REFERENCES

1. De Rocker N, Vergult S, Koolen D, et al. Refinement of the critical 2p25.3 deletion region: the role of *MYT1L* in intellectual disability and obesity. *Genet Med* 2015;17:460–466.
2. Doco-Fenzy M, Leroy C, Schneider A, et al. Early-onset obesity and paternal 2pter deletion encompassing the ACP1, TMEM18, and MYT1L genes. *Eur J Hum Genet* 2014;22:471–479.
3. World Health Organization. Obesity and overweight. Fact sheet 311. http://www.who.int/mediacentre/factsheets/fs311/en/ (updated January 2015).

doi:10.1038/gim.2015.86

A *PMS2*-specific colorectal surveillance guideline

To the Editor: We read the review by Goodenberger et al.[1] on colorectal surveillance guidelines for *PMS2* mutation carriers with great interest. However, we would like to address two issues by adding data from our cohort consisting of 415 confirmed *PMS2* mutation carriers (the majority of which were recently published (n = 367) but not included in the article by Goodenberger et al.[1]) to offer further perspective on *PMS2* specific guidelines.[2]

First, we would like to emphasize the difference between index carriers and mutation-positive family members when assessing the appropriateness of surveillance guidelines. As the authors rightly point out, colorectal cancer (CRC) at less than 30 years of age could be due to digenic inheritance or a modifier gene because young CRC patients appear to have a relatively low incidence in *PMS2* families. Indeed, the authors note that none of the index carriers with CRC at more than 30 years of age reported a positive family history for CRC diagnosed at younger than 30 years. All colorectal cancers diagnosed at an age younger than 30 (n = 7) except one belonged to an index carrier. In the family in which a nonindex individual developed CRC before age 30, the patient died soon after diagnosis and before a *PMS2* mutation in the index was identified. There is thus no evidence in either of the two cohorts, with a combined number of ~300 families, that family members have a high or even moderate risk of developing CRC before age 30, even in this group of highly selected families. Therefore, surveillance starting at age 25—as advised by Goodenberger and colleagues—is not appropriate in our opinion. However, we do agree with the authors that first-degree family members of a young patient with CRC should be counseled accordingly about the possibility of another mutation in a modifier gene and given appropriate surveillance advice, i.e., start surveillance 2–5 years earlier than the age at which the index carrier was diagnosed.

Second, the authors note that the group of mutation carriers with CRC diagnosed before age 30 appears to be a distinct group, indicating the possibility of an additional—second—germ-line mutation. One notable finding herein is that in their cohort all cases had left-side CRC, a nontypical location for Lynch syndrome–associated CRC. Even though this finding was statistically significant, we advise caution in the interpretation of these findings because in our cohort 57% (4/7) of the young CRC patients presented with right-side CRC. This difference illustrates the need for very large cohorts, which can be achieved only through global collaboration.

In conclusion, we believe that, although patient preference should always be taken into account, the combined data from Goodenberger and colleagues' study and ours provide enough evidence to support starting CRC surveillance in monoallelic *PMS2* mutation carriers at age 30. First-degree relatives of index carriers (siblings and children) who presented with CRC before age 30 should be exempt from this rule and start 2–5 years earlier than the age at which this index was diagnosed with CRC.

ACKNOWLEDGMENT

This study was supported by the Dutch Cancer Society (KWF UL 2012-5155).

DISCLOSURE

The authors declare no conflict of interest.

Sanne W. ten Broeke, MD[1] and Maartje Nielsen, MD, PhD[1]

[1]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands. Correspondence: Sanne W. ten Broeke (tenbroeke@lumc.nl)

REFERENCES

1. Goodenberger ML, Thomas BC, Riegert-Johnson D, et al. *PMS2* monoallelic mutation carriers: the known unknown. *Genet Med*; e-pub ahead of print 9 April 2015.
2. ten Broeke SW, Brohet RM, Tops CM, et al. Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. *J Clin Oncol* 2015;33:319–325.

doi:10.1038/gim.2015.91

Response to ten Broeke and Nielsen

To the Editor: Thank you for the opportunity to respond to the letter from ten Broeke and Nielsen[1] regarding our review article "*PMS2* Monoallelic Mutation Carriers: The Known Unknown."[2] We were delighted to see the publication of data from 98 mostly unpublished families with germ-line *PMS2* mutations, including 2,548 family members with 377 proven carriers, by ten Broeke et al.[3] while our review was in press. Their study greatly expands the number of known families with *PMS2* mutations.

As noted in our article, a major impediment to developing recommendations for these families has been the paucity of quality data. The article by ten Broeke and colleagues[3] represents a significant step toward improving that situation.

On the basis of the data we had available, we concluded that initiation of colon surveillance at age 25 still seems reasonable for *PMS2* mutation carriers because 8% of gene carriers in our series of 234 putative, monoallelic carriers developed colorectal cancer (CRC) before age 30. In the new cohort studied by ten Broeke et al., six of seven cases of CRC that developed before age 30 occurred in the index patient, again raising the specter of a possible undetected biallelic process or digenic process in some families. Accordingly, ten Broeke et al[3] divided screening recommendations for first-degree relatives by index cases diagnosed before age 30 and index cases diagnosed after age 30. They recommend starting screening 2–5 years earlier than the age at diagnosis of the index family member for first-degree relatives of individuals with CRC before age 30 and initiating CRC screening at age 30 for all other *PMS2* monoallelic mutation carriers.

Based on their data, this does not seem unreasonable, and such a recommendation would be consistent with an assumption that the very-early-onset cases are somehow different, perhaps because of a missed biallelic/digenic mutation. Still, whether early onset of CRC in some individuals is caused by an alternative mechanism or is simply part of the range experienced by monoallelic *PMS2* mutation carriers is currently unknown. Unfortunately, until this issue can be fully resolved, the decision of whether to start colon screening at age 25 or 30 in *PMS2* monoallelic mutation carriers will rely on patient and provider preferences, resources, and tolerance for risk, with no definite right or wrong approach.

DISCLOSURE

The authors declare no conflict of interest.

Noralane M. Lindor, MD[1] and McKinsey L. Goodenberger, MS[2]

[1]Department of Health Sciences Research, Mayo Clinic, Scottsdale, Arizona, USA; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA. Correspondence: McKinsey L. Goodenberger (goodenberger.mckinsey@mayo.edu)

REFERENCES

1. Ten Broeke SW, Nielsen M. A *PMS2*-specific colorectal surveillance guideline. *Genet Med* 2015;17:684.
2. Goodenberger ML, Thomas BC, Riegert-Johnson D, et al. *PMS2* monoallelic mutation carriers: the known unknown. *Genet Med*; e-pub ahead of print 9 April 2015.
3. Ten Broeke SW, Brohet RM, Tops CM, et al. Lynch syndrome caused by germline *PMS2* mutations: delineating the cancer risk. *J Clin Oncol* 2015;33:319–325.

doi:10.1038/gim.2015.90