Meeting Summary

Report From the Jerusalem Workshop on Lynch Syndrome-Hereditary Nonpolyposis Colorectal Cancer

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Albert de la Chapelle (The Ohio State University) discussed the population incidence of Lynch syndrome and suggested possible screening strategies for the disease. Previous estimates of the proportion of Lynch syndrome among all colorectal cancer (CRC) patients have shown considerable variation (0.9%–2.7%), mainly because the studies have not been population based and inclusive, and only *MSH2* and *MLH1* have been studied. Other reasons for variation include the inability to detect all mutations, and real differences in prevalence between populations. A population-based study from Columbus, Ohio, investigated all 4 major mismatch repair (MMR) genes in unselected consecutive patients with CRC as well as endometrial cancer. This study estimated the prevalence of detectable disease at 2.8% of all CRC and 2.5% of all endometrial cancer patients.[1–3] Based on these prevalence figures, the lifetime risks for CRC (6%) and endometrial cancer (4%) in the general population, and the average penetrance of approximately 50%, he estimated that perhaps 1 in 300 to 1 in 500 individuals in the general population has Lynch syndrome. That would make Lynch syndrome the most common Mendelian genetic predisposition to cancer. He further reported that genetic screening of all CRC patients who meet the Amsterdam criteria would still fail to detect half of all cases; likewise, screening only those aged ≤50 would detect only half of all cases; and screening all patients using the Bethesda guidelines for microsatellite instability (MSI) testing would fail to detect at least one third of all cases. On this basis, he recommended that all incident CRC and endometrial cancer cases should be screened for the disease. Although MSI testing is highly sensitive (89.3% in the Columbus study), immunohistochemistry (IHC) is equally sensitive (91.2%), is inexpensive, is more readily available, and predicts the nonworking gene. Consequently, he suggested this might be the preferred method to screen cancer cases for Lynch syndrome.[4]

Sapna Syngal (Dana Farber Cancer Institute and Brigham and Women's Hospital, Boston) discussed the clinical features of Lynch syndrome, and discussed methods for making better use of the family history in identifying cases. The variability of the incidence of CRC based on the MMR gene affected in the family was discussed with the highest incidence observed for *MLH1* and *MSH2* mutation carriers (approximately 50%) to lowest for *PMS2* and *MSH6* mutation carriers (approximately 20%–30%). She discussed the PREMM1,2 model, an open-access, Internet-based program that uses personal and family history to provide an estimate that genetic testing for *MLH1* and *MSH2* would identify a disease-causing mutation using current testing strategies. An extended program, PREMM1,2,6, which incorporates *MSH6* testing, is in development. A discussion was held reviewing the currently available prediction models: MMRpro, MMRPredict, PREMM1,2, and the Wijnen models.[5]

Robert Kurtz (Memorial Sloan Kettering Cancer Center, New York) discussed the impact of upper gastrointestinal cancers in Lynch syndrome. The incidence of upper gastrointestinal tumors varies by registry, reflecting the apparent role of geographically related environmental factors. A Korean registry estimated that gastric cancer was the second most common cancer (after CRC), as did a German registry, whereas registries from the United States, Denmark, and The Netherlands listed the stomach as the third most prevalent site for cancer in Lynch syndrome. All cases were >35 years of age. The lifetime prevalence of small intestinal cancers is 4.2%, with a relative risk >50-fold greater than in the general population. Small intestinal tumors are most common in the duodenum, followed by the jejunum and ileum with an average age of onset of 39 years. Pancreatic cancer is increased in Lynch syndrome, with a lifetime prevalence of ~2.8%, and clustering has been observed in some families with *MSH2* mutations, where the risk can be as high as 8.6%.[6] The lifetime prevalence of cancers of the liver and biliary tree was estimated to be ~2%.

Zsofia Stadler (Memorial Sloan Kettering Cancer Center, New York) reviewed the incidence of nongastrointestinal cancers in Lynch syndrome. It is estimated that 2.3% of all endometrial cancers are caused by Lynch syndrome.[2,3] Endometrial cancer is the most prominent risk, reaching up to 60%, in families with *MSH6* mutations. The median age of onset was ~47, which compares with ~63 in the general population. In 1 study, in women

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with Lynch syndrome who developed both endometrial cancer and CRC, the endometrial cancer was the first cancer in 50% of the cases and preceded the CRC by roughly 11 years. Endometrial cancers are found simultaneously with CRC in 14% of cases. These tumors frequently have an endometrioid histological pattern, and most are early stage tumors (stage I or II). There does not seem to be a difference in survival between Lynch syndrome–associated and sporadic endometrial cancer. Lynch syndrome has been reported in 5%–9% of unselected cases of endometrial cancer. Optimal appropriate screening measures were considered. About 20% of all endometrial cancers have MSI, mostly owing to non–Lynch syndrome inactivation of *MLH1*, and MSI may be spuriously negative in association with *MSH6* mutations, depending on the screening strategy. Ovarian cancers occur in 4%–12% of women with the Lynch syndrome, compared with 1.5% in the general population. The disease has an earlier onset in association with *MSH2* mutations, and the risk is greater for patients born before 1946. Urinary tract cancers are principally transitional cell cancers, and occur in about 8% of Lynch syndrome patients. However, the risk is substantially greater in *MSH2* disease, and in men, reaching 28% in men with *MSH2* mutations.[7,8] Other tumors of concern are the Muir-Torre syndrome skin tumor spectrum, and brain tumors, which are mainly glioblastomas.

Jinru Shia (Memorial Sloan Kettering Cancer Center, New York) discussed the pathologic features of CRCs in the Lynch syndrome. The characteristic features include large numbers of tumor-infiltrating lymphocytes (TIL), medullary pattern (which is quite specific for MSI tumors), mucinous type, stromal lymphocytes (which are made up of mostly B cells, and can create a "Crohn's-like" reaction), prominent neutrophilic infiltration in some cases, and poor differentiation.[9] There was discussion about the technical challenges with IHC, and it was generally thought that this might be the optimal way to screen for Lynch syndrome tumors given its routine availability. As with immunostaining assays, a key to the success of this strategy is the development of standard criteria for determining the expression of the MMR genes.

Paivi Peltomaki (University of Helsinki, Finland) discussed the unique features of the 4 genes involved in Lynch syndrome: *MSH2*, *MLH1*, *MSH6*, and *PMS2*. Large genetic rearrangements may occur in as many as 42% of the pathologic *MSH2* mutations, underscoring the importance of these alterations, which are usually not detected with classical sequencing strategies. Epimutations are associated with *MLH1*, occurring most commonly in a sporadic setting, but rarely occurs as a systemic disorder (see the discussion by Hitchins and Goel). Secondary methylation of the *MSH2* gene is associated with rearrangements of the *Epcam/TACSTD1* gene, which is immediately 3′ (upstream) of the *MSH2* gene. Over 400 sequence variants that are not pathogenic have been identified. Numerous founder mutations have been identified that have a disproportionate impact on populations that are relatively inbred. A full catalog of these and known pathogenic germline mutations associated with the Lynch syndrome can be found at the InSiGHT website (available: http://www.insight-group.org). At least 2 Lynch syndrome–causing germline mutations have been identified that are not associated with MSI: *MLH1* c415G>C (D132H), and *MSH2* c2245G>A (E749K). Changes in MMR gene dosage may occur with some missense mutations in evolutionarily conserved domains. No truncating mutations have been found in the *MSH3* gene. Finally, she reported that 88% of clinical diagnoses of the Lynch syndrome can be associated with definite germline mutations, but only 30% of these families meet the Amsterdam criteria.[10,11]

Rick Fishel (The Ohio State University, Columbus) discussed the biophysics of the interactions between the MMR proteins and DNA. The MMR proteins diffuse through the nucleus bound to adenosine diphosphate, in an "open clamp" configuration. Interaction with DNA triggers the exchange of adenosine triphosphate for adenosine diphosphate, changing the configuration of the proteins into a sliding clamp that diffuses along the nascent double-stranded DNA. Eventually, the clamps release from the DNA, to be recycled. Some of the sliding clamps encounter the DNA polymerase complex, recruit exonuclease I, and excise the daughter strand back to the mismatch, permitting resynthesis along the template. He described the mechanisms responsible for histone modification and nucleosome "plowing," which is necessary for efficient DNA MMR activity. He reviewed experiments demonstrating that aspirin and sulindac can suppress MSI in cultured cell models, which provides a theoretical basis for a protective effect of these agents against MSI cancers. He also described animal models under development to help identify effective preventive strategies in the Lynch syndrome.

Juul Wijnen (Leiden University Medical Center, The Netherlands) reviewed the technical complexities inherent in the genetic diagnosis of Lynch syndrome. First, the 4 DNA MMR genes consist of 59 coding exons, and there is 20 fold more non-coding DNA in these genes, most of which is not assayed in current diagnostic strategies. The *PMS2* gene creates the greatest challenges, as it is a 35 kb gene with 15 exons, and there are multiple pseudogenes, which obscure analysis of the authentic genetic sequence; these also predispose to gene conversion. One way to deal with this problem is to sequence mRNA, but one must inhibit nonsense-mediated RNA decay with this approach. To find all pathogenic mutations, one must use a comprehensive strategy employing testing for all types of genetic alterations, and integrate this information

with IHC and MSI testing. Using current technology for mutation analysis, Dr. Wijnen estimated that approximately 30% of MMR mutations cannot be detected.

Steven Gruber (University of Michigan School of Medicine, Ann Arbor) discussed the challenge created by familial clusters of familial CRC that are not Lynch syndrome. A growing number of studies have reported that as many as 40%–50% of familial clusters of CRC meeting the Amsterdam criteria are not associated with a germline mutation in a DNA MMR gene, abnormal IHC, or MSI. CRC in these families is less highly penetrant, they occur at an older median age, and the non-CRC cancers of the Lynch syndrome spectrum are not increased in these families. He pointed out that germline mutations in DNA MMR genes that are not associated with MSI can create a diagnostic problem, although the frequency of these seems to be low. Several groups are looking for genetic explanations for this group of families. Nomenclature for these families is a problem. A current term for this is Familial CRC-type X, which is generally felt to be nondescript or potentially misleading (ie, it implies that a genetic cause is located on the X chromosome). In addition, there is little evidence to support the possibility that these families represent just 1 disease.

Megan Hitchins (University of New South Wales, Australia) and Ajay Goel (Baylor University Medical Center, Dallas) discussed "constitutional epimutations" in the MMR genes.[12] Patients have been described in whom there is not only methylation of the promoters of *MLH1* or *MSH2* in the tumor cells, but there is mono-allelic methylation of the DNA in somatic tissues, which clinically give rise to a Lynch syndrome-like disease, with young-onset tumors that have MSI. There have been rare instances in which this has been inherited in a non-Mendelian fashion; this is unexpected, because methylation is thought to be erased early in germ cells. *MLH1* epimutations should be considered when there is a CRC with MSI and absent expression of *MLH1* and *PMS2* at IHC, and no genetic mutation in MLH1. Constitutional epimutations of *MLH1* require demonstration of methylated CpG sites in the 3′ region of the promoter closest to the start site, and should be confirmed by bisulfite sequencing, or mono-allelic expression of *MLH1* should be demonstrated in non-neoplastic tissues. In 28 cases of *MLH1* constitutional epimutations, there is no apparent gender bias, and some patients develop multiple Lynch syndrome–associated cancers. Two new cases of *MLH1* epimutation were discussed that were 18 and 20 years old, both had mono-allelic epimutations in all 3 germ cell layers (hair, blood, cheek swab), and both were de novo events, one occurring through the paternal allele, and the other through the maternal allele. Abnormalities in genome-wide methylation were discussed. The mechanism responsible for the epimutations is not known. Dr Goel presented a case of an individual with constitutional methylation of *MLH1* who had variable proportions of methylated alleles in different tissues (ie, 48% in hair follicles, 20% in buccal mucosa, etc).

James Eshleman (The Johns Hopkins University, Baltimore) reviewed MSI, and noted that mutation rates at the *HPRT* locus are elevated 100-fold in the absence of DNA MMR activity. Mutation rates are higher yet at repetitive sequences (ie, microsatellites), and there is a 600-fold range of mutation between dinucleotide and hexanucleotide repeats, inversely related to the length of the repetitive element, but directly related to the number of repeated units in the microsatellite sequence. The first Bethesda workshop recommended a panel of 5 microsatellite sequences to measure MSI (3 dinucleotide and 2 mononucleotide repeats),[13] but the second workshop also endorsed the use of 5 mononucleotide repeats.[14] Microsatellite "stutter" (ie, the appearance of multiple polymerase chain reaction products after amplification of DNA) is progressively greater in trinucleotide repeats, dinucleotide repeats, and mononucleotide repeats, respectively, which must be appreciated when interpreting these studies.

C. Richard Boland (Baylor University Medical Center, Texas) discussed the mutational target sequences of MSI that cause cancer, which should be distinguished from the microsatellite targets that are amplified during analysis for MSI. A group of ~41 genes encode mononucleotide repeats that run for ≥6 units, and these are common targets of mutation in MMR deficiency.[15] The first discovered was the *transforming growth factor β-receptor* II (*TGFβ-RII*), which encodes an A_{10} sequence that is mutated in ~85% of CRCs with MSI.[16] The functional significance of this mutation, which inactivates a critical tumor-suppressor gene, has been demonstrated. Other mutational targets of functional significance are the *BAX* gene and *caspase-5*, both of which are involved in apoptosis, the insulin-like growth factor 2 receptor (which is functionally similar to *TGFβ-RII*), and most of the DNA MMR genes themselves.[17,18] It was speculated that the presence of vulnerable coding microsatellite sequences in these genes, and their roles in regulating tissue-specific growth and differentiation, are responsible for the spectrum of tumors seen in the Lynch syndrome. Also, a distinct mechanism is involved in the genesis of low level MSI (ie, MSI-L), which is a consequence of the non-genetic down-regulation of the *MSH3* gene, and this is manifested as instability at dinucleotide, trinucleotide, and tetranucleotide sequences.[19]

William M. Grady (Fred Hutchison Cancer Research Center, Seattle) discussed the issue of "second hits" at DNA MMR genes in tumor DNA. The germline mutations in DNA MMR genes affect only 1 of the 2 alleles, and a somatic alteration at the wild-type allele is required

to inactivate MMR activity in a cell. The mechanism and timing of the second event were discussed. Allelic loss owing to large or small chromosomal deletions, or mitotic recombination-mediated gene conversion, may occur in CRCs with MSI, occurring in a range from 4% to 46% of tumors. Methylation of the promoter of the wild-type allele occurs in some cases, particularly at the *MLH1* locus, and rarely at the *MSH2* locus as a somatic event. Somatic point mutations are thought to be the least common mechanism involved, occurring in 0% to 20% of *MLH1* cases, and in ~20% of *MSH2* tumors. Also, constitutional MMR haploinsufficiency was discussed, which results in low-level MSI in the lymphocytes of carriers of certain hypomorphic MMR alleles. Finally, the timing of these mutations was discussed, and it was suggested that genetic events resulting in neoplastic growth antedate the second hit at the MMR locus, which may occur in the adenoma stage. The transformation from adenoma to carcinoma occurs in association with mutation of the A_{10} sequence of the *TGFβ-RII* gene, which seems to be among the genes susceptible to mutation in the setting of MMR deficiency that can mediate progression events in the adenoma–carcinoma sequence. A major question that remains to be answered is when the second hit occurs in the polyp–cancer sequence and whether haploinsufficiency of MMR activity is sufficient to initiate this process.

Steven Gruber (University of Michigan School of Medicine, Ann Arbor) reprised with a review of the growth pathways associated with MSI in the colon. He discussed the possibility that serrated adenomas may be the precursor lesion for sporadic MSI CRCs, but pointed out that it is uncertain whether this is relevant to Lynch syndrome. Adenomatous polyps are frequently found and removed during surveillance colonoscopy for Lynch syndrome patients, and these are often flat in appearance, similar to sessile adenomas. A marked increase in TIL, perhaps even more prominent than in the CRCs, is a feature of adenomas in Lynch syndrome, as is increased apoptosis. Unique microarray signatures are also seen in these neoplasms, presumably reflecting the contribution of the lymphocyte populations. Improved markers of Lynch syndrome –associated adenomas would be a valuable asset, and the use of mutational analysis of the *β-catenin* gene was proposed as a promising avenue of research in this context.

Hans Vasen (Leiden University Medical Center, The Netherlands) also reviewed the organ distribution of cancer risk in Lynch syndrome, which has been published recently.[8] He reported that cancers of the colon, rectum, endometrium, urinary collecting system, stomach, ovary, brain, and sebaceous glands (Muir-Torre syndrome) were definite members of the Lynch syndrome tumor spectrum, whereas there have been mixed reports on the roles of tumors of the pancreas, breast, and prostate in this disease. Gastric cancers occur in 10% of Lynch syndrome patients in a Korean registry, but only 2% of the Dutch registry,[20] underscoring the impact of local, probably environmental, factors in this disease. Bi-allelic MMR gene mutations give rise to a different tumor spectrum, including pediatric tumors, brain tumors, leukemias, and lymphomas. Future research into the gene–environment interaction was suggested.

Wolf Fridman (Cordeliers Research Center, Paris) discussed the local immune response to colorectal neoplasms. He noted the better prognosis for CRC patients when the tumor had MSI, and suggested that stage IV CRCs were underrepresented in Lynch syndrome registries. TILs are commonly seen in Lynch syndrome CRCs, and TILs are associated with a better prognosis for multiple types of tumors, including melanoma and breast cancer. The presence of $CD45RO^+$ memory cells and a TH1 response are specifically associated with improved survival in CRC. This TIL pattern is associated with increased numbers of CD8 cells, increased expression of granulysin, and decreased expression of vascular endothelial growth factor (which prevents maturation of dendritic cells and induces T-regulatory cells). $CD45RO^+$ memory cells indicate a protective response. The Crohn's-like response associated with MSI CRCs reflects maturing germinal centers formed by memory T cells, follicular dendritic cells, and antibody-secreting B cells. Possible therapeutic strategies based on the types of immune responses were discussed.

Jerome Galon (Cordeliers Research Center, Paris) followed with more details on the type of immune response that might control the development of metastases.[21] Because the TILs are heterogeneous, he emphasized the importance of noting the cell types, the cell density, and their location in the tumor. Two important regions of the tumors are the invasive margins and the center of the tumors. It was suggested that a proper interpretation of the TIL response is more predictive of clinical outcome than traditional TNM staging. Multivariate analyses showed that the immune criteria had independent effects on the rates of complete remission and survival, whereas T-stage, N-stage, and tumor differentiation were no longer significant.[22,23] Studies of the predictive values of these responses using traditional IHC on tumor specimens were suggested. Furthermore, the impact of cytotoxic therapeutic approaches on the immune response was thought to be an important area to explore, to better individualize treatment.

Deborah Schrag (Dana Farber Cancer Institute, Boston) discussed prognosis with Lynch syndrome–associated tumors. Several large studies have agreed that the prognosis is better with Lynch syndrome tumors, or with CRCs that have MSI unassociated with familial clustering. The hazard ratio for overall mortality in MSI CRCs

ranges from 0.63 to 0.74. Dr Schrag also discussed a recent study of patients enrolled in CALGB 89803 (5-fluorouracil vs 5-fluorouracil and irinotecan for stage III colon cancer), which showed that individuals with a family history had a better prognosis regardless of MSI status.

David Kelsen (Memorial Sloan Kettering Cancer Center, New York) discussed the implications of systemic therapy for patients with Lynch syndrome. This is an area of substantial controversy. One of the earliest reports of the use of systemic therapy in patients with colon cancer in the setting of Lynch syndrome, which was not randomized or prospectively designed, suggested that patients with MSI CRCs would benefit from 5-fluorouracil–based adjuvant chemotherapy. The patients selected for adjuvant therapy were significantly younger and had less comorbidity. Subsequent studies have not confirmed this, and some studies suggested that MSI predicted harm from the adjuvant therapy, particularly in stage II tumors. On the other hand, other retrospective reviews of the subgroup of patients in large, random assignment, adjuvant studies suggested that patients with MSI high did not have a worse outcome. More recently, there have been conflicting reports regarding the benefit or lack of benefit for the use of irinotecan as part of the treatment of MSI colon cancers. This is an area in need of additional prospective studies in which CRC patients are randomized to treatment groups based on MSI status. It was also recognized that sporadic MSI tumors may respond differently than Lynch syndrome MSI tumors to chemotherapy.

Hans Vasen (Leiden University Medical Center, The Netherlands) discussed cancer surveillance in Lynch syndrome. He noted that men have greater risks for CRC in this disease than women, that there are certain gene-specific differences in risk, and in some instances, different risk estimates between registries. Recommendations need to be made on the basis of the gene involved and gender. Some important clinical observations regarding surveillance were made. Colonoscopy was the only surveillance approach recommended for CRC, and data support a surveillance interval of every 1 or 2 years. Transvaginal ultrasound is ineffective in detecting early stage endometrial or ovarian cancers, and urinary cytology is ineffective in the diagnosis of urinary tract cancers; both of these areas require the development of better clinical tools for surveillance. About 30% of small intestinal cancers were metastatic at the time of diagnosis (vs 50% of sporadic tumors), and there have been no studies of surveillance measures of this cancer. The lifetime risk of gastric cancer is 8% in male Lynch syndrome patients, and in 5% in women. Because most of the small intestinal cancers occur in the duodenum and jejunum, it was suggested that upper endoscopy would be of value to screen for gastric and duodenal cancers. There does not seem to be familial clustering of gastric or genitourinary tract cancer, making this aspect of family history uninformative for developing specific surveillance plans for a Lynch syndrome family member.

John Burn (Newcastle University, UK) discussed chemoprevention in Lynch syndrome. He reviewed his previously published CAPP2 study in which 600 mg of aspirin plus 30 g of resistant starch (Novelose) were administered to an international cohort of 937 Lynch syndrome patients in an attempt to inhibit adenoma formation. The relative risk of adenomas was unchanged by this intervention after a mean of 29 months.[24] However, the post trial analysis of the clinical follow-up data 10 years after the initiation of the study showed a significant reduction in the incidence of new Lynch syndrome–related cancers. In the course of the study and follow-up period, 17 participants on aspirin developed CRC compared with 34 of those not given the active agent. There was also a significant reduction in endometrial cancer. This suggests a provocative, new, preventive approach to the disease.

Antoni Castells (Hospital Clinic of Barcelona, Spain) discussed strategies for the identification of Lynch syndrome cases. In the Spanish EPICOLON study, it was found that the use of MSI testing was approximately equivalent to the use of IHC for case finding. The revised Bethesda guidelines (which help to identify CRC cases to be tested for MSI) were only 81% sensitive, but were 95% specific for *MSH2* or *MLH1* mutation carriers. Universal screening of CRCs for MSI is expensive, but still misses 19% of the cases. They developed and tested a Bayesian model to predict MMR mutation carriers, and this was compared with other computer-based predictive models, including PREMM1,2, the Leiden model, MMR Predict, MsPath and others.[5,25–28] Some of the technical hurdles with MSI and IHC testing were discussed, such as the problem of detecting MSI in mucinous tumors, and the problem of falsely negative IHC when dealing with certain missense mutations in MMR genes.[1,29–31]

Yael Goldberg (Hadassah Medical Center, Hebrew University, Jerusalem) discussed the identification of Lynch syndrome in Israel, and the unique challenges presented by the presence of distinct ethnic groups, including Ashkenazi Jews, Sephardic Jews, and non-Jewish, mostly Arab groups. The role of founder mutations becomes more important in this setting. The potential for inbreeding raises the risk of bi-allelic mutations in MMR genes. Some specific founder mutations with reduced penetrance create special surveillance challenges. Overlap was noted with Lynch syndrome and the hereditary breast and ovarian cancer syndrome, which carries an increase risk for ovarian, pancreas, and colon cancer. These data are derived from a registry that contains approximately

900 patients from 700 families. Approximately 50% of these families do not meet clinical criteria for Lynch syndrome.

Peter Propping (University of Bonn, Germany) discussed the German Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Consortium. The HNPCC Core Initiative was started in 1999. There are now approximately 4,500 families and 6,000 individuals enrolled in the registry. The inclusion criteria are the Amsterdam II criteria, Bethesda guidelines, and an MSI cancer or MMR-absent tumor. He presented data regarding the results of surveillance in this group. Colon cancer surveillance is carried out with colonoscopy starting at age 25 years at annual intervals. Compliance was good with 81% of colonoscopies completed within 15 months. He noted that only 2 of 43 CRCs detected by prospective follow-up colonoscopy were regionally advanced. The German Consortium recommends annual surveillance.

Workshop Participants

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Conflicts of interest

The authors disclose no conflicts.

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