Genetics Primer – Genetics for Central Cancer Registries

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Topics to be Covered

- Why collect genomic tumor data?
- Genomic data routinely generated for clinical oncology
- A central registry approach to surveillance of genomic data
- Central registry infrastructure needed

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Why Collect Genomic Tumor Data?

A Public Health Cancer Surveillance Imperative

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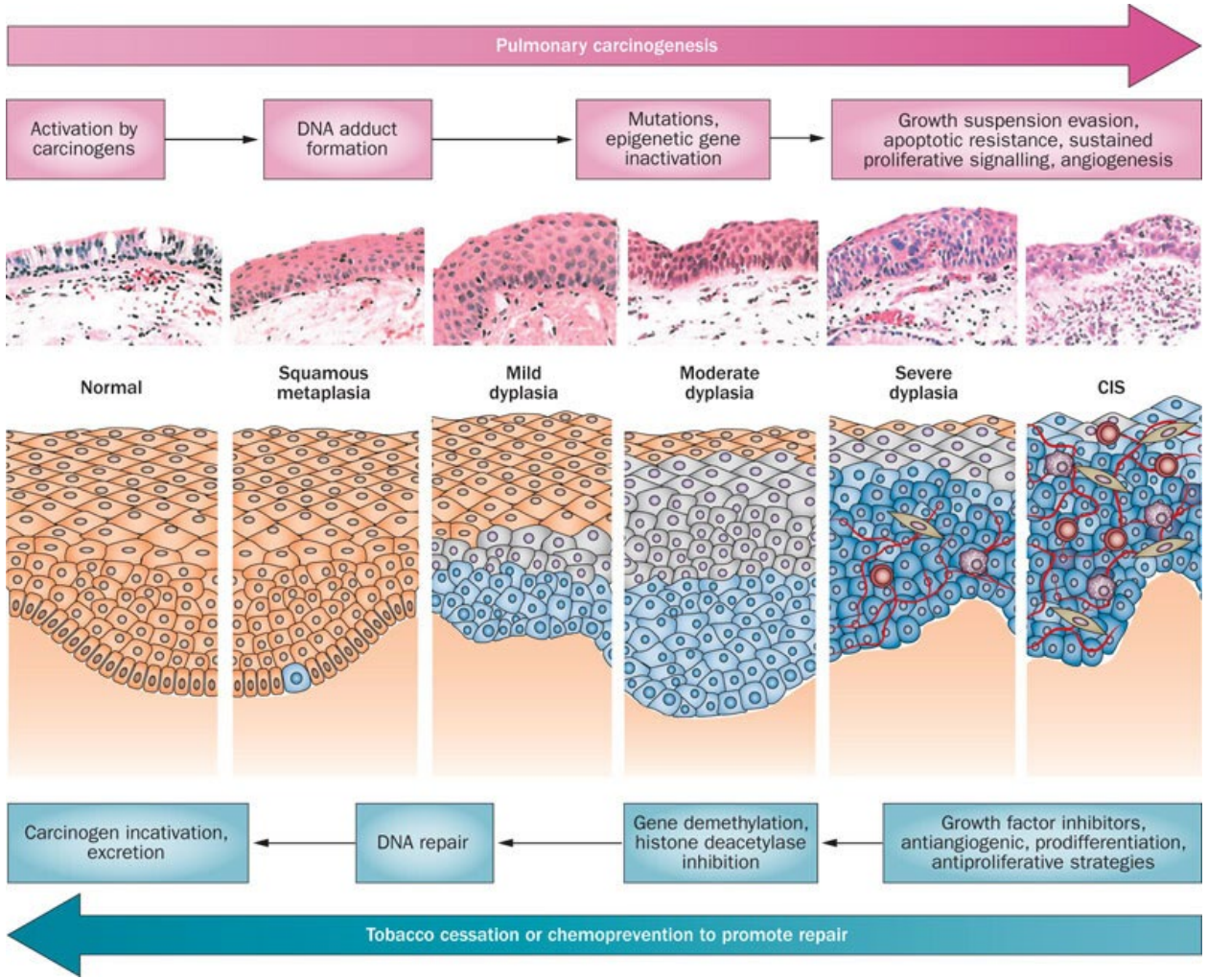
Carcinogenesis: A Genomic Process



Keith, R., Miller, Y. Lung cancer chemoprevention: current status and future prospects. *Nat Rev Clin Oncol* **10**, 334–343 (2013). https://doi.org/10.1038/nrclinonc.2013.64

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NSCLC Treatment Before Genomics

2-drug platinum-based regimens

Stratification

Performance status
0-1 vs. 2

Weight loss in previous 6 months
<5% vs. ≥5%

Disease stage IIIB or IV

Presence or absence of brain metastases

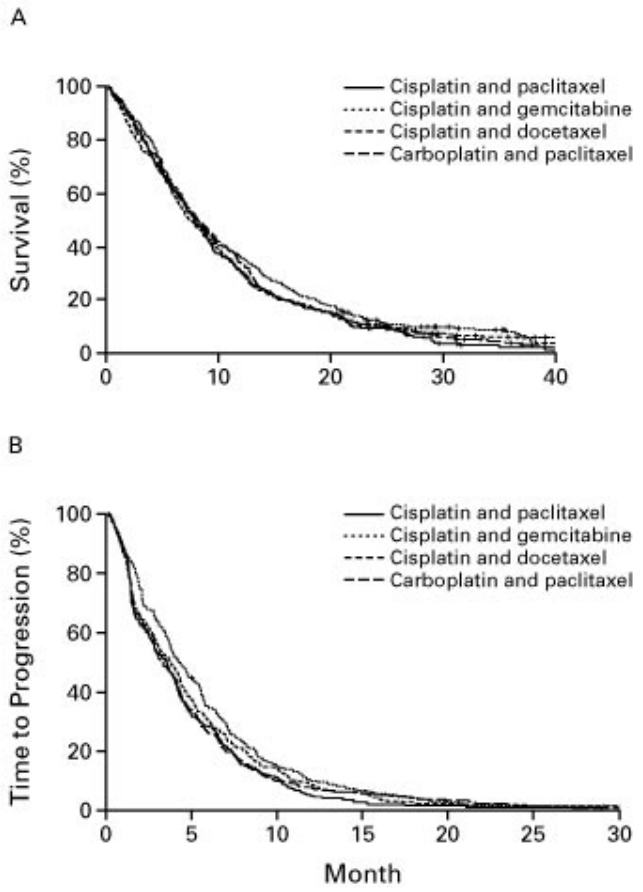
RANDOMIZE

Arm A: Cisplatin + Paclitaxel
Paclitaxel: 135 mg/m² over 24 hours, day 1
Cisplatin: 75 mg/m² day 2
3-week cycle

Arm B: Cisplatin + Gemcitabine
Gemcitabine: 1,000 mg/m² days 1,8,15
Cisplatin: 100 mg/m² day 1
4-week cycle

Arm C: Cisplatin + Docetaxel
Docetaxel: 75 mg/m² day 1
Cisplatin: 75 mg/m² day 1
3-week cycle

Arm D: Carboplatin + Paclitaxel
Paclitaxel: 225 mg/m² over 3 hours, day 1
Carboplatin: AUC 6.0 day 1
3-week cycle



Median survival
8 mo.

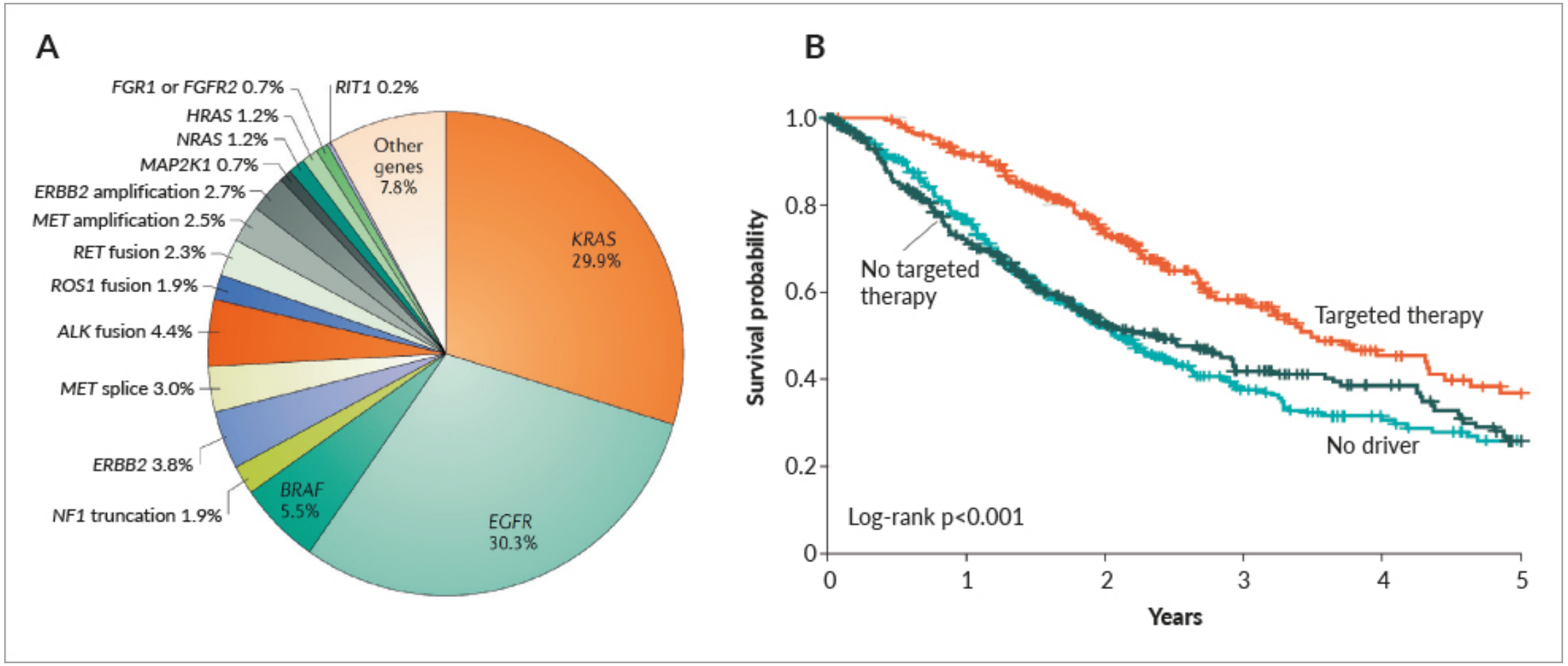
Response rate
19%

Median time to tumor progression (TTP) 3.7 mo.

Schiller JH. NEJM 2002; 346:92-98

Slide courtesy of Dr. Jill Kolesar

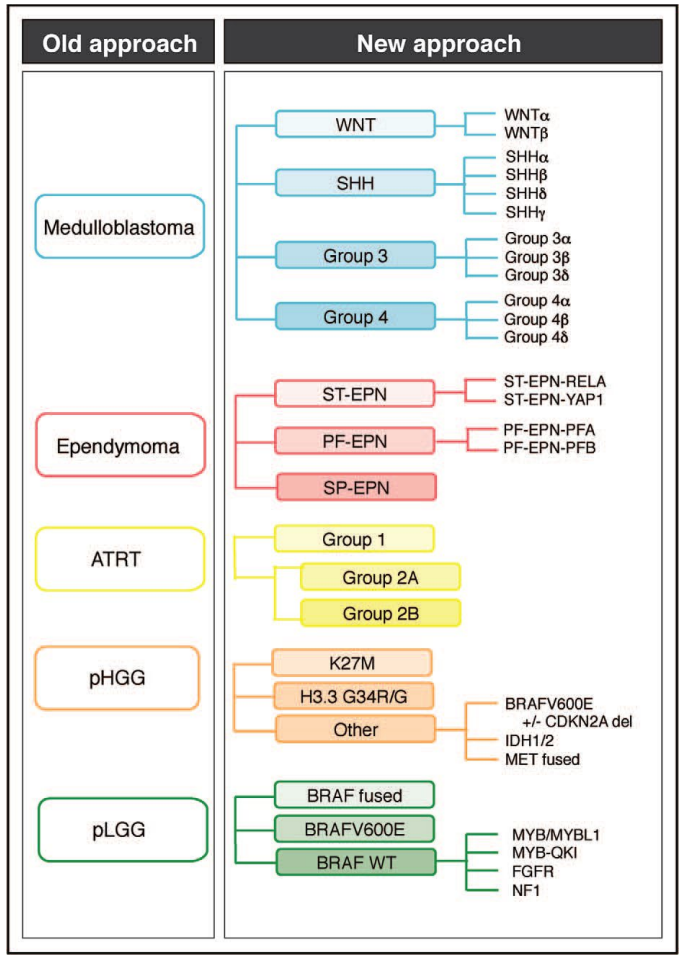
Current and Future Targets in NSCLC



Meisel 2020, Healthbook

Slide courtesy of Dr. Jill Kolesar

Shifting Paradigm in Treatment of Pediatric Brain Tumors



- Medulloblastoma – Subgroup of Embryonal Tumors
- Ependymoma – A type of CNS Tumor
- Atypical Teratoid/Rhabdoid Tumors (ATRT) – Rhabdoid tumors of the CNS, common in very young children
- Pediatric High-Grade Glioma (pHGG) – heterogenous malignant tumors
- Pediatric Low-Grade Glioma (pLGG) – histologically diverse benign tumors of glial origin

Guerreiro Stucklin, Ana S, Ramaswamy, Vijay, Daniels, Craig, and Taylor, Michael D. "Review of Molecular Classification and Treatment Implications of Pediatric Brain Tumors." Current Opinion in Pediatrics. 30.1 (2018): 3-9. Web.

Genomic Data Capture: A Public Health Imperative

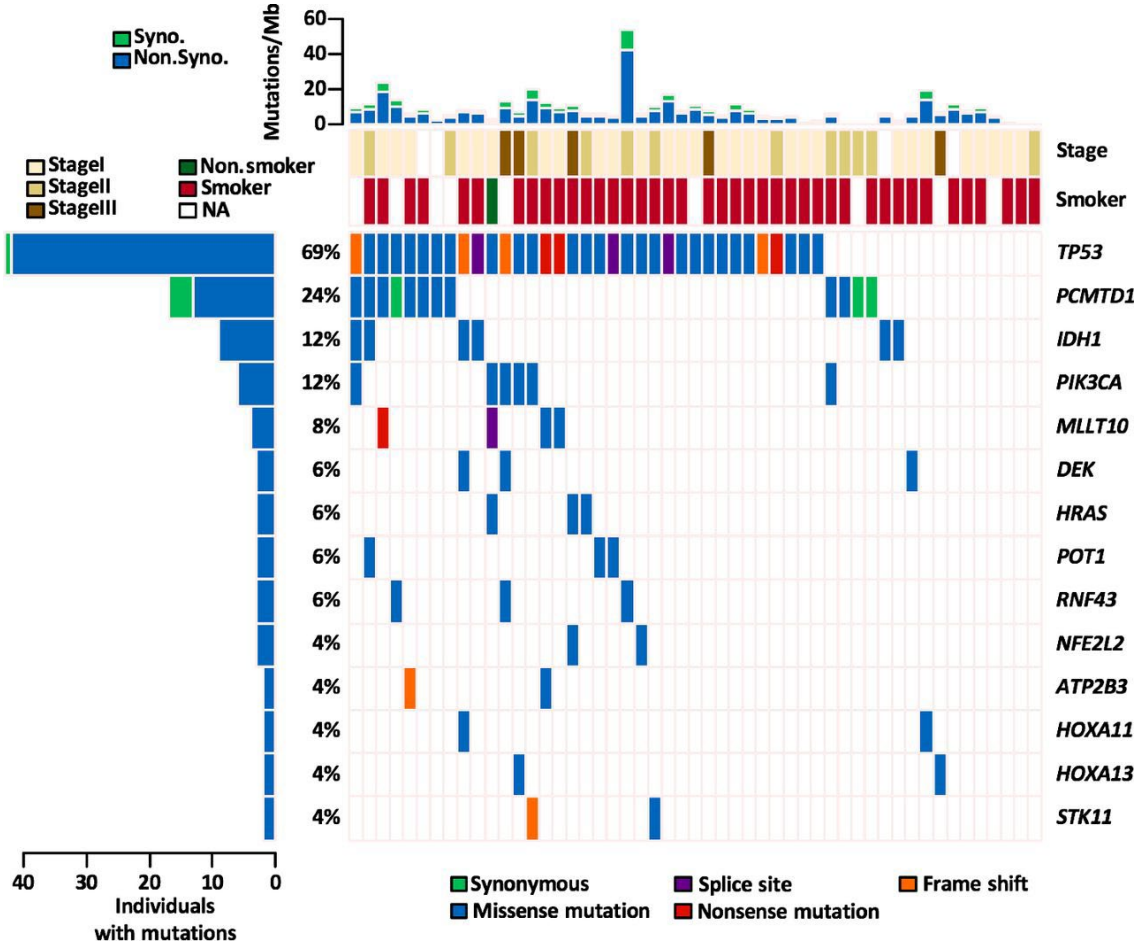
How do genomic variants impact treatment, treatment response, and survival in the population?

Do disparities exist in patients who have access to molecular testing and targeted therapy?

Do molecular profiles vary by geography, race/ethnicity, or socio-economic status?

Can genetic testing be used to identify cancer risk, diagnose cancer sooner or prevent cancer?

Appalachian KY vs TCGA Mutations in Whole Exome Sequencing of Squamous Cell Lung Cancer (N=51)



This study identified an increased percentage of IDH1 and PCMTD1 mutations in SQCC arising in the Appalachian KY residents versus TCGA, with population-specific implications for the personalized treatment of this disease.

Characterization of Squamous Cell Lung Cancers from Appalachian Kentucky. Jinpeng Liu, Thilakam Murali, Tianxin Yu, Chunming Liu, Theru A. Sivakumaran, Hunter N.B. Moseley, Igor B. Zhulin, Heidi L. Weiss, Eric B. Durbin, Sally R. Ellingson, Jinze Liu, Bin Huang, Brent J. Hallahan, Craig M. Horbinski, Kurt Hodges, Dana L. Napier, Thèrése Bocklage, Joseph Mueller, Nathan L. Vanderford, David W. Fardo, Chi Wang and Susanne M. Arnold. Cancer Epidemiol Biomarkers Prev February 1 2019 (28) (2) 348-356; DOI: 10.1158/1055-9965.EPI-17-0984

EGFR Testing and Erlotinib Use in Non-Small Cell Lung Cancer Patients in Kentucky

Modeling Had EGFR Testing		
Variable	**OR (95% CI)**	**P-Value**
Age (ref = 75+)		0.0001
20–49	4.15 (2.17–7.91)	
50–64	1.76 (1.16–2.67)	
65–74	1.39 (0.98–1.98)	
Sex (ref = Male)		0.0142
Female	1.44 (1.08–1.93)	
Appalachian Status (ref = Non-Appalachia/Metro)		0.0011
Appalachian/Metro	0.67 (0.28–1.59)	
Appalachian/Non-Metro	0.51 (0.36–0.73)	
Non-Appalachian/Non-Metro	0.60 (0.40–0.89)	
Year of Diagnosis (ref = 2007)		<0.0001
2008	3.81 (0.43–34.68)	
2009	22.30 (3.00–165.41)	
2010	58.56 (8.12–422.26)	
2011	113.47 (15.81–814.21)	
Insurance (ref = Private)		<0.0001
Medicaid	0.19 (0.09–0.40)	
Medicare	0.61 (0.44–0.84)	
Smoking (ref = No)		0.0266
Yes	0.54 (0.32–0.91)	
Unknown	0.83 (0.42–1.66)	

OR = odds ratio; CI = confidence interval; (ref) = reference variable

https://doi.org/10.1371/journal.pone.0237790.t003

Modeling Receive Erlotinib		
Variable	**OR (95% CI)**	**P-Value**
Age (ref = 75+)		0.0077
20–49	2.05 (1.02–4.14)	
50–64	1.97 (1.31–2.95)	
65–74	1.56 (1.10–2.21)	
Sex (ref = Male)		0.0045
Female	1.49 (1.13–1.97)	
Insurance (ref = Private)		0.0074
Medicaid	0.55 (0.33–0.93)	
Medicare	0.63 (0.46–0.87)	
Poverty (ref = Low)		0.0081
Moderate	1.90 (1.24–2.91)	
High	1.84 (1.22–2.79)	
Very High	1.33 (0.85–2.09)	

OR = odds ratio; CI = confidence interval; (ref) = reference variable

https://doi.org/10.1371/journal.pone.0237790.t004

Larson KL, Huang B, Chen Q, Tucker T, Schuh M, et al. (2020) EGFR testing and erlotinib use in non-small cell lung cancer patients in Kentucky. PLOS ONE 15(8): e0237790. https://doi.org/10.1371/journal.pone.0237790

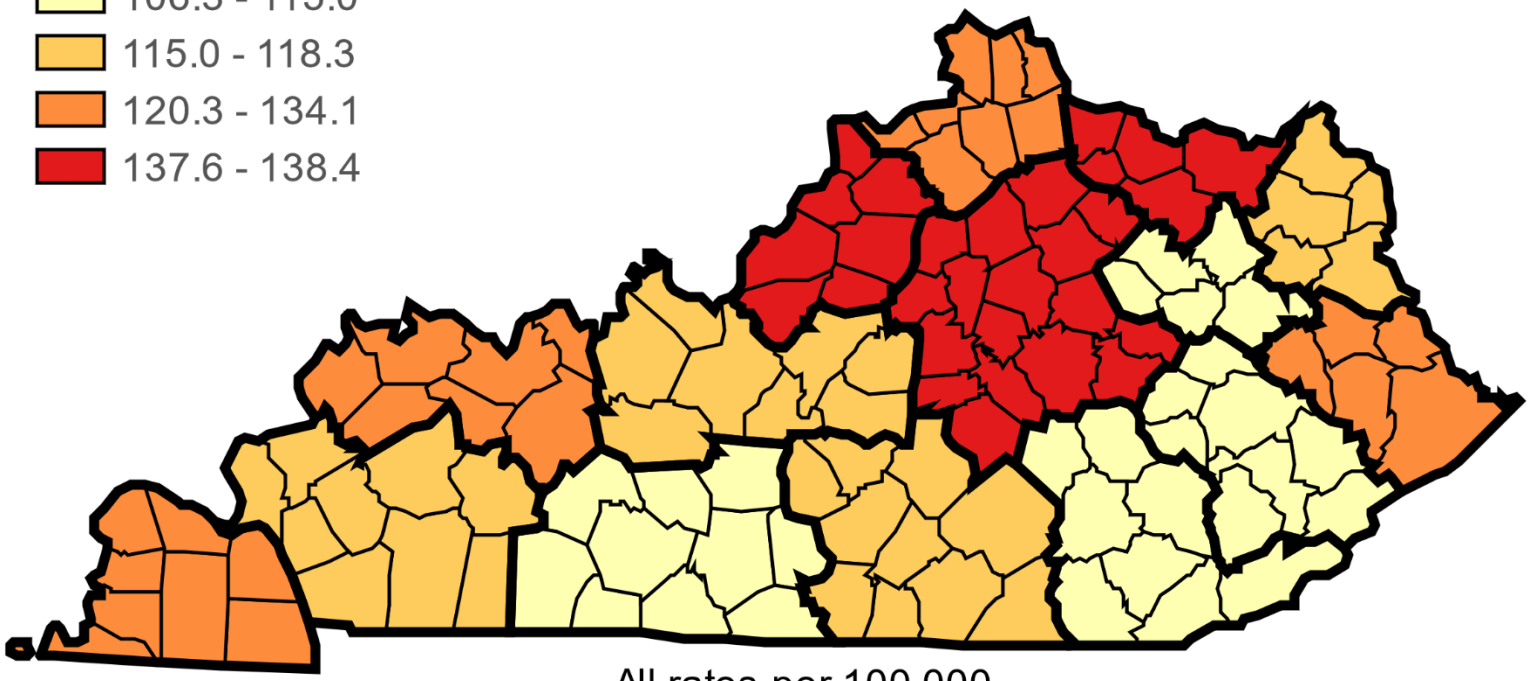
Age-Adjusted Invasive Cancer Incidence Rates in Kentucky

Breast, Female, 2014 - 2018

By Area Development District

Age-Adjusted to the 2000 U.S. Standard Million Population

Kentucky Rate: 128.0 / per 100,000



All rates per 100,000.

Data accessed July 26, 2022. Based on data released Nov 2021.

Age-Adjusted Invasive Cancer Incidence Rates in Kentucky

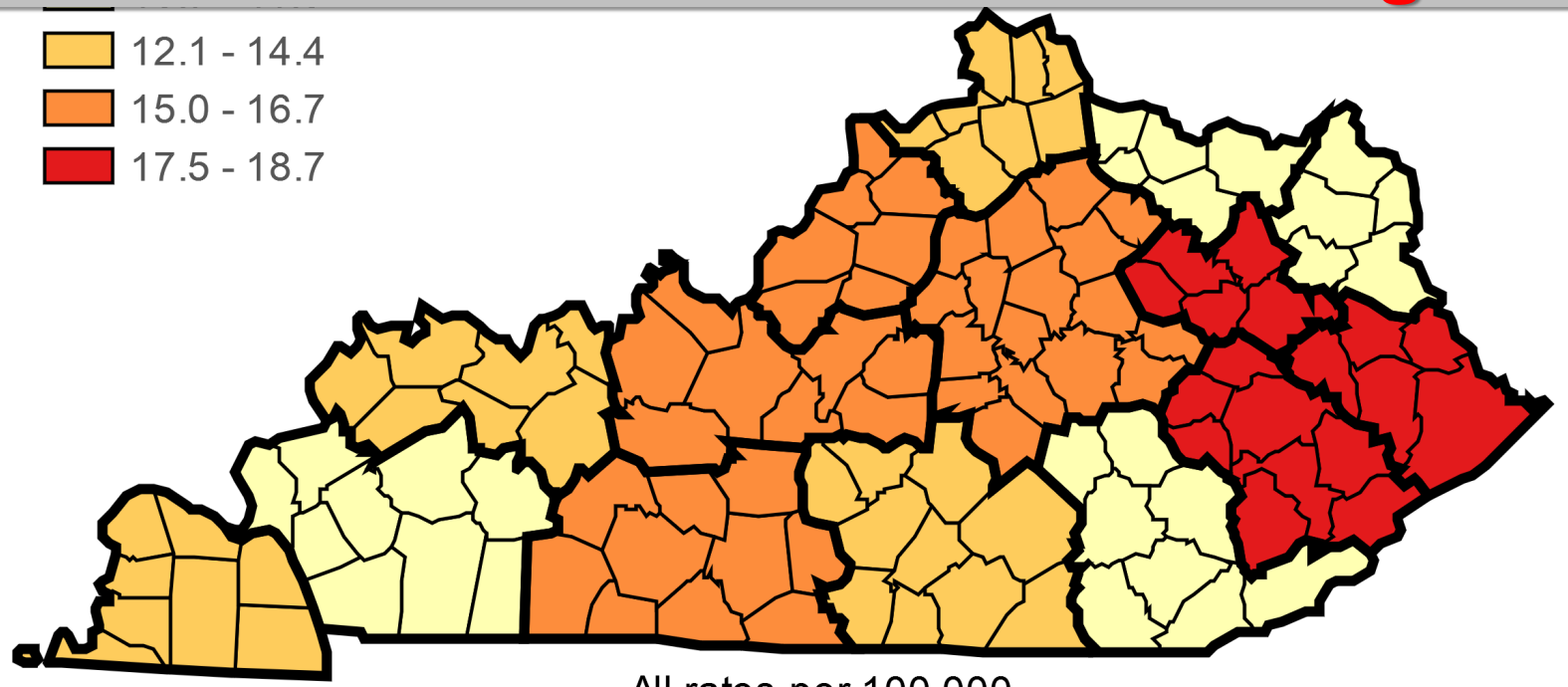
Triple Negative (HR-/HER2-) - Breast, Female, 2014 - 2018

By Area Development District

Age-Adjusted to the 2000 U.S. Standard Million Population

Kentucky Rate: 14.7 / per 100,000

Do geographic variations also exist in incidence of cancer genomic subtypes?



All rates per 100,000.

Data accessed September 16, 2021. Based on data released Nov 2020.

Genomic Data Generated for Clinical Oncology

New Challenges in Cancer Surveillance

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Next Generation Sequencing (NGS) Multi-Gene Targeted Panels

Kentucky Cancer Registry (KCR) Cancer Genomics Data Sources

- Clinical NGS reports
- Research NGS Reports Oncology Research Information Exchange Network (ORIEN)
- Pediatric Brain Tumor Study

Common Clinical NGS Service Providers in U.S.

- Guardant Health
- Foundation Medicine
- Caris Life Sciences
- Tempus
- Others

Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11ORF30 (EMSY)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*	*EPHB4*
ERBB2	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*	*FAM46C*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17ORF39)*	*GNA11*	*GNAQ13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*IDH1*	*ID3*	*IDH2*	*IGF1R*	*IKBKE*
IKZF1	*IL7R*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
KAT6A	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*	
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NOTCH1*	*NOTCH2*	*NOTCH3*	
NPM1	*NRAS*	*NTRK3*	*NTRK1*	*NTRK2*	*NUP93*	*PALB2*	*PARK2*	
PARP1	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*	*PDGFRB*
PDK1	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*	*POLD1*
POLE	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*	*PTEN*
PTPN11	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*
RAD52	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*	*RICTOR*
RNF43	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*	*SOX2*
SOX9	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*	*SYK*
TBX3	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*
TSC2	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1 (MMSET)*	*WHSC1L1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

Select Rearrangements[2,3]

Genes with select intronic regions for the detection of gene rearrangements, one gene with a promoter region and one non-coding RNA gene.

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT (PROMOTER ONLY)***	
TMPRSS2								

**TERC* is non-coding RNA gene.
***TERT* is gene with promoter region.

FoundationOne®CDx is a qualitative next-generation sequencing based in vitro diagnostic test for advanced cancer patients with solid tumors and is for prescription use only. The test analyzes 324 genes as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) and is a companion diagnostic to identify patients who may benefit from treatment with specific therapies in accordance with the approved therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the test does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Some patients may require a biopsy. For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com.

Next-Generation Sequencing Expanded NGS Gene List

Mutations (DNA)									
ABI1	BRD4	CRLF2	FOXO4	HOXC11	KLF4	MUC1	PAK3	RHOH	TAL2
ABL1	BTG1	DDB2	FSTL3	HOXC13	KLK2	MUTYH	PATZ1	RNF213	TBL1XR1
ACKR3	BTK	DDIT3	GATA1	HOXD11	LASP1	MYCL (MYCL1)	PAX8	RPL10	TCEA1
AKT1	C15orf65	DNM2	GATA2	HOXD13	LMO1	NBN	PDE4DIP	SEPT5	TCL1A
AMER1 (FAM123B)	CBLC	DNMT3A	GNA11	HRAS	LMO2	NDRG1	PHF6	SEPT6	TERT
AR	CD79B	EIF4A2	GPC3	IKBKE	MAFB	NKX2-1	PHOX2B	SFPQ	TFE3
ARAF	CDH1	ELF4	HEY1	INHBA	MAX	NONO	PIK3CG	SLC45A3	TFPT
ATP2B3	CDK12	ELN	HIST1H3B	IRS2	MECOM	NOTCH1	PLAG1	SMARCA4	THRAP3
ATRX	CDKN2B	ERCC1	HIST1H4I	JUN	MED12	NRAS	PMS1	SOCS1	TLX3
BCL11B	CDKN2C	ETV4	HLF	KAT6A (MYST3)	MKL1	NUMA1	POU5F1	SOX2	TMPRSS2
BCL2	CEBPA	FAM46C	HMGN2P46	KAT6B	MLLT11	NUTM2B	PPP2R1A	SPOP	UBR5
BCL2L2	CHCHD7	FANCF	HNF1A	KCNJ5	MN1	OLIG2	PRF1	SRC	VHL
BCOR	CNOT3	FEV	HOXA11	KDM5C	MPL	OMD	PRKDC	SSX1	WAS
BCORL1	COL1A1	FOXL2	HOXA13	KDM6A	MSN	P2RY8	RAD21	STAG2	ZBTB16
BRD3	COX6C	FOXO3	HOXA9	KDSR	MTCP1	PAFAH1B2	RECQL4	TAL1	ZRSR2
Mutations and Copy Number Variations (DNA)									
ABL2	BRCA2[1]	COPB1	ESR1	FUS	KIT	MYB	PER1	RUNX1	TFG
ACSL3	BRIP1	CREB1	ETV1	GAS7	KLHL6	MYC	PICALM	RUNX1T1	TFRC
ACSL6	BUB1B	CREB3L1	ETV5	GATA3	[illegible](MLL)	MYCN	PIK3CA	SBDS	TGFBR2
AFF1	C11orf30 (EMSY)	CREB3L2	ETV6	GID4 (C17orf39)	KMT2C (MLL3)	MYD88	PIK3R1	SDC4	TLX1
AFF3	C2orf44	CREBBP	EWSR1	GMPS	KMT2D (MLL2)	[illegible]	[illegible]	SDHAF2	TNFAIP3
AFF4	CACNA1D	CRKL	EXT1	GNA13	KRAS	MY[illegible]	[illegible]	SDHB	TNFRSF14
AKAP9	CALR	CRTC1	EXT2	GNAQ	KTN1	[illegible]	[illegible]	SDHC	TNFRSF17
AKT2	CAMTA1	CRTC3	EZH2	GNAS	LCK	NCOR[illegible]	[illegible]	SDHD	TOP1
AKT3	CANT1	CSF1R	EZR	GOLGA5	[illegible]	[illegible]	[illegible]	SEPT9	TPM3
ALDH2	CARD11	CSF3R	FANCA	GOPC	LGR5	NCOA2	POT1	SET	TPM4
ALK	CARS	CTCF	FANCC	GPHN	LHFP	NCOA4	POU2AF1	SETBP1	TPR
APC	CASC5	CTLA4	FANCD2	GPR124	LIFR	NF1	PPARG	SETD2	TRAF7
ARFRP1	CASP8	CTNNA1	FANCE	GRIN2A	LPP	NF2	PRCC	SF3B1	TRIM24
ARHGAP26	CBFA2T3	CTNNB1	FANCG	GSK3B	LRIG3	NFE2L2	PRDM1	SH2B3	TRIM26
ARHGEF12	CBFB	CYLD	FANCL	H3F3A	LRP1B	NFIB	PRDM[illegible]	SH3GL1	TRIM27
ARID1A	CBL	CYP2D6	FAS	H3F3B	LYL1	NFKB2	PRKAR[illegible]	SLC3[illegible]	TRIM33
ARID2	CBLB	DAXX	FBXO11	HERPUD1	MAF	NFKBIA	PRRX1	SMA[illegible]	TSHR
ARNT	CCDC6	DDR2	FBXW7	HGF	MALT1	NIN	PSIP1	SMAD4	U2AF1
ASPSCR1	CCNB1IP1	DDX10	FCRL4	HIP1	MAML2	NOTCH2	PTCH1	SMARCB1	USP6
ASXL1	CCND1	DDX5	FGF10	HMGA1	MAP2K1	NPM1	PTEN	SMARC[illegible]	VEGFA
ATF1	CCND2	DDX6	FGF14	HMGA2	MAP2K2	NR4A3	PTPN11	SMO	VEGFB
ATIC	CCND3	DEK	FGF19	HNRNPA2B1	MAP2K4	NSD1	PTPRC	SNX29	VTI1A
ATM	CCNE1	DICER1	FGF23	HOOK3	MAP3K1	NT5C2	RABEP1	SOX10	WHSC1
ATP1A1	CD274 (PDL1)	DOT1L	FGF3	HSP90AA1	MCL1	NTRK1	RAC1	SPECC1	WHSC1L1
ATR	CD74	EBF1	FGF4	HSP90AB1	MDM2	NTRK2	RAD50	SPEN	WIF1
AURKA	CD79A	ECT2L	FGF6	IDH1	MDM4	NTRK3	RAD51	SRGAP3	WISP3
AURKB	CDC73	EGFR	FGFR1	IDH2	MDS2	NUP214	RAD51B	SRSF2	WRN
AXIN1	CDH11	ELK4	FGFR1OP	IGF1R	MEF2B	NUP93	RAF1	SRSF3	WT1
AXL	CDK4	ELL	FGFR2	IKZF1	MEN1	NUP98	RALGDS	SS18	WWTR1
BAP1	CDK6	EML4	FGFR3	IL2	MET (cMET)	NUTM1	RANBP17	SS18L1	XPA
BARD1	CDK8	EP300	FGFR4	IL21R	MITF	PALB2	RAP1GDS1	STAT3	XPC
BCL10	CDKN1B	EPHA3	FH	IL6ST	MLF1	PAX3	RARA	STAT4	XPO1
BCL11A	CDKN2A	EPHA5	FHIT	IL7R	MLH1	PAX5	RB1	STAT5B	YWHAE
BCL2L11	CDX2	EPHB1	FIP1L1	IRF4	MLLT1	PAX7	RBM15	STIL	ZMYM2
BCL3	CHEK1	EPS15	FLCN	ITK	MLLT10	PBRM1	REL	STK11	ZNF217
BCL6	CHEK2	ERBB2 (HER2)	FLI1	JAK1	MLLT3	PBX1	RET	SUFU	ZNF331
BCL7A	CHIC2	ERBB3 (HER3)	FLT1	JAK2	MLLT4	PCM1	RICTOR	SUZ12	ZNF384
BCL9	CHN1	ERBB4 (HER4)	FLT3	JAK3	MLLT6	PCSK7	RMI2	SYK	ZNF521
BCR	CIC	ERC1	FLT4	JAZF1	MNX1	PDCD1 (PD1)	RNF43	TAF15	ZNF703
BIRC3	CIITA	ERCC2	FNBP1	KDM5A	MRE11A	PDCD1LG2 (PDL2)	ROS1	TCF12	
BLM	CLP1	ERCC3	FOXA1	KDR (VEGFR2)	MSH2	PDGFB	RPL22	TCF3	
BMPR1A	CLTC	ERCC4	FOXO1	KEAP1	MSH6	PDGFRA	RPL5	TCF7L2	
BRAF	CLTCL1	ERCC5	FOXP1	KIAA1549	MSI2	PDGFRB	RPN1	TET1	
BRCA1[1]	CNBP	ERG	FUBP1	KIF5B	MTOR	PDK1	RPTOR	TET2	
	CNTRL							TFEB	

Gene Fusions (RNA)								Variant Transcripts (RNA)
ALK	BRAF	NTRK1	NTRK2	NTRK3	RET	ROS1	RSPO3	EGFR viii	MET Exon 14 Skipping

[1] *May not be available for Medicare patients. Medicare reimburses BRCA1-2 for breast and ovarian cases only.*
Next-Generation Sequencing may not be available in New York State. For testing available in New York, please view the online New York Profile Menu (www.CarisMolecularIntelligence.com/solid_tumors-NY).

To order or learn more, visit **www.CarisMolecularIntelligence.com.**
US: 888.979.8669 | MIClientServices@carisls.com
Intl: 00 41 21 533 53 00 | EUCustomerServices@carisls.com

CARIS MOLECULAR INTELLIGENCE®
ENABLING PRECISION MEDICINE

Tumor Profiling Services from Caris Molecular Intelligence®

	MI PROFILE™ Multi-platform, solid tumor biomarker analysis for therapeutic decision support	Next-Generation Sequencing Next-Generation Sequencing for additional biomarker analysis
Chemotherapy	✔	–
Immunotherapy	✔	–
Targeted Therapy	✔	✔
Protein Expression via IHC	✔	–
DNA Analysis via Pyro Sequencing	✔	–
DNA/RNA Analysis via Fragment Analysis	✔	–
Molecular Analysis via Next-Generation Sequencing	592 Genes	592 Genes
Clinical Trial Opportunities	✔	✔

Technical Specifications

Sufficient tumor must be present to complete all analysis. If you have any questions, please contact Client Services at (888) 979-8669.

Technical Information	IHC	CISH	FISH
Sample Requirements *(see requisition for full details)*	1 unstained slide at 4µm thickness from FFPE block, with evaluable tumor present, per IHC test	1 unstained slide at 4µm thickness from FFPE block, with at least 20-100 evaluable tumor cells present, per CISH test	2 unstained slides at 4µm thickness from FFPE block, with at least 100 evaluable cells present and 10% tumor, per FISH test
Sensitivity/Specificity	>95%	>95%	>95%

Technical Information	Next-Generation Sequencing	
	Mutations and Copy Number Variations (DNA)	Fusions (RNA)
Sample Requirements	FFPE block or 15 unstained slides with a minimum of 20% malignant origin. Needle biopsy is also acceptable (4-6 cores).	FFPE block or 2-5 unstained slides with a minimum of 20% malignant origin. Needle biopsy is also acceptable (4-6 cores).
Tumor Enrichment	Microdissection performed on all cases resulting in ~25% increase in tumor nuclei and enhances detection of minor clonal variants	
Amount of DNA Required	200ng input (50ng)	
PPV	>99%	>98%
Sensitivity	> 99% for base substitutions at ≥ 5% mutant allele frequency; > 99% for indels at ≥ 5% mutant allele frequency; >95% for copy number variations (amplifications ≥ 8 copies)	>91%
Average Depth of Coverage (DNA) Average Depth/Count (RNA)	>750X	>30,000 Unique RNA Fragments
Number of Genes	592 genes	10 genes

Gene **List**

Guardant360 CDx is indicated to provide tumor mutation profiling for advanced cancer patients with any solid malignant neoplasm.
Guardant360 CDx report contains both professional services, which includes 74 genes, in addition to the FDA-approved report, which includes 55 genes.

Point Mutations (SNVs) and Deletion Variants (Indels) *(74 Genes)*

AKT1	*CDH1*	*FGFR2*	***KRAS***	*NPM1*	*RIT1*
ALK	*CDK4*	*FGFR3*	*MAP2K1*	*NRAS*	***ROS1***
APC	*CDK6*	*GATA3*	*MAP2K2*	*NTRK1*	*SMAD4*
AR	*CDK12*	*GNA11*	*MAP3K1*	*NTRK3*	*SMO*
ARAF	*CDKN2A*	*GNAQ*	*MAPK3*	*PDGFRA*	*STK11*
ARID1A	*CTNNB1*	*GNAS*	***MET***	*PIK3CA*	*TERT^*
ATM	*DDR2*	*HNF1A*	*MLH1*	*PTEN*	*TP53*
BRAF	***EGFR***	*HRAS*	*MPL*	*PTPN11*	*TSC1*
BRCA1	***ERBB2***	*IDH1*	*MTOR*	*RAF1*	*VHL*
BRCA2	*ESR1*	*IDH2*	*MYC*	*RB1*	
CCND1	*EZH2*	*JAK2*	*NF1*	***RET***	
CCND2	*FBXW7*	*JAK3*	*NFE2L2*	*RHEB*	
CCNE1	*FGFR1*	*KIT*	*NOTCH1*	*RHOA*	

Amplifications *(18 Genes)*

AR	*FGFR1*
BRAF	*FGFR2*
CCND1	*KIT*
CCNE1	***MET***
CDK4	*MYC*
CDK6	*PDGFRA*
EGFR	*PIK3CA*
ERBB2	*RAF1*

Fusions *(6 Genes)*

ALK
FGFR2
FGFR3
NTRK1
RET
ROS1

Critical or all exons* completely sequenced and all four major classes of alterations

NSCLC guideline-recommended genes shown in bold / *Exons selected to maximize detection of known somatic mutations / ^ Includes TERT promoter region

Traditional Abstraction of Gene Mutations?

- Site Specific Data Items (SSDIs) take years to approve
  - Long after testing and clinical use have become standards of clinical care
- Registrars do not have time to review and manually code hundreds of gene mutations per case
- Obtaining test results directly from sequencing providers will be much more efficient and complete

Central Registry Infrastructure Needed to Capture Genomic Test Data

Moving Beyond the Limitations

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Commercial Laboratory NGS Panel Testing and Reporting

Clinical Report

- Specific gene mutations from tumor tissue
- Suggestions for FDA approved targeted agents and clinical trials
- May or may not report variants of unknown significance

Raw Data used to Generate Clinical Report

- Sequencer -> FastQ -> BAM -> VCF -> Clinical Report

- Clinical report based upon current knowledge of mutation variants
- FastQ and BAM files contain information that may prove important in future
- At minimum, BAM files important for surveillance

FOUNDATIONONE®

Patient Name	Report Date	Tumor Type
Patient, Test	**09 December 2016**	**Breast carcinoma (NOS)**

Date of Birth	12 December 1942	**Medical Facility**	ABC Oncology		
Sex	Female	**Ordering Physician**	Smith, John	**Specimen Received**	01 December 2016
FMI Case #	SMP60684	**Additional Recipient**	Not Given	**Specimen Site**	Breast
Medical Record #	12345678	**Medical Facility ID #**	200313	**Date of Collection**	08 December 2016
Specimen ID	Not Given	**Pathologist**	Public, John Q	**Specimen Type**	Slide

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

4 genomic findings

2 therapies associated with potential clinical benefit

0 therapies associated with lack of response

10 clinical trials

TUMOR TYPE: BREAST CARCINOMA (NOS)

Genomic Alterations Identified†

PIK3CA E545K
ATM T2333fs*40
BCL2L1 amplification – equivocal#
MYST3 amplification – equivocal#

Additional Disease-relevant Genes with No Reportable Alterations Identified†

ERBB2

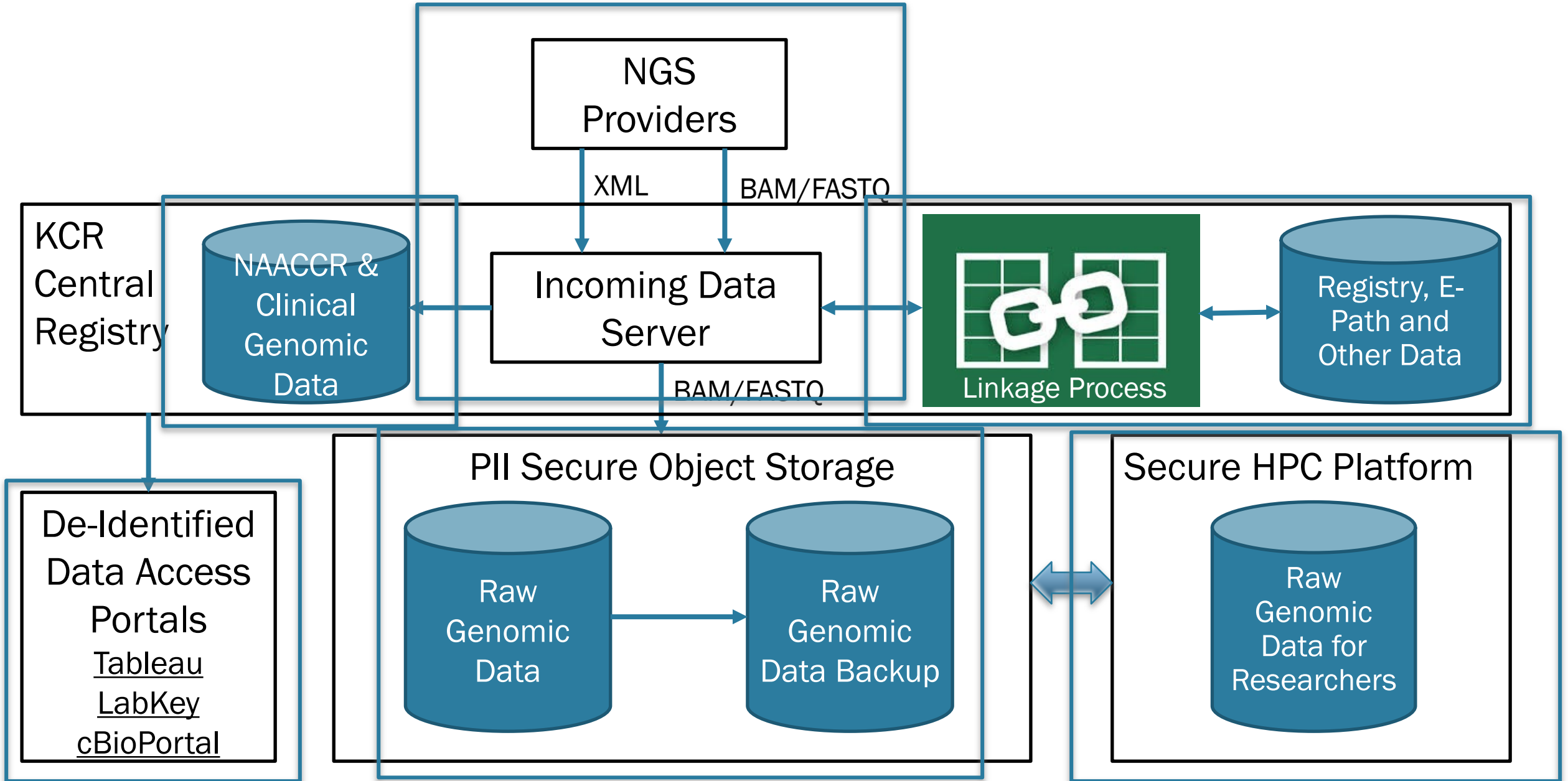
† For a complete list of the genes assayed and performance specifications, please refer to the Appendix
# See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
PIK3CA E545K	Everolimus	Temsirolimus	Yes, see clinical trials section
ATM T2333fs*40	None	None	Yes, see clinical trials section
BCL2L1 amplification - equivocal	None	None	None
MYST3 amplification - equivocal	None	None	None

Note: Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have little or no evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Genomic Data Flow into the Central Registry



KCR/MCC cBioPortal for Cancer Genomics

I. The cBioPortal for Cancer Genomics is an open-access, open-source resource for interactive exploration of multidimensional cancer genomics data sets. The goal of cBioPortal is to significantly lower the barriers between complex genomic data and cancer researchers by providing rapid, intuitive, and high-quality access to molecular profiles and clinical attributes from large-scale cancer genomics projects, and therefore to empower researchers to translate these rich data sets into biologic insights and clinical applications.

II. Provide representative, de-identified, population-based data from Kentucky cancer patients annotated with high quality KCR data

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cBioPortal for Cancer Genomic

https://cbioportal.kcr.uky.edu/study/summary?id=FMUK_CSCLC%2CFMUK_LUNE%2CFMUL_LUNE%2CFMUK_SCLC%2CFMUK_NSCLC%

Search

cBioPortal FOR CANCER GENOMICS

Data Sets | Web API | Tutorials/Webinars | Visualize Your Data

Logged in as ericd@kcr.uky.edu

Combined Study

This combined study contains samples from 14 studies

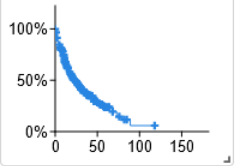
Click gene symbols below or enter here | Query

Summary | Clinical Data

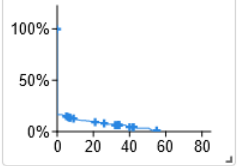
Selected: 298 patients | 304 samples

Custom Selection | Charts | Groups

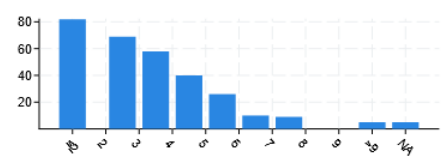
KM Plot: Overall Survival (months)



KM Plot: Disease Free Survival (...



Mutation Count



Mutated Genes (302 profiled samples)

Gene	# Mut	#	Freq
TP53	267	233	77.2%
KRAS	99	98	32.5%
STK11	46	46	15.2%
CDKN2A	33	32	10.6%
SMARCA4	31	31	10.3%
KEAP1	27	27	8.9%
ARID1A	26	25	8.3%
NF1	27	24	7.9%
RBM10	22	22	7.3%
PIK3CA	21	20	6.6%
LRP1B	22	20	6.6%

Search...

Structural Variant Genes (288 profiled samples)

Gene	# SV	#	Freq
ALK	4	4	1.4%
STK11	4	4	1.4%
BRCA1	3	3	1.0%
NF1	3	3	1.0%
LRP1B	3	3	1.0%
CDC73	3	3	1.0%
RB1	2	2	0.7%
RET	2	2	0.7%
ROS1	2	2	0.7%
APC	1	1	0.3%
CD74	1	1	0.3%

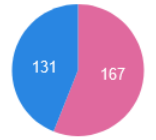
Search...

CNA Genes (295 profiled samples)

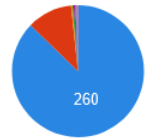
Gene	Cytoband	CNA	#	Freq
MYC	8q24.21	AMP	34	11.5%
SOX2	3q26.33	AMP	28	9.5%
RICTOR	5p13.1	AMP	27	9.2%
NKX2-1	14q13.3	AMP	24	8.1%
PIK3CA	3q26.32	AMP	21	7.1%
FGF10	5p12	AMP	19	6.4%
NFKBIA	14q13.2	AMP	19	6.4%
TERC	3q26.2	AMP	19	6.4%
PRKCI	3q26.2	AMP	17	5.8%
CCND1	11q13.3	AMP	16	5.4%
FGF19	11q13.3	AMP	16	5.4%

Search...

Sex



Race



Histology

	#	Freq
ADENOCARCINOMA, NOS	161	53.0%
SQUAMOUS CELL CARCINOM...	67	22.0%
NON SM CELL CARCINOMA	19	6.3%
LARGE CELL NEUROENDOCR...	9	3.0%
MUCINOUS ADENOCARCINOMA	7	2.3%
SMALL CELL CARCINOMA, NOS	7	2.3%
ACINAR CELL CARCINOMA	4	1.3%
ACINAR CELL CYSTADENOCA...	4	1.3%
NEUROENDOCRINE CARCINO...	3	1.0%
PAPILLARY ADENOCARCINO...	3	1.0%
PLEOMORPHIC CARCINOMA	3	1.0%

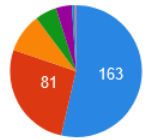
Search...

Histology Code

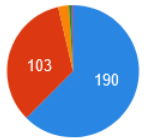
	#	Freq
8140	161	53.0%
8070	67	22.0%
8046	19	6.3%
8013	9	3.0%
8041	7	2.3%
8480	7	2.3%
8550	4	1.3%
8551	4	1.3%
8022	3	1.0%
8246	3	1.0%
8260	3	1.0%

Search...

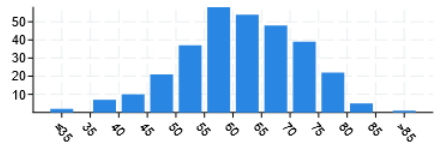
Topography Code



Laterality



Diagnosis Age

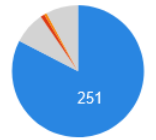


Best Stage Group

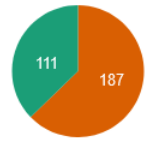
	#	Freq
Stage IV	87	28.6%
Clinical Stage IVB	34	11.2%
Pathologic Stage IVB	24	7.9%
Stage IB	23	7.6%
Stage IIIB	21	6.9%
Pathologic Stage IVA	18	5.9%
Stage IA	18	5.9%
Stage IIIA	18	5.9%
Clinical Stage IVA	8	2.6%
Stage IIB	8	2.6%
Clinical Stage IIIA	6	2.0%

Search...

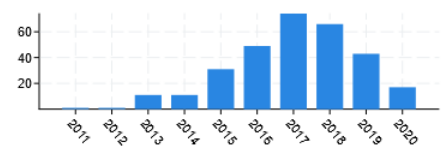
Microsatilite Status



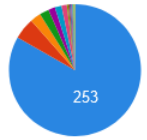
Overall Survival Status



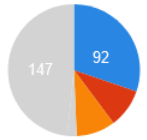
Diagnosis Year



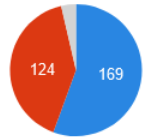
Recurrance Status



Tumor Mutation Burden



Urban/Rural



Transmission and Storage Requirements

- Secure FTP between central registry and sequencing provider
  - Push or pull
- Molecular data files must contain linkage identifiers
  - Patient: Last Name, First Name, Date of Birth, SSN, Medical Record Number
  - Case: Diagnosis (Site/Histology), Diagnosis Date, Path Report Number (Specimen), Specimen Date
- Data storage needed

Data Type	Average Size	Storage for 1000 Records
XML (Mutations)	< 1 Mb	< 1 GB
PDF (Clinical Reports)	< 1 Mb	< 1 GB
BAM (Processed Raw Data)	2.3 GB (+10MB Index)	~3 TB
FASTQ (WES Raw Data)	20-40GB	20-40 TB

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Other Resource Considerations

- Legal
  - Data Use Agreements with Sequencing Providers
  - Hospital Agreements (permission to send results to registry)
- Staffing
  - Technical infrastructure development
  - PII security (protecting germline sequencing)
  - Bioinformatics support
  - Cancer registrars for reviewing and linking genomic reports with path reports and registry data

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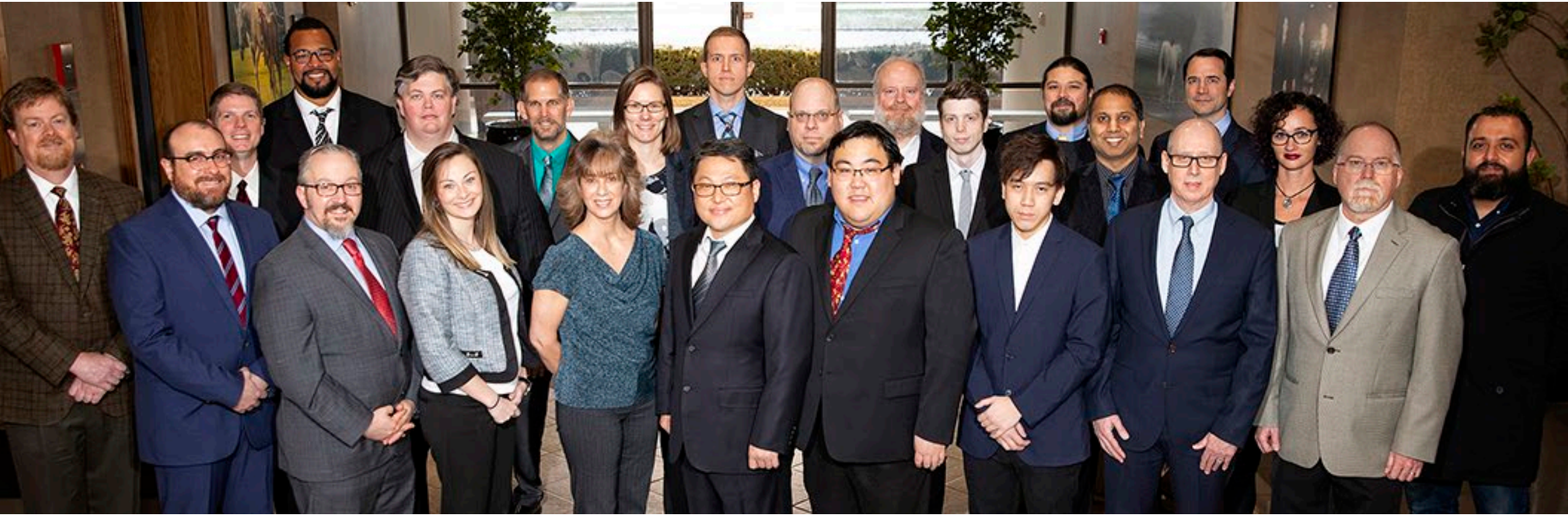
Acknowledgements: KCR/Markey Informatics Teams



Questions/Discussion

- Contact Information:

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  - NCI/SEER: HHSN261201000131, P30CA177558

https://www.kcr.uky.edu/KCRChildhoodLegislativeReport_006-2021-12.pdf