Re: Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability

The revised Bethesda Guidelines were long awaited by practitioners in the field. The commentary on the new guidelines (1), however, raises concerns. Two versions of the revised Bethesda Guidelines that were determined at the 2002 National
Cancer Institute hereditary nonpolyposis colorectal cancer (HNPCC) workshop were published in February 2004. One version was published in the Journal (1) and the other in Nature Reviews Cancer (2); both were written by nearly the same group of authors. The suggested five guidelines are not the same in each publication, so it is not clear which set of guidelines reflects the true consensus. We have issues with both publications. Parts of the commentary published in the Journal are poorly worded and hence confusing. In particular, Guidelines 4 and 5 in the JNCI presentation should have been introduced with a reference to a presenting patient with colorectal cancer, as was done in the Nature Reviews Cancer presentation. Thus, the guidelines should read as follows:

4. Colorectal cancer with one or more first-degree relatives with colorectal cancer or other HNPCC-related tumors. One must be diagnosed before the age of 50 years.…

5. Colorectal cancer with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.

In Guideline 4, the Nature Reviews Cancer report includes an alternative to one of the cancers diagnosed before 50 years of age—“(this includes adenoma, which must have been diagnosed before the age of 40 years).” This qualification is not mentioned in the version of the Guideline 4 published in the Journal. It is important for practitioners to know whether the consensus was for adenomas to be “in” or “out” of the revised guidelines. Emerging data suggest that adenomas in young patients have a low rate of microsatellite instability and may be best removed from this classification (3).

We also have concerns about the evidence supporting revised Guideline 5. The existing Bethesda Guidelines already have high sensitivity and low specificity. The new Guideline 5 will certainly further reduce specificity. For example, this guideline could be used to justify microsatellite instability (MSI) testing in an 80-year-old person with bowel cancer who has both a maternal uncle who was diagnosed with bowel cancer at age 95 years and a grandfather (either maternal or paternal) who was diagnosed at age 98 years. The Nature Reviews Cancer report included no restriction on the degree of relatedness. Indeed, everybody with bowel cancer is likely to have at least two relatives with colorectal cancer if the pedigree is pursued extensively enough. Revised Guideline 5 should be restricted to the same side of the family among first- and second-degree relatives.

Further detail is also required to determine how many of the described pathologic features are required to meet Guideline 3. The criterion shorthands this as “MSI-H histology.” The discussion in the text is diffuse on the details of this, without clear direction as to which and/ or how many of the features need to be present to qualify for this criterion. Mention is made of mucinous and signet-ring cell carcinoma, poor differentiation, and tumor-infiltrating lymphocytes.

The evidence to support the removal of patients with endometrial cancer diagnosed before age 50 years (with no family history) from the original Bethesda Guidelines is not clear.

If the revised Bethesda Guidelines are to be taken and applied internationally as the “gold standard” for immunohistochemistry/MSI testing, the issues outlined above need to be addressed. Failing this, we suggest that the original 1997 Bethesda Guidelines (4) remain the standard for deciding which patients and families should have immunohistochemistry/MSI testing performed as a screening test for HNPCC.

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REFERENCES


NOTES

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RESPONSE

Investigators have just started to evaluate the Revised Bethesda Guidelines by examining their sensitivity, specificity, and positive predictive value in various populations. How these new revised guidelines will compare with the Amsterdam criteria, the revised Amsterdam criteria, the Japanese guidelines (1), or even the original Bethesda Guidelines over time is a valid scientific question. This question must be answered in the light of scientific data rather than the belief that the Revised Bethesda Guidelines seem to be less effective if the commentary accompanying them was “poorly worded or confusing.”

The Revised Bethesda Guidelines published in the Journal (1) represent a close consensus of the overall recommendations made at the workshop of hereditary nonpolyposis colorectal cancer (HNPCC; Lynch syndrome) experts, including Dr. Lynch (2) and other pioneers in the field, whereas the Nature Reviews Cancer publication is a perspective on the guidelines across the world and more of a discussion (3). Despite some editorial variations (adenoma diagnosis before age 40 years was not finalized at the point of the Nature Reviews Cancer publication), the Revised Bethesda Guidelines presented in the two publications are identical [Table 1 and (1)]. Inclusion or exclusion of adenomas was a topic of discussion at the workshop and led to the decision to revise the original Bethesda Guidelines, as discussed in the JNCI commentary (1). In addition, we have also contributed to the publication of a dedicated issue of the journal Disease Markers (4) with a detailed commentary and point of view from many of the investigators present at the workshop of HNPCC (Lynch syndrome) experts who suggested changes to the guidelines.
The suggestion of Macrae and Harris that everyone with bowel cancer is likely to have at least two relatives with colorectal cancer if the pedigree is pursued extensively enough is not justified by the available data. Approximately 15% of individuals with colorectal cancer will have a first-degree relative with the disease; very little data are currently available regarding the prevalence of colorectal cancer in second-degree relatives among colorectal cancer patients. Adding second-degree relatives to the guidelines may decrease specificity, but it will also increase sensitivity by identifying cases that would have been missed using first-degree family history alone. Limiting Guideline 5 to the same side of the family may increase specificity and reflect the Mendelian nature of HNPCC inheritance. We do still include endometrial cancer in the revised guidelines as an HNPCC-associated tumor in footnote 1 (Table 1). A detailed discussion of HNPCC-related pathology can be found in the special issue of Disease Markers (4).

The meeting’s participants recognized that a fair amount of data exist that are too controversial to develop a consensus for many of these guidelines. The Revised Bethesda Guidelines should be considered a work in progress and by no means suggest that the original Bethesda Guidelines are obsolete; one should see them as milestones toward achieving general agreement for use by practicing physicians.

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**REFERENCES**


**NOTE**

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**Table 1.** The Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI) [Table from (1)]

Tumors from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, *regardless of age.*
3. Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is less than 60 years of age.§
4. Colorectal cancer or HNPCC-associated tumor* diagnosed under age 50 years in at least one first-degree relative.||
5. Colorectal cancer or HNPCC-associated tumor* diagnosed at any age in two first or second-degree relatives.||

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*Hereditary nonpolyposis colorectal cancer (HNPCC)-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.

†MSI-H = microsatellite instability-high in tumors refers to changes in two or more of the five National Cancer Institute–recommended panels of microsatellite markers.

‡Presence of tumor infiltrating lymphocytes. Crohn disease–like lymphocytic reaction, mucinous/signet–ring differentiation, or medullary growth pattern.

§There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

||Criteria 4 and 5 have been reworded to clarify the Revised Bethesda Guidelines.