(or hyperfluorescein spots) observed on postoperative fluorescein angiography were located at the preoperative trunk of a sea-fan-shaped vascular network of polypoidal choroidal vasculopathy (Fig. S1A in the Supplementary Appendix, available with the full text of this letter at NEJM.org), and because these hyperfluorescein spots seemed to indicate pooling rather than leakage, we interpreted them as an abnormal vessel structure that remained at the trunk after the removal of choroidal neovascularization. The preoperative optical coherence tomographic images also showed a trunk-like vessel with accompanying network vessels, some part of which remained, as shown on the optical coherence tomographic image obtained 3 days after transplantation. The elevation under the graft over the trunk area was continuously observed by means of optical coherence tomography throughout the follow-up period (Fig. 2 of our article, and Fig. S11 in the Supplementary Appendix of our article; see also Fig. S1B in the Supplementary Appendix available with this letter). On the basis of fluorescein angiograms obtained during the first year and also at 22 months after transplantation, we concluded that there was no evidence of new exudative neovascularization in this area. On review of the optical coherence tomographic images, we agree that the results support the presence of a vessel structure under the transplanted iPSC-RPE sheet at 4 weeks after transplantation and thereafter (Fig. S1B in the Supplementary Appendix available with this letter, and Fig. S11 in the Supplementary Appendix of our article). This structure could indicate the

growth of new vessels or the reperfusion of existing, nonleaky vessels, a finding consistent with the interpretation by Souied et al. We do not interpret the results obtained by means of indocyanine green angiography as supporting a change in vascular pattern (Fig. S1C in the Supplementary Appendix available with this letter).

Optical coherence tomographic angiography would disclose the presence of a vascular network or nonexudative vasculature in more detail, but we could not obtain an informative image because of the unstable fixation of the eye. Sheets of iPSC-RPE cells secrete vascular endothelial growth factor from the basal surface, and the choroid seems to be relatively well maintained under and near the transplanted iPSC-RPE graft (Table S6 and Fig. S11 in the Supplementary Appendix of our article). At present, we cannot determine whether these vessels are benign or pathogenic.

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More on Co-Occurrence of *COMT* and *BRCA1/2* Variants in a Population

TO THE EDITOR: Movassagh et al. (May 25 issue)¹ report an association between a synonymous variant (rs165631) in *COMT* and a reduced risk of cancer among female carriers of the mutation *BRCA1* or *BRCA2*. The result was based on an analysis involving 25 patients with breast cancer who had germline *BRCA1/2* alterations in the Cancer Genome Atlas and 15 presumably cancer-free women with *BRCA1/2* nonsense and

frameshift alterations in the Exome Sequencing Project of the National Heart, Lung, and Blood Institute (NHLBI). Given the potential for misinterpretation of the results, we feel obliged to correct the impression that rs165631 protects carriers of the *BRCA1* or *BRCA2* mutation from cancer.

On behalf of the Consortium of Investigators of Modifiers of *BRCA1/2*,² we examined existing

Table 1. The rs165631 Variant and the Risk of Breast or Ovarian Cancer among BRCA1/2 Mutation Carriers.*

Table 1. The rs165631 Variant and the Risk of Breast or Ovarian Cancer among BRCA1/2 Mutation Carriers.*										
Type of Cancer	BRCA1					BRCA2				
	Unaffected	Affected	Total	Hazard Ratio (95% CI)	P Value for Trend	Unaffected	Affected	Total	Hazard Ratio (95% CI)	P Value for Trend
Breast										
Genotype (no. of patients)										
GG	7523	7632	15,155			5216	5411	10,627		
GA	273	248	521			165	185	350		
AA	1	2	3			1	3	4		
Total	7797	7882	15,679	0.93 (0.79–1.10)	0.39	5382	5599	10,981	1.02 (0.84–1.24)	0.82
Minor allele frequency (%)†	1.76	1.60	1.68			1.55	1.71	1.63		
Ovarian										
Genotype (no. of patients)										
GG	12,875	2280	15,155			9808	819	10,627		
GA	446	75	521			326	24	350		
AA	2	1	3			4	0	4		
Total	13,323	2356	15,679	1.00 (0.77–1.32)	0.97	10,138	843	10,981	0.81 (0.53–1.25)	0.35
Minor allele frequency (%)†	1.69	1.63	1.68			1.65	1.42	1.63		

* Hazard ratios and estimates for 95% confidence intervals (CIs) were obtained from a retrospective cohort analysis that was corrected for the nonrandom ascertainment of mutation carriers with respect to their disease phenotypes. This analytic approach maximizes the retrospective likelihood of observing the modifier single-nucleotide polymorphism genotype conditional on the disease phenotype (unaffected status vs. affected status and censoring time) to obtain association estimates.

† The minor allele is the effect allele. Hazard ratios were calculated per allele.

data from 26,660 women with pathogenic variants of *BRCA1* or *BRCA2* and found no evidence of an association between rs165631 and the risk of either breast cancer or ovarian cancer among *BRCA1/2* carriers (Table 1). The effect sizes for established genetic modifiers of the risk of breast and ovarian cancer among *BRCA1/2* carriers are modest. Very large sample sizes are required to reliably identify associations between such modifiers and the relative risk of cancer.³

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Movassagh et al. report an association between the *COMT* variant rs165631 and a reduced risk of breast cancer among female carriers of a *BRCA1/2* pathogenic variant. The result was reported to be based on an analysis involving 40 carriers of truncating variants: 25 patients with breast cancer identified in the Cancer Genome Atlas and 15 women in the Exome Sequencing Project of the NHLBI who were assumed to be unaffected. The Supplementary Appendix provided with their letter (available at NEJM.org) indicates that the analysis included carriers of missense variants. Most troubling, the data set included 8 carriers of the common *BRCA2* c.9976A→T (p.Lys3326Ter) variant associated with only a modest risk of breast or ovarian cancer (odds ratio approximately 1.3 per allele),¹ and four additional missense variants listed as benign in the BRCA Exchange. These 12 women are thus irrelevant to analyses of modifiers of the high-risk *BRCA1/2* pathogenic variants used in clinical practice. These observations, and the fact that rs165631

has not been revealed as a potential modifier in previous large-scale genomewide association studies involving *BRCA1/2* carriers, indicate that it is premature to consider rs165631 as a potential modifier of cancer risk among such women.

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DOI: 10.1056/NEJMc1708425

THE AUTHOR REPLIES: Our decision to highlight the rs165631 variant was based on three coinciding observations: overrepresentation in a subgroup of *BRCA1/2* carriers selected from non-cancer-related studies, its position in a gene (*COMT*) with high biologic relevance,¹ and its synonymous nature in one of the very few genes in which synonymous variants have been shown to affect the protein function.² We computed overrepresentation using the minor allele frequency of rs165631, which was calculated on the basis of 60,418 persons and ranged between 0 and 0.19, depending on ethnicity; the 25 patients with *BRCA1/2* in the Cancer Genome Atlas were not included in any of our statistical analyses. We found the above coincidence intriguing and reported it as a preliminary observation in our letter in order to allow for testing in larger data sets of *BRCA1/2* carriers and perhaps in experimental settings. The overrepresentation was not seen in an analysis involving the 26,660 carriers of the *BRCA1/2* mutation, with and without cancer, that Chenevix-Trench et al. report. Therefore, unless different supportive data are presented, observations regarding rs165631 can be considered only as preliminary.

Spurdle et al. comment on the size of our data set. We appreciate the high power of the large, *BRCA1/2*-positive data sets, such as the one

presented by Chenevix-Trench et al., for the purpose of identifying risk modifiers, including those with modest effects. It is clear that the public population data sets do not support such high-powered design and have additional drawbacks, such as the assumption of noncancer status, the limited nature of individual-level information, and of course the lower frequency of cancer-predisposing alleles. However, we believe that the population-based sets offer an alternative advantage in allowing searches for potential modifiers, functional variants, or both. In contrast with cancer-based data sets, which are often enriched in their inclusion of clinic-referred patients, family members, and persons using preventive measures owing to awareness of carrier status (all of which are taken into account by the prospective statistical approaches used), population-based data sets are likely to be more representative of participants who are unaware of their carrier status. In the current era of genetic awareness, this factor alone could indicate the absence of family history or the presence of a weak family history and might (theoretically) suggest the presence of stronger modifiers. Our analysis shows that the NHLBI data set contains more than 12,000 rare alleles classified in the Human Genome Mutation Database³ as causative of disease for 1 or more of 18 hereditary cancer-implicating syndromes with autosomal dominant inheritance. We believe that these data sets, when used with awareness of their limitations, are worth exploring in the search for potential hereditary cancer-preventive signatures.

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Since publication of her letter, the author reports no further potential conflict of interest.

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