Author’s response to reviews

Title: HEREDITARY PANCREATIC CANCER: RELATED SYNDROMES AND CLINICAL PERSPECTIVE

Authors:

Sergio Carrera (sergio.carrerarevilla@osakidetza.net)
Aintzane Sancho (aintzane.sanchogutierrez@osakidetza.net)
Eider Azkona (eider.azkonauribelarrea@osakidetza.net)
Josune Azkuna (josune.azcunasagarduy@osakidetza.net)
Guillermo López-Vivanco (guillermo.lopezvivanco@osakidetza.net)

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Author’s response to reviews:

First of all, I would like to thank you all for your time and consideration; all the suggested corrections have been included and taken into consideration in order to improve the review.

Reviewer #1: The paper is a good review in its field; maybe the references could be increased with more articles.

I have some suggestions and corrections

Pg.2 line 55; incidence of 5/100,000 for only pancreatic neuroendocrine neoplasms (NEN) is not correct; this value is more attributable to all gastroenteropancreatic (GEP) NENs. I suggest this reference Frilling A, et al Neuroendocrine tumor disease: an evolving landscape. Endocr Relat Cancer. 2012 Sep 14;19(5):R163-85. But I think you can also better check on your references this data.

Response: the value data has been corrected and the suggested reference also aforementioned: "Estimated incidence for PNETs is less than 1/100,000 per year although their relative indolent nature could underestimate these numbers [5, 6]."

In hereditary pancreatic neuroendocrine neoplasms I suggest to add for completeness also tuberous sclerosis; this association is rare but it's generally described in this field. Look at Arva NC, et al. Well- differentiated pancreatic neuroendocrine carcinoma in tuberous sclerosis-case report and review of the literature. Am J Surg Pathol 2012; 36:149-153.
RESPONSE: a brief resume-mention of tuberous sclerosis has been added. The suggested reference, plus another one, have also been included: TSC is a rare entity inherited in an autosomal dominant manner, characterized mainly by multiple hamartomatous lesions, epilepsy and intellectual disability, and it is produced by mutations in TSC1 and TSC2 genes [35]. Although there is scarcity of data about TSC and increased risk of PNETs, insulinomas and non-functioning tumors have been reported in patients with TSC [36].

When discussing CDKN2A mutations associated with melanoma, the article Borroni RG, et al Genetic counselling and high-penetrance susceptibility gene analysis reveal the novel CDKN2A p.D84V (c.251A>T) mutation in melanoma-prone families from Italy. Melanoma Res. 2017 Apr;27(2):97-103, could be mentioned.

RESPONSE: a comment and the reference has been added: Recently, a novel CDKN2A pathogenic variant, p.D84V (c.251A>T) has been described in an Italian study which included patients with multiple primary cutaneous melanomas or with primary cutaneous melanoma associated with family history of melanoma and/or PDAC [67].

Thank you for the suggestions.

Reviewer #2: In general reiew is nicely written, clear and concise. Only thing what I would suggest author's is to avoid usage of term"mutation". HGVS (http://varnomen.hgvs.org/; Cotton, Human Mut.2002, 19, 203.) and ACMG (Richards et al., 2015, Genet. Med., 17, 405-424.) strongly recommends to use term "variant" with appropriate modifier. Authors do use term "variant" a couple of times: p.5 line 14 it is "pathogenic BRCA1 and BRCA2 variants" but on p.7 line21 - "deleterious ATM variants". While in both cases meaning is clear the second one doesn't correspond to guidelines. Term "mutation" has a strong inertia and appears in many papers but this isn't excuse not to use proper nomenclature.

RESPONSE: the term "deleterious" has been corrected, and pathogenic variant used now as proper nomenclature when cited in the text. Thank you for the suggestion.