Author's response to reviews

Title: Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest)

Authors:

Thierry Poynard (tpoynard@teaser.fr)
Pascal Lebray (plebray@hotmail.com)
Patrick Ingiliz (p_ingiliz@web.de)
Anne Varaut (anne.varaut@hotmail.fr)
Brigitte Varsat (brigitte.varsat@cpam-paris.cnamts.fr)
Yen Ngo (ngokimphuongyen@yahoo.com)
Pascal Nohra (pascalnohra@hotmail.com)
Mona Munteanu (mona.munteanu@biopredictive.com)
Fabienne Drane (fabienne.drane@biopredictive.com)
Djamila Messous (djamila.messous@psl.ap-hop-paris.fr)
Françoise Imbert-Bismut (francoise.bismut@psl.aphp.fr)
Jean Pierre Carrau (jp.carrau@cpam-paris.cnamts.fr)
Julien Massard (julienmassard@free.fr)
Vlad Ratziu (vratziu@teaser.fr)
Jean Pierre Giordanella (jp.giordanella@cpam-paris.cnamts.fr)

Version: 2 Date: 23 March 2010

Author's response to reviews:

Responses to editor
1. Authors' contributions section have been placed before the references.
2. Competing interests section have been placed before the authors' contributions.

Responses to reviewers

Referee 1.
1. As discussed in the manuscript we do believe that it will be never possible to perform ethically such screening in a large general population using standard liver biopsy as reference. Biopsy is far from a perfect gold standard and still has a mortality rate in adults. We also believe that the repeated studies including independent studies had demonstrated that the FibrotTest has sufficient accuracy, including high negative predictive value to be used as a screening biomarker.

2. According to the reviewer comment the references 18 and 26 have been checked re-included in the list. Sorry. We used the very recent reference by Castera Hepatology 2010 et al as new reference 18 and Pendino et al as reference 26.
Referee 2 (JG).
1. According to the reviewer comment we have given in the revised version the details of the 33 subjects with not interpretable FibroTest: excluded: "Majority were 24 abnormally low haptoglobin (hemolysis or anhaptoglobin), 4 subjects had abnormally high apoA1 value, 1 abnormally low ApoA1, 2 abnormally high GGT, one Gilbert syndrome with 72 micromol unconjugated bilirubin, and one abnormally high A2M."

2. According to the reviewer comment we have added in the revised version the following sentences related to drugs consumption:
in the results section:" A total of 3362/7482 (45%) subjects received at least one treatment at the time of inclusion, but no specific details were available."
in the discussion section: "This study was not designed to estimate the possible role of drugs in inducing liver injury."

3. According to the reviewer comment we have added the details concerning the subjects with FibroTest high risk of false positives/negatives. (see response 1)

4. According to the reviewer comment the following sentence describing the repeated FibroTest for those with initial presumed advanced fibrosis has been added in the results section: "Correlation between first and second FT was 0.77 (P<0.0001) with a significant concordance between cirrhosis/non cirrhosis (kappa=0.76; P<0.001)."

5. To our knowledge, this is the first published study on the prevalence of advanced fibrosis in a general population.

Referee 3. (GP)
1. Results. We agree with the reviewer that we performed no statistical test between included patients and French population. With the sample size of the French population (43 millions 18-80 years) all differences are highly significant. The purpose is only to identify major bias in the selection of our population. We did not state that there was "no difference" but prudently that the populations characteristics "were similar".

2. Results. According to the reviewer comment we have homogenized the reported results all along the manuscript using N (%; 95%CI), when appropriate.

"In the naïve population, 209/7463 (2.8%; 2.4%-3.2%) subjects [N (%;95%CI)] had a FT with presumed fibrosis and 25 with presumed cirrhosis (0.3%; 0.2%-0.5%); 1336/7395 (18.1%; 17.2%-18.9%) had a SteatoTest with presumed steatosis (over 5% of hepatocytes) and 80/7463 (1.1%; 0.8%-1.3%) had a NashTest with presumed steato-hepatitis."

3. Table 1: According to the reviewer comment the 95% CI has been added for all parameters.

4. According to reviewer suggestion Table S1 has been merged with Table 1.
We do think that supplementary Table S5 (revised TableS4) is useful for readers interested in the predictive value of strategy using CDT. Furthermore according to the reviewer suggestion we have reduced the number of supplementary tables from 7 to 4 in the revised version.

5. According to the reviewer comment Table S4 has been simplified focusing on cirrhosis.

6. According to reviewer suggestion, Table 1 has not be cited in the revised version.

7. Results. Last paragraph. LCM has been replaced by LSM.

8. Discussion. “was” has been deleted from “permitted to was attribute”

Discretionary Revisions

1. We are modest knowing that most of scientific findings are false, 50 years later. Thanks to the reviewer.

2. According to the reviewer suggestion we have included now previous Tables S6 and S7 as Table 6 and Table 7 and the legend's details in the results section.

3. We apologize for this inconvenience but most of open source journals do not want page numbers.

Referee 4.

1. According to the reviewer comment, we have been very modest in our discussion, even starting with limitations of our study. According also to another reviewer comment (referee #3 we have detailed the discordant cases between the FT and FS.

2. According to the reviewer suggestion we have added in the reference the excellent study recently published in Hepatology. (Castera et al. Hepatology 2010).