

Table S3. Dates of translational milestones for cancer genomic tests

Cancer Type(s)	Test	Purpose(s)	Discovery	First Human Study	First Demonstration of Test (by purpose)	First Recommendation Statement (by purpose) ^a	FDA Approval/Clearance
Acute lymphocytic leukemia	TPMT	Pharmacogenomic	September 1980 ²²	September 1980 ²²	June 1999 ³³	March 2011	--
Acute myeloid leukemia	CEBPA	Prognostic	January 1997 ³⁴	March 2001 ³⁵	October 2002 ³⁶	November 2011	--
	FLT3-ITD	Prognostic	December 1996 ³⁷	December 1996 ³⁷	May 1999 ³⁸	November 2011	--
	FLT3-TKD	Prognostic	April 2001 ³⁹	April 2001 ³⁹	April 2001 ³⁹	November 2011	--
	IDH1	Prognostic	September 2009 ⁴⁰	September 2009 ⁴⁰	May 2010 ⁴¹	November 2011	--
	IDH2 c.515G>A p.R172K	Prognostic	May 2010 ⁴¹	May 2010 ⁴¹	May 2010 ⁴¹	November 2011	--
	IDH2 (codon 140)	Prognostic	March 2010 ⁴²	March 2010 ⁴²	May 2010 ⁴¹	November 2011	--
	KIT	Prognostic	October 1989 ⁴³	December 1991 ⁴⁴	August 2006 ⁴⁵	November 2011	--
	MLL-PTD	Prognostic	December 1991 ⁴⁶	May 1996 ⁴⁷	May 2000 ⁴⁸	November 2011	--
	NPM1	Prognostic	January 1996 ⁴⁹	January 1996 ⁴⁹	December 2005 ⁵⁰	November 2011	--
	RUNX1	Prognostic	December 1991 ⁵¹	December 1991 ⁵¹	November 1996 ⁵²	November 2011	--
Breast cancer	WT1	Prognostic	May 1992 ⁵³	May 1992 ⁵³	November 1994 ⁵⁴	November 2011	--
	H:I ratio (HOXB13:IL17BR)	Prognostic	June 2004 ⁵⁵	June 2004 ⁵⁵	October 2006 ⁵⁶	January 2009	--
	CYP2D6	Pharmacogenomic	January 1990 ⁵⁷	January 1990 ⁵⁷	January 2005 ⁵⁸	January 2005	Cleared December 2004
	MammaPrint	Prognostic	January 2002 ²³	January 2002 ²³	December 2002 ⁵⁹	January 2009	Cleared February 2007
	Oncotype DX	Prognostic; Pharmacogenomic	December 2005 ⁶⁰	December 2005 ⁶⁰	December 2004 ⁶¹ ; August 2006 ⁶²	November 2007; November 2007	--

Breast and Ovarian cancer	BRCA	Screening	December 1990 ⁶³	December 1990 ⁶³	May 1997 ⁶⁴	May 2004	--
Chronic lymphocytic leukemia	TP53	Pharmacogenomic	September 1989 ⁶⁵	June 1991 ⁶⁶	December 1993 ⁶⁷	May 2004	Cleared August 2011
Colon cancer	BRAF	Screening; Prognostic; Pharmacogenomic	June 2002 ⁶⁸	June 2002 ⁶⁸	January 2004 ⁶⁹ ; July 2005 ⁷⁰ ; December 2008 ⁷¹	January 2009; November 2011; November 2011	--
	ColoPrint	Prognostic	January 2011 ⁷²	January 2011 ⁷²	January 2011 ⁷²	November 2011	--
	Oncotype DX Colon	Prognostic	August 2007 ⁷³	August 2007 ⁷³	November 2011 ⁷⁴	November 2011	--
Colorectal cancer	18q LOH/DCC	Prognostic; Pharmacogenomic	January 1990 ⁷⁵	January 1990 ⁷⁵	December 1996 ⁷⁶ ; July 2004 ⁷⁷	February 2006; February 2006	--
	KRAS (except c.38G>A (p.G13D))	Pharmacogenomic	March 1983 ⁷⁸	June 1984 ⁷⁹	April 2006 ⁸⁰	February 2009	Approved July 2012
Lynch syndrome testing, MMR/MSI	Screening; Diagnostic; Prognostic; Pharmacogenomic	May 1993 ⁸¹	May 1993 ⁸¹	April 1996 ⁸² ; April 1996 ⁸² ; June 1996 ⁸³ ; August 2001 ⁸⁴	January 2009; January 2009; November 2006; November 2006	--	
	NRAS	Pharmacogenomic	September 1988 ⁸⁵	September 1988 ⁸⁵	August 2010 ⁸⁶	February 2013	--
	PIK3CA	Pharmacogenomic	April 2004 ⁸⁷	April 2004 ⁸⁷	March 2008 ⁸⁸	February 2013	
	PTEN	Pharmacogenomic	January 2000 ⁸⁹	January 2000 ⁸⁹	October 2007 ⁹⁰	February 2013	--
	TP53	Prognostic; Pharmacogenomic	August 1984 ⁹¹	August 1984 ⁹¹	September 1992 ⁹² ; June 1996 ⁹³	November 2006; November 2006	Cleared April 2012
	UGT1A1	Pharmacogenomic	October 1997 ⁹⁴	October 1997 ⁹⁴	December 2000 ⁹⁵	January 2010	Cleared August 2005
Glioma	1p/19q	Diagnostic; Prognostic	April 1994 ⁹⁶	April 1994 ⁹⁶	July 1999 ⁹⁷ ; October 1998 ⁹⁸	November 2011; November 2011	--
	G-CIMP	Prognostic	February 2000 ⁹⁹	February 2000 ⁹⁹	May 2010 ¹⁰⁰	November 2011	--
	IDH (IDH1) c. 395	Diagnostic; Prognostic	September 2008 ¹⁰¹	September 2008 ¹⁰¹	December 2009 ¹⁰² ; February 2009 ¹⁰³	November 2011; November 2011	--

G>A p.R132H (IDH2)							
Glioma (Glioblastoma)	MGMT	Prognostic; Pharmacogenomic	September 1991 ¹⁰⁴	September 1991 ¹⁰⁴	October 1998 ¹⁰⁵ ; November 2000 ¹⁰⁶	February 2010; November 2011	--
Glioma (Pilocytic astrocytoma)	BRAF fusion	Diagnostic	November 2008 ¹⁰⁷	November 2008 ¹⁰⁷	August 2010 ¹⁰⁸	November 2011	--
Melanoma	BRAF	Pharmacogenomic	June 2002 ⁶⁸	June 2002 ⁶⁸	September 2010 ¹⁰⁹	November 2011	Approved August 2011
Non-small cell lung cancer	ALK	Pharmacogenomic	August 2007 ¹¹⁰	August 2007 ¹¹⁰	October 2010 ¹¹¹	November 2011	Approved August 2011
	EGFR	Pharmacogenomic	August 1985 ¹¹²	August 1985 ¹¹²	May 2004 ¹¹³	July 2010	Approved May 2013
	ERCC1	Prognostic; Pharmacogenomic	July 2002 ¹¹⁴	July 2002 ¹¹⁴	July 2002 ¹¹⁴ ; September 2006 ¹¹⁵	November 2013; November 2013	--
	KRAS	Prognostic; Pharmacogenomic	June 1982 ¹¹⁶	February 1984 ¹¹⁷	August 1990 ¹¹⁸ ; September 2005 ¹¹⁹	November 2011; October 2013	--
	ROS1	Pharmacogenomic	September 1984 ¹²⁰	September 1984 ¹²⁰	September 2012 ¹²¹	September 2013	--
	RRM1	Prognostic; Pharmacogenomic	November 1997 ¹²²	September 1999 ¹²³	May 2004 ¹²⁴ ; June 2003 ¹²⁵	July 2010; July 2010	--
Prostate cancer	PCA3 (DD3)	Diagnostic	December 1999 ¹²⁶	December 1999 ¹²⁶	May 2002 ¹²⁷	November 2011	Approved February 2012
Thyroid cancer (medullary)	RET	Screening; Diagnostic	October 1990 ¹²⁸	October 1990 ¹²⁸	September 1994 ¹²⁹ ; September 1994 ¹²⁹	June 2009; June 2009	--
Various ^b	DPYD	Pharmacogenomic	September 1994 ¹³⁰	August 1996 ¹³¹	September 2001 ¹³²	August 2010	--
	TYMS	Pharmacogenomic	May 1984 ¹³³	March 1987 ¹³⁴	January 2001 ¹³⁵	August 2010	--

^a earliest recommendation statement of the same recommendation type (e.g. positive or negative) as the most recent recommendation statement

^b includes colorectal cancer, other gastrointestinal cancer, head and neck, and breast cancer

Supplementary References

33. McLeod HL, Coulthard S, Thomas AE, et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. *Br J Haematol.* Jun 1999;105(3):696-700.
34. Zhang DE, Zhang P, Wang ND, Hetherington CJ, Darlington GJ, Tenen DG. Absence of granulocyte colony-stimulating factor signaling and neutrophil development in CCAAT enhancer binding protein alpha-deficient mice. *Proc Natl Acad Sci U S A.* Jan 21 1997;94(2):569-574.
35. Pabst T, Mueller BU, Zhang P, et al. Dominant-negative mutations of CEBPA, encoding CCAAT/enhancer binding protein-alpha (C/EBPalpha), in acute myeloid leukemia. *Nat Genet.* Mar 2001;27(3):263-270.
36. Preudhomme C, Sagot C, Boissel N, et al. Favorable prognostic significance of CEBPA mutations in patients with de novo acute myeloid leukemia: a study from the Acute Leukemia French Association (ALFA). *Blood.* Oct 15 2002;100(8):2717-2723.
37. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. *Leukemia.* Dec 1996;10(12):1911-1918.
38. Kiyoi H, Naoe T, Nakano Y, et al. Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. *Blood.* May 1 1999;93(9):3074-3080.
39. Yamamoto Y, Kiyoi H, Nakano Y, et al. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. *Blood.* Apr 15 2001;97(8):2434-2439.
40. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med.* Sep 10 2009;361(11):1058-1066.
41. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *J Clin Oncol.* May 10 2010;28(14):2348-2355.

42. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell*. Mar 16 2010;17(3):225-234.
43. Wang C, Curtis JE, Geissler EN, McCulloch EA, Minden MD. The expression of the proto-oncogene C-kit in the blast cells of acute myeloblastic leukemia. *Leukemia*. Oct 1989;3(10):699-702.
44. Ikeda H, Kanakura Y, Tamaki T, et al. Expression and functional role of the proto-oncogene c-kit in acute myeloblastic leukemia cells. *Blood*. Dec 1 1991;78(11):2962-2968.
45. Paschka P, Marcucci G, Ruppert AS, et al. Adverse prognostic significance of KIT mutations in adult acute myeloid leukemia with inv(16) and t(8;21): a Cancer and Leukemia Group B Study. *J Clin Oncol*. Aug 20 2006;24(24):3904-3911.
46. Ziemin-van der Poel S, McCabe NR, Gill HJ, et al. Identification of a gene, MLL, that spans the breakpoint in 11q23 translocations associated with human leukemias. *Proc Natl Acad Sci U S A*. Dec 1 1991;88(23):10735-10739.
47. Yu M, Honoki K, Andersen J, Paietta E, Nam DK, Yunis JJ. MLL tandem duplication and multiple splicing in adult acute myeloid leukemia with normal karyotype. *Leukemia*. May 1996;10(5):774-780.
48. Schnittger S, Kinkel U, Schoch C, et al. Screening for MLL tandem duplication in 387 unselected patients with AML identify a prognostically unfavorable subset of AML. *Leukemia*. May 2000;14(5):796-804.
49. Yoneda-Kato N, Look AT, Kirstein MN, et al. The t(3;5)(q25.1;q34) of myelodysplastic syndrome and acute myeloid leukemia produces a novel fusion gene, NPM-MLF1. *Oncogene*. Jan 18 1996;12(2):265-275.
50. Dohner K, Schlenk RF, Habdank M, et al. Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. *Blood*. Dec 1 2005;106(12):3740-3746.

51. Miyoshi H, Shimizu K, Kozu T, Maseki N, Kaneko Y, Ohki M. t(8;21) breakpoints on chromosome 21 in acute myeloid leukemia are clustered within a limited region of a single gene, AML1. *Proc Natl Acad Sci U S A*. Dec 1 1991;88(23):10431-10434.
52. Tobal K, Yin JA. Monitoring of minimal residual disease by quantitative reverse transcriptase-polymerase chain reaction for AML1-MTG8 transcripts in AML-M2 with t(8; 21). *Blood*. Nov 15 1996;88(10):3704-3709.
53. Miwa H, Beran M, Saunders GF. Expression of the Wilms' tumor gene (WT1) in human leukemias. *Leukemia*. May 1992;6(5):405-409.
54. Inoue K, Sugiyama H, Ogawa H, et al. WT1 as a new prognostic factor and a new marker for the detection of minimal residual disease in acute leukemia. *Blood*. Nov 1 1994;84(9):3071-3079.
55. Ma XJ, Wang Z, Ryan PD, et al. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. *Cancer Cell*. Jun 2004;5(6):607-616.
56. Ma XJ, Hilsenbeck SG, Wang W, et al. The HOXB13:IL17BR expression index is a prognostic factor in early-stage breast cancer. *J Clin Oncol*. Oct 1 2006;24(28):4611-4619.
57. Pontin JE, Hamed H, Fentiman IS, Idle JR. Cytochrome P450dbl phenotypes in malignant and benign breast disease. *Eur J Cancer*. 1990;26(7):790-792.
58. Wegman P, Vainikka L, Stal O, et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res*. 2005;7(3):R284-290.
59. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. Dec 19 2002;347(25):1999-2009.
60. Cobleigh MA, Tabesh B, Bitterman P, et al. Tumor gene expression and prognosis in breast cancer patients with 10 or more positive lymph nodes. *Clin Cancer Res*. Dec 15 2005;11(24 Pt 1):8623-8631.

61. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* Dec 30 2004;351(27):2817-2826.
62. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* Aug 10 2006;24(23):3726-3734.
63. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science.* Dec 21 1990;250(4988):1684-1689.
64. Krainer M, Silva-Arrieta S, FitzGerald MG, et al. Differential contributions of BRCA1 and BRCA2 to early-onset breast cancer. *N Engl J Med.* May 15 1997;336(20):1416-1421.
65. Lavigne A, Maltby V, Mock D, Rossant J, Pawson T, Bernstein A. High incidence of lung, bone, and lymphoid tumors in transgenic mice overexpressing mutant alleles of the p53 oncogene. *Mol Cell Biol.* Sep 1989;9(9):3982-3991.
66. Gaidano G, Ballerini P, Gong JZ, et al. p53 mutations in human lymphoid malignancies: association with Burkitt lymphoma and chronic lymphocytic leukemia. *Proc Natl Acad Sci U S A.* Jun 15 1991;88(12):5413-5417.
67. el Rouby S, Thomas A, Costin D, et al. p53 gene mutation in B-cell chronic lymphocytic leukemia is associated with drug resistance and is independent of MDR1/MDR3 gene expression. *Blood.* Dec 1 1993;82(11):3452-3459.
68. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature.* Jun 27 2002;417(6892):949-954.
69. Deng G, Bell I, Crawley S, et al. BRAF mutation is frequently present in sporadic colorectal cancer with methylated hMLH1, but not in hereditary nonpolyposis colorectal cancer. *Clin Cancer Res.* Jan 1 2004;10(1 Pt 1):191-195.
70. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. *Cancer Res.* Jul 15 2005;65(14):6063-6069.

71. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol.* Dec 10 2008;26(35):5705-5712.
72. Salazar R, Roepman P, Capella G, et al. Gene expression signature to improve prognosis prediction of stage II and III colorectal cancer. *J Clin Oncol.* Jan 1 2011;29(1):17-24.
73. Clark-Langone KM, Wu JY, Sangli C, et al. Biomarker discovery for colon cancer using a 761 gene RT-PCR assay. *BMC Genomics.* 2007;8:279.
74. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *J Clin Oncol.* Dec 10 2011;29(35):4611-4619.
75. Fearon ER, Cho KR, Nigro JM, et al. Identification of a chromosome 18q gene that is altered in colorectal cancers. *Science.* Jan 5 1990;247(4938):49-56.
76. Shibata D, Reale MA, Lavin P, et al. The DCC protein and prognosis in colorectal cancer. *N Engl J Med.* Dec 5 1996;335(23):1727-1732.
77. Gal R, Sadikov E, Sulkes J, Klein B, Koren R. Deleted in colorectal cancer protein expression as a possible predictor of response to adjuvant chemotherapy in colorectal cancer patients. *Dis Colon Rectum.* Jul 2004;47(7):1216-1224.
78. McCoy MS, Toole JJ, Cunningham JM, Chang EH, Lowy DR, Weinberg RA. Characterization of a human colon/lung carcinoma oncogene. *Nature.* Mar 3 1983;302(5903):79-81.
79. Spandidos DA, Kerr IB. Elevated expression of the human ras oncogene family in premalignant and malignant tumours of the colorectum. *Br J Cancer.* Jun 1984;49(6):681-688.
80. Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res.* Apr 15 2006;66(8):3992-3995.
81. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science.* May 7 1993;260(5109):816-819.

82. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology*. Apr 1996;110(4):1020-1027.
83. Bubb VJ, Curtis LJ, Cunningham C, et al. Microsatellite instability and the role of hMSH2 in sporadic colorectal cancer. *Oncogene*. Jun 20 1996;12(12):2641-2649.
84. Elsaleh H, Iacopetta B. Microsatellite instability is a predictive marker for survival benefit from adjuvant chemotherapy in a population-based series of stage III colorectal carcinoma. *Clin Colorectal Cancer*. Aug 2001;1(2):104-109.
85. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med*. Sep 1 1988;319(9):525-532.
86. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol*. Aug 2010;11(8):753-762.
87. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science*. Apr 23 2004;304(5670):554.
88. Jhawer M, Goel S, Wilson AJ, et al. PIK3CA mutation/PTEN expression status predicts response of colon cancer cells to the epidermal growth factor receptor inhibitor cetuximab. *Cancer Res*. Mar 15 2008;68(6):1953-1961.
89. Guanti G, Resta N, Simone C, et al. Involvement of PTEN mutations in the genetic pathways of colorectal cancerogenesis. *Hum Mol Genet*. Jan 22 2000;9(2):283-287.
90. Frattini M, Saletti P, Romagnani E, et al. PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. *Br J Cancer*. Oct 22 2007;97(8):1139-1145.
91. Crawford LV, Pim DC, Lamb P. The cellular protein p53 in human tumours. *Mol Biol Med*. Aug 1984;2(4):261-272.
92. Starzynska T, Bromley M, Ghosh A, Stern PL. Prognostic significance of p53 overexpression in gastric and colorectal carcinoma. *Br J Cancer*. Sep 1992;66(3):558-562.

93. Hamada M, Fujiwara T, Hizuta A, et al. The p53 gene is a potent determinant of chemosensitivity and radiosensitivity in gastric and colorectal cancers. *J Cancer Res Clin Oncol.* 1996;122(6):360-365.
94. Wasserman E, Myara A, Lokiec F, et al. Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. *Ann Oncol.* Oct 1997;8(10):1049-1051.
95. Ando Y, Saka H, Ando M, et al. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res.* Dec 15 2000;60(24):6921-6926.
96. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. *Am J Pathol.* Nov 1994;145(5):1175-1190.
97. Smith JS, Alderete B, Minn Y, et al. Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype. *Oncogene.* Jul 15 1999;18(28):4144-4152.
98. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogiomas. *J Natl Cancer Inst.* Oct 7 1998;90(19):1473-1479.
99. Costello JF, Fruhwald MC, Smiraglia DJ, et al. Aberrant CpG-island methylation has non-random and tumour-type-specific patterns. *Nat Genet.* Feb 2000;24(2):132-138.
100. Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell.* May 18 2010;17(5):510-522.
101. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science.* Sep 26 2008;321(5897):1807-1812.
102. Horbinski C, Kofler J, Kelly LM, Murdoch GH, Nikiforova MN. Diagnostic use of IDH1/2 mutation analysis in routine clinical testing of formalin-fixed, paraffin-embedded glioma tissues. *J Neuropathol Exp Neurol.* Dec 2009;68(12):1319-1325.

103. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* Feb 19 2009;360(8):765-773.
104. Ostrowski LE, von Wronski MA, Bigner SH, et al. Expression of O6-methylguanine-DNA methyltransferase in malignant human glioma cell lines. *Carcinogenesis.* Sep 1991;12(9):1739-1744.
105. Jaeckle KA, Eyre HJ, Townsend JJ, et al. Correlation of tumor O6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: a Southwest Oncology Group study. *J Clin Oncol.* Oct 1998;16(10):3310-3315.
106. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med.* Nov 9 2000;343(19):1350-1354.
107. Jones DT, Kocialkowski S, Liu L, et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res.* Nov 1 2008;68(21):8673-8677.
108. Lawson AR, Tatevossian RG, Phipps KP, et al. RAF gene fusions are specific to pilocytic astrocytoma in a broad paediatric brain tumour cohort. *Acta Neuropathol.* Aug 2010;120(2):271-273.
109. Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature.* Sep 30 2010;467(7315):596-599.
110. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature.* Aug 2 2007;448(7153):561-566.
111. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* Oct 28 2010;363(18):1693-1703.
112. Hunts J, Ueda M, Ozawa S, Abe O, Pastan I, Shimizu N. Hyperproduction and gene amplification of the epidermal growth factor receptor in squamous cell carcinomas. *Jpn J Cancer Res.* Aug 1985;76(8):663-666.

113. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* May 20 2004;350(21):2129-2139.
114. Lord RV, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. *Clin Cancer Res.* Jul 2002;8(7):2286-2291.
115. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med.* Sep 7 2006;355(10):983-991.
116. Der CJ, Krontiris TG, Cooper GM. Transforming genes of human bladder and lung carcinoma cell lines are homologous to the ras genes of Harvey and Kirsten sarcoma viruses. *Proc Natl Acad Sci U S A.* Jun 1982;79(11):3637-3640.
117. Santos E, Martin-Zanca D, Reddy EP, Pierotti MA, Della Porta G, Barbacid M. Malignant activation of a K-ras oncogene in lung carcinoma but not in normal tissue of the same patient. *Science.* Feb 17 1984;223(4637):661-664.
118. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med.* Aug 30 1990;323(9):561-565.
119. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol.* Sep 1 2005;23(25):5900-5909.
120. Fasano O, Birnbaum D, Edlund L, Fogh J, Wigler M. New human transforming genes detected by a tumorigenicity assay. *Mol Cell Biol.* Sep 1984;4(9):1695-1705.
121. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. *Clin Cancer Res.* Sep 1 2012;18(17):4570-4579.

122. Fan H, Huang A, Villegas C, Wright JA. The R1 component of mammalian ribonucleotide reductase has malignancy-suppressing activity as demonstrated by gene transfer experiments. *Proc Natl Acad Sci U S A*. Nov 25 1997;94(24):13181-13186.
123. Pitterle DM, Kim YC, Jolicoeur EM, Cao Y, O'Briant KC, Bepler G. Lung cancer and the human gene for ribonucleotide reductase subunit M1 (RRM1). *Mamm Genome*. Sep 1999;10(9):916-922.
124. Bepler G, Sharma S, Cantor A, et al. RRM1 and PTEN as prognostic parameters for overall and disease-free survival in patients with non-small-cell lung cancer. *J Clin Oncol*. May 15 2004;22(10):1878-1885.
125. Rosell R, Scagliotti G, Danenberg KD, et al. Transcripts in pretreatment biopsies from a three-arm randomized trial in metastatic non-small-cell lung cancer. *Oncogene*. Jun 5 2003;22(23):3548-3553.
126. Bussemakers MJ, van Bokhoven A, Verhaegh GW, et al. DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res*. Dec 1 1999;59(23):5975-5979.
127. de Kok JB, Verhaegh GW, Roelofs RW, et al. DD3(PCA3), a very sensitive and specific marker to detect prostate tumors. *Cancer Res*. May 1 2002;62(9):2695-2698.
128. Santoro M, Rosati R, Grieco M, et al. The ret proto-oncogene is consistently expressed in human pheochromocytomas and thyroid medullary carcinomas. *Oncogene*. Oct 1990;5(10):1595-1598.
129. Wells SA, Jr., Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. *Ann Surg*. Sep 1994;220(3):237-247; discussion 247-250.
130. Yokota H, Fernandez-Salguero P, Furuya H, et al. cDNA cloning and chromosome mapping of human dihydropyrimidine dehydrogenase, an enzyme associated with 5-fluorouracil toxicity and congenital thymine uraciluria. *J Biol Chem*. Sep 16 1994;269(37):23192-23196.

131. Wei X, McLeod HL, McMurrough J, Gonzalez FJ, Fernandez-Salguero P. Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. *J Clin Invest.* Aug 1 1996;98(3):610-615.
132. Raida M, Schwabe W, Hausler P, et al. Prevalence of a common point mutation in the dihydropyrimidine dehydrogenase (DPD) gene within the 5'-splice donor site of intron 14 in patients with severe 5-fluorouracil (5-FU)- related toxicity compared with controls. *Clin Cancer Res.* Sep 2001;7(9):2832-2839.
133. Takeishi K, Ayusawa D, Kaneda S, Shimizu K, Seno T. Molecular cloning of genomic DNA segments partially coding for human thymidylate synthase from the mouse cell transformant. *J Biochem.* May 1984;95(5):1477-1483.
134. Clark JL, Berger SH, Mittelman A, Berger FG. Thymidylate synthase gene amplification in a colon tumor resistant to fluoropyrimidine chemotherapy. *Cancer Treat Rep.* Mar 1987;71(3):261-265.
135. Pullarkat ST, Stoehlmacher J, Ghaderi V, et al. Thymidylate synthase gene polymorphism determines response and toxicity of 5-FU chemotherapy. *Pharmacogenomics J.* 2001;1(1):65-70.