

Rapid Reviews COVID-19

Review 3: "Hitting the diagnostic sweet spot: Point-of-care SARS-CoV-2 salivary antigen testing with an off-the-shelf glucometer"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The paper describes the sensitive and specific qualitative detection of SARS-CoV-2 salivary antigen using off-shelf commercial glucometer as a portable readout. The transduction strategy from COVID-19 antigen to glucose directly refers from the method initially reported in the *Nat. Chem.* (2011, 3, 697) by Yi Lu group, via changing the target from cocaine to SARS-CoV-2 N or S protein. That says, the aptamer-antisense duplex pre-immobilized on the magnetic beads can be weakened in presence of the aptamer target, which released the antisense-invertase conjugation away from the beads. The invertase then turns sucrose to glucose, being detectable by a commercial glucometer.

Highlights: The paper contains highlights in multiple aspects. First, it focuses on the most concerned COVID-19 pandemic that is on extremely urgent requirement to improve detection speed, accuracy, and especially, portability. As one of the most successful and accurate point-of-care devices, glucometer is hand-held, cheap, and provides a ready-to-use readout to displace traditional signaling machines such as plate reader, electrophoresis, western blot, etc. That means the whole detection may be executed without the assistance of any high weight or high cost equipment. Therefore, detection and research like this should be encouraged in order to accelerate large area self-diagnosis and self-inspection. Second, the results are promising, practically sensitive and specific to merely infected specimens. Finally, the paper has been carefully and well written. It provides accurate description on the current situation of COVID-19 detection, meticulous discussion of the results, and objective analysis of both pros and cons of the method in current form. And the experimental details and operation schemes provided in the paper are clear, useful, informative and instructive.

Concerns: Even with above pros, the paper still remains certain concerns to clarify, and problems to be improved in future. Some of the concerns have been mentioned in the discussion section, such as hard quantitation, interference of saliva components and high background sample glucose. Based on my research background, other concerns and comments are listed below:

- 1) I don't quite agree with the claim of "point-of-care" in the title. Even if the detection is already quite easy to operate, it still needs multiple steps of manual operations, such as sample transfer, magnetic separation, transfer supernatant, sucrose addition, detection with strips, etc. I think the detection may be more like "on-site" and "portable" at this stage. Once an integrated device with automatic liquid transfer is fabricated, can it be treated as a point-of-care test.
- 2) Being limited to the less controllable bead synthesis from time to time and bench to bench, it has been found that the quality, binding capacity and performance of the magnetic might be not stable and reproducible. The paper hasn't mention about this aspect. What's the reason for the relatively big error bars in e.g. Figure 2 and 3? How about the data reproducibility day by day? And how about the reagent stability and storage condition, especially after the beads are modified with aptamer switch conjugated with invertase?
- 3) The rule set that leads to the design of aptamer antisense sequence hasn't be mentioned. According to Figure S1, how was the hybridization site of the antisense selected? Because the binding site and affinity will directly affect the targeting sensitivity, has it been optimized?