



**ESPS PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 16353

**Title:** Controversy in pediatric Non-Alcoholic Fatty Liver Disease diagnosis

**Reviewer’s code:** 02939926

**Reviewer’s country:** Germany

**Science editor:** Jing Yu

**Date sent for review:** 2015-01-13 20:22

**Date reviewed:** 2015-02-07 03:15

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

**COMMENTS TO AUTHORS**

Thank you for the opportunity to review this editorial, which summarizes current methods for non-invasive characterization of NAFLD and their (potential) role in the pediatric setting. Although the major aspects of current methods are mentioned in the article, a revision of the manuscript should consider the following points: Major aspects: 1) NAFLD in childhood: There is general consent that fatty liver can be considered as part of the metabolic syndrome which reduces overall prognosis. However, the progression from simple steatosis to advanced fibrosis, cirrhosis and further endpoints is a long term phenomenon and liver related events due to NAFLD have a low incidence in children. This is important because prevalence determines the predictive value of (non-invasive) diagnostic methods. Please add data of NASH fibrosis prevalence and incidence of NAFLD related events in childhood and discuss the potential diagnostic value of non-invasive methods against this background. 2) Beside life style modification, treatment options for NAFLD are limited, especially in the pediatric setting. What could be the role of NAFLD screening programs for children by means of non-invasive methods, if the major risk factor (obesity) is easy to diagnose? Further aspects: 1) Elastography: a) I suggest using the term “transient elastography” instead of the



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brand name “Fibroscan”. b) The cited literature on Fibroscan in the pediatric setting is outdated. Meanwhile, the manufacturer provides a small probe (S probe) dedicated to smaller children (e.g. Engelmann G et al. *Eur J Pediatr.* 2012 Feb;171(2):353-60. doi: 10.1007/s00431-011-1558-7). This probe improves feasibility and allows examination of children of younger age. c) The controlled attenuation parameter (CAP), a software module available for the Fibroscan probes M and XL, allows quantification of hepatic fat content along with assessment of liver stiffness. This is the first non-invasive method for hepatic fat quantification which can potentially be applied in larger cohorts and may be used in screening programs (de Ledinghen et al. *J Hepatol.* 2014 May;60(5):1026-31. doi: 10.1016/j.jhep.2013.12.018.). Data from adult cohorts are promising and therefore, this technology should be discussed in the manuscript: CAP merits evaluation in pediatric cohorts. d) Alternative elastography methods (e.g. Acoustic Radiation Force Impulse Imaging, ARFI) are available, have already been evaluated in the pediatric setting and should therefore be mentioned in the manuscript (e.g. Lee MJ et al. *Eur J Radiol.* 2013 Jun;82(6):e290-4. doi: 10.1016/j.ejrad.2013.01.018.) 2) MR techniques: a) Please discuss costs and availability of these techniques. What might be their role in screening programs? b) When comparing MR techniques with liver biopsy, one needs to keep in mind that histology gives a fraction of hepatocytes involved rather than fraction of tissue volume occupied by fat (MR). These different types of units of measure cannot be directly compared ... We currently do not know which method better predicts the outcome of NAFLD. 3) Computed tomography: This technique is associated with significant irradiation doses with unknown long term risks, especially when used in children. Regarding the rather benign aspect of pediatric NAFLD, there is no role for CT scans in the diagnosis of this disease. CT scans should be reserved for pediatric emergencies and malignancies. 4) Laboratory based approaches: a) Please discuss the role of age-specific upper limits of normal, e.g. for ALT, and their role for non-invasive NAFLD markers. b) Is there a potential role for ferritin / iron in the diagnosis of NAFLD severity (e.g. Kowdley KV et al. *Hepatology.* 2012 Jan;55(1):77-85. doi: 10.1002/hep.24706) Formal aspects: 1) Table one, elastography: “the probe size IN not appropriate” – please correct 2) check typesetting of reference 55



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<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input checked="" type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

**COMMENTS TO AUTHORS**

Manuscript entitled Controversy in pediatric Non-Alcoholic Fatty Liver Disease diagnosis is a comprehensive, well prepared review of the methods used in clinical practice for diagnosis of the liver steatosis and fibrosis in children. Authors in a clear way present details of the present diagnostic standard and future possibilities. The reference list contains the most important original and review papers in this field. Minor points: Page 4. The sentence: However with the rising prevalence of NAFLD, the proportion of children with both an underlying primary liver disease (e.g.; autoimmune liver disease or Wilson disease) and additional NAFLD increases, and becomes essential not to miss a treatable condition[9] is not clear. I suggest to correct it. Page 18. Reference No 55 should be corrected.



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Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various review criteria like 'Grade A: Excellent', 'Priority publishing', 'Google Search', etc.

COMMENTS TO AUTHORS

The manuscript entitled "Controversy in pediatric non-alcoholic fatty liver disease diagnosis" reviewed a hot topic for diagnosing controversy of pediatric NAFLD. For the alternatives methods for diagnosis of pediatric NAFLD, ultrasound taking the advantages of noninvasive, low cost, and feasibility is suggested a screening tool in high suspicious population (such in obesity). Although many limits (as descriptions in the text Page 6, lines 2-6) exist, authors and NSPGHAN consensus also suggest ultrasound combined with ALT are reasonable screening tool in the high risk population (such as obesity). This article is a well-written, comprehensive comparison and discussion for the dilemma of diagnosis of pediatric NAFLD. However, some suggestions are list below. The comments to authors 1. The title may change to "Controversy in the diagnosis of pediatric non-alcoholic fatty liver disease". 2. I suggest to change the order of two subtitles "What are the alternatives to a liver biopsy?" and "When to perform a liver biopsy?". It is reasonable to discuss liver biopsy, a gold standard for NAFLD diagnosis, first then talk about alternatives. 3. Reference 48. The journal Obesity needs Italic. 4. Table 1. ALT seric levels dosage change to ALT serum levels dosage.