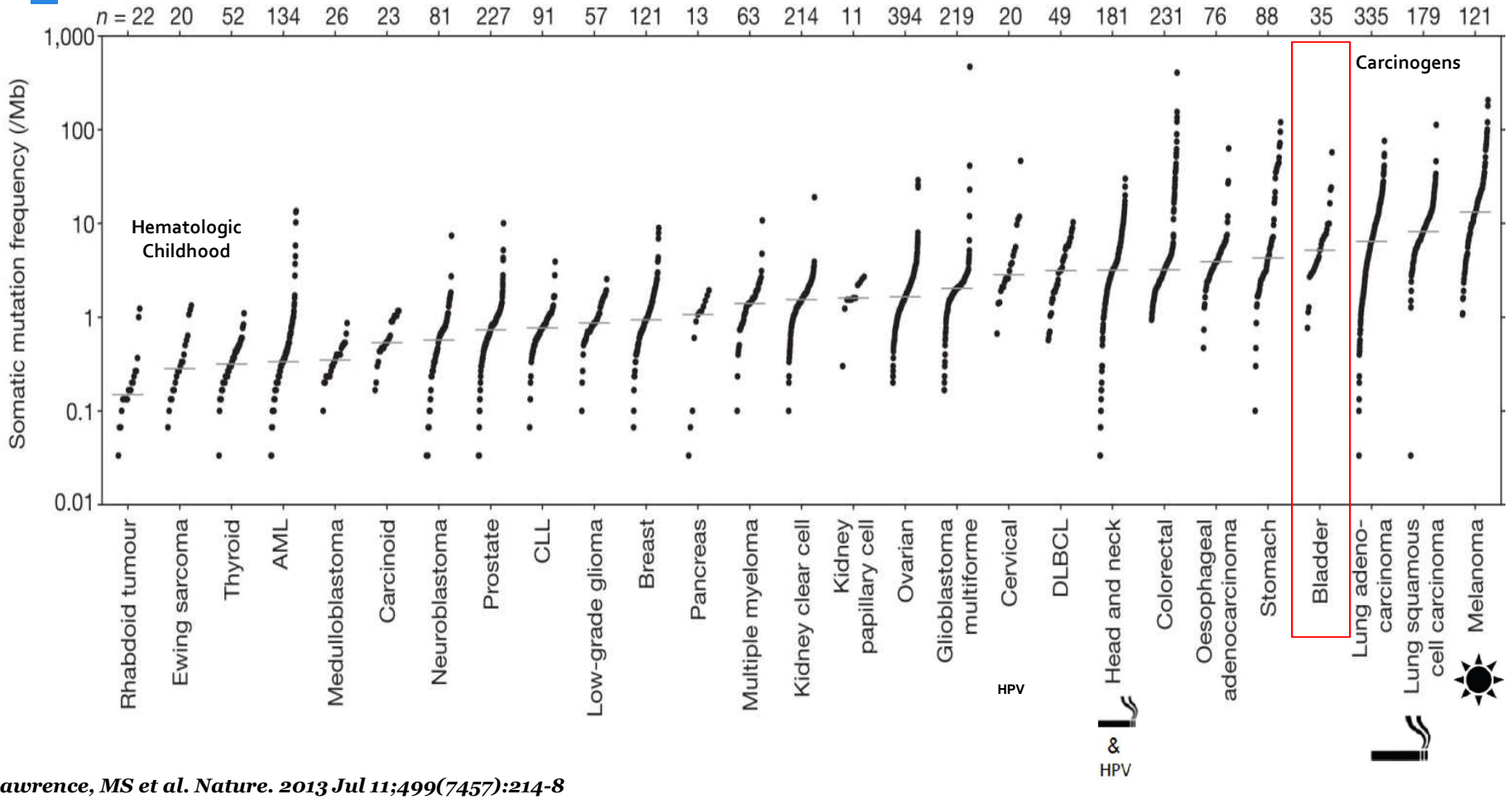
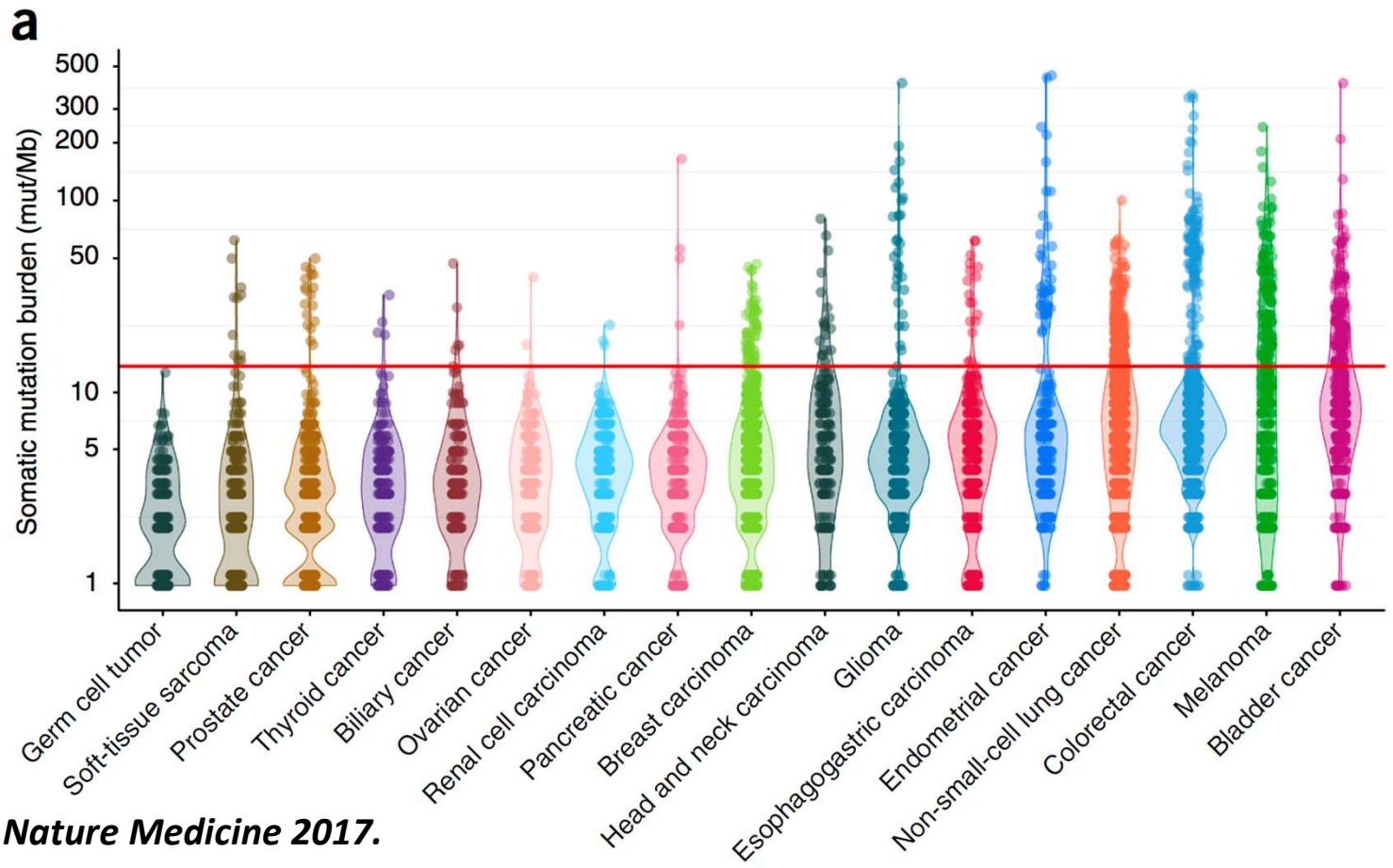


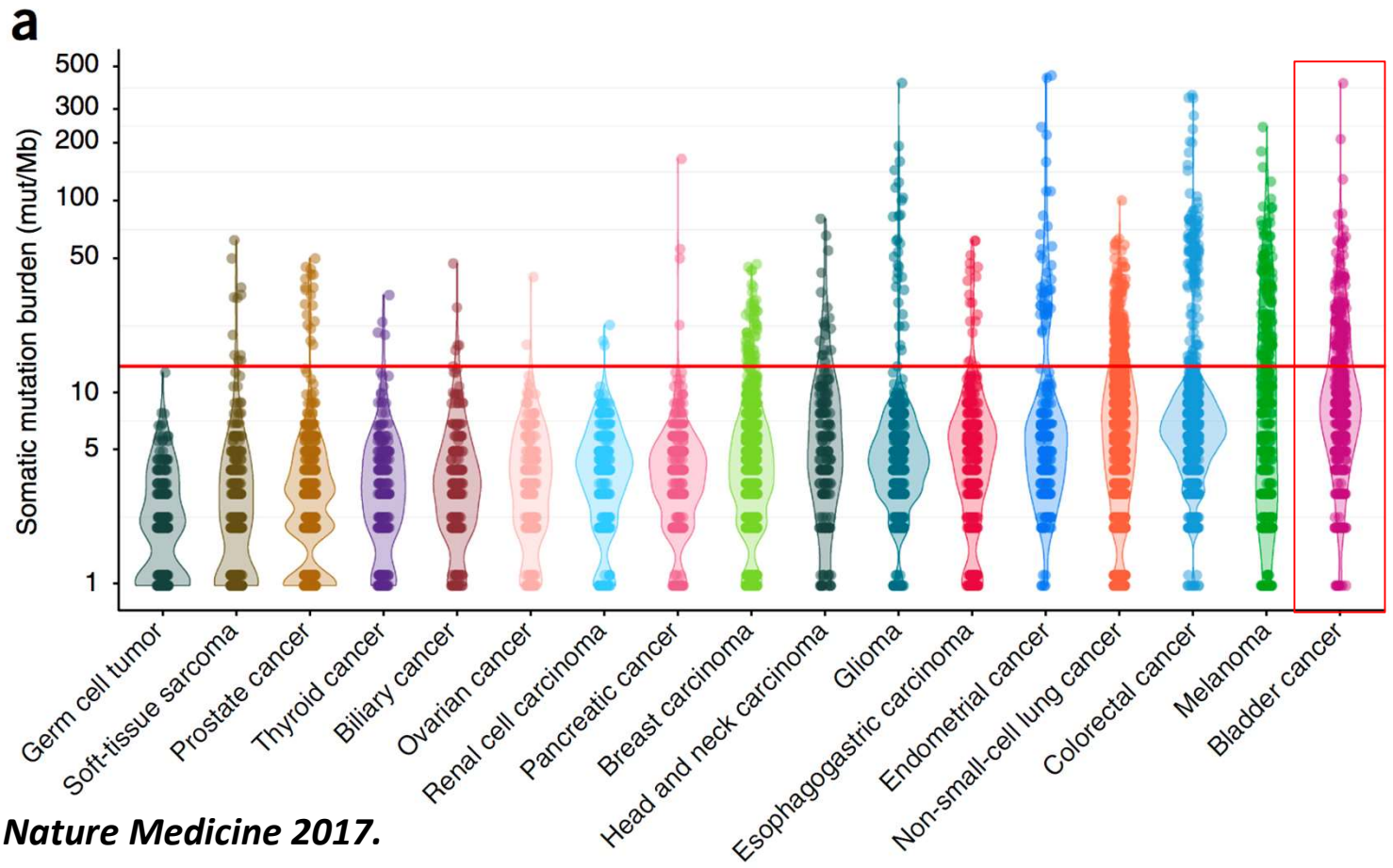
Lawrence, MS et al. Nature. 2013 Jul 11;499(7457):214-8

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

2. Prior Knowledge

3. Intuitive visualization

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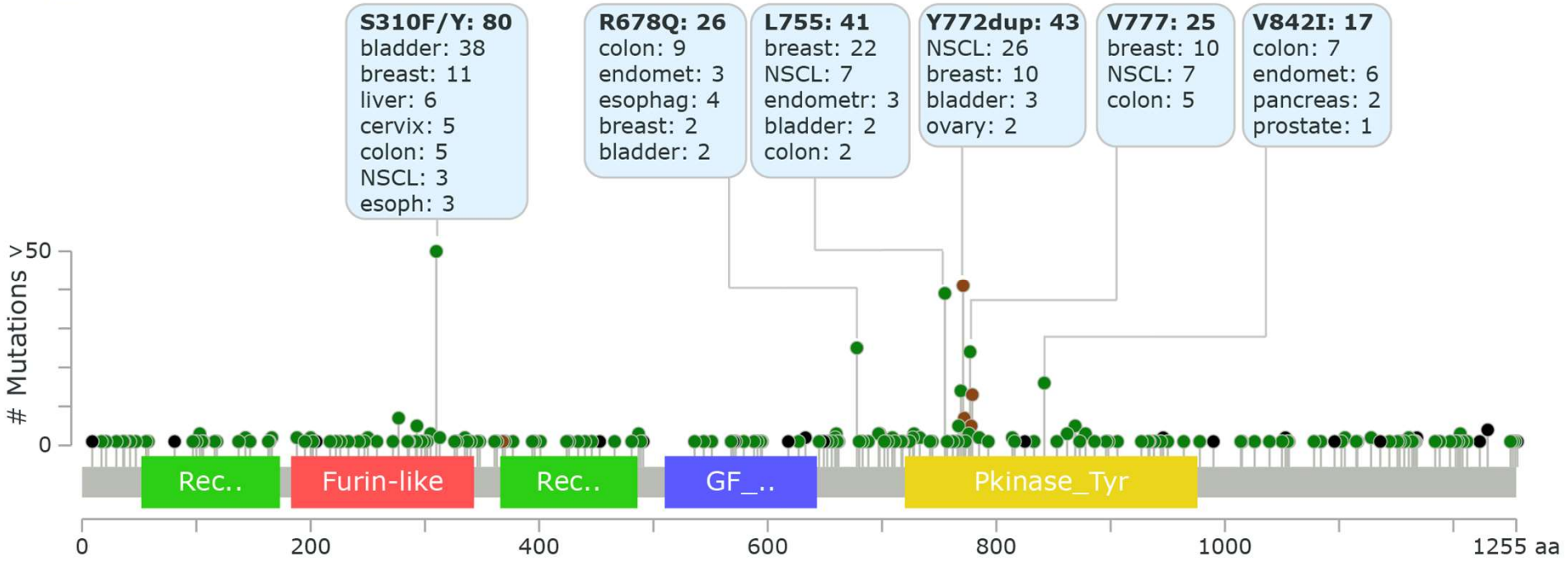
ERBB2 mutation pattern



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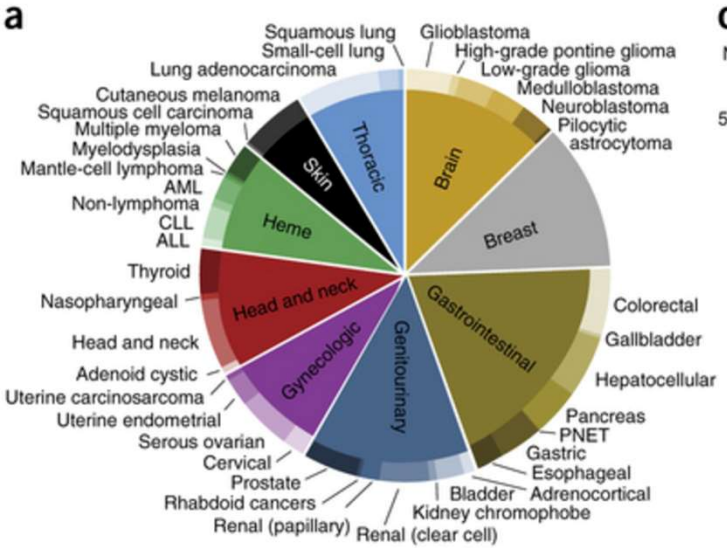
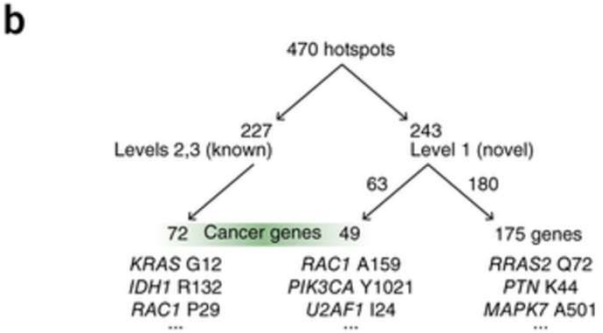
Algorithmic detection of mutational hotspots





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

11,119 human tumors in 41 cancer types

470 somatic hotspots in 275 genes

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

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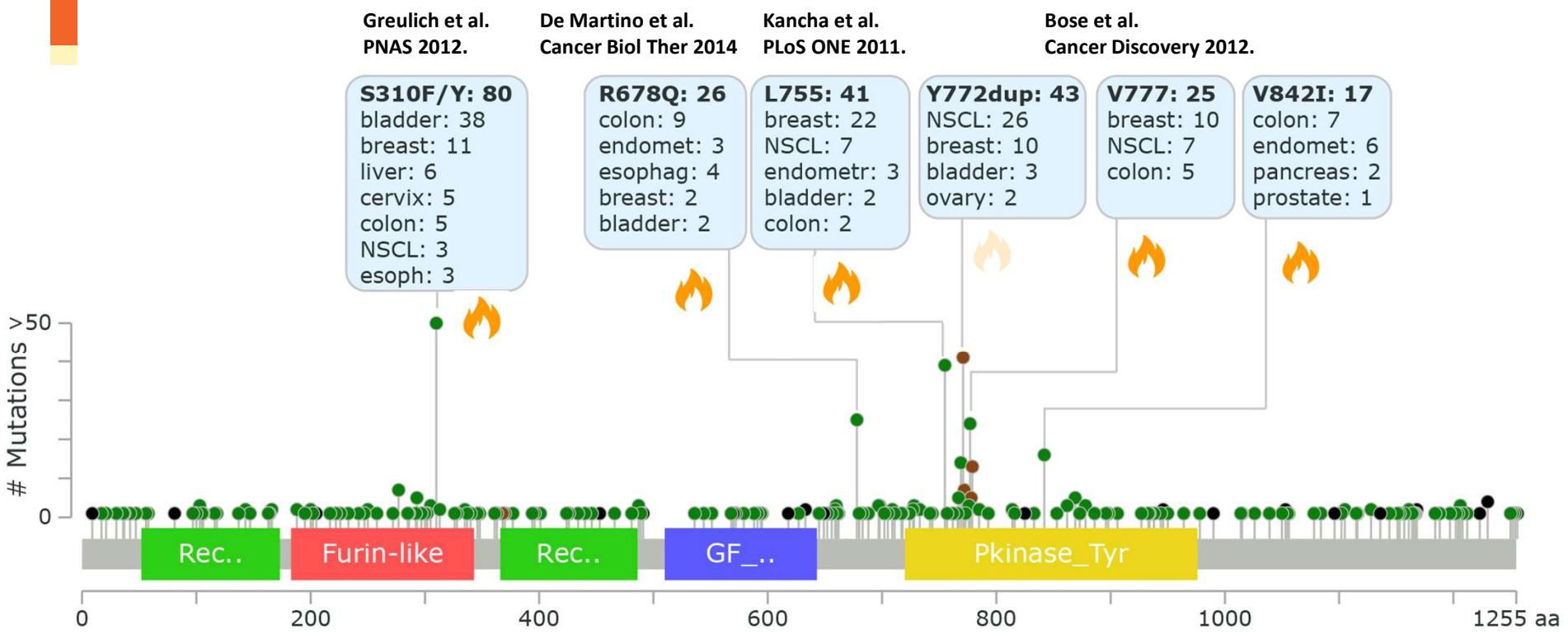
ERBB2 hotspots in 10,000 tumor samples



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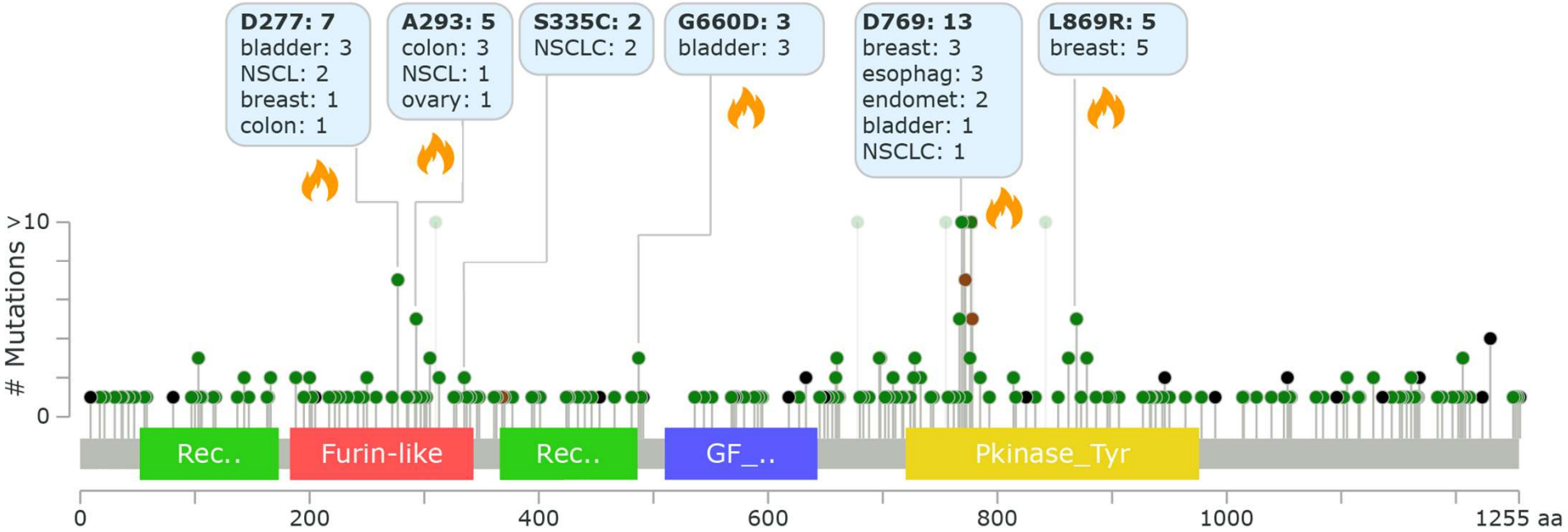
ERBB2 hotspots in 24,500 tumor samples



20 ERBB2 hotspot in analysis of 24,500 tumors

1165 hotspots in 247 genes

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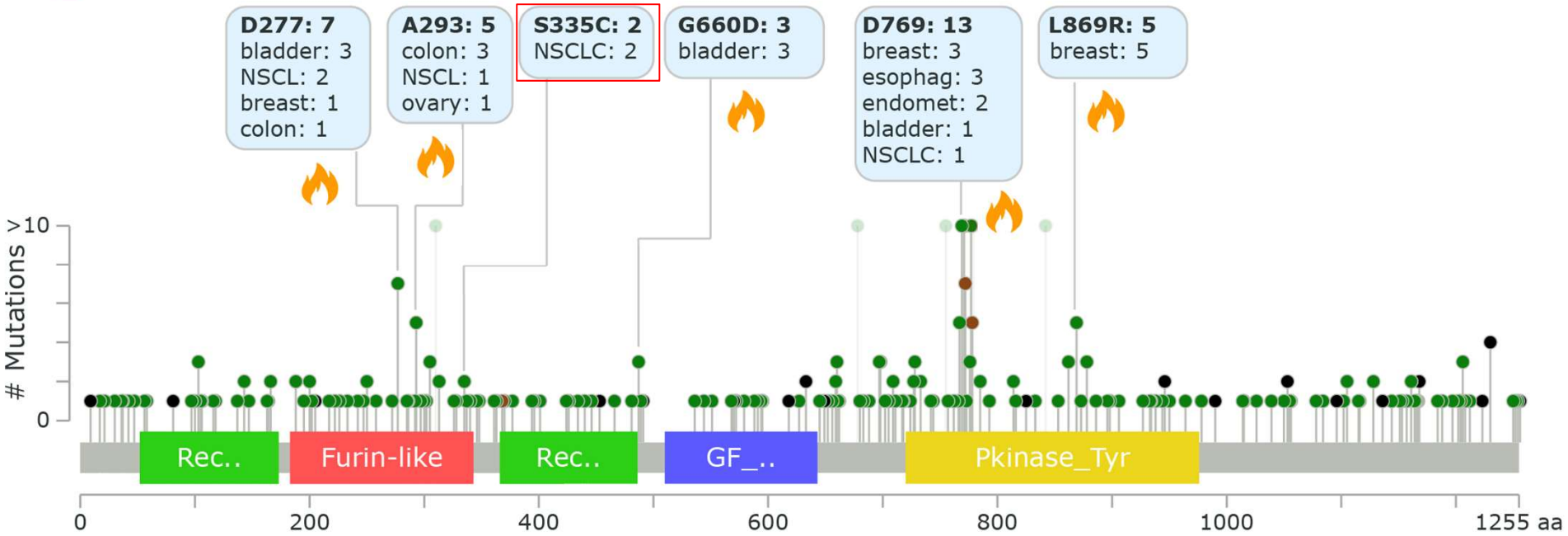
ERBB2 hotspots in 24,500 tumor samples



20 ERBB2 hotspot in analysis of 24,500 tumors

1165 hotspots in 247 genes

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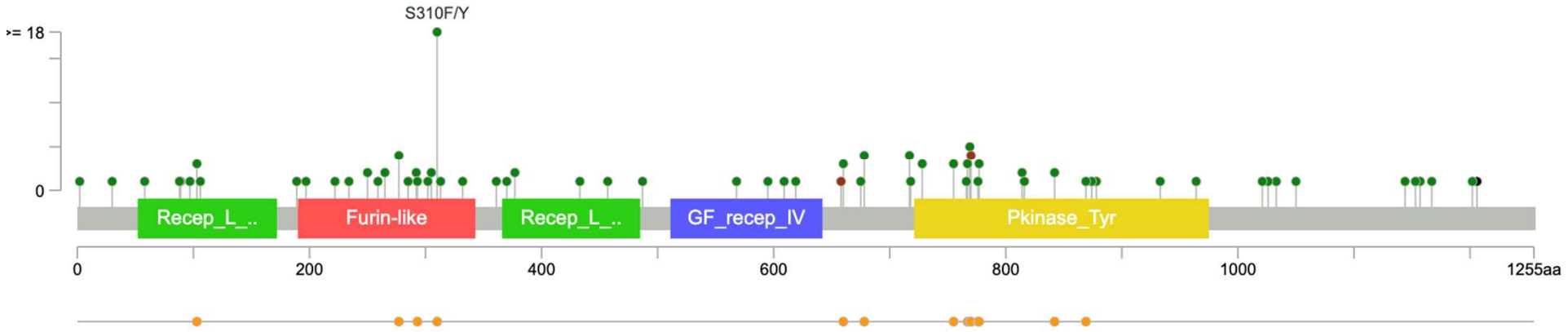
ERBB2 hotspots in bladder cancer

> 1/3 of mutations



~1/2 of mutations are known hotspots

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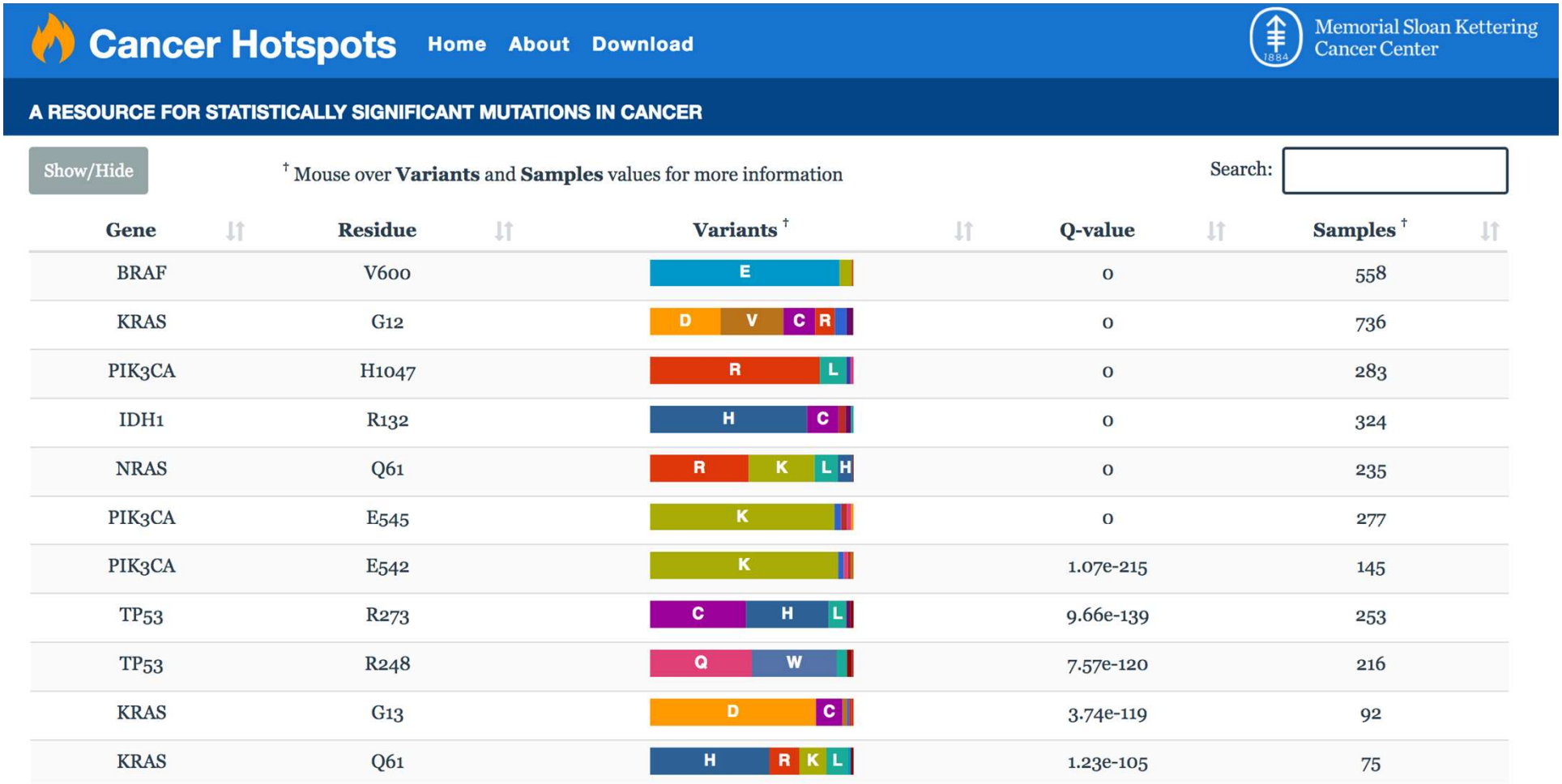

http://cancerhotspots.org/

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

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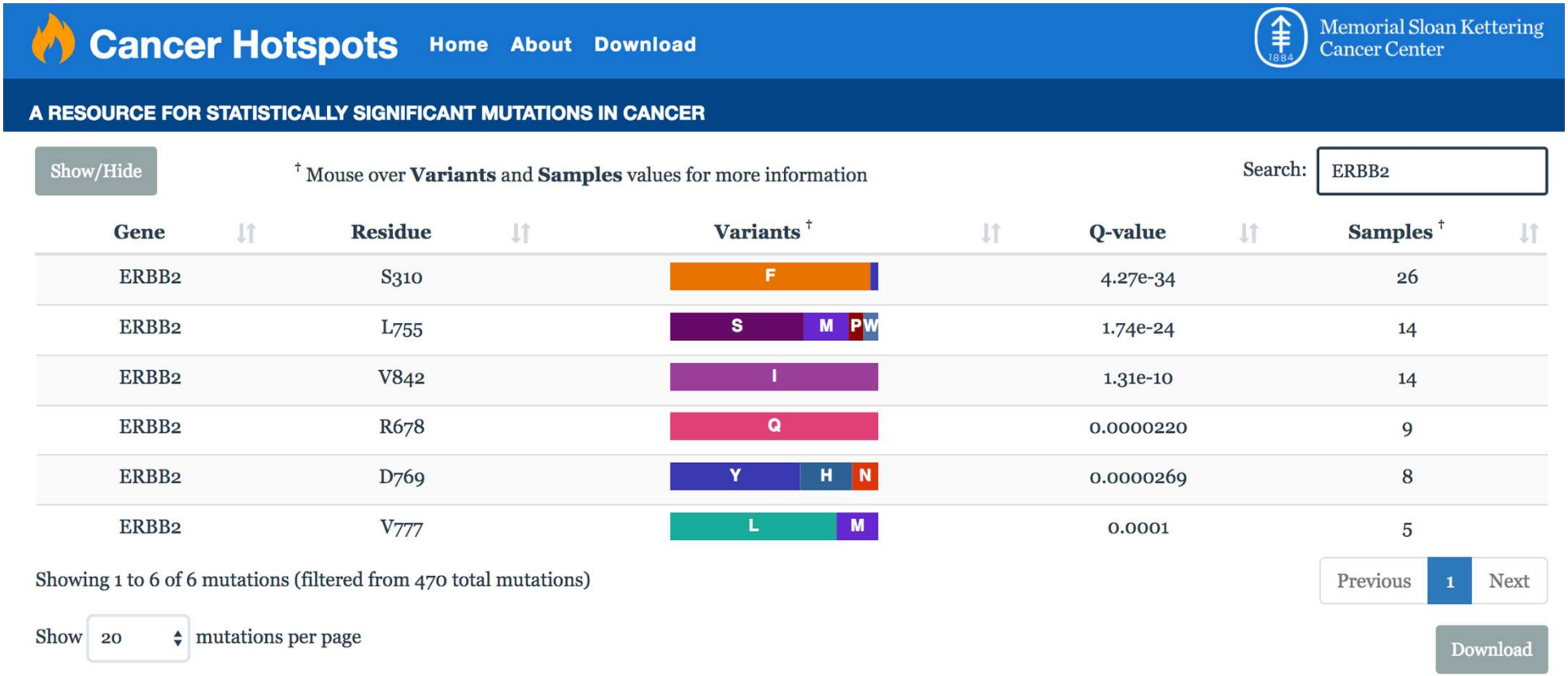

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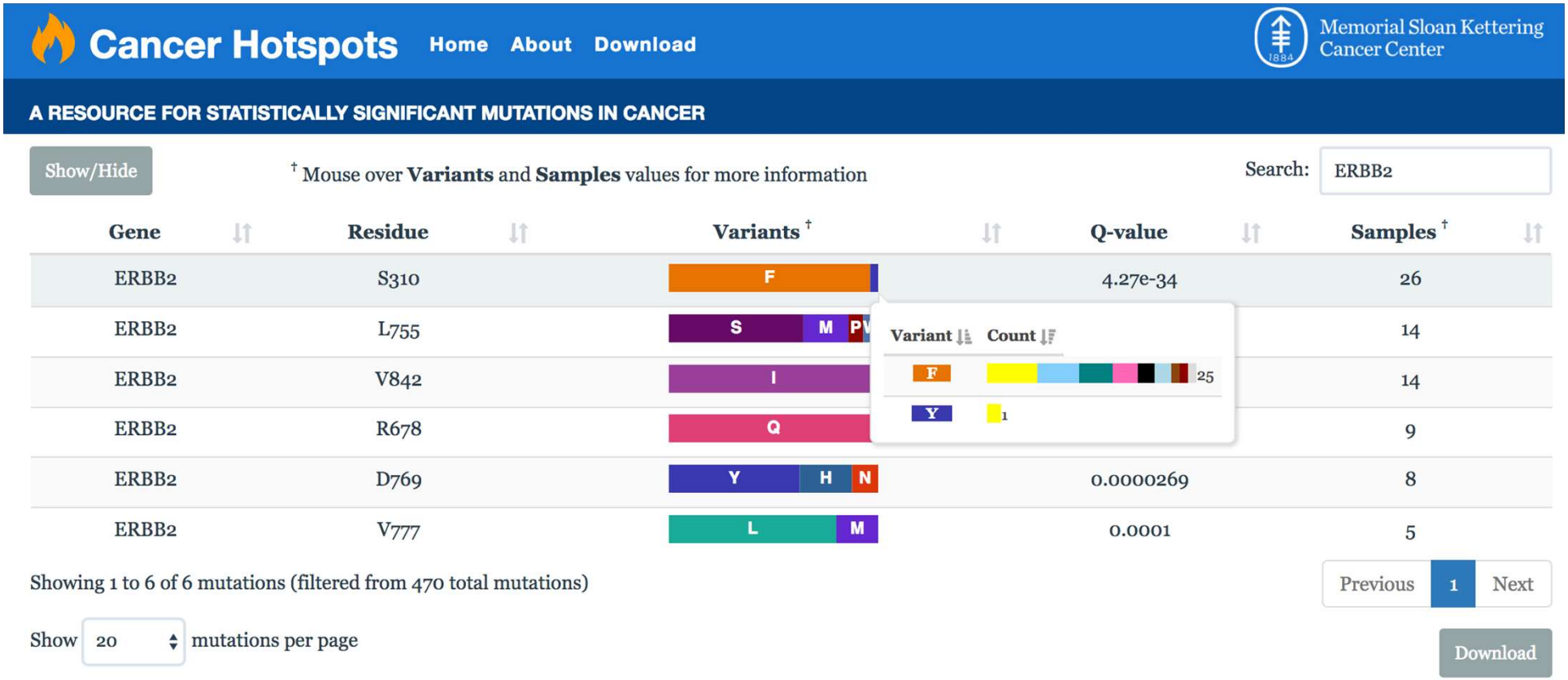

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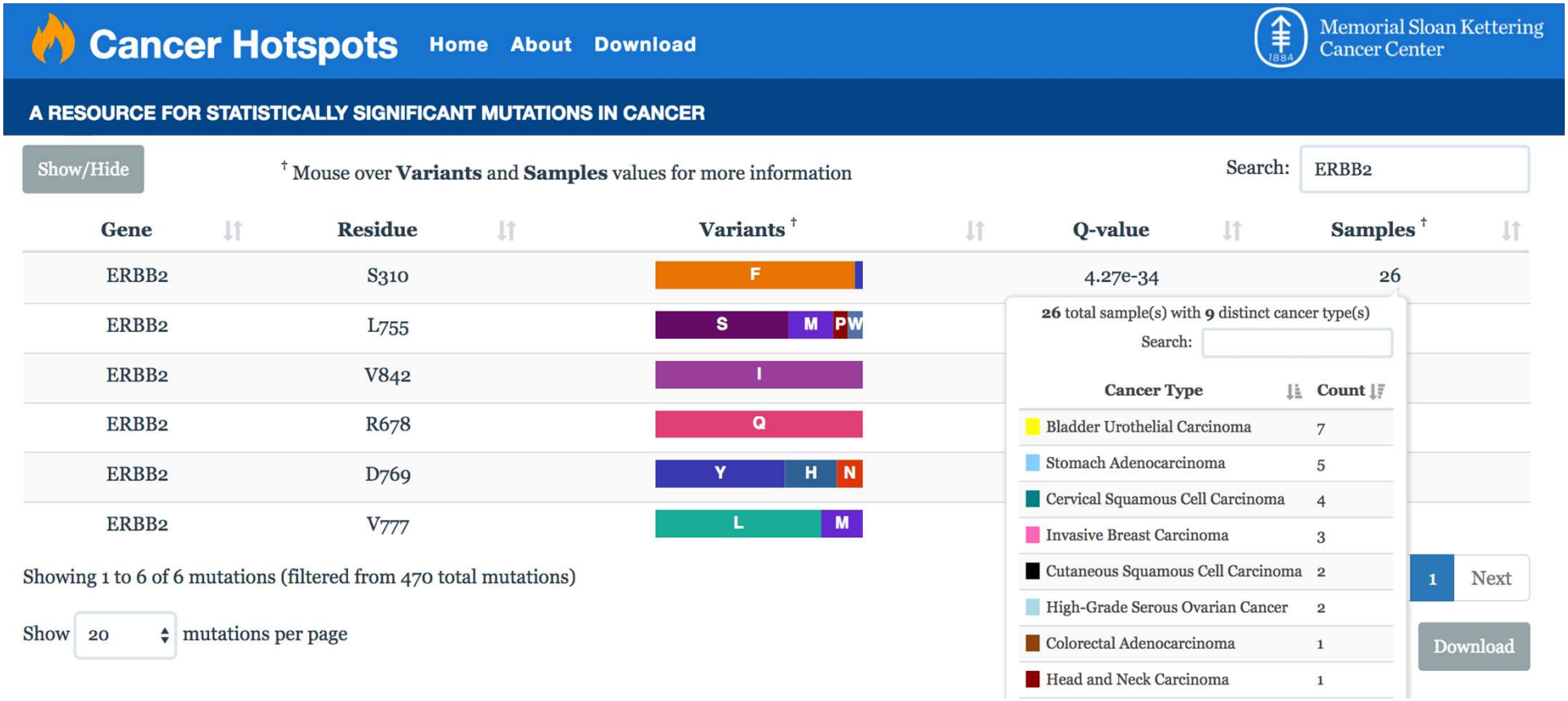

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How can we identify driver & actionable variants?

1. **Recurrence**
   Frequently mutated amino acids

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

   OncoKB
   Precision Oncology Knowledge Base

3. **Intuitive visualization**

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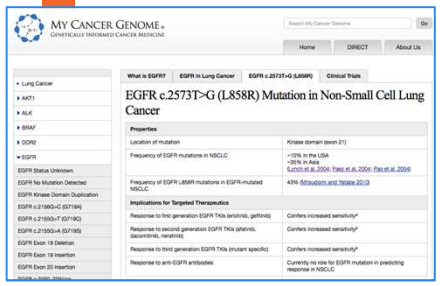
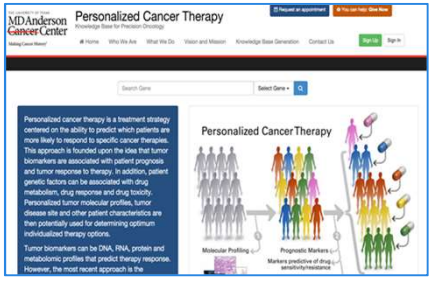
Currently available Knowledgebases (for somatic mutations)



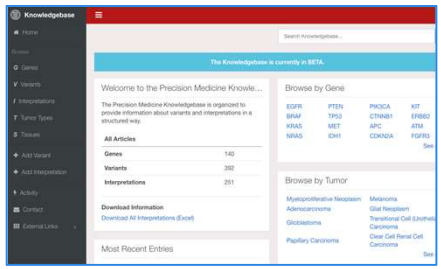
[My Cancer Genome](#)
Vanderbilt



[Personalized Cancer Medicine](#)
MD Anderson

[Targeted Cancer Care](#)
Mass General

[CKB](#)
Jackson Labs



[Precision Medicine Knowledgebase](#)
Cornell

[Cancer Driver Log](#)
Ohio State University

[CIViC](#)
Wash U

[Cancer Genome Interpreter](#)
UPF Barcelona

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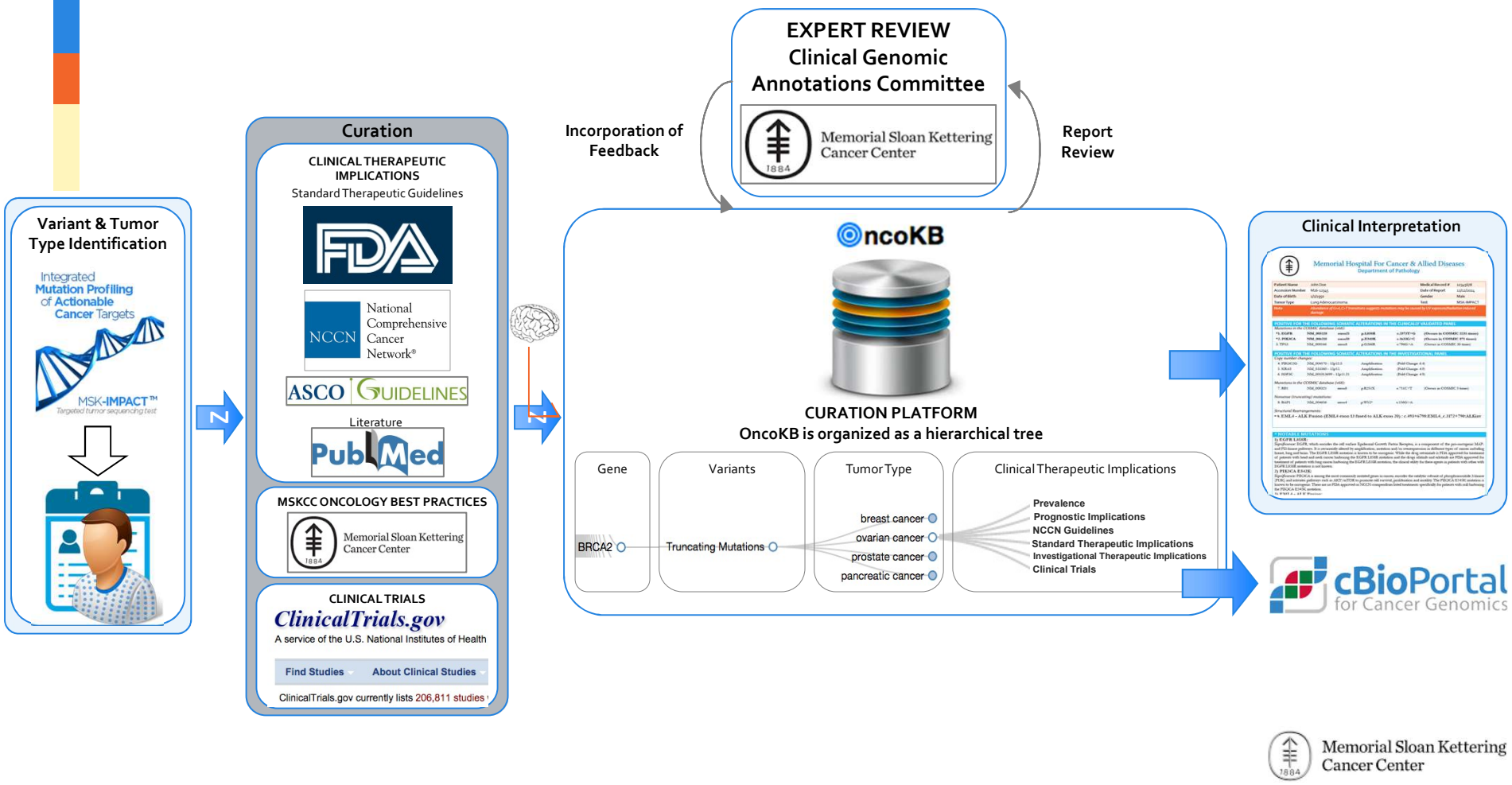
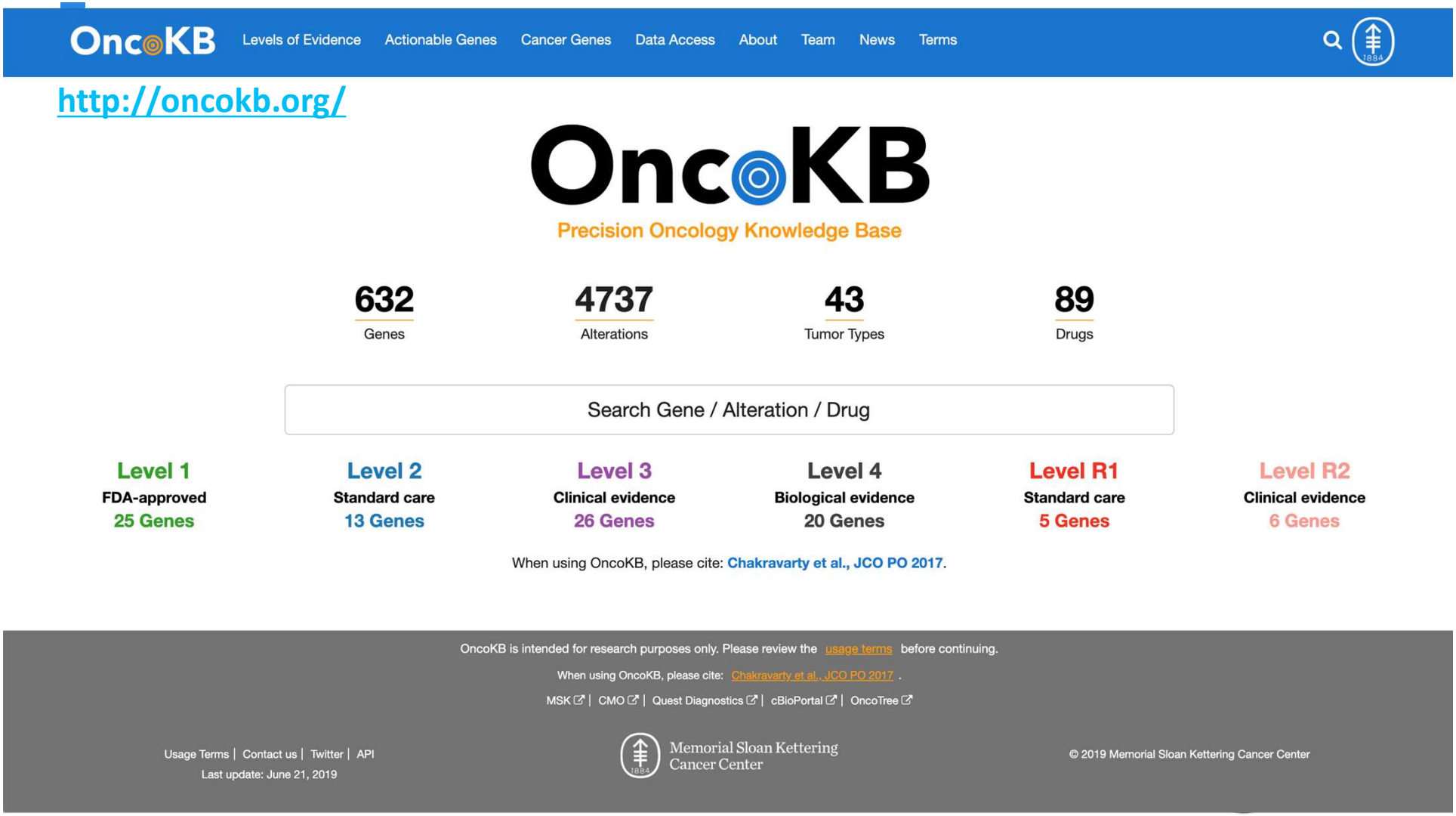
Key pieces of information about individual variants

- **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




OncoKB
Levels of Evidence
Actionable Genes
Cancer Genes
Data Access
About
Team
News
Terms
http://oncokb.org/
OncoKB
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.
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MSK | CMO | Quest Diagnostics | cBioPortal | OncoTree
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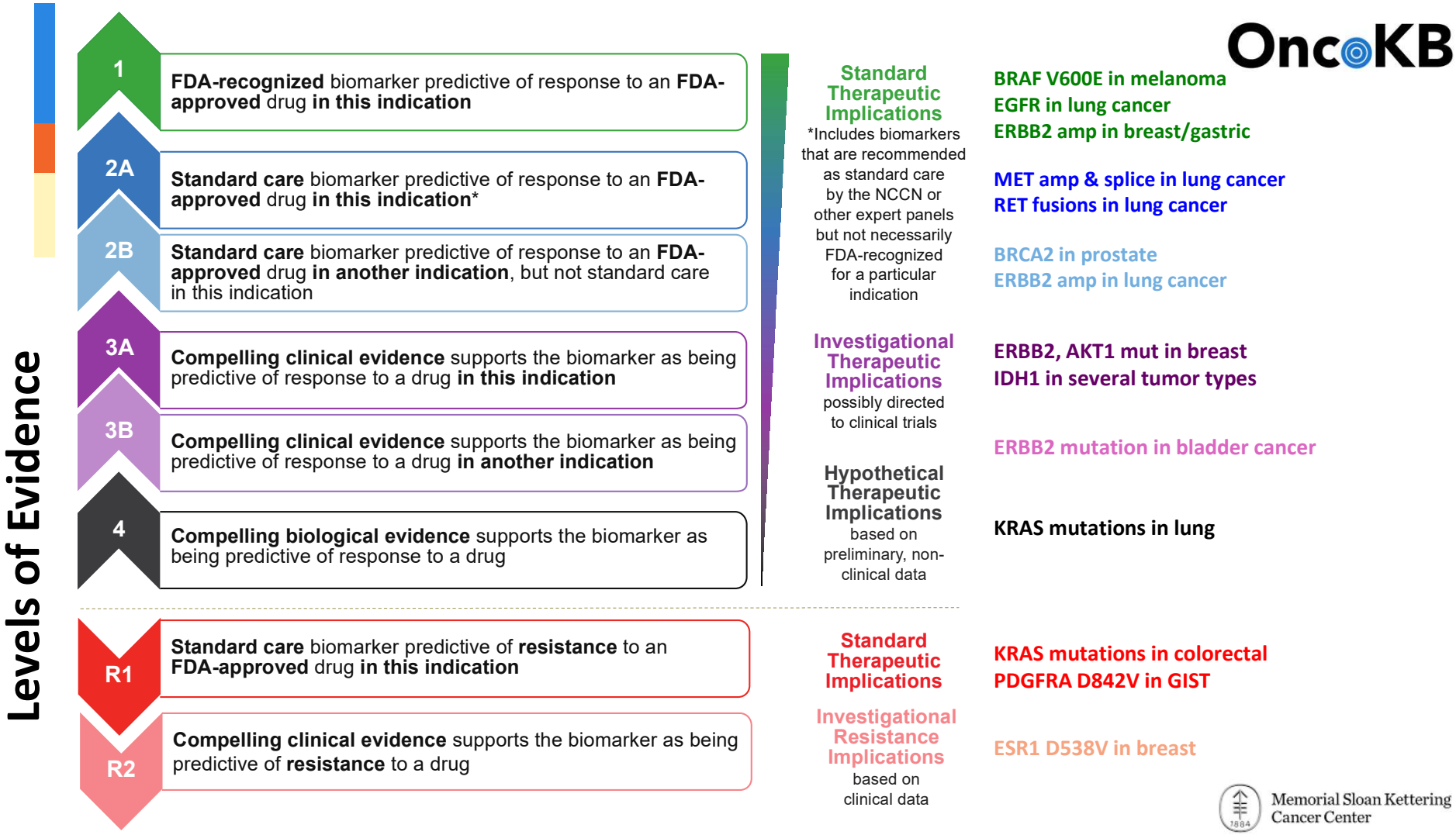
Levels of Evidence
1
FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication
2A
Standard care biomarker predictive of response to an FDA-approved drug in this indication*
2B
Standard care biomarker predictive of response to an FDA-approved drug in another indication, but not standard care in this indication
3A
Compelling clinical evidence supports the biomarker as being predictive of response to a drug in this indication
3B
Compelling clinical evidence supports the biomarker as being predictive of response to a drug in another indication
4
Compelling biological evidence supports the biomarker as being predictive of response to a drug
R1
Standard care biomarker predictive of resistance to an FDA-approved drug in this indication
R2
Compelling clinical evidence supports the biomarker as being predictive of resistance to a drug
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
OncoKB
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
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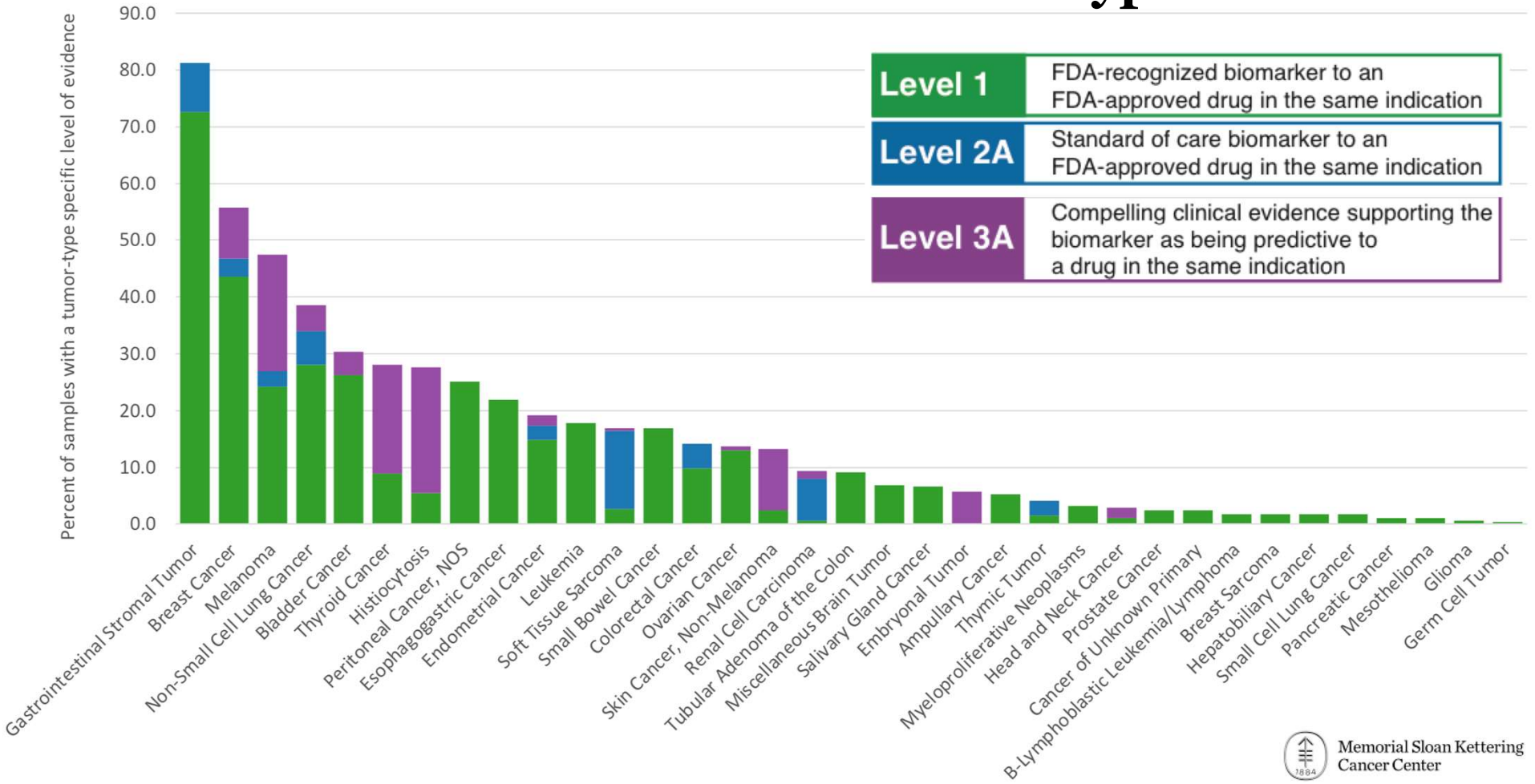
Actionable alterations across tumor types

OncoKB



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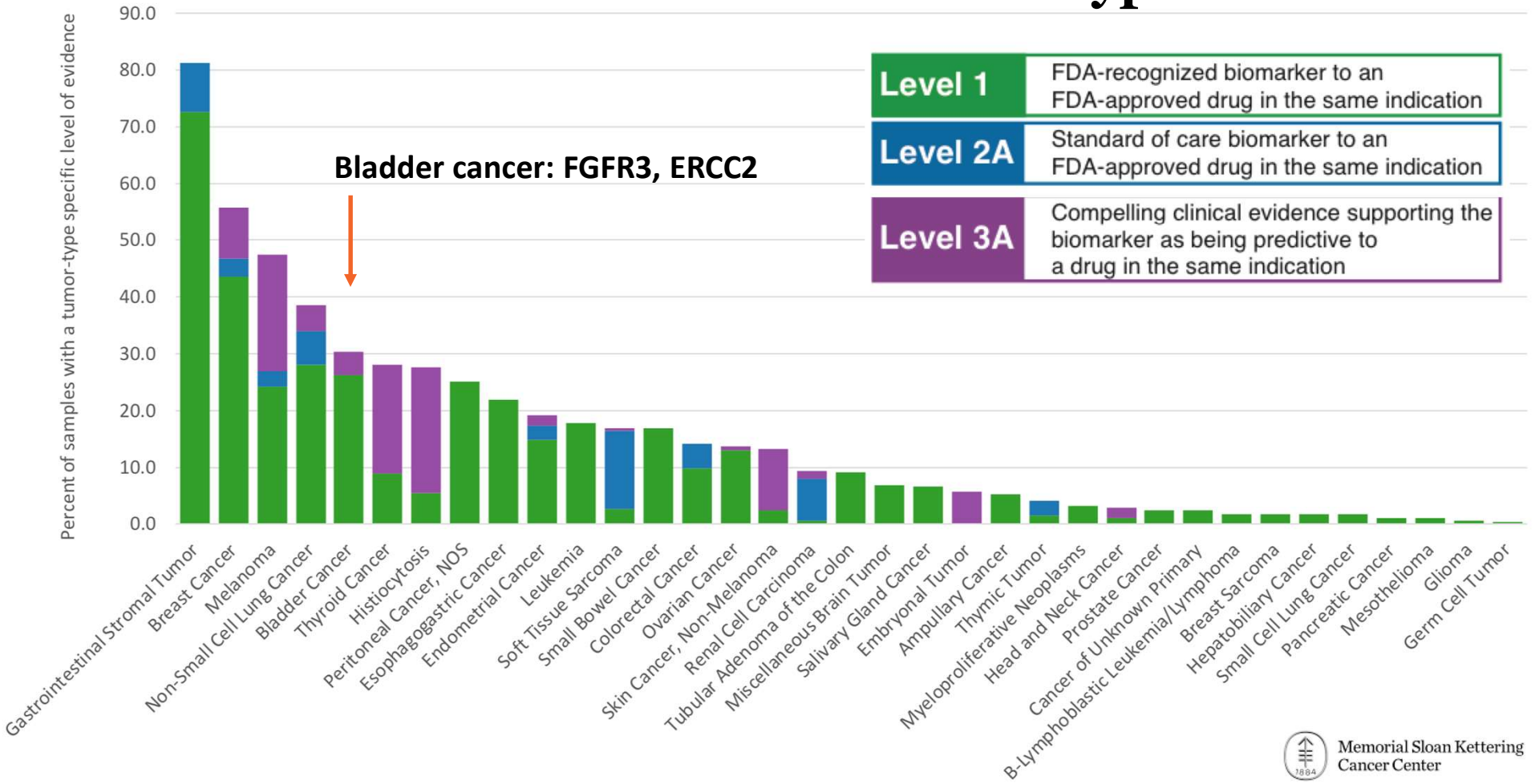

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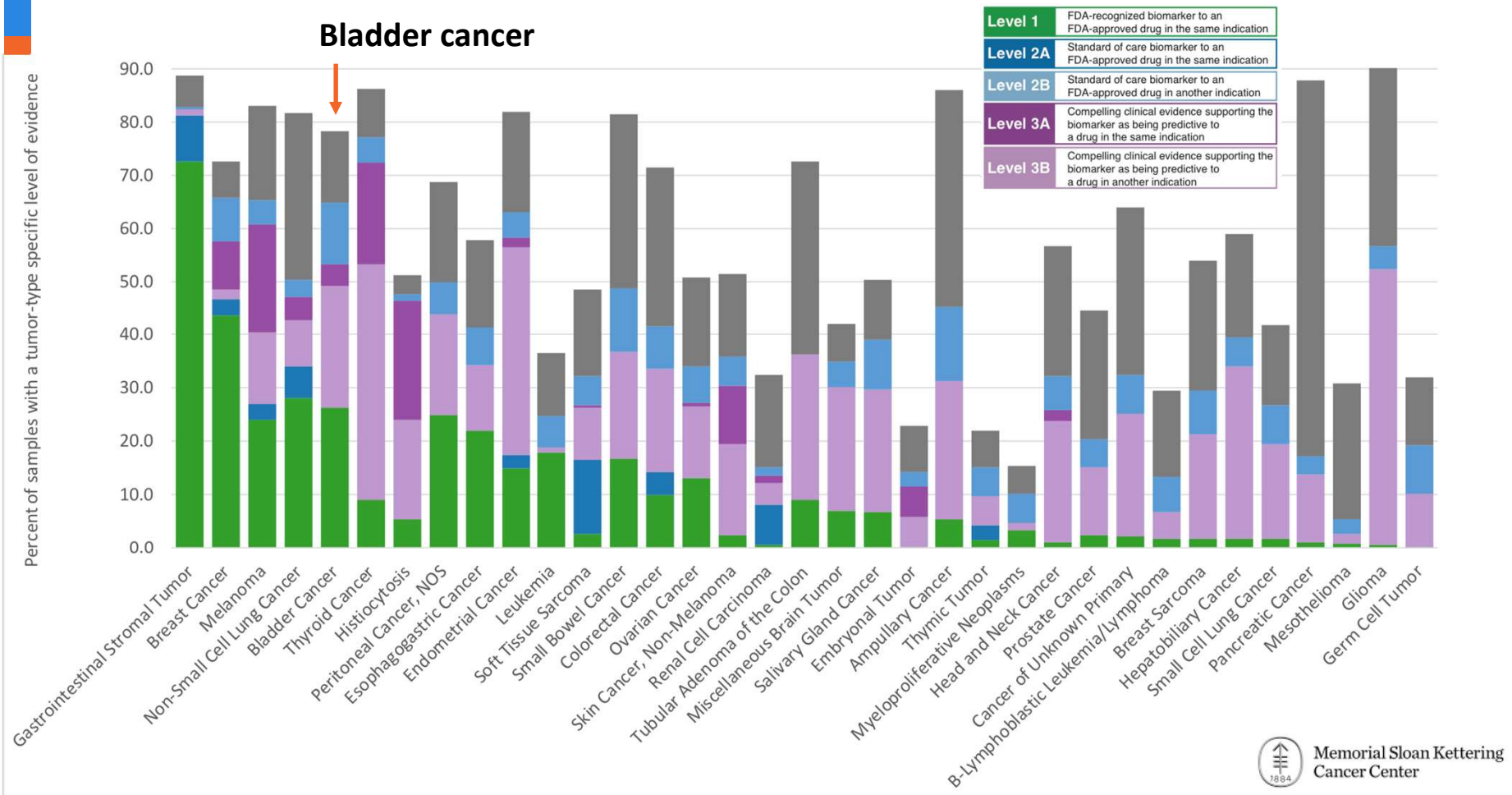
Actionable alterations across tumor types



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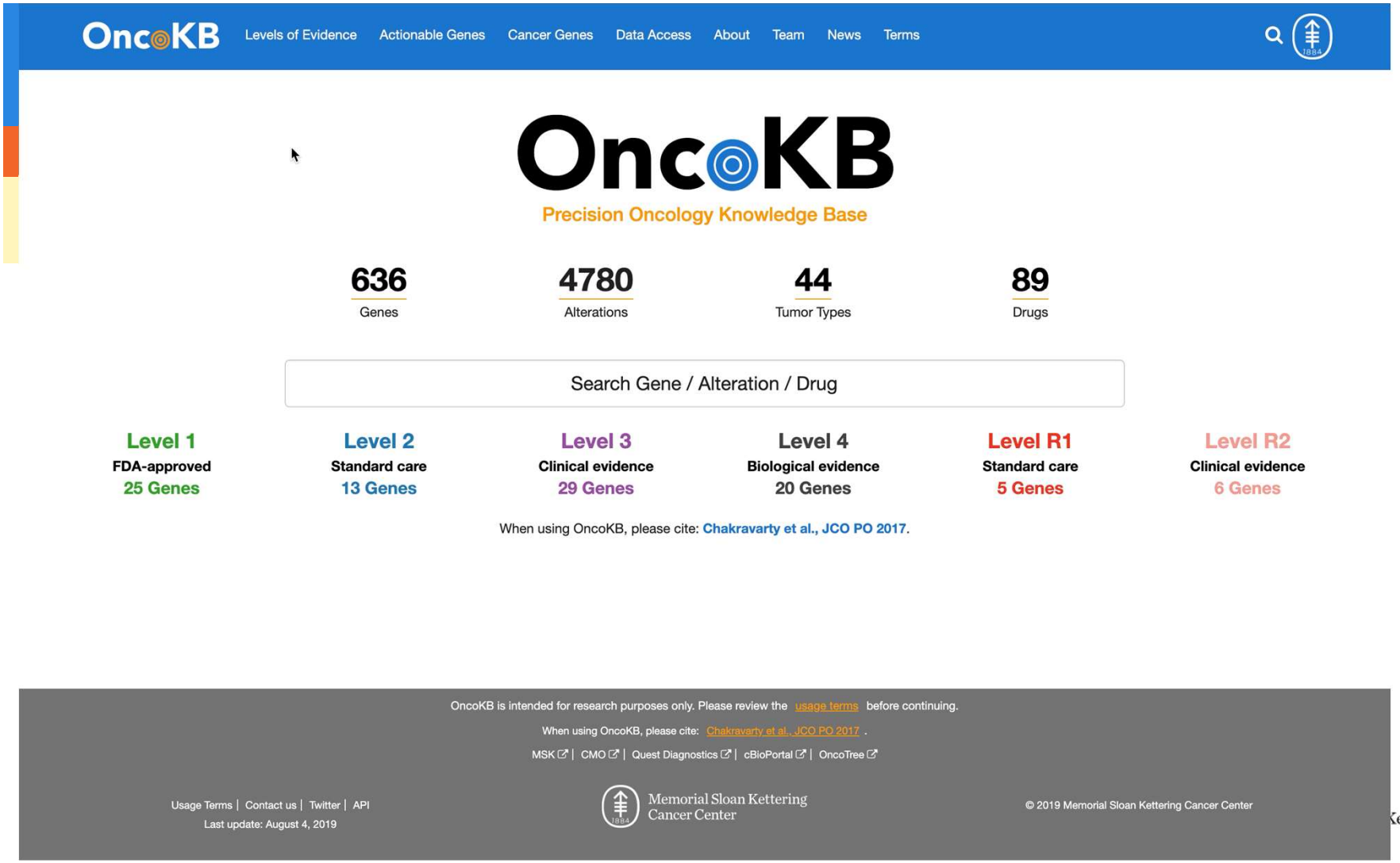
OncoKB
Levels of Evidence
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Biological evidence
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Level R1
Standard care
5 Genes
Level R2
Clinical evidence
6 Genes
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MSK-IMPACT reports

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.[β]
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.[γ]

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information	
Mutations					
ERCC2	Missense Mutation	N238S *(c.713A>G)*	exon 8	MAF: 51.9%	3A
AKT1	Missense Mutation	E17K *(c.49G>A)*	exon 3	MAF: 64.4%	3B α
ERBB2	Missense Mutation	E265K *(c.793G>A)*	exon 7	MAF: 47.7%	3B
FBXW7	Missense Mutation	R505G *(c.1513C>G)*	exon 10	MAF: 48.6%	b
TERT	Non-coding	g.1295228C>T	Promoter	MAF: 50.1%	
ELF3	Frameshift Deletion	c.1105_*1del	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%	a
RB1	Splicing Mutation	X405_splice *(c.1215+1G>C)*	exon 12	MAF: 85.7%	c
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%	

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	Q558* *(c.1672C>T)*	exon 5	MAF: 45.4%
Structural Variants				
ID3	Deletion	c.-3112_c.*1662del	exons 1-2	d

+: A glossary of terms and icons used in this report can be found after the "Test and Methodology" section .
α: Denotes clinically/analytically validated variants.
a: Note: Allele specific copy number analysis by FACETS suggests loss of heterozygosity of TP53. FACETS results are for investigational use only.
b: Note: The FBXW7 exon10 mutations occur on different alleles.
c: Note: Allele specific copy number analysis by FACETS suggests loss of heterozygosity of RB1. FACETS results are for investigational use only.
d: The ID3 rearrangement is a deletion that includes ID3 exons 1-2. The functional significance is undetermined.
β: MSI Note: The MSIsensor score is 0.06.
γ: 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

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MSK-IMPACT reports

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MSK-IMPACT reports

Memorial Hospital For Cancer & Allied Diseases

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

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How can we identify driver & actionable variants?

1. **Recurrence**
   Frequently mutated amino acids

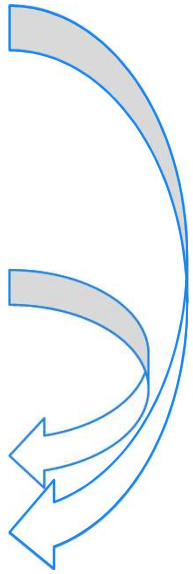
2. **Prior Knowledge**
   Driver & actionable variants

3. **Intuitive visualization**

Cancer Hotspots

OncoKB
Precision Oncology Knowledge Base

cBioPortal
FOR CANCER GENOMICS



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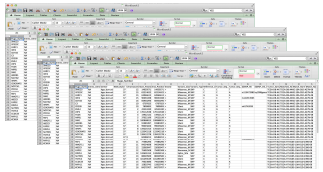
cBioPortal for Cancer Genomics: Data to knowledge / the last mile

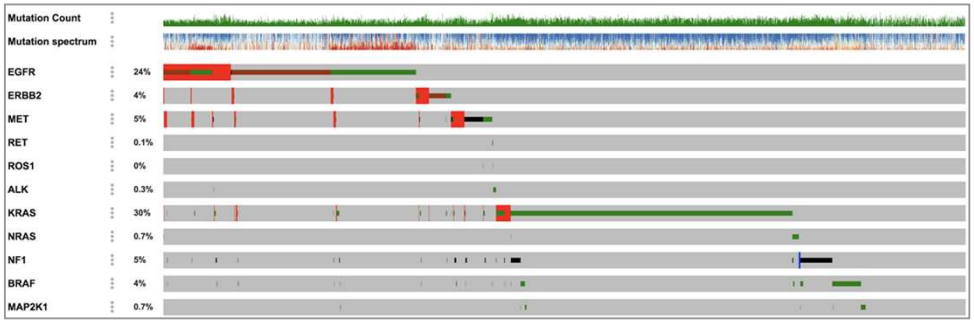
Tumor DNA, RNA

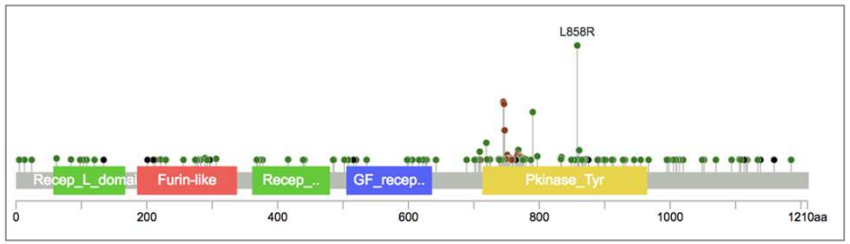
DNA sequencer, microarrays, etc.

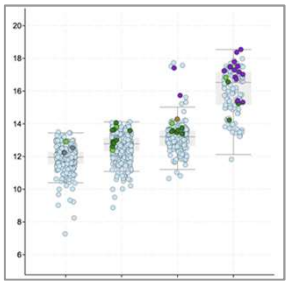
Tumor and normal sequences

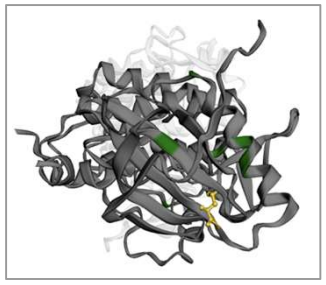


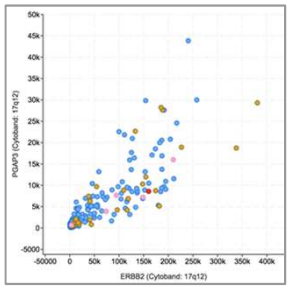
Data











Intuitive interface, quick response time, reduction of complexity

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cBioPortal is open source software

https://github.com/cBioPortal/cbioportal

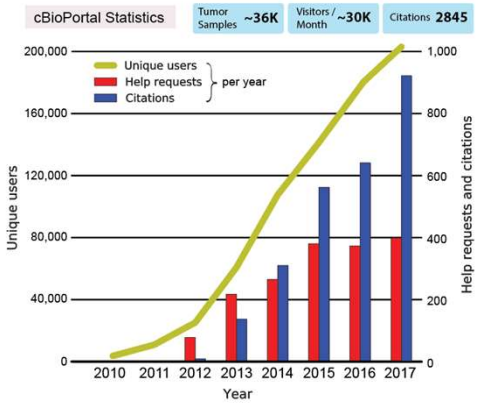
Licensed under the AGPL license
Free to download and use
Modifications welcome

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



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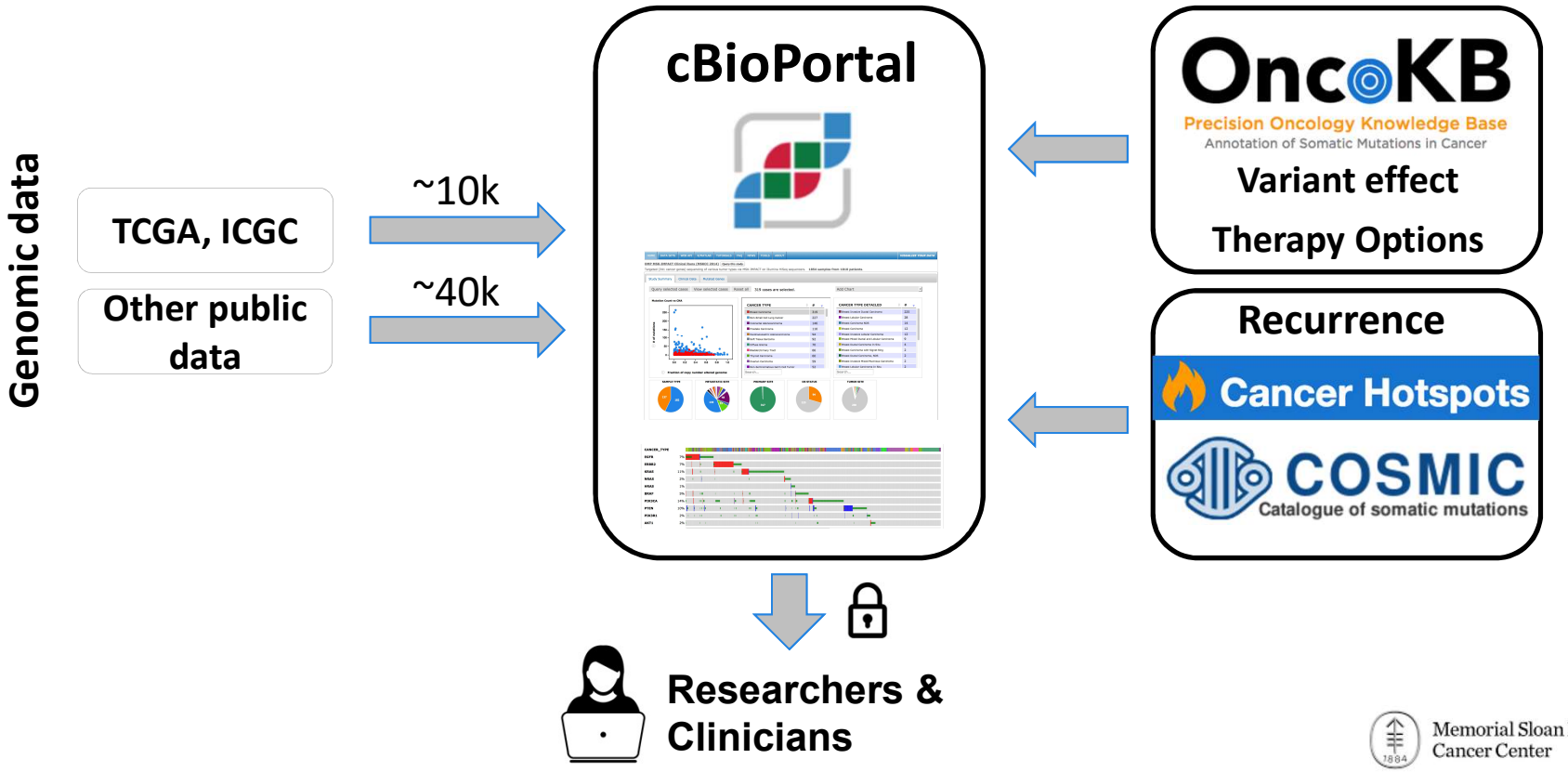
Public cBioPortal at https://cbioportal.org



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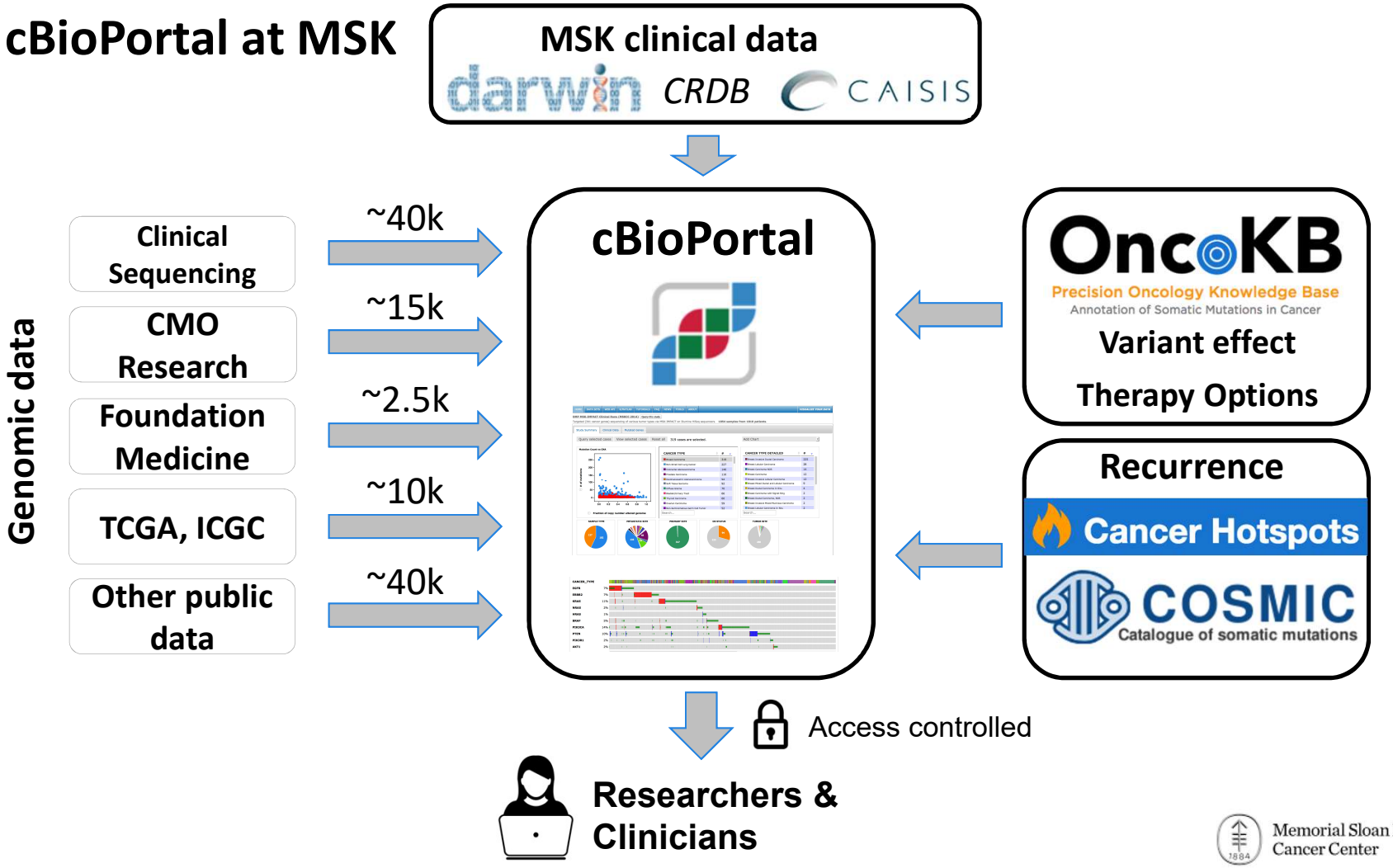
cBioPortal at MSK



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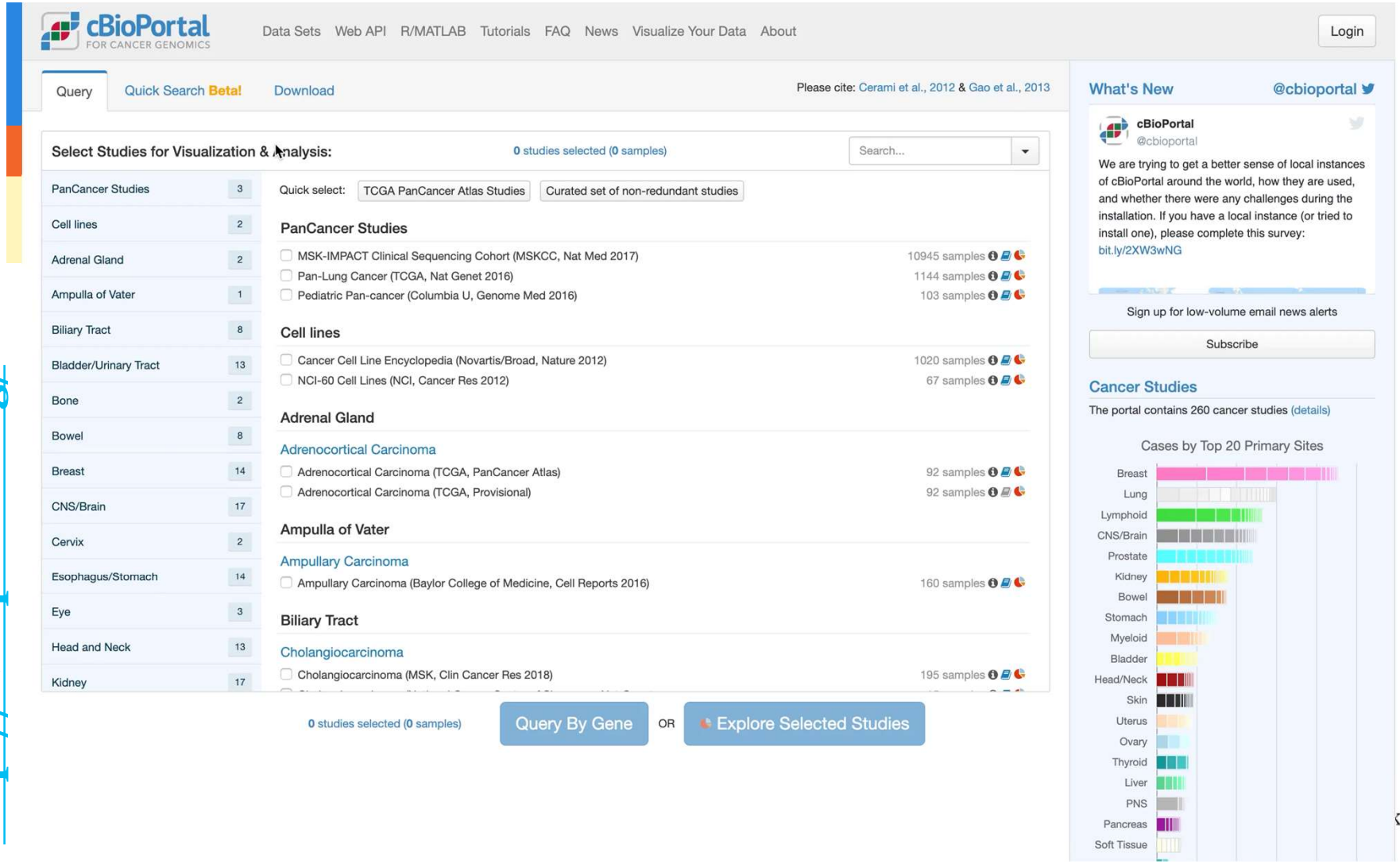
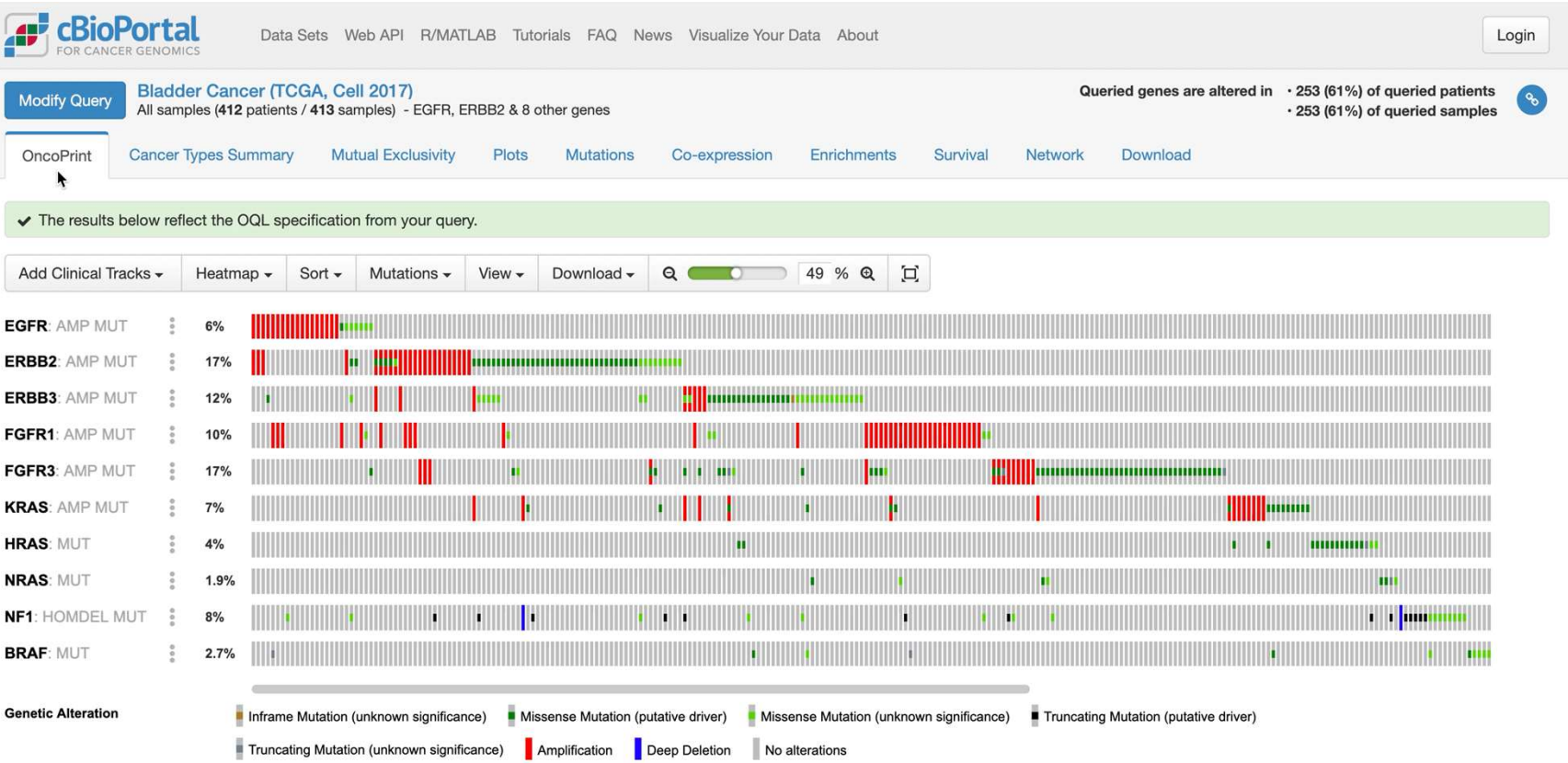
http://cbioportal.org/



Kettering

http://cbioportal.org/



Kettering

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...

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Marc Ladanyi

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Paul Sabbatini
David Hyman

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