Algorithms, rapid analyses, and data integrity in clinical practice

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University of Chicago

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Agenda

- Pediatric cancer
- Innovations in
    - data processing
    - clinical trials
    - data collection

New therapies are needed for pediatric cancer

Pediatric cancer is rare

Adult cancers	annual incidence
All	**1,688,780**
Oral	49,670
GI	310,440
Lung	222,500
Skin	95,360
Breast	255,180
Ovary	22,440
Prostate	161,360
Urinary	146,650
Lymphoma	80,500
Myeloma	30,280
Leukemia	62,130

Source: cancer.org - 2017

Pediatric cancers	annual incidence
All	**15,780**
ALL	3,080
CNS	2,780
Hodgkin lymphoma	1,180
NHL	1,040
AML	730
Neuroblastoma	710
Bone	820
Thyroid	570
Wilms	510
Germ cell	540
Rhabdomyosarcoma	340
Retinoblastoma	280
Melanoma	310
Other	2,890

Source: CDC - 2014

Children's Oncology Group

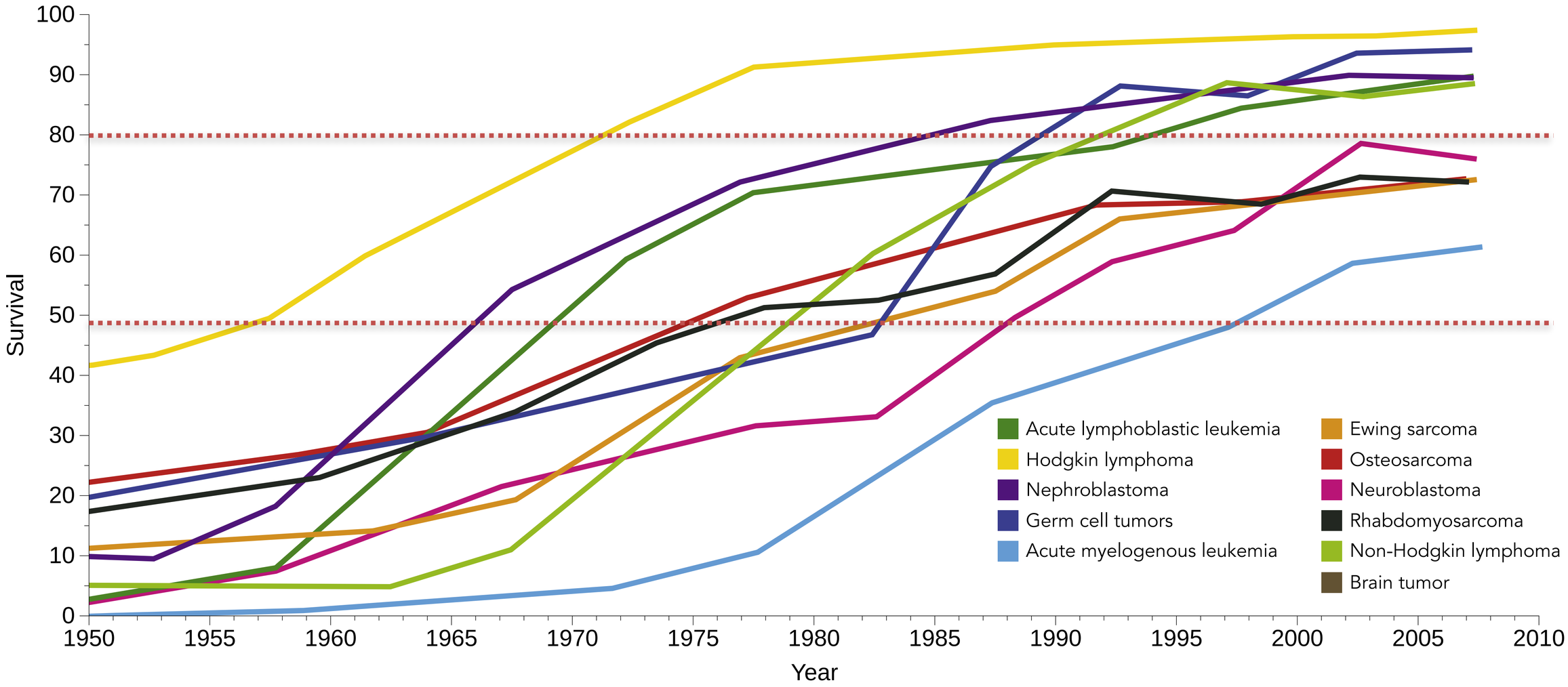
1955 — Cooperative group system for clinical research

Pediatric Oncology Group (POG)
Children's Cancer Group (CCG)
National Wilms' Tumor Study Group (NWTS)
Intergroup Rhabdomyosarcoma Study Group (IRSG)

2000 — Children's Oncology Group (COG)

200 centers in the United States, Canada, Switzerland, the Netherlands, Australia, and New Zealand

Survival - Pediatric cancer



The “long tail” of pediatric extracranial cancers

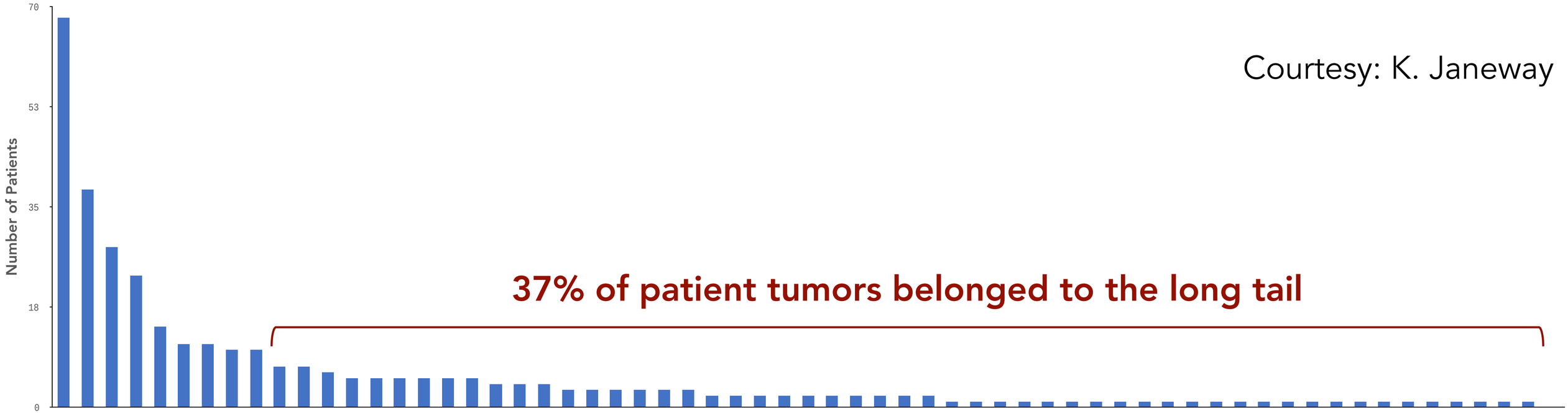
- PROFILE study (DFCI, BWH, BCH)
- All kids with suspected cancer
- DNA sequencing panel
- Used ICD-O for diagnoses
- Sequenced 338 patients

Courtesy: K. Janeway

doi:10.1172/jci.insight.87062

There were many rare diagnoses

- 63% were from nine common pediatric diagnoses
- Remaining 37% represent a “long tail”



Courtesy: K. Janeway

Diagnoses grouped into categories

Liver Tumors
Hepatoblastoma
Hepatocellular carcinoma

Germ Cell/Sex Cord Tumor
Choriocarcinoma
Germinoma
Granulosa cell tumor
Malignant teratoma
Seminoma
Sertoli-Leydig cell tumor
Yolk sac tumor

Carcinoma
Acinar cell carcinoma
Carcinoma, NOS
Embryonal carcinoma
Merkel cell carcinoma
Neuroendocrine carcinoma
Solid pseudopapillary carcinoma
Squamous cell carcinoma in situ
Adrenal cortical carcinoma
Mucoepidermoid carcinoma
Urothelial carcinoma
Renal cell carcinoma

Sarcoma (other)
Adenosarcoma (Mullerian)
Alveolar soft part sarcoma
Angiomatoid fibrous histiocytoma
Chondrosarcoma
Clear cell sarcoma of kidney
Dermatofibrosarcoma
Desmoplastic small round cell tumor
Embryonal sarcoma
Epithelioid sarcoma
Infantile fibrosarcoma
Leiomyosarcoma, NOS
Mesenchymal chondrosarcoma
Myxoid liposarcoma
Round cell sarcoma
Sarcoma, NOS
Spindle cell sarcoma
Synovial sarcoma

Rhabdomyosarcoma
Embryonal
Alveolar
Spindle cell
NOS

Other
Carcinoid tumor
Desmoid tumor
Gastrointestinal stromal tumor
Giant cell tumor of bone
Glomus tumor, malignant
Malignant melanoma
Malignant peripheral nerve sheath tumor
Malignant rhabdoid tumor
Myofibroblastic tumor
Neoplasm, NOS
Neurofibromatosis
Paraganglioma
Pheochromocytoma
Pigmented dermatofibrosarcoma protuberans
Pleuropulmonary blastoma
Retinoblastoma
Thymoma

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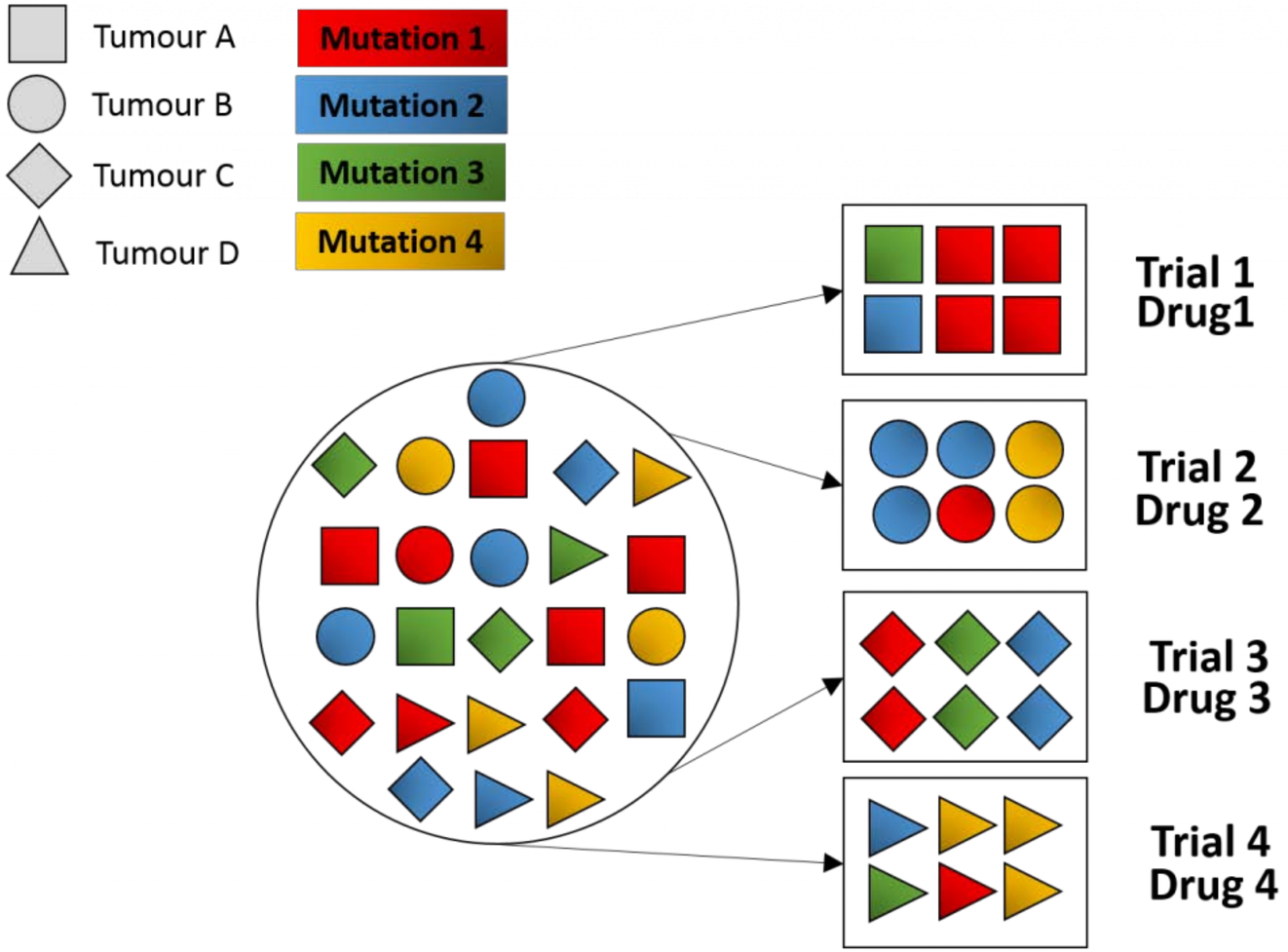
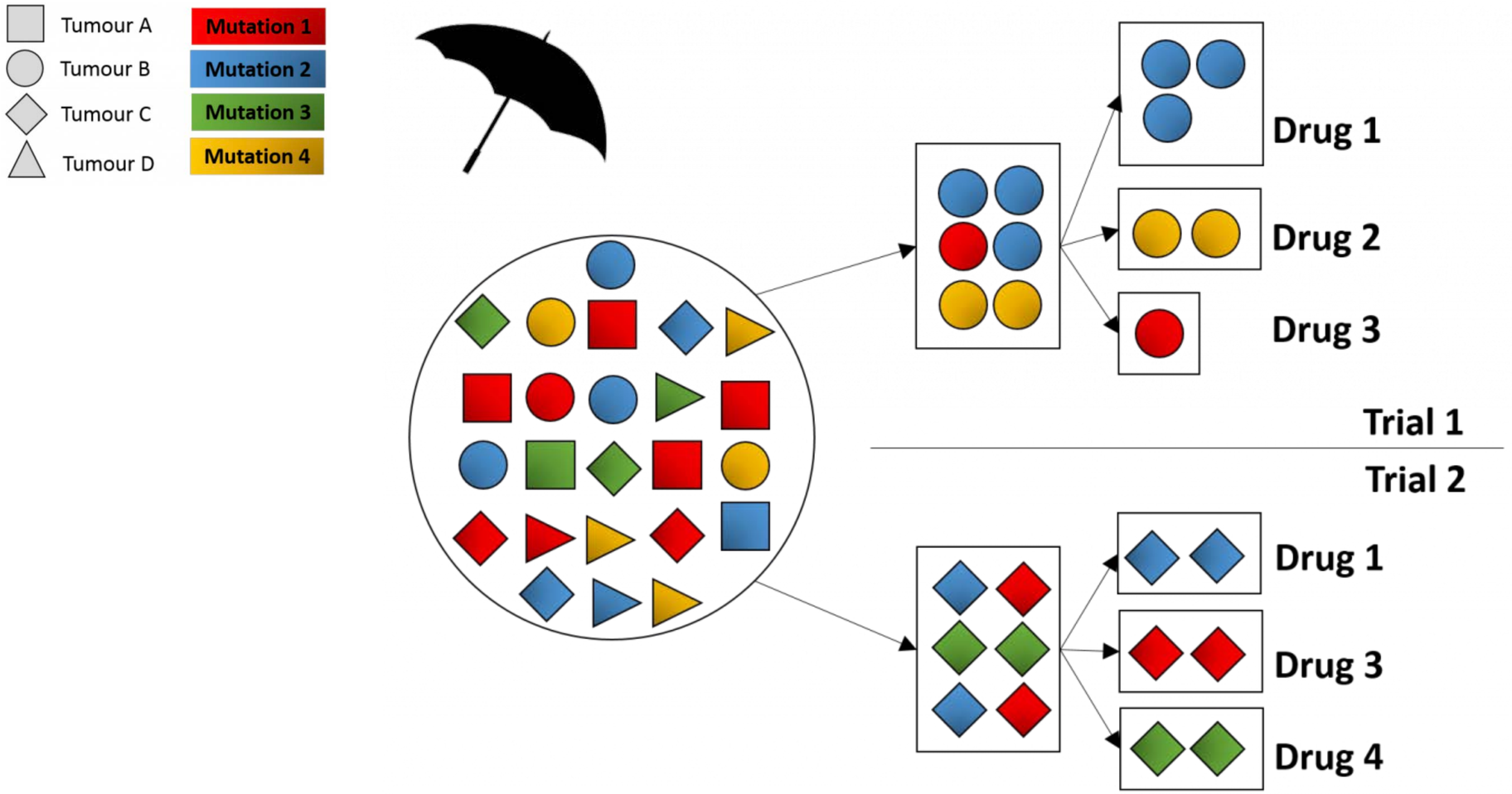
Need a new way to think about therapy

Traditional trial based on histology



https://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials/

Umbrella trial - based on tumor type and genotype



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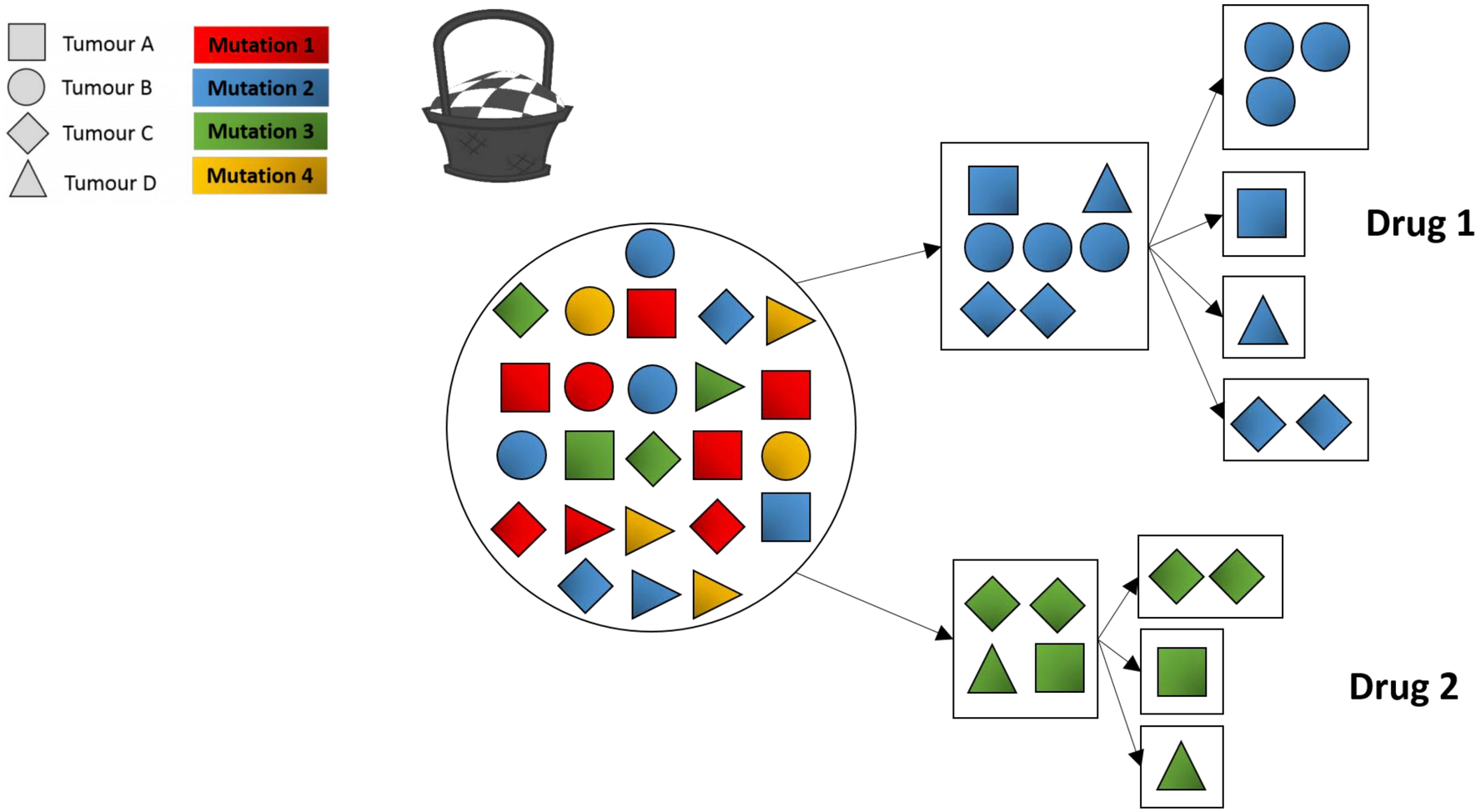
Basket trial - based on genotype



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Precision trials in pediatric oncology

Trial type	Examples	Sponsor
Basket in Relapsed/Refractory cancers across multiple diagnoses	NCI-COG Pediatric MATCH AcSé-eSMART	COG/NCI Gustave Roussy
Disease-specific umbrella in patients with progressive disease	Ruxolitinib or Dasatinib with Chemotherapy in Ph-Like ALL NEPENTHE (Neuroblastoma)	MD Anderson CHOP
Single-agent targeted therapy in advanced cancers	Larotrectinib in NTRK Fusion Positive Tumors EZH2 Inhibitor Tazemetostat in INI-1 Negative tumors Crizotinib for Tumors with an ALK, MET or ROS1 alteration LDK378 (Ceritinib) in ALK-activated Pediatric Tumors Dabrafenib with Trametinib for BRAF V600 Positive Tumors Afatinib in Pediatric Tumors with ErbB Pathway Deregulation	LOXO Oncology Epizyme UNICANCER Novartis Novartis Boehringer Ingelheim
Disease-specific trials in newly-diagnosed patients	Total Therapy XVII JAK/STAT Mutations in ALL and Lymphoma Addition of Dasatinib for ALL with TKI-targetable Fusions Combination Therapy Plus Dasatinib for Ph-Like B-ALL Clinical and Molecular Risk-Directed Therapy (Medulloblastoma) BIOMEDE (DIPG)	St. Jude DFCI COG/NCI St. Jude Gustave Roussy

Forrest SJ, Geoerger B, Janeway KA 2018 Curr Op Peds

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Single-agent targeted therapy in advanced cancers	Larotrectinib in NTRK Fusion Positive Tumors EZH2 Inhibitor Tazemetostat in INI-1 Negative tumors Crizotinib for Tumors with an ALK, MET or ROS1 alteration LDK378 (Ceritinib) in ALK-activated Pediatric Tumors Dabrafenib with Trametinib for BRAF V600 Positive Tumors Afatinib in Pediatric Tumors with ErbB Pathway Deregulation	LOXO Oncology Epizyme UNICANCER Novartis Novartis Boehringer Ingelheim
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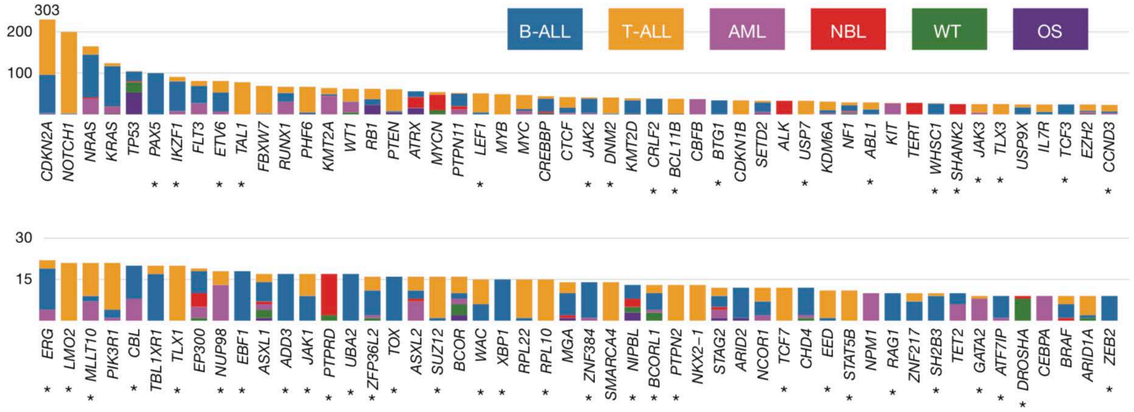
Landmark work in pediatric oncology

Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours

Xiaotu Ma[1]*, Yu Liu[1]*, Yanling Liu[1], Ludmil B. Alexandrov[2], Michael N. Edmonson[1], Charles Gawad[1], Xin Zhou[1], Yongjin Li[1], Michael C. Rusch[1], John Easton[1], Robert Huether[3]†, Veronica Gonzalez-Pena[4], Mark R. Wilkinson[1], Leandro C. Hermida[5], Sean Davis[6], Edgar Sioson[1], Stanley Pounds[7], Xueyuan Cao[7], Rhonda E. Ries[8], Zhaoming Wang[1], Xiang Chen[1], Li Dong[1], Sharon J. Diskin[9], Malcolm A. Smith[10], Jaime M. Guidry Auvil[5], Paul S. Meltzer[6], Ching C. Lau[11,12], Elizabeth J. Perlman[13], John M. Maris[9], Soheil Meshinchi[8], Stephen P. Hunger[9], Daniela S. Gerhard[5] & Jinghui Zhang[1]

doi:10.1038/nature25795

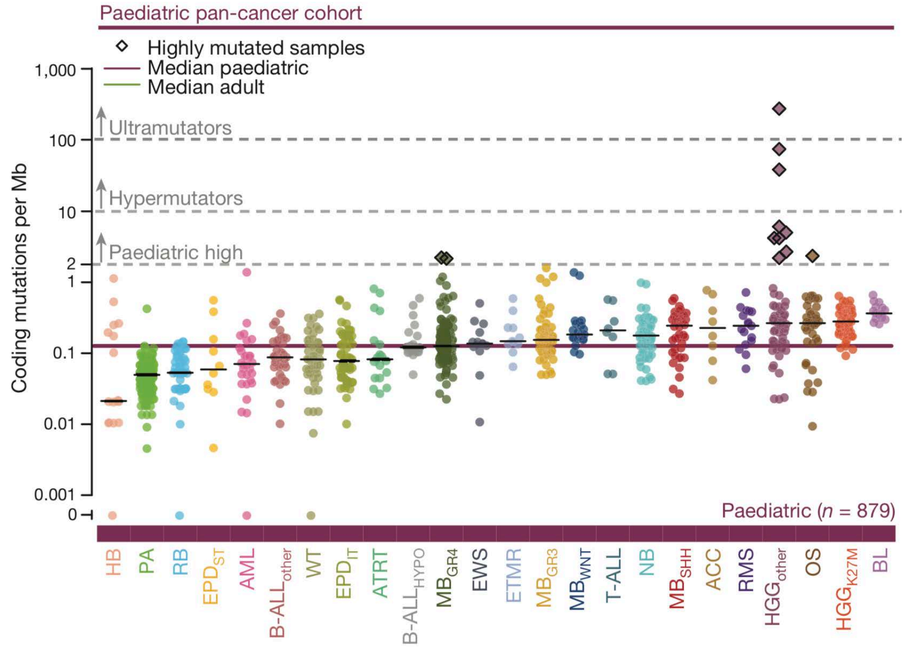


Top 100 recurrently mutated genes

The landscape of genomic alterations across childhood cancers

A list of authors and affiliations appears at the end of the paper.

doi:10.1038/nature25480



Somatic mutations

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Ongoing data aggregation studies in pediatric oncology

Repository	Notes	Cases
Genomic data commons	TARGET Basic data standardization	3,236
St. Jude Cloud	Less clinical annotation	3,054
GENIE	Hospital-based sequencing Potential for greater clinical annotation	>1000
Foundation Medicine	Limited clinical information	1,215

Courtesy: K. Janeway

Infrastructure innovations

UChicago clinical genomics lab

Illumina HiSeq 2500

MiSeq Desktop

Ion Torrent

Division of Genomic and Molecular Pathology

Clinical Genomics and Molecular Diagnostics Laboratories

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Lauren Ritterhouse, MD, PhD (Co-Dir, Molecular Laboratories)
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Megan McNerney, MD, PhD
Carrie Fitzpatrick, PhD
Nifang Niu, PhD

Bioinformatics

Sabah Kadri, PhD (Director of Bioinformatics)
Sushant Patil, PhD
Pankhuri Wanjari, PhD

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Filippo Galbo
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Clinical Genomics Laboratory

NGS Test Menu

- **OncoPlus v3.0**
  - 147 (out of 1213) gene panel for comprehensive profiling
  - Mutations, indels, structural variations, CNVs, fusions, MSI
  - Specimens: FFPE tissue, blood, bone marrow, FNAs
  - Turnaround time: 10-14 business days
- **OncoScreen v2.0**
  - 50 gene panel for hot-spot mutation detection
  - Specimens: FFPE tissue, blood, bone marrow, FNAs
  - Turnaround time: 4-10 business days
  - Minimal DNA input
- ***NPM1* MRD detection**
  - Molecular barcode amplicon sequencing for low% *NPM1* mutation detection.
  - Allelic discrimination at 1 mutant molecule per 10,000 normal molecules (0.01%)
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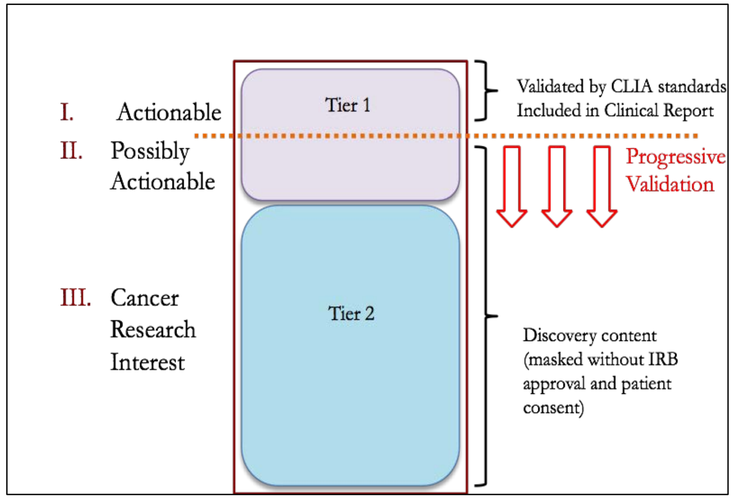
OncoPlus Comprehensive Cancer Panel

Tier 1 = 316 genes Tier 2 = 896 genes

ABCA12	COL8	ERBB4	ITPKB	NFKBIA	ROBO2	TRAF7	ALDH2	BNIP3	CHIC2	DBH	ERG	FUBP1	HLPDA	ICK	LDLR	MLF1	NEBL	PAX2	PRKDC	RPN1	SLC36A1	T	TRIM24	ZMYM2
ABCB1	CD79A	ESR1	JAK1	NKX2-1	ROBO3	TSC1	ALDH8A1	BRD3	CHMP4C	DBI	ESRP1	FUS	HIP1	IGF2	LEMD1	MLH3	NELL1	PAX3	PRRX1	RPS10	SLC38A1	TAF1	TRIM27	ZNF217
ABCD2	CD79B	ETV6	JAK2	NOTCH1	RPL22	TSC2	ALDOA	BRD4	CHN1	DCC	ETS1	FZR1	HS4H4	IGF2R	LHFP	MLLT1	NFIB	PAX6	PRSS1	RPS17	SLC38A3	TAF12	TRIM33	ZNF320
ABL1	CDC73	EZH2	JAK3	NOTCH2	RPTOR	TSHR	ALOX5	BTNL2	CIITA	DDB2	ETV1	G6PC3	HIST1H3A	IKBKB	LIFR	MLLT10	NFKB1	PAX7	PRSS37	RPS19	SLC38A6	TAF15	TRIP11	ZNF331
AFF2	CDH1	FAM46C	JAKMIP2	NPM1	RUNX1	TYK2	AMER1	BUB1B	CKS1B	DDIT3	ETV4	GABRA1	HIST1H3B	IKBKE	LMBRD1	MLLT11	NFKB2	PAX8	PRSS8	RPS24	SLC45A3	TAF1L	TRRAP	ZNF384
AKT1	CDH2	FANCA	KDM5A	NRAS	SAMHD1	U2AF1	ANKRD26	CA1D	CLCA2	DDIT4	ETV5	GALNT12	HIST1H3D	IKZF3	LMO1	MLLT3	NHP2	PBX1	PSIP1	RPS26	SLC47A1	TAL1	TSKU	ZNF423
AKT2	CDK12	FANCC	KDM5C	NTRK1	SDHA	UBR5	ANKRD37	CA9	CLP1	DDX10	EVPL	GALNT3	HIST1H3E	IL11	LMO2	MLLT4	NIN	PCDH9	PSMA7	RPS6KA2	SLC47A2	TAL2	TTL	ZNF490
AKT3	CDK4	FANCD2	KDM6A	OR2M5	SDHAF2	VHL	ANLN	CACNA1C	CLTC	DDX41	EWSR1	GAPDH	HIST1H3G	IL2	LPHN3	MLLT6	NLRP1	PCLO	PSPH	RPS7	SLC6A2	TANK	TUBA1B	ZNF521
ALK	CDK6	FANCE	KDR	PAL B2	SDHB	WISP3	ANTXR1	CACNA1S	CLTCL1	DDX5	EXO1	GAS7	HIST1H3H	IL21R	LPP	MMP2	NLRP7	PCM1	PSRC1	RQCD1	SLC6A3	TBX22	TUBA1C	ZNF668
APC	CDK8	FANCF	KIT	PAX5	SDHC	WT1	ANTXR2	CACNA2D1	CMC4	DDX6	EXT1	GCHFR	HIST1H3I	IL6ST	LRIF1	MNX1	NOA1	PCSK7	PTCH2	RRAGB	SLC6A4	TBXAS1	TUBB6	ZNF703
AR	CDKN1A	FANCG	KLHL14	PBRM1	SDHD	XIRP2	APOA1	CACNB2	CMPK1	DEK	EXT2	GDNF	HIST1H3J	ING4	LRP5	MORC2	NONO	PDCD11G2	PTGIS	RRAGC	SLC9A3R1	TC2N	TWSG1	ZSCAN20
ARAF	CDKN1B	FANCL	KLHL6	PCDH15	SEMA3A	XPO1	APOB	CAMTA1	CNBP	DEPTOR	FADD	GEN1	HIST1H4A	INHBA	LRP6	MRGBP	NOP10	PDE4DIP	PTGS1	RRAGD	SLCO1A2	TCEA1	UACA	
ARID1A	CDKN2A	FAT3	KMT2A	PCDHB6	SEMA3E	ZFHX4	ARFRP1	CANT1	CNKSR3	DICER1	FAM175A	GFI1	HIST1H4B	INPP4B	LRRC42	MRPL13	NOTCH3	PDGFB	PTGS2	RRM1	SLCO1B1	TCF12	UBE2C	
ARID2	CDKN2B	FAT4	KMT2B	PCDHGA2	SETBP1	ZIM2	ARHGAP21	CAPRIN1	CNTRL	DIS3L2	FAM175B	GID4	HIST1H4C	INSL6	LRRFIP1	MRPL15	NOTCH4	PDK1	PTHLH	RTEL1	SLCO1B3	TCF3	UGT1A1	
ASXL1	CDKN2C	FBXW7	KMT2C	PDCD1	SETD2	ZMYM3	ARHGAP26	CARS	COL11A1	DKC1	FANCB	GIMAP4	HIST1H4D	INSR	LRRTM4	MRPL19	NPAT	PDLIM3	PTK2	RUNX1T1	SLCO1C1	TCF4	UGT1A4	
ATM	CEBPA	FGF23	KMT2D	PDGFRA	SF3B1	ZNRF3	ARHGEF11	CASC5	COL1A1	DNMT1	FANCI	GIT2	HIST1H4H	IRF4	LTBP2	MRPL3	NPHS2	PDPK1	PTK2B	SAMD9	SLCO2B1	TCF7L1	UIMC1	
ATR	CHEK1	FGF3	KRAS	PDGFRB	SIGLEC10	ABCB11	ARHGEF12	CASP8	COL1A2	DNMT3B	FANCM	GLCCI1	HIST1H4I	IRF6	LTBP3	MRPS17	NPPB	PEAR1	PTPN3	SARDH	SLTM	TCF7L2	UNC13D	
ATRX	CHEK2	FGF4	LRP1B	PHF6	SLC16A1	ABCC2	ARHGEF26	CASR	COL1C2	DOCK2	FAS	GLI3	HIST1H4J	ITGA10	LTF	MSANA6A	NPR1	PEBP1	PTPRC	SBDS	SLX4	TCL1A	USB1	
AURKA	CIC	FGFR1	MAGEA6	PIK3CA	SLC16A4	ABCC5	ARHGEF7	CBFB	COMT	DOT1L	FASN	GLMN	HIST1H4K	ITGA3	LTK	MSH3	NQO1	PER1	PTPRD	SBF2	SMAD6	TCL6	USP42	
AURKB	CREBBP	FGFR2	MAP2K1	PIK3CD	SLIT2	ABCC6	ARID3A	CCDC141	CORO1C	DPYD	FAT1	GMPS	HIST1H4L	ITGA9	LYL1	MSI2	NR3C1	PFKP	PTPRJ	SCN5A	SMOX	TERC	USP6	
AXIN1	CRKL	FGFR3	MAP2K2	PIK3CG	SMAD2	ABCG5P2	ARID3B	CCDC18	COX6C	DRD1	FAT2	GOLGA4	HIST2H4A	ITGB2	MACROD1	MSN	NR3C2	PGAP3	PTPRS	SEC31A	SMUG1	TET1	USP9X	
AXL	CRLF2	FGFR4	MAP2K4	PIK3R1	SMAD3	ABCG1	ARID4A	CCDC28A	CRBN	DRD2	FBXO11	GOLGA5	HIST2H4B	ITGB3	MAD2L1BP	MSR1	NR4A3	PGK1	PTPRT	SEC61G	SNX2	TET3	UTP11L	
B2M	CSF1R	FLG	MAP3K1	PIK3R2	SMAD4	ABCG2	ARID4B	CCDC6	CREB1	DROSHA	FCGR2B	GOPC	HK2	ITK	MAD2L2	MST1R	NRP1	PGR	PXN	SEMA5B	SNX29	TFE3	UTY	
BAP1	CSF3R	FLT1	MAPK1	PIM1	SMARCA4	ACD	ARID5A	CCDC63	CREB3L1	DSP	FCRL4	GOT1	HLA-B	ITM2A	MAF	MT2A	NSD1	PHLDB1	PYGL	SENP5	SOS1	TFEB	VDR	
BARD1	CSMD1	FLT3	MCL1	PLXNA1	SMARCB1	ACE	ARID5B	CCL19	CREB3L2	DUX4	FGF10	GPC3	HLA-DQB3	JAZF1	MAF8	MTCP1	NT5C2	PHLPP2	RABEP1	"SEPT2"	SOX9	TFG	VEGFA	
BCL10	CTCF	FLT4	MDM2	PMS1	SMC1A	ACOT7	ARL11	CCNB1IP1	CRHR1	EAF2	FGF14	GPHN	HLF	JUN	MAGEA1	MTR	NTF3	PHOX2B	RAD50	"SEPT5"	SPATA17	TFPT	VKORC1	
BCL2	CTNNA1	FOXA1	MDM4	PMS2	SMC3	ACSL3	ARNT	CCND2	CRTC3	EBF1	FGF19	GPI	HMCN1	KAT6A	MAGI1	MTRR	NTRK2	PICALM	RAD51	"SEPT6"	SPECC1	TFRC	VPS45	
BCL6	CTNNB1	FOXL2	MED12	POLD1	SMO	ACSL6	ATF1	CD274	CSF1	EED	FGF6	GPR171	HMGA1	KAT6B	MALT1	MTUS2	NTRK3	PIK3C2B	RAD51B	"SEPT9"	SPI1	TGFBI	VTI1A	
BCOR	CUX1	FRMPD1	MEF2B	POLE	SOCS1	ACVR1	ATIC	CD40LG	CSMD3	EGLN1	FGFR1OP	GPR98	HMGA2	KCNH2	MAML2	MUC1	NUDT3	PIK3CB	RAD51C	SET	SPINK1	TGM7	WAS	
BCORL1	CXCR4	GATA1	MEN1	POT1	SOCS2	ACVR1B	ATP10A	CD44	CTC1	EIF4A2	FGFR1OP2	GREM1	HMGCR	KDR	MAOA	MYB	NUDT7	PIR	RAD51D	SETDB1	SRDSA2	THBS1	WISCR17	
BIRC3	DAXX	GATA2	MET	PPP2R1A	SOCS3	ACVR2A	ATP10D	CD74	CTNNA2	ELAC2	FH	GRK4	HNRNPA2B1	KEAP1	MAP3K7	MYBL2	NUF2	PKHD1	RALGDS	SF3B2	SRGAP3	THRAP3	WDR36	
BLM	DDR2	GATA3	MITF	PRDM1	SOX10	ADA	ATP2B3	CD8A	CTNNA3	ELF4	FHIT	GRK5	HOOK3	KHDC3L	MAP3K8	MYH11	NUMA1	PLAG1	RANBP17	SFPQ	SRP72	THSD7A	WDR48	
BMPR1A	DDX3X	GNA11	MLH1	PRKAR1A	SOX2	ADAMTS20	AURKC	CDC20	CTSV	ELK4	FHL1	GRM8	HOXA10	KIAA1524	MAP7D1	MYH9	NUP214	PLCB4	RAP1GDS1	SFRP1	SRRM2	TIMP3	WHSC1	
BRAF	DMD	GNA13	MPL	PTCH1	SPEN	ADAMTSL3	AXIN2	CDH10	CUL1	ELN	FIP1L1	GSK3B	HOXA11	KIAA1549	MAPK13	MYO18A	NUP93	PLCG1	RASA1	SFXN4	SRSF3	TINF2	WHSC1L1	
BRCA1	DNAH5	GNAQ	MRE11A	PTEN	SPOP	ADCY4	BAI3	CDH11	CUL3	EML1	FKBP14	GSTM1	HOXA13	KIF1B	MAPK8	MYOC	NUP98	PLCG2	RBM15	SGK1	SS18	TLR4	WIF1	
BRCA2	DNMT3A	GNAS	MSH2	PTPN11	SRC	ADD3	BAK1	CDH6	CXCR7	EML4	FKBP1B	GSTP1	HOXA3	KIF20A	MAPRE1	MYSM1	NUTM1	PLEKHG5	RBM48	SH2B3	SSX1	TLX1	WRAP53	
BRIP1	DTX1	GRIN2A	MSH6	PXDN	SRSF2	ADM	BCHE	CDK3	CYLD	ENG	FKBP5	GSTT1	HOXA9	KIF2C	MARK1	NAA16	NUTM2B	PLK1	RFFL	SH2D1A	STAT1	TMEM127	WRB	
BTG1	EGFR	H3F3A	MTOR	RAD21	STAG2	ADRB2	BCL11A	CDKN1C	CYP1A2	ENKD1	FKBP9	GUCY1A2	HOXB13	KIF4A	MARK4	NACA	OBSCN	PLK2	RGS20	SHCBP1	STAT2	TMPRSS2	WRN	
BTG2	EGR2	HIST1H1E	MUC16	RAF1	STAT3	AFF1	BCL11B	CDKN2D	CYP1B1	ENO1	FLCN	H3F3B	HOXC11	KIF5B	MAX	NAT1	OIP5	PML	RHBDF2	SHH	STAT4	TNFRSF13B	WWTR1	
BTK	EP300	HIST1H3C	MUTYH	RARA	STK11	AFF3	BCL2A1	CDKN3	CYP2A6	EP400	FLI1	HAS2	HOXC13	KL	MBD1	NAT2	OMD	PON1	RHOH	SHOC2	STAT5A	TNFRSF17	XPA	
C11orf30	EPC1	HNF1A	MXRA5	RB1	SUFU	AFF4	BCL2L1	CDX2	CYP2B6	EPAS1	FMN2	HAX1	HOXD11	KLF4	MBD4	NBN	OPTN	POR	RIMS2	SKP2	STAT5B	TNK5	XPC	
CALR	EPHA2	HRAS	MYC	REL	SYK	AHR	BCL2L2	CECR1	CYP2C19	EPCAM	FN1	HCAR1	HOXD13	KLF6	MC1R	NCKIPSD	P2RY8	POU2AF1	RIPK4	SLC15A2	STAT6	TNKS2	XRCC2	
CARD11	EPHA3	ID2	MYCL	RET	TERT	AHRR	BCL9	CENPF	CYP2C8	EPHA10	FNBP1	HDAC1	HSD17B3	KLHDC8B	MCCC1	NCOA1	P4HA1	POU5F1	RMI2	SLC1A2	STIL	TOP2A	XRCC3	
CBL	EPHA5	ID3	MYCN	RHEB	TET2	AIM2	BCL7A	CEP57	CYP2C9	EPS15	FOLR1	HDAC4	HSD17B7	KLK2	MCTS1	NCOA2	P4HA2	PPARG	RNASEL	SLC22A1	STK36	TP63	XRCC5	
CBLB	EPHA7	IDH1	MYO88	RICTOR	TGFBR2	AIP	BCL9	CES1	CYP2D6	ERC1	FOXO1	HECW1	HSD3B2	KTN1	MDS2	NCOA3	PAFAH1B2	PPM1D	RNF2	SLC22A2	STX11	TPI1	YKT6	
CBLC	EPHB1	IDH2	MYOM2	RIF1	TNFAIP3	AJUBA	BCR	CES2	CYP2R1	ERCC1	FOXO3	HERPUD1	HSP90AA1	LAMP1	MECOM	NCOA4	PAK3	PRAOC1	RNF213	SLC22A3	STXBP2	TPM3	YTHDF2	
CCND1	EPHB2	IKZF1	NALCN	RIPK1	TNFRSF14	AK3	BDNF	CHCHD7	CYP3A4	ERCC2	FOXO4	HEXIM1	HSP90AB1	LASP1	MED1	NCOR1	PAK7	PRCC	ROS1	SLC22A6	SUMF1	TPM4	YWHAE	
CCND3	EPHB4	IKZF2	NF1	RIT1	TOP1	AKIL1	BIRC2	CHD1	CYP3A5	ERCC3	FOXP1	HEY1	HTR1A	LCK	MEF2D	NCOR2	PALLD	PRDM16	RPL11	SLC25A32	SUPT3H	TPMT	ZBTB16	
CCNE1	ERBB2	IL7R	NF2	RNF43	TP53	AKAP12	BLID	CHD5	DAB2IP	ERCC4	FOXP2	HGF	HTR2A	LCP1	MKI67	NDC80	PARP1	PRDM9	RPL35A	SLC2A1	SUZ12	TRAF3	ZEB1	
CD36	ERBB3	IRS2	NFE2L2	ROBO1	TRAF2	AKR1C4	BLNK	CHD6	DAZAP1	ERCC5	FOXR2	HIF1A	ICAM2	LDHA	MKL1	NDRG1	PATZ1	PRF1	RPL5	SLC34A2	SYNE1	TRAF5	ZMIZ1	



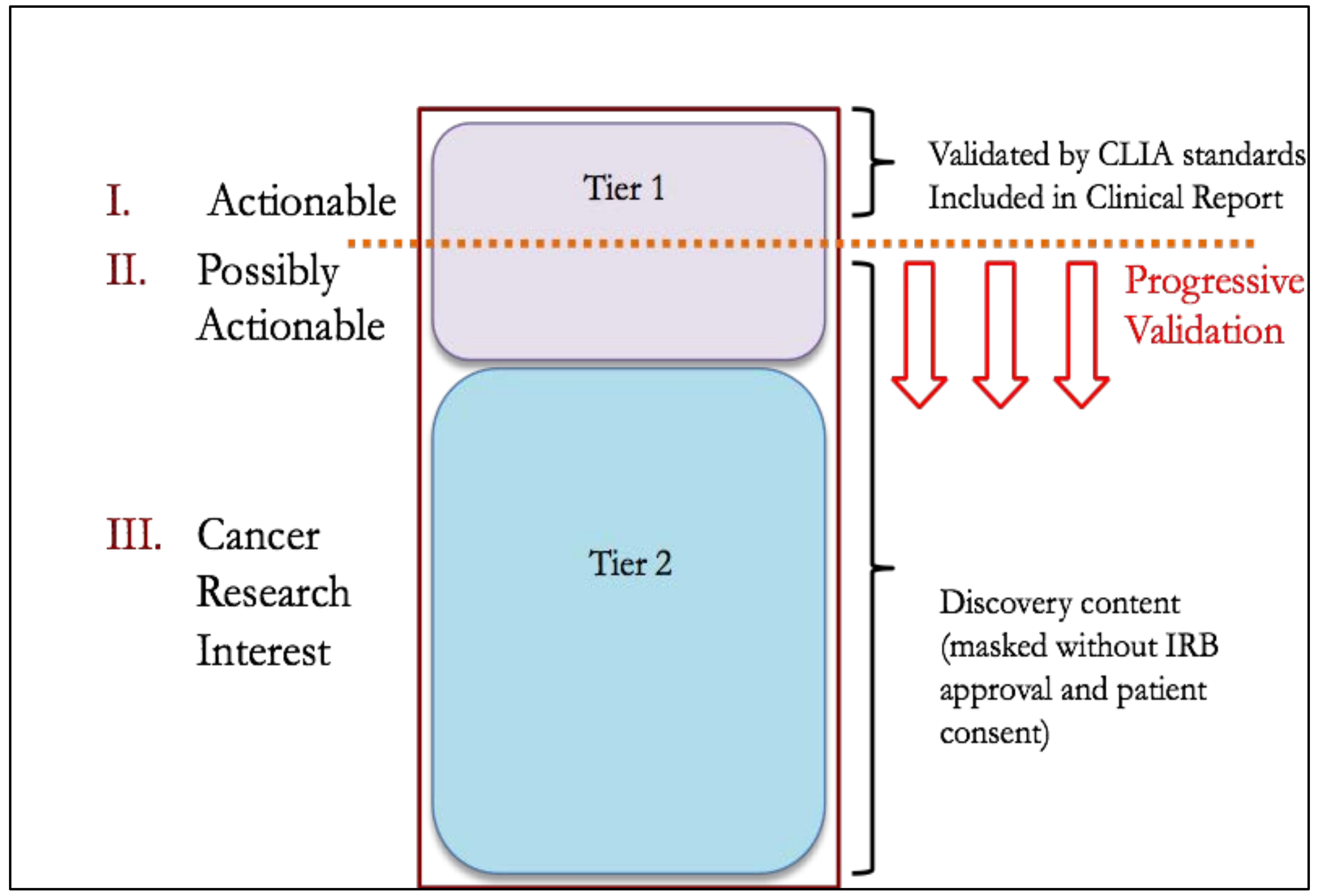
Kadri S et al. J Mol Diagn. 2017 Jan;19(1):43-56.

@samvolchenboum

OncoPlus Comprehensive Cancer Panel

Tier 1 = 316 genes   Tier 2 = 896 genes

ABCA12	CD58	ERBB4	ITPKB	NFKBIA	ROBO2	TRAF7	ALDH2	BNIP3	CHIC2	DBH	ERG	FUBP1	HILPDA	ICK	LDLR	MLF1	NEBL	PAX2	PRKDC	RPN1	SLC36A1	T	TRIM24	ZMYM2
ABCB1	CD79A	ESR1	JAK1	NKX2-1	ROBO3	TSC1	ALDH8A1	BRD3	CHMP4C	DBI	ESRP1	FUS	HIP1	IGF2	LEMD1	MLH3	NELL1	PAX3	PRRX1	RPS10	SLC38A1	TAF1	TRIM27	ZNF217
ABCD2	CD79B	ETV6	JAK2	NOTCH1	RPL22	TSC2	ALDOA	BRD4	CHN1	DCC	ETS1	FZR1	HIS4H4	IGF2R	LHFP	MLLT1	NFIB	PAX6	PRSS1	RPS17	SLC38A3	TAF12	TRIM33	ZNF320
ABL1	CDC73	EZH2	JAK3	NOTCH2	RPTOR	TSHR	ALOX5	BTNL2	CIITA	DDB2	ETV1	G6PC3	HIST1H3A	IKBKB	LIFR	MLLT10	NFKB1	PAX7	PRSS37	RPS19	SLC38A6	TAF15	TRIP11	ZNF331
AFF2	CDH1	FAM46C	JAKMIP2	NPM1	RUNX1	TYK2	AMER1	BUB1B	CKS1B	DDIT3	ETV4	GABRA1	HIST1H3B	IKBKE	LMBRD1	MLLT11	NFKB2	PAX8	PRSS8	RPS24	SLC45A3	TAF1L	TRRAP	ZNF384
AKT1	CDH2	FANCA	KDM5A	NRAS	SAMHD1	U2AF1	ANKRD26	CA10	CLCA2	DDIT4	ETV5	GALNT12	HIST1H3D	IKZF3	LMO1	MLLT3	NHP2	PBX1	PSIP1	RPS26	SLC47A1	TAL1	TSKU	ZNF423
AKT2	CDK12	FANCC	KDM5C	NTRK1	SDHA	UBR5	ANKRD37	CA9	CLP1	DDX10	EVPL	GALNT3	HIST1H3E	IL11	LMO2	MLLT4	NIN	PCDH9	PSMA7	RPS6KA2	SLC47A2	TAL2	TTL	ZNF490
AKT3	CDK4	FANCD2	KDM6A	OR2M5	SDHAF2	VHL	ANLN	CACNA1C	CLTC	DDX41	EWSR1	GAPDH	HIST1H3G	IL2	LPHN3	MLLT6	NLRP1	PCLO	PSPH	RPS7	SLC6A2	TANK	TUBA1B	ZNF521
ALK	CDK6	FANCE	KDR	PALB2	SDHB	WISP3	ANTXR1	CACNA1S	CLTCL1	DDX5	EXO1	GAS7	HIST1H3H	IL21R	LPP	MMP2	NLRP7	PCM1	PSRC1	RQCD1	SLC6A3	TBX22	TUBA1C	ZNF668
APC	CDK8	FANCF	KIT	PAX5	SDHC	WT1	ANTXR2	CACNA2D1	CMC4	DDX6	EXT1	GCHFR	HIST1H3I	IL6ST	LRIF1	MNX1	NOA1	PCSK7	PTCH2	RRAGB	SLC6A4	TBXAS1	TUBB6	ZNF703
AR	CDKN1A	FANCG	KLHL14	PBRM1	SDHD	XIRP2	APOA1	CACNB2	CMPK1	DEK	EXT2	GDNF	HIST1H3J	ING4	LRP5	MORC2	NONO	PDCD1LG2	PTGIS	RRAGC	SLC9A3R1	TC2N	TWSG1	ZSCAN20
ARAF	CDKN1B	FANCL	KLHL6	PCDH15	SEMA3A	XPO1	APOB	CAMTA1	CNBP	DEPTOR	FADD	GEN1	HIST1H4A	INHBA	LRP6	MRGBP	NOP10	PDE4DIP	PTGS1	RRAGD	SLCO1A2	TCEA1	UACA	
ARID1A	CDKN2A	FAT3	KMT2A	PCDHB6	SEMA3E	ZFHX4	ARFRP1	CANT1	CNKSR3	DICER1	FAM175A	GFI1	HIST1H4B	INPP4B	LRRC42	MRPL13	NOTCH3	PDGFB	PTGS2	RRM1	SLCO1B1	TCF12	UBE2C	
ARID2	CDKN2B	FAT4	KMT2B	PCDHGA2	SETBP1	ZIM2	ARHGAP21	CAPRIN1	CNTRL	DIS3L2	FAM175B	GID4	HIST1H4C	INSL6	LRRFIP1	MRPL15	NOTCH4	PDK1	PTHLH	RTEL1	SLCO1B3	TCF3	UGT1A1	
ASXL1	CDKN2C	FBXW7	KMT2C	PDCD1	SETD2	ZMYM3	ARHGAP26	CARS	COL11A1	DKC1	FANCB	GIMAP4	HIST1H4D	INSR	LRRTM4	MRPL19	NPAT	PDLIM3	PTK2	RUNX1T1	SLCO1C1	TCF4	UGT1A4	
ATM	CEBPA	FGF23	KMT2D	PDGFRA	SF3B1	ZRSR2	ARHGEF11	CASC5	COL1A1	DNMT1	FANCI	GIT2	HIST1H4H	IRF4	LTBP2	MRPL3	NPHS2	PDPK1	PTK2B	SAMD9	SLCO2B1	TCF7L1	UIMC1	
ATR	CHEK1	FGF3	KRAS	PDGFRB	SIGLEC10	ABCB11	ARHGEF12	CASP8	COL1A2	DNMT3B	FANCM	GLCCI1	HIST1H4I	IRF6	LTBP3	MRPS17	NPPB	PEAR1	PTPN3	SARDH	SLTM	TCF7L2	UNC13D	
ATRX	CHEK2	FGF4	LRP1B	PHF6	SLC16A1	ABCC2	ARHGEF26	CASR	COLEC12	DOCK2	FAS	GLI3	HIST1H4J	ITGA10	LTF	MS4A6A	NPR1	PEBP1	PTPRC	SBDS	SLX4	TCL1A	USB1	
AURKA	CIC	FGFR1	MAGEA6	PIK3CA	SLC16A4	ABCC5	ARHGEF7	CBFB	COMT	DOT1L	FASN	GLMN	HIST1H4K	ITGA3	LTK	MSH3	NQO1	PER1	PTPRD	SBF2	SMAD6	TCL6	USP42	
AURKB	CREBBP	FGFR2	MAP2K1	PIK3CD	SLIT2	ABCC6	ARID3A	CCDC141	CORO1C	DPYD	FAT1	GMPS	HIST1H4L	ITGA9	LYL1	MSI2	NR3C1	PFKP	PTPRJ	SCN5A	SMOX	TERC	USP6	
AXIN1	CRKL	FGFR3	MAP2K2	PIK3CG	SMAD2	ABCC6P2	ARID3B	CCDC18	COX6C	DRD1	FAT2	GOLGA4	HIST2H4A	ITGB2	MACROD1	MSN	NR3C2	PGAP3	PTPRS	SEC31A	SMUG1	TET1	USP9X	
AXL	CRLF2	FGFR4	MAP2K4	PIK3R1	SMAD3	ABCG1	ARID4A	CCDC28A	CRBN	DRD2	FBXO11	GOLGA5	HIST2H4B	ITGB3	MAD2L1BP	MSR1	NR4A3	PGK1	PTPRT	SEC61G	SNX2	TET3	UTP11L	
B2M	CSF1R	FLG	MAP3K1	PIK3R2	SMAD4	ABCG2	ARID4B	CCDC6	CREB1	DROSHA	FCGR2B	GOPC	HK2	ITK	MAD2L2	MST1R	NRP1	PGR	PXN	SEMA5B	SNX29	TFE3	UTY	
BAP1	CSF3R	FLT1	MAPK1	PIM1	SMARCA4	ACD	ARID5A	CCDC63	CREB3L1	DSP	FCRL4	GOT1	HLA-B	ITM2A	MAF	MT2A	NSD1	PHLDB1	PYGL	SENP5	SOS1	TFEB	VDR	
BARD1	CSMD1	FLT3	MCL1	PLXNA1	SMARCB1	ACE	ARID5B	CCL19	CREB3L2	DUX4	FGF10	GPC3	HLA-DQB3	JAZF1	MAFB	MTCP1	NT5C2	PHLPP2	RABEP1	"SEPT2"	SOX9	TFG	VEGFA	
BCL10	CTCF	FLT4	MDM2	PMS1	SMC1A	ACOT7	ARL11	CCNB1IP1	CRHR1	EAF2	FGF14	GPHN	HLF	JUN	MAGEA1	MTR	NTF3	PHOX2B	RAD50	"SEPT5"	SPATA17	TFPT	VKORC1	
BCL2	CTNNA1	FOXA1	MDM4	PMS2	SMC3	ACSL3	ARNT	CCND2	CRTC3	EBF1	FGF19	GPI	HMCN1	KAT6A	MAGI1	MTRR	NTRK2	PICALM	RAD51	"SEPT6"	SPECC1	TFRC	VPS45	
BCL6	CTNNB1	FOXL2	MED12	POLD1	SMO	ACSL6	ATF1	CD274	CSF1	EED	FGF6	GPR171	HMGA1	KAT6B	MALT1	MTUS2	NTRK3	PIK3C2B	RAD51B	"SEPT9"	SPI1	TGFBI	VTI1A	
BCOR	CUX1	FRMPD1	MEF2B	POLE	SOCS1	ACVR1	ATIC	CD40LG	CSMD3	EGLN1	FGFR1OP	GPR98	HMGA2	KCNH2	MAML2	MUC1	NUDT3	PIK3CB	RAD51C	SET	SPINK1	TGM7	WAS	
BCORL1	CXCR4	GATA1	MEN1	POT1	SOCS2	ACVR1B	ATP10A	CD44	CTC1	EIF4A2	FGFR1OP2	GREM1	HMGCR	KDSR	MAOA	MYB	NUDT7	PIR	RAD51D	SETDB1	SRD5A2	THBS1	WBSCR17	
BIRC3	DAXX	GATA2	MET	PPP2R1A	SOCS3	ACVR2A	ATP10D	CD74	CTNNA2	ELAC2	FH	GRK4	HNRNPA2B1	KEAP1	MAP3K7	MYBL2	NUF2	PKHD1	RALGDS	SF3B2	SRGAP3	THRAP3	WDR36	
BLM	DDR2	GATA3	MITF	PRDM1	SOX10	ADA	ATP2B3	CD8A	CTNNA3	ELF4	FHIT	GRK5	HOOK3	KHDC3L	MAP3K8	MYH11	NUMA1	PLAG1	RANBP17	SFPQ	SRP72	THSD7A	WDR48	
BMPR1A	DDX3X	GNA11	MLH1	PRKAR1A	SOX2	ADAMTS20	AURKC	CDC20	CTSV	ELK4	FHL1	GRM8	HOXA10	KIAA1524	MAP7D1	MYH9	NUP214	PLCB4	RAP1GDS1	SFRP1	SRRM2	TIMP3	WHSC1	
BRAF	DMD	GNA13	MPL	PTCH1	SPEN	ADAMTSL3	AXIN2	CDH10	CUL1	ELN	FIP1L1	GSK3B	HOXA11	KIAA1549	MAPK13	MYO18A	NUP93	PLCG1	RASA1	SFXN4	SRSF3	TINF2	WHSC1L1	
BRCA1	DNAH5	GNAQ	MRE11A	PTEN	SPOP	ADCY4	BAI3	CDH11	CUL3	EML1	FKBP14	GSTM1	HOXA13	KIF1B	MAPK8	MYOC	NUP98	PLCG2	RBM15	SGK1	SS18	TLR4	WIF1	
BRCA2	DNMT3A	GNAS	MSH2	PTPN11	SRC	ADD3	BAK1	CDH6	CXCR7	EML4	FKBP1B	GSTP1	HOXA3	KIF20A	MAPRE1	MYSM1	NUTM1	PLEKHG5	RBM8A	SH2B3	SSX1	TLX1	WRAP53	
BRIP1	DTX1	GRIN2A	MSH6	PXDN	SRSF2	ADM	BCHE	CDK3	CYLD	ENG	FKBP5	GSTT1	HOXA9	KIF2C	MARK1	NAA16	NUTM2B	PLK1	RFFL	SH2D1A	STAT1	TMEM127	WRB	
BTG1	EGFR	H3F3A	MTOR	RAD21	STAG2	ADRB2	BCL11A	CDKN1C	CYP1A2	ENKD1	FKBP9	GUCY1A2	HOXB13	KIF4A	MARK4	NACA	OBSCN	PLK2	RGS20	SHCBP1	STAT2	TMPRSS2	WRN	
BTG2	EGR2	HIST1H1E	MUC16	RAF1	STAT3	AFF1	BCL11B	CDKN2D	CYP1B1	ENO1	FLCN	H3F3B	HOXC11	KIF5B	MAX	NAT1	OIP5	PML	RHBDF2	SHH	STAT4	TNFRSF13B	WWTR1	
BTK	EP300	HIST1H3C	MUTYH	RARA	STK11	AFF3	BCL2A1	CDKN3	CYP2A6	EP400	FLI1	HAS2	HOXC13	KL	MBD1	NAT2	OMD	PON1	RHOH	SHOC2	STAT5A	TNFRSF17	XPA	
C11orf30	EPC1	HNF1A	MXRA5	RB1	SUFU	AFF4	BCL2L1	CDX2	CYP2B6	EPAS1	FMN2	HAX1	HOXD11	KLF4	MBD4	NBN	OPTN	POR	RIMS2	SKP2	STAT5B	TNKS	XPC	
CALR	EPHA2	HRAS	MYC	REL	SYK	AHR	BCL2L2	CECR1	CYP2C19	EPCAM	FN1	HCAR1	HOXD13	KLF6	MC1R	NCKIPSD	P2RY8	POU2AF1	RIPK4	SLC15A2	STAT6	TNKS2	XRCC2	
CARD11	EPHA3	ID2	MYCL	RET	TERT	AHRR	BCL3	CENPF	CYP2C8	EPHA10	FNBP1	HDAC1	HSD17B3	KLHDC8B	MCCC1	NCOA1	P4HA1	POU5F1	RMI2	SLC1A2	STIL	TOP2A	XRCC3	
CBL	EPHA5	ID3	MYCN	RHEB	TET2	AIM2	BCL7A	CEP57	CYP2C9	EPS15	FOLR1	HDAC4	HSD17B7	KLK2	MCTS1	NCOA2	P4HA2	PPARG	RNASEL	SLC22A1	STK36	TP63	XRCC5	
CBLB	EPHA7	IDH1	MYD88	RICTOR	TGFBR2	AIP	BCL9	CES1	CYP2D6	ERC1	FOXO1	HECW1	HSD3B2	KTN1	MDS2	NCOA3	PAFAH1B2	PPM1D	RNF2	SLC22A2	STX11	TPI1	YKT6	
CBLC	EPHB1	IDH2	MYOM2	RIF1	TNFAIP3	AJUBA	BCR	CES2	CYP2R1	ERCC1	FOXO3	HERPUD1	HSP90AA1	LAMP1	MECOM	NCOA4	PAK3	PRADC1	RNF213	SLC22A3	STXBP2	TPM3	YTHDF2	
CCND1	EPHB2	IKZF1	NALCN	RIPK1	TNFRSF14	AK3	BDNF	CHCHD7	CYP3A4	ERCC2	FOXO4	HEX1M1	HSP90AB1	LASP1	MED1	NCOR1	PAK7	PRCC	ROS1	SLC22A6	SUMF1	TPM4	YWHAE	
CCND3	EPHB4	IKZF2	NF1	RIT1	TOP1	AK3L1	BIRC2	CHD1	CYP3A5	ERCC3	FOXP1	HEY1	HTR1A	LCK	MEF2D	NCOR2	PALLD	PRDM16	RPL11	SLC25A32	SUPT3H	TPMT	ZBTB16	
CCNE1	ERBB2	IL7R	NF2	RNF43	TP53	AKAP12	BLID	CHD5	DAB2IP	ERCC4	FOXP2	HGF	HTR2A	LCP1	MKI67	NDC80	PARP1	PRDM9	RPL35A	SLC2A1	SUZ12	TRAF3	ZEB1	
CD36	ERBB3	IRS2	NFE2L2	ROBO1	TRAF2	AKR1C4	BLNK	CHD6	DAZAP1	ERCC5	FOXR2	HIF1A	ICAM2	LDHA	MKL1	NDRG1	PATZ1	PRF1	RPL5	SLC34A2	SYNE1	TRAF5	ZMIZ1	



Clinically reported 147 genes

ABL1	BRCA2	CXCR4	FAT3	IDH1	MTOR	POLE	SMC3
AKT1	BTK	DAXX	FBXW7	IDH2	MYD88	POT1	SMO
ALK	CALR	DDR2	FGFR1	IKZF1	NBN	PPP2R1A	SRSF2
APC	CBL	DDX3X	FGFR2	ITPKB	NF1	PTCH1	STAG2
ARID1A	CBLB	DDX41	FGFR3	JAK2	NF2	PTEN	STK11
ARID2	CCND1	DICER1	FH	KDM6A	NFE2L2	PTPN11	TERT
ASXL1	CCND2	DNMT3A	FLT3	KDR	NOTCH1	RAD21	TET2
ATM	CCND3	EGFR	FOXL2	KIT	NOTCH2	RAD51	TP53
ATR	CDH1	EP300	GATA1	KMT2A	NPM1	RB1	TSC1
ATRX	CDKN2A	EPHA3	GATA2	KRAS	NRAS	RET	TSC2
AXL	CEBPA	EPHA5	GNA11	MAP2K1	PALB2	RUNX1	U2AF1
B2M	CHEK1	ERBB2	GNAQ	MAPK1	PBRM1	SDHB	VHL
BAP1	CHEK2	ERBB3	GNAS	MET	PDGFRA	SDHC	WT1
BCOR	CSF1R	ERBB4	GRIN2A	MLH1	PDGFRB	SDHD	ZRSR2
BCORL1	CSF3R	ERCC3	H3F3A	MLH3	PHF6	SETBP1	
BIRC3	CTCF	ESR1	HIST1H3B	MPL	PIK3CA	SF3B1	
BLM	CTNNA1	ETV6	HIST1H3C	MRE11A	PIK3CB	SMAD4	
BRAF	CTNNB1	EZH2	HNF1A	MSH2	PIK3R1	SMARCB1	
BRCA1	CUX1	FANCA	HRAS	MSH6	PLCG2	SMC1A	

Kadri S et al. J Mol Diagn. 2017 Jan;19(1):43-56.

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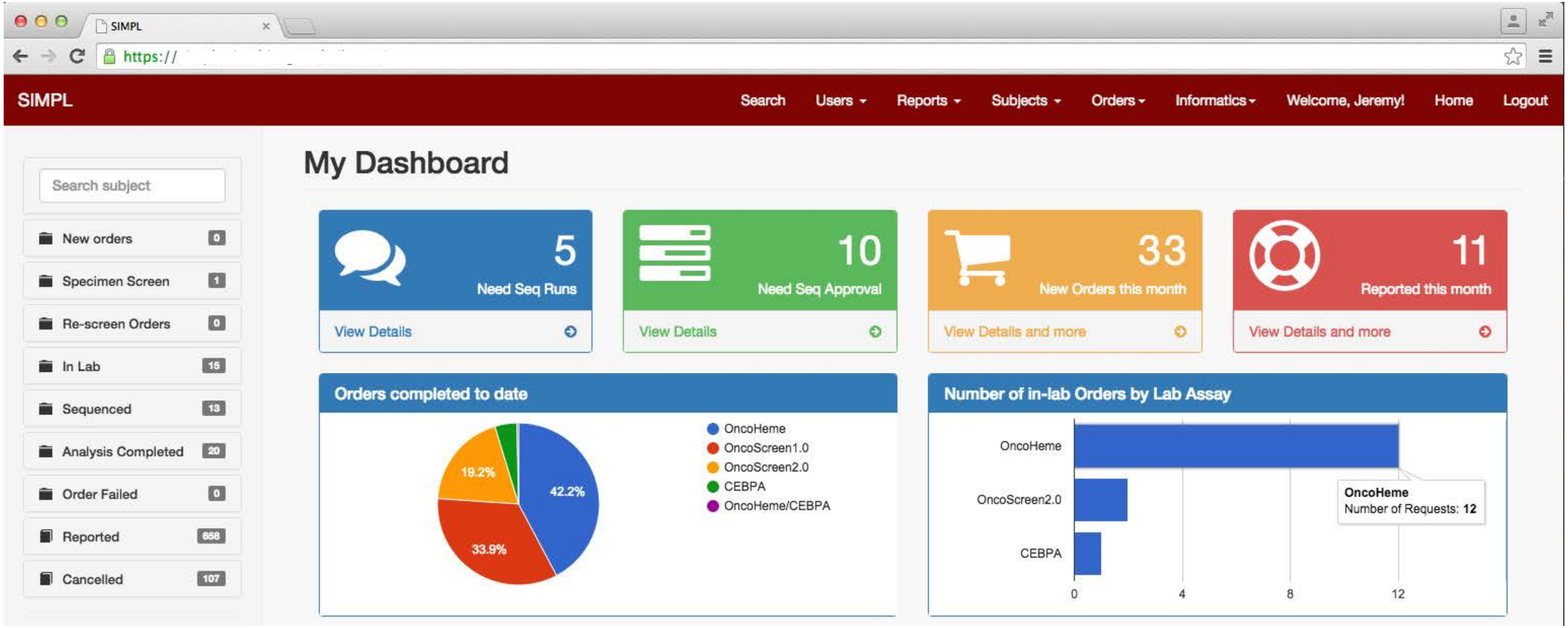
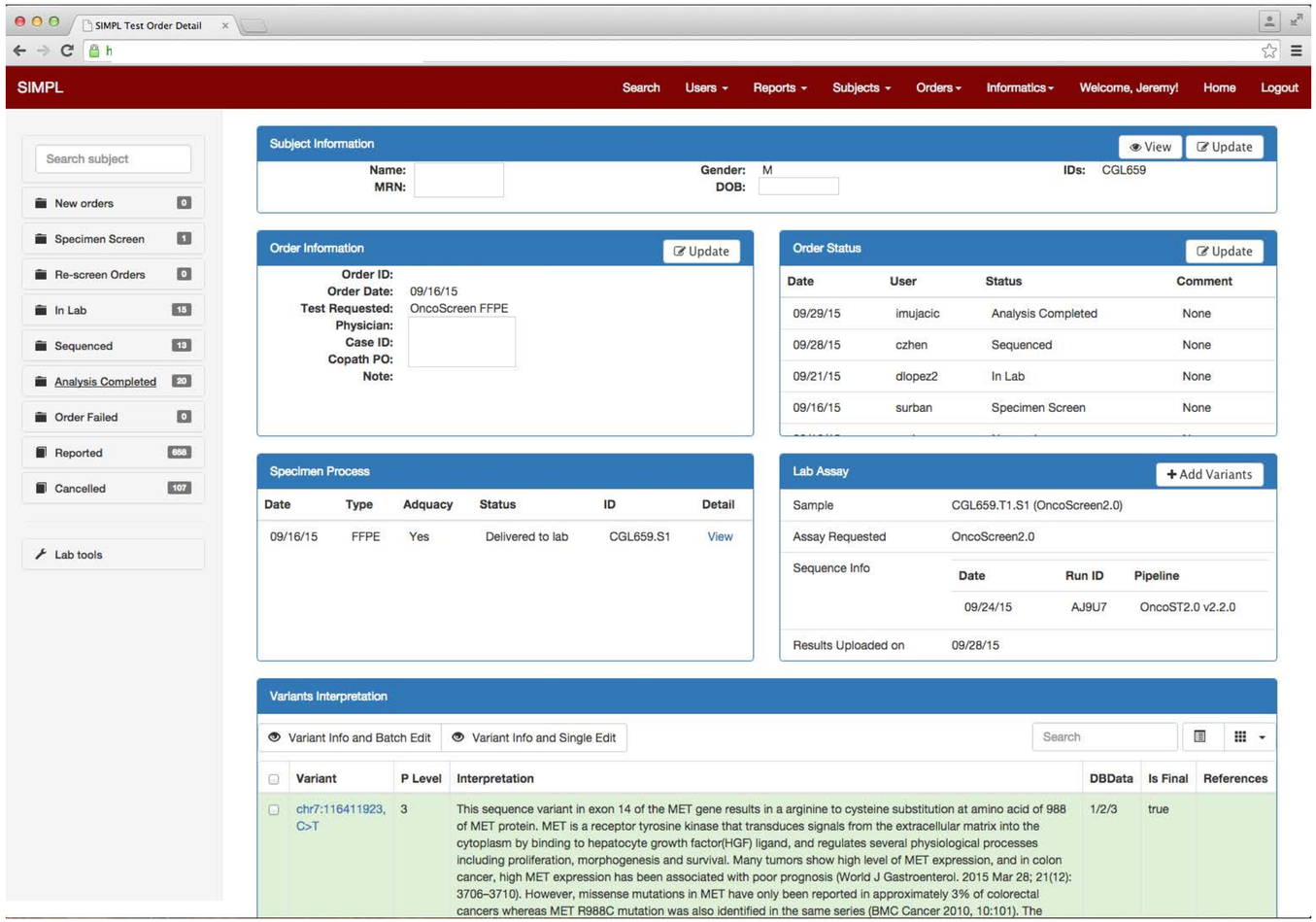
@samvolchenboum

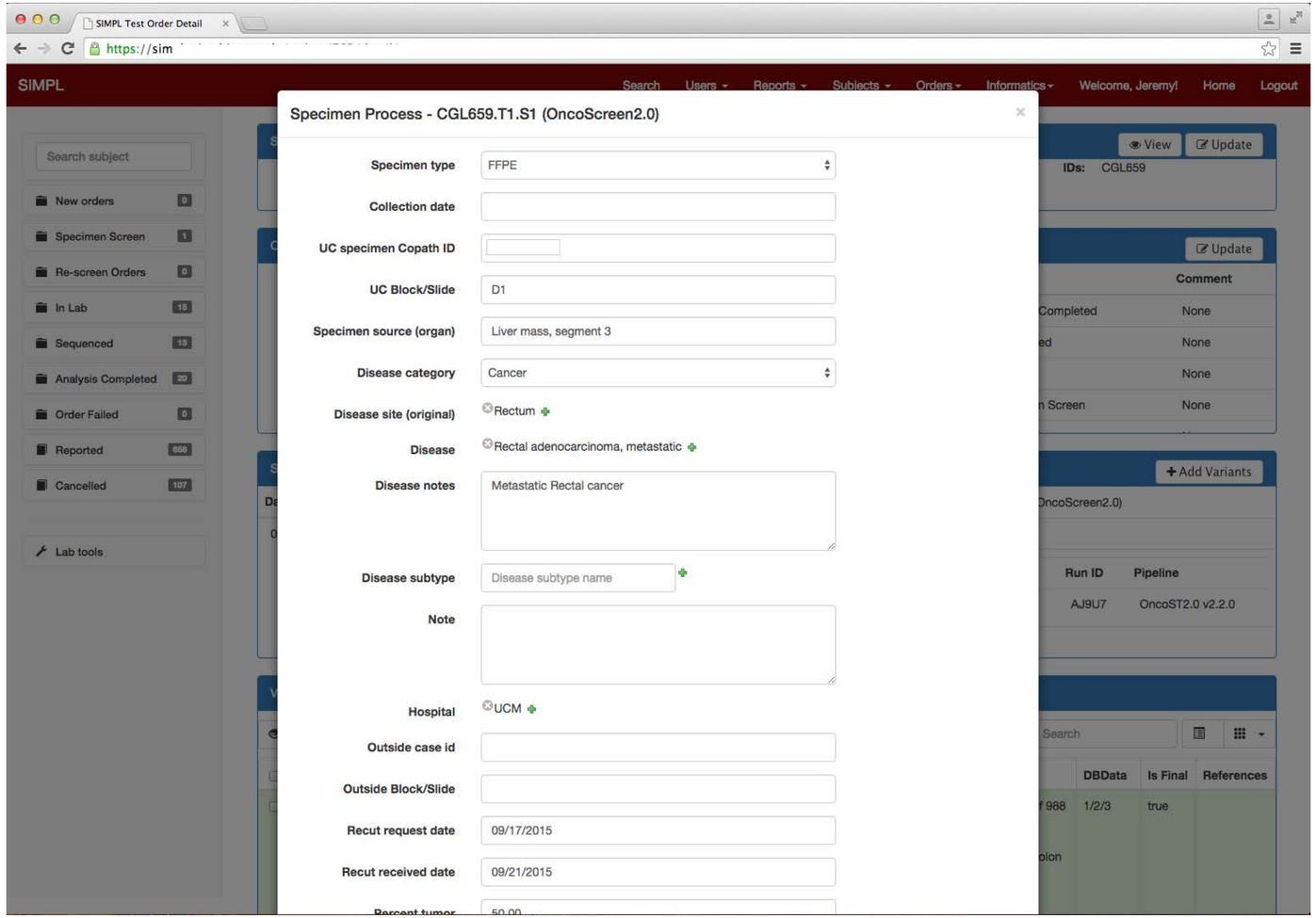
System for informatics in the molecular pathology laboratory (SIMPL)



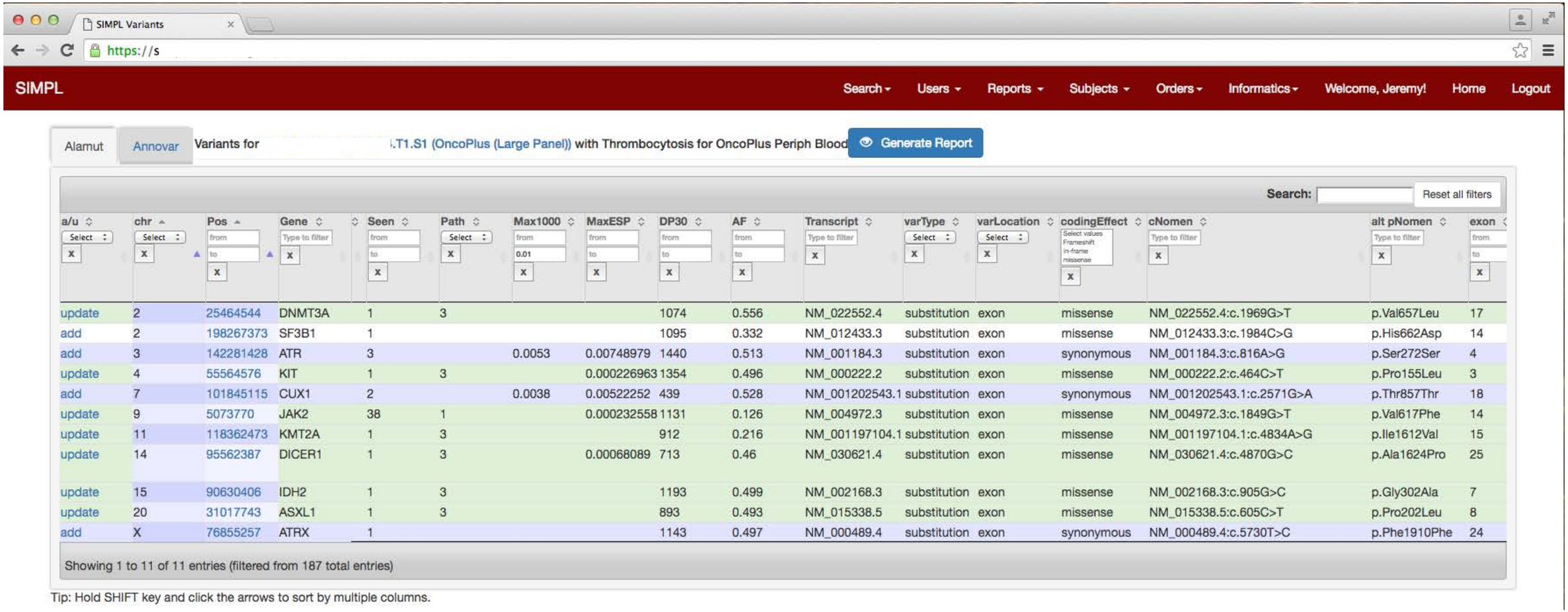
SIMPL sample tracking



SIMPL sample data annotation

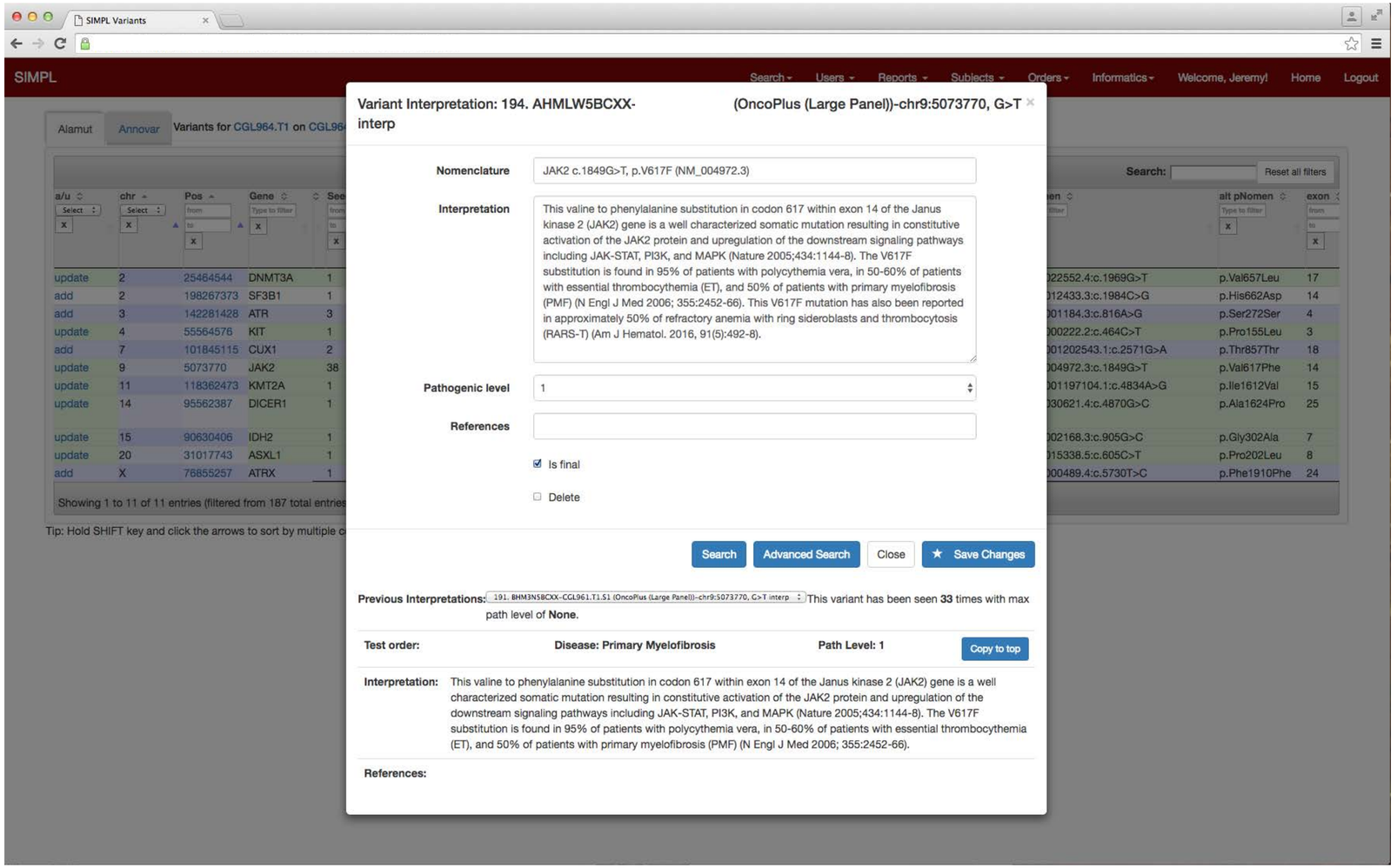


SIMPL variant report

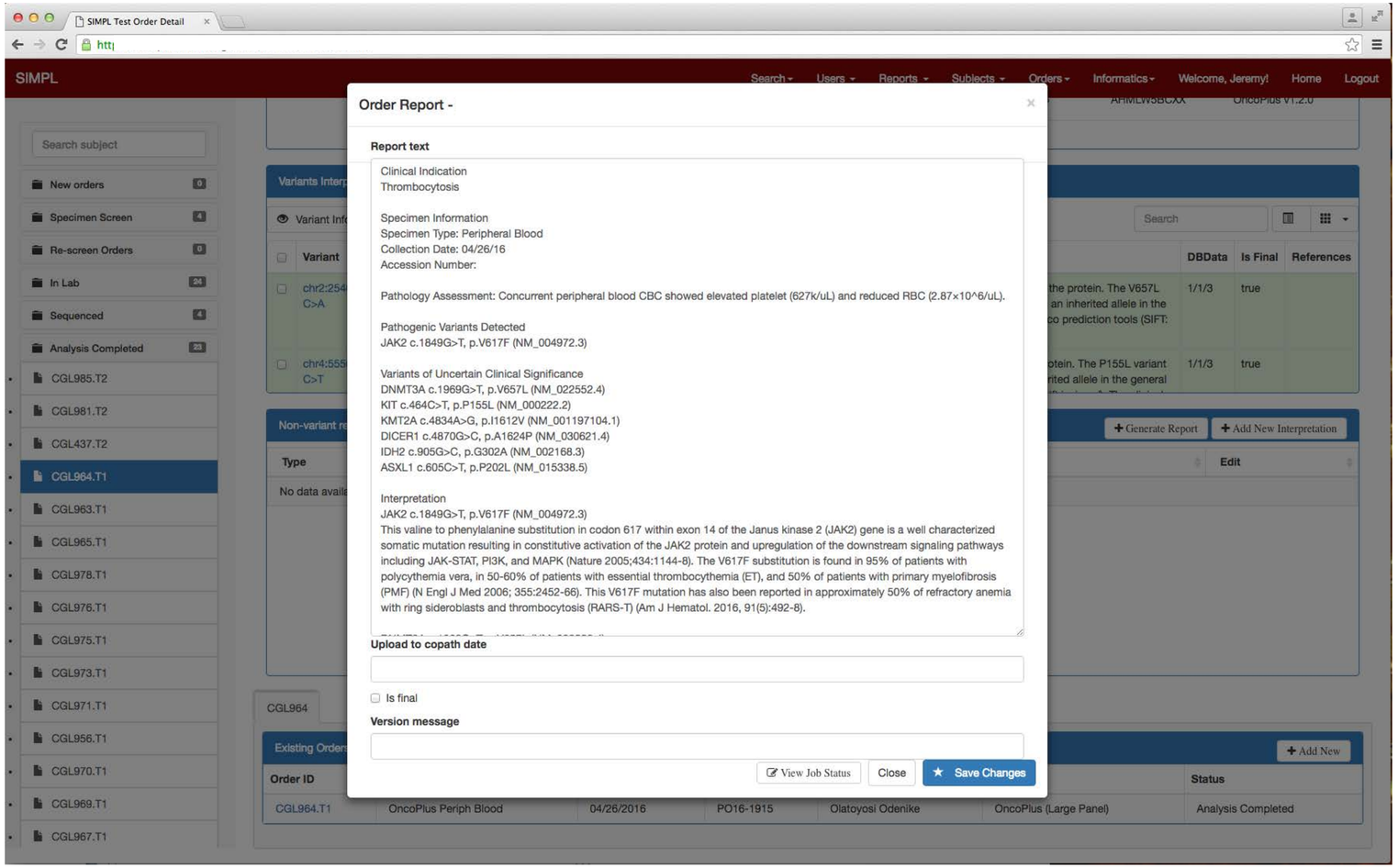


a/u	chr	Pos	Gene	Seen	Path	Max1000	MaxESP	DP30	AF	Transcript	varType	varLocation	codingEffect	cNomen	alt pNomen	exon
update	2	25464544	DNMT3A	1	3			1074	0.556	NM_022552.4	substitution	exon	missense	NM_022552.4:c.1969G>T	p.Val657Leu	17
add	2	198267373	SF3B1	1				1095	0.332	NM_012433.3	substitution	exon	missense	NM_012433.3:c.1984C>G	p.His662Asp	14
add	3	142281428	ATR	3		0.0053	0.00748979	1440	0.513	NM_001184.3	substitution	exon	synonymous	NM_001184.3:c.816A>G	p.Ser272Ser	4
update	4	55564576	KIT	1	3		0.000226963	1354	0.496	NM_000222.2	substitution	exon	missense	NM_000222.2:c.464C>T	p.Pro155Leu	3
add	7	101845115	CUX1	2		0.0038	0.00522252	439	0.528	NM_001202543.1	substitution	exon	synonymous	NM_001202543.1:c.2571G>A	p.Thr857Thr	18
update	9	5073770	JAK2	38	1		0.000232558	1131	0.126	NM_004972.3	substitution	exon	missense	NM_004972.3:c.1849G>T	p.Val617Phe	14
update	11	118362473	KMT2A	1	3			912	0.216	NM_001197104.1	substitution	exon	missense	NM_001197104.1:c.4834A>G	p.Ile1612Val	15
update	14	95562387	DICER1	1	3		0.00068089	713	0.46	NM_030621.4	substitution	exon	missense	NM_030621.4:c.4870G>C	p.Ala1624Pro	25
update	15	90630406	IDH2	1	3			1193	0.499	NM_002168.3	substitution	exon	missense	NM_002168.3:c.905G>C	p.Gly302Ala	7
update	20	31017743	ASXL1	1	3			893	0.493	NM_015338.5	substitution	exon	missense	NM_015338.5:c.605C>T	p.Pro202Leu	8
add	X	76855257	ATRX	1				1143	0.497	NM_000489.4	substitution	exon	synonymous	NM_000489.4:c.5730T>C	p.Phe1910Phe	24

SIMPL variant report



SIMPL pathology report



Clinical trial innovations

GAIN Consortium

G·A·I·N

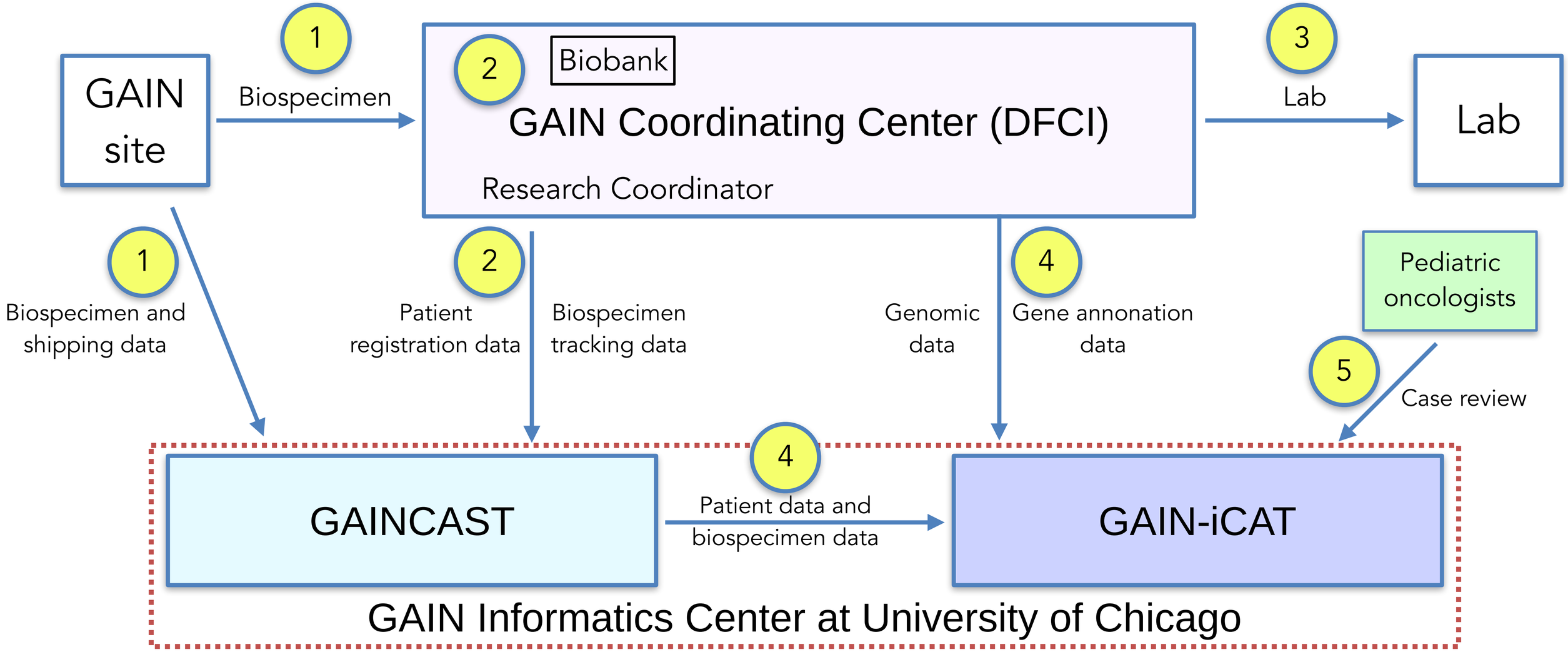
Genomic Assessment Informs Novel Therapy

CONSORTIUM

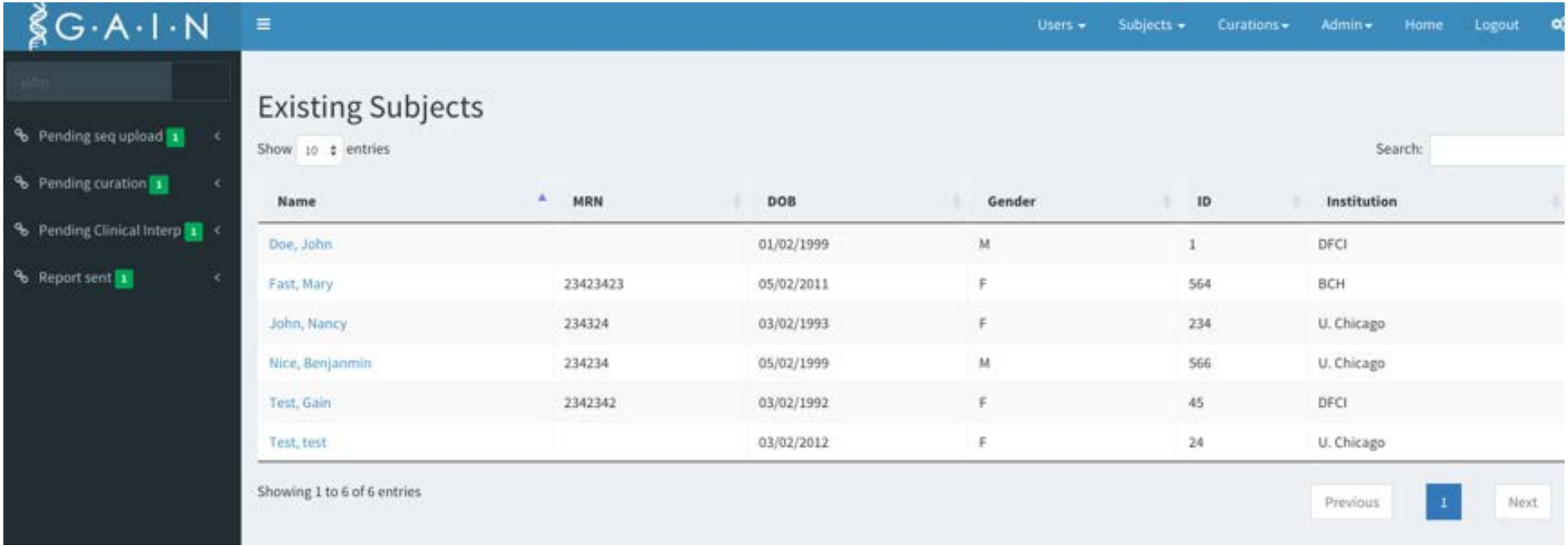
- Boston Children's Hospital
- Children's Hospital at Montefiore
- Children's Hospital of Philadelphia
- Children's National Medical Center
- Columbia University Medical Center
- Dana-Farber Cancer Institute
- Huntsman Cancer Institute, University of Utah
- Nationwide Children's Hospital
- Seattle Children's Hospital
- UCSF Benioff Children's Hospital
- University of Chicago Comer Children's Hospital
- Children's Hospital Colorado
- UT Southwestern Medical Center

Multi-institutional collaboration in precision oncology for children with difficult-to-cure cancers

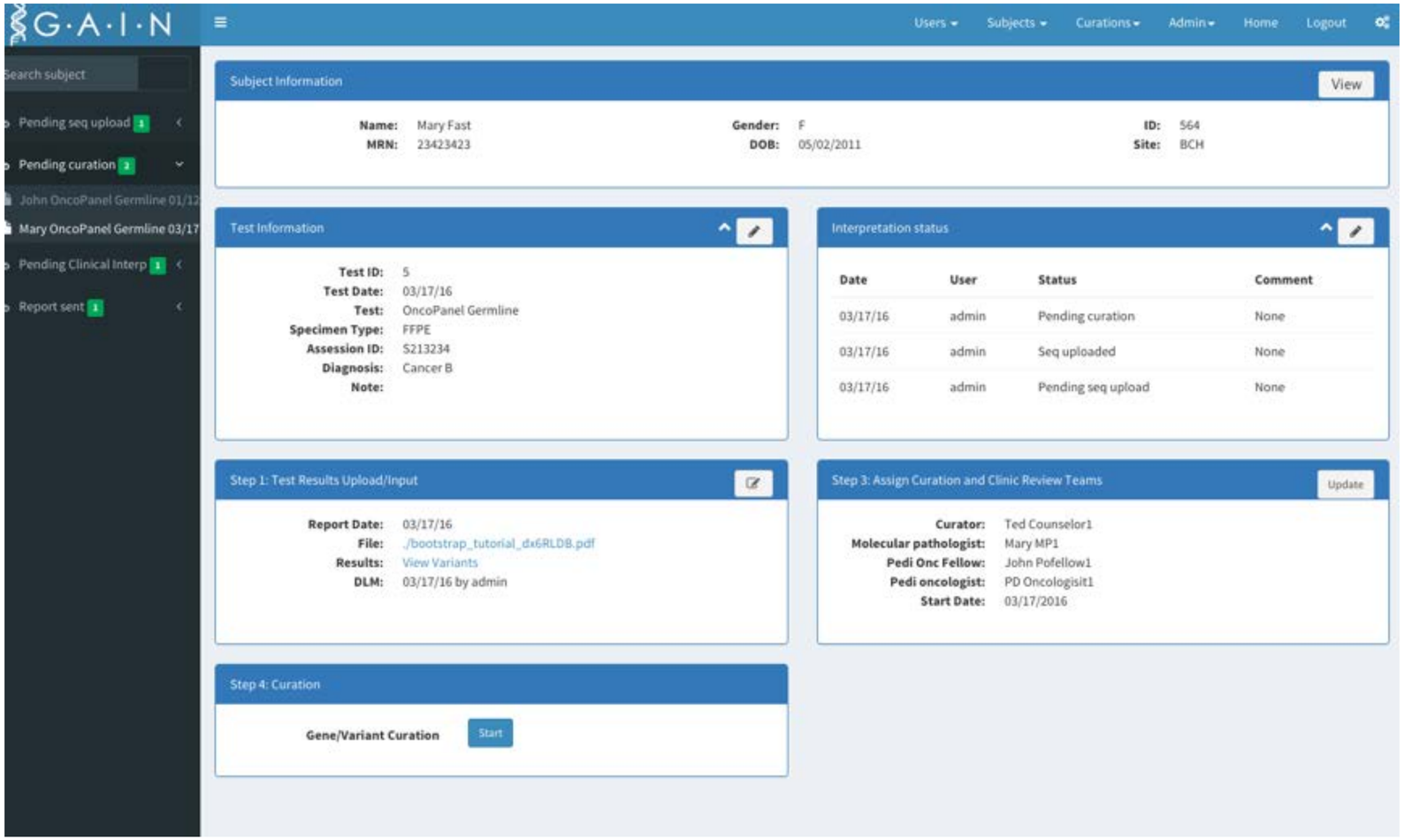
GAIN Consortium - infrastructure



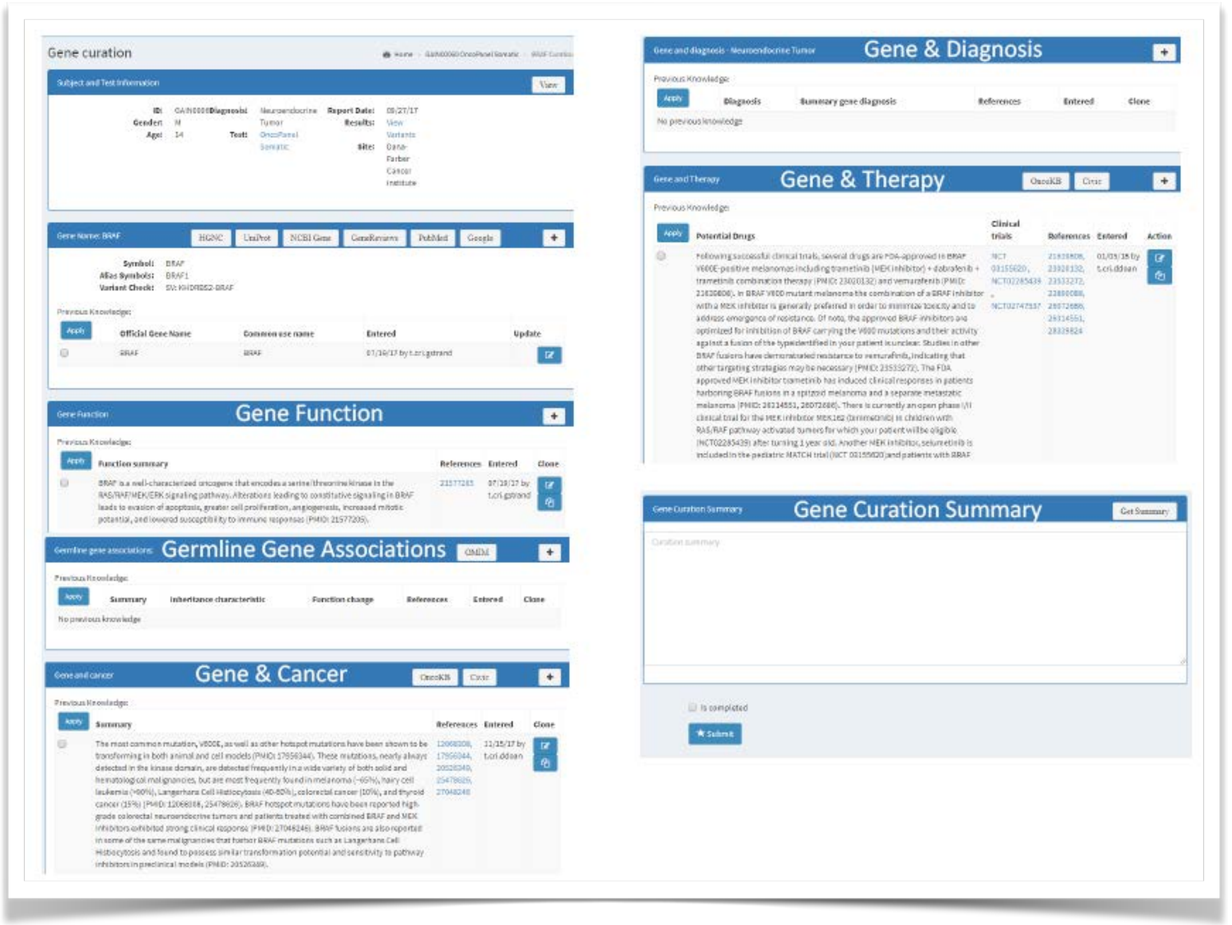
GAIN iCAT - patient tracking



GAIN iCAT - analysis tracking



GAIN iCAT - Facilitated gene curation



GAIN iCAT - variant curation summary

variant curation summary

CCNE1 amplification (~6 copies) was detected in this tumor. CCNE1 amplification in ovarian, uterine, and endometrial cancers has been associated with poor prognoses (PMID: 20336784, 26647729). Preclinical studies have shown that CCNE1 amplification sensitized ovarian or uterine carcinoma cells to CDK2 knockdown or CDK2 inhibitors (PMID: 24004674, 27351214). Numerous companies are developing cyclin dependent kinase inhibitors (PMID: 28127048). It should be noted however that these are not selective CDK2 inhibitors and efficacy specific for CCNE1-amplified tumors has not been conclusively demonstrated. Below are several CDK inhibitor clinical trials that are actively recruiting patients at least 18 years of age for which your patient may be eligible.

(1) NCT01434316 is a phase I clinical trial of dinaciclib (CDK2/5/1/9 inhibitor) in combination with veliparib (PARP inhibitor) in advanced solid tumors.

(2) NCT00999401 is a phase I clinical trial of seliciclib (CDK2/7/1 & ERK2 inhibitor) in combination with sapacitabine (a DNA damaging agent) in advanced solid tumors.

(3) NCT02503709 is a phase I clinical trial of AT7519 (CDK9/5/2/4/6/1 & GSK3B inhibitor) in combination with onalespib (HSP90 inhibitor) in metastatic solid tumors.

Number of iCat recommendations (for this variant): 2

- iCat recommendation therapeutic class: CDK2 Inhibitors
  - iCat recommendation tier: 4B
    - iCat recommendation specific drugs: dinaciclib
      - Treatment availability: Clinical trial active and currently open for enrollment
    - iCat recommendation specific drugs: seliciclib
      - Treatment availability: Clinical trial active and currently open for enrollment
    - iCat recommendation specific drugs: AT7519
      - Treatment availability: Clinical trial active and currently open for enrollment
- iCat recommendation therapeutic class: DNA Damage Response Inhibitor
  - iCat recommendation tier: 5A
    - iCat recommendation specific drugs: AZD1775
      - Treatment availability: Clinical trial active and currently open for enrollment
    - iCat recommendation specific drugs: Prexasertib
      - Treatment availability: Clinical trial active and currently open for enrollment
    - iCat recommendation specific drugs: VX-970
      - Treatment availability: Clinical trial active and currently open for enrollment

Variant curation summary

GAIN iCAT - Final curation report

A TP53 p.R290H variant was identified in this tumor with an allelic frequency of 51%. This represents a modest change from arginine to histidine (Grantham distance of 29) at a moderately conserved residue at the edge of the DNA binding domain. This missense variant, p.R290H, is frequently reported in multiple cancer databases (COSMIC, cBioPortal, TCGA). However, it has also been reported in population databases at a frequency of up to 0.046%. It has been submitted to ClinVar multiple times with conflicting interpretations. The p.R290H variant was identified in 6 families with inherited cancer predisposition, 2 with classic clinical criteria for LFS (PMID: 28861920). However, the variant scored as having wild type activity in a transactivation assay (PMID: 12826609). Coupled with the low penetrance with which carriers develop cancer, this variant likely has reduced pathogenicity. This test does not distinguish between germline and somatic alterations. If clinically indicated, genetic counseling and germline testing may be helpful.

Number of iCat recommendations (for this variant): 1

iCat recommendation therapeutic class: WEE1 Inhibitors

iCat recommendation tier: 2A

iCat recommendation specific drugs: AZD1775

Treatment availability: Drug in clinical development but no appropriate trial for this patient

Curation Report:

POLB p.I260M 56.7% in 171 reads

POLB is a DNA polymerase involved in base excision and repair, also called gap-filling DNA synthesis. POLB variants have been identified in a wide range of cancers, including colon, prostate, gastric, cervical, breast, and esophageal cancer.

A POLB p.I260M variant was identified in the tumor with an allelic frequency of 56%. This represents a seemingly modest change from an isoleucine to a methionine (Grantham distance of 10) at a highly conserved residue in the nucleotidyltransferase (NT) domain. It has been identified in population databases at frequencies as high as 0.001%. p.I260 is a key residue of the hydrophobic hinge important for polymerase closing, which is critical for polymerase fidelity (PMID: 22914675). The p.I260M variant alters protein function and is a sequence-context-dependent mutator in preclinical models (PMID: 16313169, 28862868, 22914675). This variant is included in the Curation Section as it likely contributes to an increased mutation rate in this cancer.

RAD51 p.G305Efs*68 57.5% in 153 reads

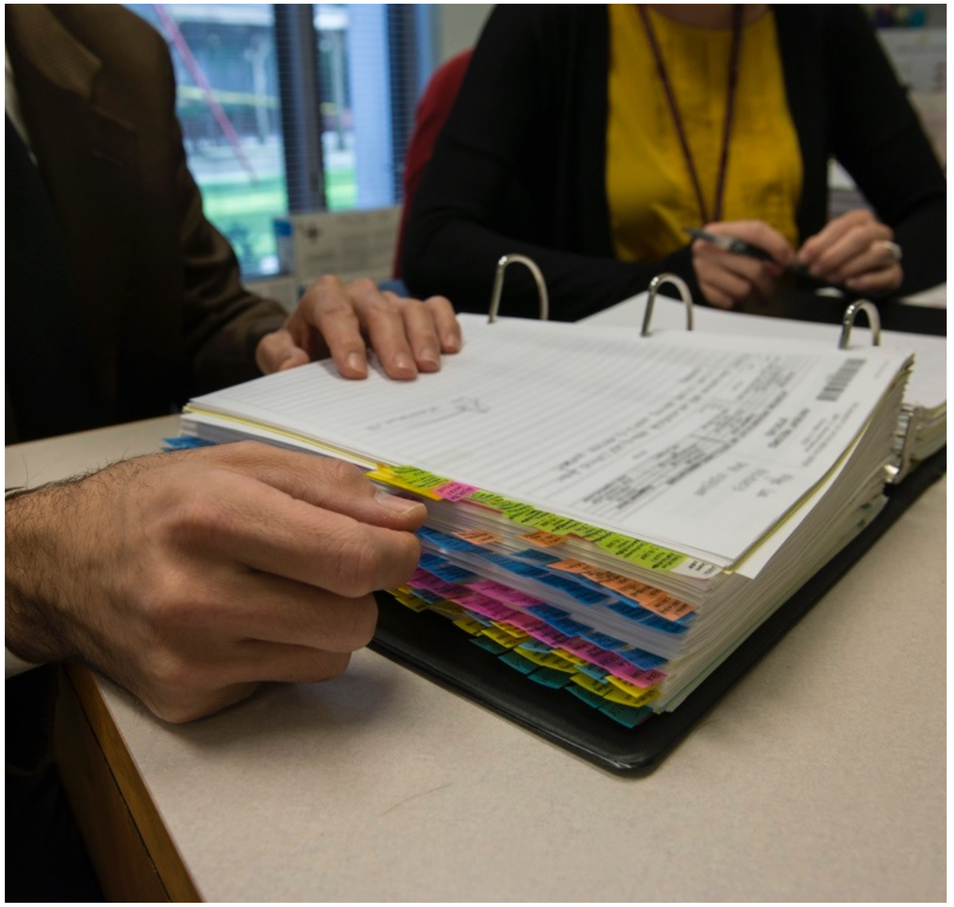
RAD51 functions in homologous recombination (HR)-mediated repair of double-stranded DNA breaks. RAD51 germline mutations may increase breast cancer risk in certain populations (PMID: 10807537, 26108708). Heterozygous truncating mutations have also been associated with mirror movements-2 (MRMV2) while dominant-negative missense mutations have been linked with an atypical form of Fanconi anemia. RAD51 is infrequently mutated in human cancer. However, RAD51 overexpression has been linked to increased oncogenic potential in several tumor

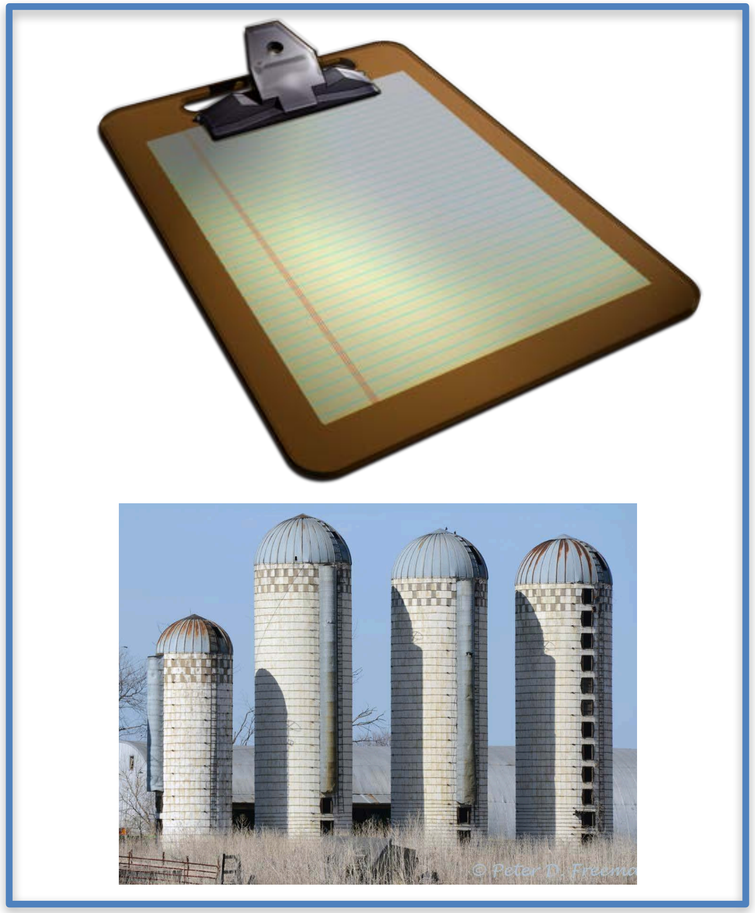
Innovations in data collection

Lack of rich phenotype data hinders progress

- Many samples for genomics lack sufficient clinical information
- Without deep phenotype data, analyses are limited
- Deep phenotype data should be collected at the time of sample acquisition, directly from electronic health record systems

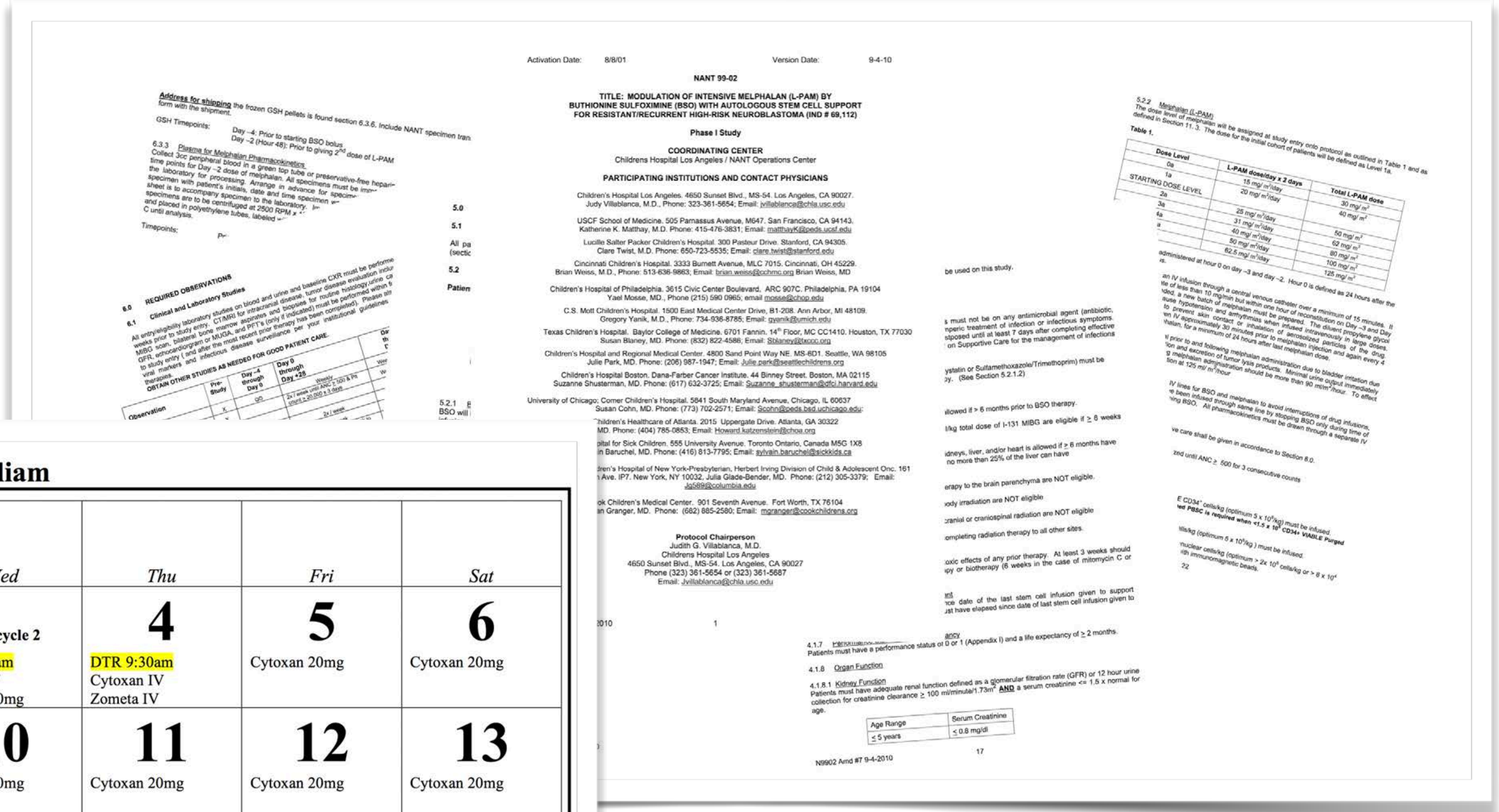
Manual processes and lack of data standards for clinical trials





Manual processes and lack of data standards for clinical trials

CTCAE CODE (per protocol)	CTCAE SHORT NAME (per protocol)	Current Grade	Maximum Grade This Course* (for occurrence)	Maximum Grade This Occurrence **	Attribu -tion	Date Onset	Resolved Yes / No	Date Resolved	Comments
10020943	Hypo albuminemia	0	1	1	3	05/23	Yes	06/02	
10020943	Hypo albuminemia	0	1	1	3	06/05	Yes	06/09	
10021038	Hypo natremia	0	1	1	3	05/26	Yes	05/27	
10021038	Hypo natremia	0	1	1	3	05/29			
10021059	Hypo phosphatemia	0	1	1	3	05/0			
10021059	Hypo phosphatemia	0	1	1	3	05/23			
10016256	Fatigue	0	1	1	3	05/2			

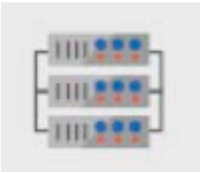


October — William

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	1 Bactrim Cytoxan 20mg	2 Bactrim Cytoxan 20mg	3 cycle 2 DTR 9:30am Avastin IV Cytoxan 20mg	4 DTR 9:30am Cytoxan IV Zometa IV	5 Cytoxan 20mg	6 Cytoxan 20mg
7 Cytoxan 20mg	8 Bactrim Cytoxan 20mg Labs and blood pressure at home	9 Bactrim Cytoxan 20mg	10 Cytoxan 20mg	11 Cytoxan 20mg	12 Cytoxan 20mg	13 Cytoxan 20mg
14 Cytoxan 20mg	15 Bactrim Cytoxan 20mg	16 Bactrim Cytoxan 20mg	17 DTR 9:30am Avastin IV Cytoxan 20mg	18 Cytoxan 20mg	19 Cytoxan 20mg	20 Cytoxan 20mg
21 Cytoxan 20mg	22 Bactrim Cytoxan 20mg SSKI	23 Bactrim Cytoxan 20mg MIBG, x-ray knees Bone marrow biopsies SSKI	24 Cytoxan 20mg MIBG CT scan SSKI	25 Cytoxan 20mg SSKI	26 Cytoxan 20mg SSKI	27 Cytoxan 20mg
28 Cytoxan 20mg	29 Bactrim Cytoxan 20mg	30 Bactrim Cytoxan 20mg	31 Cycle 3 DTR 9:30am Avastin IV Cytoxan 20mg	1 DTR 9:30am Cytoxan IV Zometa IV		

Why do we need data commons?

Too much data to store

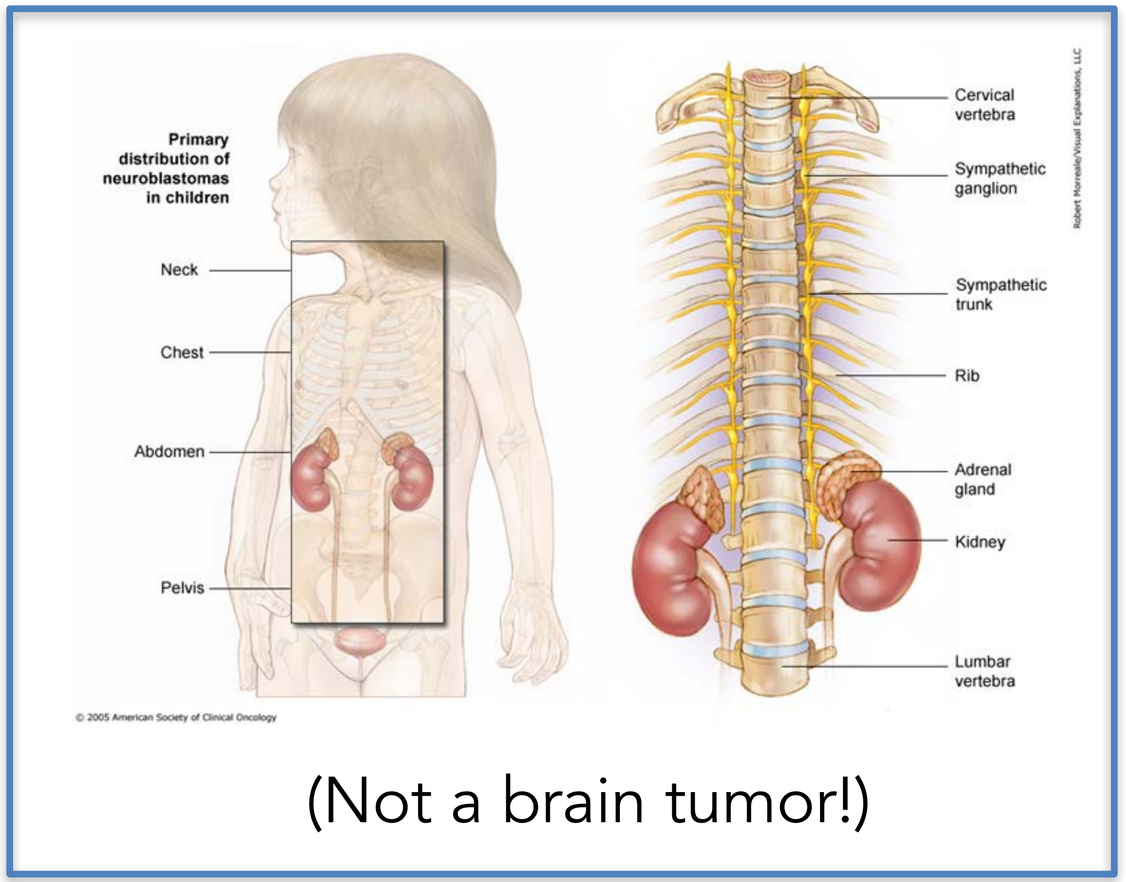


Takes too long to transfer

Too expensive to analyze

Lack of data standardization

Neuroblastoma



(Not a brain tumor!)

International Neuroblastoma Research Group (2004)

Children's Oncology Group (COG)

Germany

Japan

SIOPEN

International Neuroblastoma Research Group (2004)

Children's Oncology Group (COG)

Germany

Japan

SIOPEN

COG	SIOPEN	Japan	Germany
Study 1	Study 4	Study 7	Study 10
Study 2	Study 5	Study 8	Study 11
Study 3	Study 6	Study 9	Study 12
COG Consensus	**SIOPEN Consensus**	**Japan Consensus**	**Germany Consensus**

International Neuroblastoma Research Group (2004)

Children's Oncology Group (COG)

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SIOPEN

COG	SIOPEN	Japan	Germany
Study 1	Study 4	Study 7	Study 10
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COG Consensus	**SIOPEN Consensus**	**Japan Consensus**	**Germany Consensus**

Consensus standard

International Neuroblastoma Research Group (2004)

Children's Oncology Group (COG)

Germany

Japan

SIOPEN

International Neuroblastoma Research Group (2004)

Children's Oncology Group (COG)

Germany

Japan

SIOPEN

Group	Number
COG	4235
Germany	1938
Japan	470
SIOPEN	936
Total	8800

>15 high-impact publications that changed clinical practice

International Neuroblastoma Research Group (2004)

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The good news: 8800 patients

The bad news:

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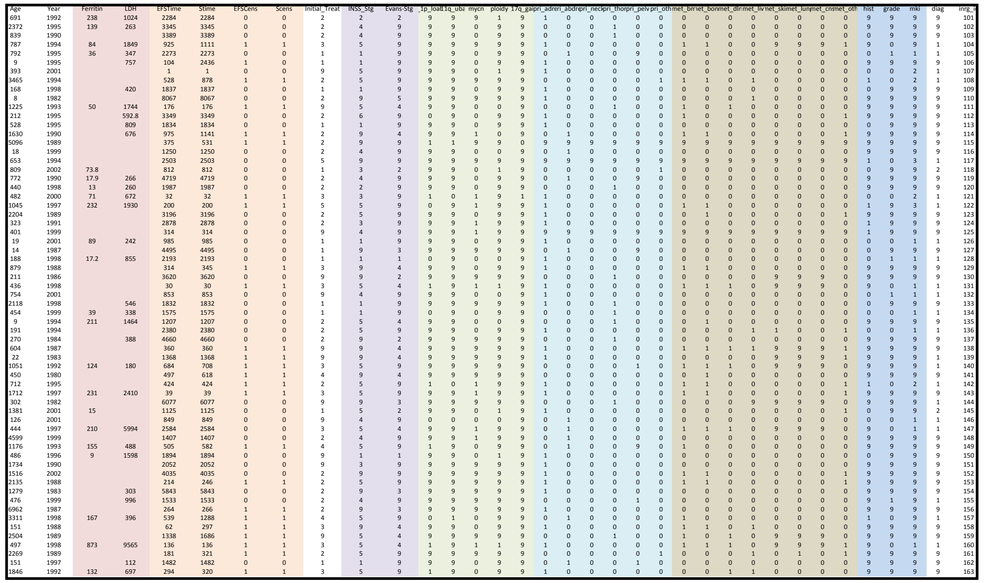
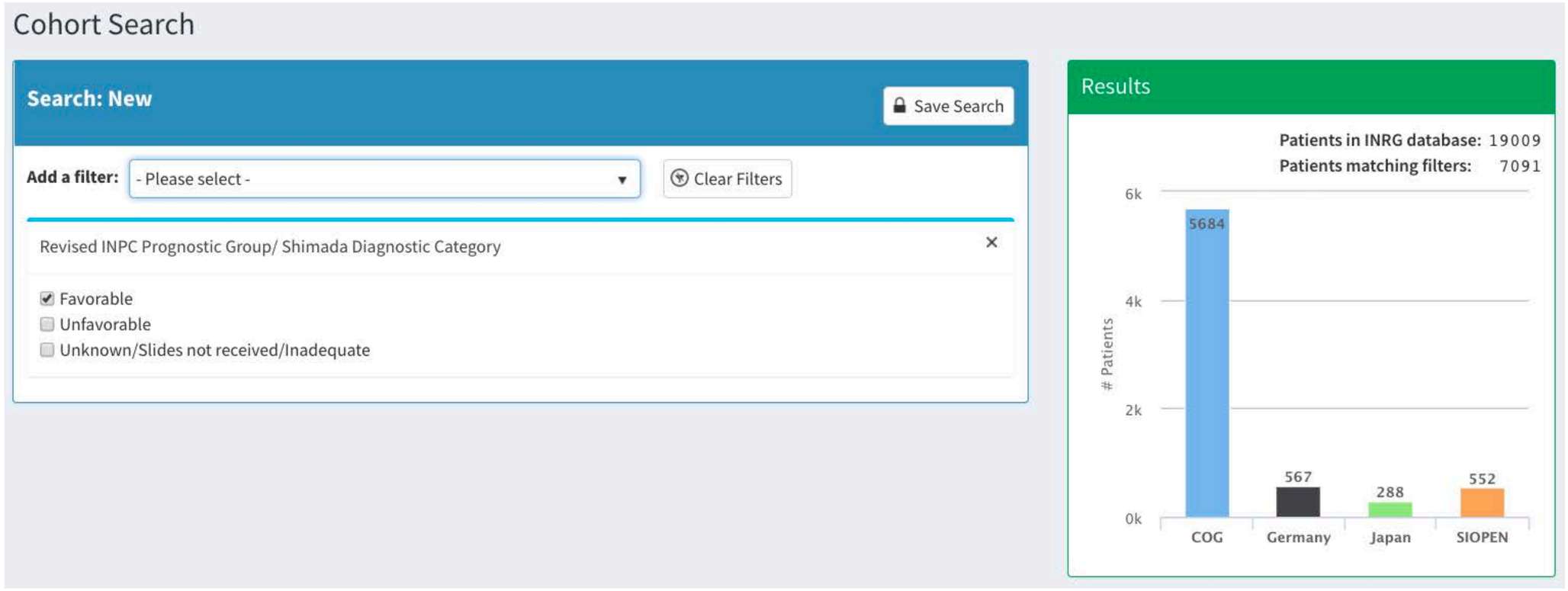


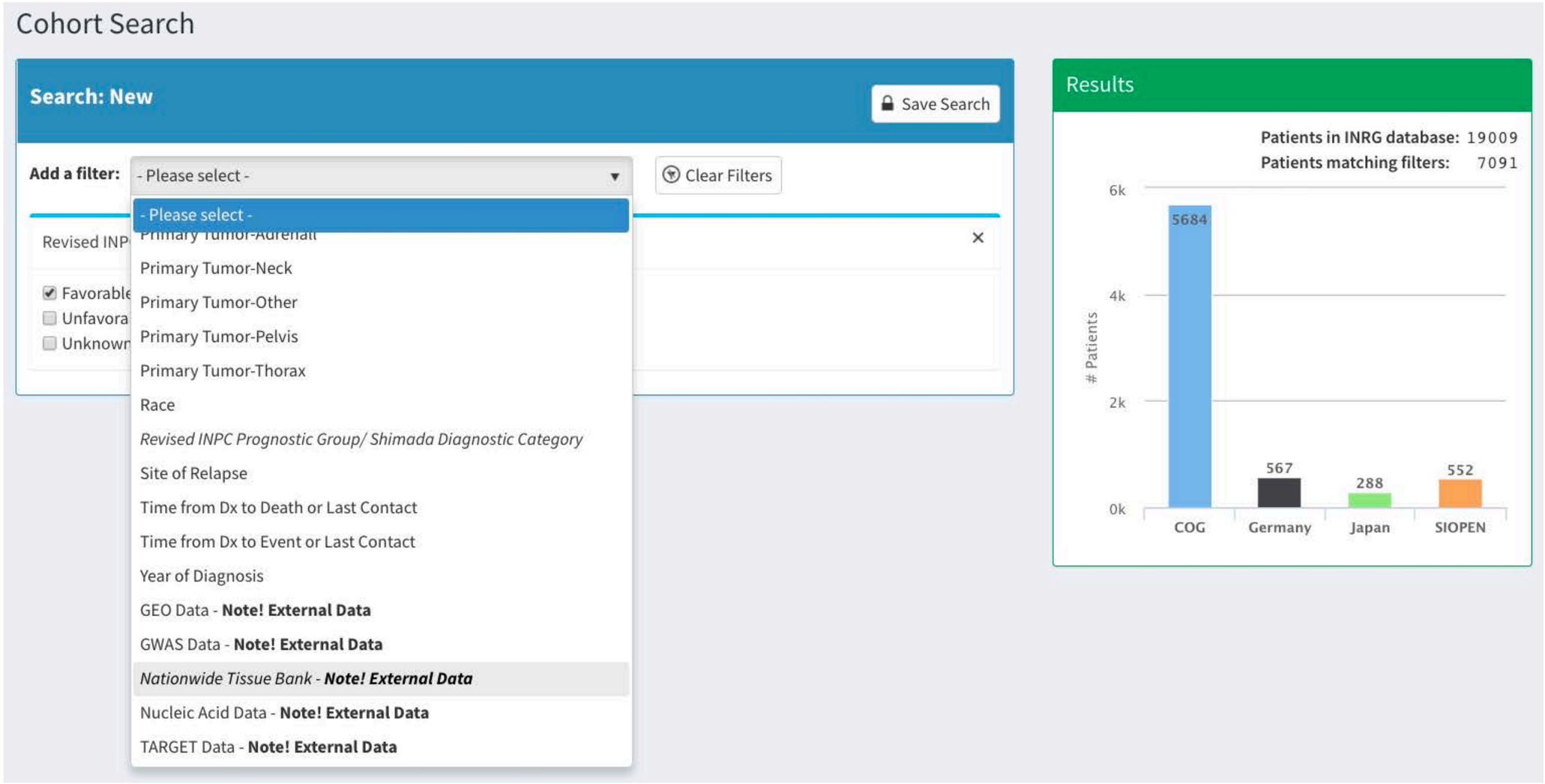
>15 high-impact publications that changed clinical practice

Neuroblastoma Commons Cohort Discovery

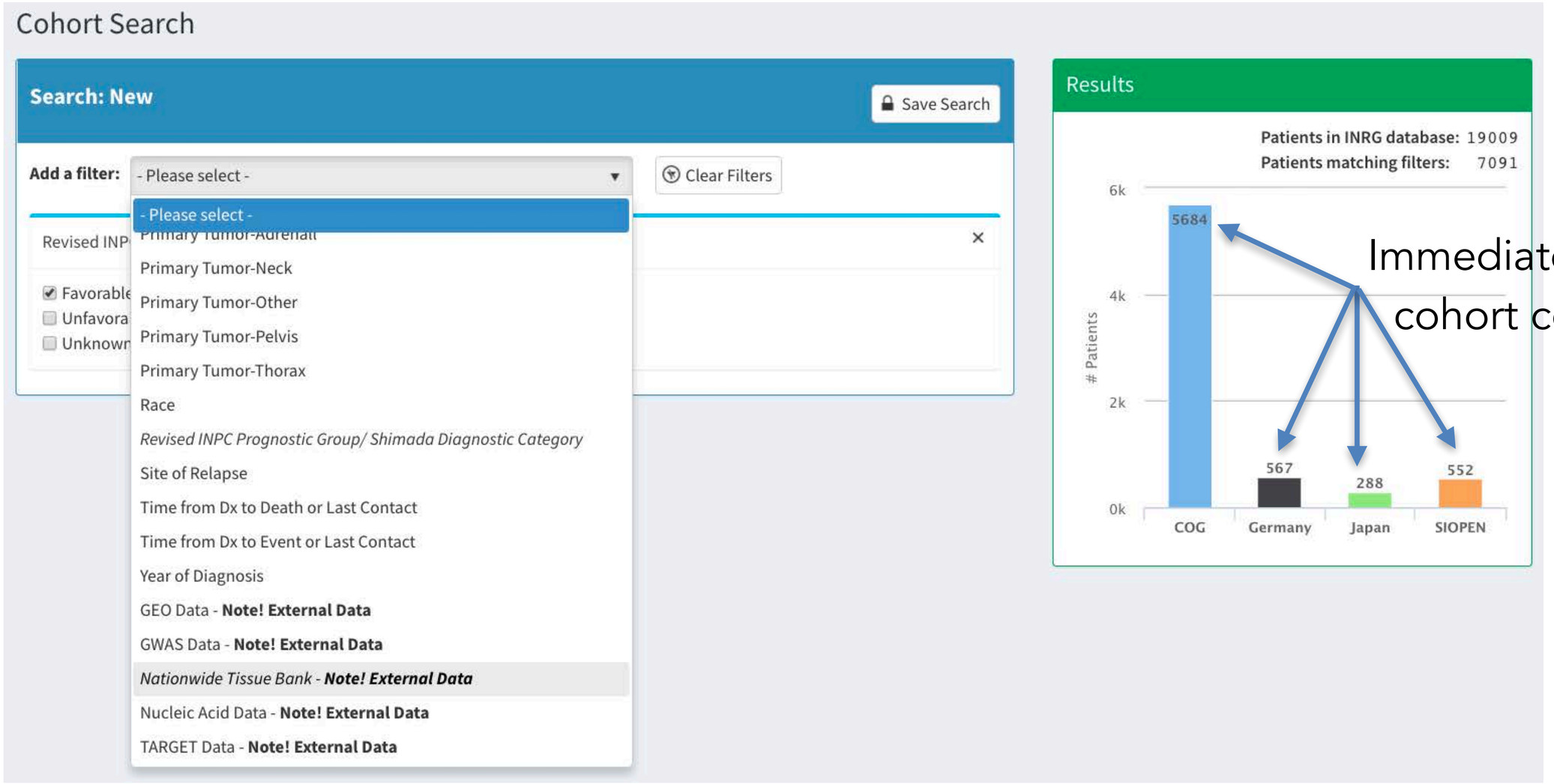
Favorable tumor biology, tissue available



Neuroblastoma Commons Cohort Discovery



Neuroblastoma Commons Cohort Discovery



Immediately see cohort counts

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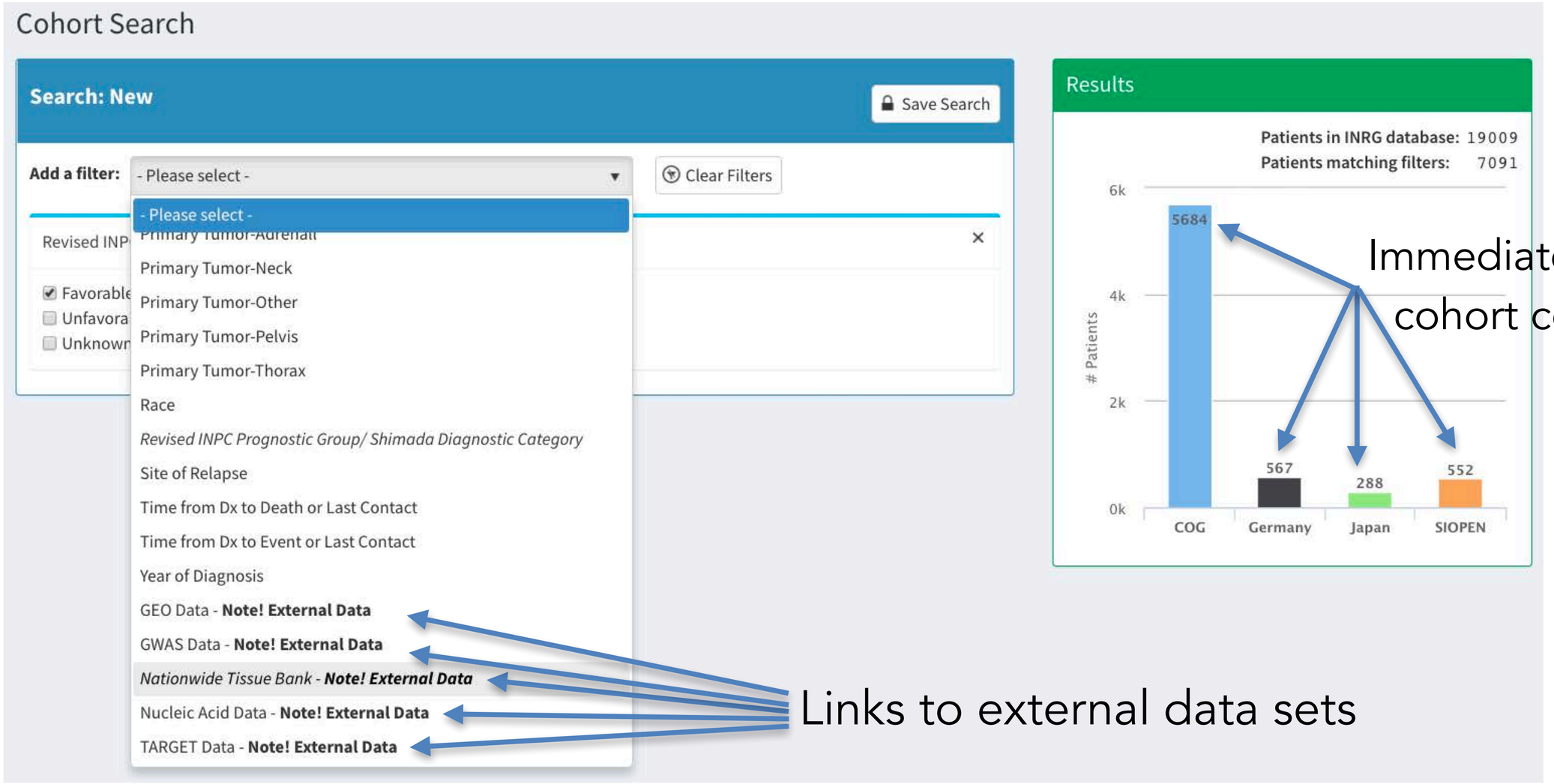
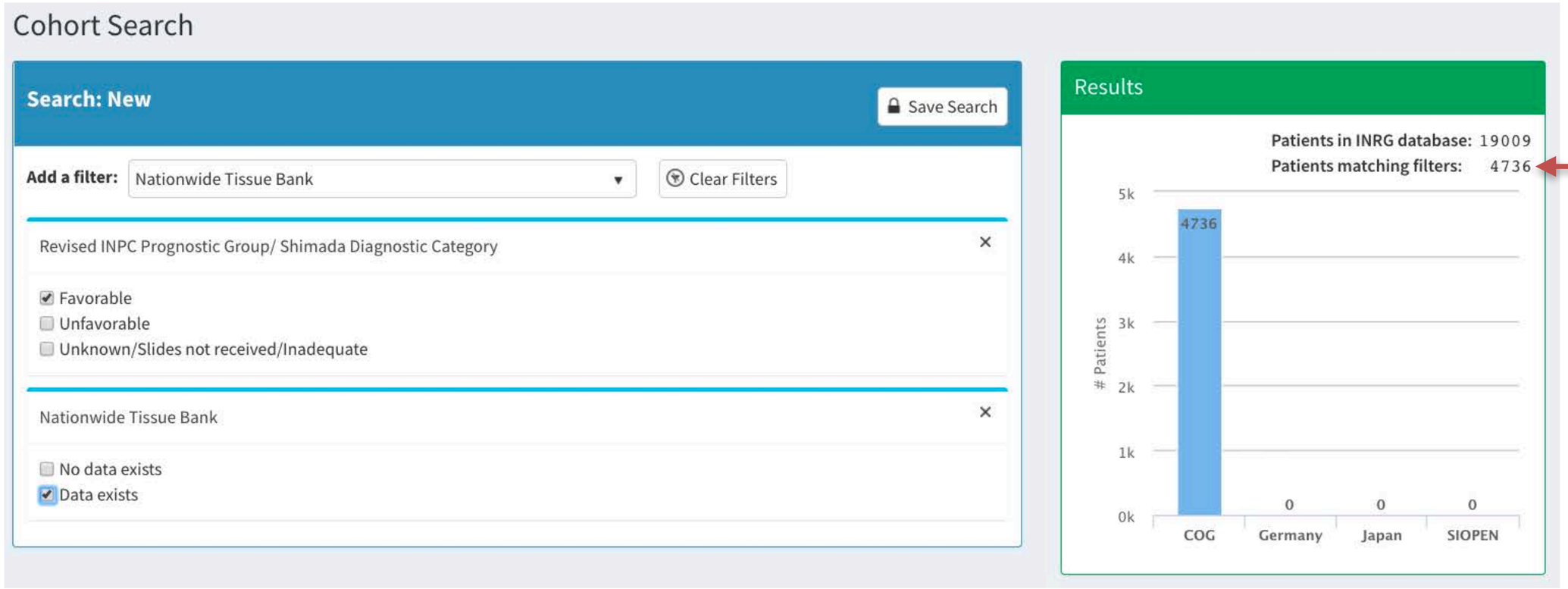
Publicly available at inrgdb.org

@samvolchenboum

Neuroblastoma Commons Cohort Discovery



Neuroblastoma Commons Cohort Discovery



Favorable biology, tissue available

Neuroblastoma data commons growth

Year	COG	SIOPEN	GPOH	Japan	Total
2004	4235	2157	1938	470	**8800**
2012	6127	2504	1938	470	**11039**
2013	11642	2504	1938	470	**16554**
2015	13060	2504	1938	470	**17972**
2016	13937	2664	2154	470	**19225**

Data upload can be automated using a standardized data dictionary with error and consistency checking.

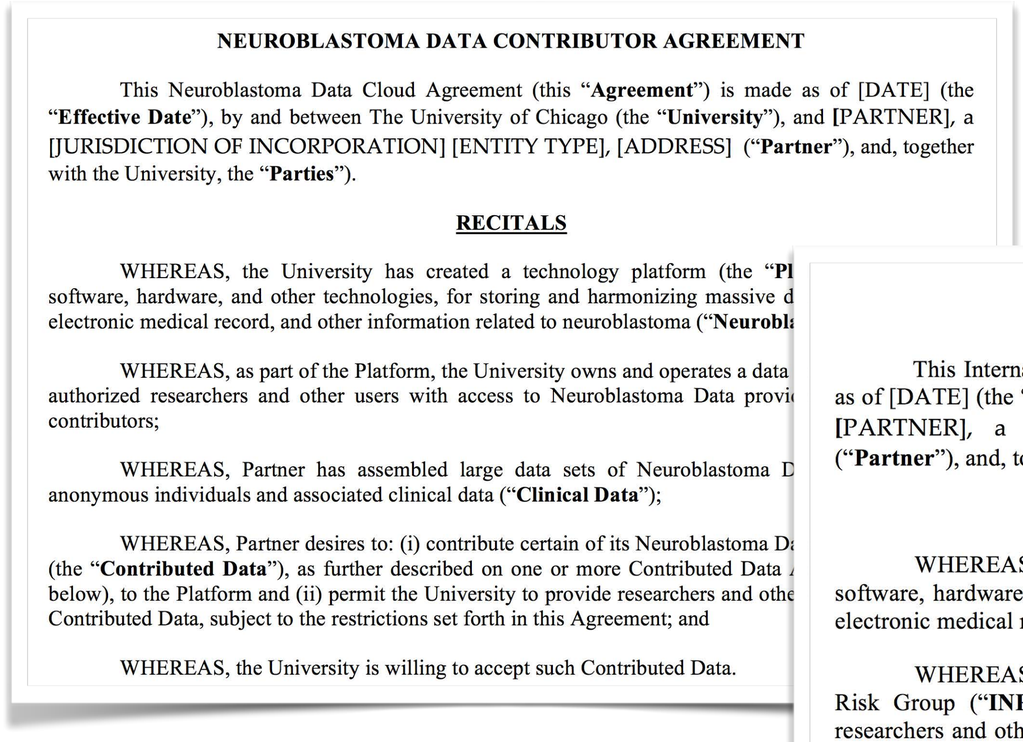
Paradigm for building a pediatric cancer commons

1. Engage cooperative group(s)
2. Define scope
3. Identify funding source
4. Identify infrastructure
5. Engage project team
6. Identify data sources
7. Establish governance, create policies and procedures
8. Create contributor / use agreements
9. Create standards working group to create data dictionary, map elements
10. Create database
11. Build front-end query engine
12. Create and execute communication and education plans
13. Create sustainability model

Volchenboum SL, Cox SM, Heath A, Resnick A, Cohn SL, Grossman R
"Data Commons to Support Pediatric Cancer Research"

Governance / Regulation / Compliance

Data contributor agreement



NEUROBLASTOMA DATA CONTRIBUTOR AGREEMENT

This Neuroblastoma Data Cloud Agreement (this "**Agreement**") is made as of [DATE] (the "**Effective Date**"), by and between The University of Chicago (the "**University**"), and [PARTNER], a [JURISDICTION OF INCORPORATION] [ENTITY TYPE], [ADDRESS] ("**Partner**"), and, together with the University, the "**Parties**").

RECITALS

WHEREAS, the University has created a technology platform (the "**Pl**
software, hardware, and other technologies, for storing and harmonizing massive d
electronic medical record, and other information related to neuroblastoma ("**Neurobla**

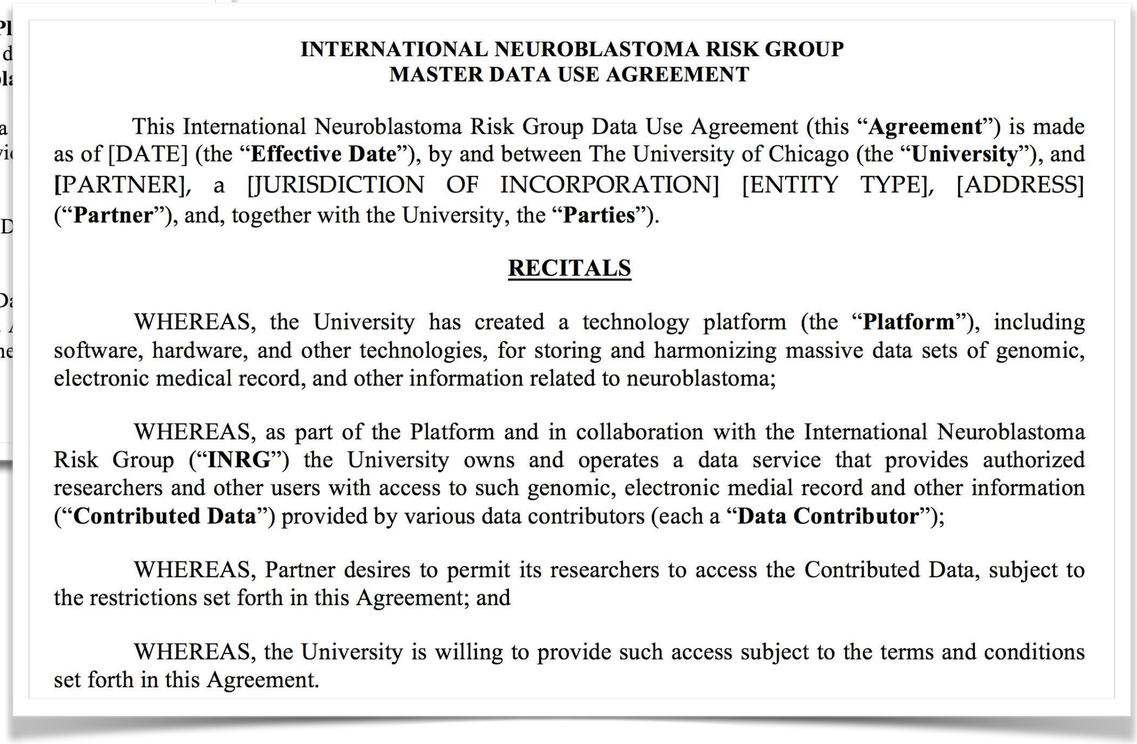
WHEREAS, as part of the Platform, the University owns and operates a data
authorized researchers and other users with access to Neuroblastoma Data provi
contributors;

WHEREAS, Partner has assembled large data sets of Neuroblastoma D
anonymous individuals and associated clinical data ("**Clinical Data**");

WHEREAS, Partner desires to: (i) contribute certain of its Neuroblastoma Da
(the "**Contributed Data**"), as further described on one or more Contributed Data A
below), to the Platform and (ii) permit the University to provide researchers and othe
Contributed Data, subject to the restrictions set forth in this Agreement; and

WHEREAS, the University is willing to accept such Contributed Data.

Data sharing agreement



INTERNATIONAL NEUROBLASTOMA RISK GROUP
MASTER DATA USE AGREEMENT

This International Neuroblastoma Risk Group Data Use Agreement (this "**Agreement**") is made as of [DATE] (the "**Effective Date**"), by and between The University of Chicago (the "**University**"), and [PARTNER], a [JURISDICTION OF INCORPORATION] [ENTITY TYPE], [ADDRESS] ("**Partner**"), and, together with the University, the "**Parties**").

RECITALS

WHEREAS, the University has created a technology platform (the "**Platform**"), including software, hardware, and other technologies, for storing and harmonizing massive data sets of genomic, electronic medical record, and other information related to neuroblastoma;

WHEREAS, as part of the Platform and in collaboration with the International Neuroblastoma Risk Group ("**INRG**") the University owns and operates a data service that provides authorized researchers and other users with access to such genomic, electronic medial record and other information ("**Contributed Data**") provided by various data contributors (each a "**Data Contributor**");

WHEREAS, Partner desires to permit its researchers to access the Contributed Data, subject to the restrictions set forth in this Agreement; and

WHEREAS, the University is willing to provide such access subject to the terms and conditions set forth in this Agreement.

COG RMS data dictionary

Field Name	Data Type	Description	Value Constraints	Notes
PATIENT_ID	INTEGER	Unique Patient Identification number, assigned after data submission		
USI	TEXT	Universal specimen index (COG patients)		
STUDY	TEXT	Protocol Number		
AGE	INTEGER	Age (in years) at date of diagnosis	99 = Unknown	
GENDER	INTEGER		1 = Male 2 = Female	
HISTOLOGY	INTEGER	Type of Rhabdomyosarcoma	1 = ARMS 2 = ERMS 3 = BRMS 4 = NOS 5 = Undifferentiated Sarcoma 6 = Sarcoma, not classifiable 7 = Spindle cell 8 = Ectomesenchymoma 9 = Other 10 = Mixed RMS 99 = Unknown	
STAGE	INTEGER	IRS TMN classification for pretreatment clinical assessment of disease	1 = Favorable Site, M0 2 = Other Site, any T, a, N0, M0 3 = Other Site, any T, a, N1, M0, any T, b, N0/N1, M0 4 = Metastases, M1	
GROUP	INTEGER	IRS Surgical-Pathologic Grouping System	1 = Completely removed 2 = IIA Microscopic residual, Margin + Nodes - 3 = IIB Microscopic residual, Margin - Nodes +	
PRI_ORBIT	INTEGER	Pr		
PRI_HN	INTEGER	Pr		
				93 = Marrow & Skin 94 = Marrow & Other 95 = Meninges 96 = Multiple Sites, Excl. Lung 97 = Muscle 98 = Peripheral Nerves 99 = Pineal 100 = Pituitary 101 = Skin 102 = Spinal Cord 103 = Spleen 104 = Subcutaneous 105 = Unknown 106 = Other
METASTATIC	INTEGER	Metastases is distant	0 = No 1 = Yes 9 = Unknown	
MET_LUNG	INTEGER	Metastatic site of tumor at the time of diagnosis is lung	0 = No 1 = Yes 9 = Unknown	
MET_BONE	INTEGER	Metastatic site of tumor at the time of diagnosis is bone or bone marrow	0 = No 1 = Yes 9 = Unknown	
MET_NODE	INTEGER	Metastatic site of tumor at the time of diagnosis is distant lymph nodes	0 = No 1 = Yes 9 = Unknown	
MET_STS	INTEGER	Metastatic site of tumor at the time of diagnosis is soft tissue sites	0 = No 1 = Yes 9 = Unknown	
MET_PE	INTEGER	Metastatic site of tumor at the time of diagnosis is pleural effusion	0 = No 1 = Yes 9 = Unknown	
MET_OTHER	INTEGER	Metastatic site of tumor at the time of diagnosis is other	0 = No 1 = Yes 9 = Unknown	
MEASUREMENT	INTEGER	Maximum diameter of tumor (cm)	99 = Unknown	
INVASIVE	INTEGER	Tumor invasiveness	1 = Yes [confined to organ of origin], T1 2 = No [not confined to organ of origin], T2 9 = Unknown	
NODAL_CLINICAL	INTEGER	Clinical or imaging evidence for nodal Involvement	0 = No, N0 1 = Yes, N1 9 = Not Evaluated/Unknown	

				12 = Other Head & Neck
PRI_PM	INTEGER	Primary site of tumor is parameningeal	0 = No 1 = Yes 9 = Unknown	13 = Infratemporal Fossa 14 = Middle Ear 15 = Nasal Cavity & Sinus 16 = Nasopharynx 17 = Paranasal Sinus 18 = Parapharyngeal Area 19 = Pterygopalatine 20 = Cheek & PM Extension 21 = Larynx & PM Extension 22 = Orbit & PM Extension 23 = Oropharynx & PM Extension 24 = Other H&N & PM Extension 25 = Parotid & PM Extension 26 = Scalp & PM Extension
PRI_GU	INTEGER	Primary site of tumor is GU, non- te	0 = No 1 = Yes 9 = Unknown	27 = Cervix 28 = Epididymis 29 = Kidney 30 = Ovary 31 = Penis 32 = Spermatic Cord 33 = Testis-Paratestis 34 =
		tumor is bladder/prostate	0 = No 1 = Yes 9 = Unknown	35 = 36 = 37 = 38 = 39 = 40 = 41 = 401 =
		tumor is extremity	0 = No 1 = Yes 9 = Unknown	42 = 43 = 44 = 45 = 46 = 47 = 48 = 49 = 50 = 51 =
		tumor is intrathoracic	0 = No	62 =
			1 = Yes 9 = Unknown	63 = Diaphragm 64 = Heart 65 = Hilum 66 = Lung & Local Sites 67 = Lung & Other Sites 68 = Lung 69 = Mediastinum 70 = Pericardium 71 = Pleura 72 = Pleural Effusion 73 = Thymus 74 = Trachea
PRI_PERI_ANUS	INTEGER	Primary site of tumor is perineum/anus	0 = No 1 = Yes 9 = Unknown	75 = Anus 76 = Perineum
PRI_RETROPERI	INTEGER	Primary site of tumor is retroperineum	0 = No 1 = Yes 9 = Unknown	77 = Pelvis, Site Indeterminate 78 = Retroperitoneum
PRI_TRUNK	INTEGER	Primary site of tumor is trunk	0 = No 1 = Yes 9 = Unknown	79 = Abdominal Wall 80 = Breast 81 = Chest Wall 82 = Paraspinal
PRI_OTHER	INTEGER	Primary site of tumor is other	0 = No 1 = Yes 9 = Unknown	52 = Esophagus 53 = Gall Bladder & Biliary Tree 54 = Intestine, large 55 = Intestine, small & duodenum 56 = Liver 57 = Omentum 58 = Pancreas 59 = Peritoneal Nodules 60 = Peritoneum 61 = Stomach 83 = Adrenal Glands 84 = Ascites 85 = Bone

NODAL_PATH	INTEGER	Pathological evidence for Nodal Involvement	0 = No, N0 1 = Yes, N1 9 = Not Evaluated/Unknown	
FUSION	INTEGER	Fusion Status	0 = FOX01- 1 = FOX01+ 9 = Unknown	
PAX	INTEGER	PAX fusion partner	3 = PAX3 7 = PAX7 9 = Unknown	
ANAPLA	INTEGER	Anaplasia status	0 = None 1 = Focal 2 = Diffuse 9 = Unknown	
EFS_EVENT	INTEGER	Censoring flag for event	0 = Patient is Censored (No Event) 1 = Patient had an event	Event = first occurrence of relapse, progression, secondary malignancy, or death from any cause
EVENT_TYPE	INTEGER	Type of first event	0 = No Event 1 = Relapse/Progression 2 = Second Malignancy 3 = Death 9 = Cannot determine if first event	
EFS_TIME	INTEGER	Time (in days) from diagnosis/enrollment to first event, or to last contact if no event occurred		
OS_EVENT	INTEGER	Censoring flag for death	0 = Patient is Censored (No Death) 1 = Patient died	Death = death from any cause
OS_TIME	INTEGER	Time (in days) from diagnosis/enrollment to death, or to last contact if patient is alive		

International RMS meeting - October 2017

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES | CENTER FOR RESEARCH INFORMATICS

INSTRuCT

(INternational Soft Tissue saRcoma ConsorTium)

Chicago Meeting

Tuesday, October 17 8:00am – Wednesday, October 18 4:00pm

Polsky Exchange North
1452 East 53rd Street, 2nd floor
Room: Promontory Point
Chicago, IL 60615
773-795-0209

Consensus harmonization of primary site

	CWS	COG	EpSSG
Major Primary Site	**CWS**	**COG**	**EpSSG/MMT Name**
ORBIT	Eyelid	1=Eye	Eyelid
	Orbit	2=Orbit	Orbit
HEAD & NECK (non PM)	Scalp	10=Scalp	Soft tissue of scalp
			External auricular canal
			Ear soft tissue, external ear
			Temporal muscle
	Parotid	9=Paratoid	Parotid, soft tissue
	Oral Cavity	7=Oral cavity	Gum
			Base of tongue
			Lip
			Lower lip
			Upper lip
			Tongue
	Larynx	5=Larynx	Larynx
	Oropharynx	8=Orophaynx	Oropharynx
			Lingual tonsil
			Mandible soft tissue
			Bone of face (Maxillar)
			Masseter
			Oral cavity
	Cheek	3=Cheek	Cheek
	Hypopharynx	4=Hypopharynx	Hypopharynx
	Thyroid & Parathyroid	11=Thyroid & Parathyroid	Thyroid
	Neck	6=Neck	Neck
			Neck Supra-clavicular soft tissues
			Neck, nodes Nos
		12=Other Head & Neck	Chin
			Soft tissue face (non specified region)
			Face specified region
			Nasolabial fold (skin)
			Nostril

Consensus harmonization of primary site

CWS COG EpSSG

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			Face specified region
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			Nostril

Orbit		CUI
	Eyelid	C0015426
	Orbit	C0029180
	Other orbit	C0700042
Head and Neck		
	Scalp	C0036270
	Parotid	C0030580
	Oral cavity	C0226896
	Larynx	C0023078
	Oropharyngeal	C0521367
	Cheek	C0007966
	Hypopharynx	C0020629
	Thyroid and/or parathyroid	C0574117
	Neck	C0027530
	Other head and neck	C0460004

Consensus example: Maximum tumor diameter

Old

- Maximum diameter
  or
- X,Y,Z
  or
- >5 cm vs. <5 cm

Consensus example: Maximum tumor diameter

Old

- Maximum diameter
  or
- X,Y,Z
  or
- >5 cm vs. <5 cm

New

- Discrete measurement (in cm)
  - X (or max diameter if single)
  - Y
  - Z
- Category (if no discrete meas.)
  - <=5 cm
  - >5 cm
  - Unknown

Building pediatric cancer data commons

April 10 COG meeting to engage all disease groups

- Acute myeloid leukemia
- Acute lymphoblastic leukemia
- Bone tumors
- Central nervous system tumors
- Germ cell tumors
- Hodgkin Disease
- Neuroblastoma
- Non-Hodgkin lymphoma
- Renal tumors
- Soft tissue sarcoma

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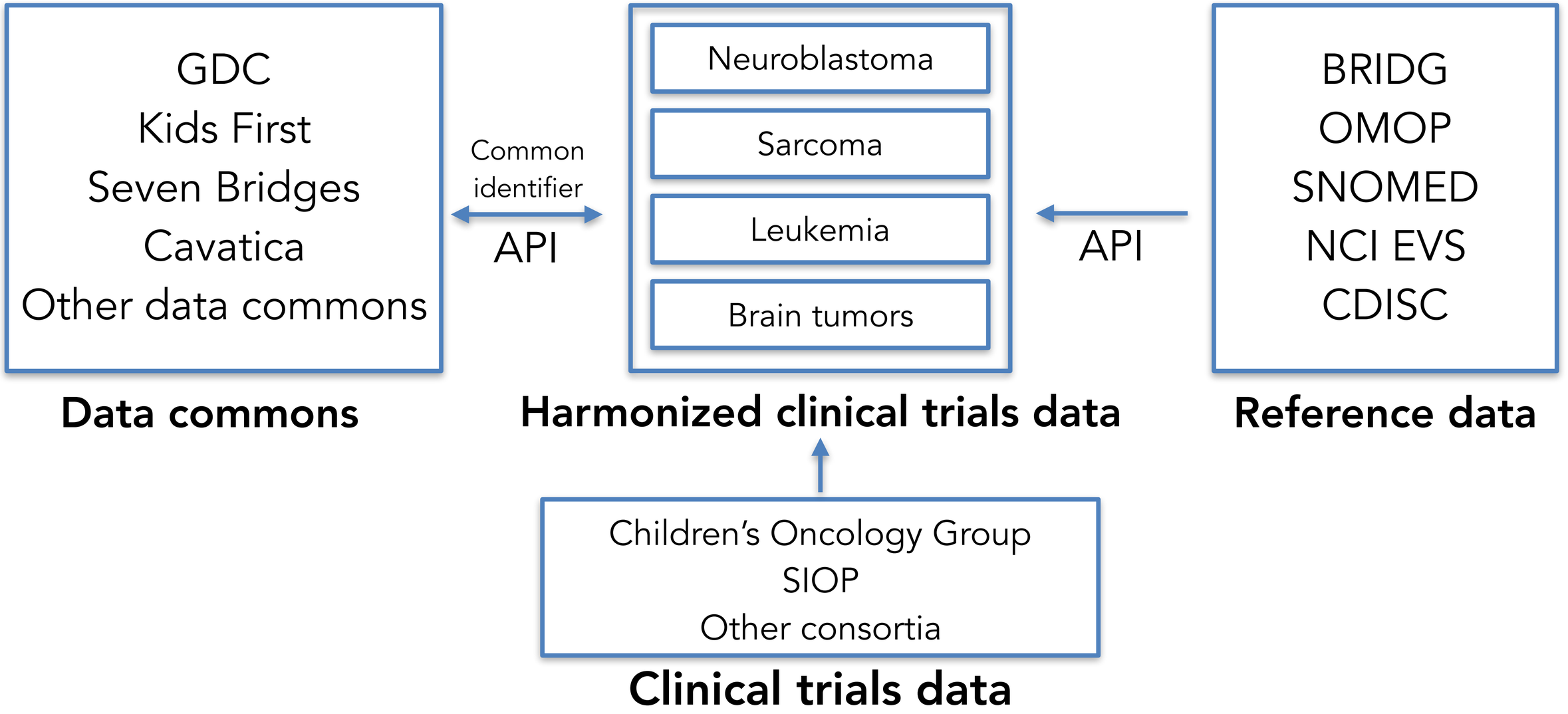
Goal to discuss data and sample collection for all pediatric oncology.

Paradigm for pediatric cancer clinical trials data commons



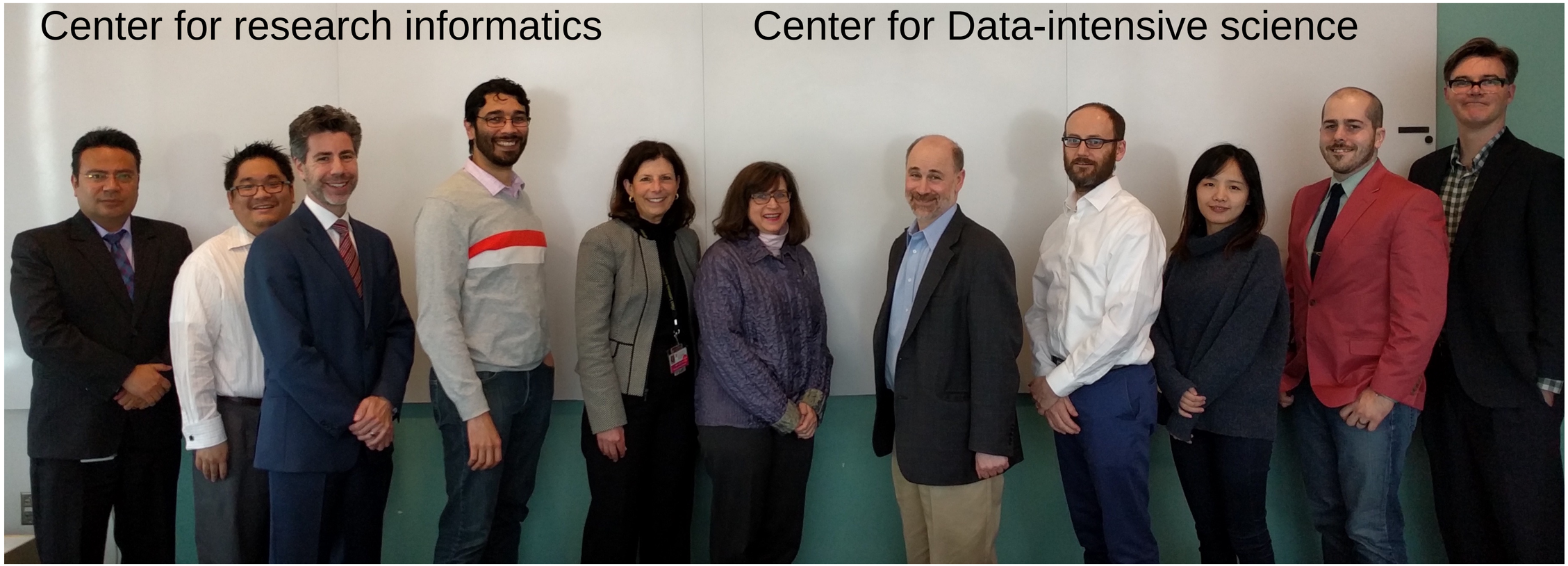
Summary / Call to action

- Pediatric cancer requires novel, genotype-based therapies
- Discovery requires innovations in sample collection, processing, and annotation
- Harmonized data leads to shared phenotype/clinical data
- Data and samples must have universal identifiers
- We must envision data collection and sharing at all stages of care
- The goal is all data from all patients at all times

Center for Research Informatics

Applications - Systems - Bioinformatics - Data warehousing - Clinical trials

Acknowledgements



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St. Baldrick's FOUNDATION
Conquer Childhood Cancers

Alex's Lemonade Stand

The Super Jake Foundation

LITTLE HEROES

Children's Neuroblastoma Cancer Foundation

FOR CHILDHOOD CANCER RESEARCH
Rally! FOUNDATION

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