100,000 Genomes Cancer Programme
South London GMC Teaching Cases

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Overview

- Three patients enrolled in 100,000 Genomes cancer programme
- Paired tumour and cancer genome analysis
- Clinical and molecular information
- Impact on patient management

Case One

- Rectal adenocarcinoma (70) August 2016
  - Dukes A, pT1 25mm, EMVI negative, no LNs involved
  - Laparoscopic low anterior resection with loop ileostomy
  - Resection specimen showed loss of MSH2 and MSH6 on immunohistochemistry (IHC)
- Consented for 100,000 Genomes Project Cancer Programme
- Referred to clinical genetics

Case One

- Did not attend genetics appointment
- Results of cancer genome analysis
  - 10 Tier 1 variants
  - >100 Tier 2 variants
  - High mutational burden
  - Mutational signature = mismatch repair deficiency
  - Germline mutation in *MSH2* gene

100,000 Genomes report

Participant information

Participant name	D.O.B	Gender	NHS number	Laboratory sample ID	GeL participant ID	GMC	Sample date	Date analysis issued
		F		1018174223	212000082	RJ1	24-08-2016	11-04-2017

Tumour information

Tumour type	Tumour subtype	ICD10 code	Sample type	Reported tumour content	Tumour sample cross-contamination
Colorectal	unknown	C189	FF	High >60%	Pass

Pathogenic germline cancer susceptibility variants

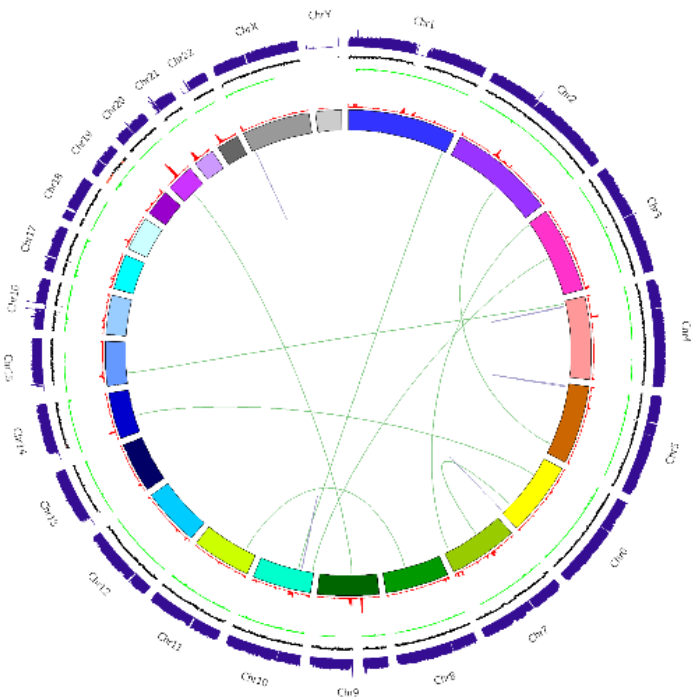
The following variants have been identified on analysis for pertinent germline findings (known pathogenic or likely pathogenic variants in cancer susceptibility genes relevant to the tumour type).

Gene	GRCh38 coordinates ref/alt allele	Transcript	cDNA and protein change	Predicted consequences	Population germline allele frequency (1KG)	Alt allele/total read depth	Genotype	ClinVar ID	Gene mode of action
MSH2	2:47466756 A>T	ENST00000233146	c.1609A>T p.(Lys537*)	stop_gained	N/A	27/46	0/1	N/A	N/A

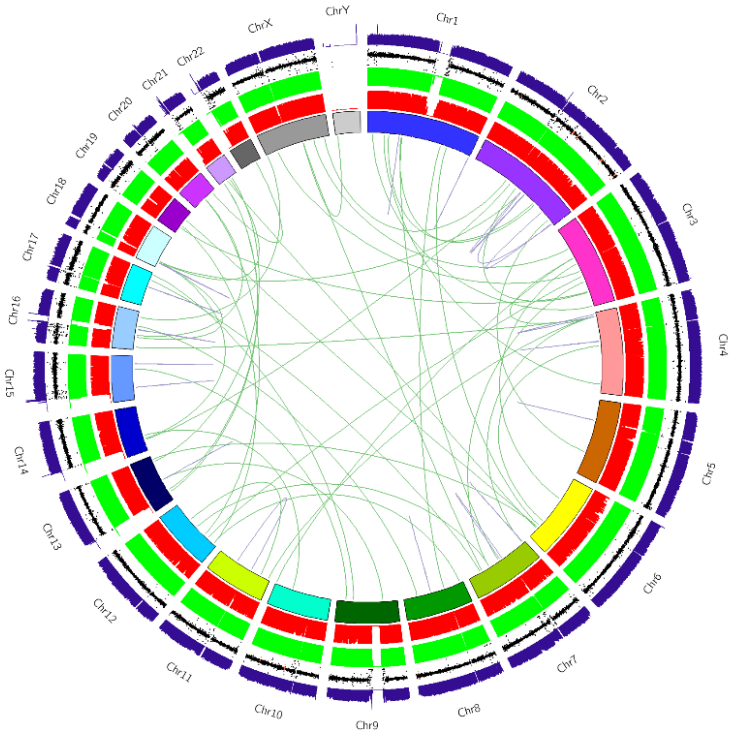
For more details of analysis and the genes included for pertinent germline findings, please refer to Technical Information v1.4.main.

Comparison with MMR proficient colorectal tumour – Circus plot

MMR proficient



MMR deficient



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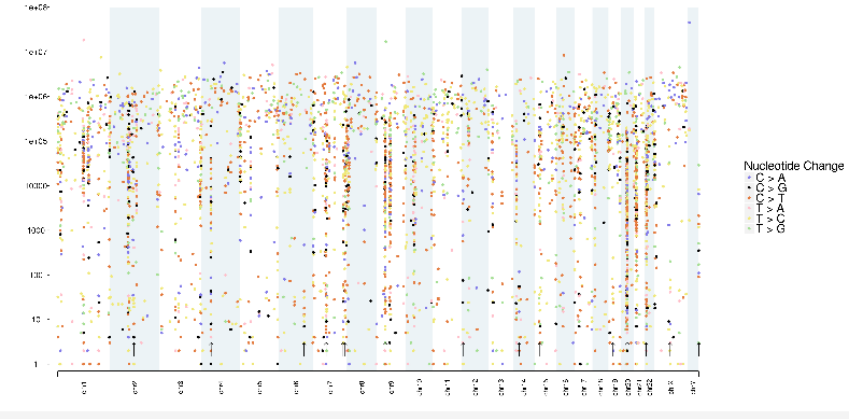
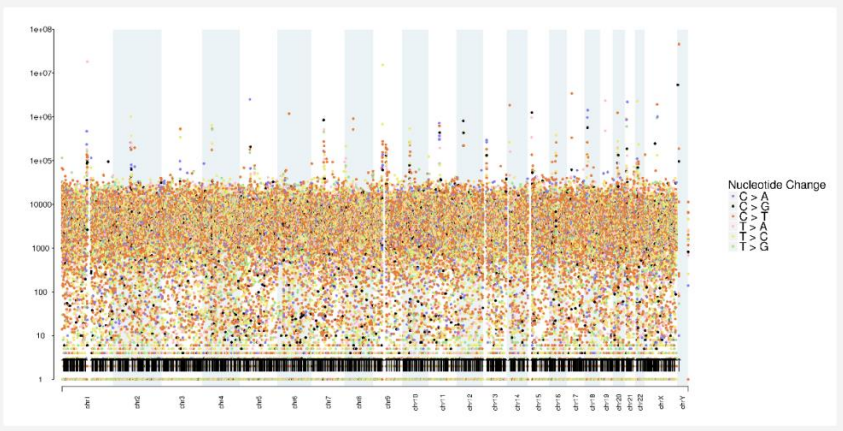
Comparison with MMR proficient colorectal tumour – Rain plot

MMR proficient

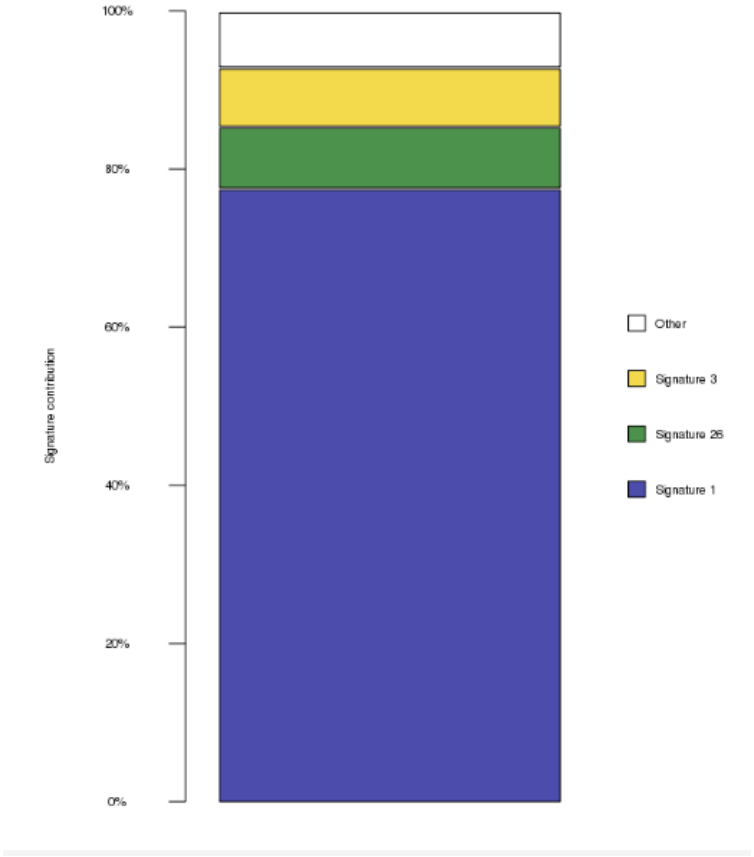


MMR deficient

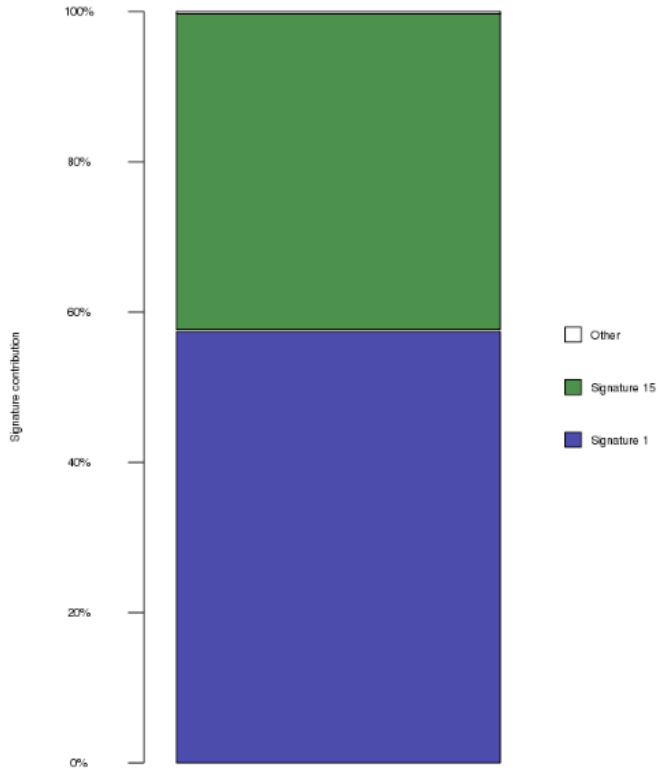


Comparison with MMR proficient colorectal tumour – Mutational signature

MMR proficient



MMR deficient



Clinical impact of germline MMR deficiency

- Treatment – limited benefit of single agent 5FU, doublet chemo regime with oxalaplatin and 5FU
- Less conservative surgery (significant second primary risk)
- Prophylactic aspirin reduces likelihood of second cancer
- Prophylactic gynaecological surgery – TAH and BSO greatly reduces risk of endometrial and ovarian cancers
- Cascade screening of relatives

Case Two

- 55 year old diagnosed with triple negative breast cancer (right breast) July 2016
- No family history or Jewish ancestry
- Referred to Genetics August 2016
- Not offered germline *BRCA1/BRCA2* testing as outside standard Pan-Thames BRCA testing criteria

Clinical management

- Right mastectomy Sept 2016
- Chemotherapy 6# FEC complicated by co-existing COPD and cellulitis
- Radiotherapy June 2017
- Enrolled in 100,000 genome study and consented to receive germline results

100,000 Genome Report

Whole Genome Analysis

100,000 Genomes Project Cancer Programme

Preliminary analysis: somatic small non-synonymous variants and pertinent germline findings in cancer susceptibility genes v1.4

Genomics england

Participant information

Participant name	D.O.B	Gender	NHS number	Laboratory sample ID	GeL participant ID	GMC	Sample date	Date analysis issued
		F		1018173889	212000085	RJ1	09-09-2016	24-04-2017

Tumour information

Tumour type	Tumour subtype	ICD10 code	Sample type	Reported tumour content	Tumour sample cross-contamination
Breast	ductal	C509	FF	High >60%	Pass

Pathogenic germline cancer susceptibility variants

The following variants have been identified on analysis for pertinent germline findings (known pathogenic or likely pathogenic variants in cancer susceptibility genes relevant to the tumour type).

Gene	GRCh38 coordinates ref/alt allele	Transcript	cDNA and protein change	Predicted consequences	Population germline allele frequency (1KG)	Alt allele/total read depth	Genotype	ClinVar ID	Gene mode of action
BRCA2	13:32340432 C>CA	ENST00000544455	c.6079dupA p.(Arg2027fs)	frameshift_variant	N/A	21/36	0/1	RCV000044837 RCV000076953 RCV000132018	tumour suppressor

For more details of analysis and the genes included for pertinent germline findings, please refer to Technical Information v1.4.main.

Pathogenic variant in BRCA2

Confirmed in diagnostic lab, seen in clinic August 2017 with result

Change in management

- Now eligible for Olaparib - PARPi (tablet chemotherapy that specifically targets cancers in BRCA carriers) via OLYMPIA trial
- Increased lifetime risk ovarian cancer (10-30%) –recommend bilateral salpingo-oophorectomy
- Predictive genetic testing for specific *BRCA2* mutation can be offered to children
  - daughter is a carrier and is now due for MRI breast screening

Case Three

- Lung adenocarcinoma

100,000 Genome Report

Whole Genome Analysis

100,000 Genomes Project Cancer Programme

Preliminary analysis: somatic small non-synonymous variants and pertinent germline findings in cancer susceptibility genes v1.3

Genomics england

Participant information

Participant name	D.O.B	Gender	NHS number	Laboratory sample ID	GeL participant ID	GMC	Sample date	Date analysis issued
		F		1023650796	212000226	RJ1	22-11-2016	24-03-2017

Tumour information

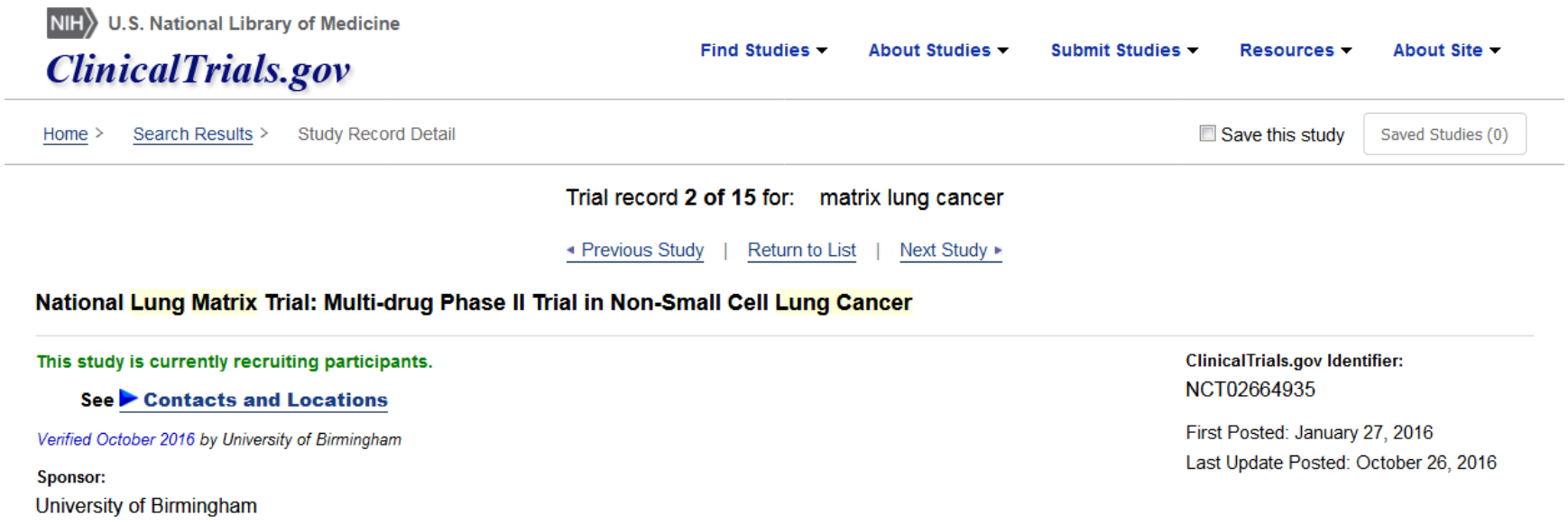
Tumour type	Tumour subtype	ICD10 code	Sample type	Reported tumour content	Tumour sample cross-contamination
Lung	adenocarcinoma	N/A	FF	High >60%	Pass

Gene	GRCh38 coordinates ref/alt allele	Transcript	cDNA and protein change	Predicted consequences	Population germline allele frequency (1KG)	VAF	Alt allele/ total read depth	COSMIC ID	Gene-level actionability	Variant-level actionability	Gene mode of action
BRCA2	13:32338167 C>A	ENST00000544455	c.3812C>A p.(Ser1271*)	stop_gained	N/A	0.06	7/123	N/A	Therapeutic (ovarian ca); Therapeutic (fallopian tube ca); Therapeutic (peritoneal ca); Trial (fallopian tube ca); Trial (fallopian tube ca); Trial (ovarian ca); Trial (ovarian ca); Trial (ovarian ca); Trial (prim peritoneal ca); Trial (prim peritoneal ca); Trial (solid neoplasm)	Therapeutic (ovarian ca); Trial (fallopian tube ca); Trial (ovarian ca); Trial (ovarian ca); Trial (prim peritoneal ca); Trial (prim peritoneal ca)	tumour suppressor
EGFR	7:55191822 T>G	ENST00000275493	c.2573T>G p.(Leu858Arg)	missense_variant	N/A	0.23	25/107	COSM6224	Therapeutic (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (breast ca); Trial (colorectal ca); Trial (endometrial ca); Trial (melanoma); Trial (ovarian ca); Trial (pancreatic ca); Trial (RCC); Trial (solid neoplasm); Trial (solid neoplasm); Trial (SCC Lung); Trial (thyroid ca)	Therapeutic (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca); Trial (NSC lung ca)	N/A
FGF3	11:69816341 C>G	ENST00000334134	c.303G>C p.(Lys101Asn)	missense_variant	N/A	0.06	5/89	N/A	Trial (solid neoplasm)		N/A
FGFR4	5:177090544 G>C	ENST00000292408	c.246G>C p.(Trp82Cys)	missense_variant	N/A	0.05	5/101	N/A	Trial (solid neoplasm); Trial (urothelial ca)		N/A
NF1	17:31219095 G>C	ENST00000358273	c.1618G>C p.(Glu540Gln)	missense_variant	N/A	0.06	7/127	COSM5963097 COSM5963098	Trial (breast ca); Trial (colorectal ca); Trial (endometrial ca); Trial (melanoma); Trial (NSC lung ca); Trial (NSC lung ca); Trial (ovarian ca); Trial (pancreatic ca); Trial (RCC); Trial (solid neoplasm); Trial (solid neoplasm); Trial (SCC Lung); Trial (thyroid ca); Trial (glioma); Trial (glioma); Trial (MPNST); Trial (neuroblastoma); Trial (neurofibroma); Trial (rhabdoid tu); Trial (rhabdomyosarcoma); Trial (schwannoma); Trial (sarcoma-ST)		N/A

EGFR mutations in lung cancer

- **EGFR inhibitors used in NSCLC with *EGFR* gene mutations**
- **Erlotinib (Tarceva)**
- **Afatinib (Gilotrif)**
- **Gefitinib (Iressa)**
- These drugs can be used alone (without chemo) as the first treatment for advanced NSCLCs that have certain mutations in the *EGFR* gene. These are more common in women and people who haven't smoked. Erlotinib can also be used for advanced NSCLC without these mutations if chemo isn't working. All of these medicines are taken as pills.
- **EGFR inhibitors that also target cells with the T790M mutation**
- EGFR inhibitors can often shrink tumors for several months or more. But eventually these drugs stop working for most people, usually because the cancer cells develop another mutation in the *EGFR* gene. One such mutation is known as T790M. But some newer EGFR inhibitors also work against cells with the T790M mutation, including **osimertinib (Tagrisso).**
- Doctors now commonly get another tumor biopsy when EGFR inhibitors have stopped working to see if the patient has developed the T790M mutation.
- **EGFR inhibitors used for squamous cell NSCLC**
- **Necitumumab (Portrazza)** is a monoclonal antibody (a man-made version of an immune system protein) that targets EGFR. It can be used along with chemotherapy as the first treatment in people with advanced squamous cell NSCLC. This drug is given as an infusion into a vein (IV).

Clinical trial links



Clinical trial links