

Transforming the care of people with Lynch syndrome: a system-wide approach

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In this issue, Monahan *et al*¹ describe progress in addressing the lack of diagnosis of Lynch syndrome in the English National Health Service with a bold attempt to fix a leaking pathway.

Lynch syndrome (LS) describes a cluster of overlapping phenotypes resulting from a germline loss of function in an allele at four loci responsible for mismatch repair (MMR) proteins. These proteins act together to identify and facilitate repair of replication errors in DNA, a system fundamental to all cellular organisms.

This year marks the 30th anniversary of the breakthrough that identified the first of these genes to be the underlying cause of multiple cancers in families with hereditary on-polyposis colon cancer.² The proband from a Northumberland family whose DNA was shared had had three gastrointestinal cancers and nine skin cancers; the Boston yeast genetics team published an *MSH2* variant, which proved not to be pathogenic but provided us with an intragenic marker of the pathogenic allele allowing us to be the first to begin predictive testing. The other three genes were soon identified, and the detailed prior knowledge of this repair system promised rapid progress in identifying and preventing cancer in what was becoming recognised as a 'common rare syndrome'. This first family illustrated the challenge; incomplete penetrance, different cancers, wide range of onset age, variants of uncertain significance and possible genetic heterogeneity.

Careful population studies suggest that more than 1 in 300 people carry a pathogenic variant in one of the four genes: *MSH2*, *MLH1*, *MSH6* and *PMS2*.³ A review by NHS England indicated fewer than 10% of the expected number had been identified by 2019 despite 2017 NICE guidance requiring all colorectal cancers (CRCs) be tested for

MMR deficiency as a prelude to referral for germline testing.⁴

The obvious challenge was the complex logistics of the pathway; testing of biopsy blocks or resected tumours using immunohistochemistry for the four MMR proteins or microsatellite instability on molecular testing then led to a second test for the driver point mutation *BRAF V600E* and/or methylation testing for *MLH1* promoter methylation. These latter tests identify changes largely confined to sporadic CRCs and reduce the target group for germline testing to a more manageable 6–8% of the 37000 reported cases per annum. The eligible patients would then be referred to the regional genetics service to be advised of the benefits of germline testing in terms of routine surveillance and eligibility for prophylactic aspirin to half their cancer risk.^{5 6} With consent, samples would be referred to one of the seven regional Genomics Laboratory Hubs. Gene carriers would then be contacted, and their families traced to offer intervention.

Analysis by the National Disease Registration Service showed around 50% attrition at every step and estimated around 700 people with LS among those presenting with CRC had been missed in 2019. Monahan and colleagues discovered multiple issues; a survey of 126 multi-disciplinary teams revealed lack of clarity on responsibility. It was no-one's 'job' and only a little over half discussed MMR results. While most believed they offered universal testing, there was uncertainty on how genetic testing was organised and its outcome. Delays meant patients had left the hospital or died before the relevant information arrived. The potential to use MMR data and *BRAF* status in selection of the latest therapies has added urgency but did nothing to resolve the logistic barriers.

The new programme, led by experts in the field and supported by the Genomic Medicine



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Service Alliances allied to each of the seven Genomic Laboratory Hubs, has set out to remedy the many problems. Additional non-recurrent support was provided to pathology services to expand IHC capacity while each Cancer Alliance was called on to identify a Lynch Champion in each multi-disciplinary team to ensure the condition was considered and information followed up. Lynch nurses in each region would promote testing and help educate frontline teams about the potential for early detection with colonoscopy, prevention with aspirin and the benefits to other family members. Mainstreaming the germline test would greatly reduce delays by ensuring sampling by the coloproctology team rather than a long wait for genetic referral.

Has the investment worked? It is a little early to say. This is a time of extreme system stress, but there is a real sense that the professional community have grasped the challenge. The National Bowel Cancer Screening programme has accepted responsibility for all LS carriers which should ensure regular high-quality colonoscopies for all and initial MMR plus BRAF screening can now be done more rapidly on biopsy blocks.⁷ Growing numbers of coloproctology nurse practitioners have embraced the mainstreaming, with others soon to follow, ensuring eligible patients are offered germline testing while still under their care. The next traffic jam is getting the germline gene sequencing done in a timely fashion, but this will improve as technology advances alongside international efforts to curate the many thousands of gene variants in these genes.

There remains much to do, not least inclusion of the many other tumour types seen in LS, but this programme has demonstrated the power of a national system of health provision and the willingness of the professional community to work together to improve the care of people with this common rare disorder.

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