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30th Jan 24

Dear Professor Han,

Thank you for submitting your manuscript, "Challenges and opportunities for wearable kidney healthcare systems", to Communications Materials. It has now been seen by 2 referees, whose comments are appended below. You will see that while they find your work of interest, some important points are raised.

In particular, you will see that Reviewer 2 requests clarification on key biomarkers for CKD, currently available test kits, and challenges in measurement. Also, Reviewer 1 requests a table summary and discussions about the challenges in transitioning sensors into wearable devices. We are not strict on the allowed word limit, and we feel that the requested revisions from the referees would substantially improve the paper.

We are interested in the possibility of publishing your study in Communications Materials, but would like to consider your response to these concerns in the form of a revised manuscript before we make a decision on publication.

We therefore invite you to revise and resubmit your manuscript, taking into account the points raised.

We are committed to providing a fair and constructive peer-review process. Please don't hesitate to contact us if you wish to discuss the revision in more detail.

When submitting your revised manuscript, please include the following:

-A response letter with a point-by-point reply to each of the referee comments and a description of changes made. Please include the complete referee report in the response letter. Please note that the response letter must be separate to the cover letter to the editors.

-A marked-up version of the manuscript with all changes to the text in a different colored font. Please do not include tracked changes or comments. Please select the file type 'Revised Manuscript - Marked Up' when uploading the manuscript file to our online system.

-A clean version of the manuscript. Please select the file type 'Article File'.

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We hope to receive your revised paper within three months; please let us know if you aren't able to submit it within this time so that we can discuss how best to proceed. If we don't hear from you, and the revision process takes significantly longer, we will close your file. In this event, we will still be happy to reconsider your paper at a later date, as long as nothing similar has been accepted for publication at Communications Materials or published elsewhere in the meantime.

Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further. We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

Best regards,

Rona Chandrawati, PhD

Editorial Board Member

Communications Materials

orcid.org/0000-0002-9780-8844

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

This Perspective article highlights the evolving landscape of wearable sensors and their potential in advancing personalized medicine and real-time disease management. Despite the significant progress in wearable sensors for various medical applications, there is a notable gap in the development of such technology for CKD detection. The article proposes a wearable digital healthcare concept for non-invasive, continuous CKD monitoring, discussing optimal biofluids, biomarkers, bioreceptors, and the current trend in sensor development for a wearable CKD sensing platform. These concepts are well updated and valuable to the researchers working in this area. However, to reach the standard for publication, a more thorough picture on the working principles or improvements on key parameter should be provided. Below are suggestions and inquiries that should be addressed before recommending this paper for acceptance:

1. A comprehensive table is needed to provide literature comparison. Key parameters, such as sensitivity, stability, and detection limits, related to CKD should be well listed and compared to address the recent breakthroughs.
2. Is there additional literature available in the last section of the article to provide a more comprehensive review on the challenges and developments in wearable devices?
3. The transition from sensors to actual wearable devices presents numerous challenges. The article extensively discusses challenges related to sensing materials, but it seems that the difficulties associated with the integration of wearable devices are not thoroughly addressed in detail.

Reviewer #2 (Remarks to the Author):

In this perspective, the authors discussed the existing challenges in detecting of chronic kidney diseases and proposed possible improvements using wearable biomarker sensing technologies to continuously measure more easily accessible biofluids with low invasiveness. While the topic is

timely and important, I believe the perspective requires more original and in-depth discussions regarding the future development of this specific field. Furthermore, some additional information can be useful in strengthening the discussion within this perspective. I have the following comments:

1. The authors only briefly covered the blood and urine testing in centralized hospital setting but did not mention the already existing blood/urine-based test kits available for home-use. For frequent, convenient self-monitoring, these existing technologies/products with their advantages and disadvantages should also be discussed.
2. The current diagnosis standard of various chronic kidney diseases should be mentioned. The key biomarkers for blood and urine tests as well as their typical range should be summarized (e.g., glomerular filtration rate, blood urea nitrogen, urine albumin-creatinine ratio)
3. While the authors raised the topic of wearable sensing for CKD, most of the body discussed the sensing of creatinine. What about other important biomarkers for kidney functions?
4. Much of the discussion on the form factors and biofluid extraction mechanisms is quite general for all wearable biomarker sensors. Special consideration for the detection of CKD-related biomarkers that is different from other metabolites/electrolytes should be emphasized.
6. Can the authors share more insights into how the individuality/conversion is accounted for sweat or ISF sensing, considering the dilution effect from blood to these alternative biofluid options?
7. The authors discussed the challenges of biofouling or leaching for extended sensor usage. However, to my knowledge, most of the invasive wearable sensors with similar form factors to Abbott Freestyle Libre can be worn for over 2 weeks without suffering from significant biofouling due to the use of polymeric coating and other surface chemistries. Furthermore, most microneedle-based devices are designed to be worn for much less time than the invasive needle-based wearable patches. Seeing the problem already addressed and existing CGM receiving much commercial success, why do the authors claim that biofouling/leaching are still key challenges for the commercialization of wearable CKD sensors?
8. In the introduction, the authors claimed that blood/urine test "does not allow real-time monitoring of the kidney function, and thus largely fails in early detection of CKD". Why would continuous measurement be so important for a chronic disease? Are there any dynamic events in a day that cannot be captured using a single-use testing device that is key to the early diagnosis of CKD? The authors can expand on the importance of the sensing continuity.

Point-by-point response to the reviewers

We wish to thank the reviewers for their comments. Our response and revisions are outlined below:

Reviewer #1

1. A comprehensive table is needed to provide literature comparison. Key parameters, such as sensitivity, stability, and detection limits, related to CKD should be well listed and compared to address the recent breakthroughs.

As the reviewer's comment, we have added a table including the key parameters to provide literature comparison, and also added contents regarding the recent breakthroughs just below the table in yellow.

2. The transition from sensors to actual wearable devices presents numerous challenges. The article extensively discusses challenges related to sensing materials, but it seems that the difficulties associated with the integration of wearable devices are not thoroughly addressed in detail. Is there additional literature available in the last section of the article to provide a more comprehensive review on the challenges and developments in wearable devices?

In a revised manuscript, we have added other challenges to wearable sensing and their possible solutions: the effects of interfering species, sweat secretion rate and pH in the section "Considerations for developing wearable sensors" in yellow.

Additionally, we have cited a Perspective paper discussing other challenges to wearables, for example, sensor integration, user acceptance and power consumption in the last part of the first paragraph on the section "Considerations for developing wearable sensors".

- Philipp Gutruf, "Towards a digitally connected body for holistic and continuous health insight", *Communications Materials* 5, 2 (2024).

Reviewer #2

1. The authors only briefly covered the blood and urine testing in centralized hospital setting but did not mention the already existing blood/urine-based test kits available for home-use. For frequent, convenient self-monitoring, these existing technologies/products with their advantages and disadvantages should also be discussed.

We agree with the reviewer's comment. The contents have been added in the second paragraph of the "Introduction" section in yellow.

2. The current diagnosis standard of various chronic kidney diseases should be mentioned. The key biomarkers for blood and urine tests as well as their typical range should be summarized (e.g., glomerular filtration rate, blood urea nitrogen, urine albumin-creatinine ratio).

As the reviewer's comment, we have added the contents including the current diagnosis standard and the typical ranges of the key biomarkers in the beginning of the section "Selection of biomarkers".

3. While the authors raised the topic of wearable sensing for CKD, most of the body discussed the sensing of creatinine. What about other important biomarkers for kidney functions?

As the reviewer's comment, we have added the contents of other biomarkers (urea, cystatin C) in the section "State-of-the-art sensing technology" in yellow.

4. Much of the discussion on the form factors and biofluid extraction mechanisms is quite general for all wearable biomarker sensors. Special consideration for the detection of CKD-related biomarkers that is different from other metabolites/electrolytes should be emphasized.

We have added special considerations for the detection of CKD biomarkers in the last paragraph of the "Considerations for developing wearable sensors" section in yellow.

5. Can the authors share more insights into how the individuality/conversion is accounted for sweat or ISF sensing, considering the dilution effect from blood to these alternative biofluid options?

We agree with the reviewer's comment. The contents have been added at the end of the last paragraph of the "Selection of biomarkers" section in yellow.

6. The authors discussed the challenges of biofouling or leaching for extended sensor usage. However, to my knowledge, most of the invasive wearable sensors with similar form factors to Abbott Freestyle Libre can be worn for over 2 weeks without suffering from significant biofouling due to the use of polymeric coating and other surface chemistries. Furthermore, most microneedle-based devices are designed to be worn for much less time than the invasive needle-based wearable patches. Seeing the problem already addressed and existing CGM receiving much commercial success, why do the authors claim that biofouling/leaching are still key challenges for the commercialization of wearable CKD sensors?

We completely agree with the reviewer's comment, and the contents have been removed accordingly.

7. In the introduction, the authors claimed that blood/urine test "does not allow real-time monitoring of the kidney function, and thus largely fails in early detection of CKD". Why would continuous measurement be so important for a chronic disease? Are there any dynamic events in a day that cannot be captured using a single-use testing device that is key to the early diagnosis of CKD? The authors can expand on the importance of the sensing continuity.

As the reviewer's comment, we have added the contents highlighting the importance of the sensing continuity for CKD in the last paragraph of the Introduction in yellow.

31st Jul 24

Dear Professor Han,

Your manuscript titled "Challenges and opportunities for wearable kidney healthcare systems" has now been seen again by Reviewer 1, whose comments appear below. Reviewer 2 did not respond to our requests to look at the revised paper, and we have therefore assessed your replies to their previous comments ourselves. In light of that, I am delighted to say that we are happy, in principle, to publish a suitably revised version in Communications Materials.

We therefore invite you to edit your manuscript to comply with our journal policies and formatting style in order to maximise the accessibility and therefore the impact of your work.

EDITORIAL REQUESTS

- * Your manuscript should comply with our policies and format requirements, detailed in our style and formatting guide (<https://www.nature.com/documents/commsj-phys-style-formatting-guide-accept.pdf>).
- * Please edit your manuscript according to the editorial requests in the attached table, and outline revisions made in the right hand column. If you have any questions or concerns about any of our requests, please do not hesitate to contact me. It is important that each request be addressed in order to avoid delays in accepting your manuscript. Please upload the completed table with your manuscript files as a Related Manuscript file.
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- * An updated editorial policy checklist that verifies compliance with all required editorial policies must be completed and uploaded with the revised manuscript. All points on the policy checklist must be addressed; if needed, please revise your manuscript in response to these points. Please note that this form is a dynamic 'smart pdf' and must therefore be downloaded and completed in Adobe Reader. Clicking this link will download a zip file containing the pdf.

Editorial policy checklist: <https://www.nature.com/documents/nr-editorial-policy-checklist.zip>

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We hope to hear from you within two weeks; please let us know if the process may take longer.

Best regards,

Rona Chandrawati, PhD

Editorial Board Member

Communications Materials

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REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

The authors revised the manuscript according to the review comments with updated results. It is okay for publication.