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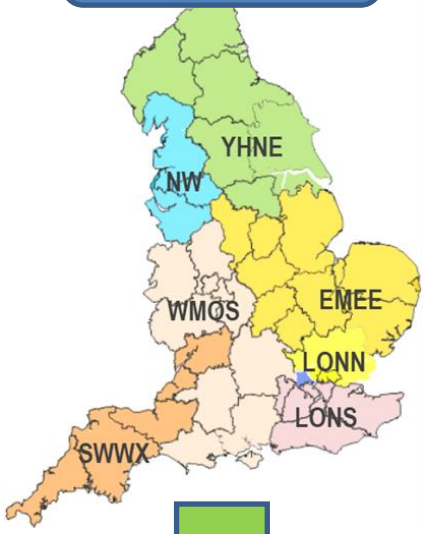
# Cancer Genomic NHS Services

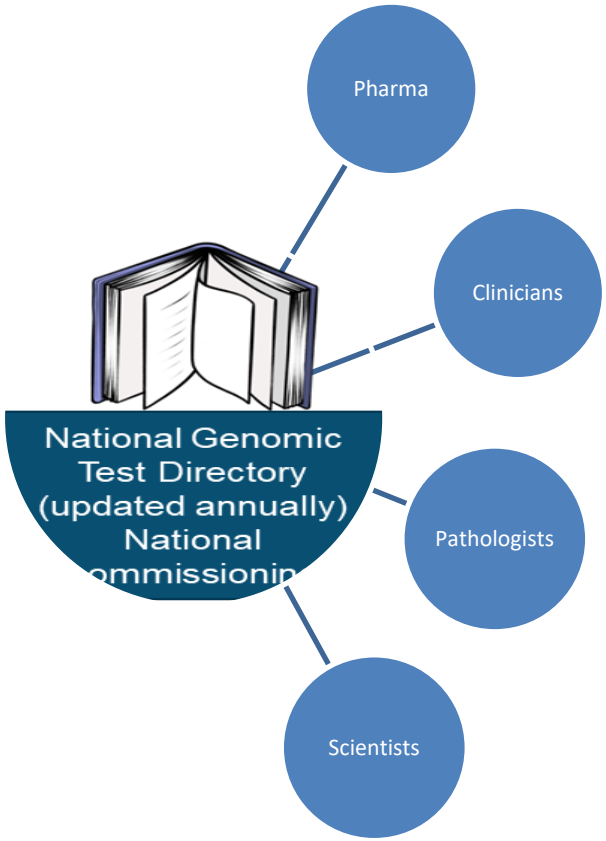
Professor Rachel Butler, MBE
Operational Director of SW GLH

# NHSE Genomics Unit

7 GLHs




Tests according to the NGTD




## Cancer services

Clinical teams
Genomic education
Cancer alliances
Pharma

Ref: Professor Rachel Butler, personal data

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National Genomic Test Directory (updated annually) National commissioning

# National Genomic Test Directory

| | | | Essential gene targets | *Desirable gene targets* |
|---|---|---|---|---|
| Non-Small Cell Lung Cancer | M4.1 | Multi-target NGS panel - small variant (EGFR, ALK, BRAF, KRAS) | **EGFR**, ALK, BRAF, KRAS | |
| | M4.2 | Multi-target NGS panel - structural variant (ROS1, RET, ELM4-ALK, NTRK1, NTRK1, NTRK3) | ROS1, RET, EML4-ALK, NTRK1, NTRK2, NTRK3 | |
| | M4.3 | Multi-target NGS panel - copy number variant (MET) | MET | |
| | M4.5 | EGFR hotspot ctDNA | **EGFR** | |
| | M4.11 | ALK hotspot ctDNA | ALK | |
| | | | | *ERBB2, AKT1, ARID1A, ARID1B, ARID2, ATM, BRCA1, BRCA2, BRIP1, CDK12, CDK4, CDKN2A, ERBB3, ERBB4, FGFR1, FGFR2, FGFR3, KEAP1, MAP2K1, MET, MET ctDNA, MDM2, NF1, NFE2L2, PALB2, PIK3CA, PTEN, RAD51C, RAD51D, RB1, RBM10, RIT1, SETD2, SMARCA4, STK11, TP53, TSC1, TSC2, U2AF1, NRAS* |
| | | | | *CCND1, CCND3, CCNE1, CDKN2A, ERBB2, ERBB3, FGFR3, MDM2, RICTOR* |
| | | | | *TMB* |
| | | | | *Microsatellite instability analysis* |
| | | | | *NRG1, MET* |
| | | | | *MET exon 14 skipping* |
| | | | | *ALK, ROS1, RET ctDNA testing* |

https://www.england.nhs.uk/publication/national-genomic-test-directories/

# New services – summer 2020

- Gene panel analysis
- BRCA for ovarian cancer
- Gene fusion analysis for NTRK
- Gene fusion analysis in NSCLC
- MSI analysis in newly diagnosed CRC
- DPYD analysis to predict toxicity to fluoropyrimidines
- EGFR ctDNA in NSCLC

# Gene panel strategy: Tumour agnostic

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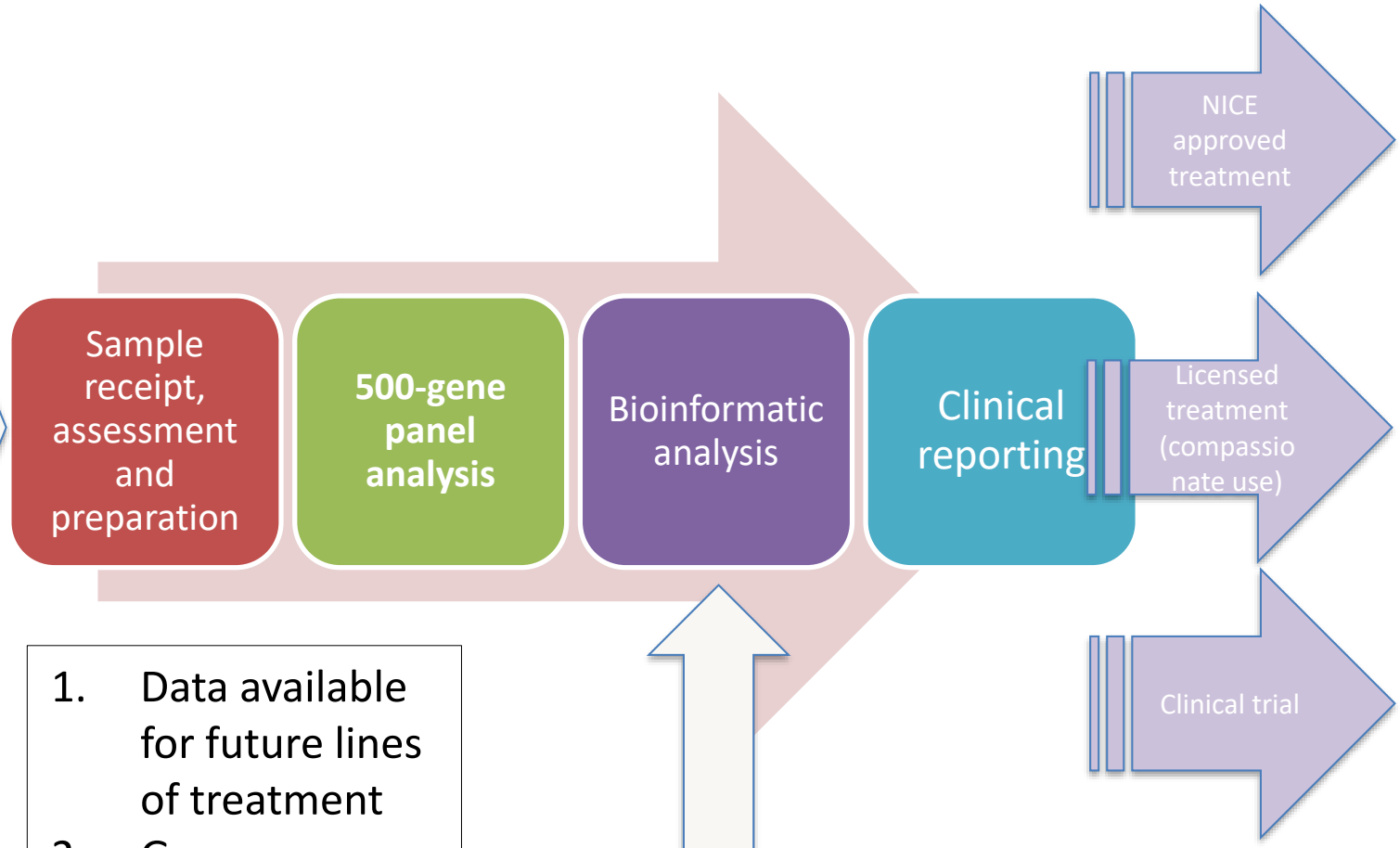
**Tumour types:**
Lung
CRC
Melanoma
Neuro
Pancreatic
Prostate
Ovarian
Breast
Bladder
Thyroid
H&N
Renal

Haem ….

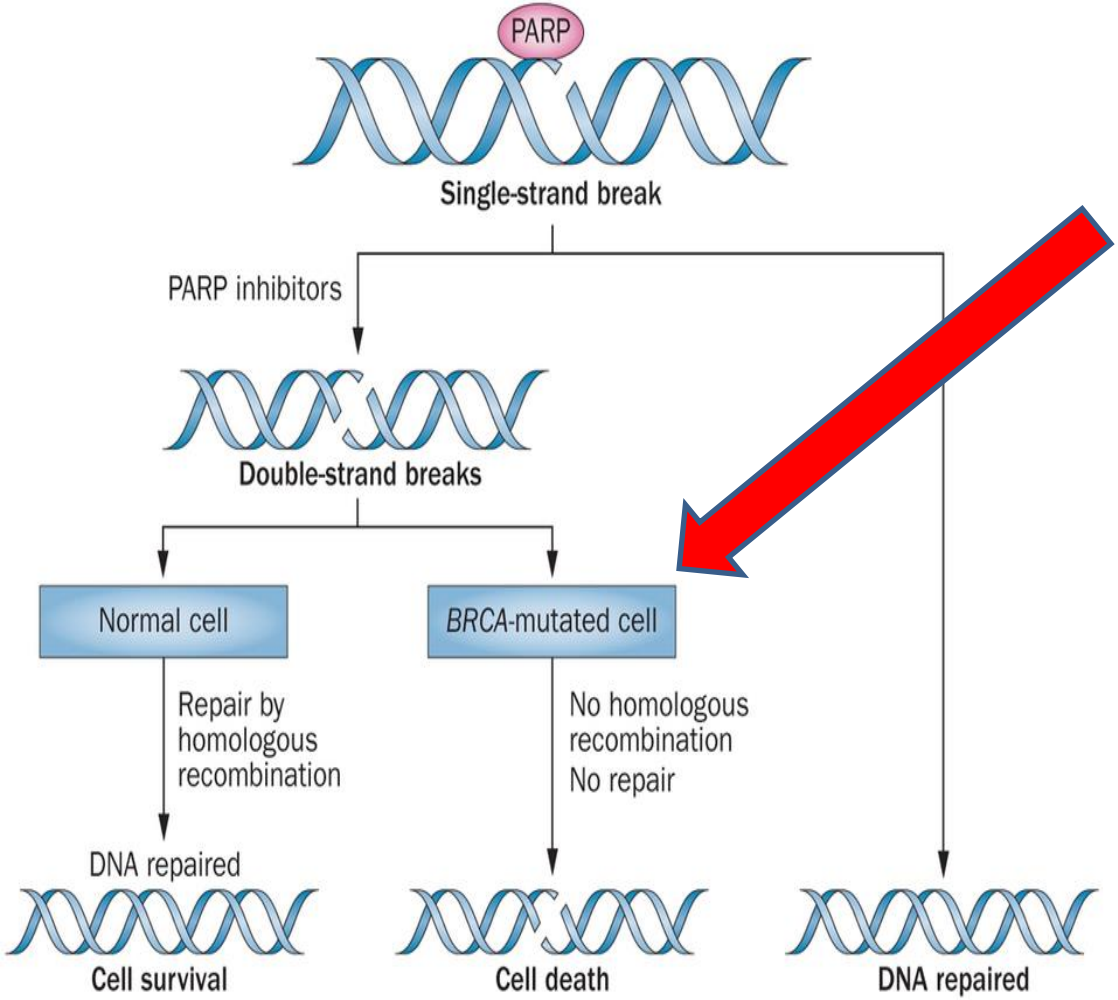



1. Data available for future lines of treatment
2. Gene re-analysis can be requested

Genes selected according to tumour type

# BRCA analysis in HGS ovarian cancer

# PARPi and synthetic lethality




Homologous recombination deficient (HRD)

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# High grade serous ovarian cancer

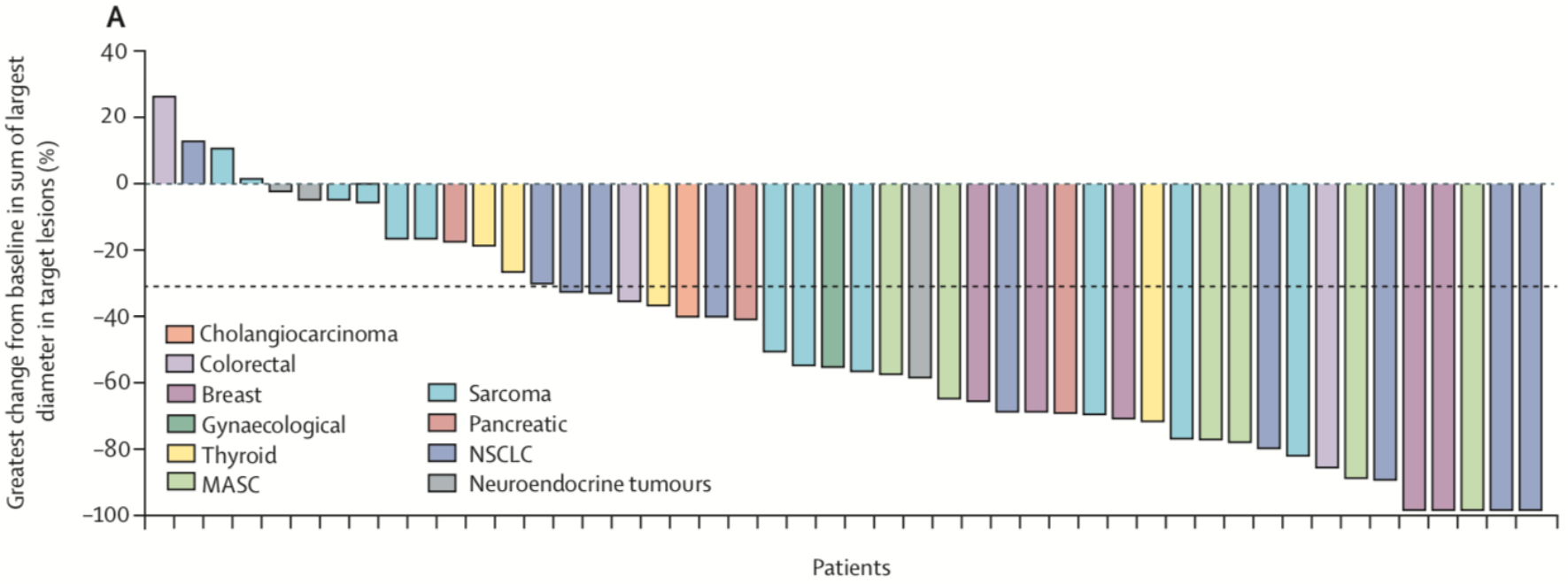
- ~15% have a BRCA1 or 2 mutation
  - 2/3 are germline
  - 1/3 somatic (tumour only)
  - The majority will be detected by sequencing the tumour
- High response rate to PARP inhibitors (much better than chemo)

# Gene fusion analysis
# Tumour agnostic strategy

- This is applied to both NTRK and also gene fusions in NSCLC, thyroid, H&N…..

# Benefits: NTRK – multiple childhood and adult cancers

- Neurotropin Receptor Tyrosine Kinase oncogenic gene fusions
- TRK inhibitors - Entrectinib / Larotrectinib
- Phase I / II trials – 75% objective response across 17 cancer types




*Lancet Oncol.* 2019 Dec 11. pii: S1470-2045(19)30691-6.

*Exp Rev of Anticancer Therapy*, 2018. 19:1, 1-10, DOI: 10.1080/14737140.2019.1538796

# Roll-out of NTRK fusion services

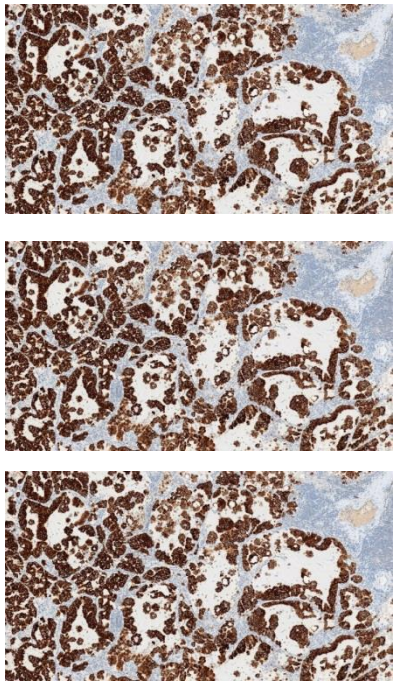
Phase 1 – From April 20

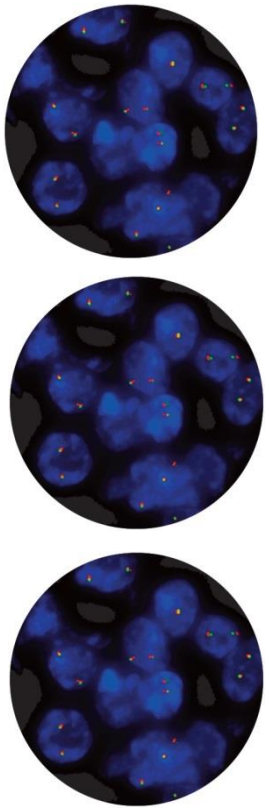
- Rare cancers that have a very high incidence of NTRK gene fusion ie >90%:
  - Paediatric - infantile fibrosarcoma and congenital mesoplastic nephroma
  - Adult cancers - mammary variant salivary gland carcinoma and secretory breast cancer
- Cancers in which NTRK gene fusions account for 5-25%: gastrointestinal stromal tumours (GISTs), thyroid cancers and spitzoid neoplasms.
- Paediatric patients who are being seen in PTCs and TYA (would normally be patients up to the age of 25 in line with NHS England definition of cancer services for children and young people).

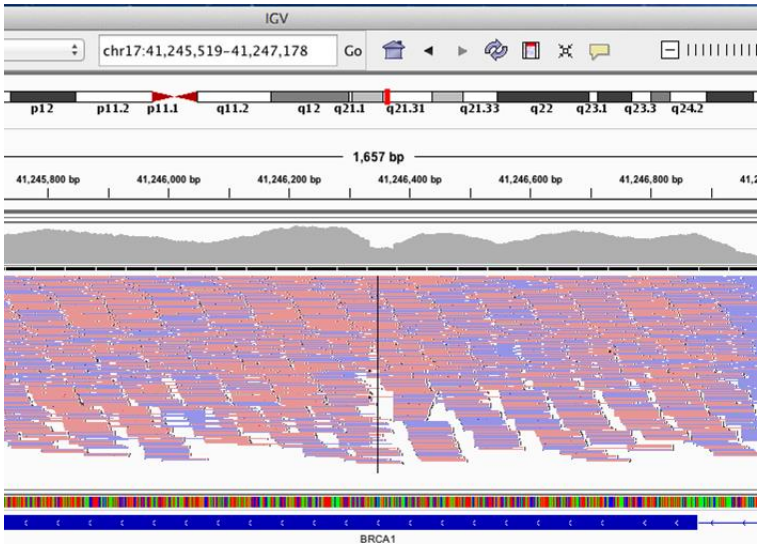
Phase 2 – From August 20

- Larotrectinib is approved for use through the CDF and indicated for NTRK gene fusion-positive solid tumour patients with locally-advanced or metastatic disease, or where surgical resection is likely to result in severe morbidity, for whom standard therapies have failed, or none are available, and are fit for further treatment.

# NSCLC – ALK, ROS and RET fusions








Plus bonus additional gene fusions. e.g. NTRK, and information about gene partners

**3 x IHC and FISH** **OR** **1 NGS**

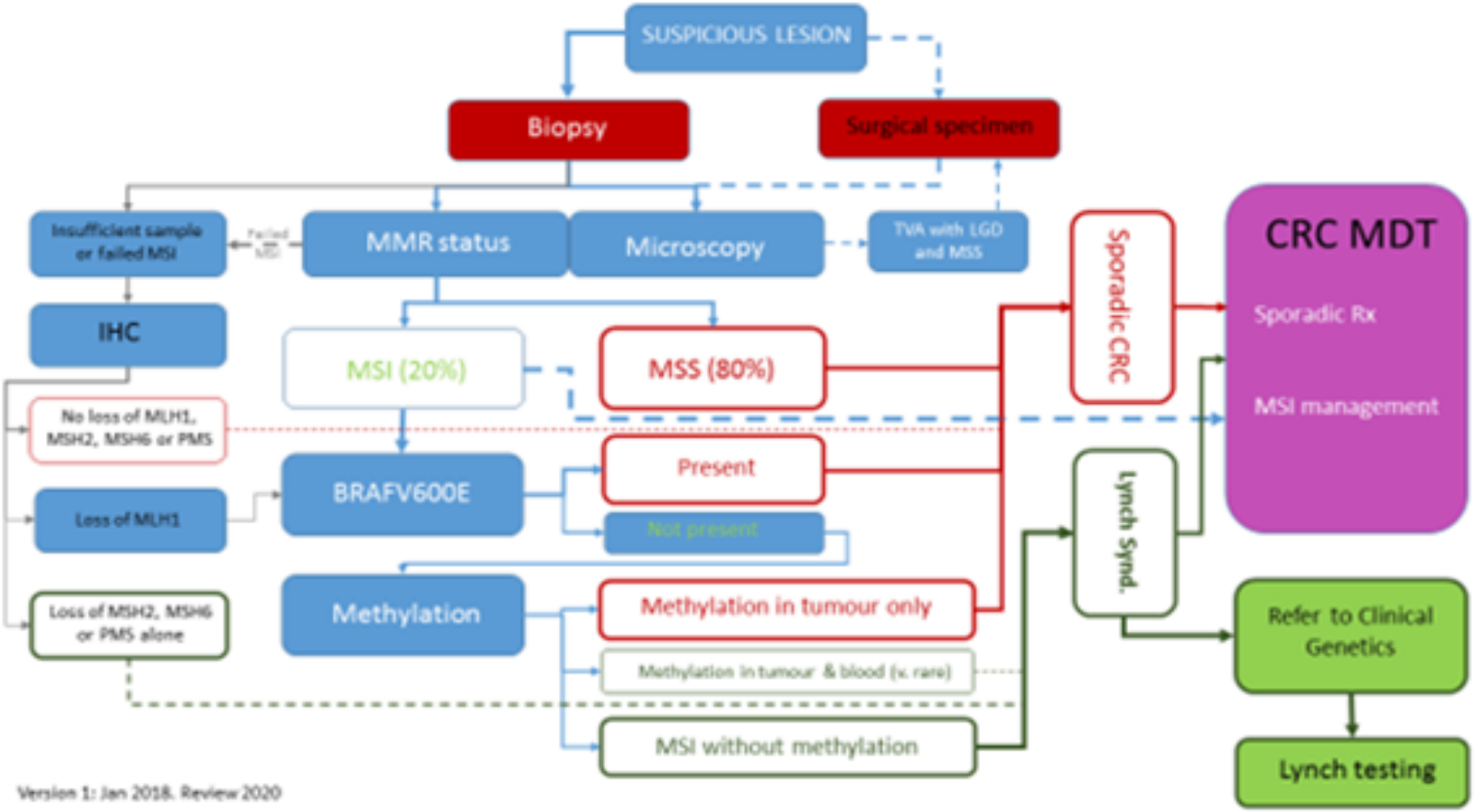
Gene fusion analysis will be run in parallel to DNA analysis for EGFR, KRAS, BRAF etc.

# MSI analysis in newly diagnosed CRC

- MSI will be performed for sporadic CRC patients at diagnosis in accordance with NICE guidance (DG27), with the aim of identifying those patients (and their families) at risk of Lynch syndrome. The test has the benefit of also identifying those stage II patients who will not benefit from chemotherapy, and those patients who are likely to benefit from immunotherapy.

- MMR immunohistochemistry (IHC) may be used to supplement MSI analysis where tissue is scarce or unsuitable for genetic analysis.

# Pathway


SUSPICIOUS LESION
Biopsy
Surgical specimen
Insufficient sample or failed MSI
MMR status
Microscopy
TVA with LGD and MSS
IHC
MSI (20%)
MSS (80%)
No loss of MLH1, MSH2, MSH6 or PMS
Loss of MLH1
Loss of MSH2, MSH6 or PMS alone
BRAFV600E
Present
Not present
Methylation
Methylation in tumour only
Methylation in tumour & blood (v. rare)
MSI without methylation
Sporadic CRC
Lynch Synd.
CRC MDT
Sporadic Rx
MSI management
Refer to Clinical Genetics
Lynch testing
Version 1: Jan 2018. Review 2020

# MSI: Patient outcomes

80% of samples will test **Normal for MSI** i.e. stable.
These patients are at negligible risk of their cancer being associated with Lynch syndrome

20% of samples will be **MSI unstable**

Patients whose tumour samples exhibit MSI instability are more likely to respond to immunotherapy, stage II patients show no benefit to chemotherapy.

Further tests are required to identify which of the MSI unstable patients are likely to have Lynch syndrome. Patients for whom the both the *BRAF* p. V600E and *MLH1* promoter methylation is absent will be reported as **MSI unstable – an increased likelihood of Lynch syndrome** (~2%). A recommendation for referral to Clinical Genetics will be included in these reports.

# DPYD deficiency – A pharmacogenetic test

Mail Online

# The NHS still isn't warning bowel cancer patients that their chemo can kill them - despite eight months passing since the alarm was raised

- Lynn Stevens was diagnosed with bowel cancer after a routine test screening
- After successful surgery in January this year, Lynn appeared to be in the clear
- Doctors advised a course of chemotherapy, to wipe out any rogue cells
- On March 21 Lynn had her first and only dose of intravenous fluorouracil
- Less than four weeks later, she was dead, aged just 66 - poisoned by the very drug that was supposed to prolong her life

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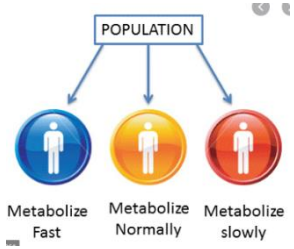
# Pharmacogenomics




Genetic prediction of drug metabolism

e.g. DPYD for fluoropyrimidines

- Fluoropyrimidine anticancer drugs have been widely used for more than 60 years.
- Over 2 million newly diagnosed patients each year are treated with fluoropyrimidines.
- 5-Fluorouracil (5FU)
  - IV - colon, oesophageal, stomach, pancreatic, breast and cervical cancer
  - cream – actinic keratosis, basal cell carcinoma, skin warts
  - oral prodrug capecitabine (Xeloda)
- Generally 6 cycles of treatment – each lasting 2-4 weeks

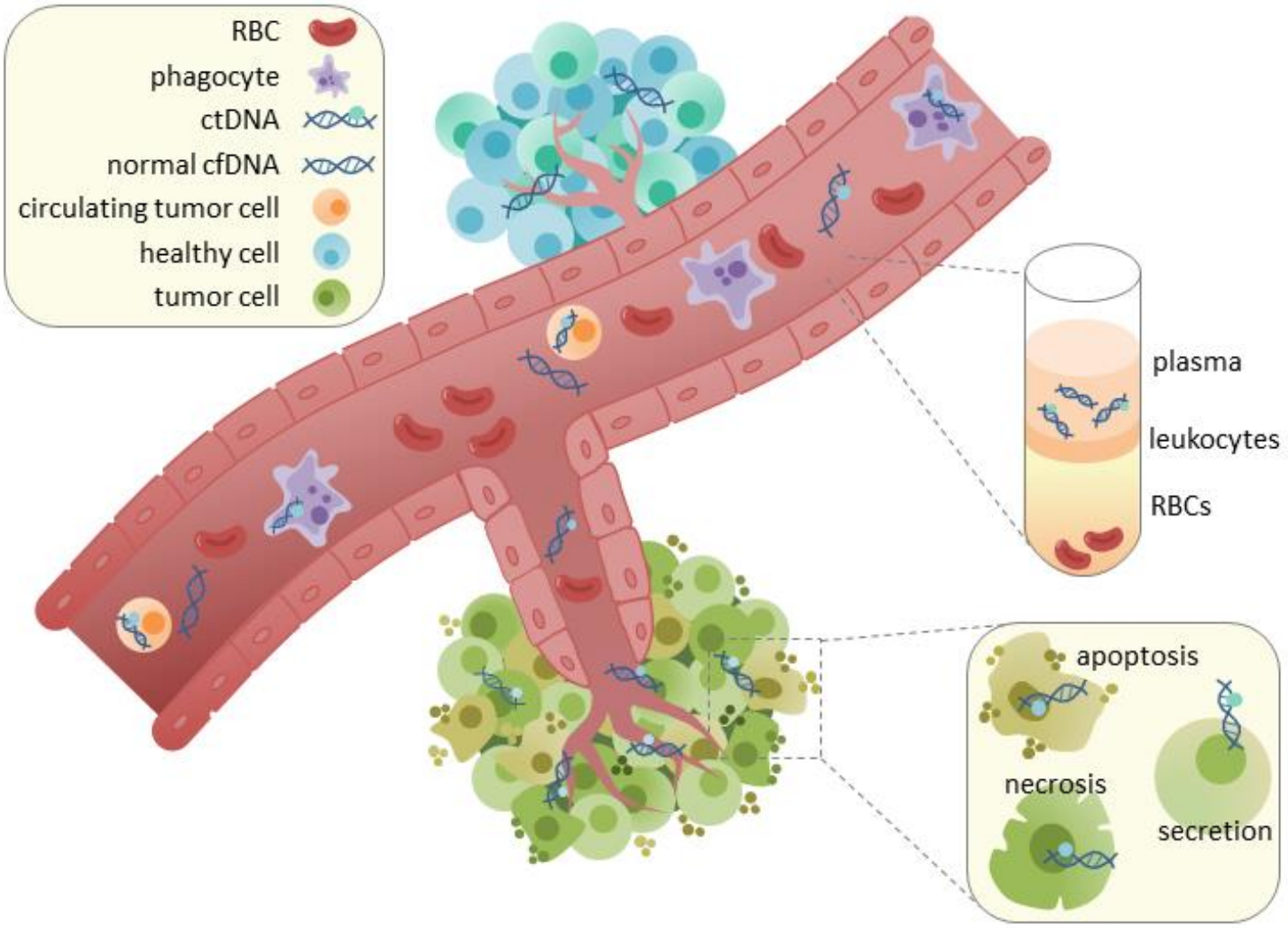
- Up to 30% of patients have severe treatment related toxicity:
  - diarrhoea, mucositis, myelosuppression, hand-foot syndrome

- NHSE has currently approved testing for 4 DPYD variants based on :
  - Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines - 2017
  - Population frequency
  - Established impact on enzyme function and toxicity risk
  - Approx. 7% of Europeans carry at least one of these 4 *DPYD* variants

# ctDNA analysis of EGFR in NSCLC

- ctDNA has many applications in cancer diagnostics.
- We currently have 1 clinical diagnostic service approved on the NGTD, for EGFR testing in NSCLC. This is for 2 applications:
  - For EGFR mutation-positive patients who are progressing on an EGFR TKI, where we specifically look for the p.T790M variant
  - For NSCLC patients where an EGFR test has not been possible, or has failed due to the lack of tissue

# Circulating tumour DNA



- There are many more new services to come
  - New gene targets
  - **New tumour types**

- Service consolidation
  - NHSE model is for all tests in 1 lab per GLH: Efficiencies, patient equity, standardisation, access to new tests / treatment
  - Not supported by some path labs in SW