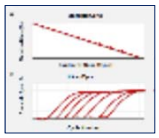
RECENT DEVELOPMENTS IN CANCER DIAGNOSIS AND TREATMENT

FCDS Annual Educational Conference

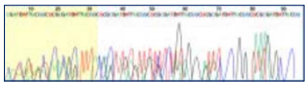
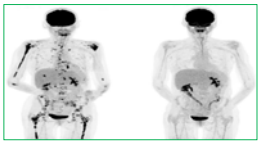
Orlando, Florida

July 28, 2017




Steven Peace, CTR

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CDC & Florida DOH Attribution

"We acknowledge the Centers for Disease Control and Prevention, for its support of the Florida Cancer Data System, and the printing and distribution of the materials for the 2015-2016 FCDS Webcast Series under cooperative agreement DP003872-03 awarded to the Florida Department of Health. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention".

CDC Centers for Disease Control and Prevention

Florida HEALTH

FCDS would also like to acknowledge the Florida Department of Health for its support of the Florida Cancer Data System, including the development, printing and distribution of materials for the 2015-2016 FCDS Webcast Series under state contract CODJU. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Florida Department of Health.

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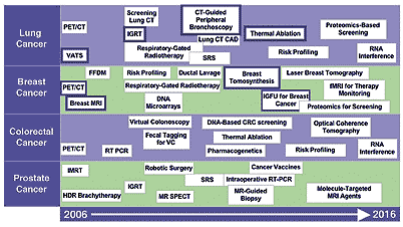
Outline

- Revised Common Rule and Cancer Surveillance
- 2017 Incidence & Mortality Estimates
- AACR Cancer Progress Report 2016
- National Toxicology Program - 14th Report on Carcinogens
- ASCO 2017 Clinical Cancer Advances
- NCCN Annual Report 2016 – At Our Core
- Explosion of Data / Fragmented Data Sources
- CAP Solid Tumor Selected Tests by Tumor Type
- New Diagnostic Tools & Techniques
- Next Generation Genomic Sequencing
- Next Generation Immuno & Precision Therapies
- Questions

Emerging Technologies Are More Complex and Tumor-Specific



Timings reflect consensus adoption. VATS = video-assisted thoracic surgery; PCR = polymerase chain reaction; VC = virtual colonoscopy.
Source: SgE Analysis, 2006.

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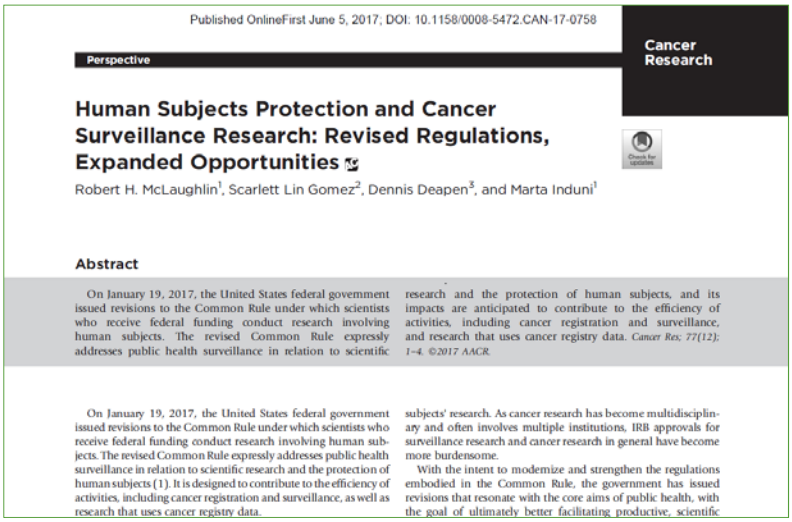
Revised Common Rule and Cancer Surveillance



Published OnlineFirst June 5, 2017; DOI: 10.1158/0008-5472.CAN-17-0758

Perspective

Cancer Research

Human Subjects Protection and Cancer Surveillance Research: Revised Regulations, Expanded Opportunities

Robert H. McLaughlin[1], Scarlett Lin Gomez[2], Dennis Deapen[3], and Marta Induni[1]

Abstract

On January 19, 2017, the United States federal government issued revisions to the Common Rule under which scientists who receive federal funding conduct research involving human subjects. The revised Common Rule expressly addresses public health surveillance in relation to scientific research and the protection of human subjects, and its impacts are anticipated to contribute to the efficiency of activities, including cancer registration and surveillance, and research that uses cancer registry data. *Cancer Res; 77(12); 1–4. ©2017 AACR.*

On January 19, 2017, the United States federal government issued revisions to the Common Rule under which scientists who receive federal funding conduct research involving human subjects. The revised Common Rule expressly addresses public health surveillance in relation to scientific research and the protection of human subjects (1). It is designed to contribute to the efficiency of activities, including cancer registration and surveillance, as well as research that uses cancer registry data.

subjects' research. As cancer research has become multidisciplinary and often involves multiple institutions, IRB approvals for surveillance research and cancer research in general have become more burdensome.

With the intent to modernize and strengthen the regulations embodied in the Common Rule, the government has issued revisions that resonate with the core aims of public health, with the goal of ultimately better facilitating productive, scientific

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Revised Common Rule and Cancer Surveillance

Intent to modernize and strengthen the regulations embodied in the Common Rule

Goal is to make significant improvements in facilitating productive, scientific research outcomes which continue to support the ethics of public health activities in disease surveillance

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1) The recognition and exclusion from IRB oversight of public health surveillance activities, including the collection and testing of bio specimens;
2) The requirement that a research study in which more than one institution located in the United States is engaged be reviewed by a single IRB with the others entering a relationship of reliance; and
3) The expansion of exemption categories to include many research studies involving the collection of identifiable human subjects' data through survey and interview procedures.

The definition of public health surveillance activities is, nevertheless, broadly consistent with the data collection and analyses performed by state cancer registries and the activities of registries that participate in federal cancer surveillance programs, such as database linkages.

Source: American Association for Cancer Research (AACR), June 5, 2017 - doi: 10.1158/0008-5472.CAN-17-0758

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2017 Incidence & Mortality Estimates

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2017 Estimates

Estimated New Cases

Male			Female		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All sites	**836,150**	**100%**	**All sites**	**852,630**	**100%**

Estimated Deaths

Male			Female		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All sites	**318,420**	**100%**	**All sites**	**282,500**	**100%**

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Source: American Cancer Society – 2017 Cancer Facts and Figures

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2017 Survival Rate Estimates

Table 7. Trends in 5-year Relative Survival Rates* (%) by Race, US, 1975-2012

	All races			White			Black		
	1975-77	1987-89	2006-12	1975-77	1987-89	2006-12	1975-77	1987-89	2006-12
Brain & other nervous system	22	29	35	22	28	33	25	32	44
Breast (female)	75	84	91	76	85	92	62	71	82
Colon & rectum	50	60	66	50	60	67	45	52	59
Esophagus	5	9	21	6	11	22	4	7	13
Hodgkin lymphoma	72	79	89	72	80	89	70	72	86
Kidney & renal pelvis	50	57	75	50	57	75	49	55	75
Larynx	66	66	62	67	67	64	58	56	52
Leukemia	34	43	63	35	44	64	33	35	58
Liver & intrahepatic bile duct	3	5	18	3	6	18	2	3	13
Lung & bronchus	12	13	19	12	13	19	11	11	16
Melanoma of the skin	82	88	93	82	88	93	57†	79†	69
Myeloma	25	27	50	24	27	50	29	30	52
Non-Hodgkin lymphoma	47	51	73	47	51	74	49	46	65
Oral cavity & pharynx	53	54	67	54	56	69	36	34	47
Ovary	36	38	46	35	38	46	42	34	38
Pancreas	3	4	9	3	3	9	2	6	8
Prostate	68	83	99	69	84	>99	61	71	97
Stomach	15	20	31	14	18	30	16	19	30
Testis	83	95	97	83	95	97	73‡	88	90
Thyroid	92	94	98	92	94	99	90	92	97
Urinary bladder	72	79	79	73	80	79	50	63	66
Uterine cervix	69	70	69	70	73	71	65	57	58
Uterine corpus	87	82	83	88	84	86	60	57	66

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 9 areas from 1975 to 77, 1987 to 89, and 2006 to 2012, all followed through 2013. †The standard error is between 5 and 10 percentage points. ‡Survival rate is for cases diagnosed from 1978 to 1980.

Source: Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review, 1975-2013*, National Cancer Institute, Bethesda, MD, www.seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER website April 2016.

Source: American Cancer Society – 2017 Cancer Facts and Figures

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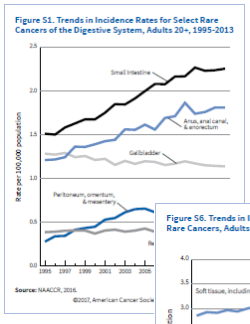
2017 Trends in Rare Cancers

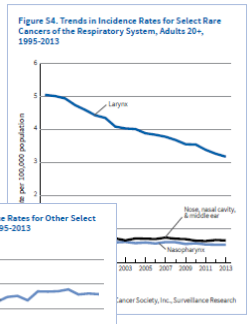
Table S1. Statistics for Select Rare Cancers, Ages 20+ Years

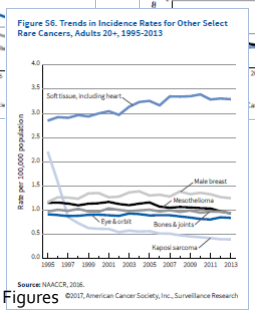
	Incidence				Mortality		Relative survival
	Rate* 2009-2013	Male: female rate ratio	Trend (APC) 2004-2013	% local stage 2009-2013	Rate* 2010-2014	Trend (APC) 2005-2014	5-year (%) 2006-2012
Oral cavity & pharynx							
Lip	0.8	3.4	-2.4†	83	<0.1	-3.4†	89
Tongue	4.7	2.8	1.9†	33	0.9	-0.3†	65
Salivary gland	1.7	1.8	0.3†	43	0.3	1.0†	72
Floor of mouth	0.8	2.5	-3.2†	44	<0.1	-8.1†	52
Gum & other mouth	2.2	1.5	-0.2	40	0.5	-0.2	59
Nasopharynx‡	0.7	2.7	-0.9†	9	0.3	-1.4†	60
Tonsil	2.9	4.9	3.1†	12	0.3	1.3†	73
Oropharynx	0.7	3.6	1.3†	14	0.3	2.5†	43
Hypopharynx	0.9	4.7	-2.6†	17	0.1	-1.3	33
Digestive system							
Small intestine	3.2	1.3	1.7†	32	0.5	0.1	67
Anus, anal canal, & anorectum	2.5	0.7	1.6†	47	0.3	3.0†	66
Gallbladder	1.6	0.6	-0.6†	10	0.9	-0.7†	19
Retroperitoneum	0.5	1.1	-0.2	43	0.1	-3.4†	53
Peritoneum, omentum, & mesentery	0.8	0.1	-2.3†	18	0.4	0.0	33
Respiratory system							
Nose, nasal cavity, & middle ear	0.9	1.8	-0.6†	27	0.2	-2.0†	56
Larynx	5.0	4.5	-2.5†	53	1.4	-2.1†	61
Trachea, mediastinum	0.2	2.5	-1.3†	30	0.1	-3.8†	46
Genitourinary system							
Vagina	1.0	–	-0.9†	32	0.3	-1.3†	47
Vulva	3.6	–	0.5†	60	0.7	0.6	72
Penis	1.2	–	-0.1	57	0.2	-0.6†	69
Testis	7.2	–	0.2	68	0.3	-0.4†	95
Ureter	0.8	2.2	-1.5	45	0.2	-0.7†	47
Other rare cancers							
Male breast cancer	1.9	–	0.2	47	0.4	-1.1†	84
Bones & joints	1.0	1.4	-0.2†	40	0.5	-0.4†	66
Soft tissue, including heart	4.2	1.5	0.4	58	1.8	0.5†	64
Eye & orbit	1.0	1.4	-0.7	73	0.1	1.5	80
Mesothelioma	1.4	4.3	-1.8†	9	1.1	-1.4†	10
Kaposi sarcoma	0.5	9.6	-3.4†	56	<0.1	1.3	73

APC= annual percent change. *Rate per 100,000 population. †Indicates APC significantly different from zero, p<0.05. ‡Nasopharyngeal cancers are classified with oral cavity/pharynx here, consistent with SEER coding, but are described in the section on respiratory cancers in the text because the nasopharynx is technically part of the respiratory system. Note: All male:female incidence rate ratios are significantly different from 1.0, p<0.05.

Sources: Data for overall incidence rate, male: female rate ratio, and percent local stage are from the North American Association for Central Cancer Registries (NAACCR) and include information from all states and DC, except MN, NM, and NV. Incidence trends are based on NAACCR data from 1995 to 2013 from 26 states, representing 67% of the US population. Data for 5-year relative survival are from the Surveillance, Epidemiology, and End Results (SEER) program, 18 SEER registries, covering approximately 28% of the US population. Mortality data for rates and trends cover the entire US and are from the National Center for Health Statistics.







American Cancer Society – 2017 Cancer Facts and Figures

8

Annual Report to the Nation on the Status of Cancer Featuring Survival – 1975-2014

- The American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate to provide annual updates on cancer occurrence and trends in the United States. This Annual Report highlights survival rates.
- Overall cancer death rates from 2010 to 2014 decreased by 1.8% (95% confidence interval [CI] ¼ –1.8% to –1.8%) per year in men, by 1.4% (95% CI ¼ –1.4% to –1.3%) per year in women, and by 1.6% (95% CI ¼ –2.0% to –1.3%) per year in children.
- Death rates decreased for 11 of the 16 most common cancer types in men and for 13 of the 18 most common cancer types in women, including lung, colorectal, female breast, and prostate, whereas death rates increased for liver (men and women), pancreas (men), brain (men), and uterine cancers.
- In contrast, overall incidence rates from 2009 to 2013 decreased by 2.3% (95% CI ¼ –3.1% to –1.4%) per year in men but stabilized in women.
- For several but not all cancer types, survival statistically significantly improved over time for both early and late-stage diseases. Survival varied by race/ethnicity and state.
- Conclusions: Cancer death rates continue to decrease in the United States. However, progress in reducing death rates and improving survival is limited for several cancer types, underscoring the need for intensified efforts to discover new strategies for prevention, early detection, and treatment and to apply proven preventive measures broadly and equitably.

Source: JNCI J Natl Cancer Inst (2017) 109(9): djx030

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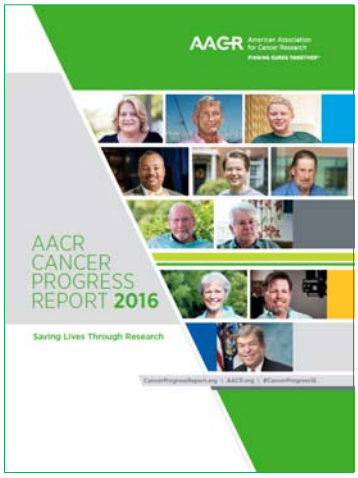
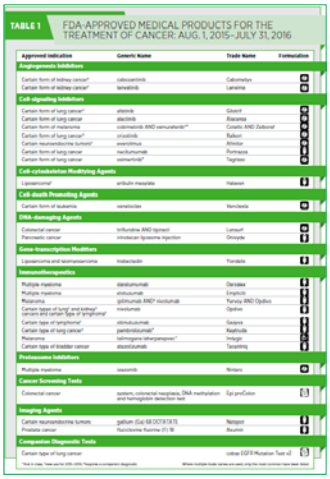
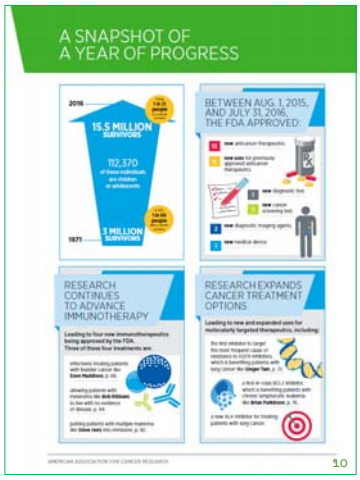
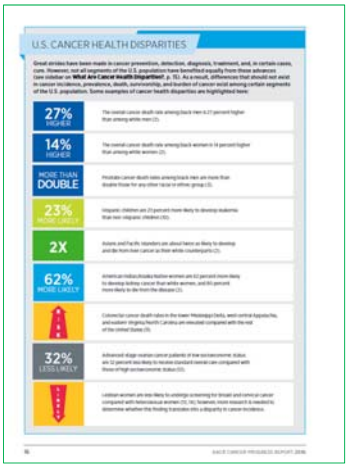
AACR Cancer Progress Report 2016

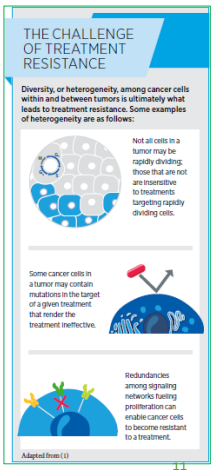






AACR Cancer Progress Report 2016





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National Toxicology Program 14th Report on Carcinogens

14th Report on Carcinogens 2016

Five viruses, a chemical, and a metallic element listed in new HHS report.
Total # Carcinogenic Substances = 248

Newly reviewed substances		
Substance	**Listing Status**	**Description**
Human immunodeficiency virus type 1 (HIV-1)	Known to be a human carcinogen	Virus
Human T-cell lymphotropic virus type 1 (HTLV-1)	Known to be a human carcinogen	Virus
Epstein-Barr virus (EBV)	Known to be a human carcinogen	Virus
Kaposi sarcoma-associated herpesvirus (KSHV)	Known to be a human carcinogen	Virus
Merkel cell polyomavirus (MCV)	Known to be a human carcinogen	Virus
Trichloroethylene (TCE)	Known to be a human carcinogen	Industrial solvent
Cobalt and cobalt compounds that release cobalt ions in vivo	Reasonably anticipated to be a human carcinogen	A metal and its compounds

"Given that approximately 12 percent of human cancers worldwide may be attributed to viruses, and there are no vaccines currently available for these five viruses, prevention strategies to reduce the infections that can lead to cancer are even more critical," said Linda Birnbaum, Ph.D., director National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP).

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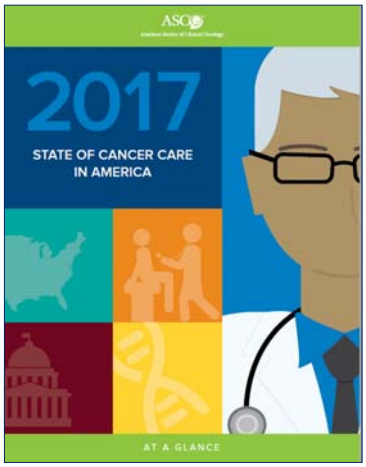
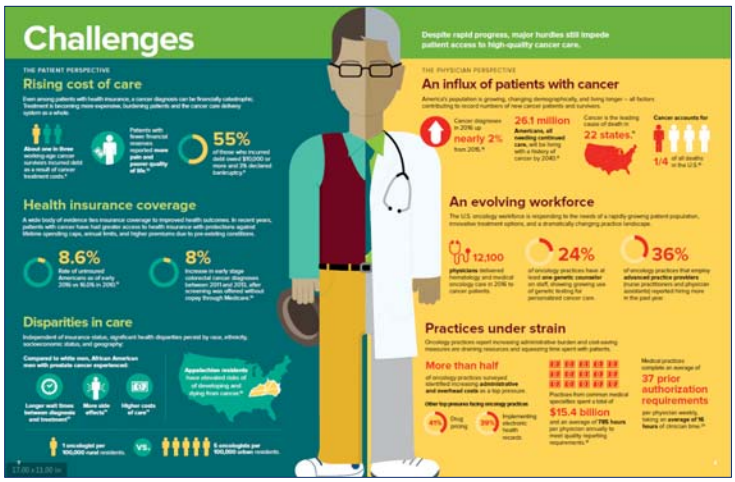
ASCO 2017 State of Cancer Care in America



ASCO 2017 State of Cancer Care in America



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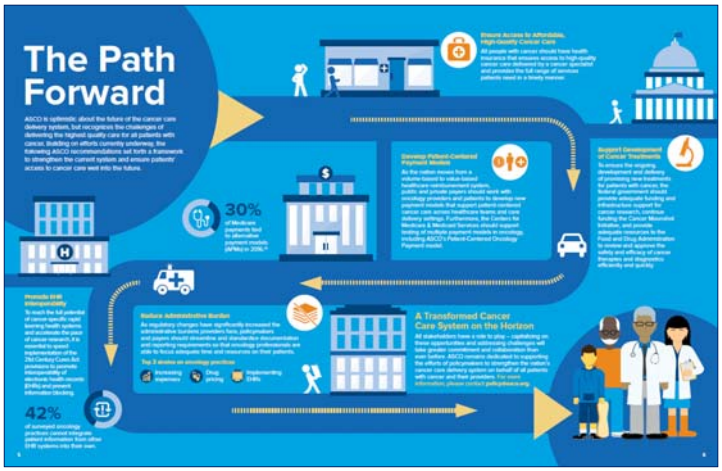

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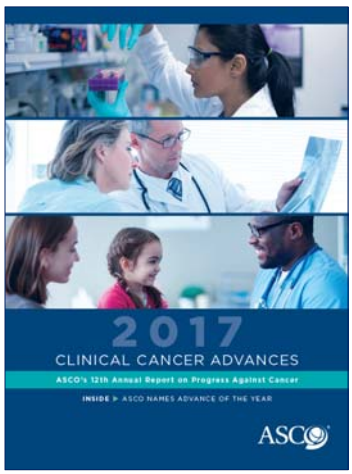
ASCO 2017 Clinical Cancer Advances



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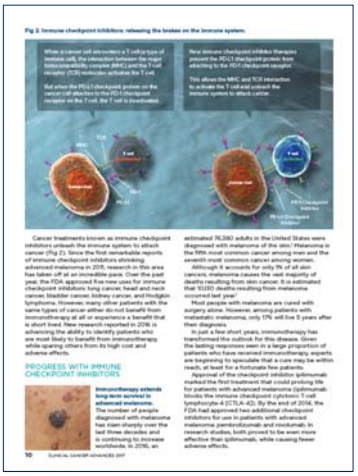
ASCO 2017 Clinical Cancer Advances



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ASCO "Hot Topics" from ASCO Meeting

- Combination Clinical Trials – 765 drug combination studies available
  - One or More Immunotherapy Agent(s)
  - One or More Targeted Agent(s)
  - One or More Conventional Therapies – chemotherapy, radiation therapy, etc.
- Keytruda in Combination for Many Cancers – 268 Keytruda drug combination studies available
- The Looming New Epidemic – "Financial Toxicity" from New Expensive Drug Costs
- Larotrectinib – TRK Fusion Gene – 17 different types of cancer – not organ specific
- Zytiga (abiraterone) + standard hormone therapy for Advanced Prostate Cancer – reduced chance of death by 40% for men with newly diagnosed advanced disease.
- CAR T-cell Therapy for Multiple Myeloma - removing T cells from patients' blood, genetically altering them to boost their cancer-fighting potential and infusing them back into the patient.

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Keytruda's Fast Track for Approvals

- Pembrolizumab is approved to treat:
  - US Brand Name(s) – Keytruda
  - Type: Immune Checkpoint Inhibitor
  - FDA Approved - Yes
- FDA Approval for Pembrolizumab for Microsatellite Instability - High
- FDA Approval for Pembrolizumab for Urothelial Carcinoma
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2017)
- FDA Approval for Pembrolizumab for Hodgkin Lymphoma
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2016)
- FDA Approval for Pembrolizumab for Head and Neck Cancer
- FDA Approval for Pembrolizumab for Melanoma (2015)
- FDA Approval for Pembrolizumab for Non-Small Cell Lung Cancer (2015)
- FDA Approval for Pembrolizumab for Melanoma (2014)

The process of mismatch repair enables cells to correct mistakes in their DNA code that sometimes occur during DNA replication. It's "like a spell-checker" for DNA, explained Dr. Gulley. Mismatch repair deficient (dMMR) cells, which lack this failsafe process, acquire multiple DNA mutations. Some dMMR cells acquire alterations in short, repetitive DNA sequences called microsatellites and are referred to as microsatellite instability-high (MSI-H).

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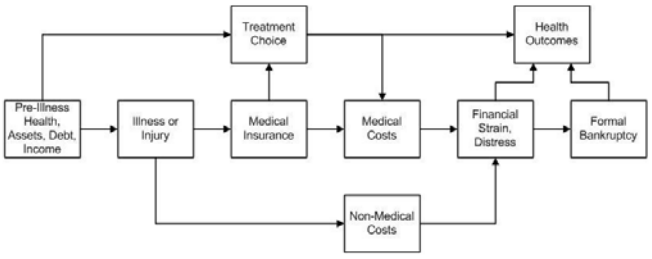
Financial Toxicity and Cancer Treatment

Financial Toxicity and Cancer Treatment (PDQ®)–Health Professional Version

Go to Patient Version

Financial Toxicity Associated with Cancer Care–Background and Prevalence

- Introduction
- Background
- Etiology and Risk Factors
- Prevalence
  - Prevalence of high out-of-pocket costs
  - Prevalence of productivity loss
  - Prevalence of asset depletion and medical debt
  - Incidence and prevalence of bankruptcy
  - Prevalence of financial stress, distress, or worry
  - Prevalence of financial hardship as a composite measure



Source: https://www.cancer.gov/about-cancer/managing-care/financial-toxicity-hp-pdq

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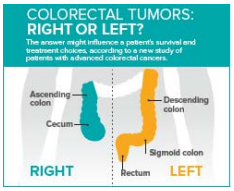
Colon Tumor Location and Treatment

- Analysis of data from a large clinical trial showed patients with advanced colorectal cancer live longer if the cancer begins on the left side of the colon rather than on the right side
- Patients received a combination of FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) chemotherapy with either of the two standard targeted therapies for advanced colorectal cancer: cetuximab or bevacizumab
- Median survival for patients with left-sided tumors was 33 months
- Median survival for patients with right-sided tumors was only 19 months
- Overall, patients with left-sided tumors had a 20% lower risk of death.



- Conclusion: the location of primary tumor should be considered when establishing prognosis and designing future clinical trials in both early and advanced colorectal cancers.
- Patients with a right-sided colorectal cancer, cetuximab may not provide a benefit. However, for those patients whose tumors originate in the left colon, either a bevacizumab- or cetuximab-based regimen is effective, with cetuximab seeming to produce the best outcomes when combined with chemotherapy.

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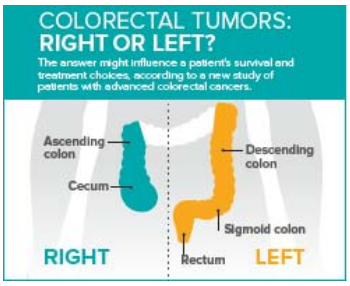
Colon Tumor Location and Treatment

Median Overall Survival by Tumor Location and Therapy

	Left-Sided Tumors	Right-Sided Tumors
All Patients	33.3 months	19.4 months
Patients Treated with Cetuximab	36 months	16.7 months
Patients Treated with Bevacizumab	31.4 months	24.2 months



Although patients whose tumors originated in the left colon lived substantially longer after treatment than patients whose tumors originated in the right colon, the survival improvement for patients treated with cetuximab was more pronounced. And patients with right-sided tumors had better outcomes when treated with bevacizumab.

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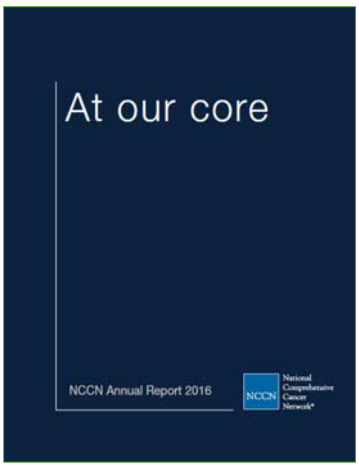
NCCN Annual Report 2016 – At Our Core



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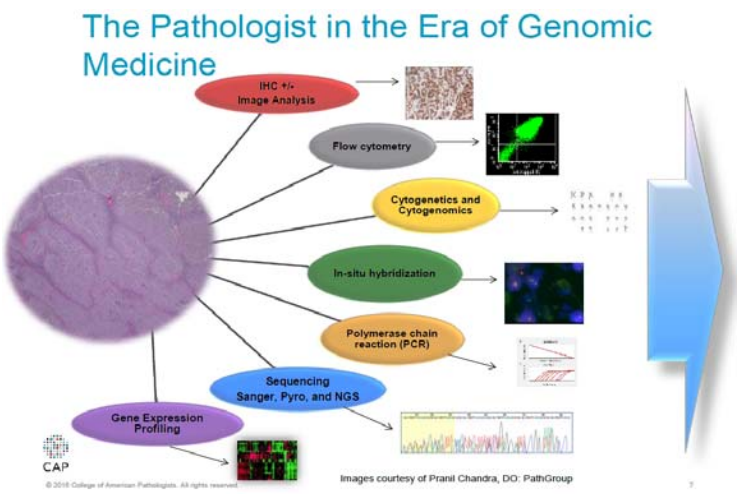
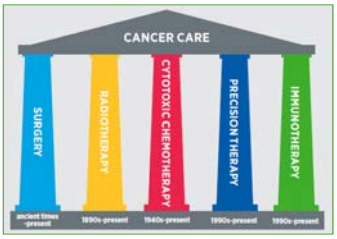
Explosion of Data / Fragmented Data Sources





Multiplex Testing May Become Standard

Combination Therapy Means Managing Multiple Treatment Data Sources

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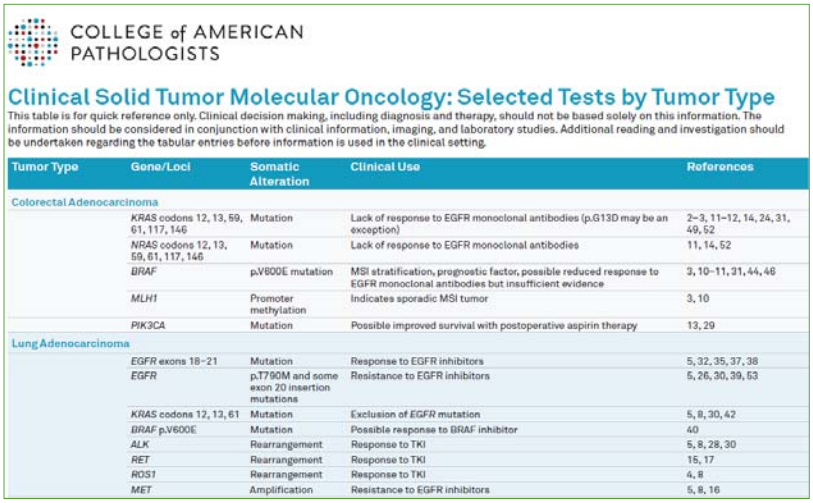
CAP Solid Tumor Selected Tests by Tumor Type



COLLEGE of AMERICAN PATHOLOGISTS

Clinical Solid Tumor Molecular Oncology: Selected Tests by Tumor Type

This table is for quick reference only. Clinical decision making, including diagnosis and therapy, should not be based solely on this information. The information should be considered in conjunction with clinical information, imaging, and laboratory studies. Additional reading and investigation should be undertaken regarding the tabular entries before information is used in the clinical setting.

Tumor Type	Gene/Loci	Somatic Alteration	Clinical Use	References
Colorectal Adenocarcinoma				
	KRAS codons 12, 13, 59, 61, 117, 146	Mutation	Lack of response to EGFR monoclonal antibodies (p.G13D may be an exception)	2–3, 11–12, 14, 24, 31, 49, 52
	NRAS codons 12, 13, 59, 61, 117, 146	Mutation	Lack of response to EGFR monoclonal antibodies	11, 14, 52
	BRAF	p.V600E mutation	MSI stratification, prognostic factor, possible reduced response to EGFR monoclonal antibodies but insufficient evidence	3, 10–11, 31, 44, 48
	MLH1	Promoter methylation	Indicates sporadic MSI tumor	3, 10
	PIK3CA	Mutation	Possible improved survival with postoperative aspirin therapy	13, 29
Lung Adenocarcinoma				
	EGFR exons 18–21	Mutation	Response to EGFR inhibitors	5, 32, 35, 37, 38
	EGFR	p.T790M and some exon 20 insertion mutations	Resistance to EGFR inhibitors	5, 26, 30, 39, 53
	KRAS codons 12, 13, 61	Mutation	Exclusion of *EGFR* mutation	5, 8, 30, 42
	BRAF p.V600E	Mutation	Possible response to BRAF inhibitor	40
	ALK	Rearrangement	Response to TKI	5, 8, 28, 30
	RET	Rearrangement	Response to TKI	15, 17
	ROS1	Rearrangement	Response to TKI	4, 8
	MET	Amplification	Resistance to EGFR inhibitors	5, 8, 16

Source: College of American Pathologists (CAP) Allison M. Cushman-Vokoun, MD, PhD

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CAP Solid Tumor Selected Tests by Tumor Type

Breast Carcinoma				
	HER2/ERBB2	Amplification	Response to HER2 monoclonal antibodies	18, 51
Gastric Adenocarcinoma				
	HER2/ERBB2	Amplification	Response to HER2 monoclonal antibodies	45
Thyroid Carcinoma				
Papillary Thyroid Carcinoma / Anaplastic Thyroid Cancer	*BRAF*	p.V600E mutation	Preoperative FNA diagnosis and prognosis, potential therapeutic target	9, 36, 43
	NRAS, HRAS, KRAS	Mutation	Preoperative FNA diagnosis	36
	RET-PTC	Rearrangement	Preoperative FNA diagnosis	36
Follicular Thyroid Carcinoma	*NRAS, HRAS, KRAS*	Mutation	Preoperative FNA diagnosis	36
	PAX8-PPAR$_\gamma$	Rearrangement	Preoperative FNA diagnosis	36
Melanoma				
Cutaneous & Mucosal	*BRAF* codon 600	Mutation	Response to BRAF inhibitors	19–20, 33
	KIT	Mutation	Response to TKI	7
Uveal	*GNAQ* or *GNA11*	Mutation	Diagnostic	50
	Chromosome 3	Loss (monosomy)	Unfavorable prognosis	23
GIST				
	KIT	Mutation	Response to TKI	41
	PDGFRA	Mutation	Response to TKI	41
	BRAF p.V600E	Mutation	Possible imatinib resistance	1, 34

Source: College of American Pathologists (CAP) Allison M. Cushman-Vokoun, MD, PhD

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CAP Solid Tumor Selected Tests by Tumor Type

CNS Neoplasms				
Glioma	*MGMT*	Promoter methylation	Favorable response to alkylating agents	21
	IDH1 and *IDH2*	Mutation	Distinguishes reactive gliosis from glioma, favorable prognosis	27, 54
Oligodendroglioma	Chromosome 1p and 19q	Co-deletion	Favorable prognosis and response to therapy	6, 22
Pilocytic Astrocytoma	*BRAF*	Duplication/ fusion and p.V600E mutation (extracere-bellar)	Diagnostic	27, 47
Pleomorphic Xanthoastrocytoma and Ganglioglioma	*BRAF*	p.V600E mutation	Diagnostic	47
Cholangiocarcinoma/Pancreatic Carcinoma				
	KRAS codons 12, 13, 61	Mutation	Preoperative bile duct brushing diagnosis	25
Oropharyngeal Squamous Cell Carcinoma				
	HR HPV-related	Positive detection	Favorable response to chemoradiation therapy	48

Source: Allison M. Cushman-Vokoun, MD, PhD

MSI = Microsatellite Instability; TKI = Tyrosine-Kinase Inhibitors; HR HPV= High-Risk Human Papillomavirus
This table is meant to be a list of selected tests and is not a comprehensive resource.

August 2016

Source: College of American Pathologists (CAP) Allison M. Cushman-Vokoun, MD, PhD

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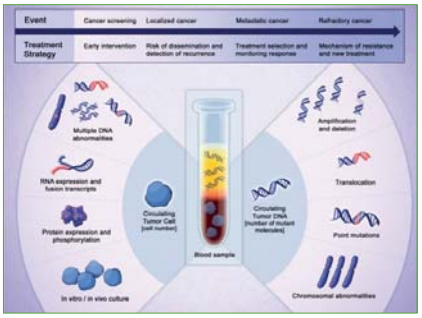
New Diagnostic Tools & Techniques

Major trends shaping healthcare and life science markets in genomics:

1) Integration of Genomic Data into Clinical Workflows
2) On the Rise: Pharmacogenomic
3) Emergence of Advanced Genomic Editing Techniques
4) Noninvasive Cancer Screening – Liquid Biopsy
5) More Direct-to-Consumer Genetics
6) Growth of Newborn Genetic Screening Programs
7) Integration of New Data Streams



Gene-Quantification – Liquid Biopsy

Source: *Genetic Engineering & Biotechnology News*, "A Look Ahead: Seven Trends Shaping Genomics in 2017 and Beyond"

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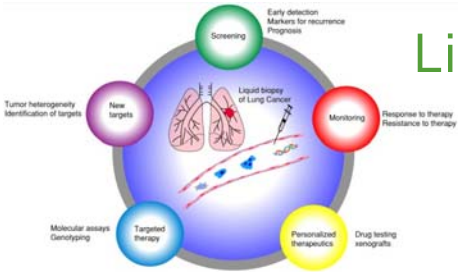
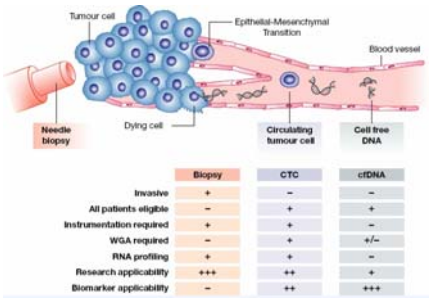
Liquid Biopsy





	Biopsy	CTC	cfDNA
Invasive	+	–	–
All patients eligible	–	+	+
Instrumentation required	+	+	–
WGA required	–	+	+/–
RNA profiling	+	+	–
Research applicability	+++	++	+
Biomarker applicability	–	++	+++

- Liquid biopsy is a minimally invasive technology for detection of molecular biomarkers without the need for costly or invasive procedures.
- Circulating cancer cells or traces of the cancer's RNA or DNA in the blood can give clues about which treatments are likely to work for a patient.
- Circulating nucleic acids are protected by extracellular micro-vesicles, mainly exosomes.
- Exosomes are cell-derived vesicles that are present in many and perhaps all eukaryotic fluids, including blood, urine, and cultured medium of cell cultures.
- Exosomes maintain specified "compartments" of micro and macro molecules. Cancers create an expulsion of key proteins and microRNAs resulting in mis-expression of intracellular molecules which in turn interrupt cancer's intra and extra cellular communications pathways

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Next Generation Genomic Sequencing

- Advances in Genome Sequencing, Pharmacogenomics, Gene Editing, and Biometric Wearables Will Provide New Pathways to Improve Cancer Therapy Options – fast, reliable, standardized, portable, and beyond proof of concept
- Next-generation sequencing (NGS) is arguably one of the most significant technological advances in the biological sciences of the last 30 years. NGS has evolved to point where now in routine use when establishing cancer diagnosis.
- NGS in turn is translating to rapid development and approvals for ne diagnostic, prognostic & therapeutic targets
- Multi-Gene Assays cropping up everywhere – these are not standardized and are often proprietary and under study
- Example: Prostate - New three-in-one blood test could transform treatment of advanced prostate cancer through use of precision drugs such as PARP Inhibitor, olaparib, designed to target mutations in BRCA2 and PALB2 genes
  - Olaparib is good at killing cancer cells that have errors in genes that have a role in repairing damaged DNA.
  - Some patients respond to the drug for years
  - Other patients, the treatment either fails early, or the cancer evolves resistance.
  - Study also identified specific genetic mutations used to resist treatment with olaparib
  - The test is designed for use both before and after treatment
- Using the absolute amounts of cancer DNA in the bloodstream and also a readout of the specific mutations within that genetic material – researchers believe the test can usher in a new era of precision medicine for prostate cancer.

Source: *ICR, The Royal Marsden, UCL and Imperial College London*

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Next Generation Immuno & Precision Therapies

- Checkpoint Inhibitors – Keytruda – "humanized" monoclonal antibodies
- PARP Inhibitors - PARP enzymes help repair damaged DNA. PARP inhibitors block this repair mechanism, causing some cancer cells to die.
- CAR-T Cells – immunotherapy using patient's own immune cells
- CRISPR/Cas9 – intentional gene sequence alteration – gene editing technique
- Cellular Immunotherapy – targeted immunotherapy
  - G12D is a Target for KRAS, NRAS, HRAS Mutant Cancers – mutations in KRAS gene
    - 95% of all pancreatic cancers
    - 50% of all colorectal cancers
  - Infusion of the patient's own Tumor Infiltrating Lymphocytes (TILs), called adoptive T cell transfer immunotherapy, to mediate effective antitumor immune responses against cancers that express the KRAS G12D mutation "presenting" the neoplasm as foreign to immune system
- Limitations: Managing Cytokine Release Syndrome (CRS) – CRS can be fatal

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Next Generation Precision Therapies Checkpoint Inhibitors

- Immune checkpoint inhibitors are drugs – often made of antibodies – that unleash an immune system attack on cancer cells.
- When immune system T-cells encounter another cell, they probe certain proteins on its surface, which serve as insignia of the cell's identity.
- If the proteins indicate the cell is normal and healthy, the T cell leaves it alone.
- If the proteins suggest the cell is infected or cancerous, the T cell will lead an attack against it.
- Once T cells initiate an attack, the immune system increases a series of additional molecules to prevent the attack from damaging normal tissues in the body.
- These molecules are known as immune checkpoints.
- Cancer cells use immune checkpoint molecules to trick the immune system such that the immune system identifies the cancer cells as normal cells with normal proteins on its surface, and leaves the cancer cell alone to reproduce and proliferate unfettered.
- Example: genomic alterations in 196 tumors related to development of Hepatocellular Carcinoma include mutations in the *TERT* gene promotor, mutations in the *TP53* and *CTNNB1* (β-catenin) genes, and elevated expression of several immune checkpoint genes. These are now therapies for therapeutic intervention using Checkpoint Inhibitors targeting TERT, TP53 and CTNNB1.

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Next Generation Precision Therapies CAR-T and CRISPR/CAS9

- **CAR-T = Chimeric Antigen Receptor T Cells**
  - Aim is to "reprogram" the immune system to target specific proteins on cancer cell
  - New Therapy Based on Anti-CD19 CAR-T cells
  - BCMA-targeted CAR T-Cells for Plasma Cell Myeloma
  - KTE-C19 for Diffuse Large B-Cell Lymphoma
  - CTL019 for Acute Lymphoblastic Leukemia
  - JCAR015 for Leukemia

- **CRISPR/CAS9 – Gene Editing Approach**
  - Specific Manipulation of the Defective Gene Sequence Targets Errant DNA in Cancer Cells
  - Intentional Break in Gene Sequence Used to Trigger Self-Repair Mechanism in Cellular DNA
  - Inject Genome-Edited Immune Cells into Patient – NSCLC
  - Gene Editing Approach more promising for solid tumors

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Next Generation Precision Therapies PARP Inhibitors

- PARP enzymes help repair damaged DNA. Below example is olaparib (Lynparaza) for glioma.
- PARP inhibitors block this repair mechanism, causing some cancer cells to die.
- How It Works - some cancer therapies, like chemotherapy and radiation, damage DNA. If the damage is not extensive, cells can often repair it and carry on. But if cells have defects in their ability to repair DNA, they may not be able to recover and die. Ex: BRCA1 & BRCA2 genes have reduced DNA-repair abilities.
- Cancer cells with DNA repair mechanism mutations, which in low grade glioma affect a gene called IDH, similar to BRCA1 or BRCA2 gene mutation, have an impaired ability to repair DNA damage. Treating these cells with PARP inhibitors, drugs that further disrupt DNA repair, effectively killed the cancer cells.
- IDH-mutant gliomas are more vulnerable to chemotherapy
- Amplifying this vulnerability enhanced toxic effects resulting in kill of more glioma cells.
- PARP inhibitors killed glioma cells with IDH mutations but not cells with normal IDH.
- PARP inhibitor enhanced the toxic effects of chemotherapy treatment on IDH-mutant cells
- Combining olaparib with temozolomide (alkylating chemo agent) enhanced DNA-damage and killing effects

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Update on NCI MATCH Trial & SubProtocols

(**M**olecular **A**nalysis for **T**herapy **Ch**oice)

Sub Protocol	MATCH	Restrictions	Treatment
EAY131 – **A**	Solid tumors or lymphomas with **activating mutations of EGFR** that progressed after standard TX	Small Cell and Non-Small cell Lung cancer excluded	Afatinib 40 mg QD PO
EAY131 – **B**	**HER2 activating**	Non-Small cell lung cancer excluded. No	Afatinib 40 mg QD PO
EAY131 – **C1**	Tumors with **MET amplification**		Crizotinib 250 mg BID PO
EAY131 – **C2**	Tumors with **MET Exon 14 deletion**		Crizotinib 250 mg BID PO
EAY131 – **E**	Tumors with **EGFR T790M mutation** or **rare activating mutations of EGFR**	Non-Small Cell Lung Cancer	AZD9291 80 mg QD PO
EAY131 – **F**	Tumors with **ALK translocations**	Adenocarcinoma of lung or	Crizotinib 250 mg BID PO
EAY131 – **G**	**ROS1 Translocations or Inversion**	Non-Small Cell Lung Cancer	Crizotinib 250 mg BID PO
EAY131 – **H**	Tumors with **BRAF V600E, V600K, V600R or V600D** Mutations	Metastatic melanoma from	Trametinib 2 mg QD PO + Drabrafenib 150 mg BID
EAY131 – **I**	**PIK3CA mutation**	Breast cancer, squamous cell	GDC-0032 (Taselisib) 4 mg QD PO
EAY131 – **J**	**HER2 amplifications (> 7 copies/cell)**	Breast, gastric/GEJ/Es	Pertuzumab IV 840 mg + Trastuzumab IV 8 mg/kg

Sub Protocol	MATCH	Restrictions	Treatment
EAY131 – **L**	**mTOR**	Patients with brain mets must not have progression for over 1 month prior to start of tx.	TAK228 (MLN0128) 3 mg QD PO
EAY131 – **M**	**TSC1 or TSC2**	Patients with brain mets must not have progression for over 1 month prior to start of tx.	TAK228 (MLN0128) 3 mg QD PO
EAY131 – **N**	Tumors with **PTEN mutation/deletion**, with PTEN	PTEN mutation 225% variant	PI3K Beta Specific inhibitor GSK2636771 400 mg QD
EAY131 – **P**	**PTEN loss** via IHC	Non-Small Cell Lung Cancer	GSK2636771 400 mg QD PO
EAY131 – **Q**	Tumors with **HER 2 amplification** (> 7)	Breast, Gastric, Gastroesophageal Junction	Ado-trastuzumab Emtansine 3.6mg/kg IV once every 3 weeks
EAY131 – **R**	**BRAF fusions**, or with **non V600E**, or **non V600K** mutations	HX of interstitial lung disease or	Trametinib 2 mg QD PO
EAY131 – **S1**	Tumors with **NF1** mutations	Must have deleterious inactivating NF-	Trametinib 2 mg QD PO
EAY131 – **S2**	Tumors with **GNAQ or GNA11** mutations	No HX of interstitial lung	Trametinib 2 mg QD PO

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Update on NCI MATCH Trial & SubProtocols

(**M**olecular **A**nalysis for **T**herapy **Ch**oice)

Sub Protocol	MATCH	Restrictions	Treatment
EAY131 – **T**	Tumors with **Smoothened (SMO)** or **Patched 1 (PTCH1)** mutations	Basal Cell skin carcinoma	GDC-004 (Vismodegib) 150 mg QD PO
EAY131 – **U**	Tumors with **NF2 Loss**	Inactivating mutation of	VS-6063 (Defactinib) 400 mg BID PO
EAY131 – **V**	Tumors with **c-KIT** mutations (Exon 9, 11, 13 or 14) Exon 17 or 18 excluded.	GIST (Gastrointestinal	Sunitinib 50 mg QD PO for 28 consecutive days
EAY131 – **W**	Tumors with **aberrations in FGFR** pathway	FGFR 1-3 amplification,	AZD4547 80 mg BID PO
EAY131 – **X**	Tumors with **DDR2** mutations	Must have one DDR2 mutation: S768R, I638F,	Dasatinib 140 mg QD PO
EAY131 – **Y**	Tumors with **AKT** mutations	KRAS, NRAS, HRAS or BRAF mutations	AZD5363 480 mg BID PO (4 days on, 3 days off) for each week of the 28 day
EAY131 – **Z1A**	Tumors with **NRAS** mutations (Codon 12, 13, 61)	Melanoma excluded. Active CNS lesion	Binimetinib 45 mg BID PO
EAY131 – **Z1B**	Tumors with **CCND1, 2 or 3 amplification**	Rb protein expression by	Palbociclib 125 mg QD PO for 21 consecutive days and
EAY131 – **Z1C**	**CDK4 or CDK6 Amplifications**	Rb protein expression by	Palbociclib 125 mg QD PO for 21 consecutive days and
EAY131 – **Z1D**	Tumors with **Mismatch repair deficiency**	Colorectal cancer excluded.	Nivolumab 240 mg IV at Days 1 & 15 of each cycle;
EAY131 – **Z1E**	**NTRK Fusions (NTRK1, 2 or 3 gene fusion)**		LOXO-101 100 mg PO BID
EAY131 – **Z1I**	**BRCA 1 or BRCA 2 gene**	Patients with ovarian cancer	AZD1775 300 mg QD PO 5 days on, 2 days off. (2

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Information Sources and Resources

- American Association for Cancer Research (AACR), June 5, 2017 - doi: 10.1158/0008-5472.CAN-17-0758
- American Cancer Society – 2017 Cancer Facts and Figures
- JNCI J Natl Cancer Inst (2017) 109(9): djx030 - Annual Report to the Nation on the Status of Cancer
- Featuring Survival – 1975-2014
- AACR Cancer Progress Report - 2016
- National Toxicology Program - 14th Report on Carcinogens (2016)
- ASCO 2017 State of Cancer Care in America
- ASCO 2017 Clinical Cancer Advances
- NCCN Annual Report 2016 – At Our Core
- The Pathologist in the Era of Genomic Medicine – PathGroup - College of American Pathology (CAP)
- CAP Solid Tumor Selected Tests by Tumor Type - College of American Pathologists (CAP) A. M. Cushman-Vokoun, MD, PhD
- Genetic Engineering & Biotechnology News, "A Look Ahead: Seven Trends Shaping Genomics in 2017 and Beyond"
- Institute of Cancer Research, The Royal Marsden, UCL and Imperial College London
- NCI MATCH Trial – National Cancer Institute

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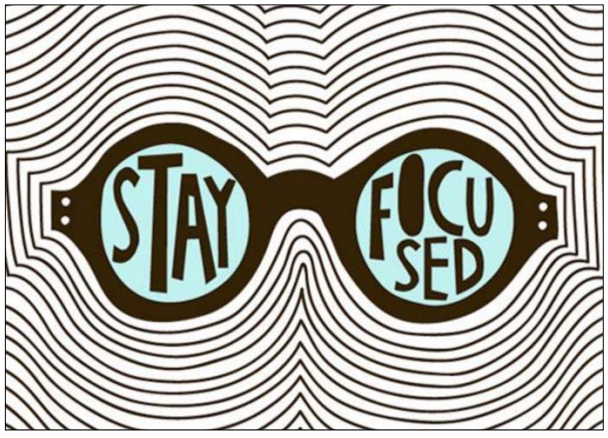
Questions



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