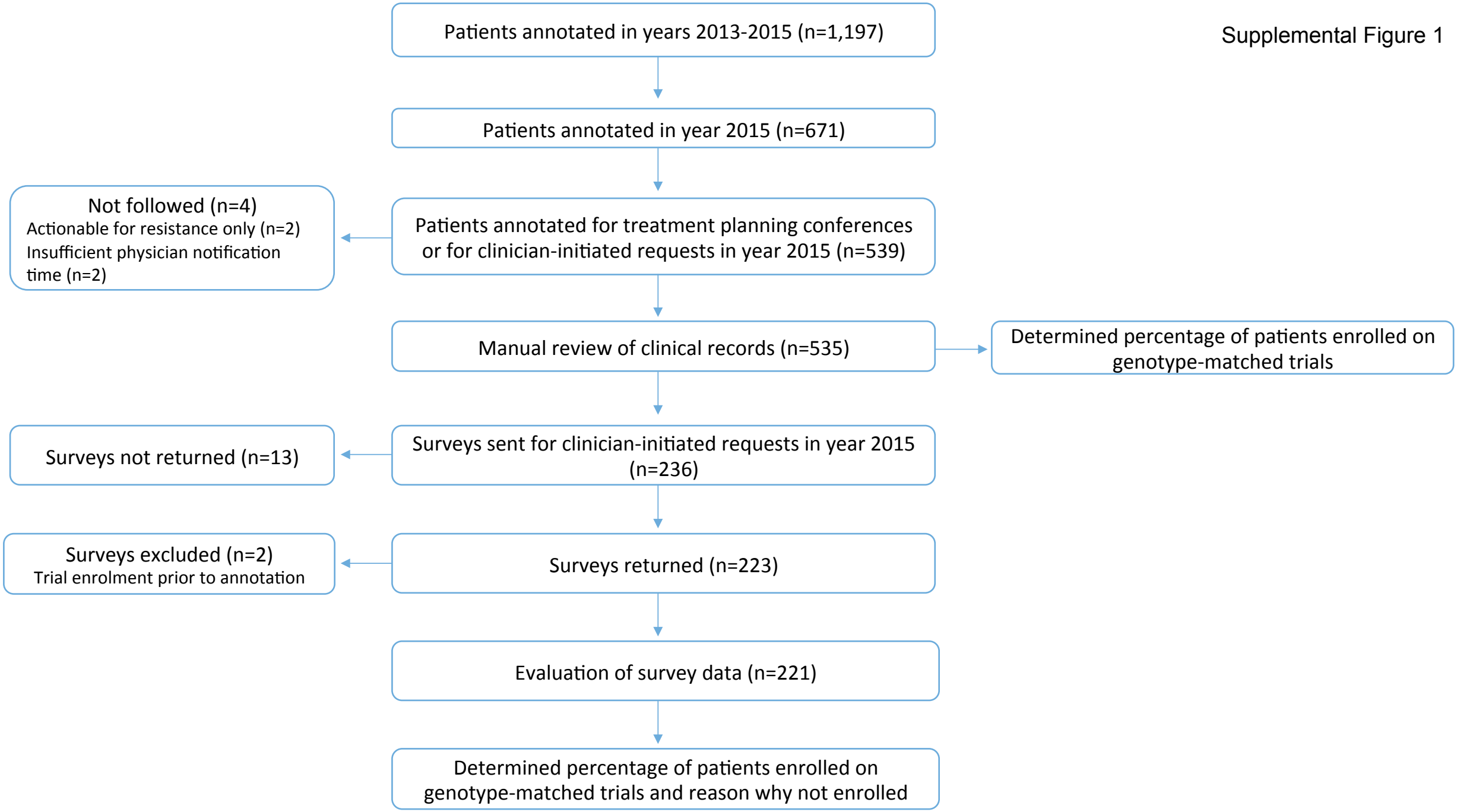
Supplemental Figure 1



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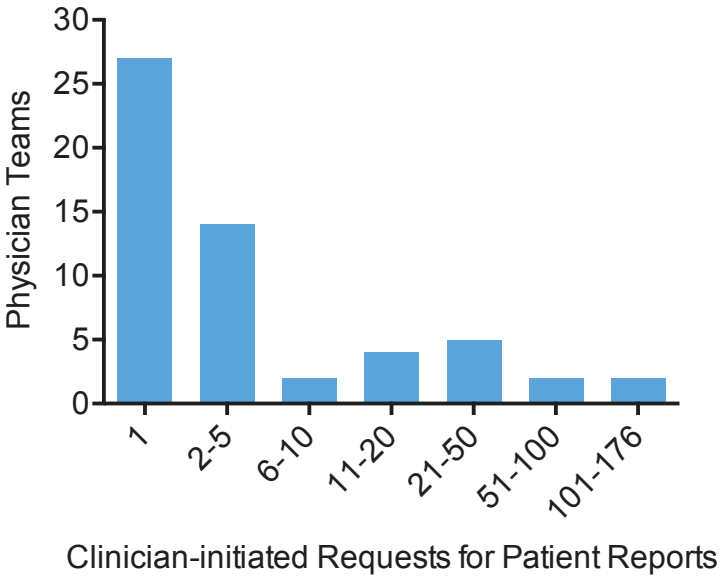
Physician Teams
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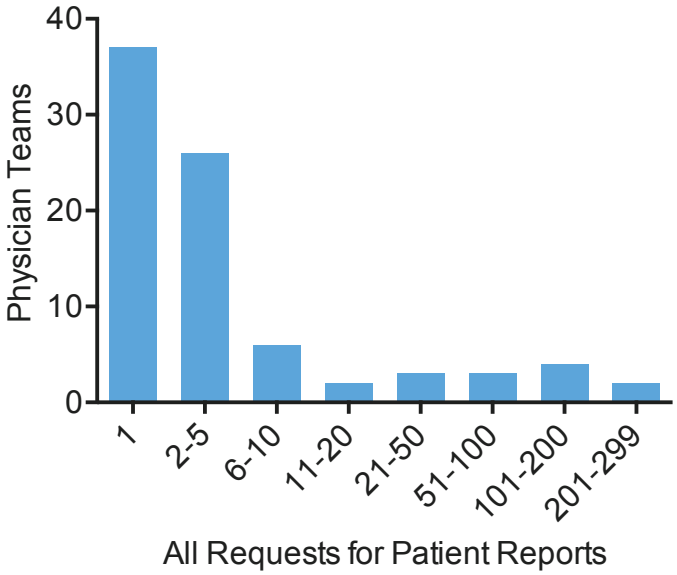
25
20
15
10
5
0
1
2-5
6-10
11-20
21-50
51-100
101-176
Clinician-initiated Requests for Patient Reports

B


Physician Teams
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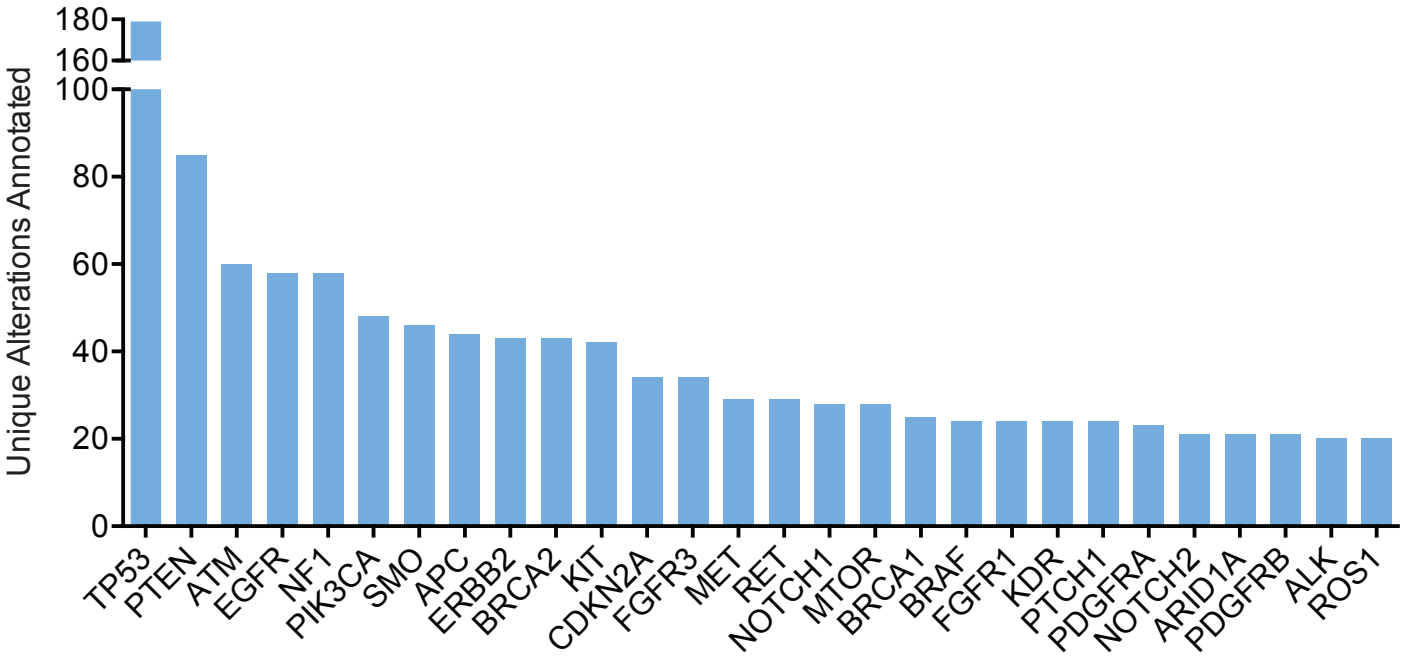
101-200
201-299
All Requests for Patient Reports

Supplemental Figure 3



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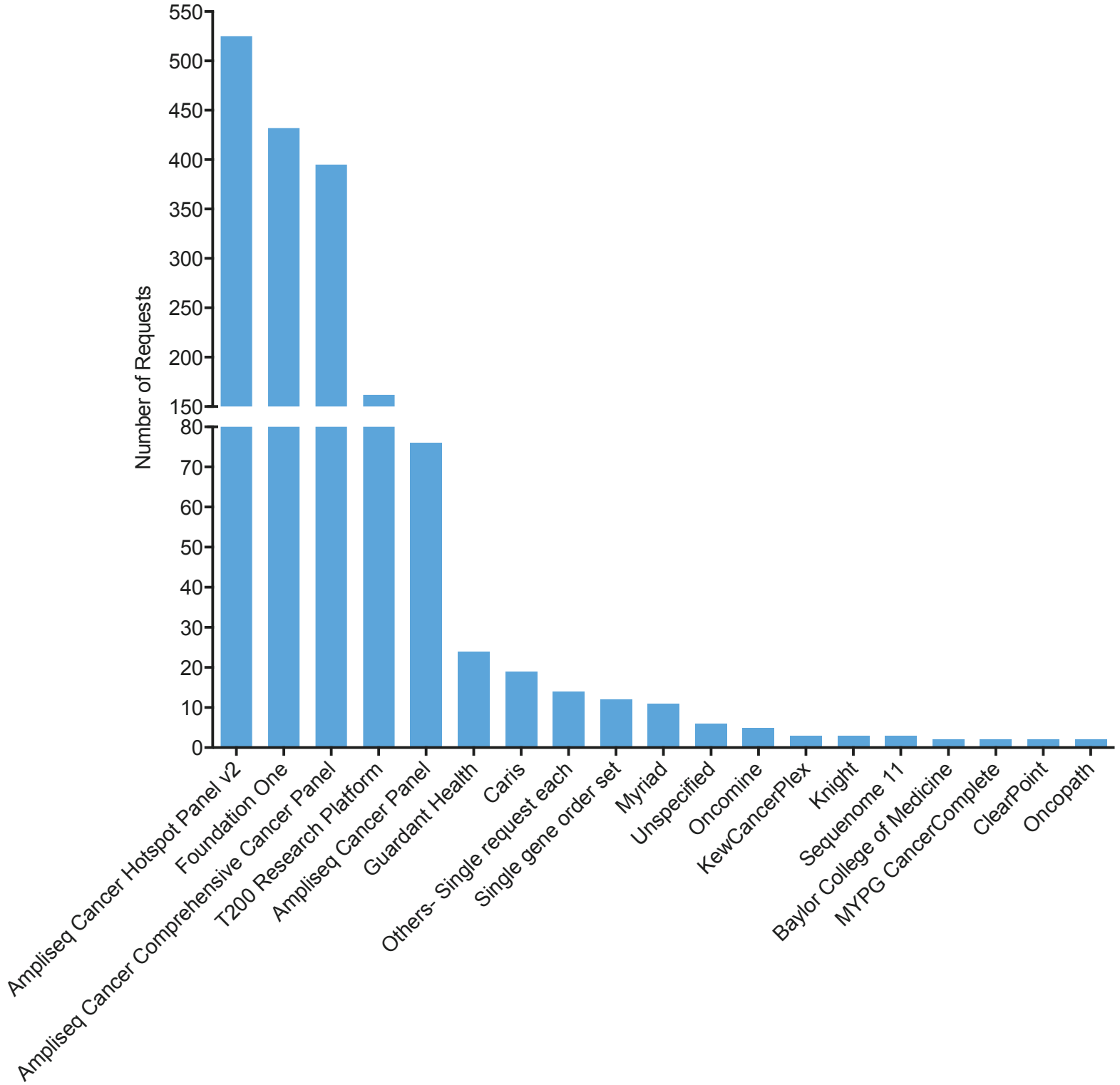

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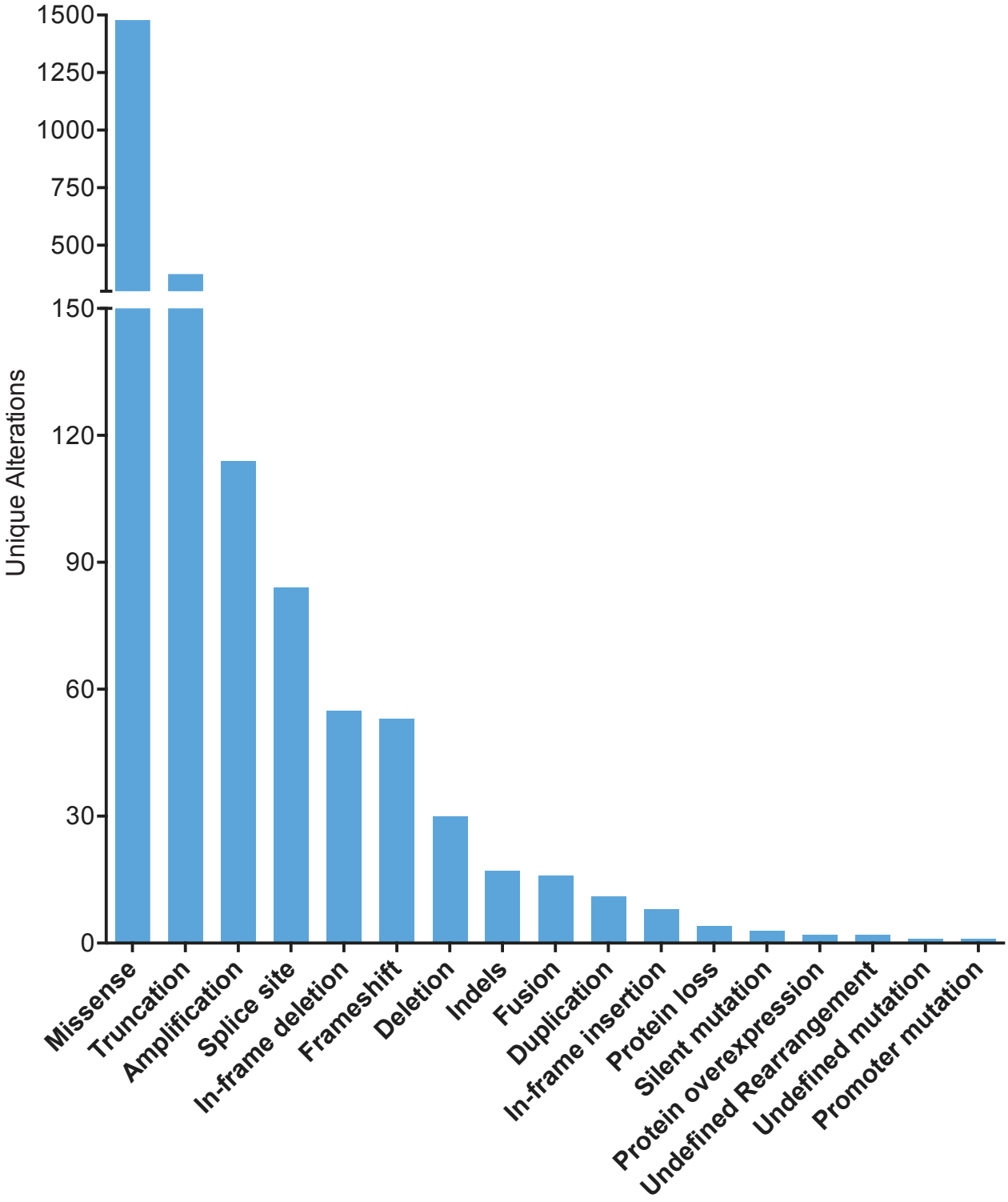

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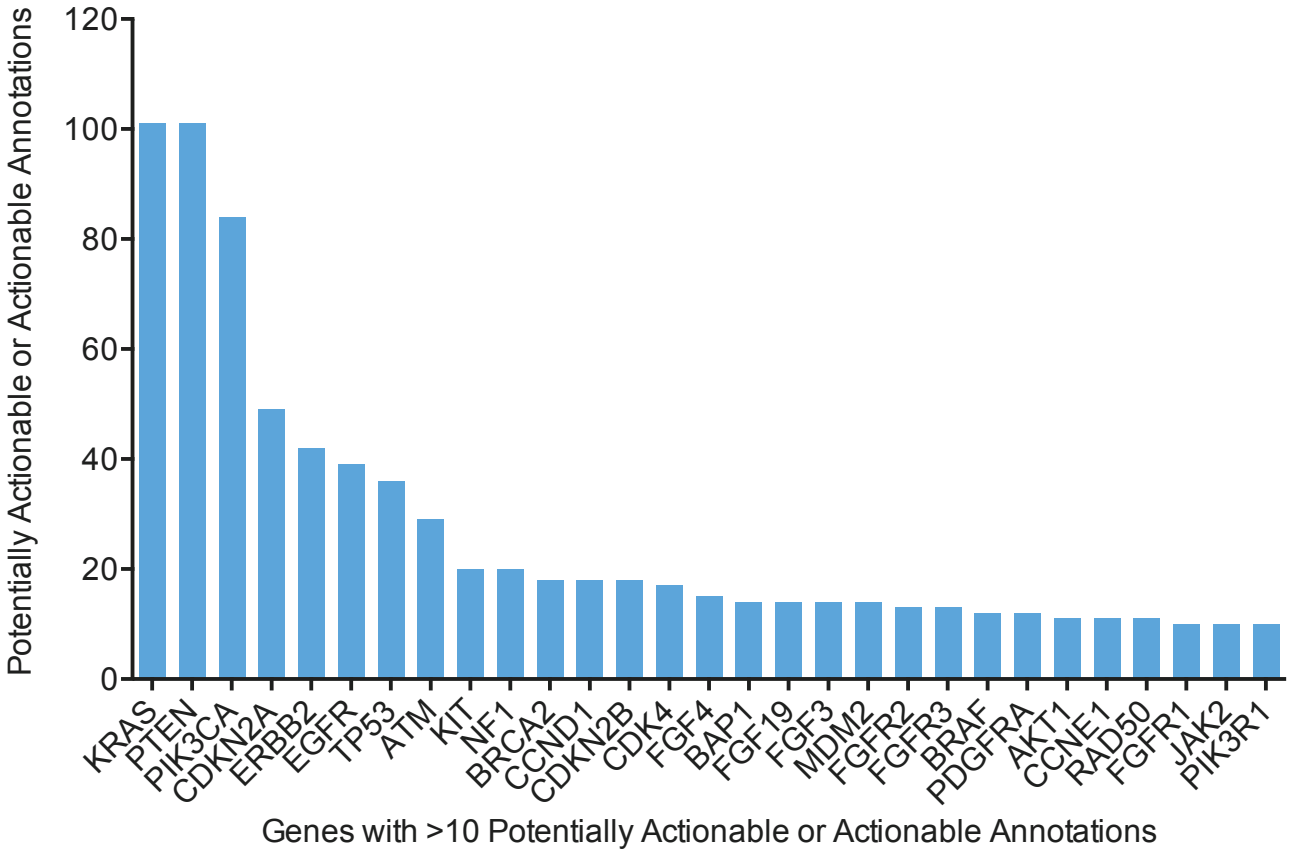
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60
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PTEN
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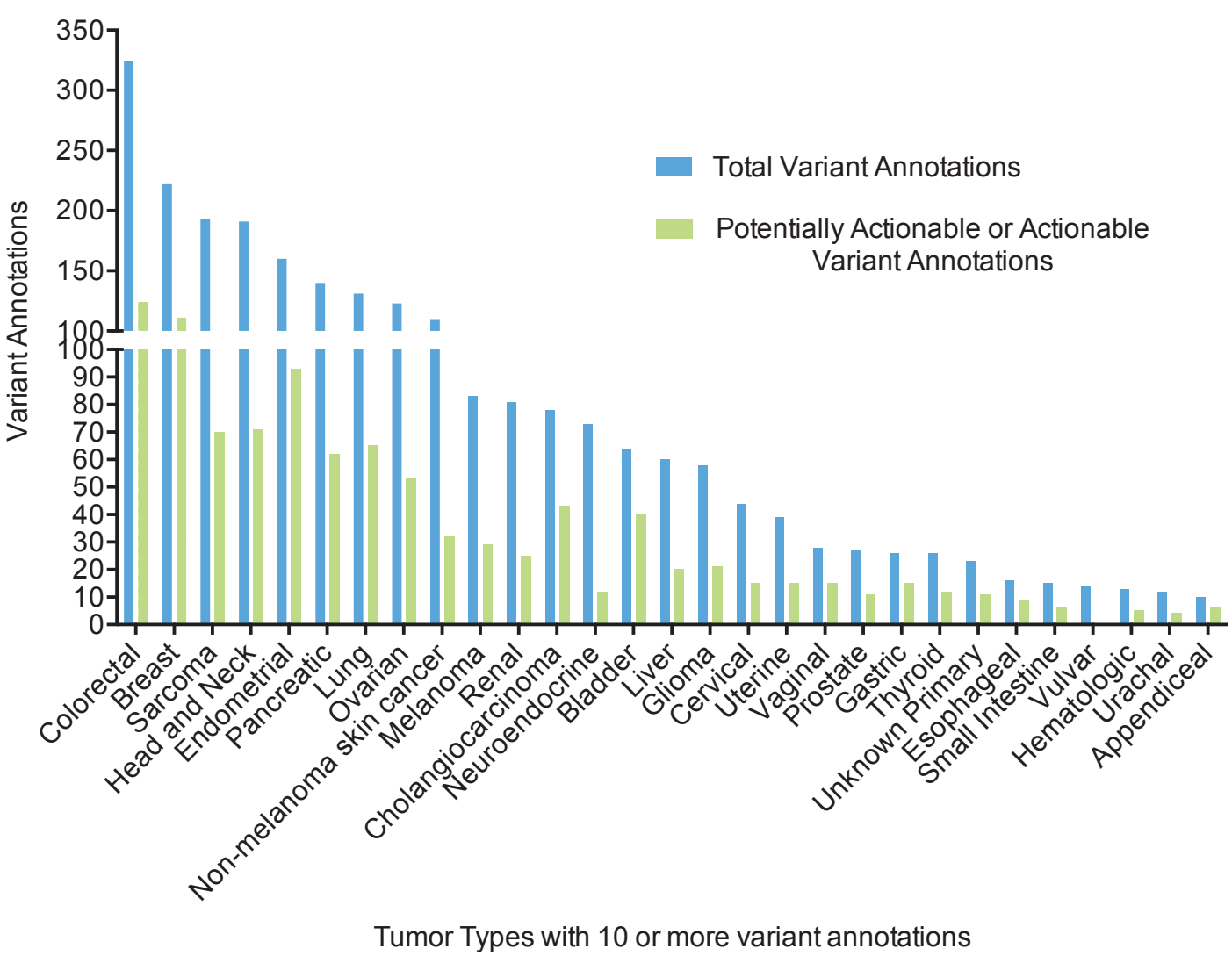
CDKN2A
ERBB2
EGFR
TP53
ATM
KIT
NF1
BRCA2
CCND1
CDKN2B
CDK4
FGF4
BAP1
FGF19
FGF3
MDM2
FGFR2
FGFR3
BRAF
PDGFRA
AKT1
CCNE1
RAD50
FGFR1
JAK2
PIK3R1
Genes with >10 Potentially Actionable or Actionable Annotations

B


Variant Annotations
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150
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100
90
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70
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40
30
20
10
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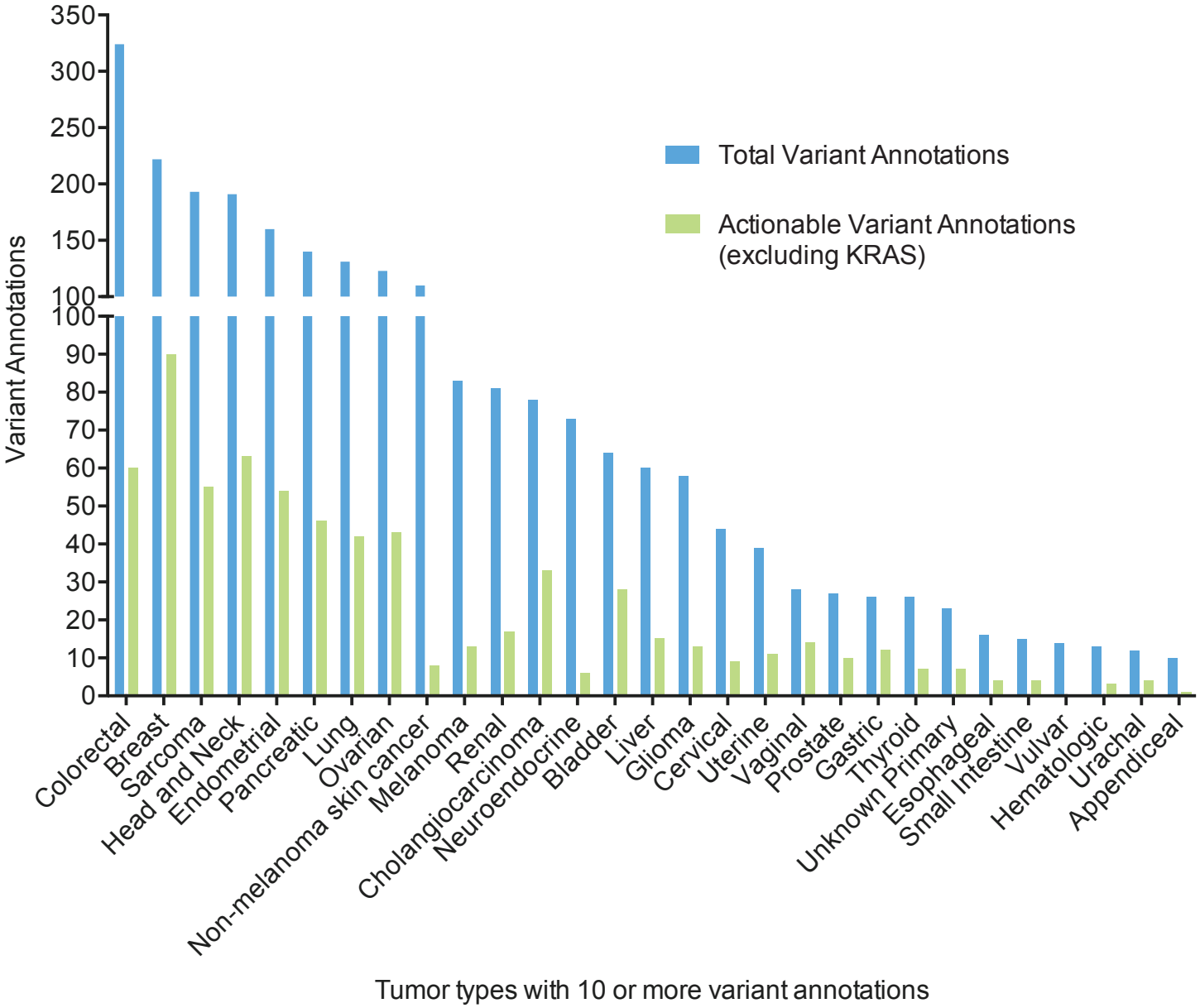
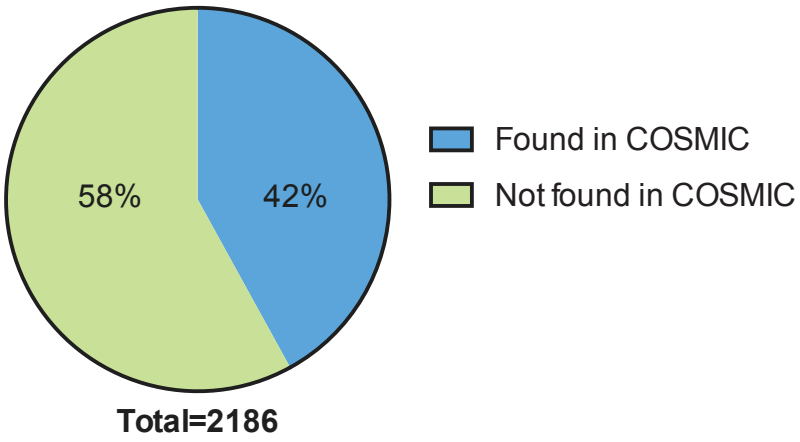
Total Variant Annotations
Potentially Actionable or Actionable Variant Annotations
Colorectal
Breast
Sarcoma
Head and Neck
Endometrial
Pancreatic
Lung
Ovarian
Non-melanoma skin cancer
Melanoma
Renal
Cholangiocarcinoma
Neuroendocrine
Bladder
Liver
Glioma
Cervical
Uterine
Vaginal
Prostate
Gastric
Thyroid
Unknown Primary
Esophageal
Small Intestine
Vulvar
Hematologic
Urachal
Appendiceal
Tumor Types with 10 or more variant annotations

Supplemental Figure 7

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Supplemental Table 1.

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
ABL1	Activating mutations, gene amplification, or BCR-ABL1 fusion	Treatment with ABL or BCR-ABL inhibitors
ABL2	Activating mutations or gene amplification	Treatment with ABL inhibitors
AKT1	Activating mutations or gene amplification	Treatment with AKT or mTOR inhibitors
AKT2	Activating mutations or gene amplification	Treatment with AKT or mTOR inhibitors
AKT3	Activating mutations or gene amplification	Treatment with AKT or mTOR inhibitors
ALK	Activating mutations, gene amplification, or gene fusions	Treatment with ALK inhibitors
AR	Specific mutations, splicing variants, and gene amplification	Resistance to anti-hormone therapy
ARAF	Activating mutations	Treatment with RAF inhibitor
ARID1A	Loss of ARID1A function mutations or deletion	Treatment with PARP inhibitors
ATM	Inactivating mutations or deletions	Treatment with PARP inhibitors
ATR	Inactivating mutations or deletions	Treatment with PARP inhibitors
AURKA	Activating mutations or gene amplification	Treatment with AURKA inhibitors
AURKB	Activating mutations or gene amplification	Treatment with AURKB inhibitors
AURKC	Activating mutations or gene amplification	Treatment with AURKC inhibitor
BAP1	Inactivating mutations or deletions	Treatment with HDAC inhibitors
BCL2	Gene amplification or gene fusion	Treatment with BCL2 inhibitor and potential resistance to mTOR inhibitors
	Mutations	Resistance to BCL2 inhibitor
BCR	Fusion with ABL1	Trials selecting for BCR-ABL fusions
BRAF	Activating V600 mutations	Treatment with BRAF/ MEK/ERK inhibitors
	Activating non-V600 mutations	Treatment with MEK and ERK inhibitors
	Intermediate or inactivating mutations	Treatment with pan-RAF or ERK Inhibitors
	Gene amplification	Treatment with MEK, ERK or pan-RAF inhibitors

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
	Fusions	Treatment with MEK, ERK or pan-RAF inhibitors
BRCA1	Inactivating mutations or deletions	Treatment with PARP inhibitors
BRCA2	Inactivating mutations or deletions	Treatment with PARP inhibitors
CBFB	Gene fusions	Clinical trial selection criteria
CCND1	Gene amplification or gene fusion	Treatment with CDK 4/6 inhibitors
CCND2	Gene amplification or gene fusion	Treatment with CDK 4/6 inhibitors
CCND3	Gene amplification or gene fusion	Treatment with CDK 4/6 inhibitors
CCNE1	Gene amplification or gene fusion	Treatment with CDK 2 Inhibitors
CDK4	Activating mutations or gene amplification	Treatment with CDK 4/6 inhibitors
CDK6	Activating mutations or gene amplification	Treatment with CDK 4/6 inhibitors
CDKN1B	Inactivating mutations or deletions	Treatment with CDK 2 Inhibitors
CDKN2A	Inactivating mutations or deletions	Treatment with CDK 4/6 inhibitors
CDKN2B	Inactivating mutations or deletions	Treatment with CDK 4/6 inhibitors
CDKN2C	Inactivating mutations or deletions	Treatment with CDK 4/6 inhibitors
CHEK2	Activating mutations or gene amplification	Treatment with Chk2 inhibitor
CSF1R	Activating mutations or gene amplification	Treatment with CSF1R monoclonal antibody and inhibitors
DDR1	Activating mutations or gene amplification	Treatment with DDR1 inhibitor
DDR2	Activating mutations or gene amplification	Treatment with DDR2 inhibitor
DNMT3A	Mutations	Eligibility factor for specific clinical trials recruiting myelodysplastic or myeloproliferative disorders
DOT1L	Activating mutations or gene amplification	Treatment with DOT1L inhibitor
EGFR	Activating mutations or gene amplification	Treatment with EGFR inhibitors
EMSY	Amplification	Treatment with PARP inhibitors
EPHA3*	Amplification	Treatment with Dasatinib
ERBB2 (HER2)	Activating mutations or gene amplification	Treatment with HER2 inhibitors, monoclonal antibodies, and targeted vaccines
ERBB3 (HER3)	Activating mutations or gene amplification	Treatment with HER3 inhibitors

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
ERBB4 (HER4)	Activating mutations or gene amplification	Treatment with HER4 inhibitors
ESR1	Mutations	Anti-hormone resistance
EZH2	Mutations	Treatment with EZH2 inhibitors
FANCA	Loss of function mutation or deletions	Clinical trial selection criteria
FANCC	Loss of function mutation or deletions	Clinical trial selection criteria
FANCD2	Loss of function mutation or deletions	Clinical trial selection criteria
FANCE	Loss of function mutation or deletions	Clinical trial selection criteria
FANCF	Loss of function mutation or deletions	Clinical trial selection criteria
FANCG	Loss of function mutation or deletions	Clinical trial selection criteria
FANCL	Loss of function mutation or deletions	Clinical trial selection criteria
FGF3	Mutations or amplification	Clinical trial selection criteria
FGF4	Mutations or amplification	Clinical trial selection criteria
FGF6	Mutations or amplification	Clinical trial selection criteria
FGF10	Mutations or amplification	Clinical trial selection criteria
FGF14	Mutations or amplification	Clinical trial selection criteria
FGF19	Mutations or amplification	Clinical trial selection criteria
FGF23	Mutations or amplification	Clinical trial selection criteria
FGFR1	Activating mutations, gene amplification, or gene fusions	Treatment with FGFR1 inhibitors
FGFR2	Activating mutations, gene amplification, or gene fusions	Treatment with FGFR2 inhibitors
FGFR3	Activating mutations, gene amplification, or gene fusions	Treatment with FGFR3 inhibitors
FGFR4	Activating mutations or gene amplification	Treatment with FGFR4 inhibitors
FLT1	Activating mutations or gene amplification	Treatment with FLT1 inhibitors
FLT3	Activating mutations, gene amplification, or gene fusions	Treatment with FLT3 inhibitors
FLT4	Activating mutations or gene amplification	Treatment with FLT4 inhibitors
GNA11	Activating mutations or gene amplification	Treatment with PKC and MEK inhibitors

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
GNAQ	Activating mutations or gene amplification	Treatment with PKC and MEK inhibitors
HDAC9	Activating mutations or gene amplification	Treatment with HDAC9 inhibitors
HGF	Gene amplification	Treatment HGF monoclonal antibody
HRAS	Activating mutations or gene amplification	Treatment with MEK inhibitors
IDH1	Activating mutations	Treatment with IDH1 inhibitors
IDH2	Activating mutations	Treatment with IDH2 inhibitors
IGF1R	Activating mutations or gene amplification	Treatment with IGF1R monoclonal antibodies or inhibitors
IGF2	Gene amplification	Treatment with IGF1R monoclonal antibodies or inhibitors
JAK1	Activating mutations or gene amplification	Treatment with JAK inhibitors
JAK2	Activating mutations or gene amplification	Treatment with JAK inhibitors
JAK3	Activating mutations or gene amplification	Treatment with JAK inhibitors
KDR	Activating mutations or gene amplification	Treatment with KDR inhibitors
KIT	Activating mutations or gene amplification	Treatment with KIT inhibitors
KRAS	Activating mutations, gene amplification, or gene fusions	Treatment with MEK Inhibitors
MAP2K1	Activating mutations or gene amplification	Treatment with MEK Inhibitors
MAP2K2	Activating mutations or gene amplification	Treatment with MEK Inhibitors
MAP2K4	Activating mutations or gene amplification	Treatment with JNK1 inhibitor
MAP3K1	Activating mutations or gene amplification	Treatment with JNK1 inhibitor
MAP3K4	Activating mutations or gene amplification	Treatment with JNK1 inhibitor
MAPK1	Activating mutations or gene amplification	Treatment with p38 MAPK1 inhibitor
MAPK8	Activating mutations or gene amplification	Treatment with JNK1 inhibitor

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
MDM2	Activating mutations or gene amplification	Treatment with MDM2 inhibitor or Nutlins that inhibit MDM2-p53 interaction.
MET	Activating mutations, gene amplification, or gene fusion	Treatment with MET inhibitors
MLL (KMT2A)	Gene fusions	Treatment with MEK, VEGFR2, AURKA, and DOT1L inhibitors.
MPL	Activating mutations	Treatment with JAK2 inhibitors.
MRE11A	Loss of function Mutation or Deletions	Treatment with PARP inhibitors
MTOR	Activating mutations or gene amplification	Treatment with mTOR inhibitors
	Selected binding domain mutations	Resistance to rapalogs
MYCN	Gene amplification	Treatment with BET inhibitors
NBN	Loss of function mutation or deletions	Treatment with PARP inhibitors
NF1	Inactivating mutations or deletions	Treatment with PI3K pathway inhibitors (PI3K/AKT/MTOR), MAPK pathway inhibitors (RAF/MEK/ERK), or HSP90 inhibitors
NF2	Inactivating mutations or deletions	Treatment with PI3K pathway inhibitors (PI3K/AKT/MTOR), MAPK pathway inhibitors (RAF/MEK/ERK), HSP90 inhibitors, or FAK inhibitors
NOTCH1	Activating mutations, gene amplification, or gene fusion	Treatment with Gamma Secretase inhibitors (GSIs)
NOTCH2	Activating mutations or gene amplification	Treatment with Gamma Secretase inhibitors (GSIs)
	Gene fusion	Resistance to Gamma Secretase inhibitors (GSIs)
NOTCH3	Activating mutations or gene amplification, or gene fusion	Treatment with Gamma Secretase inhibitors (GSIs)
NOTCH4	Activating mutations or gene amplification	Treatment with Gamma Secretase inhibitors (GSIs)
NPM1	Mutations	Correlate with positive response to all-trans retinoic acid therapy and chemotherapy in AML.
NRAS	Activating mutations or gene amplification	Treatment with MEK inhibitors
NTRK1	Activating mutations, gene amplification, gene fusions	Treatment with NTRK1 (TrkA) inhibitor

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
NTRK2	Activating mutations or gene amplification	Treatment with NTRK2 (TrkB) inhibitor
NTRK3	Activating mutations, gene amplification, gene fusions	Treatment with NTRK3 (TrkC) inhibitor
PALB2	Mutations or homozygous deletion	Treatment with PARP inhibitors
PDGFB	Gene fusions	Treatment of DFSP tumors with t(17;22) translocation with Imatinib.
PDGFRA	Activating mutations, gene amplification, or gene fusions	Treatment with PDGFRA inhibitors
PDGFRB	Activating mutations, gene amplification, or gene fusions	Treatment with PDGFRB inhibitors
PIK3CA	Activating mutations or gene amplification	Treatment with PI3K, AKT, or mTOR inhibitors
PIK3CB	Activating mutations or gene amplification	Treatment with PIK3CB inhibitors
PIK3CD	Activating mutations or gene amplification	Treatment with PIK3CD inhibitors
PIK3R1	Inactivating mutations	Treatment with PI3K, AKT or mTOR inhibitors
PIK3R2	Inactivating mutations	Treatment with PI3K, AKT or mTOR inhibitors
PML	Gene fusions with RARA	Treatment of PML-RARA tumors with all trans retinoic acid (ATRA) or HDAC inhibitors
PTCH1	Inactivating mutations or deletions	Treatment with SMO inhibitors
PTEN	Inactivating mutations or deletions	Treatment with p110beta, AKT, or mTOR inhibitors
PTPN11	Activating mutations or gene amplification	Treatment with MEK Inhibitors
RAD50	Inactivating mutations or deletions	Treatment with PARP inhibitors
RAF1	Gene amplification	Potential resistance to RAF inhibitors
	Gene amplification, activating mutations, or gene fusions	Treatment with MEK inhibitors
	Deletion or loss-of-function mutations	Resistance to Dasatinib
RARA	Gene fusions with PML or co-amplification with HER2	Treatment of ERα(-) breast cancer with HER2/RARA co-amplification with ATRA and anit-HER2 therapy. Treatment of PML-RARA tumors with ATRA or HDAC inhibitors

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
RET	Activating mutations, gene amplification, or gene fusions	Treatment with Ret inhibitors
RNF43	Inactivating Mutations and Gene Deletions	Treatment to Porcupine inhibitors and selection criteria for trial enrollment
RICTOR	Activating mutations or gene amplification	Treatment with AKT or mTORC2 inhibitors
ROS1	Gene fusions	Treatment with Crizotanib or ROS1/ALK inhibitor, PF-06463922
	Mutations, Amplification, and Gene Fusion	Clinical trial selection criteria
RSPO	Gene fusions	Sensitivity to Wnt signaling inhibitor and selection criteria for trial enrollment
RUNX1	Gene fusions	Trials selecting for RUNX1 gene fusions. Treatment with AML1(RUNX1)-ETO chemical inhibitors, cotricosteroids, and methylprednisolone.
SMARCB1	Loss of function mutation or deletions	Clinical trial selection criteria
SDHA	Loss of function mutation or deletions	Clinical trial selection criteria
SDHB	Loss of function mutation or deletions	Clinical trial selection criteria
SDHC	Loss of function mutation or deletions	Clinical trial selection criteria
SDHD	Loss of function mutation or deletions	Clinical trial selection criteria
SMO	Activating mutations or gene amplification	Treatment with SMO inhibitors
SRC	Activating mutations or gene amplification	Treatment with SRC inhibitors
STK11	Inactivating mutations or deletions	Treatment with mTOR inhibitors or AMPK activators
SYK	Activating mutations or gene amplification	Treatment with Syk inhibitors
TET2	Mutations	"High risk" factor of myelodysplastic or myeloproliferative disorders required for trial enrollment.

Gene	Potentially Actionable Alterations	Potential Therapeutic Implications
TOP2A	Copy number changes	Treatment with topoisomerase 2A inhibitors
TSC1	Inactivating mutations or deletions	Treatment with mTOR inhibitors
TSC2	Inactivating mutations or deletions	Treatment with mTOR inhibitors