Oxford University Hospitals NHS
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The Evolution of Genetic Testing for Hereditary Bowel Cancer at Oxford Medical Genetics Laboratories

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Introduction

- Inherited predisposition to bowel cancer is genetically and phenotypically heterogeneous.
- Transition from traditional stepwise gene analysis to panel testing is standardising service, improving test sensitivity and turnaround time.
- Historically, analysis of individual genes was undertaken using Sanger sequencing and MLPA.
  - Phenotype driven
  - Each individual gene screen had a target turnaround of 56 calendar days (40 working days)
- 17 gene panel introduced July 2014 – available to clinically selected patients who had complex family histories or had previously been mutation negative on individual gene screen
  - Average panel turnaround time was 92 calendar days

Current Strategy

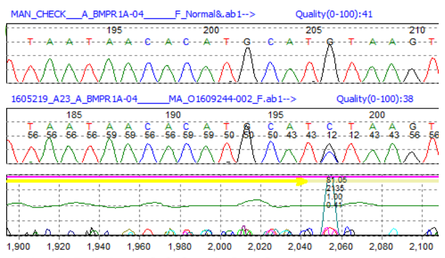
- Introduced September 2016
- All patients screened using one of two panels based on clinical grounds
- Target turnaround 56 calendar days
- **Polyp panel** – 50 reports issued:
  - 5 class 5 variants (10%); 1 class 4; 7 class 3; 2 individuals with heterozygous pathogenic variants in recessive genes
- **Lynch-like panel** – 25 reports issued:
  - 3 class 5 variants (12%); 2 class 3

Polyp Panel FH CRC and proband with >10 polyps / CRC	Lynch like Panel MSI high/IHC abnormal/ not fulfilling polyp criteria
MLH1 (&MLPA)	*MLH1* (&MLPA)
MSH2 (&MLPA)	*MSH2* (&MLPA)
MSH6 (&MLPA)	*MSH6* (&MLPA)
POLD1	*PMS2* (sanger)
POLE	*POLD1*
MUTYH	*POLE*
APC (+MLPA)	*MUTYH*
BMPR1A	
PTEN (+promoter)	
SMAD4	
STK11	
NTHL1	
Average TAT 55 calendar days	Average TAT 53 calendar days

Unexpected Case Studies

BMPR1A

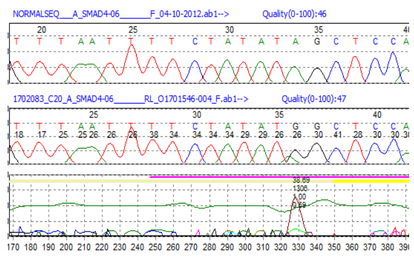
- Proband with Bowel cancer (37) , tubular adenoma and TVA, no juvenile polyps
- *BMPR1A* consensus splice variant consistent with molecular diagnosis of juvenile polyposis
- Result not consistent with phenotype



BMPR1A c.230+1G>C

SMAD4

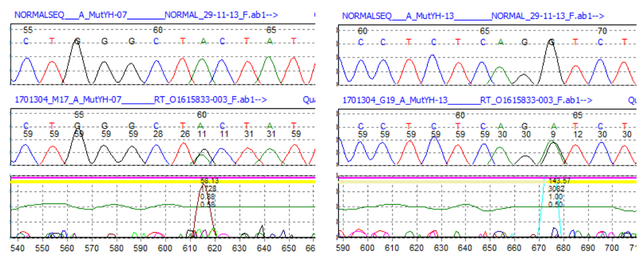
- Proband with serrated polyposis and sigmoid cancer
- *SMAD4* consensus splice variant suggesting juvenile polyposis; this diagnosis was not supported by histopathology



SMAD4 c.455-2A>G

MutYH

- Individual tested normal for familial pathogenic *MSH2* variant
- Bowel panel undertaken due to polyps
- Molecular diagnosis of *MUTYH* associated polyposis
- Co-occurrence of two bowel cancer susceptibility genes in one family



MUTYH c.536A>G *MUTYH* c.1187G>A

Conclusions and Future Directions

- Access to constitutional analysis for bowel cancer predisposition is standardised in Oxford.
- Panels have the potential to reveal novel genotype-phenotype correlations through analysis of a standardised gene list, rather than selection based on currently recognised phenotype.
- This service has made a significant positive impact on turnaround to reach molecular diagnosis.