mulation of mutations may lead to acceleration of tumor development and to presentation of breast cancer at a much earlier age. The normal lifetime risk of developing breast cancer in HNPCC patients may indicate that the MMR defect is not involved in the initiation of breast cancer.

The answer to the question whether breast cancer is part of the tumor spectrum of HNPCC should be "no" if we consider the absence of an increased lifetime risk. Yet this question should be answered with "yes" if we take into account the possible role of the MMR defect in the progression of a breast tumor. Application of the latter criterion implies that a large variety of tumor types should in fact be regarded as part of the tumor spectrum of HNPCC. We believe that decisions as to whether surveillance should be advised for a specific type of cancer should be based on the age-specific cancer risk and the availability of sensitive and specific screening tools. Many cancers that are currently not included in the surveillance program may develop at an early age in patients with HNPCC. Therefore, we urge clinicians managing HNPCC to be especially alert when the patient presents with unusual symptoms.

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## Electronic-Database Information

The accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for HNPCC [MIM 120435 and 120436])

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## Reply to Vasen et al.

*To the Editor:*

Hereditary nonpolyposis colorectal cancer (HNPCC) is associated, at least in part, with germline mutations in genes involved in DNA mismatch repair. Two genes, termed "*hMSH2*" and "*hMLH1,*" account for HNPCC in ~60% of families whose symptoms adhere to the Amsterdam Criteria (Syngal et al. 2000). Three other genes—*hPMS1, hPMS2,* and *hMSH6*—account for an additional 5%–10%, the exact percentage not being known at this time. There remains a significant proportion of families, ~30%, in which HNPCC does not appear to be accounted for by these genes, suggesting that additional genes, which may or may not have anything to do with DNA mismatch repair, are involved. Given that errors in DNA mismatch repair result in the characteristic signature of microsatellite instability (MSI), it should be relatively straightforward to determine whether families whose symptoms adhere to the Amsterdam Criteria but who do not harbor changes in known DNA mismatch-repair genes display MSI. To our knowledge, little information exists that indicates which of these two scenarios is most likely.

The letter by Vasen et al. (2001) questions the association between mutations in the DNA mismatch-repair gene *hMLH1* and breast cancer, which we identified in a report published at the beginning of this year (Scott et al. 2001). In our report, we presented data that indicated a statistically significant difference between the likelihood of developing breast cancer in the *hMLH1* mutation–positive group and the mutation-negative group compared with the likelihood in *hMSH2* mutation–positive families. One of the reasons we focused on breast cancer was precisely because there was little or no agreement as to whether it was part of the disease spectrum of HNPCC. Furthermore, there were sufficient anecdotal reports of breast cancer occurring at an earlier

age within the context of HNPCC to suggest that it is part of the disease spectrum.

The results that were obtained reflect breast cancer incidence observed in our population. We cannot explain why the findings for our population differ from those observed in the Dutch families with HNPCC or those reported by Watson et al. (1993) or Aarnio et al. (1999), who showed that there was no increased risk of breast cancer in HNPCC. In the analysis of Dutch families with HNPCC, either no association or indeed a slight protective effect of DNA mismatch-repair errors was reported.

There are several interesting differences between our population and the Dutch population. The most interesting is the relative percentage of families with linkage to *hMSH2* and *hMLH1*. In Holland, the ratio of *hMSH2* to *hMLH1* mutation carriers is ~1:1, compared with our findings, which suggest a 1:2 ratio of *hMSH2* to *hMLH1* mutations. This difference does not account for the discrepancy seen between our population and the Dutch population, but it does suggests that there are significant differences between the two. We are currently accumulating more HNPCC families (>230) and will reanalyze the data when mutation analysis is complete, to determine whether the results of our initial analysis of the first 95 families hold true or were a result of a bias within our population.

Finally, we agree with the notion put forward by Vasen et al. (2001) that breast cancer development may be accelerated in persons who are deficient in DNA mismatch repair.

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## Mitochondria and the Quality of Human Gametes

*To the Editor:*

Ruiz-Pesini et al. (2000) cleverly show that extant human mtDNA variation affects sperm function. They find that mitochondrial haplogroup T is overrepresented in asthenozoospermic populations and shows reduced sperm oxidative phosphorylation pathway (OXPHOS) activity, relative to the H haplogroup that is overrepresented in nonasthenozoospermic populations. These authors—as well as Moore and Reijo-Pera (2000), in the accompanying invited editorial—stress that, because of the exclusive matrilinear inheritance of mitochondria, mutations of mtDNA purely affecting male fertility are not selected against and therefore can become fixed. The absence of a direct check against mitochondrial mutations that affect male fertility is unfortunate and begs the question of why such a pattern became established.

In keeping with an earlier suggestion (Giannelli 1986), I propose that the exclusion of sperm mitochondria from the zygote is part of a scheme enabling mitochondria to provide an indirect measure of sperm quality and, hence, to favor fertilization by optimal spermatozoa while avoiding the risk of passing on mtDNA exposed to high physiological stress and, hence, potential damage. This would clearly have adaptive value and could help justify the establishment of matrilineal mitochondrial inheritance.

There is evidence that mitochondria have a role in germ-cell selection. Krakauer and Mira (1999), in a phylogenetic study, note that species producing fewer offspring have fewer egg mitochondria and experience greater ovarian atresia, and these authors conclude that lower numbers of mitochondria offer greater opportunities for variation in mitochondrial function and, thus, for elimination of eggs with poor mitochondria. This results in purifying selective pressure on mitochondrial genomes. Some proof of a mitochondrial role in ovarian