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Carrier testing for partners of *MUTYH* variant carriers: UK Cancer Genetics Group recommendations

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MUTYH-associated polyposis (MAP) is an autosomal recessive condition caused by biallelic constitutional pathogenic variants in the *MUTYH* gene. MAP is associated with colonic polyposis (typically adenomas, but less commonly hyperplastic, serrated or mixed) and increased cancer (colorectal, duodenal and others) risk. Variable expressivity has been noted; polyp burden has often been reported in the order of 100s and rarely greater than a thousand,[1] but colorectal cancer has also been reported in affected individuals in the absence of many, or any, preceding polyps.[2] MAP-associated penetrance is incomplete, but the risk of colorectal cancer in the absence of intervention is high. Although age at diagnosis of cancer is typically younger than sporadic cancers, at 47, phenotypic expression is usually adult in onset.[3] Recommended surveillance includes biannual colonoscopy from 18 to 20, and oesophagogastroduodenoscopy from 35.[4]

The frequency of MAP is estimated to be at least 1 in 40 000, but the condition is likely underrecognised, given recessive inheritance pattern and variable phenotype. It is estimated that approximately 1%–2% of individuals of White European ancestry are heterozygous carriers of a pathogenic variant in *MUTYH*.[5–7] It is estimated that two pathogenic founder variants, c.536A>G (p.Y179C) and c.1187G>A (p.G396D), account for greater than 80% of pathogenic variants in this gene, with approximately 70% of affected individuals carrying at least one of these variants.[8] Several other recurrent variants have been identified in different groups (table 1).

In the UK, *MUTYH* testing is currently offered as part of a panel of genes for investigation of individuals with a personal and/or family history of polyposis or early-onset colorectal cancer.[9] While the intention of testing of *MUTYH* is to identify individuals with MAP, testing frequently identifies heterozygous carriers of *MUTYH* variants, which, in isolation, would not account for the patient phenotype, as heterozygous carriers of this recessive trait do not have a significantly increased cancer risk.[10] Identification of a single *MUTYH* variant in an individual with a convincing MAP phenotype suggests another unidentified contributing risk allele. Outside NHS testing criteria, *MUTYH* is frequently included in commercial pan-cancer predisposition panels available in the private sector. Identification of a heterozygous *MUTYH* variant in an individual without a clinically relevant phenotype may represent an incidental finding. Such variants may also be ascertained through other routes, such as whole genome sequencing or tumour-based testing, depending on technology/filtering applied, research-based testing or direct-to-consumer testing,[11] although some companies/groups now recommend reporting only biallelic status.[12]

Table 1 Recurrent *MUTYH* variants in different populations

MUTYH variant	Population	Variant allele frequency (population)[16]
c.1187G>A (p.Gly396Asp)	European	0.005885 (NFE)
c.536A>G (p.Tyr179Cys)	European	0.002332 (NFE)
c.934–2A>G (p.?)	East Asian (Japanese)	0.01863 (East Asian)
c.1118C>T (p.Ala373Val)	Japanese, Korean	0.006105 (East Asian, 0.0003952 (South Asian)
c.1227_1228dup (p.Glu410GlyfsTer43)	Spanish, Portuguese, Tunisian, Moroccan	0.0009875 (Middle Eastern) 0.0009666 (Admixed American)
c.312C>A (p.Tyr104Ter)	South Asian	0.0007356 (South Asian)
c.1438G>T (p.Glu480Ter)	South Asian (Indian Gujarati)	0.0007578 (South Asian)
c.857G>A (p.Gly286Glu)	Japanese	0.0002450 (East Asian)
c.933+3A>C (p.?)	Italian	0.001096 (Amish) 0.0001195 (NFE)
c.1437_1439del (p.Glu480del)	Italian	0.0009862 (Middle Eastern) 0.00003983 (NFE)
c.734G>A (p.Arg245His)	Russian, Hungarian	0.0001336 (East Asian) 0.00006695 (NFE)
c.1147delC (p.Ala385ProfsTer23)	Northern European	0.0001042 (NFE)
c.1214C>T (p.Pro405Leu)	Dutch	0.00008813 (NFE)
Deletions exon 4–16	Brazilian, French, Spanish	

NFE, Non-Finnish European.

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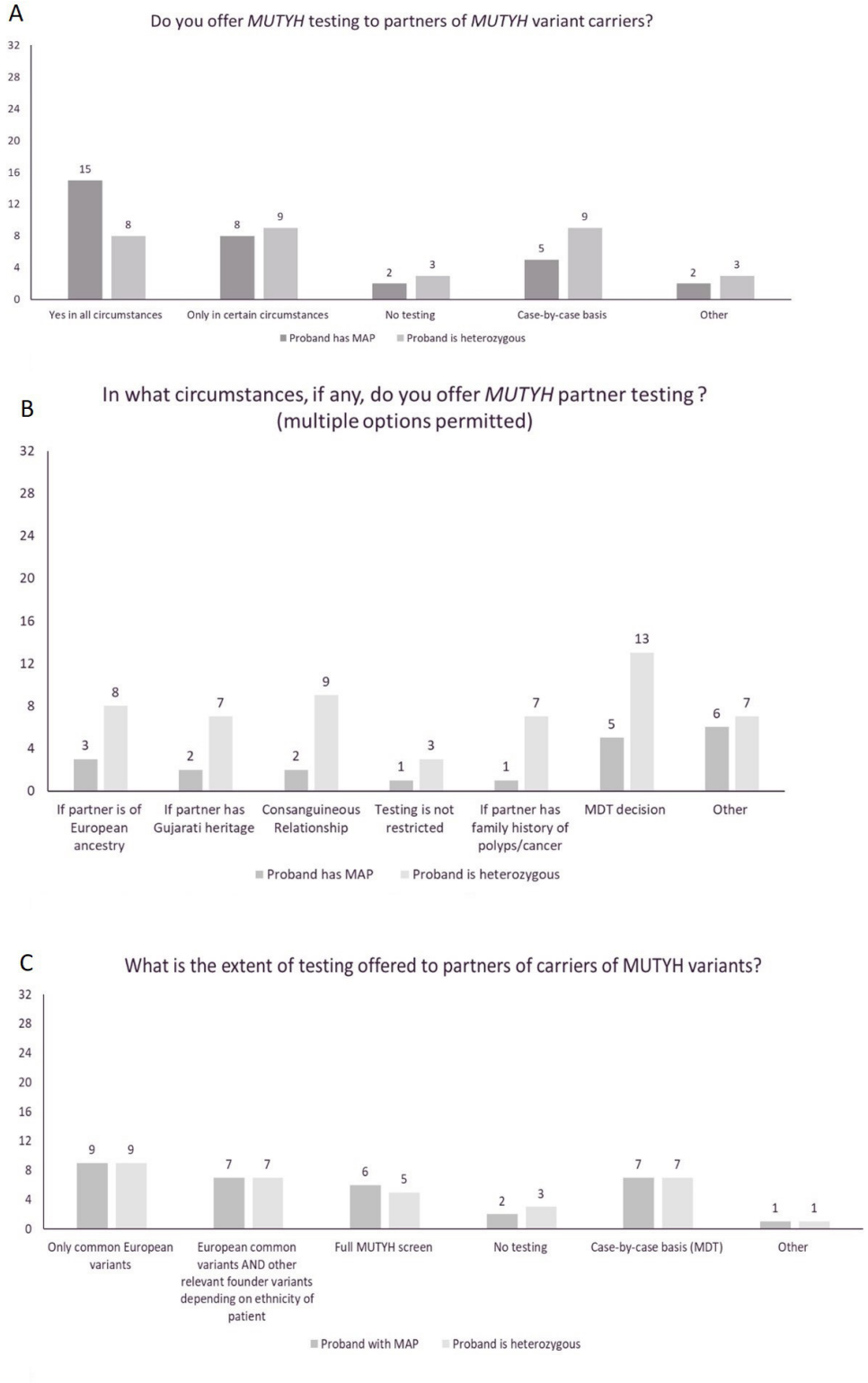

Figure 1 Survey of practice for MUTH carrier testing in UK Cancer Genetics/Specialist services. (A) Practice of carrier testing in partners of carriers of *MUTYH* variants. (B) Indications for carrier testing in partners of carriers of *MUTYH* variants. (C) Extent of testing in partners of carriers of *MUTYH* variants. MAP, *MUTYH*-associated polyposis.

The NHS England Genomic testing directory outlines indications for carrier testing in partners of individuals who carry recessive traits, to enable accurate and informed reproductive decision-making. Presently, criteria are reasonably broad, suggesting that such testing can be considered where the result would influence reproductive decision-making, if the carrier frequency of pathogenic variants in the associated gene is at least one in 70 (or if consanguinity is a consideration). While the carrier frequency of the common founder *MUTYH* variants in White Europeans is higher than this threshold, the frequency of these and other variants in *MUTYH* in non-European populations is not well established.

Although MAP is a high-risk heritable genetic disorder with a reported carrier frequency (at least in some populations) in excess of 1 in 70, the phenotype is adult in onset; and variants in this gene are much more likely to be ascertained incidentally compared with other recessive traits associated with highly penetrant disorders.

Previous work has demonstrated that testing of partners of patients with MAP is cost-effective.[13] However, ascertainment of heterozygous carriers of *MUTYH* variants is increasing, given associated growth in genetic testing using pan-cancer predisposition panels in patients with and without a *MUTYH*-related phenotype. Because of the relatively high carrier frequency of *MUTYH* variants in the general population, incidental detection of carrier status is not rare and represents a commonly encountered clinical challenge for genetics services, without a precedent in clinical guidelines to inform decision-making.[14] Cascade testing is associated with significant workload, particularly in countries with large family sizes. In England, Wales and Scotland, the average size of an extended three-generation family totals 19 individuals, and in Northern Ireland and Ireland, 64.[15] The potential workload is associated with testing of relatives and partners of heterozygous carriers, in the absence of proven cost-effectiveness needs due consideration. There are no specific guidelines related to testing of partners of carriers of recessive traits associated with later onset cancer risk. Considering this, we aimed to establish current practice (and variability thereof) in *MUTYH* cascade and partner/spousal carrier testing in the UK and Ireland, and to suggest *MUTYH*-specific modifications to existing criteria for testing for recessive traits.

To establish current practice, we surveyed lead genetic counsellors, cancer genetic consultant leads and clinical scientists in each regional genetics service in the four devolved nations in the UK, and in the Republic of Ireland, and clinicians in the specialist familial clinic in St Mark's Polyposis Registry. Data collection was considered complete once at least one response (Microsoft form) was received from every relevant regional service (n=32). Variability was noted in practice of offering spousal testing and extent of testing (common variants or full gene sequencing) (figure 1).

In order to standardise practice, we discussed indications for, and extent of partner testing at a virtual meeting involving clinical and scientific leads from each genomic laboratory hub, in August 2023, facilitated by the UK Cancer Genetics Group. At this meeting, we agreed that clinical services were becoming increasingly inundated with requests to facilitate carrier testing for partners of heterozygous carriers of *MUTYH* variants ascertained via non-standard testing as well as extended cascade testing in families where the presence of *MUTYH* in the family was ascertained as an incidental finding, rather than in individuals with a matching polyposis phenotype.

Mindful of current pressures on NHS genomic laboratories and clinical genetics services, we agreed that:

- Carrier testing for *MUTYH* should be prioritised for partners of patients with MAP (ie, biallelic carriers).
- Testing should not be limited to recurrent variants (ie, full gene sequencing should be undertaken).
- Testing should be offered irrespective of the ethnicity of the partner, given that the carrier frequency in populations outside of white Europeans is not well established.
- Full *MUTYH* gene testing may be offered directly to children of patients with MAP in the event that their other parent is not available for carrier testing.

We agreed that carrier testing should *not* routinely be offered to partners of heterozygotes in the absence of consanguinity or a personal or family history of polyposis or colorectal cancer, particularly if reproductive decision-making will not be influenced (eg, in older individuals).

We believe that bespoke criteria for partner testing of *MUTYH* are required compared with other recessive traits and hope that these recommendations provide guidance to address the current inconsistencies in clinical practice.

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REFERENCES

1 Grover S, Kastrinos F, Steyerberg EW, *et al*. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. *JAMA* 2012;308:485–92.
2 Sieber OM, Lipton L, Crabtree M, *et al*. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med* 2003;348:791–9.
3 Poulsen MLM, Bisgaard ML. MUTYH associated polyposis (MAP). *Curr Genomics* 2008;9:420–35.
4 Monahan KJ, Bradshaw N, Dolwani S, *et al*. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United kingdom cancer Genetics group (UKCGG). *Gut* 2020;69:411–44.
5 Al-Tassan N, Chmiel NH, Maynard J, *et al*. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. *Nat Genet* 2002;30:227–32.
6 Cleary SP, Cotterchio M, Jenkins MA, *et al*. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology* 2009;136:1251–60.

7 Win AK, Jenkins MA, Dowty JG, *et al*. Prevalence and penetrance of major genes and polygenes for colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2017;26:404–12.
8 Nielsen M, Morreau H, Vasen HFA, *et al*. MUTYH-associated polyposis (MAP). *Crit Rev Oncol Hematol* 2011;79:1–16.
9 NHS National Genomic Test Directory Testing Criteria for Rare and Inherited Disease version 6, 2024. Available: https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-6-January-2024.pdf
10 Theodoratou E, Campbell H, Tenesa A, *et al*. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. *Br J Cancer* 2010;103:1875–84.
11 23andme. MUTYH-associated Polyposis. 2024. Available: https://www.23andme.com/en-gb/topics/health-predispositions/mutyh-associated-polyposis/
12 Green RC, Berg JS, Grody WW, *et al*. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013;15:565–74.
13 Nielsen M, Hes FJ, Vasen HFA, *et al*. Cost-utility analysis of genetic screening in families of patients with Germline MUTYH mutations. *BMC Med Genet* 2007;8:42.
14 Yap TA, Ashok A, Stoll J, *et al*. Prevalence of Germline findings among tumors from cancer types lacking hereditary testing guidelines. *JAMA Netw Open* 2022;5:e2213070.
15 McVeigh TP, Donnelly D, Al Shehhi M, *et al*. Towards establishing consistency in triage in a tertiary specialty. *Eur J Hum Genet* 2019;27:547–55.
16 gnomAD. gnomAD V4.0.0. 2024 Available: https://gnomad.broadinstitute.org/