Reviewer's report

Title: Thyroid Cancer Complicating Familial Adenomatous Polyposis: Mutation spectrum of At-Risk Individuals

Version: 1 Date: 18 June 2013

Reviewer: Larry Geier

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Major compulsory revisions: None recommended

Minor essential revisions:
1) Introduction, para 3: Should there be a reference after "correlations?"

Discretionary revisions:

1) Introduction, para 1: This refers to the "classic" form of FAP, which would be the only form seen in childhood. It is currently believed that "attenuated" FAP is likely to be much more common, and that many of the extraintestinal manifestations are similar to the classic form. It would be useful to at least describe and distinguish the two forms, or at the very least indicate that the statement applies only to classic FAP. This same suggestion applies elsewhere in the manuscript as well.

2) Introduction, para 3: Recommend replacing "involvement" with "manifestations" or "expression." Also recommend summarizing some of these manifestations in addition to hepatoblastoma, many of which can occur in childhood: CHRPE, osteomas, supernumerary or missing teeth, etc.

3) Introduction, para 4: I find this paragraph unnecessary. The paper is not really addressing thyroid ca in children, as even those with high risk mutations are not recommended for enhanced surveillance until age 18.

4) Introduction, para 5: "higher in some populations".....what populations?

5) Introduction, para 5: If paragraph 4 is omitted, consider replacing the sentence "The increased incidence of sporadic.....17:1" with something like the following:

"While the female: male ratio in sporadic cases of PTC is 3-4:1, the magnitude of the disparity appears to be even higher in PTC associated with FAP. In such patients, the female predominance is reported to be 10-17:1."

6) Introduction, para 6: Second sentence needs to be reworded. "described as more prevalent when the mutation occurs between codons 140-1309."

7) Introduction, para 7: Reword the last sentence: "for patients with FAP, potentially using the specific APC gene mutation to guide strategies for thyroid
cancer surveillance."

8) Results: General comment that it seems hard to believe that only 48 pts have ever been reported with FAP, thyroid cancer, and a specified mutation. This underscores the need for such patients to be included in registries/databases. You might consider making a recommendation along these lines in the discussion, as the low number of patients weakens the correlations that are made.

9) Results, para 2: I found this paragraph confusing until I read it several times. The third sentence is too long. Recommend breaking this up into smaller sentences, and rewording for clarity.

10) Results, para 3. Again, confusing. I don't challenge the results, but the observations that mutations distal to codon 938 confer the least risk of PTC, while the two codons with the greatest risk (1061 and 1039) are in that same range seem rather discordant. As a critical reader, whenever I see such apparent discordance, I start to wonder about the statistical relevance of the results, particularly with small sample size. The issue is addressed somewhat in the discussion, but I would look for ways to make it more clear, or attempt to explain the apparent paradox.

11) Discussion, para 1: Change the word "contextualize." Perhaps "correlate?"

12) Discussion, para 2: First sentence is too long, or at least needs some punctuation.

13) Discussion, para 5 and para 7: While I have no doubt that ultrasound is more sensitive than physical exam, I am wondering if there is any data that supports that it makes a difference in these patients? To recommend a routine surveillance procedure in a high-risk individual, there should ideally be some evidence that it leads to either earlier diagnosis and better outcomes (survival benefit), or the finding of precursor lesions that can be excised or handled with medication (prevention benefit). Is there evidence for either in this situation? Also, is there evidence that the PTC associated with FAP is either more or less aggressive than sporadic PTC? If any of this information exists, I would consider expanding the discussion to include this.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.