

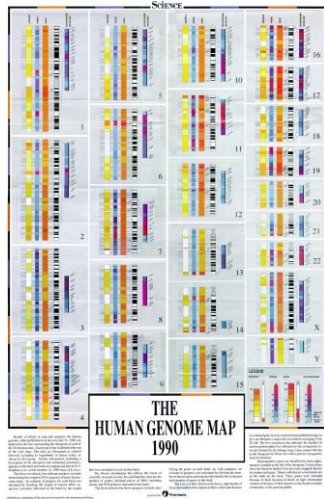
Molecular biology of colorectal cancer

Phil Quirke

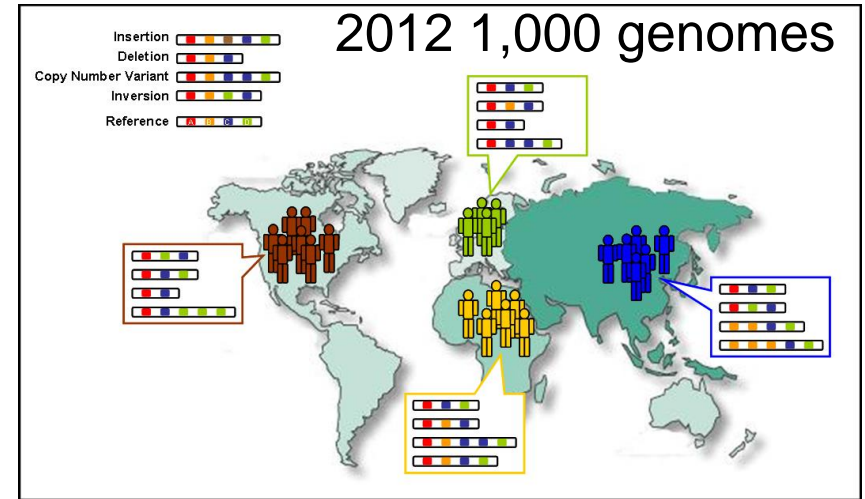
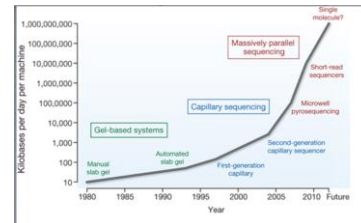
Yorkshire Cancer Research
Centenary Professor of Pathology
University of Leeds, UK



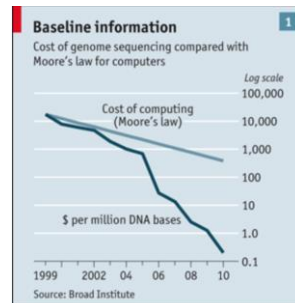
Rapid pace of molecular change



Sequencing changes



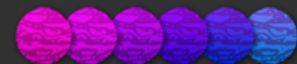
2000



100,000 Genomes Project



"It is crucial that we continue to push the boundaries and this new plan will mean we are the first country in the world to use DNA codes in the mainstream of the health service"
The Rt Hon David Cameron MP
The Prime Minister
10 December 2012

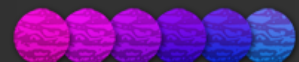
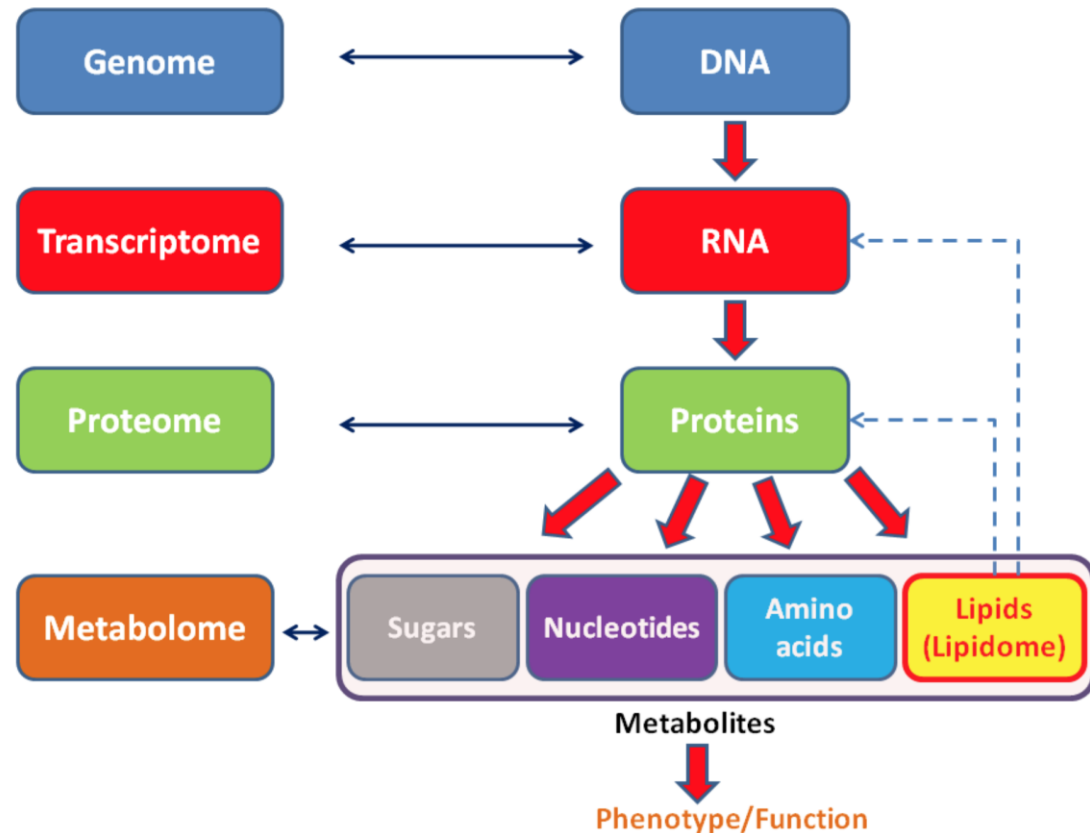


Which technologies should we use?



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- Genomics- DNA/RNA
- Proteomics
- Metabolome
- Pathways
- Phenotype
- Test
 - Fit for purpose
 - Cost
 - Changing

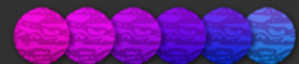
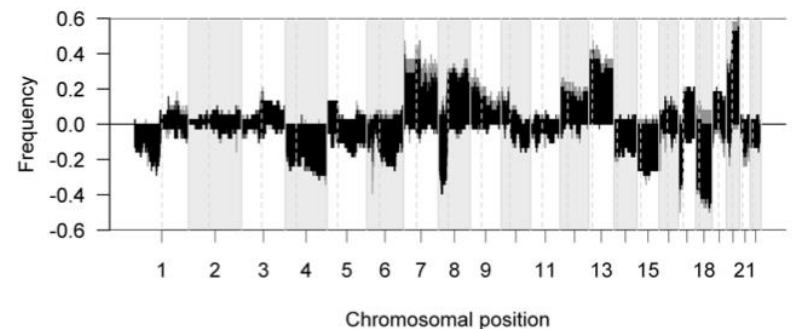
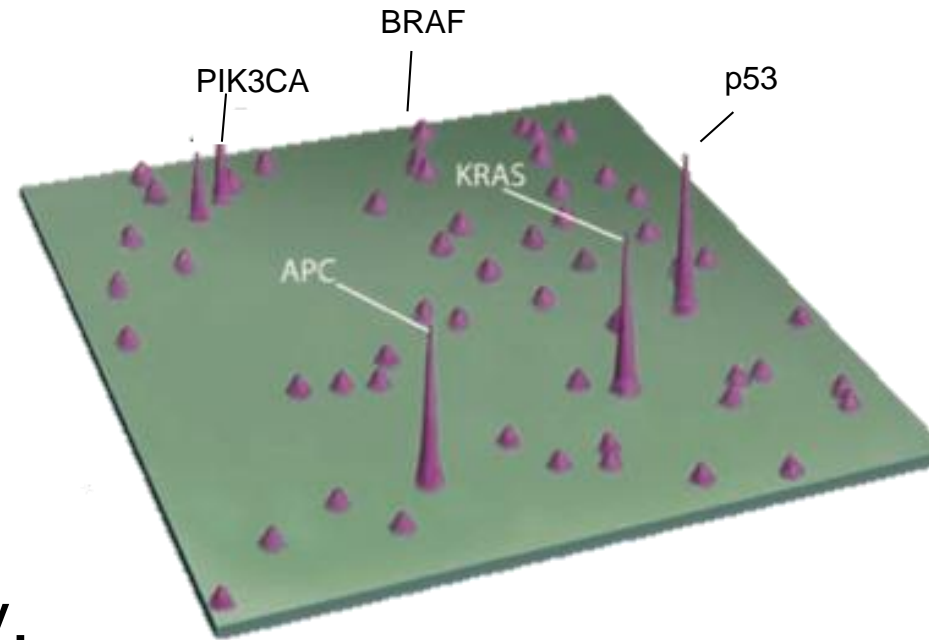


Molecular changes in bowel cancer



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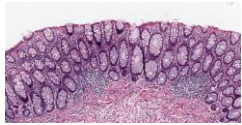
- DNA
 - Mutations – driver and passenger
 - Amplifications
 - Deletions
 - Chromosomal instability,
 - Microsatellite instability
 - Fusion genes
 - Methylation



Increasing complexity with time



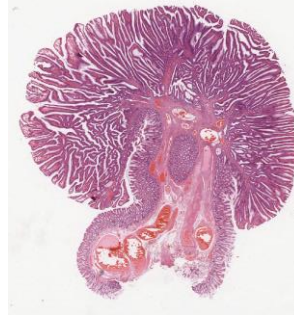
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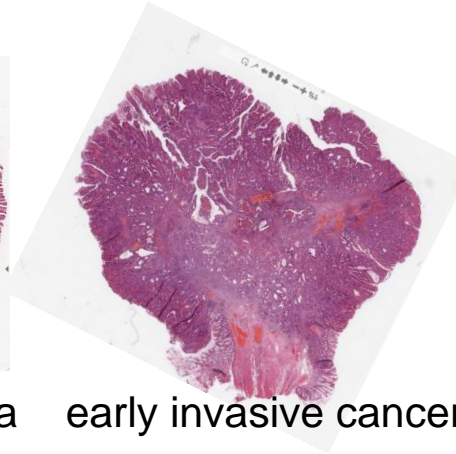
Normal



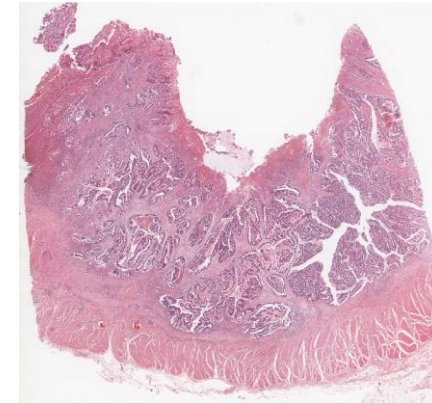
early adenoma



later adenoma



early invasive cancer



colorectal cancer



Early

APC, Ras, PIK3CA, BRaf

Later

p53, SMAD4 DNA repair, Copy number

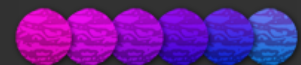
Gradual increase in genomic changes

Increasing mutations

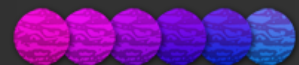
Increasing genomic instability

Classical adenomas, Serrated pathway, mismatch repair

Identification of subtypes



- Genetic syndromes
- Outcomes
 - DNA
 - Deficient mismatch repair
 - Kras/Braf/PIK3CA
 - RNA –
 - oncotype Dx ?
 - RNA subtypes?
- Prediction of response
 - Anti-EGFr abs
 - Ras
 - Epiregulin/amphiregulin
 - Her3
 - Braf inhibitor
 - Braf
 - Her2
 - Aspirin PIK3CA
 - Immunotherapy
 - dMMR and anti PD1/PDL1



Genetic syndromes



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HHS Public Access

Author manuscript

Surg Clin North Am. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Surg Clin North Am. 2015 October ; 95(5): 1067–1080. doi:10.1016/j.suc.2015.05.004.

Hereditary Colorectal Cancer: Genetics and Screening

Lodewijk A.A. Brosens, MD, PhD^{1,2}, G. Johan A. Offerhaus, MD, PhD, MPH³, and Francis M. Giardiello, MD⁴

TABLE 1

Colorectal cancer syndromes

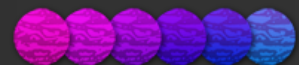
Syndrome	Genes	Mode of inheritance
Lynch syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , or <i>EpCAM</i>	Autosomal dominant
(Attenuated) Familial adenomatous polyposis	<i>APC</i>	Autosomal dominant
MUTYH-associated polyposis	<i>MUTYH</i> (<i>MYH</i>)	Autosomal recessive
Peutz-Jeghers syndrome	<i>LKB1</i> (<i>STK11</i>)	Autosomal dominant
Juvenile polyposis syndrome	<i>SMAD4</i> (~30%) <i>BMPRI1A</i> (~20%)	Autosomal dominant
Hereditary mixed polyposis syndrome	<i>GREM1</i>	Autosomal dominant
Serrated polyposis syndrome	unknown	unknown

3%
1%

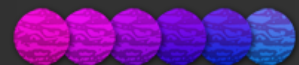
Polymerase proof reading associated polyposis

POLE & *POLD1*

Autosomal dominant



- HNPPCC 3%
- Germ line mutations in DNA repair genes leads to hyper mutation
- Inactivates key genes leading to CRC and other cancers
- Truncated proteins appear on cell surface – immune response
- Screening via MSI or immunohistochemistry
 - dMMR proteins
 - hMSH2 (40%), hMLH1 (40%), hMSH6 (10%), PMS2 (6%) POLD (1%) and POLE (1%)
 - BRAF V600E wild type
- Germ line sequencing



Nice recommendations Feb 2017 Routine testing in England



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Molecular testing strategies for Lynch syndrome in people with colorectal cancer

In development [GID-DG10001] Expected publication date: February 2017 [Register as a stakeholder](#)

Project information

Project documents

Status	In progress
Process	DT
Provisional Schedule	
Expected publication	February 2017
Project Team	
Project lead	Robert Fernley

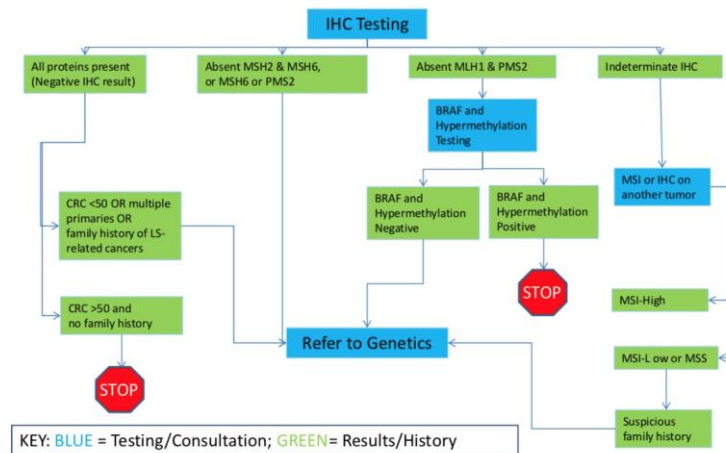
Molecular testing for Lynch syndrome in people with colorectal cancer

Produced by Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU

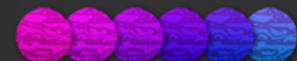
Authors Tristan Showell, *Research Fellow*¹
Helen Coshio, *Research Fellow*¹
Nicola Huxley, *Research Fellow*¹
Tracey Jones-Hughes, *Research Fellow*¹
Simon Briscoe, *Information Specialist*¹
Ian Frayling, *Consultant in Genetic Pathology*²
Chris Hyde, *Professor of Public Health and Clinical Epidemiology*¹

IHC Testing Schematic

(With BRAF and Hypermethylation)



The base case results in the economic evaluation suggest that screening for LS in CRC patients using IHC, *BRAF* V600E and *MLH1* methylation testing would be cost-effective at a threshold of £20,000 per quality-adjusted life year (QALY). The incremental cost-effectiveness ratio for this strategy is £11,008 per QALY compared to no screening. Screening without tumour tests is not predicted to be cost-effective (more costly and less effective than another strategy).



Classification - DNA



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- Prognosis
 - dMMR/hypermethylated 12-15%
 - Genomic instability Rest

Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network*

330 | NATURE | VOL 487 | 19 JULY 2012

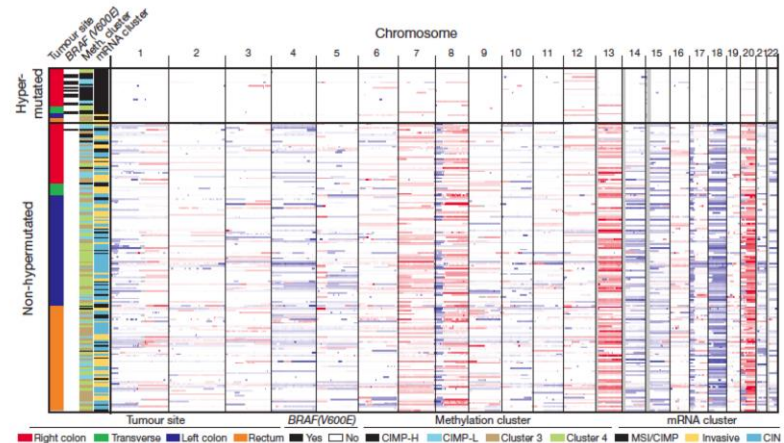
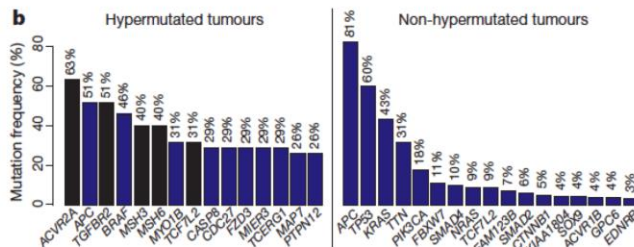
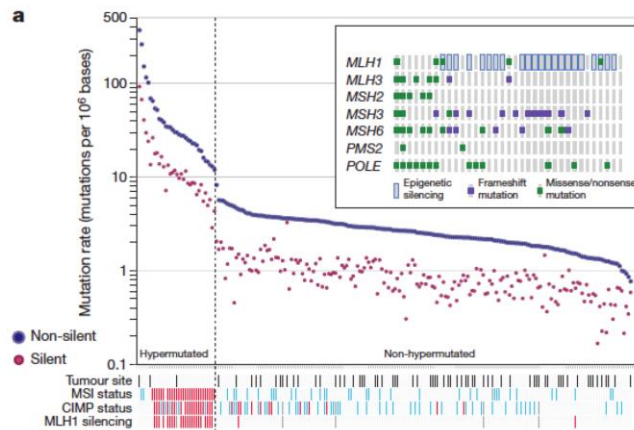
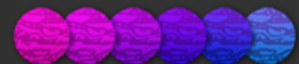


Figure 2 | Integrative analysis of genomic changes in 195 CRCs.

Hypermethylated tumours have near-diploid genomes and are highly enriched for hypermethylation, CIMP expression phenotype and *BRAF(V600E)* mutations. Non-hypermethylated tumours originating from different sites are virtually

indistinguishable from each other on the basis of their copy-number alteration patterns, DNA methylation or gene-expression patterns. Copy-number changes of the 22 autosomes are shown in shades of red for copy-number gains and shades of blue for copy-number losses.

N= 276 with 97 undergoing WGS

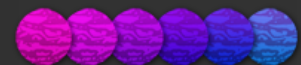
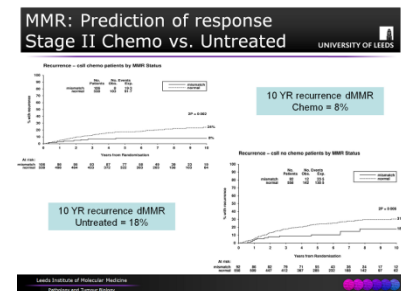
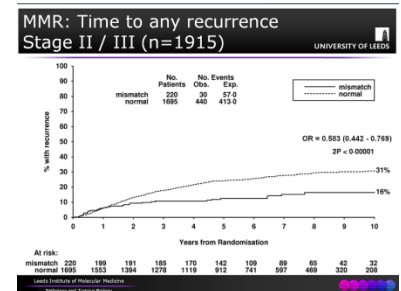
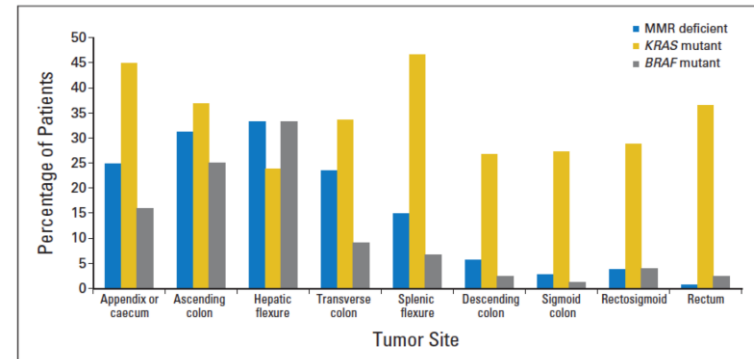


Sporadic deficient Mismatch Repair (dMMR) Hyper mutated tumours



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- Demographics
 - HNPCC dMMR/Braf wild type
 - Sporadic
 - Colon > rectum
 - Females
 - Stage II 12% Stage III 7%, Stage 4 4%
- Prognosis
 - 50% lower recurrence risk in stage II dMMR tumours
 - Prognostic effect dMMR remains in treated group
- Prediction
 - US data suggests less responsive to chemotherapy
 - NO evidence of worse outcome on chemo in Quasar



Other mutations and prognosis



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Recurrence Quasar1 – by KRas 12,13,61

N=789 MRC Focus stage IV

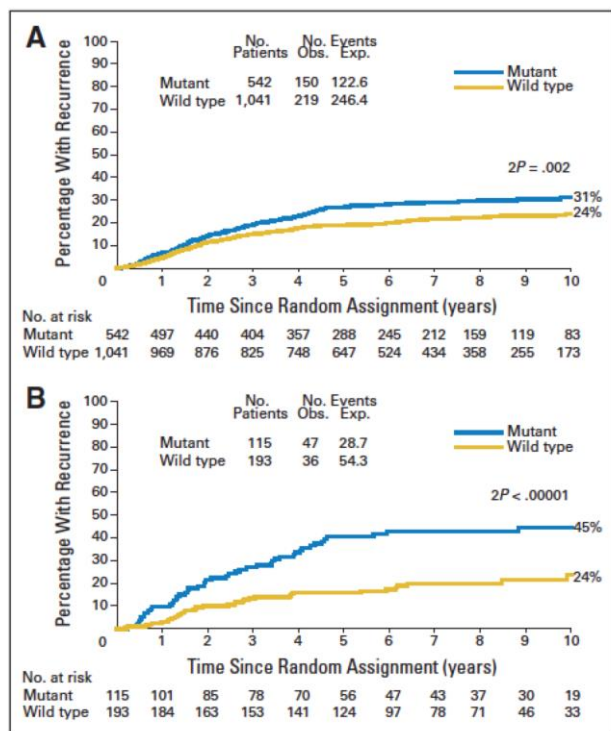
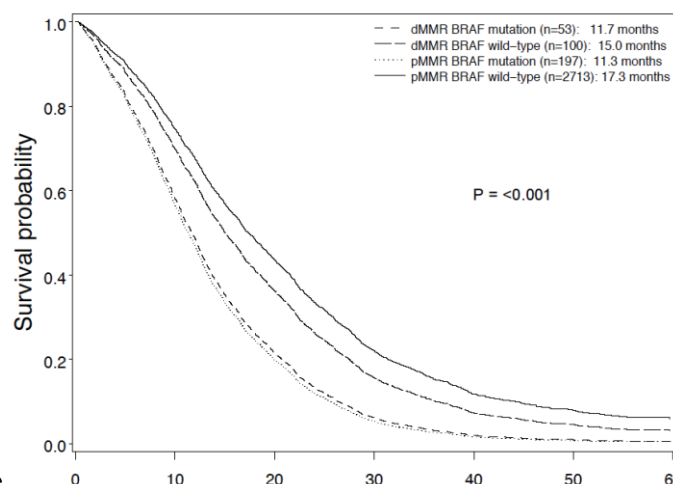


Fig 5. Recurrence by KRAS status: (A) all patients, (B) rectum stage II only. Obs., observed number of recurrences; Exp., expected number of recurrences; Var, variance of O-E.

Braf V600E not prognostic
PIK3CA mutations not prognostic

Marker	Endpoint	Group	n	Hazard Ratio* (95% CI)	p-value
KRAS	PFS	W/T KRAS	322	1.0	0.06
		Any KRAS mutation	311	1.17 (1.00, 1.36)	
	OS	W/T KRAS	324	1.0	0.02
		Any KRAS mutation	314	1.23 (1.04, 1.44)	

Marker	Endpoint	group	n	Hazard Ratio* (95% CI)	p-value
BRAF	PFS	W/T BRAF	679	1.0	0.80
		BRAF mutation	54	1.04 (0.78, 1.38)	
	OS	W/T BRAF	684	1.0	<0.0001
		BRAF mutation	54	1.69 (1.26, 2.27)	



BRAF/dMMR
3063 cases
Braf poor
prognosis



Multi-Gene RT-PCR Colon Cancer Assay – Oncotype Dx colon



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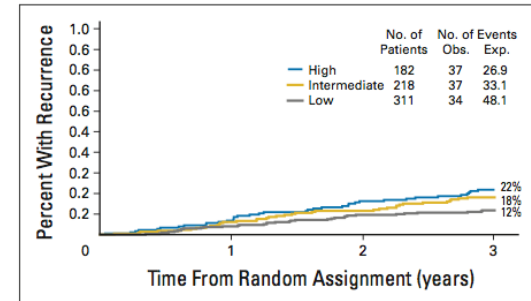
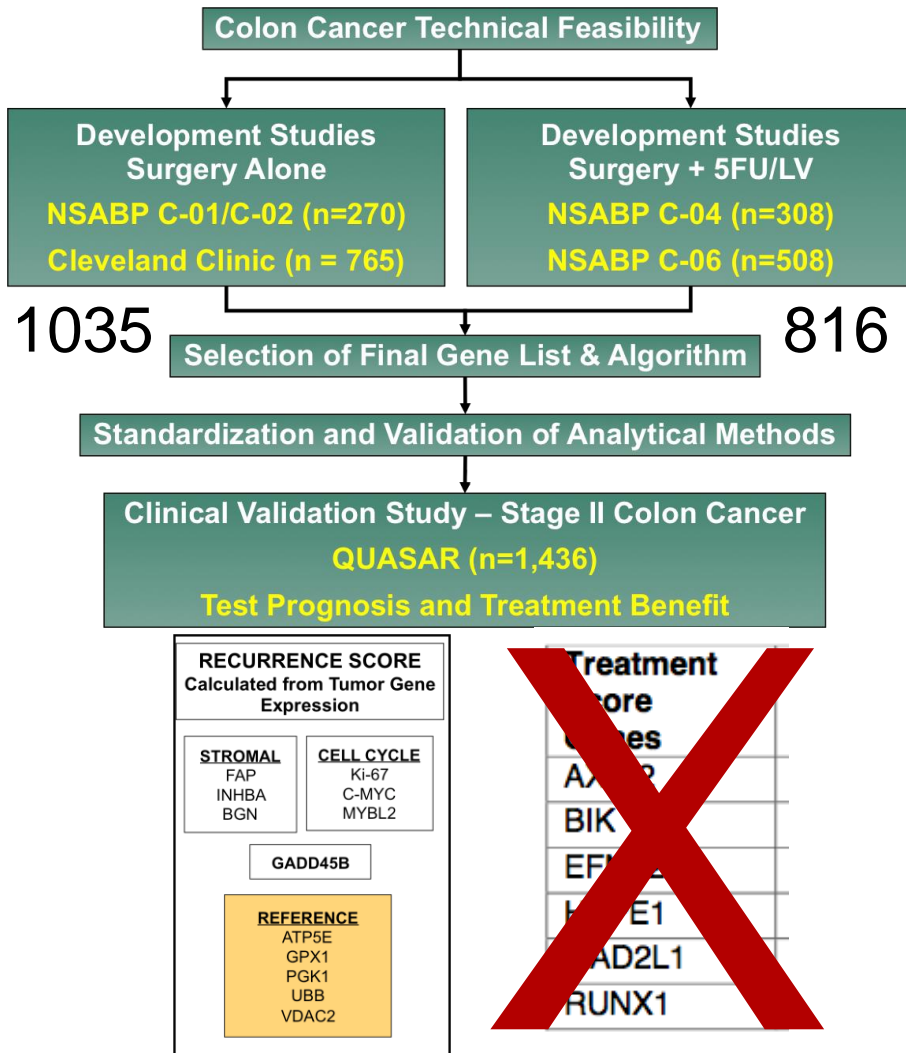
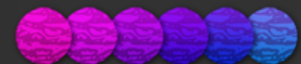
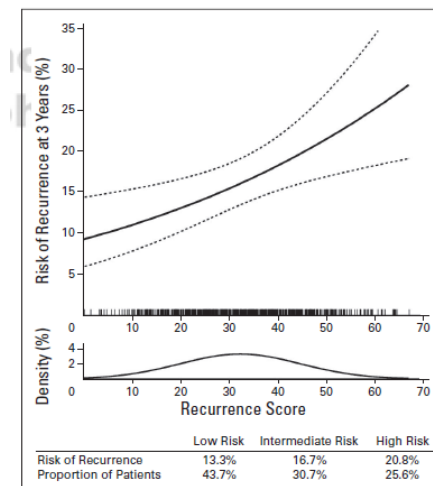


Fig 3. Kaplan-Meier estimates of 3-year recurrence in surgery-alone patients by risk group. Obs, observed; Exp, experienced.

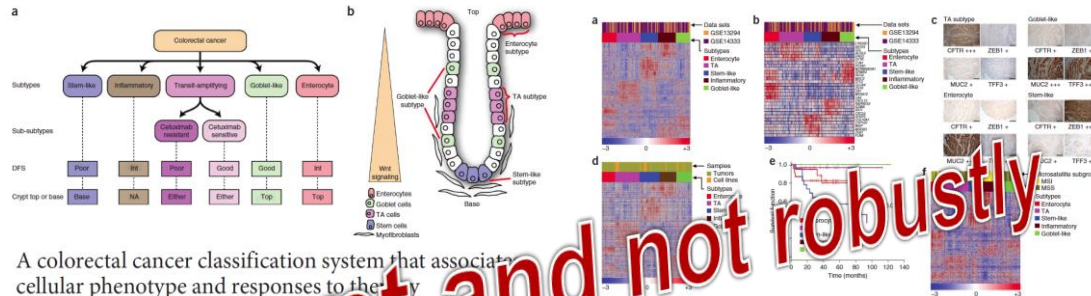
HR = 1.47 (p=0.046)



New RNA array patterns



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A colorectal cancer classification system that associates cellular phenotype and responses to therapy

Anguraj Sadana^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220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Transcriptome/Protein characterisation



UNIVERSITY OF LEEDS

A pathology atlas of the human cancer transcriptome

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Cancer is one of the leading causes of death, and there is great interest in understanding the underlying molecular mechanisms involved in the pathogenesis and progression of individual tumors. We used systems-level approaches to analyze the genome-wide transcriptome of the protein-coding genes of 17 major cancer types with respect to clinical outcome. A general pattern emerged: Shorter patient survival was associated with up-regulation of genes involved in cell growth and with down-regulation of genes involved in cellular differentiation. Using genome-scale metabolic models, we show that cancer patients have widespread metabolic heterogeneity, highlighting the need for precise and personalized medicine for cancer treatment. All data are presented in an interactive open-access database (www.proteinatlas.org/pathology) to allow genome-wide exploration of the impact of individual proteins on clinical outcomes.

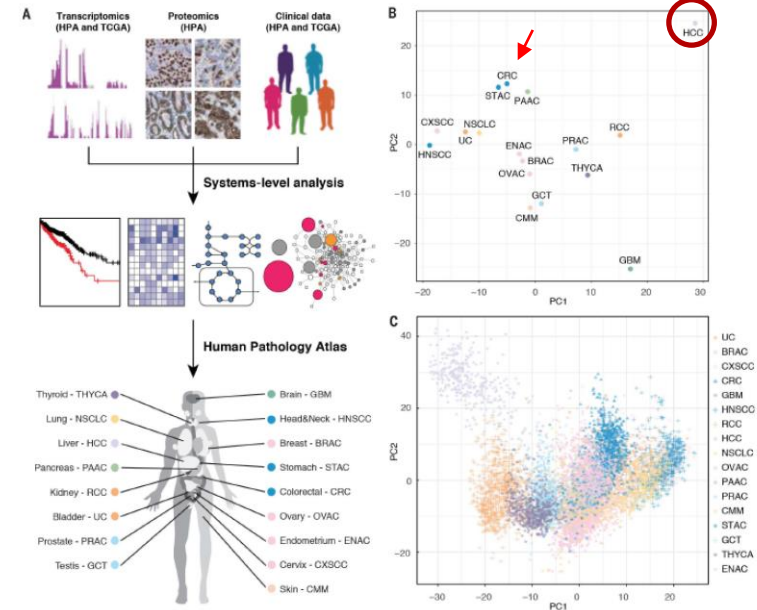


Fig. 1. Analysis of the global expression patterns of protein-coding genes in human cancers. (A) Schematic drawing of the Human Pathology Atlas effort described herein. (B) Principal components analysis (PCA) showing the similarities in expression of 19,571 protein-coding genes

among 17 cancer types. See Fig. S4 for additional PCA analysis with more stratified patient cohorts. (C) PCA plot showing the individual differences in the genome-wide global expression profiles among the 17 cancer types in 9666 individual patients.

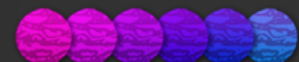
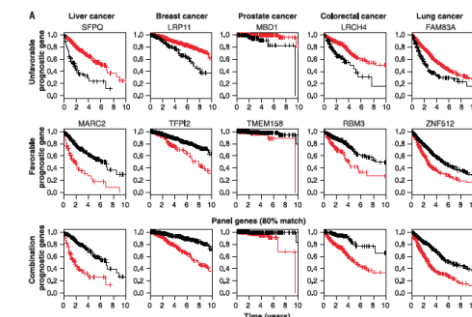
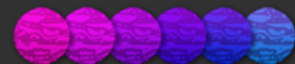


Table 1. Targeted Therapeutics in Cancer.*

Gene	Genetic Alteration	Tumor Type	Therapeutic Agent
Receptor tyrosine kinase			
EGFR	Mutation, amplification	Lung cancer, glioblastoma	Geftinib, erlotinib
ERBB2	Amplification	Breast cancer	Lapatinib
FGFR1	Translocation	Chronic myeloid leukemia	PKC412, BIBF-1120
FGFR2	Amplification, mutation	Gastric, breast, endometrial cancer	PKC412, BIBF-1120
FGFR3	Translocation, mutation	Multiple myeloma	PKC412, BIBF-1120
PDGFRA	Mutation	Glioblastoma, gastrointestinal stromal tumor	Sunitinib, sorafenib, imatinib
PDGFRB	Translocation	Chronic myelomonocytic leukemia	Sunitinib, sorafenib, imatinib
ALK	Mutation or amplification	Lung cancer, neuroblastoma, anaplastic large-cell lymphoma	Crizotinib
c-MET	Amplification	Geftinib-resistant non-small-cell lung cancer, gastric cancer	Crizotinib, XL184, SU11274
IGF1R	Activation by insulin-like growth factor II ligand	Colorectal, pancreatic cancer	CP-751,871, AMG479
c-KIT	Mutation	Gastrointestinal stromal tumor	Sunitinib, imatinib
FLT3	Internal tandem duplication	Acute myeloid leukemia	Lestaurtinib, XL999
RET	Mutation, translocation	Thyroid medullary carcinoma	XL184
Non-receptor tyrosine kinase			
ABL	Translocation (BCR-ABL)	Chronic myeloid leukemia	Imatinib
JAK2	Mutation (V617F), translocation	Chronic myeloid leukemia, myeloproliferative disorders	Lestaurtinib, INCB018424
SRC	Overexpression	Non-small-cell lung cancer; ovarian, breast cancer; sarcoma	KX2-391, dasatinib, AZD0530
Serine-threonine-lipid kinase			
BRAF	Mutation (V600E)	Melanoma; colon, thyroid cancer	SB-590885, PLX-4032, RAF265, XL281
Aurora A and B kinases	Overexpression	Breast, colon cancer; leukemia	MK-5108 (VX-689)
Polo-like kinases	Overexpression	Breast, lung, colon cancer; lymphoma	BI2536, GSK461364
MTOR	Increased activation	Renal-cell carcinoma	Temsirolimus (CCI-779), BEZ235
PI3K	PIK3CA mutations	Colorectal, breast, gastric cancer; glioblastoma	BEZ235
DNA damage or repair			
BRCA1 and BRCA2	Mutation (synthetic lethal effect)	Breast, ovarian cancer	Olaparib, MK-4827 (PARP inhibitors)

* PARP denotes poly(adenosine diphosphate-ribose) polymerase.

- Targeted therapies CRC
 - Anti EGFR ab's
 - Braf inhibitors
 - Anti PD1 and dMMR
 - Others
 - Herceptin – anti Her2
 - Aspirin – PIK3CA mutations

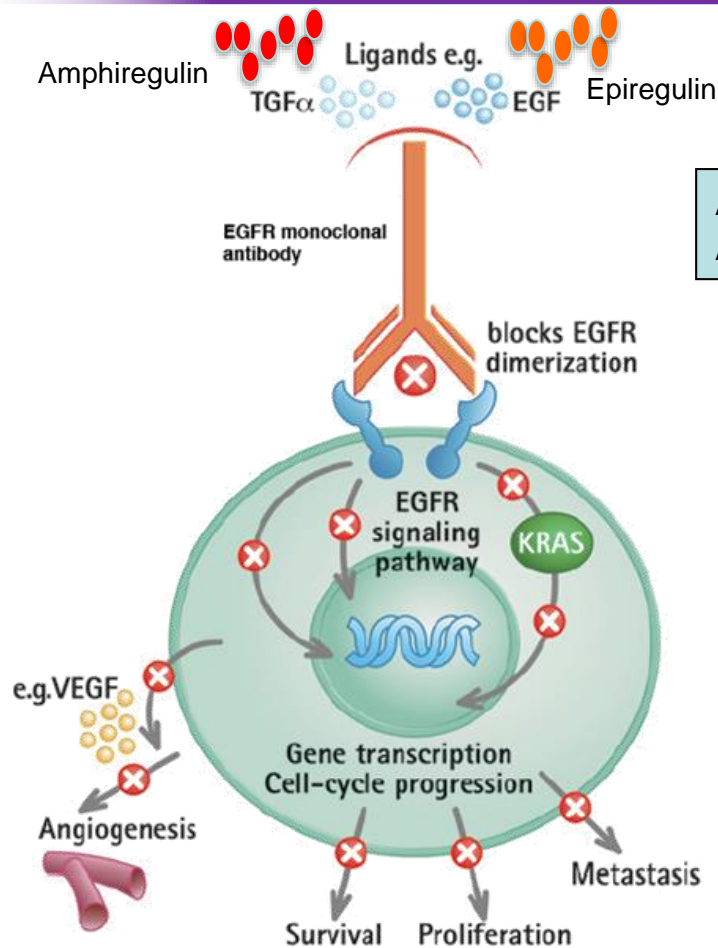


KRAS and the EGFr signalling pathway in KRAS-wild type and KRAS-mutant patients

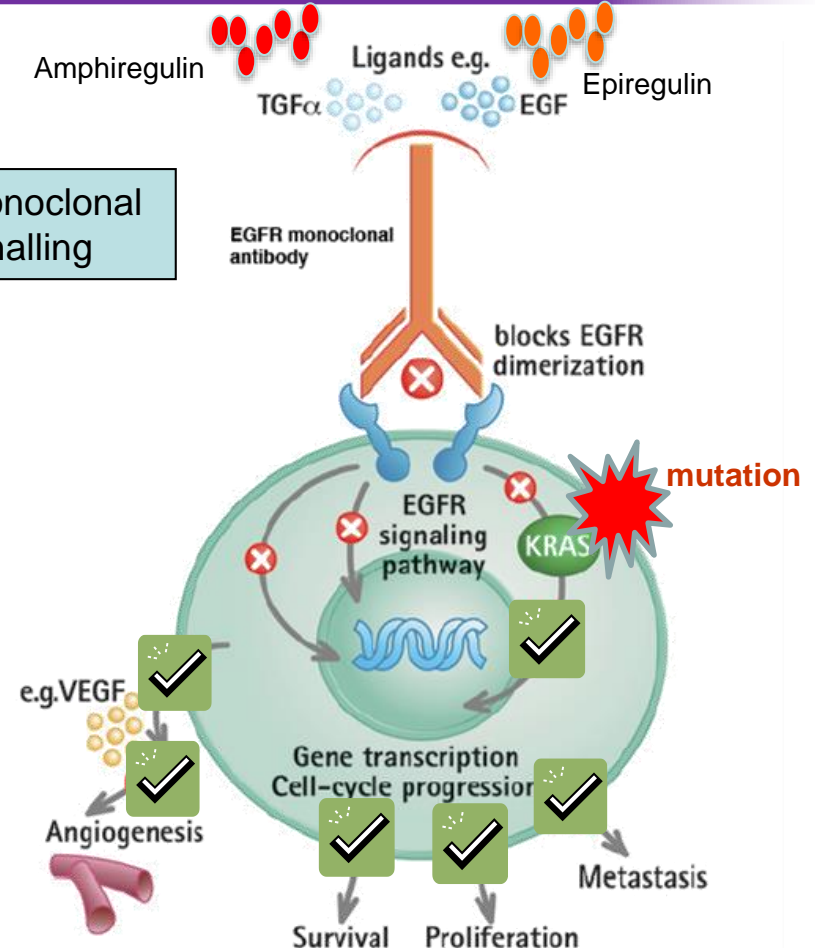


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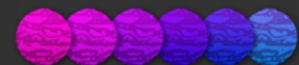
Anti-EGFr monoclonal
Abs block signalling



KRAS-WT



KRAS-MUTANT

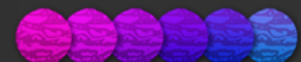
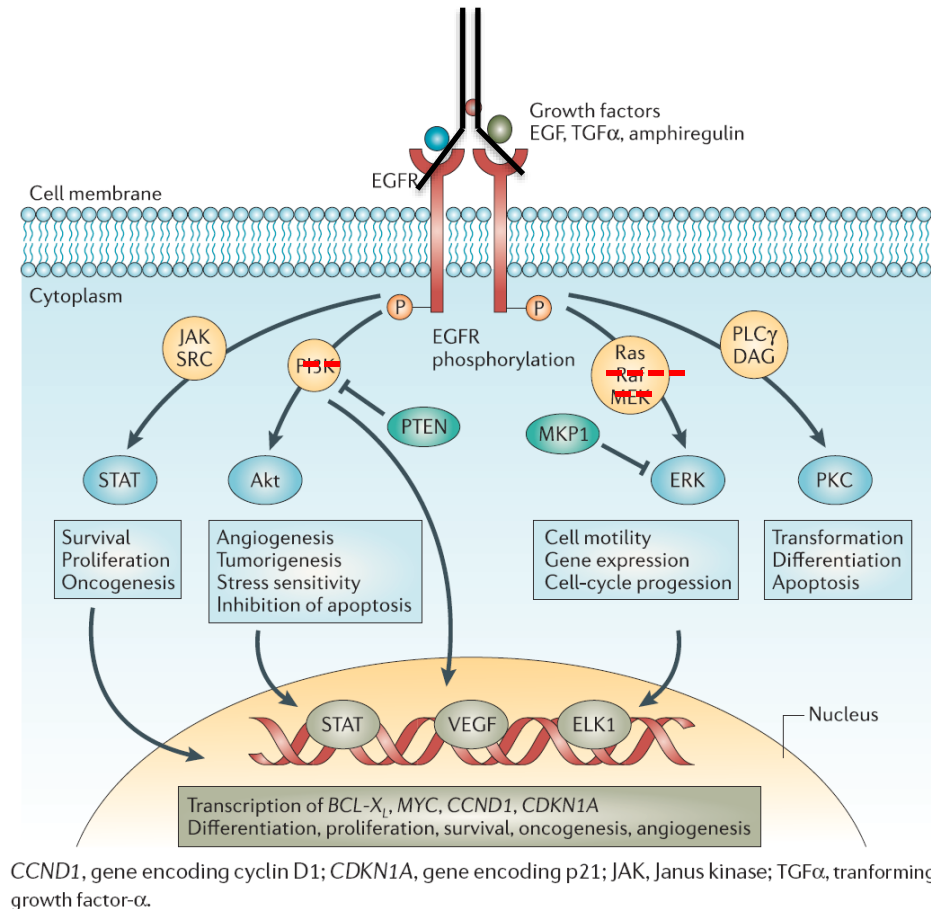


BRAF mutants



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- BRAFinhibitors negative
- Block BRAF and others ?
- Early reports
 - No
 - BRAFi and MEK
 - Yes 26-35% RR
 - BRAFi, anti EGFr and anti PIK3CA
 - BRAFi, anti EGFr and Mek inhibitor
 - BRAFi, antiEGFr and Irinotecan
- Looks likely that dual inhibition BRAFi and antiEGFr works



PD-1 blockade phase 2 data



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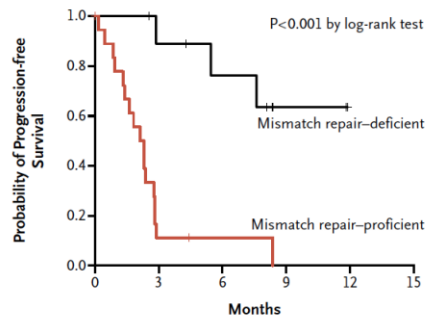
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiiji, F. Bhajee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

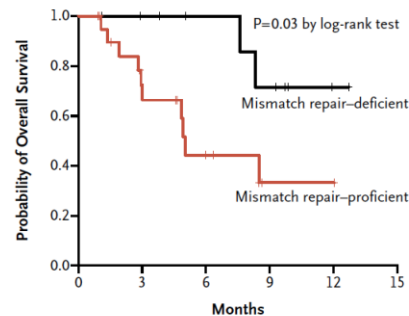
N Engl J Med 2015;372:2509-20.

A Progression-free Survival in Cohorts with Colorectal Cancer



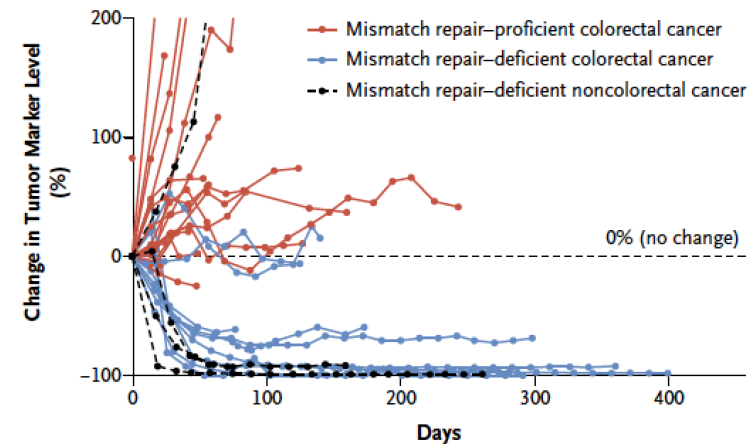
No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	8	6	2	0	0
Mismatch repair-proficient	21	2	1	0	0	0

B Overall Survival in Cohorts with Colorectal Cancer

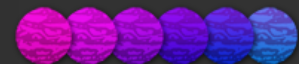
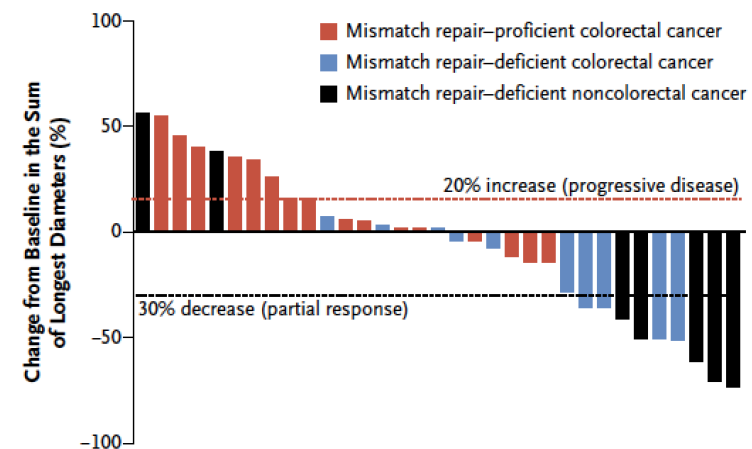


No. at Risk	0	3	6	9	12	15
Mismatch repair-deficient	11	9	7	5	1	0
Mismatch repair-proficient	21	12	5	1	1	0

A Biochemical Response



B Radiographic Response



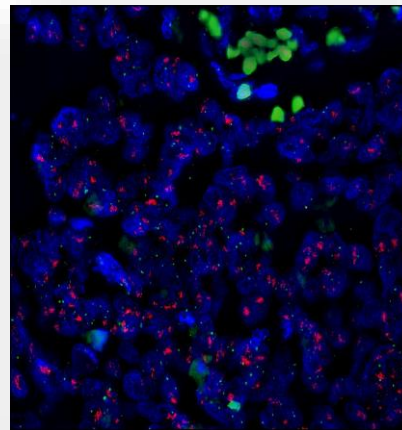
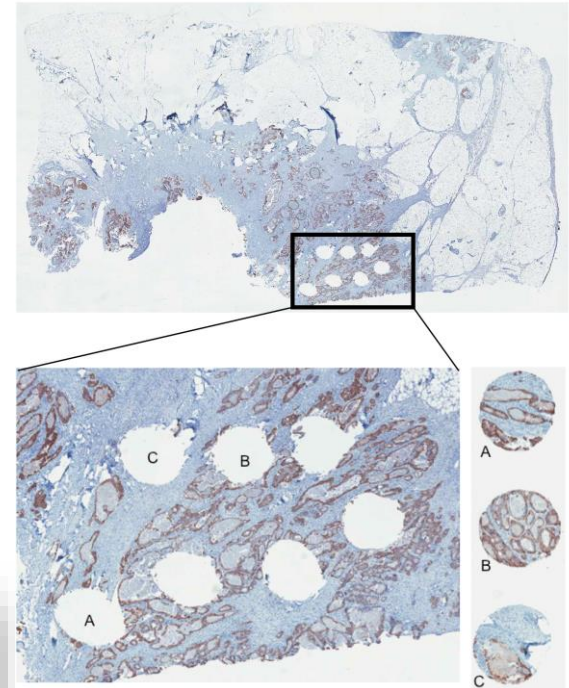
Reapplying drugs from other sites

- small populations

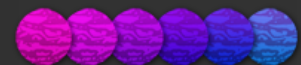


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- Challenge
 - Agents positive in other cancers
 - Her-2
 - Stage II Quasar 25/1767 (1.4%) all pMMR
 - Stage IV CRC 29/1340 (2.2%)
 - Ki ras/Braf wild type 24/461 (5.2%)
 - Ki ras/Braf mutant 5/527 (0.95%)
- 96.4% amplified
- ? Others –fusion genes



Susan Richman
Katie Southward
Gemma Hemmings



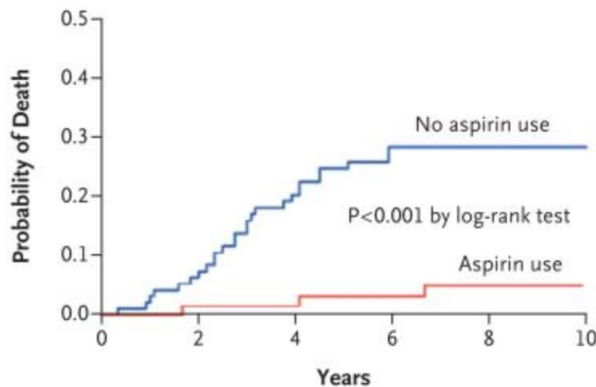
PIK3CA mutations



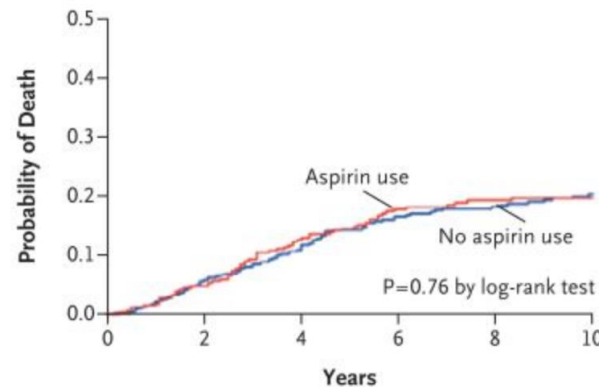
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- Quasar1
 - 874 cases PIK3CA mutations 13.9 %. 83 exon 9 (9.5%) exon 20 (4.4%).
 - No prognostic effect in stage II
- Aspirin
 - PIK3CA mutations reduced recurrence
 - NEJM HR 0.18 New Engl J Med. 2012 Oct 25;367(17):1596-606.
 - Victor HR 0.11 J Clin Oncol. 2013 Dec 1;31(34):4297-305.

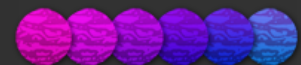
A Colorectal Cancer–Specific Mortality, Mutant *PIK3CA*



B Colorectal Cancer–Specific Mortality, Wild-Type *PIK3CA*



Add Aspirin trials



Changing clinical trials – Focus 4



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EME/CRUK Focus 4
n = 3,500

Testing NGS

Kras 12,13, 59, 61,146

Nras 12,13, 61

PIK3CA exon 9 & 20

Braf V600E

p53

PTEN immuno

dMMR immuno

Labs

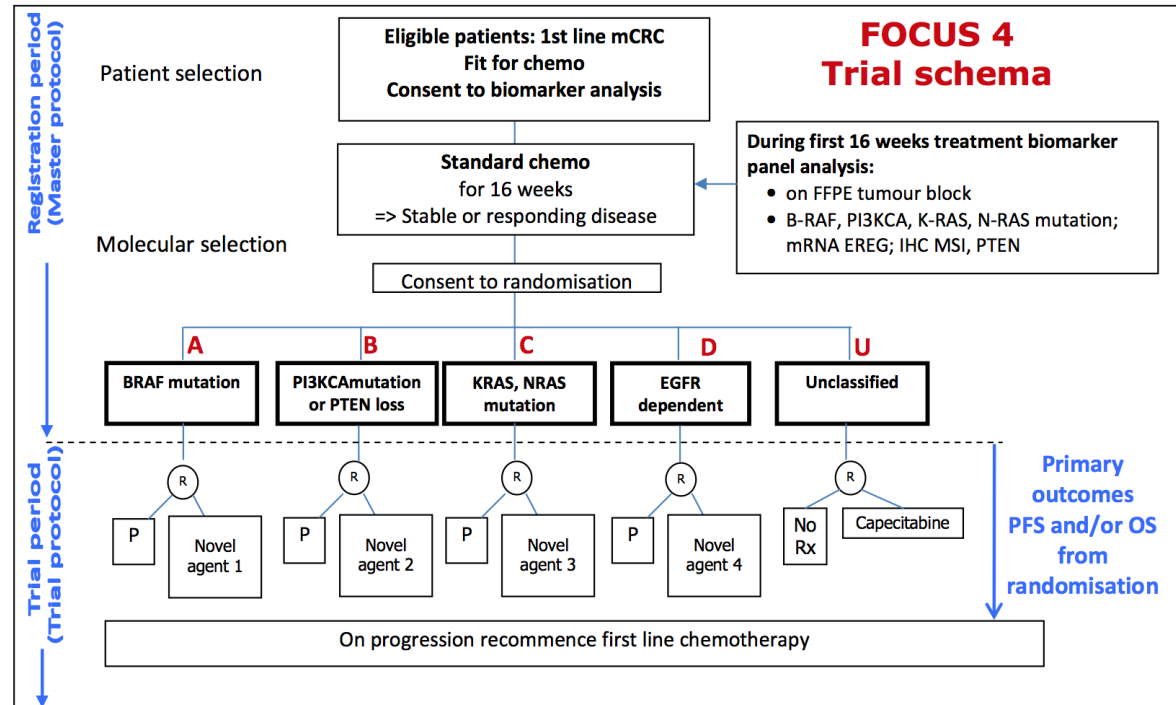
Leeds and Cardiff

Susan Richman

Gemma Hemmings

Pathology, Anatomy and Tumour Biology

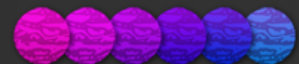
Leeds Institute of Cancer and Pathology



aspirin

oral Her 1,2,3 inhibitor (AZD8931)

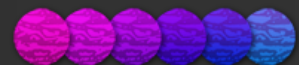
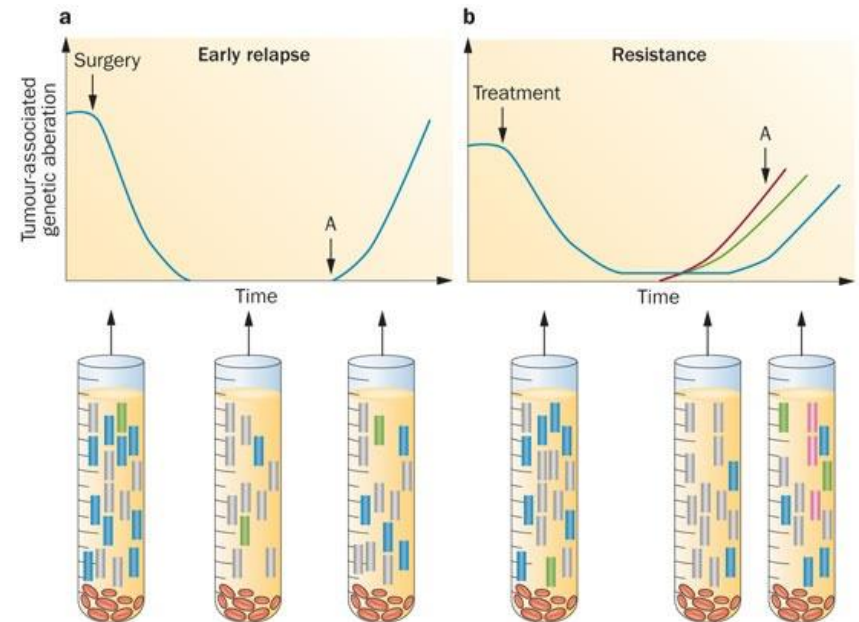
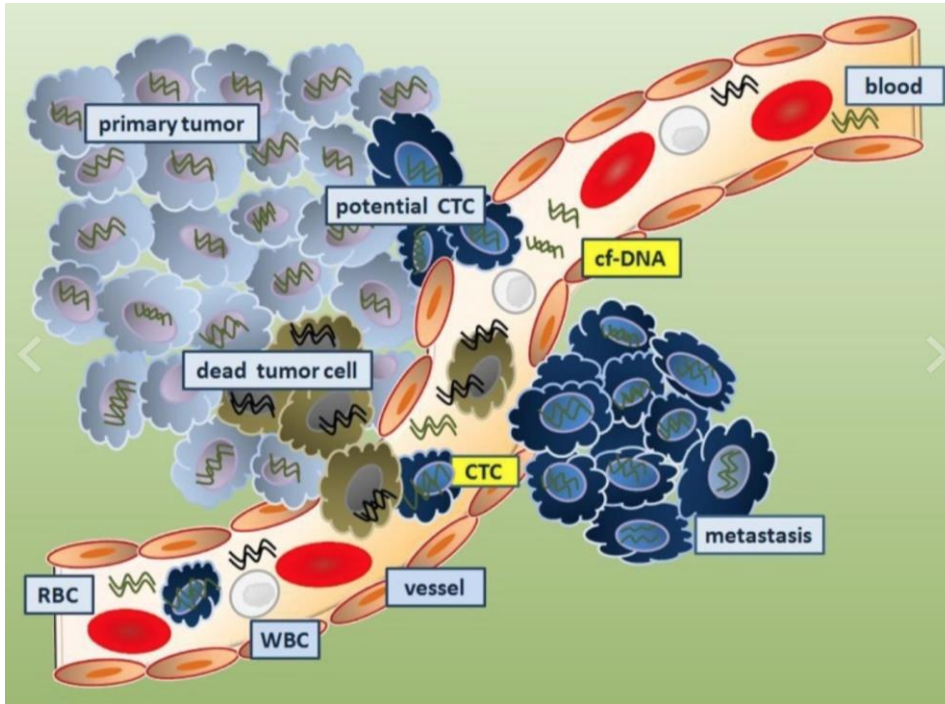
WEE-1 inhibitor



Following disease



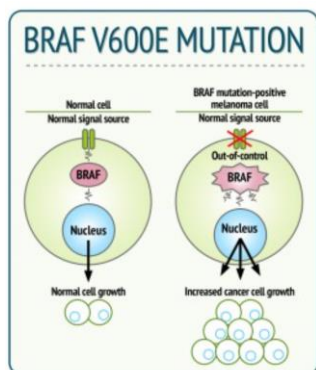
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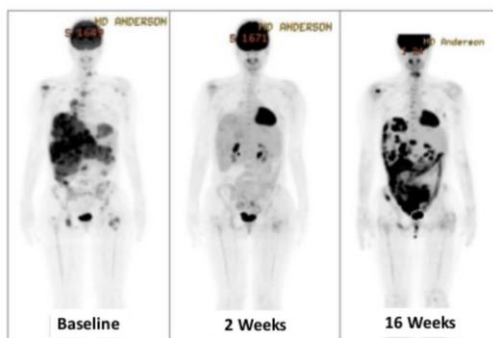
Resistance develops on therapy



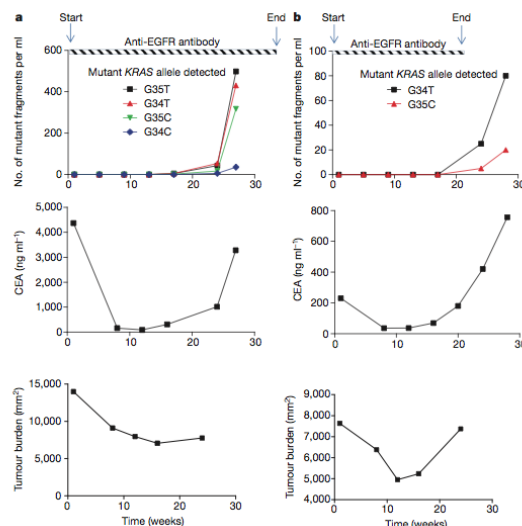
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Resistance to BRAF Inhibitors



Average response duration ~6 months



Emerging mutational
Resistance Ras in CRC
with anti-EGFr Rx

BJC
British Journal of Cancer (2017), 1–9 | doi: 10.1038/bjc.2017.294

Keywords: locally advanced rectal cancer; cetuximab-containing chemoradiation; RAS mutations; intra-tumoural clonal heterogeneity; treatment response; next generation sequencing

Preoperative chemoradiation with capecitabine, irinotecan and cetuximab in rectal cancer: significance of pre-treatment and post-resection RAS mutations

Simon Collins^{1,1}, Nick West², David Sebag-Montefiore³, Arthur Sun Myint⁴, Mark Saunders⁵, Shabbir Susenwala⁶, Phil Quirke⁷, Sharadah Essapen⁸, Leslie Samuel⁹, Bruce Sizer¹⁰, Jane Worthing¹¹, Katie Southward², Gemma Hemmings², Emma Tinkler-Hundal², Morag Taylor², Daniel Bottomley², Philip Chambers², Emma Lawrie¹², Andre Lopes¹² and Sandy Beare¹²

Excite phase 2
Rectal cancer
19% gained mutations
35% lost mutations
after treatment



Screening - DNA

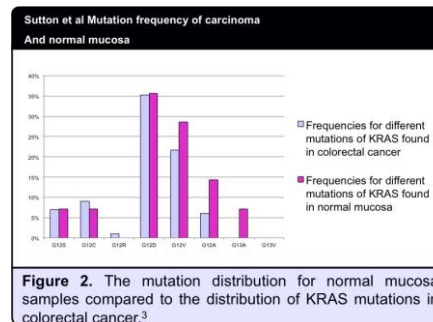
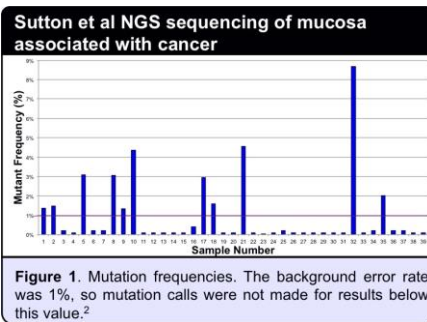


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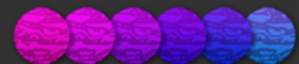
- Screening/diagnosis
- Cologuard
- DNA mutations in stool



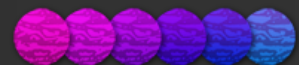
Imperiale TF, Ransohoff DF, Itzkowitz SH, et al.
Multitarget stool DNA testing for colorectal-cancer
screening. *N Engl J Med.* 2014;370(14):1987-97.



Kate Sutton



- **Diagnosis of hereditary disease**
- **Routine screening for HNPCC**
- **DNA subtypes**
 - **Hypermotators/dMMR are important 12%**
 - **Worse prognosis RAS mutants and BRAF in stage 4**
 - RNA profiles not yet clinically usable
- **Predictors**
 - **K and NRas mutations present insensitive to an**
 - Anti PD1/PDL1 and dMMR story developing
 - Braf - ?anti EGFr and Brafi
 - ? Her-2 and anti-Her2 therapy
 - ? PIK3CA,
- **New trial methods**



Thanks to:



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- Yorkshire Cancer Research
- Quasar1 Richard Gray, Kelly Handley, Gordon Hutchins
- Focus 1-4, Piccolo, Susan Richman, Matt Seymour, Jenny Barrett, Gemma Hemmings
- Tim Palmer, Susan Richman, Morag Taylor
- Trialists, collaborators and colleagues
- MRC, CRUK and Yorkshire Trials Units

