Memorial Sloan Kettering Cancer Center

Identifying Driver Alterations and Therapeutic Options using the cBioPortal for Cancer Genomics & OncoKB

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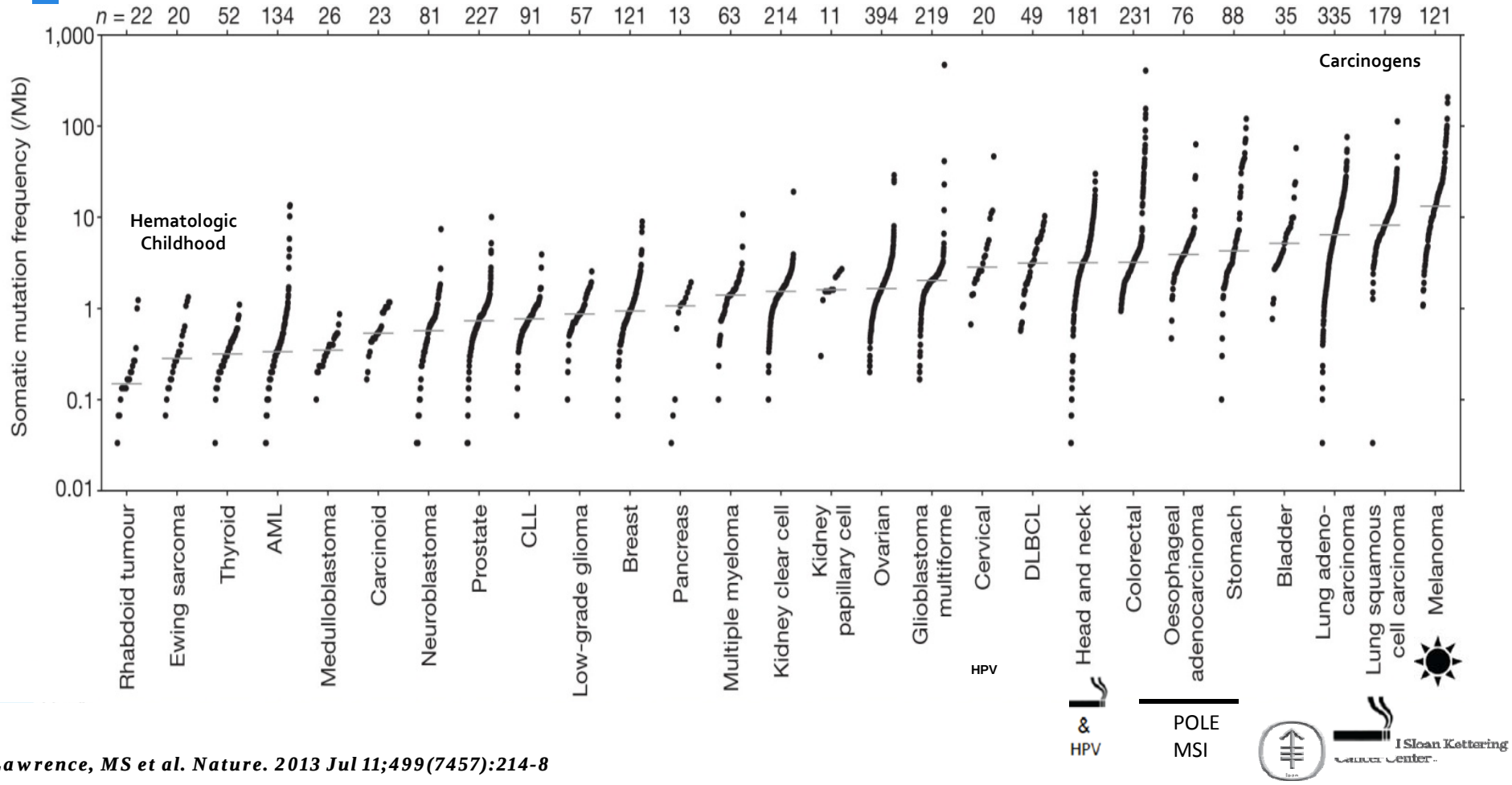
Associate Member, Computational Oncology
Head, Knowledge Systems
Kravis Center for Molecular Oncology

October 4, 2018

Most mutations found in cancer samples are “passengers”



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

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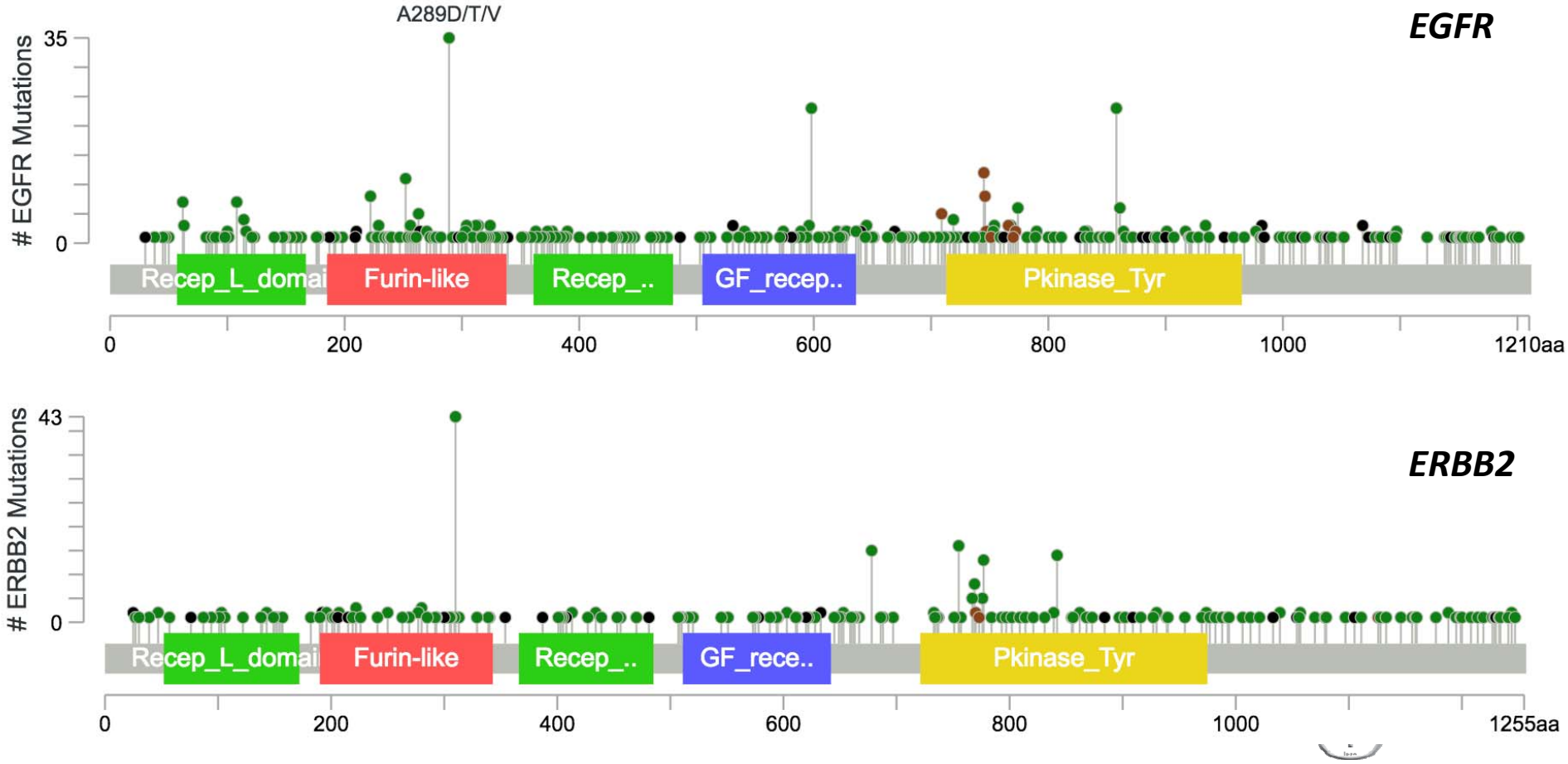

Among driver variants, only a subset or clinically actionable

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

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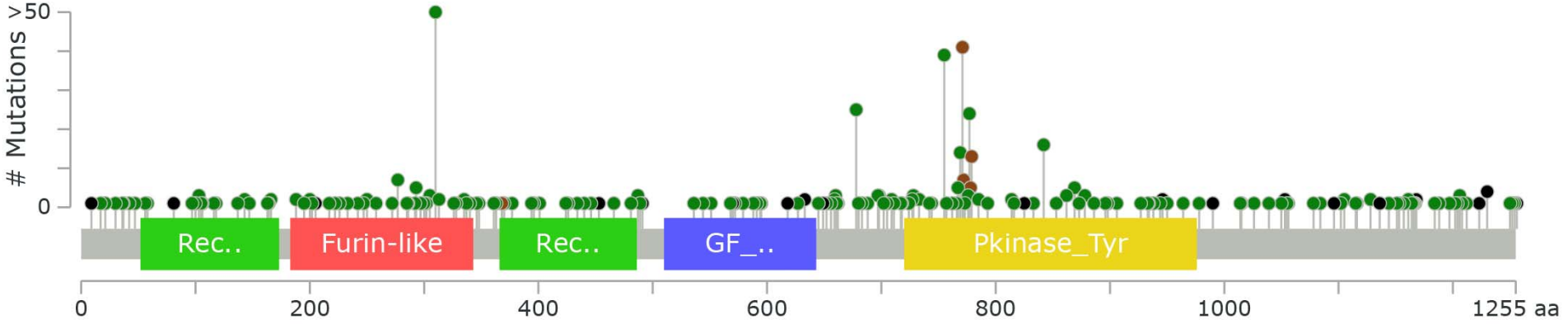
How can we identify driver variants and act on them?

1 Recurrence

Frequently mutated amino acids

Cancer Hotspots

http://www.cancerhotspots.org/



ERBB2 mutations in 24,500 tumors

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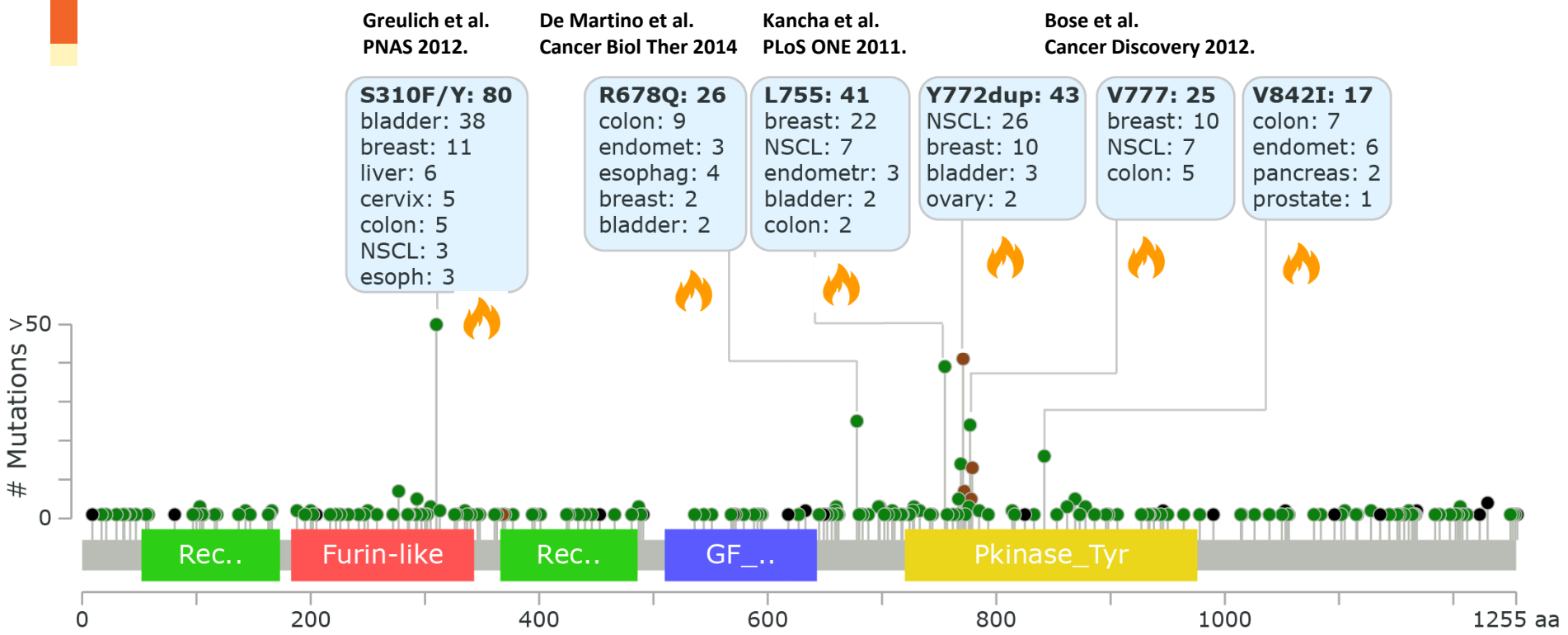
ERBB2 hotspots in 24,500 tumor samples

Cancer Hotspots

http://www.cancerhotspots.org/



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ERBB2 hotspots in 24,500 tumor samples

Cancer Hotspots

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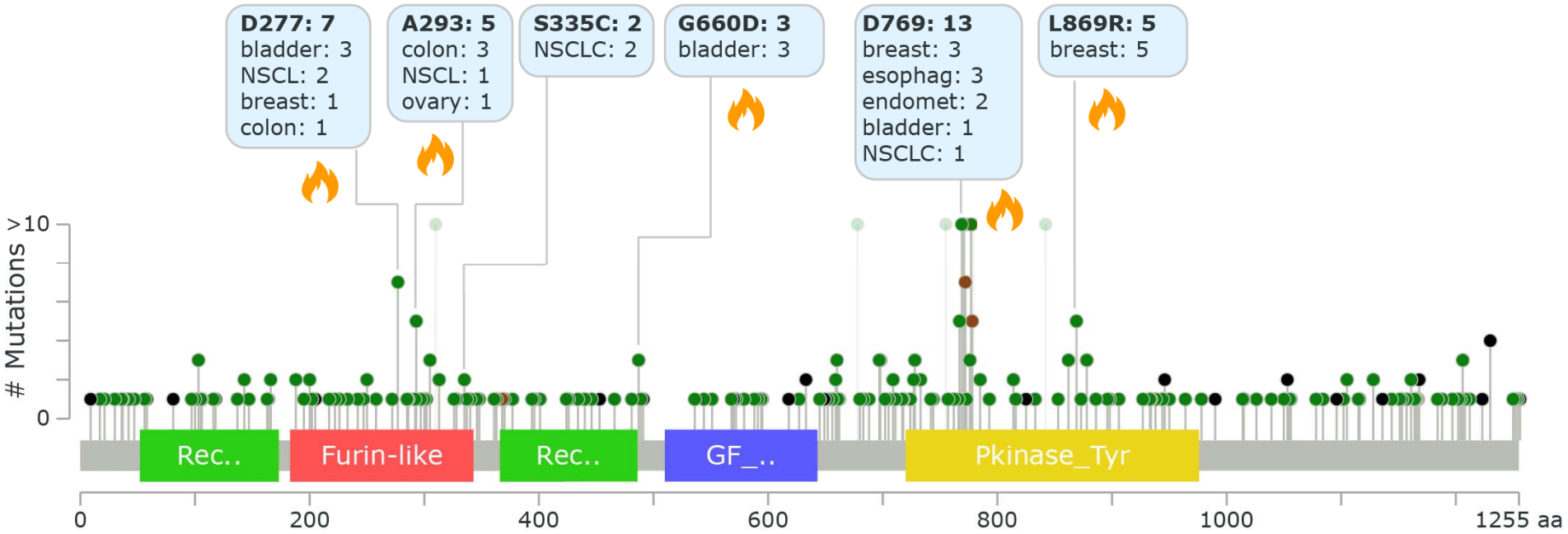

20 ERBB2 hotspots in analysis of 24,500 tumors

1165 hotspots in 247 genes

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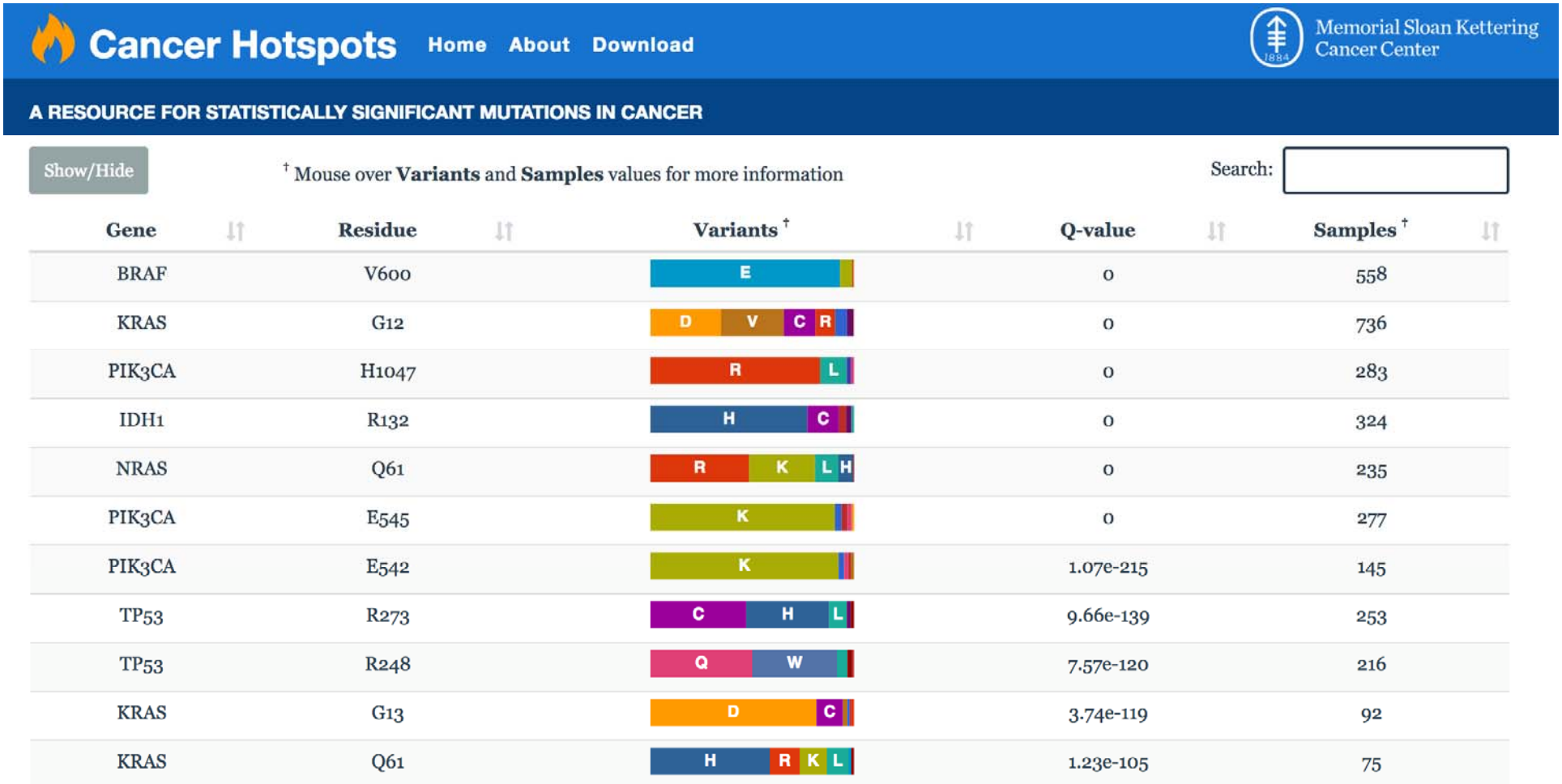

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Chang, MT et al. Nat Biotechnol. 2016 Feb;34(2):155-63

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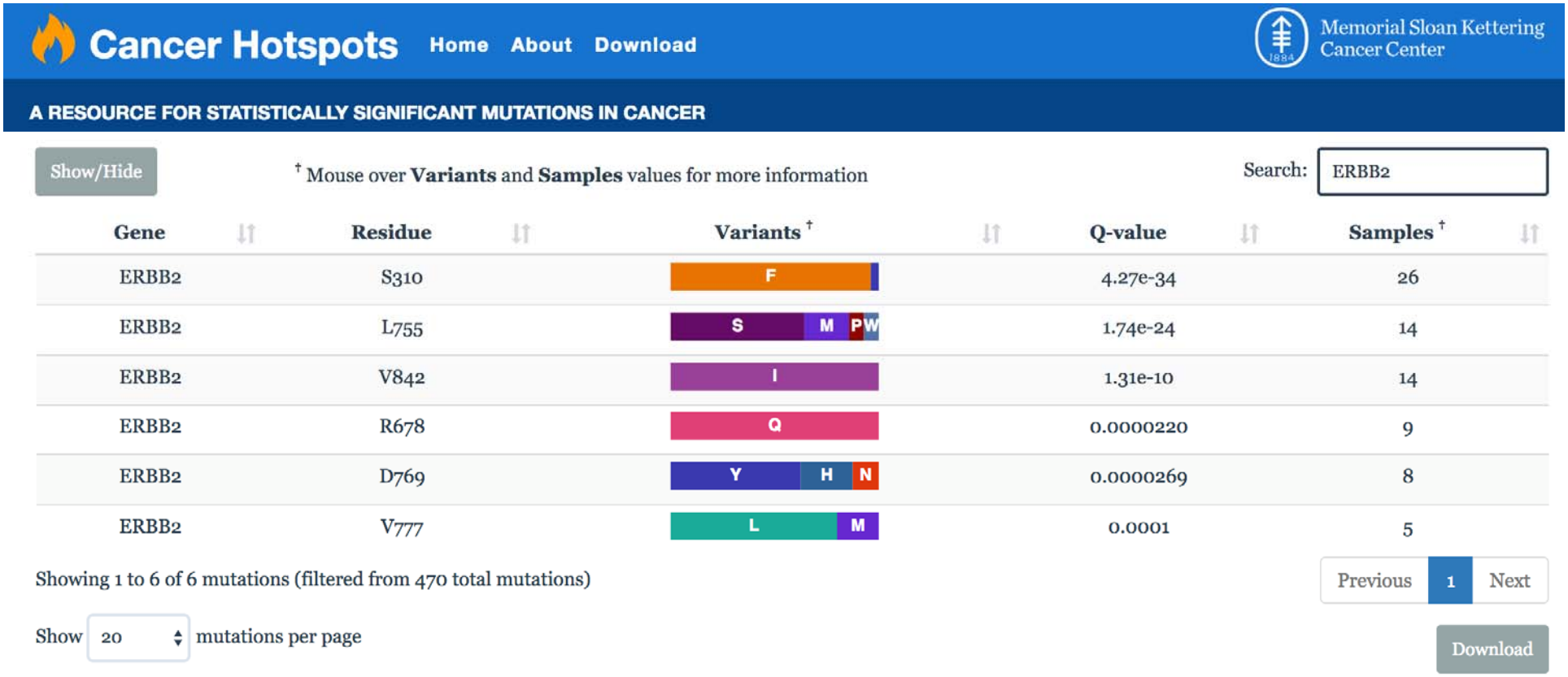

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Chang, MT et al. Nat Biotechnol. 2016 Feb;34(2):155-63

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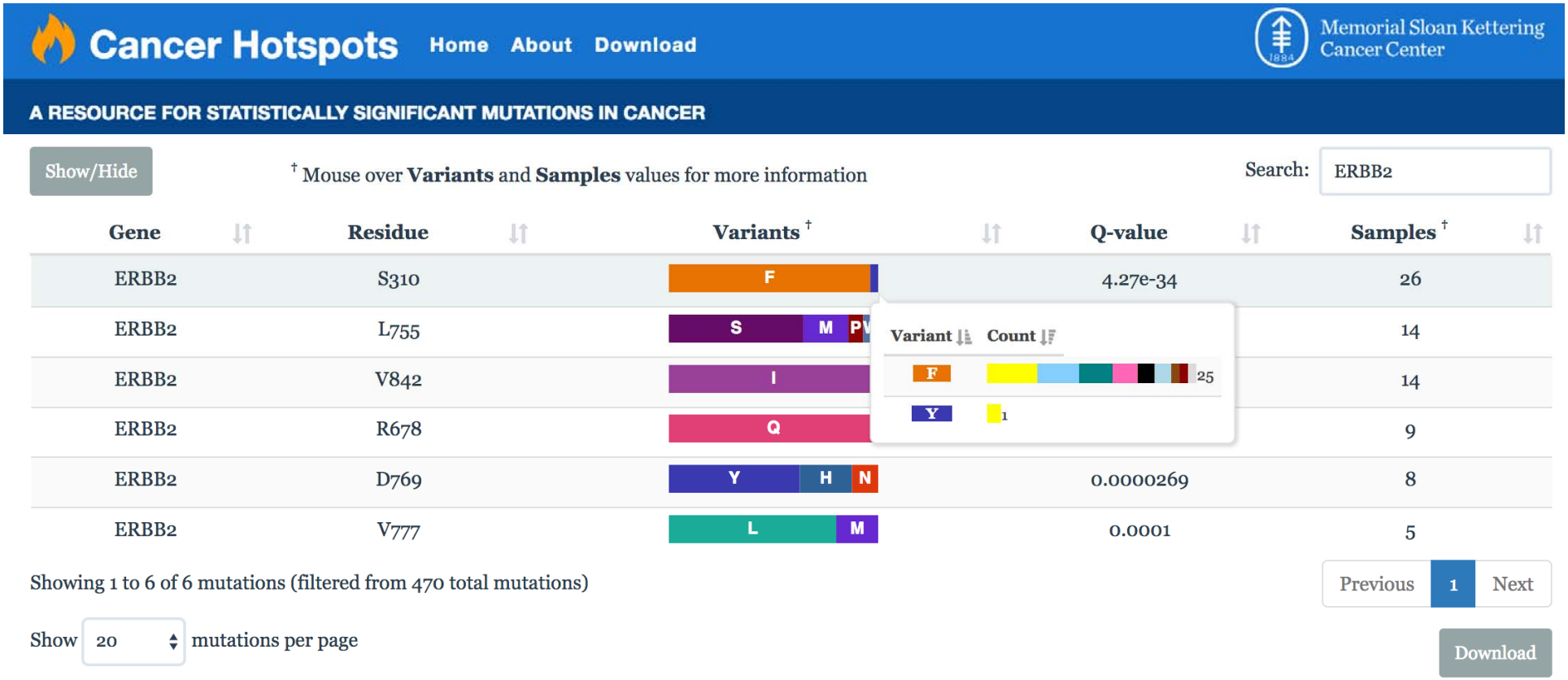

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Chang, MT et al. Nat Biotechnol. 2016 Feb;34(2):155-63

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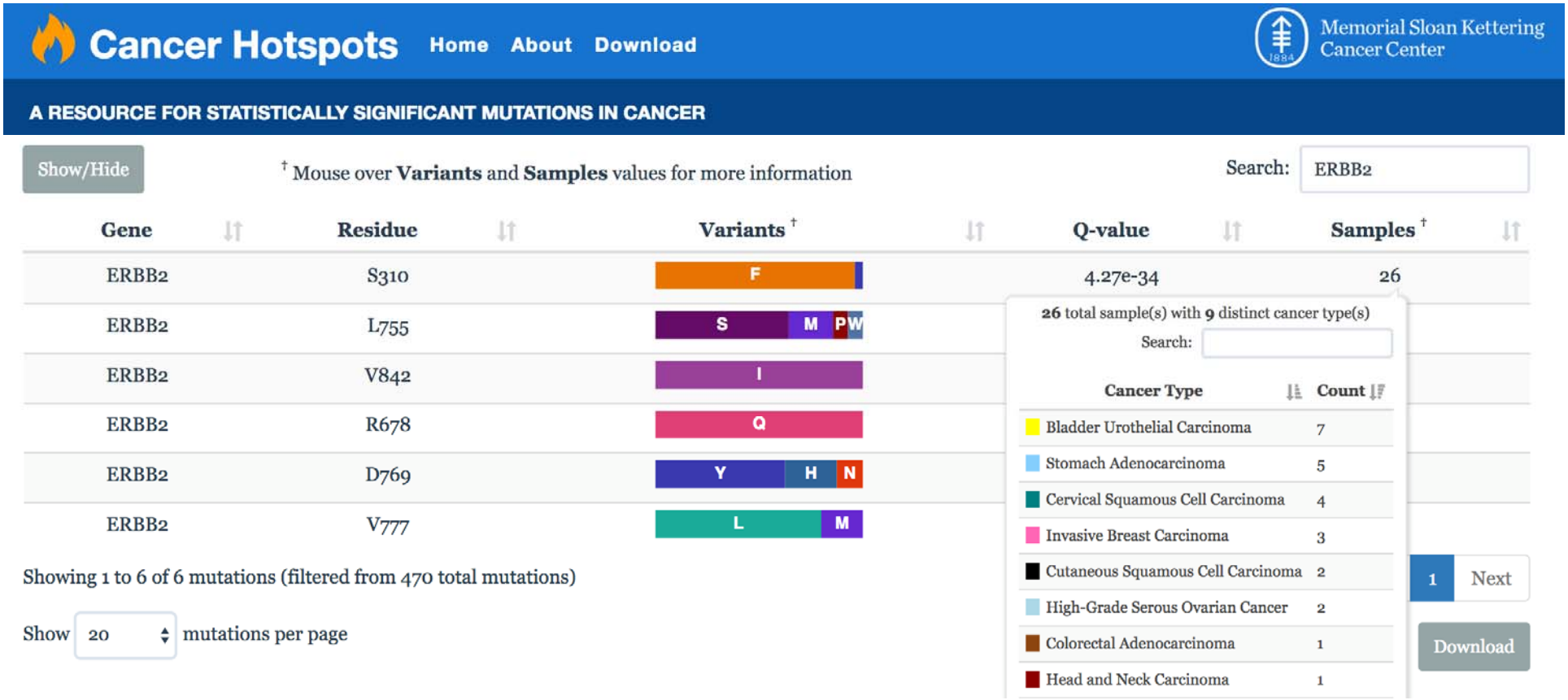

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How can we identify driver & actionable variants?

1 **Recurrence**

Frequently mutated amino acids

2 **Prior Knowledge**

Driver & actionable variants

3 **Intuitive visualization**

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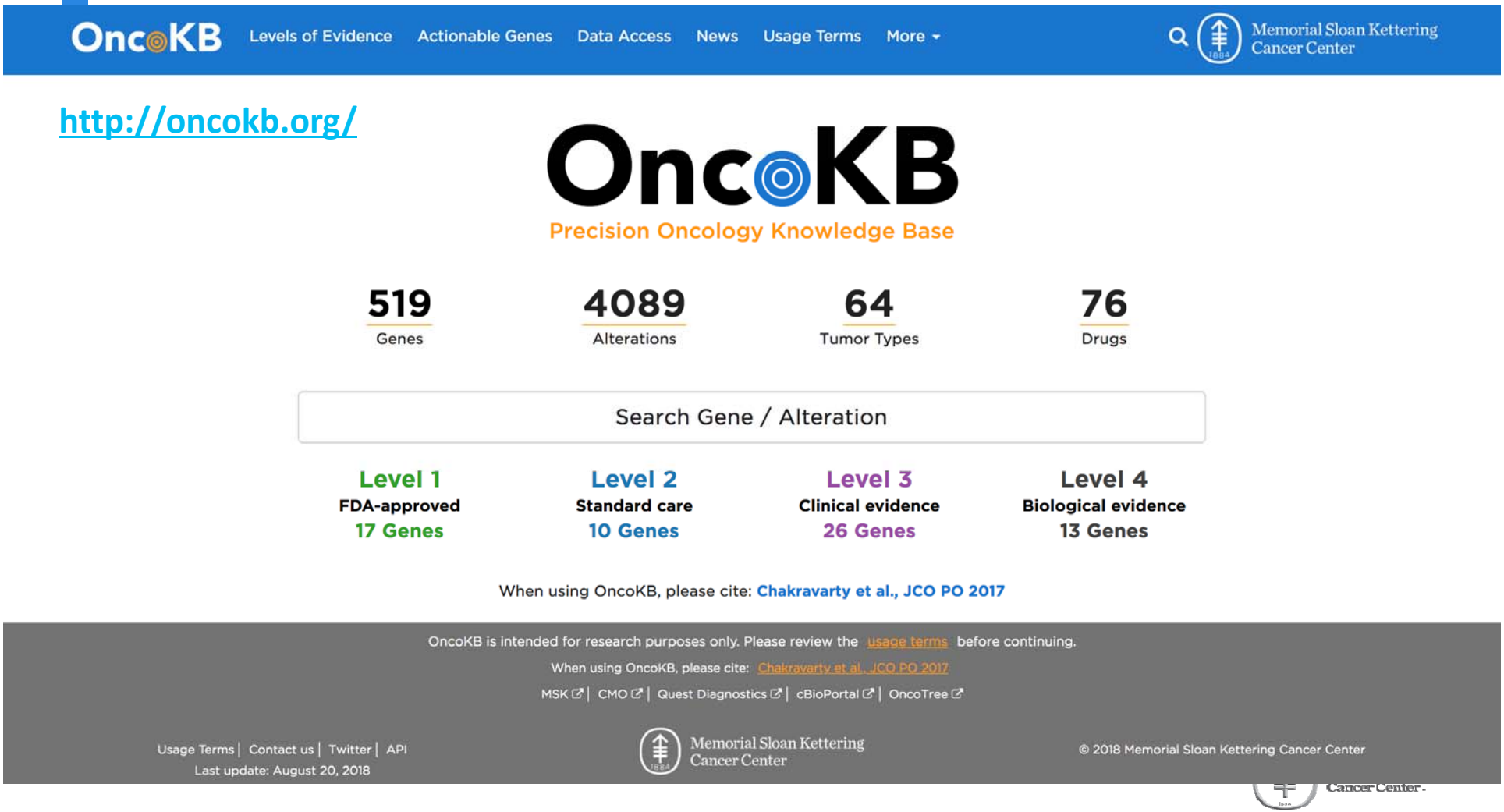
OncoKB
Levels of Evidence
Actionable Genes
Data Access
News
Usage Terms
More
Memorial Sloan Kettering Cancer Center
http://oncokb.org/
OncoKB
Precision Oncology Knowledge Base
519
Genes
4089
Alterations
64
Tumor Types
76
Drugs
Search Gene / Alteration
Level 1
FDA-approved
17 Genes
Level 2
Standard care
10 Genes
Level 3
Clinical evidence
26 Genes
Level 4
Biological evidence
13 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
Usage Terms | Contact us | Twitter | API
Last update: August 20, 2018
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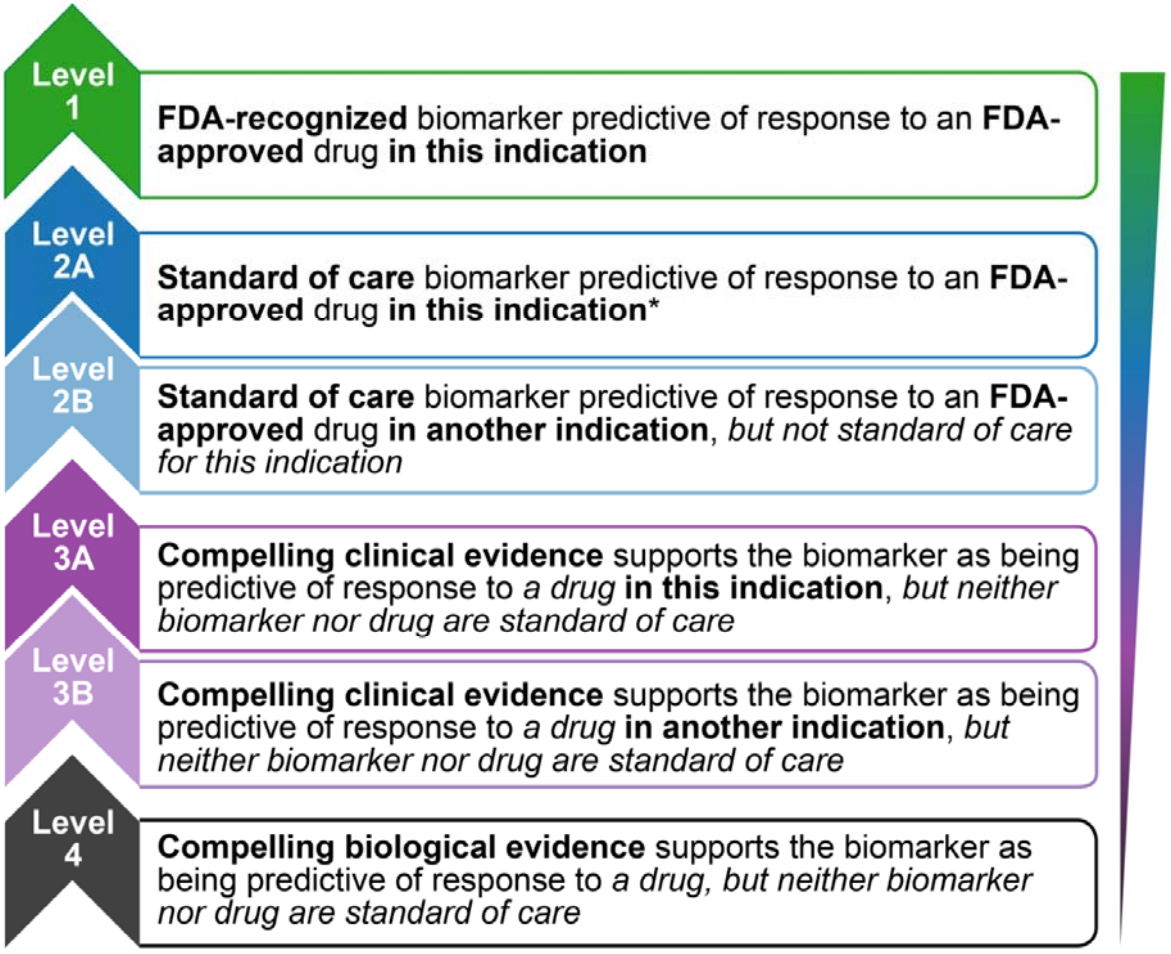
OncoKB Levels of Evidence



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

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

BRAF V600E in lung cancer
MET amp & splice in lung cancer

BRAF V600E in thyroid
ERBB2 amp in lung cancer

Investigational Therapeutic Implications
possibly directed to clinical trials

ERBB2, AKT1, PIK3CA mut in breast
IDH1 in several tumor types

ERBB2 mutation in bladder cancer

Hypothetical Therapeutic Implications
based on preliminary, non-clincial data

EGFR exon 20 mutation in lung

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OncoKB Metrics

519 Genes

4089 Alterations

64 Tumor Types

76 Drugs

Level 1
FDA-approved
17 Genes

ABL1, ALK, BRAF, BRCA1, BRCA2, EGFR, ERBB2, IDH2, KIT, KRAS, PDGFRA, PDGFRB, ROS1
(and MSI-H)

Level 2
Standard care
10 Genes

ALK, BRAF, BRCA1, BRCA2, CDK4, KIT, MET, PDGFRA, RET, TSC1, TSC2

Level 3
Clinical evidence
26 Genes

AKT1, ARAF, BRAF, ERBB2, ERCC2, ESR1, FGFR1, FGFR2, FGFR3, FLT3, IDH1, JAK2, MAP2K1, MDM2, MET, MTOR, NRAS, NTRK1, NTRK2, NTRK3, PIK3CA, PTCH1, RET

Level 4
Biological evidence
13 Genes

ATM, BRAF, EGFR, ERBB2, EWSR1, EZH2, HRAS, KIT, KRAS, MTOR, NF1, NOTCH1, NTRK1, NTRK3, PDGFRB, PTEN

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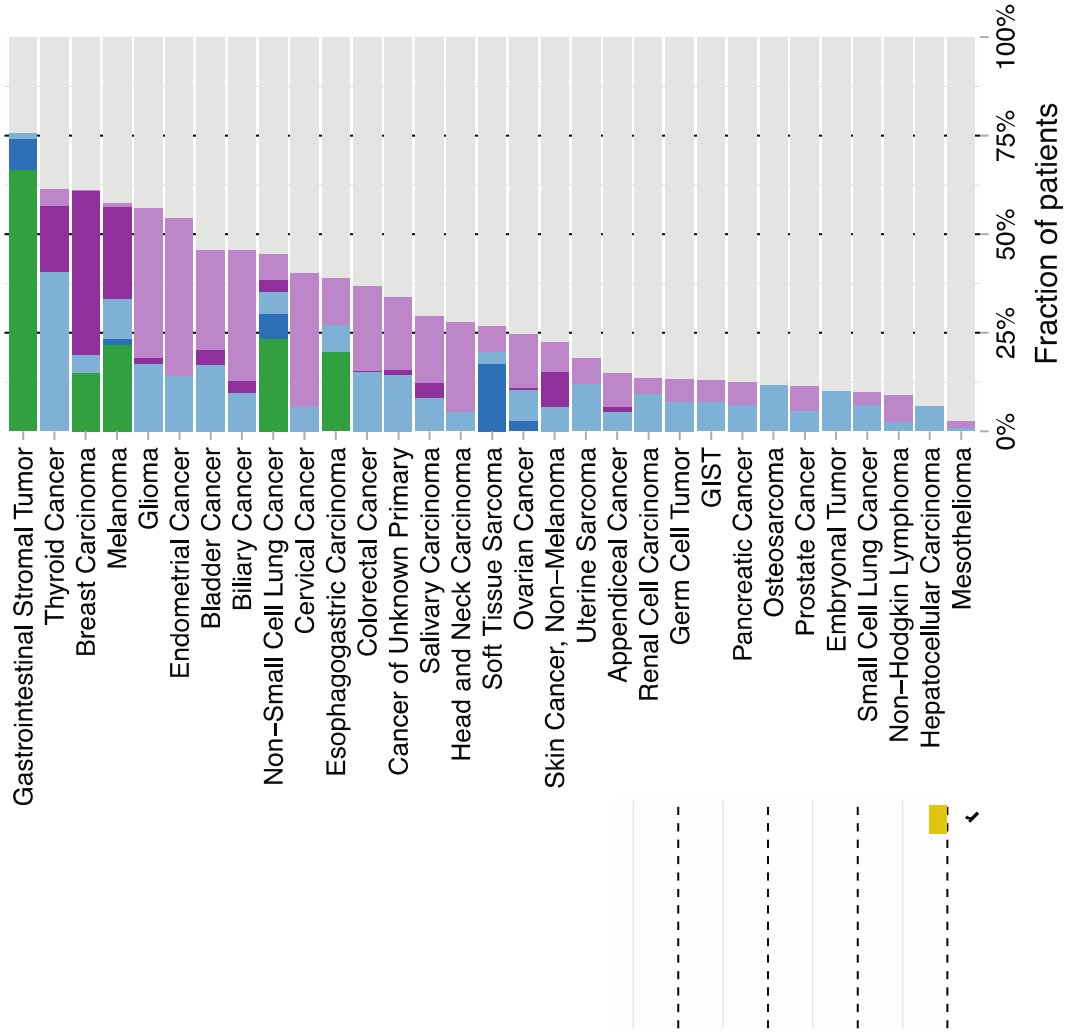
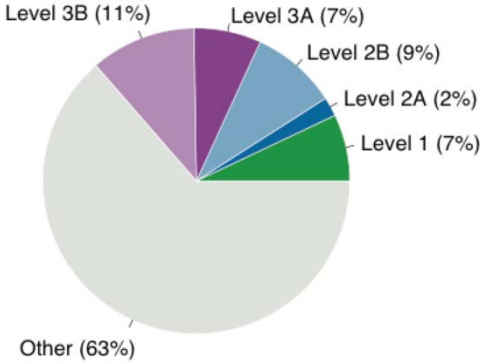
Actionable alterations per tumor type in MSK-IMPACT



Level 1	FDA-recognized biomarker to an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker to an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker to an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive to a drug in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive to a drug in another indication



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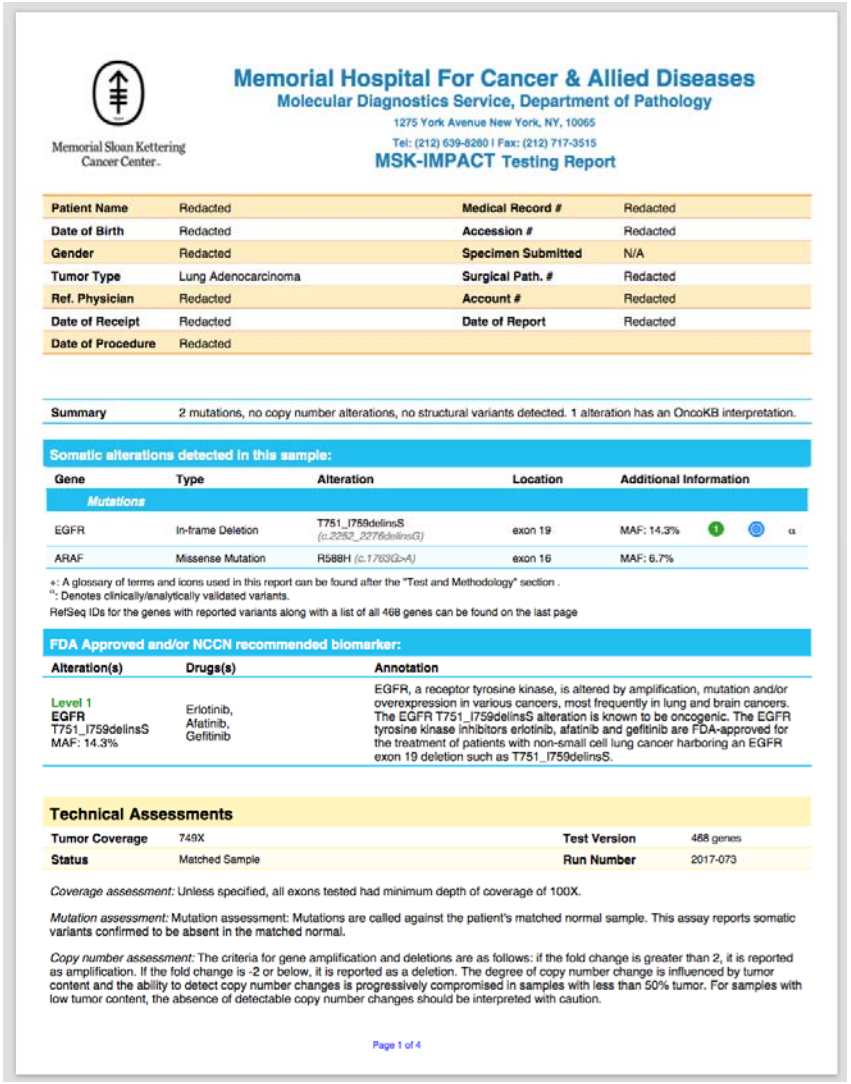

Memorial Hospital For Cancer & Allied Diseases
Molecular Diagnostics Service, Department of Pathology
1275 York Avenue New York, NY, 10065
Tel: (212) 639-6280 | Fax: (212) 717-3515
MSK-IMPACT Testing Report

Memorial Sloan Kettering Cancer Center

Patient Name	Redacted	**Medical Record #**	Redacted
Date of Birth	Redacted	**Accession #**	Redacted
Gender	Redacted	**Specimen Submitted**	N/A
Tumor Type	Lung Adenocarcinoma	**Surgical Path. #**	Redacted
Ref. Physician	Redacted	**Account #**	Redacted
Date of Receipt	Redacted	**Date of Report**	Redacted
Date of Procedure	Redacted		

Summary 2 mutations, no copy number alterations, no structural variants detected. 1 alteration has an OncoKB interpretation.

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Mutations				
EGFR	In-frame Deletion	T751_I759delinsS (c.2252_2276delinsG)	exon 19	MAF: 14.3%
ARAF	Missense Mutation	R588H (c.1763G>A)	exon 16	MAF: 6.7%

+: A glossary of terms and icons used in this report can be found after the "Test and Methodology" section .
°: Denotes clinically/analytically validated variants.
RefSeq IDs for the genes with reported variants along with a list of all 468 genes can be found on the last page

FDA Approved and/or NCCN recommended biomarker:

Alteration(s)	Drugs(s)	Annotation
Level 1 **EGFR** T751_I759delinsS MAF: 14.3%	Erlotinib, Afatinib, Gefitinib	EGFR, a receptor tyrosine kinase, is altered by amplification, mutation and/or overexpression in various cancers, most frequently in lung and brain cancers. The EGFR T751_I759delinsS alteration is known to be oncogenic. The EGFR tyrosine kinase inhibitors erlotinib, afatinib and gefitinib are FDA-approved for the treatment of patients with non-small cell lung cancer harboring an EGFR exon 19 deletion such as T751_I759delinsS.

Technical Assessments

Tumor Coverage	749X	**Test Version**	468 genes
Status	Matched Sample	**Run Number**	2017-073

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

Mutation assessment: 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.

Copy number assessment: The criteria for gene amplification and deletions are as follows: if the fold change is greater than 2, it is reported as amplification. If the fold change is -2 or below, it is reported as a deletion. The degree of copy number change is influenced by tumor content and the ability to detect copy number changes is progressively compromised in samples with less than 50% tumor. For samples with low tumor content, the absence of detectable copy number changes should be interpreted with caution.

Page 1 of 4

MSK-IMPACT reports

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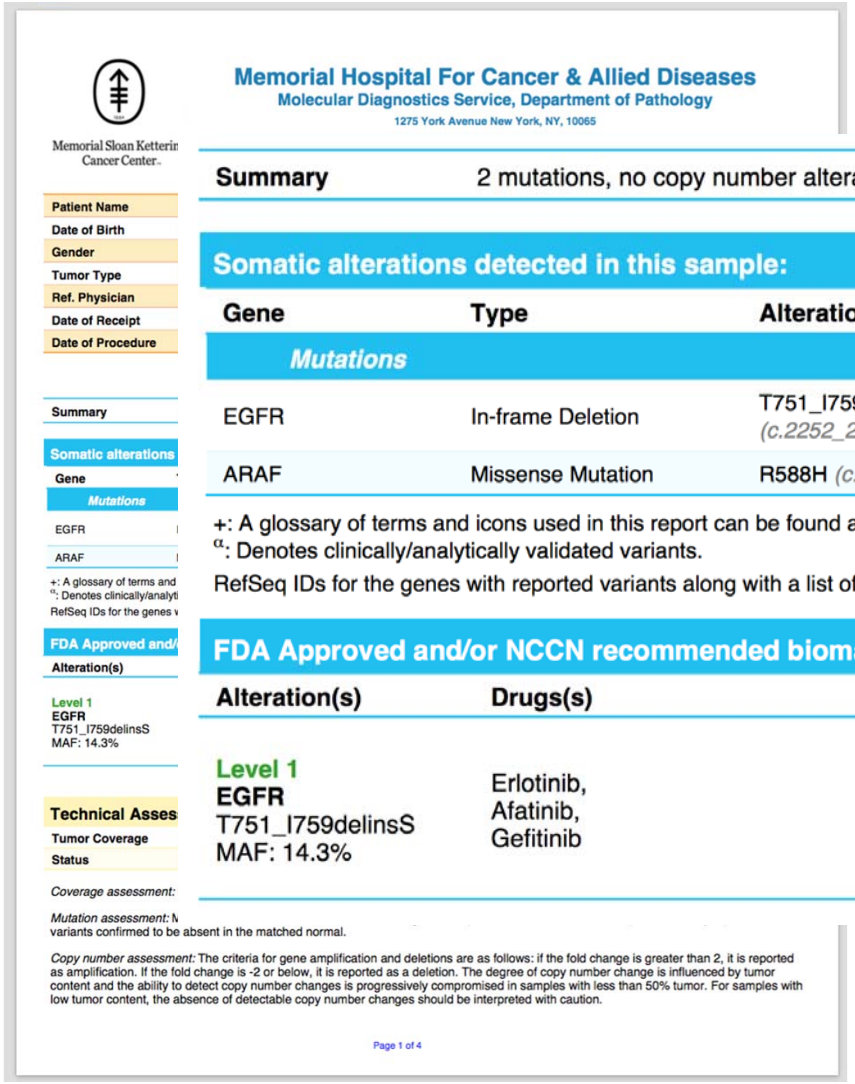
MSK-IMPACT reports



Memorial Hospital For Cancer & Allied Diseases
Molecular Diagnostics Service, Department of Pathology
1275 York Avenue New York, NY, 10065

Memorial Sloan Kettering Cancer Center

Patient Name
Date of Birth
Gender
Tumor Type
Ref. Physician
Date of Receipt
Date of Procedure

Summary
Somatic alterations
Gene
Mutations
EGFR
ARAF
+: A glossary of terms and
α: Denotes clinically/analyti
RefSeq IDs for the genes
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Alteration(s)
Level 1
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Technical Asses
Tumor Coverage
Status

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Page 1 of 4

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How can we identify driver & actionable variants?

1. **Recurrence**
   Frequently mutated amino acids

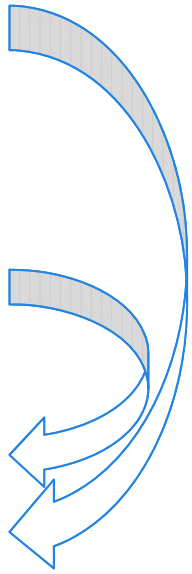
2. **Prior Knowledge**
   Driver & actionable variants

3. **Intuitive visualization**

Cancer Hotspots

OncoKB
Precision Oncology Knowledge Base

cBioPortal
FOR CANCER GENOMICS



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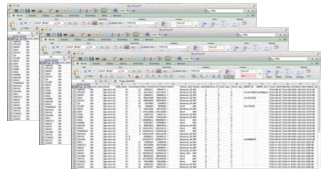
cBioPortal for Cancer Genomics: Data to knowledge

Tumor DNA

DNA sequencer, microarrays …

Tumor and normal sequences



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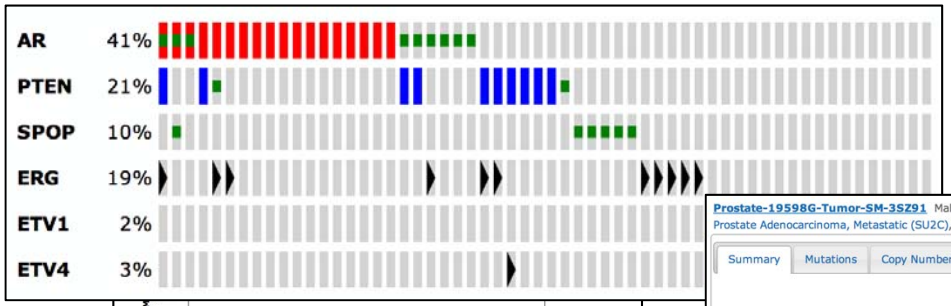

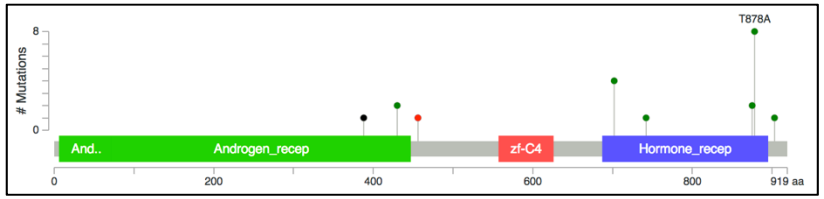

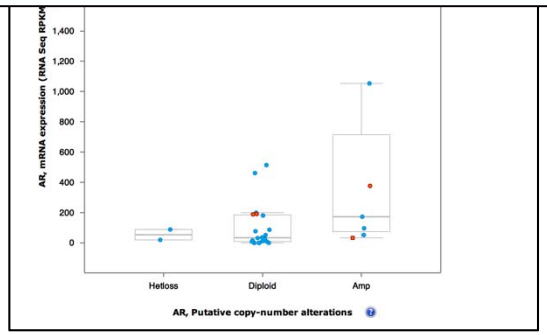

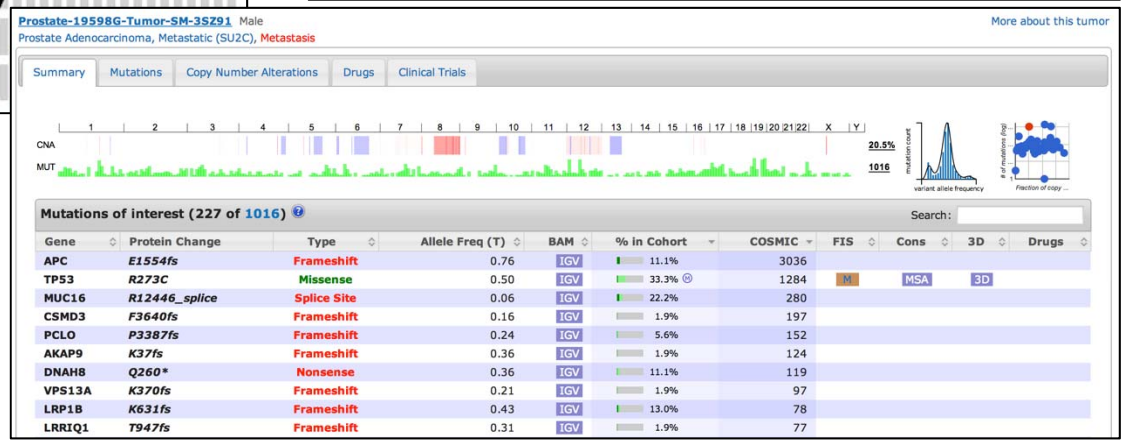

Intuitive interface, quick response time, reduction of complexity

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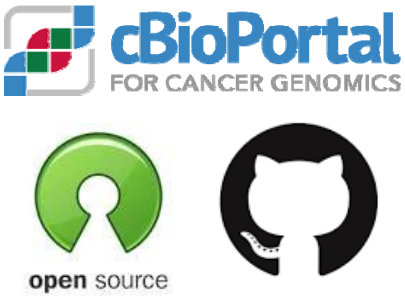
cBioPortal is open source software

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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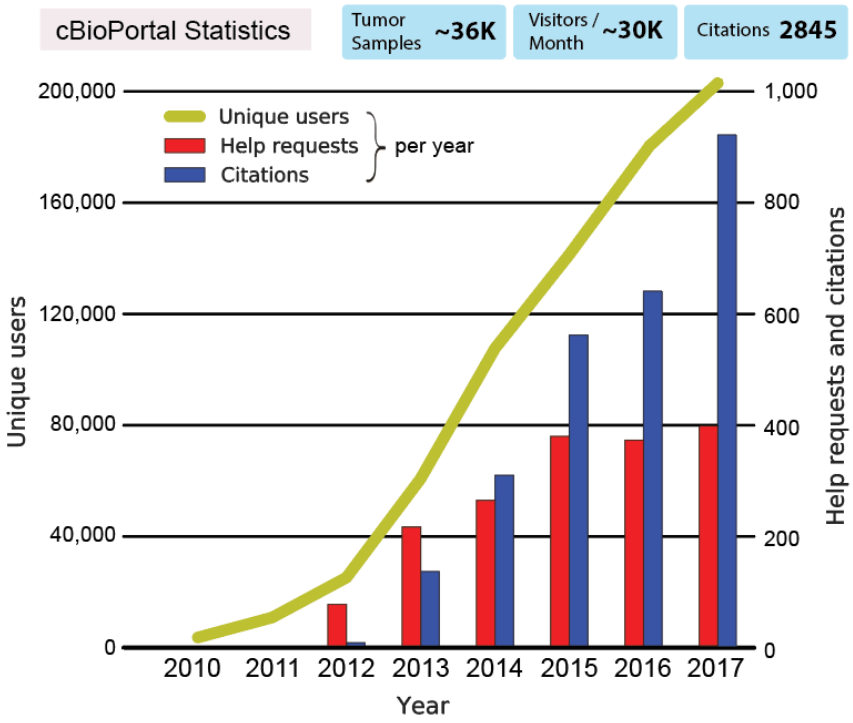
cBioPortal use

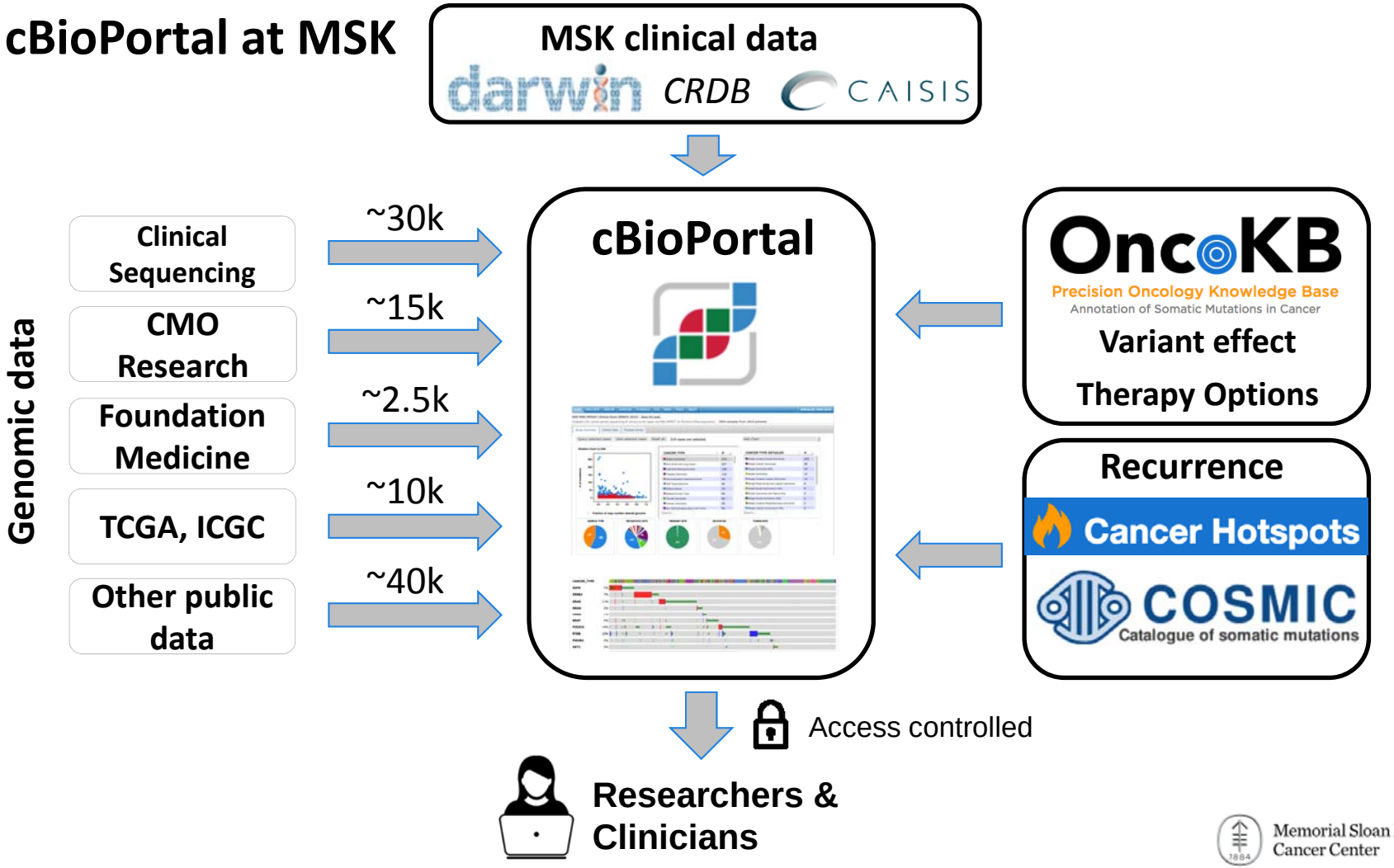


http://cbioportal.org/

AACR Project GENIE
+ SU2C, BCRF PDX, TCGA, POETIC, …

Local instances →

cBioPortal at MSK



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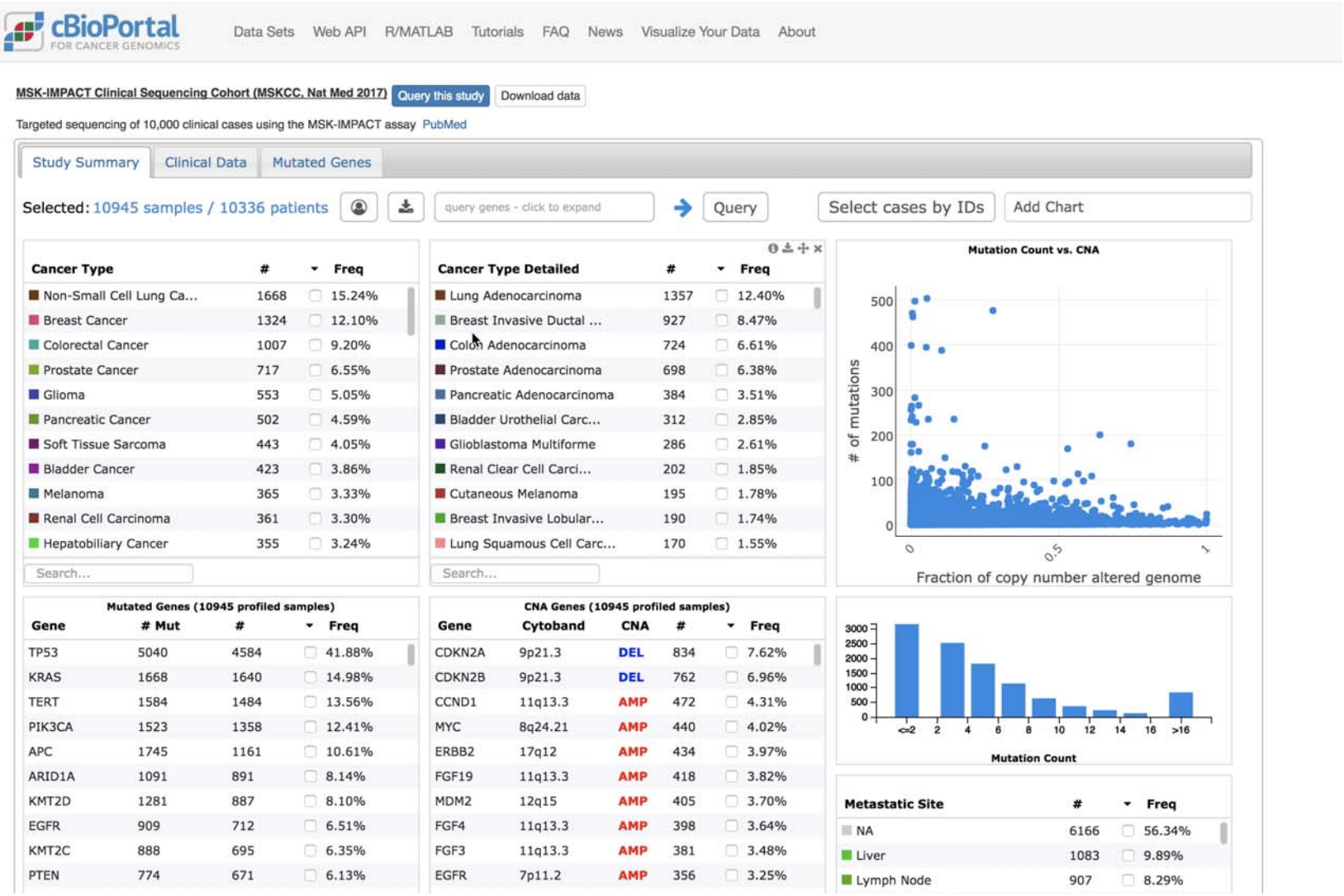
http://cbioportal.org/



http://cbioportal.org/

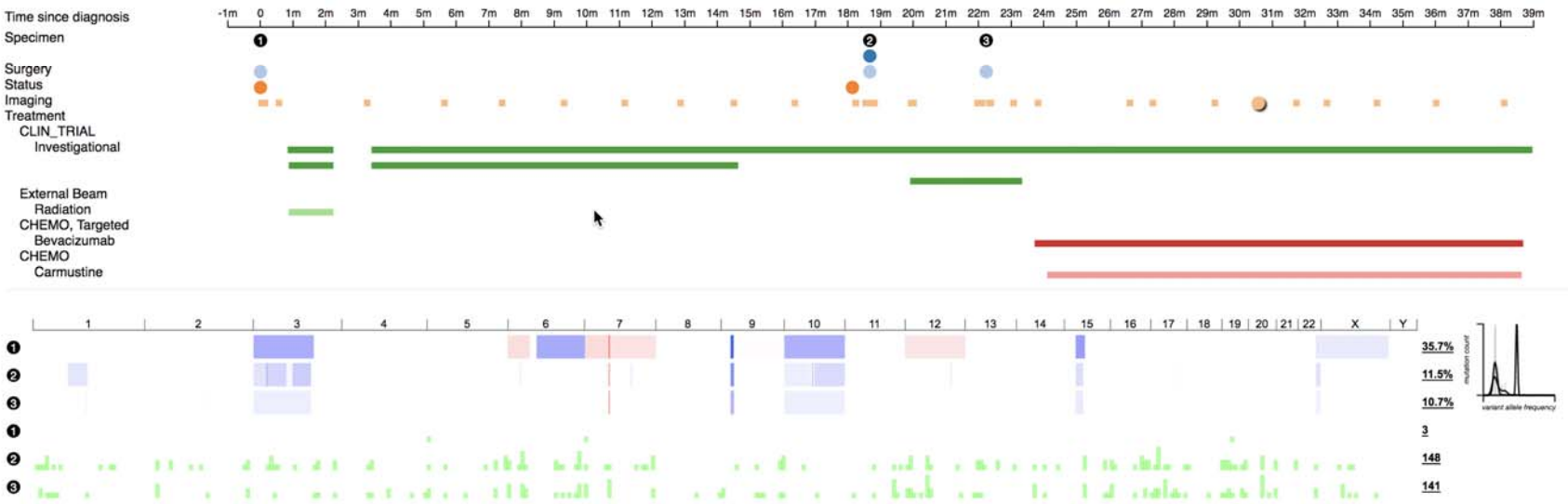
Patient: P-0002265, Male, 70 years old, Glioma (Glioblastoma Multiforme), LIVING (38 months), Recurred/Progressed (18 months) darwin

Samples: ❶ P-0002265-T01-IM3, Primary (Brain) ❷ P-0002265-T02-IM5, Primary (Brain) ❸ P-0002265-T04-IM5, Primary (Brain)

MSK-IMPACT Clinical Sequencing Cohort (MSKCC)

« ‹ 1 of 5 patients › »

Summary | Clinical Data



255 Mutations (page 1 of 26)

Columns ▾

Tumors ▼	Gene	Protein Change	Annotation	Mutation Type	Allele Freq	Cohort	COSMIC
❶ ❷ ❸	TERT	*Promoter*		5'Flank		13.7%	
❶ ❷ ❸	EGFR	*EGFR-intragenic*		Fusion			
❶ ❷ ❸	PIK3R2	*S144C*		Missense		1.1%	
❷ ❸	EGFR	*R108K*		Missense		6.2%	17
❷ ❸	EPHA5	*L113F*		Missense		3.2%	1
❷ ❸	ATM	*W1710**		Nonsense		5.4%	1
❷ ❸	PRKN	*A371T*		Missense		1.1%	2
❷ ❸	POLD1	*V759I*		Missense		1.6%	1
❷ ❸	FLT4	*D214N*		Missense		2.6%	

Summary

1. **Recurrence**
   Frequently mutated amino acids

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

3. **Intuitive visualization**

Acknowledgements

Schultz lab / Knowledge Systems
JianJiong Gao
Benjamin Gross
Debyani Chakravarty
Hongxin Zhang
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Ritika Kundra
Robert Sheridan
Onur Sumer
Sarah Phillips
Moriah Nissan
Jiajiao Wang
Francisco Sanchez-Vega
Joshua Armenia
Walid Chatila

CMO
Barry Taylor
Michael Berger
David Solit
Agnes Viale
Matthew Chang
Cyriac Kandoth
Nicholas Socci
Kristina Knapp
Ederlinda Paraiso

cBioPortal network
Ethan Cerami
Chris Sander
James Lindsay
Priti Kumari
Pichai Raman
Alex Sigaras
The Hyve

Clinical Leadership
Paul Sabbatini
David Hyman

OncoKB curators / clinical committee
Lindsay Saunders
Tara Soumerai
Rona Yaeger
Sarat Chandarlapaty
Alan Ho
Paul Paik
Tiffany Traina

Information Systems
Mike Eubanks
Stu Gardos

Molecular Diagnostics
Ahmet Zehir
Aijaz Syed
Michael Berger
Maria Arcila
Marc Ladanyi

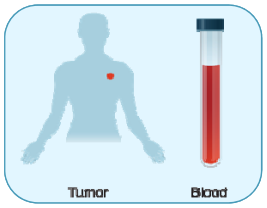
Bioinformatics Core
Joanne Edington

NIH NATIONAL CANCER INSTITUTE Office of Cancer Genomics
STARR CANCER CONSORTIUM
PROSTATE CANCER FOUNDATION
Quest Diagnostics
POETIC
S2C
Memorial Sloan Kettering Cancer Center

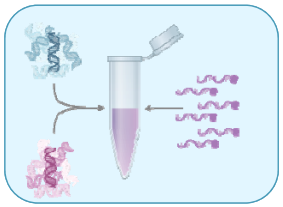
MSK-IMPACT Integrated Mutation Profiling of Actionable Cancer Targets

Tumor / normal
600x coverage

Patient Consent

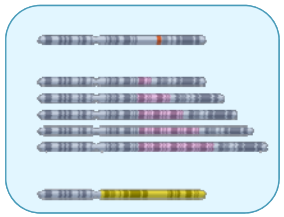


Sample Accessioning

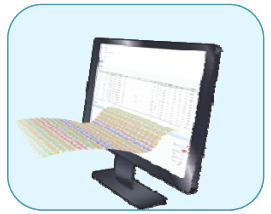


Sample Preparation

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)

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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

16,182 cases: 341 genes (n=2,894), 410 genes (n=9,880), 468 genes (n=18,000)

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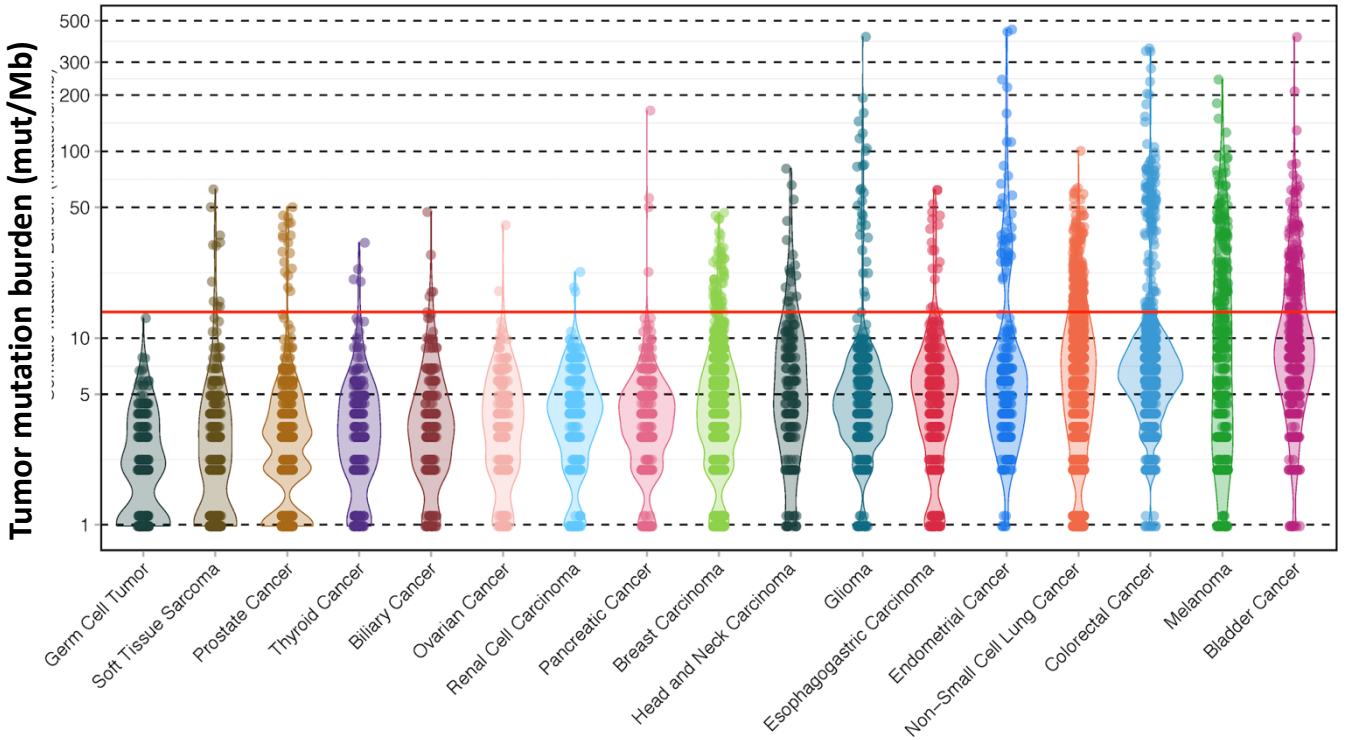
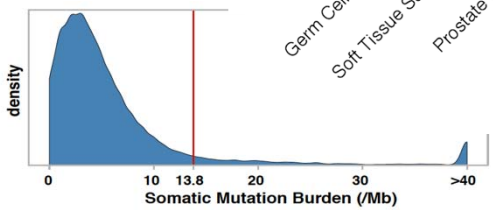
Somatic mutation rates in MSK-IMPACT

Wide range of tumor mutation burden across and within cancer types





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