

Reviewer 1 v.1

Comments to the Author

This paper is sort of ok. It's a little strange that it's a systematic review of 3000+ papers but then they only include 5. It seems like they could just cut out all or most of the systematic review folderol, and just get to the 5 papers they decided to use. The English is maybe average, but it could use some editing since the meaning is frequently unclear. The main results are essentially unsupported by the methods.

I have two major concerns.

First, is that this is a prediction paper wherein a predictive model is built and tested, and there's no information whatsoever about how this is done. There's also no information about how the predictive models were built in each of the 5 source papers. This is a major weakness, since it's likely there was no separate training populations and the models were probably learned on the same data they were tested upon. It's also possible that the models changed through each of the five datasets.

What kind of predictive models were used and how they were created must be explained. Were the models trained on the entire dataset then tested on the entire dataset? How many datasets does that encompass? Were model parameters retained from the sources? Were model parameters retrained on each separate data source?

There's also a lot of ambiguity of the originally reported effects of the five miRs in each of the five papers. It seems like the authors assume that 1 miR comes from one publication, but the other miRs were clearly available in those datasets.

The second major concern is sort of philosophical, but there should be some deeper motivation for a biomarker test of asthma. It'd be a powerful test if you could predict which children will develop asthma before they develop asthma; ie, before they show symptoms, but that's not what's going on here. In the Introduction the authors state: "The FEV1 increased by at least 12% in children with asthma [6], whereas, there is a natural decline for FEV1 in adults [8]." This doesn't make sense. One likely interpretation is that it might be saying that changes in FEV1 throughout the lifecourse invalidate it as a diagnostic measure for asthma, which is false. This issue comes up again later when they say "These results indicate that the combination of these miRNA could greatly increase the diagnosis rates of asthma." This statement must be evaluated against the current standard method of diagnosis for asthma. Since asthma is defined by reversible airflow restriction, diagnosing asthma by spirometry tests - by definition - can't be more accurate.

Smaller points:

Abstract: OK.

Methods: This section is written a little less like a paper and more like a fill-in-the-blanks worksheet.

Abbreviations should be spelled out the first time they're used.

Results:

Table 2: did each study identify only a single differentially expressed miRNA?

Figure 2 pie chart doesn't match text. Blood samples (49%) takes up more area than the alternative.

Figure 2 caption doesn't match image. "Forest plots for the diagnostic value of the combined of 5 miRNAs in asthma. Left is the pooled sensitivity analysis. Right is the pooled specificity analysis. And the combined miRNAs contain miR-185-5p, miR-155, Let-7a, miR-21, and miR-1165-3p."

Need to define I-squared.

Figure 6: need to define ESS. It seem like drawing a regression line through six points is pretty arbitrary, and likely influenced by outliers.

Discussion: Some rationale should be provided for which of the many predictive accuracy metrics should be most relevant; why we should consider the other metrics, and under what circumstances the others should take precedence.