Writing the Discussion Section

Overview

The Discussion is the last major section in the body of a scientific article:

Introduction:	Why did you do the study? What was your hypothesis or purpose?
Methods:	What did you do?
Results:	What did you find?
Discussion:	**What do your findings mean?**

Topics to be covered in this chapter include

- Features of the Discussion
- Stating your conclusions
- Interpreting your findings
- Describing your study's relationship to other studies
- Describing your study's limitations
- Explaining the implications of your findings
- Introducing speculation in the Discussion

Features of the Discussion

The Discussion is basically an essay on the importance of your findings—how they fit into what is already known in the field, how they affect current scientific thought or medical practice, and what further research they suggest. An objective of the Discussion is to make sure readers do not misunderstand your research findings and their place in the research literature.

To write the Discussion, address all of the following that apply to your study:

- Begin by stating your conclusions based on your findings.
- Interpret your findings—say what the results mean and how they relate to each other.
- Indicate how your findings fit in with the existing literature:
  - Studies that agree.
  - Studies that disagree, and possible explanations for the differences between your results and theirs.
- State the novelty or exceptional strengths of your study.
- Acknowledge the limitations and any other potential valid criticisms of your study (and if possible, give reasons why they may not be serious problems).
- State the extent to which your findings can be generalized to other populations.
- Describe why having filled the knowledge gap is important.
- Explain the implications of your findings, for example, how they may affect current scientific thought or medical practice.
- Describe avenues for further study that your findings suggest.

You should not use the Discussion to repeat the background information and results presented earlier in the paper.

Generally, Discussions do not have subheadings, but the ideas in the Discussion must flow from one to another, leading the reader along. Transitional phrases are thus very important in the Discussion. The relationship between the paragraphs also needs to be apparent.

Examples of Poorly Written and Well-Written Discussions

On pages 5-16 to 5-22 are Discussions that contain the kinds of mistakes authors often make in the first drafts of their Discussion and well-written versions of the same poor Discussions. How the well-written examples fit the model of a well-written Discussion is indicated on each well-written example, and how the poorly written examples fail to follow the model is indicated on them.

Stating Your Conclusions

Start your Discussion with a statement of your conclusions based on your findings. These conclusions are tied to your hypothesis or purpose, so use wording similar to that in your hypothesis or purpose (as stated at the end of the Introduction). Also point out the major findings that support your conclusions (but do not simply repeat all your results).

Consider the following example:

> *At the end of the Introduction:* "To further the understanding of the role of CFTR gene dysfunction in the development of the cystic fibrosis phenotype, we extensively analyzed CFTR genes in 74 patients with nonclassic cystic fibrosis who were referred for confirmatory genetic diagnosis."
>
> *At the beginning of the Discussion:* "The identification of mutations in the CFTR gene in a large fraction of our patients confirms the involvement of this gene in nonclassic cystic fibrosis. **[Conclusion]** Indeed, each of the 29 patients with two identified CFTR mutations had at least one mutation that was predicted to be associated with residual CFTR function." **[Major finding that supports the conclusion]** (Adapted from Groman JD et al. Variant cystic fibrosis phenotypes in the absence of CFTR mutations. N Engl J Med 347:401–407, 2002.)

It is helpful in writing your conclusions to think of your hypothesis as a question ("Does X lead to Y?"), and then write the answer to the question ("Our study showed that X leads to Y.").

Activity 1

Stating the Conclusions of a Study

Write a conclusion for each of the following pairs of hypothesis/purpose statements and findings.

1. Hypothesis: We hypothesized that the *Q* gene is associated with life span in mice.
   Finding: Seventy percent of the mice not expressing the *Q* gene lived 1 year longer than the mice that expressed the gene.

2. Purpose statement: The goal of our study was to determine the toxic effects of drug X in patients with advanced solid tumors.
   Finding: In our study, 20 of 25 patients developed hand-foot syndrome after exposure to drug X.

Possible solutions will be handed out after discussion.

Please also see the examples of well-written Discussions (pages 5-18 and 5-21) for other examples of how to phrase the conclusions in the Discussion.

Interpreting Your Findings

The Discussion section is where you interpret your findings—that is, explain what they mean. This can involve putting your findings into perspective, explaining interesting or unexpected findings, correcting possible misperceptions, increasing readers' appreciation of your findings, showing the value of or compensating for disappointing or negative findings, or just giving readers a broader understanding of your findings and their significance.

To decide what to include, you can ask yourself, "What further explanation should I give to help readers understand and appreciate the importance of my research?" There could be 1 or several answers to this question. For example:

- In a study that shows that 2 or more agents have similar clinical benefits, you might compare the cost of the agents or their ease of administration.
- In a study that shows an increased incidence of a disorder, you might discuss how improvements in diagnostic techniques or varying definitions of the disorder over time may have contributed to the perceived increase.
- In a study with somewhat contradictory findings, you might analyze the potential reasons for the discrepant findings.
- In a study that shows that an agent has unexpected side effects, you might theorize how the properties or mechanisms of action of the agent might be responsible for the side effects.
- In a study of a gene's function in the development of an organism, you might relate your findings to those in evolutionarily related organisms.
- In a study that shows that an agent is ineffective, you might explain why continued research on this agent or related agents is still called for, why this agent might work better in a different group of patients, or why this agent might be effective in combination with other therapies.
- In a study of the mechanism of action of a molecule, you might relate the pathway you describe to pathways that together might affect activity.

Such descriptions can vary in length, from just a couple of sentences to several paragraphs.

Here are 2 examples from the literature:

> There are many possible causes of a relationship between hospital volume and mechanical ventilation outcome among patients receiving critical care. High-volume hospitals may improve outcomes by implementing a broad range of best practices, including higher nurse-to-patient ratios, multidisciplinary care teams, a ventilation strategy involving a low tidal volume for lung injury, and protocols for sedation, weaning, and glycemic control.[25–30] Clinicians at high-volume hospitals may also gain experience in the care of the critically ill, which could translate into improved rates of survival. More experienced as opposed to less experienced clinicians may be better at recognizing and treating the complications of critical illness or may be better at translating evidence into practice. (From Kahn JM et al. Hospital volume and the outcomes of mechanical ventilation. N Engl J Med 355:41–50, 2006.)

> Since elevated serum RBP4 levels lead to insulin resistance in mice,[9] our observations raise the possibility that the serum RBP4 level might contribute to systemic insulin resistance in humans. In mice, increased serum RBP4 levels impair postreceptor insulin signaling at the level of phosphoinositide-3 kinase in muscle and enhance the expression of phosphoenolpyruvate carboxykinase in liver.[9] Therefore, increased serum RBP4 levels in humans might contribute to impaired insulin-stimulated glucose uptake in muscle and elevated hepatic glucose production, both of which are characteristic of type 2 diabetes.[1] Regions near the *RBP4* locus on human chromosome 10q have been linked to hyperinsulinemia or early onset of type 2 diabetes in 2 populations, a finding consistent with a pathogenic role for RBP4 in insulin resistance and type 2 diabetes.[32,33] (From Graham TE et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 354:2552–2563, 2006.)

If your study included several experiments, you will also use the Discussion to explain how the findings of the individual experiments relate to each other and what they mean when considered together. Here's an example:

> [Preceding paragraph: The in vivo activity of AMG 706 is attributed to its activity against all VEGFRs tested. . . .] The high selectivity of AMG 706 is evidenced by the lack of activity against a variety of other kinases tested. Furthermore, no activity against bFGF-induced HUVEC proliferation was observed, implying that AMG 706 does not inhibit the receptor for bFGF or any downstream kinases or other proteins that mediate the proliferative signals of bFGF. Examination of the physiologic response of established tumors to treatment with

> AMG 706 provided direct evidence that the mechanism of tumor regression in A431 xenografts is the antiangiogenic effects of AMG 706. Increased endothelial cell apoptosis in association with decreased blood vessel area was the first event observed after administration of AMG 706. This was followed by significant increases in tumor cell apoptosis. The sequence of these observations is consistent with targeting of tumor-associated endothelial cells and blood vessels as a primary mechanism of the antitumor activity of AMG 706 in the model systems explored in this study. (From Polverino A et al. AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and Kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. Cancer Res 66:8715–8721, 2006.)

The following sections describe elements of the Discussion that are an extension of interpreting your findings.

Describing Your Study's Relationship to Other Studies

An important component of the Discussion is a description of the most relevant studies that directly support your findings and the most relevant studies that disagree with your findings. For studies that disagree, you should include possible reasons why the studies disagree with yours. For example, perhaps you used a different technique, studied a different population or ethnic group, or had a larger sample and so detected effects too small to be seen in smaller studies.

Discussing work by others that disagrees with yours is one of the hardest things to do in the Discussion. On the one hand, you want to be respectful and objective and give credit to those who published first because they may have laid the foundation for your work. On the other hand, you also must convince readers to accept your conclusions and must suggest plausible explanations for the discrepancy.

Some authors try to avoid criticizing other studies by simply naming the studies or just stating the studies' results without explaining how the results differ from the authors' own. But then the readers must identify the discrepancies themselves, which can lead to misunderstanding.

When explaining a discrepancy between your results and those previously published by another group, it is best to focus on a strength of your study rather than a weakness of theirs. In other words, instead of stating that the other study's approach was inferior to yours, state that

yours was better and give reasons to support this. Also, avoid all-or-nothing statements about the reasons for the discrepancy or the validity of the other study's findings. Phrase your explanations as suggestions, or assume that the discrepancy could be due to more than 1 factor.

Consider the following example:

> *Not useful (study merely named):* We found that drug B was not effective. Smith et al.[1] also studied drug B.
>
> *Not useful (discrepancies not stated):* We found that drug B was not effective. In the study of Smith et al.,[1] 15 of 40 patients responded to drug B.
>
> *Negative tone (focuses on other study's shortcoming):* Unlike our study, a previous trial showed that drug B was effective.[1] However, the patient selection criteria used in that trial were unrealistic. Failure of the previous trial to include patients with advanced disease probably accounts for the positive findings of that trial.
>
> *Positive tone (focuses on present study's strength):* Unlike our study, a previous trial showed that drug B was effective.[1] However, unlike the previous trial, our study group included a high proportion of patients with advanced disease. This difference in patient groups may account for the different results.

It is also important to distinguish your work from corroborating studies. A string of sentences about similar studies with similar results can raise doubts about whether your study is novel. You should therefore point out how the previous studies differed from yours (for example, a different patient population or different cell line). You also may discover that the gap in knowledge, as stated in the Introduction, should be refined to emphasize the differences between your study and those that preceded it.

Describing Others' Findings

Describing other researchers' findings in your own words is an important part of explaining your study's relationship to other studies. Occasionally, a direct quotation is appropriate, because you wish to reuse a short phrase that is particularly apt and memorable or because repeating the exact words of a recognized authority gives those words extra weight. Most of the time, however, you will be paraphrasing or summarizing.

Paraphrasing means rewriting, or "translating," the written text from another source into your own words without changing the original

meaning. When you paraphrase, take care to substantially reword and restructure the sentences rather than replacing or rearranging only a few words.

Consider the following example:

> *Original:* Chronic hepatitis C virus infection is most frequently associated with remote or current intravenous drug use and blood transfusions before 1992, although as many as 20% of infected patients have no identifiable risk factor. (Adapted from Herrine SK. Approach to the patient with chronic hepatitis C virus infection. Ann Intern Med 136:747–757, 2003.)
>
> *Poor paraphrase:* Chronic hepatitis C virus infection is most often associated with past or current intravenous drug use and with blood transfusions before 1992, but up to 20% of infected patients do not have an identifiable risk factor.[1]
>
> *Good paraphrase:* The most common risk factors for chronic hepatitis C virus infection are use of intravenous drugs, either currently or in the past, and receipt of blood transfusions before 1992. However, in up to 20% of patients with chronic hepatitis C virus infection, no risk factor can be identified.[1]

Summarizing involves creating a concise, shortened version of the original text that includes the main information but not all the details. This technique is the one used most often in describing others' studies. Like paraphrasing, summarizing involves putting others' statements into your own words. However, whereas paraphrasing often involves rewording individual sentences, summarizing usually involves a larger amount of information.

Consider the following example:

> *Original:* We observed a striking inhibition of hepatic preneoplasia by upregulation of insulin-like growth factor binding protein-I (IGFBP-I) in transgenic mice. This inhibition may have been caused by increased binding of insulin-like growth factor-I and/or -II by IGFBP-I within the preneoplastic lesions, which would decrease the mitogenic activity of the growth factors. Our results suggest that liver cancer development might be affected by glucoregulatory hormones, growth factors, cytokines, and nutritional factors that regulate hepatic IGFBP-I expression. The study added new evidence to the notion that the insulin-like growth factor axis plays a critical

role in liver cancer development. (Reprinted with permission from Lu S, Archer MC. Insulin-like growth factor binding protein-I overexpression in transgenic mice inhibits hepatic neoplasia. Mol Carcinog 36:142–146, 2003.)

Summary: Using a transgenic mouse model, Lu and Archer[3] showed that glucose regulation is involved in hepatocellular carcinogenesis.

Attribution Signals

Attribution signals are words, phrases, and verb forms used to identify, or signal, someone else's work and to distinguish between studies. Examples of attribution signals are "others have shown," "their findings demonstrate," "Smith et al. reported," and "our previous study showed." You may combine these attribution signals with phrases that suggest contrast or similarity between your findings and others', such as "in contrast," "however," and "likewise." In the Discussion, this technique is highly useful to synthesize your findings with others' research and to clarify the relationships among the studies.

In the paragraph below, the words in bold signal a particular study.

We found that the WW–WW–WW haplotype was the most prevalent haplotype in the lung cancer patients and control subjects but was more common in the control subjects than in the patients. **A similar observation** has been documented for colorectal cancer and breast cancer.[35,37] The haplotype for distribution **in this study is similar to that found by Weston et al.,**[38] who suggested that rare p53 minor haplotypes are associated with increased risk of breast cancer in some racial groups. **Similarly, we found** that the rare haplotypes were statistically significantly associated with an elevated risk of lung cancer, with the highest risk found in individuals with the W–M–M alleles. **In addition, we found, as did Sjolander et al.,**[53] that the 3 loci are in strong linkage disequilibrium. (Adapted from Wu X et al. p53 genotypes and haplotypes associated with lung cancer susceptibility and ethnicity. J Natl Cancer Inst 94:681–690, 2002. Reprinted with permission.)

Activity 2

Effective Paraphrasing and Summarizing

Here are 2 passages that might be found in the general medical literature.

1. Paraphrase this sentence for inclusion in the Discussion of a research article.

   However, because our previous trial showed that 6 of 10 patients who had previously been treated with regimen R had a minor response to drug Z, one could envision that drug Z might be a useful salvage therapy in patients with disease resistant to regimen R.

2. Summarize this paragraph by "Smith et al (4)" for inclusion in the Discussion of a research article.

   We observed the following in the patients with colon cancer who underwent the new, more radical surgical procedure. In group A, which received radical resection followed by adjuvant chemotherapy, the 5-year survival rates were 95% in those with stage I disease, 65% in those with stage II disease, and 25% in those with stage III disease. In group B, which received the standard treatment consisting of less radical resection followed by chemotherapy, the respective 5-year survival rates were 50%, 35%, and 10%. There were also acceptable (considering the more radical nature of the procedure) long-term surgical morbidity rates of 18%, 23%, and 28% for group A and 15%, 18.5%, and 19% for group B.

Possible solutions will be handed out after discussion.

Describing Your Study's Limitations

It is also important in the Discussion to anticipate reviewers' criticisms and acknowledge possible limitations of your study. For example:

> Our subjects were non-Hispanic whites, so it is not known whether our results are applicable to other groups. Further studies with additional populations are needed.
>
> Because we examined only 50 patients, our results may have been due to chance. The results must be confirmed in a larger study.
>
> These conclusions were based on the responses of 5 cell lines and so might not reflect processes in the intact body. We are now confirming our results in mice.
>
> In this study, gene expression was measured by Northern blotting, which may not have been sensitive enough to detect low-level expression.

If perceived limitations of your study might not be true limitations, give the reasons why. Please see the examples of well-written Discussions (pages 5-18 and 5-21) for examples of this.

Explaining the Implications of Your Findings

Explaining the implications of your findings is an essential part of your Discussion. A study's findings are specific but may have far-reaching implications—identifying disease characteristics that predict response to therapy, for example, or providing a rationale for a change in clinical practice.

To describe the implications, think of how your findings will affect scientific thought or medical practice or how your findings will be applied and what will happen when they are. To determine the implications of your study, try answering 1 or more of the following questions:

- How do these findings advance our understanding of disease prevention, treatment, or cure?
- On the basis of these findings, what should now be done differently in research or clinical practice?

- What do these findings tell us about the agent or disease model being studied?
- How should any novel materials or methods used in the study be applied in future studies or clinical practice?

Here are some examples:

> *Major finding:* We found that most early liver tumors have mutations in the X gene promoter.
>
> *Implication:* Therefore, mutation screening of the X gene promoter may be a useful tool for early detection of liver tumors.
>
> *Major finding:* We found that mouse Z tumors are genetically and histologically different from human Z tumors.
>
> *Implication:* Therefore, future studies of chemotherapy for Z cancer should be conducted in a different animal model.

Implications of a clinical trial may be self-evident, showing whether a new therapy should be tested in future trials. However, articles on basic science, such as those examining specific molecular, genetic, or cellular behavior, often require an explicit statement of the implications of the results. Including this information in your Discussion shows that you have thought critically about your results and their practical value.

Activity 3

Explaining the Implications of Your Findings

Write the conclusions of your current research based on the assumption that your hypothesis is true. Remember, these can be stated by answering your research question ("Does X lead to Y?" "Our study showed that X leads to Y."). Then write 1 or more sentences describing the implications of your presumed findings. Some implications will be discussed in class. If yours is not discussed in class, we will be happy to review it afterward and send you our comments. Please put your name on it before giving it to an instructor.

Introducing Speculation in the Discussion

When you state your conclusions, why filling the gap is important, and how your results may change scientific thought or medical practice, you may be tempted to speculate about implications that your current data do not support. Speculation is the formation of new hypotheses. Sometimes journal reviewers and readers disapprove of speculation, but often that is because the writer has not made it clear that the speculation is a hypothesis rather than a conclusion. How much can you speculate about your findings? Assuming you have firm data for your conclusions, it is probably all right to speculate 1 step further to another, more long-ranging conclusion.

Following are 2 examples in which the authors add phrases or sentences that indicate that the ideas are speculations, not conclusions:

> On the basis of our data, we conclude that overexpression of protein ABC in tumors from patients with disease XYZ is associated with a decreased survival rate. We *further speculate* that ABC is involved in the initiation of XYZ.

> Given our results, *it is likely* that ABC is involved in the initiation of XYZ. *However, this hypothesis needs to be tested*.

Speculation can also be a way of introducing what you will do next. It is useful to mention the next step: it shows you are thinking ahead in your research plan. For example:

> Our findings *suggest* that ABC is a predictor of response to chemotherapy with XYZ in patients with breast cancer. *The next step* is to study the relationship between ABC level and response to XYZ in a clinical trial.

If you are actually doing the next step, say so, to let your competitors know you have a head start:

> The results of our study imply that bone growth is slowed by this gene, *but this must be tested in other experiments. These experiments are under way in our laboratory*.

Activity 4

Outlining Your Discussion

Write either an informal outline or a list of phrases or statements for the Discussion section of a paper on your current research. Some outlines will be discussed in class. If yours is not discussed in class, we will be happy to review it afterward and discuss it with you later. Please put your name on it before giving it to an instructor.

Example of a Poorly Written Discussion (Basic Science Study)

Previous data suggested that BRCA1/2 mutation status influences the clinical characteristics and outcome in breast and ovarian cancers. However, mutations in these genes alone are unlikely to account for all of the variation observed; tumor formation results from an accumulation of somatic genetic alterations in several different genes, of which many may influence tumor phenotype. In support of this, some studies have shown associations between the clinical characteristics of tumors and multiple differences in gene expression (14).

Previously, we determined the BRCA1 and BRCA2 mutation status in 288 epithelial ovarian cancer families (Ref. 3; unpublished data). The purpose of the study reported here was to establish whether the spectrum of somatic genetic events that may influence tumor phenotype during ovarian cancer development differs with respect to BRCA1/2 mutation status and/or a family history of the disease. To do this, we have compared the frequencies of genomic alterations identified using metaphase comparative genomic hybridization (CGH) between ovarian tumors from BRCA1 and BRCA2 mutation carriers, familial cases in which no BRCA1/2 mutation could be identified, and sporadic cases.

Table 1 summarizes the frequencies with which genetic alterations were identified for each chromosome arm. Several alterations occurred with a particularly high frequency (in 42–76% of all tumors); these were losses on chromosomes 4q, 5q, 6q, 13q, 18q, and X and gains on chromosomes 1, 3q, 6p, 7q, 8q, 19q, and 20q. Several regions of relatively frequent loss or gains (in >30% of all tumors) were also identified. For most alterations, we were able to define single critical regions in common between tumors. In some cases, it was possible to define more than 1 region of interest (Table 1).

High levels of amplifications were identified at several sites throughout the genome. In some instances, the same region of high-level amplification was common to multiple tumors, which possibly indicates the location of a single gene target. In general, high-level amplifications were not frequent events. However, they tended to occur in regions that also showed frequent gain, which may suggest a shared target (Table 2).

We used 2 different approaches to determine whether the pattern of somatic genetic alterations during tumor development differs between BRCA1, BRCA2, familial non-BRCA1/2, and sporadic ovarian cancers. Firstly, we performed a systematic comparison of the frequency of genetic alterations between the 4 tumor groups. Secondly, we performed hierarchical cluster analysis to identify alterations that tended to occur together during tumor development. For the purpose of these analyses, we divided the genome into 100 nonoverlapping regions of similar size based on the 4´,6-diamidino-2-phenylindole banding on the CGH profile and recorded the presence of loss or gain at every region for each tumor.

Significant differences in the frequency of loss or gain between 1 or more groups of tumors were identified at 20 different chromosome regions; in total, 41 significant differences were observed between the 4 groups (Table 3). Notably, deletions of the region containing the BRCA1 gene (17q12–21) were significantly more frequent in tumors from BRCA1 mutation carriers than in non-BRCA1 tumors ($P = 0.014$). Similarly, deletions of the region containing the BRCA2 gene (13q12–13) were significantly more frequent in tumors from BRCA2 mutation carriers than in non-BRCA2 tumors ($P = 0.006$). This is consistent with data from loss of heterozygosity studies, which indicate that deletion of the wild-type BRCA1 or BRCA2 allele is a frequent and nonrandom event in tumors from mutation carriers.

Cluster analysis of all tumors grouped together could not differentiate between the groups. These data are illustrated in Fig. 1. However, there were several changes that were not common in the clusters of all tumor types, which may indicate differences in the molecular genetic pathways of tumor progression between different tumor types.

In conclusion, we have used metaphase CGH to characterize the spectrum of somatic genetic events that occur in the development of epithelial ovarian cancer in tumors from BRCA1 and BRCA2 mutation carriers, familial non-BRCA1/2, and sporadic cases. In doing so, we have identified molecular genetic differences between these 4 tumor groups that suggest there are different mechanisms for tumor development, which may influence the phenotype and clinical outcome of ovarian cancers.

Adapted from the well-written Discussion in Ramus SJ et al. BRCA1/2 mutation status influences somatic genetic progression in inherited and sporadic epithelial ovarian cancer cases. Cancer Res 63:417–423, 2003.

Example of a Well-Written Discussion (Basic Science Study)

Our finding of molecular genetic differences between ovarian cancers from BRCA1 and BRCA2 mutation carriers, familial non–BRCA1/2-related ovarian cancers, and sporadic ovarian cancers suggests that BRCA1/2 mutation status and family history of ovarian cancer influence the somatic genetic pathway of ovarian cancer progression.

Some of the data from this study are consistent with previous metaphase comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) studies in ovarian cancer (18–20); for example, regions of common deletion on chromosomes 4p, 6q, 9p, 13q, 18q, and Xp have frequently been identified using LOH analysis (18). Similarly, a previous study in which metaphase CGH was used to analyze 100 sporadic ovarian tumors identified multiple regions of loss and gain that are consistent with our findings (19).

However, some of our data differ from those in previous studies (18–20); for example, there are notable differences in the frequency with which alterations on chromosomes 3q, 5q, 6p, 12q, 17, 19p, 22q, and Xq were detected between this and other studies. Some of the disparity between CGH and LOH data may be explained by differences between the 2 methods in their ability to resolve genetic alterations. Metaphase CGH paints a picture of gross genomic alterations, including changes in chromosome copy number, whereas LOH analysis produces better, locus-specific resolution. However, LOH analysis is limited as a genome-wide screen because it requires high-density microsatellite mapping, which is both time-consuming to perform and a considerably greater drain on DNA resources than is CGH. Another reason for some of the differences between this and other metaphase CGH studies could be that whereas most previously published CGH data are from sporadic ovarian cancers only, approximately half of all tumors in this study were from BRCA1/2 mutation carriers and only a fifth from sporadic cases. Previous studies in breast cancer suggested that the presence of a germ-line BRCA1/2 mutation can influence the pattern of somatic genetic alterations during tumor development (21, 22).

We found evidence of a similar influence when the frequencies with which somatic genetic changes in tumors from BRCA1, BRCA2, familial non-BRCA1/2, and sporadic cases were compared. We identified multiple differences between the 4 tumor groups, which suggests that they differ in some aspects of tumor development. However, we carried out a large number of significance tests, and it is likely that some of these differences are chance occurrences. There were 200 individual comparisons between the 4 tumor groups, and 32 alterations with a P value of <0.2 were selected for additional analyses in which an additional 320 pair-wise comparisons were performed. Applying the Bonferroni correction to the results of these analyses would require a P value of <0.00016 to achieve a conventional level of significance of $P < 0.05$. The sample size of this study was not large enough to generate such a small P value, and indeed the smallest observed P value was 0.001. However, we observed 41 pair-wise comparisons with significant differences at the 0.05 level, compared with 16 expected if there were no true differences in frequency of alteration between tumor types; and 8 significant differences at the 0.01 level, compared with 3 expected. This suggests that a substantial proportion of these differences are real.

This assertion is supported by the observation, as expected, of significant increases in the frequencies of loss at the BRCA1 and BRCA2 loci in tumors from BRCA1 and BRCA2 carriers, respectively. To provide a better indication of the most critical events, we used a hierarchical cluster algorithm to group alterations that tended to occur together. The apparent clustering of a limited number of regions of loss and gain indicates a select series of targets for future studies aimed at identifying genes in ovarian cancer.

Some studies indicate that there are differences in the clinical and/or histopathological characteristics of breast and ovarian tumors between tumors from BRCA1, BRCA2, and non-BRCA1/2 mutation carriers (7–13). The reasons for this variation are unknown. BRCA1 and BRCA2 may have a direct effect on the behavior of breast and ovarian epithelial cells, which could vary depending on germ-line BRCA1/2 mutation status. Alternatively, BRCA1/2 mutation status might influence subsequent somatic genetic events in tumorigenesis, with these events being responsible for the observed variation in tumor phenotype. The somatic genetic differences that we observed between BRCA1, BRCA2, non-BRCA1/2, and sporadic ovarian tumors provide support for the latter of these hypotheses. A more detailed comparison of the histopathological characteristics of ovarian tumors in BRCA1/2 mutation and nonmutation carriers will be needed to obtain a better understanding of this association.

In conclusion, we used metaphase CGH to characterize the spectrum of somatic genetic events that occur in the development of epithelial ovarian cancer in tumors from BRCA1 and BRCA2 mutation carriers, familial non-BRCA1/2, and sporadic cases. In doing so, we identified molecular genetic differences between these 4 tumor groups that suggest there are different mechanisms for tumor development that may influence the phenotype and clinical outcome of ovarian cancers. The genetic differences we found may be useful in tailoring treatment for breast cancer patients.

Adapted with permission from Ramus SJ et al. BRCA1/2 mutation status influences somatic genetic progression in inherited and sporadic epithelial ovarian cancer cases. Cancer Res 63:417–423, 2003.

Example of a Poorly Written Discussion (Clinical Study)

Before our study, the clinical importance of ventricular ectopy during exercise stress testing was uncertain. There was conflicting evidence about the relationship of exercise-induced ventricular ectopy to coronary artery disease and to cardiovascular risk.[1–10] In addition, the prognostic implications of when ventricular ectopy occurs (i.e., during or after exercise) had not been well characterized.

A recent study established that vagal reactivation normally occurs early in recovery, immediately after exercise.[11] In the absence of normal vagal reactivation, heart-rate recovery is attenuated and mortality increases.[12–15] Therefore, attenuated vagal reactivation during recovery might be associated with ventricular ectopy that is not suppressed. Thus, we prospectively tested the hypothesis that ventricular ectopy during recovery is a stronger predictor of an increased risk of death than ectopy during exercise.

Consecutive patients referred for symptom-limited treadmill exercise testing at the Cleveland Clinic Foundation in Cleveland between 1990 and 1999 were eligible for our study. Information regarding ventricular ectopy at rest as well as during each stage of exercise and recovery was systematically recorded according to prespecified definitions. We prospectively defined frequent ventricular ectopy as the presence of 7 or more ventricular premature beats per minute during any given stage, ventricular bigeminy, ventricular trigeminy, ventricular couplets, ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation. The primary end point was death from all causes, which is an objective, clinically relevant, and unbiased end point.[20,21]

After adjustment for the variables listed in Table 1 and for frequent ventricular ectopy during exercise, frequent ventricular ectopy during recovery was a predictor of an increased risk of death (adjusted hazard ratio, 1.6; 95 percent confidence interval, 1.3 to 1.9; P<0.001). The prognostic importance of frequent ventricular ectopy during recovery in this propensity-matched cohort is shown in Figure 2. Patients with frequent ventricular ectopy during recovery had decreased survival, particularly after three to four years of follow-up. After adjustment for the propensity score, frequent ventricular ectopy during exercise, and the other variables listed in Table 2, frequent ventricular ectopy during recovery predicted an increased risk of death (adjusted hazard ratio, 1.5; 95 percent confidence interval, 1.1 to 1.9; P=0.003). A similar analysis was performed regarding frequent ventricular ectopy during exercise. Frequent ventricular ectopy during exercise was not associated with decreased survival in this propensity-matched cohort (adjusted hazard ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; P=0.53).

In conclusion, frequent ventricular ectopy during recovery from exercise was found to be an important, independent predictor of an increased risk of death in a large clinical cohort. Frequent ventricular ectopy that occurred only during exercise did not independently predict an increased risk. In accordance with previous findings of a strong relationship between attenuated recovery of the heart rate after exercise and an elevated risk of death, these results support the central importance of vagal mediation in cardiac function. They also underscore the value of the exercise stress test as a tool for prognosis and risk stratification.

Adapted from the well-written Discussion in Frolkis JP et al. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 348:781–790, 2003.

Example of a Well-Written Discussion (Clinical Study)

In a large cohort of patients referred for exercise stress testing, we found that ventricular ectopy after exercise (during the recovery phase) was a better predictor of increased risk of death than was ventricular ectopy during exercise only. The occurrence of frequent ventricular ectopy during recovery was strongly predictive of an increased risk of death from all causes over a 5-year follow-up period, whereas the occurrence of frequent ventricular ectopy only during exercise was not. This association persisted even after propensity-based adjustment for clinical and exercise characteristics known to predict an increased risk of death.

Until recently, it was thought that exercise-induced ventricular ectopy was not independently related to an increased risk of coronary heart disease, the extent of coronary artery disease, mortality from all causes, or the risk of major cardiac events.[4,8,16,31] However, one recent report showed that among over 6000 asymptomatic men, ventricular ectopy during exercise was associated with a relative risk of death from cardiovascular disease of approximately 3 when the cohort was followed for 23 years.[6]

The current study clarifies these previous findings and extends them to a large cohort likely to be representative of patients seen in clinical practice. Because of the size of the study sample, we were able to examine carefully the prognostic importance of frequent ventricular ectopy during and after exercise in large numbers of subjects (more than 1000 patients in each group). The large cohort also made it possible for us to perform propensity matching,[27] thus allowing a more valid comparison of patients with and without frequent ventricular ectopy than would have been possible by standard regression techniques.[28] Finally, our observations were consistent with our a priori hypothesis that frequent ventricular ectopy during recovery would be a stronger predictor of risk than ectopy during exercise, which had been based on the recognition of recovery as a period of rapid vagal reactivation.[11]

Because the cohort was a heterogeneous one, including patients who underwent stress testing with electrocardiography only, with echocardiography, or with nuclear perfusion scintigraphy, we did not have systematic data on left ventricular systolic function and myocardial ischemia in all patients. Nonetheless, it is noteworthy that in the subgroup of 6421 patients for whom ejection-fraction data were available, a low ejection fraction (40 percent or less) was associated with frequent ventricular ectopy during recovery. Furthermore, both ventricular ectopy during recovery and a low ejection fraction were independent predictors of death. We focused on death from all causes and could not differentiate among deaths due to arrhythmias, those due to other cardiac causes, and those due to noncardiac causes. We and others have commented on this issue before, pointing out that only death from all causes can be considered a truly unbiased and objective end point that is also clinically relevant when arrhythmia-related outcomes are studied.[20,21]

How should the finding of an association between frequent ventricular ectopy during recovery from exercise and mortality from all causes be incorporated into clinical practice? Because this was a prospective, observational study, making treatment recommendations on the basis of our results is problematic. Nonetheless, it is clear that frequent ventricular ectopy during recovery is a marker of an increased risk of death. Accordingly, comprehensive risk-factor assessment and aggressive management of the risk factors identified may well be justified in patients with this finding. In addition, the association of asymptomatic left ventricular dysfunction with frequent ventricular ectopy during recovery suggests that echocardiography may be indicated, since treatment of asymptomatic left ventricular dysfunction is of clinical benefit.[32]

Frequent ventricular ectopy during recovery from exercise was found to be an important, independent predictor of an increased risk of death in a large clinical cohort. Frequent ventricular ectopy that occurred only during exercise did not independently predict an increased risk. In accordance with previous findings of a strong relation between attenuated recovery of the heart rate after exercise and an elevated risk of death, these results support the central importance of vagal mediation in cardiac function. They also underscore the value of the exercise stress test as a tool for prognosis and risk stratification.

From Frolkis JP et al. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 348:781–790, 2003. Reprinted with permission.

Example of a Poorly Written Discussion (Basic Science Study)

Previous data suggested that BRCA1/2 mutation status influences the clinical characteristics and outcome in breast and ovarian cancers. However, mutations in these genes alone are unlikely to account for all of the variation observed; tumor formation results from an accumulation of somatic genetic alterations in several different genes, of which many may influence tumor phenotype. In support of this, some studies have shown associations between the clinical characteristics of tumors and multiple differences in gene expression (14).

Previously, we determined the BRCA1 and BRCA2 mutation status in 288 epithelial ovarian cancer families (Ref. 3; unpublished data). The purpose of the study reported here was to establish whether the spectrum of somatic genetic events that may influence tumor phenotype during ovarian cancer development differs with respect to BRCA1/2 mutation status and/or a family history of the disease. To do this, we have compared the frequencies of genomic alterations identified using metaphase comparative genomic hybridization (CGH) between ovarian tumors from BRCA1 and BRCA2 mutation carriers, familial cases in which no BRCA1/2 mutation could be identified, and sporadic cases. **[Instead of starting with a statement of the conclusions, this Discussion starts with unnecessary background information and restates the purpose of the study. All of that information was stated in the Introduction and should not be repeated in the Discussion.]**

Table 1 summarizes the frequencies with which genetic alterations were identified for each chromosome arm. Several alterations occurred with a particularly high frequency (in 42–76% of all tumors); these were losses on chromosomes 4q, 5q, 6q, 13q, 18q, and X and gains on chromosomes 1, 3q, 6p, 7q, 8q, 19q, and 20q. Several regions of relatively frequent loss or gains (in >30% of all tumors) were also identified. For most alterations, we were able to define single critical regions in common between tumors. In some cases, it was possible to define more than 1 region of interest (Table 1). **[In this paragraph and the next 4, the methods and results are repeated. This much detail on methods and results should not be included in the Discussion.]**

High levels of amplifications were identified at several sites throughout the genome. In some instances, the same region of high-level amplification was common to multiple tumors, which possibly indicates the location of a single gene target. In general, high-level amplifications were not frequent events. However, they tended to occur in regions that also showed frequent gain, which may suggest a shared target (Table 2).

We used 2 different approaches to determine whether the pattern of somatic genetic alterations during tumor development differs between BRCA1, BRCA2, familial non-BRCA1/2, and sporadic ovarian cancers. Firstly, we performed a systematic comparison of the frequency of genetic alterations between the 4 tumor groups. Secondly, we performed hierarchical cluster analysis to identify alterations that tended to occur together during tumor development. For the purpose of these analyses, we divided the genome into 100 nonoverlapping regions of similar size based on the 4´,6-diamidino-2-phenylindole banding on the CGH profile and recorded the presence of loss or gain at every region for each tumor.

Significant differences in the frequency of loss or gain between 1 or more groups of tumors were identified at 20 different chromosome regions; in total, 41 significant differences were observed between the 4 groups (Table 3). Notably, deletions of the region containing the BRCA1 gene (17q12–21) were significantly more frequent in tumors from BRCA1 mutation carriers than in non-BRCA1 tumors ($P = 0.014$). Similarly, deletions of the region containing the BRCA2 gene (13q12–13) were significantly more frequent in tumors from BRCA2 mutation carriers than in non-BRCA2 tumors ($P = 0.006$). This is consistent with data from loss

of heterozygosity studies, which indicate that deletion of the wild-type BRCA1 or BRCA2 allele is a frequent and nonrandom event in tumors from mutation carriers.

Cluster analysis of all tumors grouped together could not differentiate between the groups. These data are illustrated in Fig. 1. However, there were several changes that were not common in the clusters of all tumor types, which may indicate differences in the molecular genetic pathways of tumor progression between different tumor types.

In conclusion, we have used metaphase CGH to characterize the spectrum of somatic genetic events that occur in the development of epithelial ovarian cancer in tumors from BRCA1 and BRCA2 mutation carriers, familial non-BRCA1/2, and sporadic cases. In doing so, we have identified molecular genetic differences between these 4 tumor groups that suggest there are different mechanisms for tumor development, which may influence the phenotype and clinical outcome of ovarian cancers. **[Conclusions are given, but readers are not given the information to assess the conclusions for themselves (which would be the possible limitations of the study and its relationship to other studies).]**

Adapted from the well-written Discussion in Ramus SJ et al. BRCA1/2 mutation status influences somatic genetic progression in inherited and sporadic epithelial ovarian cancer cases. Cancer Res 63:417–423, 2003.

Example of a Well-Written Discussion (Basic Science Study)

Our finding of molecular genetic differences between ovarian cancers from BRCA1 and BRCA2 mutation carriers, familial non–BRCA1/2-related ovarian cancers, and sporadic ovarian cancers suggests that BRCA1/2 mutation status and family history of ovarian cancer influence the somatic genetic pathway of ovarian cancer progression. **[Conclusion and supporting finding]**

Some of the data from this study are consistent with previous metaphase comparative genomic hybridization (CGH) and loss of heterozygosity (LOH) studies in ovarian cancer (18–20); for example, regions of common deletion on chromosomes 4p, 6q, 9p, 13q, 18q, and Xp have frequently been identified using LOH analysis (18). Similarly, a previous study in which metaphase CGH was used to analyze 100 sporadic ovarian tumors identified multiple regions of loss and gain that are consistent with our findings (19). **[Studies that agree]**

However, **[A good transition word; it links the ideas in this paragraph to those in the previous paragraph and indicates that this paragraph contains ideas that differ from those in the previous paragraph]** some of our data differ from those in previous studies (18–20); for example, there are notable differences in the frequency with which alterations on chromosomes 3q, 5q, 6p, 12q, 17, 19p, 22q, and Xq were detected between this and other studies. **[Studies that disagree]** Some of the disparity between CGH and LOH data may be explained by differences between the 2 methods in their ability to resolve genetic alterations. Metaphase CGH paints a picture of gross genomic alterations, including changes in chromosome copy number, whereas LOH analysis produces better, locus-specific resolution. However, LOH analysis is limited as a genome-wide screen because it requires high-density microsatellite mapping, which is both time-consuming to perform and a considerably greater drain on DNA resources than is CGH. Another reason for some of the differences between this and other metaphase CGH studies could be that whereas most previously published CGH data are from sporadic ovarian cancers only, approximately half of all tumors in this study were from BRCA1/2 mutation carriers and only a fifth from sporadic cases. Previous studies in breast cancer suggested that the presence of a germ-line BRCA1/2 mutation can influence the pattern of somatic genetic alterations during tumor development (21, 22). **[Gives explanations for the disagreements, and interprets current findings]**

We found evidence of a similar **[A transition word that links the ideas in this paragraph to those in the previous one and indicates that the ideas in this paragraph are similar to those in the last paragraph]** influence when the frequencies with which somatic genetic changes in tumors from BRCA1, BRCA2, familial non-BRCA1/2, and sporadic cases were compared. We identified multiple differences between the 4 tumor groups, which suggests that they differ in some aspects of tumor development. However, we carried out a large number of significance tests, and it is likely that some of these differences are chance occurrences. **[Possible limitation of the study]** There were 200 individual comparisons between the 4 tumor groups, and 32 alterations with a P value of <0.2 were selected for additional analyses in which an additional 320 pair-wise comparisons were performed. Applying the Bonferroni correction to the results of these analyses would require a P value of <0.00016 to achieve a conventional level of significance of $P < 0.05$. The sample size of this study was not large enough to generate such a small P value, and indeed the smallest observed P value was 0.001. However, we observed 41 pair-wise comparisons with significant differences at the 0.05 level, compared with 16 expected if there were no true differences in frequency of alteration between tumor types; and 8 significant differences at the 0.01 level, compared with 3 expected. This suggests that a substantial proportion of these differences are real. **[Reason why the possible limitation might not be a true limitation, and interpretation of findings]**

This assertion is supported by the observation, as expected, of significant increases in the frequencies of loss at the BRCA1 and BRCA2 loci in tumors from BRCA1 and BRCA2 carriers, respectively. **[Interpretation of findings]** To provide a better indication of the most critical events, we used a hierarchical cluster algorithm to group alterations that tended to occur together. The apparent clustering of a limited number of regions of loss and gain indicates a select series of targets **[The targets do not have to be named here, because they were named in the Results section]** for future studies aimed at identifying genes in ovarian cancer. **[Avenue for further studies]**

Some studies indicate that there are differences in the clinical and/or histopathological characteristics of breast and ovarian tumors between tumors from BRCA1, BRCA2, and non-BRCA1/2 mutation carriers (7–13). The reasons for this variation are unknown. BRCA1 and BRCA2 may have a direct effect on the behavior of breast and ovarian epithelial cells, which could vary depending on germ-line BRCA1/2 mutation status. Alternatively, BRCA1/2 mutation status might influence subsequent somatic genetic events in tumorigenesis, with these events being responsible for the observed variation in tumor phenotype. The somatic genetic differences that we observed between BRCA1, BRCA2, non-BRCA1/2, and sporadic ovarian tumors provide support for the latter of these hypotheses. A more detailed comparison of the histopathological characteristics of ovarian tumors in BRCA1/2 mutation and nonmutation carriers will be needed to obtain a better understanding of this association. **[Avenue for further study]**

In conclusion, we used metaphase CGH to characterize the spectrum of somatic genetic events that occur in the development of epithelial ovarian cancer in tumors from BRCA1 and BRCA2 mutation carriers, familial non-BRCA1/2, and sporadic cases. In doing so, we identified molecular genetic differences between these 4 tumor groups that suggest there are different mechanisms for tumor development that may influence the phenotype and clinical outcome of ovarian cancers. The genetic differences we found may be useful in tailoring treatment for breast cancer patients. **[Implication of findings]**

Adapted with permission from Ramus SJ et al. BRCA1/2 mutation status influences somatic genetic progression in inherited and sporadic epithelial ovarian cancer cases. Cancer Res 63:417–423, 2003.

Example of a Poorly Written Discussion (Clinical Study)

Before our study, the clinical importance of ventricular ectopy during exercise stress testing was uncertain. There was conflicting evidence about the relationship of exercise-induced ventricular ectopy to coronary artery disease and to cardiovascular risk.[1–10] In addition, the prognostic implications of when ventricular ectopy occurs (i.e., during or after exercise) had not been well characterized.

A recent study established that vagal reactivation normally occurs early in recovery, immediately after exercise.[11] In the absence of normal vagal reactivation, heart-rate recovery is attenuated and mortality increases.[12–15] Therefore, attenuated vagal reactivation during recovery might be associated with ventricular ectopy that is not suppressed. Thus, we prospectively tested the hypothesis that ventricular ectopy during recovery is a stronger predictor of an increased risk of death than ectopy during exercise. **[Instead of starting with a statement of the conclusions, this Discussion starts with unnecessary background information and restates the purpose of the study. All that information was stated in the Introduction and should not be repeated in the Discussion.]**

Consecutive patients referred for symptom-limited treadmill exercise testing at the Cleveland Clinic Foundation in Cleveland between 1990 and 1999 were eligible for our study. Information regarding ventricular ectopy at rest as well as during each stage of exercise and recovery was systematically recorded according to prespecified definitions. We prospectively defined frequent ventricular ectopy as the presence of 7 or more ventricular premature beats per minute during any given stage, ventricular bigeminy, ventricular trigeminy, ventricular couplets, ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, torsade de pointes, or ventricular fibrillation. The primary end point was death from all causes, which is an objective, clinically relevant, and unbiased end point.[20,21] **[This paragraphs is about the design and conduct of the study, which was described in the Materials and Methods section. This information should not be restated in the Discussion.]**

After adjustment for the variables listed in Table 1 and for frequent ventricular ectopy during exercise, frequent ventricular ectopy during recovery was a predictor of an increased risk of death (adjusted hazard ratio, 1.6; 95 percent confidence interval, 1.3 to 1.9; P<0.001). The prognostic importance of frequent ventricular ectopy during recovery in this propensity-matched cohort is shown in Figure 2. Patients with frequent ventricular ectopy during recovery had decreased survival, particularly after three to four years of follow-up. After adjustment for the propensity score, frequent ventricular ectopy during exercise, and the other variables listed in Table 2, frequent ventricular ectopy during recovery predicted an increased risk of death (adjusted hazard ratio, 1.5; 95 percent confidence interval, 1.1 to 1.9; P=0.003). A similar analysis was performed regarding frequent ventricular ectopy during exercise. Frequent ventricular ectopy during exercise was not associated with decreased survival in this propensity-matched cohort (adjusted hazard ratio, 1.1; 95 percent confidence interval, 0.9 to 1.3; P=0.53). **[In this paragraph, the Results are described again in detail, which is not necessary, and they are not interpreted.]**

In conclusion, frequent ventricular ectopy during recovery from exercise was found to be an important, independent predictor of an increased risk of death in a large clinical cohort. Frequent ventricular ectopy that occurred only during exercise did not independently predict an increased risk. In accordance with previous findings of a strong relationship between attenuated recovery of the heart rate after exercise and an elevated risk of death, these results support the central importance of vagal mediation in cardiac function. They also underscore the value of the exercise stress test as a tool for prognosis and risk stratification.
[Conclusions are given and their clinical implication is discussed, but readers are not given the information to assess the conclusions for themselves (which would be the possible limitations of the study and its relationship to other studies).]

Adapted from the well-written Discussion in Frolkis JP et al. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 348:781–790, 2003.

Example of a Well-Written Discussion (Clinical Study)

In a large cohort of patients referred for exercise stress testing, we found that ventricular ectopy after exercise (during the recovery phase) was a better predictor of increased risk of death than was ventricular ectopy during exercise only. **[Conclusion]** The occurrence of frequent ventricular ectopy during recovery was strongly predictive of an increased risk of death from all causes over a 5-year follow-up period, whereas the occurrence of frequent ventricular ectopy only during exercise was not. This association persisted even after propensity-based adjustment for clinical and exercise characteristics known to predict an increased risk of death. **[Supporting findings]**

Until recently, it was thought that exercise-induced ventricular ectopy was not independently related to an increased risk of coronary heart disease, the extent of coronary artery disease, mortality from all causes, or the risk of major cardiac events.[4,8,16,31] However, one recent report showed that among over 6000 asymptomatic men, ventricular ectopy during exercise was associated with a relative risk of death from cardiovascular disease of approximately 3 when the cohort was followed for 23 years.[6] **[How study fits with existing literature; restatement of the gap in knowledge]**

The current study clarifies these previous findings and extends them to a large cohort likely to be representative of patients seen in clinical practice. **[How the study fills the gap]** Because of the size of the study sample, we were able to examine carefully the prognostic importance of frequent ventricular ectopy during and after exercise in large numbers of subjects (more than 1000 patients in each group). The large cohort also made it possible for us to perform propensity matching,[27] thus allowing a more valid comparison of patients with and without frequent ventricular ectopy than would have been possible by standard regression techniques.[28] **[Strengths of study, and interpretation of findings]** Finally, our observations were consistent with our a priori hypothesis that frequent ventricular ectopy during recovery would be a stronger predictor of risk than ectopy during exercise, which had been based on the recognition of recovery as a period of rapid vagal reactivation.[11]

Because the cohort was a heterogeneous one, including patients who underwent stress testing with electrocardiography only, with echocardiography, or with nuclear perfusion scintigraphy, we did not have systematic data on left ventricular systolic function and myocardial ischemia in all patients. Nonetheless, it is noteworthy that in the subgroup of 6421 patients for whom ejection-fraction data were available, a low ejection fraction (40 percent or less) was associated with frequent ventricular ectopy during recovery. Furthermore, both ventricular ectopy during recovery and a low ejection fraction were independent predictors of death. We focused on death from all causes and could not differentiate among deaths due to arrhythmias, those due to other cardiac causes, and those due to noncardiac causes. We and others have commented on this issue before, pointing out that only death from all causes can be considered a truly unbiased and objective end point that is also clinically relevant when arrhythmia-related outcomes are studied.[20,21] **[A possible limitation of the study (and why it's not a limitation), and interpretation of findings]**

How should the finding of an association between frequent ventricular ectopy during recovery from exercise and mortality from all causes be incorporated into clinical practice? Because this was a prospective, observational study, making treatment recommendations on the basis of our results is problematic. Nonetheless, it is clear that frequent ventricular ectopy during recovery is a marker of an increased risk of death. Accordingly, comprehensive risk-factor assessment and aggressive management of the risk factors identified may well be justified in patients with this finding. In addition, the association of asymptomatic left

ventricular dysfunction with frequent ventricular ectopy during recovery suggests that echocardiography may be indicated, since treatment of asymptomatic left ventricular dysfunction is of clinical benefit.[32] **[Implication of findings, or suggested change in current medical practice]**

Frequent ventricular ectopy during recovery from exercise was found to be an important, independent predictor of an increased risk of death in a large clinical cohort. Frequent ventricular ectopy that occurred only during exercise did not independently predict an increased risk. In accordance with previous findings of a strong relation between attenuated recovery of the heart rate after exercise and an elevated risk of death, these results support the central importance of vagal mediation in cardiac function. They also underscore the value of the exercise stress test as a tool for prognosis and risk stratification. **[Another implication of findings]**

From Frolkis JP et al. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med 348:781–790, 2003. Reprinted with permission.

Discussion Section Worksheet

- Do not repeat background information, methods, or results.
- Make it clear whose study you are discussing each time you switch between yours and someone else's.
- Use transitions between sentences and paragraphs to link ideas.
- Include the information below if appropriate and in the most logical sequence.

Conclusion (based on major findings and relating to study's purpose or hypothesis)

(first paragraph in section)

O*ur findings that… confirm….*

In this study, we found that….

Our results indicate/show/suggest that….

Interpretation of your findings—What further explanation should you give to help readers understand and appreciate the importance of your research?

How findings fit in with existing literature

studies that agree

Our data are consistent with…

Our findings on… agree with those reported by… et al., who….

studies that disagree, with possible explanations for differences

Our data differ from....

Unlike [authors' names] et al., we observed that….

Novelty/strength of study (optional)

In this study, we showed for the first time that.…

The major strength of this study was.…

Limitations of study and other valid criticisms

Our study subjects were…, so it is not known whether our results are applicable to other groups.… Further studies….

In this study, …was measured by…, which may not have….

It is possible, however, that other agents not tested could….

Our study had several limitations. First….

Generalizations to other populations (if possible)

Although our cohort was limited to…, the results suggest that….

Why filling the knowledge gap is important

Our findings will allow us to take the next step in….

Implications of findings / speculation

Our findings may be useful in….

Our findings support the premise that…,

We speculate that….

Our findings further suggest that…

Our results imply that…, but this must be tested further….

Our study adds to the accumulating evidence that suggests.…

These findings are important for… and point to the need for.…

Further study is warranted so that.…

These results suggest that …. should be reinvestigated for.…

Our findings raise the possibility that.…

Adaptations of this study to other….. could result in.…

Avenues for further study

The next step is to….

We have begun investigating....

Our findings suggest issues that should be explored further….

Additional studies are needed to confirm….

Larger studies with longer follow-up are needed to….