JYVÄSKYLÄN YLIOPISTO
885/03.06.00.00/2017

Unofficial translation - In case of discrepancies between the Finnish and the English text, the Finnish text shall prevail.

RECTOR'S DECISION ON AN ALLEGED VIOLATION OF THE RESPONSIBLE CONDUCT OF RESEARCH

TARGET OF THE DECISION:

Articles

1. A multiplex and multifunctional enzyme linked immunosorbent assay for microbes associated with tick-borne diseases[1]
2. Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases[2]

According to the written notification received by the Rector, Article 1 has been used to scientifically validate the Tickplex test. However, this investigation has not been targeted to the Tickplex test itself but only to the articles. The investigation has revealed that the Pockit test mentioned in the notification is based on different technology. Therefore, the investigation has not been targeted to Pockit.

RESOLUTION

In the abovementioned articles, Leona Gilbert and Kunal Garg are guilty of research misconduct, disregard for the responsible conduct of research and other irresponsible practices as depicted in the Finnish Advisory Board on Research Integrity (TENK) guidelines for the responsible conduct of research[3].

Leena Meriläinen, Marco Quevedo-Diaz, Oliver Hendricks, Heidi Pirttinen, Stephen Croucher and Ole Franz are not guilty of a misconduct of responsible conduct of research.

The investigation, the justification of the decision, the informing process and the appeal process are clarified below.

Jyväskylä, 4 September 2020

Keijo Hämäläinen
Rector

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[1] Published online in 2017; no more available publicly.
[2] Published in the Scientific Reports journal on 29 October 2018. https://www.nature.com/articles/s41598-018-34393-9#MOESM1
[3] Finnish Advisory Board on Research Integrity: Responsible conduct of research and procedures for handling allegations of misconduct in Finland (2012). https://tenk.fi/sites/tenk.fi/files/HTK_ohje_2012.pdf

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Abbreviations:

Bbsl	Borrelia burgdorferi sensu lato
ELISA	Enzyme-linked immunosorbent assay
RCR	Responsible conduct of research
RCR guidelines	The Finnish Advisory Board on Research Integrity guidelines "Responsible conduct of research and procedures for handling allegations of misconduct in Finland"

KSSHP	Central Finland Health Care District
PSSHP	Kuopio University Hospital District Municipal Federation
THL	National Institute for Health and Welfare
TENK	Finnish Advisory Board on Research Integrity
TUKIJA	National Committee on Medical Research Ethics TUKIJA
SPA	Spondyloarthritis
SR Article	Article published in *Scientific Reports* on 29 October 2018: "Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases" https://www.nature.com/articles/s41598-018-34393-9#MOESM1
Validation Paper	The article, which is the original target of the investigation. The whole title is "A multiplex and multifunctional enzyme linked immunosorbent assay for microbes associated with tick-borne diseases".

1. PRELIMINARY INQUIRY

1.1. Written notification and start of preliminary inquiry

Based on a written notification to the Rector of the University of Jyväskylä on 19 July 2017, the test kit "Tickplex", developed by Senior Lecturer Leona Gilbert (University of Jyväskylä, Faculty of Mathematics and Science, Department of Biological and Environmental Science) and her research team, is not scientifically validated in peer-reviewed publications and does not give reliable results. The instigator of the allegation was doctor Mats Reimer from Gothenburg.

The only available scientific justification was an article, written by Gilbert and five other authors and published on the website of the Gilbert's company, titled "A multiplex and multi-functional enzyme linked immunosorbent assay for microbes associated with tick-borne diseases". Garg, K. 1, Meriläinen, L. 1, 2, Pirttinen, H. 1, Quvendo-Diaz, M. 3, Hendricks, O. 4, and Gilbert, L. 1 (1. Department of Biological and Environmental Sciences, Nano Science Center, University of Jyväskylä, Jyväskylä, Finland; 2. University of Helsinki, Helsinki, Finland; 3. Biomedical Research Center SAS, Slovak Academy of Sciences, Dúbravská cesta 9, 84505 Bratislava, Slovak Republic; 4. Faculty of Health Sciences, University of Southern Denmark, Syddansk Universitet).

The notification of the allegation also mentioned another test of Gilbert's team, "Pockit", which participated in the Helsinki Challenge science competition. The instigator suggested that also Pockit may violate the responsible conduct of research.

On 16 August 2017, the Rector initiated a preliminary inquiry in compliance with the RCR guidelines with the aim to clarify if the test kit marketed through Gilbert's company was based on scientific research, what was the status of the Validation Paper, and if the Validation Paper was published or approved to be published in a peer-reviewed publication. In addition, the aim was to clarify if

research permits necessary for the research had been acquired and if an ethical review required for the research had been made.

1.2. Rector's hearing of the parties

1.2.1. Gilbert

In her statement, Gilbert denied any violations of the responsible conduct of research. She submitted a list of publications, which were intended to prove that the Tickplex test had a scientific background. As for the status of the Validation Paper, she stated that it was almost ready to be published and that cooperation partners had approved its publication on the company's website. According to Gilbert, the validation report had been required by many operators in the company's field of operation. According to Gilbert, the test is not based on a single paper or project but is a result of years of development work.

In her response, Gilbert provided a list of research permits and ethical reviews.

Gilbert was heard again and was presented specifying questions that aimed to clarify if the Tickplex and Pockit tests were based on the same research. As for the Pockit test, it still did not become clear how it essentially differs from the Tickplex test. It was noticed that an expert assessment would be needed to clarify this.

1.2.2. Reimer

Gilbert's response was submitted to Reimer for information. In his response, Reimer emphasised the clarification of an ethical review. He still questioned if Tickplex would be able to find also non-tick-borne pathogens as presented in the Validation Paper.

1.3.Expert statement

Docent (Adjunct Professor) Jussi Sane from the National Institute for Health and Welfare (THL) was invited to give an expert statement on the scientific value of the Validation Paper as the validator of the test. Sane's assessment was that the test developed by Gilbert's research team was not validated appropriately. Sane recommended a more detailed clarification in which 1) the methodology, findings and conclusions of the validation paper should be thoroughly reviewed, and 2) it would be examined more closely whether the marketing of Leona Gilbert's company is misleading.

1.4.Summary of the preliminary inquiry

The parties were submitted a summary of the preliminary inquiry and given an opportunity to give a response on it.

1.5.Gilbert's response to the summary of the preliminary inquiry

Gilbert claimed that the test was validated in compliance with the applicable laws and that required ethical permits and ethical reviews had been made. According to Gilbert, the paper was removed from the company's website because one of the authors had demanded to be removed from the list of authors. As the reason for the removal, the author had mentioned Reimer's accusations towards the author.

Gilbert explained that the research on the background of Tickplex was initiated in 2007 in a project funded by the Schwartz Foundation, then continued in the Parvovirus B19 project of the Academy of Finland in 2008 and continued further in the TICK-TAG project funded by TEKES in 2015. According to Gilbert, the Validation Paper summarised data from the earlier studies and the TICK-TAG project.

According to the response, the abovementioned studies had received necessary ethical permits and reviews.

1.6.Reimer's response on the summary of the preliminary inquiry

In his response, Reimer said that when discussing about the existence of chronic Lyme disease, the question is not about equally balanced sides. He explained that Gilbert is on the minority side and international health authorities and microbiology specialists on the other.

Reimer also stated that he was still not convinced that the validation based on published research on Tickplex was sufficient enough to make scientific decisions or that clinicians would be able to use the test.

1.7.Conclusions

The conclusion of the preliminary inquiry was that it could not indisputably prove that the responsible conduct of research had not been violated. Based on the preliminary inquiry, it was still unclear if the test had a validation to the extent claimed by Gilbert and it was not possible to clarify if the required favourable ethical review statements and research permits had been received. In addition, the preliminary inquiry could not clarify the primary difference between the two test kits (Pockit and Tickplex).

It was noticed in the preliminary inquiry that, according to TENK's RCR guidelines, the alleged violation of the responsible conduct of research belongs to the category *other irresponsible practices: misleading the general public by publicly presenting deceptive or distorted information concerning one's own research results or the scientific importance or applicability of those results.* However, it cannot be excluded that the question would be about *Research misconduct: Falsification (misrepresentation) refers to modifying and presenting original observations deliberately so that the results based on those observations are distorted. The falsification of results refers to the unfounded modification or selection of research results. Falsification also refers to the omission of results or information that are essential for the conclusions.*

2. INVESTIGATION PROPER

Based on the conclusions of the preliminary inquiry, the Rector decided to start an investigation proper. On 23 March 2018, he appointed Professor of Microbiology (emeritus) Olli Vainio, the University of Oulu (chair), Professor of Health Law and Administrative Chief Physician Lasse Lehtonen, the University of Helsinki and Hospital District of Helsinki and Uusimaa, Clinical Microbiology Specialist, Docent Satu Kurkela, HUSLAB laboratory of the Hospital District of Helsinki and Uusimaa, and Legal Counsel Visa Hiltunen, EduCluster Finland (secretary) as the members of the investigation committee.

To secure possible trade secrets related to Gilbert's business activities, all members of the research team signed a confidentiality agreement with the University before starting the committee work.

2.1. Content of Final Report 1

2.1.1. Target of investigation and its definition

The investigation committee defined the target of the investigation proper as to clarify if the research described in the Validation Paper was conducted following the responsible conduct of research and if the claims presented in the paper were based on scientific evidence.

The investigation committee noticed that the Validation Paper had six authors, so also other authors than Leona Gilbert needed to be heard.

The investigation committee decided to limit the following matters outside the investigation:

- The marketing of Gilbert's company or the authority approvals of the company's products. However, the investigation committee pointed out that if a violation of the responsible conduct of research is found out in the investigation proper, there is a reason to inform authorities responsible for marketing or product approvals.

- Pockit test: Gilbert had systematically described that Pockit and Tickplex are different products and based on different technologies. In addition, the development of the Pockit test was still in progress.

-Other publications than the Validation Paper, unless a considerable reason would occur to include them in the investigation. Such a reason could be a clear reference, presented by the author, how the publication helps to understand the research reported in the Validation Paper.

2.1.2. Hearing of the parties

The suspects were given an opportunity to respond to the limitation of the investigation defined by the investigation committee and to answer submitted questions.

Hendricks, Quevedo-Diaz, Pirttinen and Gilbert gave their responses. Kunal Garg and Leena Meriläinen did not submit a response.

Oliver Hendricks stated that he does not consider to be an author of the Validation Paper. In an email, he had requested Gilbert to remove his name, organisation and any elements referring to research cooperation with Gilbert from the Validation Paper immediately after becoming aware of the publication of the Validation Paper in June 2017. In November 2017, Hendricks had approached Gilbert again by email, repeating his earlier request and asking Gilbert to remove the Validation Paper from the website. Hendricks had explained problems related to the data presented about the lookalike patient cohort of SPA patients. In the dissertation, in which the cohort had originally been used, the patients had been divided into three categories: patients with SPA, patients without SPA, and patients with lower back pain. Hendricks described this division as crucial. In the Validation Paper and in the unfinished manuscript of a new article based on the Validation Paper, all these 78 patients were considered to have SPA. Hendricks notified Gilbert that this changed interpretation is not scientifically correct. The follow-up study recommended in the dissertation had also revealed that only 44 of the 78 patients in the cohort really had SPA.

Hendricks also told the investigation committee that he was not part of Gilbert's team in 2015–2017, when research leading to the Validation Paper had been conducted. According to his response, he did not know what kind of tests Gilbert used to validate Tickplex.

Gilbert and Hendricks also discussed with each other. In July 2018, Hendricks sent Gilbert an email, adding also the secretary of the investigation committee as the recipient. In the message to Gilbert, Hendricks repeated his viewpoint that the Validation Paper assumed that all 78 suspects in the lookalike patient cohort had SPA, even though this was not the case. Hendricks had told this to Garg already in 2015. Hendricks wrote to Gilbert that, according to his understanding, both the Validation Paper and the planned new article suffered from a selection bias. Tickplex and the new manuscript did not bring out the earlier negative results but led to believe that the results were positive. This is scientifically erroneous.

In her response, Pirttinen explained that cooperation clinics recruited the patients (the healthy comparison group) and that she had not participated in the categorisation. According to her knowledge, at some point the Validation Paper was sent to be published in the Scientific Reports journal but was not accepted.

In his response, Quevedo-Diaz explained to have participated in the project only within the limits of his special field (rickettsiology).

Gilbert submitted her response and 30 attachments: funding applications, research plans, research permits, raw data, patent applications and articles.

Gilbert answered all of the presented questions. According to her, the team received serum samples and related data from Germany, Finland, Sweden, Norway and the USA. To the question about the publication of the Validation Paper, Gilbert stated that the manuscript had been submitted to the Nature journal, which had required small corrections that were almost ready.

On 4 December 2018, the investigation committee sent Gilbert and Garg a request for additional information, pleading to submit the decisions of the KSSHP Ethics Committee to the investigation committee so that it would be possible to assess if the requests were related to the research related to the Validation Paper. The investigation committee also wanted to clarify if the approval of the Western Institutional Review Board had been accidentally left out from the attachments of the response. Gilbert and Garg did not submit the decision of the KSSHP Ethics Committee. On 17 December 2018, Gilbert responded that the process was still in progress in KSSHP and that it is not relevant for the ongoing investigation. Nevertheless, Gilbert submitted the missing decision of the Western Institutional Review Board.

2.1.3. The purpose of the Validation Paper

According to the investigation committee's understanding, the Validation Paper describes a clinical laboratory test method for the detection of IgM and IgG antibodies against Bbsl and other pathogens by using ELISA platform. The material used in this study consisted of serum specimens

According to the understanding of the investigation committee, the research leading to the Validation Paper had three goals:

1. To develop and evaluate a new test method for recognising Bbsl antibodies in human serum samples.

2. To develop and evaluate a new test method for recognising the antibodies of 14 other microbes in human samples.

3. By using the methods mentioned in items 1 and 2, to study the prevalence of various microbial antibodies in different patient groups and draw medical conclusions from the results.

According to the interpretation of the investigation committee, the Validation Paper aims to differentiate patients with a proven recent or earlier Bbsl infection from patients without the infection. This is made by combining information from clinical and laboratory tests and by comparing the results to the results received with the test method. The paper presents the performance parameters. In addition, the paper deals with a phenomenon called polymicrobial infection, which the researchers claim to have noticed from Bbsl patients with the test method they has developed in the research.

Upon the request of the investigation committee, Gilbert submitted a list of publications that were supposed to increase the committee's understanding on the research reported in the Validation Paper. According to the assessment of the investigation committee, the publications, in which Gilbert was not an author, had very little to do with the research behind the Validation Paper and, according to the committee's conception, did not solve the deficiencies of the Validation Paper.

2.1.4. Performance parameters

According to the investigation committee, the validation of an ordinal scale test is based on such a comparison of methods, in which the same sample entity is analysed using two different methods. The comparison method may be another laboratory test or a well-defined clinical diagnosis. In well-constructed settings, the comparative method is made using both a reference test and a clinical diagnosis.

According to the investigation committee, several requirements must be considered when using a diagnosis: Case definitions must be made clearly and the criteria for counting an individual to a certain group must be written out. The group of patients must be representative and have a relevant distribution of gender and age. In case of infectious diseases, exposure to the risk factor (in this case a tick bite) must be possible. Also epidemiological background information, in this case the pathogen's distribution in the geographical area in which the exposure to ticks occurred, must be included.

The Validation Paper describes in total eight cases. According to the investigation committee, the Validation Paper does not provide sufficiently data on how the case definitions were made. Therefore, the committee requested for this data: geographical area, place of recruitment, age, gender, ethnical background, the sampling time in relation to the outbreak of the disease, antimicrobial treatment, exposure to ticks, other illnesses, the use of CDC case definitions (standard criteria for defining an illness in the monitoring of a population's health). The data were not submitted or they were not available. Therefore, the Validation Paper and submitted additional documents do not offer exact information on the clinical case definitions, the representativeness of the patient population, exposure or geography.

Because clinical criteria had not been described appropriately considering the validation of the test, the investigation committee had to focus solely on the comparison of the tests.

An appropriate comparison of tests requires that raw data and results based on them are available. To perform the comparison, the raw data of both the existing test and the new test to be validated as well as the test results (which may be positive, negative or in the grey area) are needed. Each sample must go through the same testing process. The resulting datasets are used to calculate the performance of the new test, including relative sensitivity and specificity. The report of the investigation committee presents the calculation formulas used in the comparison of sensitivity and specificity.

In the report, the committee notes that the performance parameters have been calculated in a manner that is not acceptable for a clinical laboratory test – the values of each parameter must be calculated separately, not as combinations as has been made in the Validation Paper. The erroneous processing of data is revealed in the data analysis information of Gilbert's response (especially in the clinical competence evaluation tables). The investigation committee's final report, page 9, includes a table that summarises erroneous interpretations made in the data analysis and the correct interpretations of the observations. In all cases of the table, the authors have presented their interpretation only as true positive, whereas, according to the investigation committee, the correct interpretation would have always been false negative or false positive, indicated separately for IgM and IgG. The correct interpretations presented by the investigation

committee were always different for IgM and IgG.[4] In two cases, the IgM comparison value was not available at all, in which case, according to the committee, it was not possible to make an IgM interpretation at all. Also for these parts, the authors' interpretation was true positive.

2.1.5. Use of the new test in epidemiological research

According to the interpretation of the investigation committee, the purpose of the Validation Paper is to use the test to prove a medical phenomenon called polymicrobial infection. This has been implemented by assessing the prevalence of antibodies in different patient groups and in the reference group (healthy persons).

Because the case definitions had not been made appropriately for the validation of the test, they were not defined appropriately for the cross-sectional study either.

The investigation committee assessed the research to suffer from a selection bias. The seroprevalences reported by the authors either refer to a very atypical selection of patients (which is not explained at all) or are clearly unconvincing in comparison to the observations of other studies. According to the investigation committee, the authors' conclusions

> *"Outstandingly large immune responses to other microbes and Borrelia antigens indicated the profound polymicrobial nature of tick-borne diseases."*
>
> *"Figure 3 suggested that Lyme symptomatic patients suffer from polymicrobial infections (multiple infections) where existence of a microbe may pre-dispose a patient to colonization by other microbes."*
>
> *"Evidently, positive immune responses to Borrelia antigens either in an individual morphology or in combination, predisposed patients to multiple other microbes (figures 6B and 7B)"*

are without justification for all eight categories due to the deficiency of case definitions and for category 8 (Healthy) due to the selection bias.

2.1.6. Other observations and medical interpretations concerning the performance of the test

The investigation committee also presents the following observations:

- The justification of the cross-reactivity of antigens does not follow the standard.

-The claim about the quantitative nature of the test is misleading. According to the investigation committee, the test does not provide information on the concentrations of antibodies even though

[4] Eg. Table 8 / TBb S 116: The authors' interpretation is true positive. According to the investigation committee the correct interpretations are false positive for IgM and false negative for IgG.

the Validation Paper claims Tickplex to find positive, borderline and negative reactions to many pathogens and to give information on the concentrations of the antibody.

According to the understanding of the investigation committee, it is unquestionable that opportunistic EBV and CMC infections are observed with a quantitative nucleic acid definition from plasma. Therefore, the use of an antibody test for the same purpose is misleading.

2.1.7. Oliver Hendricks's status in the investigation

The investigation committee considered that the reprimand presented by the committee cannot be directed to Oliver Hendricks. Based on his response and additional information he submitted, he had opted out of the research leading to the Validation Paper. He had presented his concern about the data analysis already two years before the publication of the paper. The investigation committee finds it exceptional and reprehensible that the paper was published without Hendricks's consent.

2.1.8. Research permits

When assessing the research permits submitted to the investigation committee, the committee found them only partly relevant. From the submitted permits, it was not possible to clarify for all parts if they concerned the implemented research. There were no research permits from Finland, Sweden and Norway, even though samples from these countries were used in the research.

2.1.9. SR Article

Before the deadline of the investigation committee's final report, Gilbert's research team published the SR Article. The preparation of the article had been mentioned already in the responses of authors. For many parts, the content of the SR Article is similar to the Validation Paper. The most significant difference is that the article does not describe the validation of the test but focuses on the epidemiological findings produced by the new test. The research of the article uses the same data as the Validation Paper, but the category 8 values have been changed in the article, possibly because the 0% incidence of antibodies presented in the Validation Paper is not credible. The lookalike category has also been removed because it concerns Danish SPA patients and refers to cooperation with Hendricks.

The investigation committee' tentative assessment is that also the SR Article is misleading and may contain an RCR violation because the laboratory test used for epidemiological assessment in the SR Article does not have sufficient scientific validation.

2.2. Final Report 1: Conclusions about an RCR violation

At the beginning of its assessment, the investigation committee highlighted the sections of TENK's definition of responsible conduct of research, which the committee considered relevant. The parts are (numbering follows the TENK's guidelines):

1. The research follows the principles that are endorsed by the research community, that is, integrity, meticulousness, and accuracy in conducting research, and in recording, presenting, and evaluating the research results.

2. The methods applied for data acquisition as well as for research and evaluation, conform to scientific criteria and are ethically sustainable. When publishing the research results, the results are communicated in an open and responsible fashion that is intrinsic to the dissemination of scientific knowledge.

4. The researcher complies with the standards set for scientific knowledge in planning and conducting the research, in reporting the research results and in recording the data obtained during the research.

5. The necessary research permits have been acquired and the preliminary ethical review that is required for certain fields of research has been conducted.

7. Sources of financing, conflicts of interest or other commitments relevant to the conduct of research are announced to all members of the research project and reported when publishing the research results.

The investigation committee also states that TENK classifies violations against the responsible conduct of research into three categories. The main categories are research misconduct and disregard for the responsible conduct of research. In addition, TENK defines other irresponsible research practices, which may also meet the criteria of an RCR violation. In the preliminary inquiry, it was noticed that the alleged RCR violation would belong to the category of *other irresponsible practices: misleading the general public by publicly presenting deceptive or distorted information concerning one's own research results or the scientific importance or applicability of those results.* Furthermore, in the preliminary inquiry it was not possible to exclude that the question could be about research misconduct.

Of the subcategories of research misconduct, the investigation committee evaluated if the question is about falsification (misrepresentation), which "refers to modifying and presenting original observations deliberately so that the results based on those observations are distorted. The falsification of results refers to the unfounded modification or selection of research results. Falsification also refers to the omission of results or information that are essential for the conclusions."

In addition to research misconduct and other irresponsible practices, the investigation committee also assessed if the operation mode of the suspects should be evaluated as disregard for the responsible conduct of research. From the subcategories of disregard for the responsible conduct of research, the committee selected "reporting research results and methods in a careless manner, resulting in misleading claims" as the target of more specific inspection.

The investigation committee noted that an RCR violation may be committed intentionally or through negligence. In this case, a negligent violation of the responsible conduct of research could be, for example, not acquiring all research permits or processing data so that it leads to wrong conclusions in the test comparisons, if other conclusions would be obvious for an intermediate-level researcher. Unlike other RCR violations, falsification seems to require intentional actions based on its definition.

About the calculation of performance parameters, the investigation committee stated that if the incorrect processing of data and the erroneous interpretation of results have been intentional, the question is about research misconduct (falsification, referring to modifying and presenting original observations deliberately so that the results based on those observations are distorted). The committee finds it improbable that the data would have been processed and interpreted incorrectly by accident.

The committee considers that using the new test for epidemiological research is, at the least, disregard for the responsible conduct of research, in more detail "reporting research results and methods in a careless manner, resulting in misleading claims". If the activity has been intentional, the question, according to TENK's definition of falsification (omission of results or information that are essential for the conclusions), is about research misconduct. Again, the investigation committee finds if improbable that the conduct would have been unintentional.

The committee states that the Validation Paper was publicly available in the Internet and its content interests the public very much. In principle, this fulfils TENK's definition "misleading the general public by publicly presenting deceptive or distorted information concerning one's own research results or the scientific importance or applicability of those results" (TENK category *Other irresponsible practices*). Because of their company, the researchers had a financial incentive to market the test to the public. On the other hand, the Validation Paper was publicly available for a relatively short time.

Claims about the test's performance and medical interpretation may possibly mislead the science community and the public. However, according to the investigation committee's conception, the erroneous medical interpretation does not fulfil the definition of an RCR violation in this case.

As for the research permits and the ethical review, the investigation committee considers that at least negligence is involved in their documentation. The committee has not been able to confirm if all activities of the researchers had required research permits. It is possible that some parts of the research have been made without necessary statements or research permits. The clarification has been hindered by, for example, that the KSSHP Ethics Committee, Leona Gilbert or Kunal Garg have not presented any decisions from the KSSHP Ethics Committee to the statement requests. It is also possible that the research has been carried on regardless of a negative statement.

In its report, the investigation committee concludes about the Validation Paper that, according to the committee's view, the authors of the paper, excluding Oliver Hendricks, are guilty of the following violations of the responsible conduct of research defined in the RCR guidelines of TENK:

- Falsification (research misconduct)
- Reporting research results and methods in a careless manner, resulting in misleading claims (disregard for the responsible conduct of research)
- Misleading the general public by publicly presenting deceptive or distorted information concerning one's own research results or the scientific importance or applicability of those results (other irresponsible practices).

The investigation committee leaves it for the Rector to assess if the researchers' conduct has been intentional. If the Rector finds that the conduct has not been intentional, the conduct noticed as falsification in the report only fulfils the definition of disregard for the responsible conduct of research. The investigation committee reminds that regardless of the forthcoming decision on intentionality, the conduct of the suspects has been grossly negligent and indifferent.

2.3.Supplementing the investigation

On 11 February 2019, the Rector requested the investigation committee to supplement its investigation considering the SR Article. The committee was requested to assess if the article violates the responsible conduct of research and, if it does, specify the type of violation for each writer. In comparison to the authors of the Validation Paper, Oliver Hendricks had been left out and Stephen Croucher and Ole Franz had been included as new authors.

The Rector requested the investigation committee to specify its investigation also in terms of the ethical review and the research permits and to present in more detail for each alleged suspect if a violation has taken place, and, if yes, in which category of violation the suspect is guilty of as well as give a justified evaluation of the nature, seriousness and recurrence of the violation.

The Rector also prompted Gilbert to provide the documentation requested by the investigation committee, or, alternatively, inform the committee if any required research permission or ethical review is missing.

To clarify the role of Croucher and Franz in the alleged RCR violation, the Rector started an investigation proper on 4 March 2019. The purpose of the investigation was to clarify if Croucher and Franz were guilty of an RCR violation and to give a justified assessment of the nature, seriousness and recurrence of the conduct specified separately for both researchers. In this situation, a separate preliminary inquiry was considered to be unnecessary and to delay the process. The Rector appointed the same investigation committee to perform the investigation.

2.4.Content of Final Report 2

2.4.1. General

The investigation committee submitted the authors one statement request for the Validation Paper and another for the SR Article. The authors of both articles received both of the statement requests. The statement request concerning the Validation Paper requested each author to clarify their contribution, asked for more information about the research permits and requested the authors to comment on the conclusions presented by the investigation committee in Final Report 1.

The statement request concerning the SR Article dealt with differences between the Validation Paper and the SR Article, the contributions of authors, the applicability of conclusions presented in Final Report 1 to the SR Article, research permits, and how the new authors were informed of the

ongoing investigation and the conclusions of the investigation committee. All authors responded to the questions.

In addition, the investigation committee still tried to clarify the research permit matter by making an information request to KSSHP on 7 March 2019. The committee asked to see all statement requests submitted by Leona Gilbert from 2014 to 2019.

2.4.2. Responses of Croucher, Franz, Quevedo-Diaz, Meriläinen and Pirttinen

In their responses, the authors consistently explained that they had a limited role in the research, on which the Validation Paper and/or the SR Article were based, and in the writing of the articles.

2.4.3. Garg's response

Garg told to have participated in the Validation Paper for all other parts than the supervision of the research team and the acquisition of research permits. Garg also submitted four attachments, which included raw data, an excerpt of the ISO 15189 standard, descriptions of other Lyme disease tests, and the completion instructions of an IgG test. Garg also submitted the common response of the authors, which will be discussed below.

2.4.4. Gilbert's response

Similar to Garg, Gilbert submitted the authors' common response and the same four attachments. In addition, Gilbert submitted her own response and correspondence about research permits and discussions with Oliver Hendricks.

Gilbert stated that differences in the Validation Paper are related to the collection of ELISA data, statistical analyses, the removal of SPA data, causal reasoning, and an epidemiological search strategy.

According to Gilbert, required ethical reviews for the Validation Paper were acquired from Germany, Denmark and the United States. The research subjects gave a consent to participate in the study and the serum samples were anonymised before making the ELISA tests. Permits for the SR Article were acquired from Germany and the United States. Gilbert did not consider the statement requests submitted to KSSHP relevant.

According to Gilbert, anonymised leftover serum was used in the study.

According to Gilbert, the Medical Research Act and the Act of the Medical Use of Human Organs and Tissues do not require an ethical review for research that uses anonymised human samples taken earlier, such as in the research reported in the Validation Paper and the SR Article. Gilbert told to have contacted Legal Services of the University of Jyväskylä before starting the research. Legal Services gave its instructions in the matter after consulting the KSSHP Ethics Committee, the PSSHP Ethics Committee and TUKIJA. According to Gilbert, she was instructed that the permit of KSSHP would not be needed for using the serum samples for the planned use. However, Legal Services

instructed Gilbert to ask yet from Valvira if a permit to implement the research should be requested from it.

2.4.5. The common response of the authors

Final Report 2 states, at a general level, that the common response of the authors particularly comments on the following sections of Final Report 1: 8.2 Calculation of performance parameters, 8.3. Utilizing the novel test for an epidemiological study, 8.4 Other considerations concerning test performance and medical interpretations, 8.7 Scientific Reports article, 9.7 Summary of the conclusions and 10.2 Proposals on how the consequences of the violation should be rectified.

2.4.6. Contributions of authors

The investigation committee has compiled a table on the participation of authors to specify how each author has participated in the research and the writing of the article. As a summary, the committee states that only Gilbert and Garg have participated in practically all sections. The contribution of Meriläinen and Franz has been the smallest. The contribution of Pirttinen, Croucher and Quevedo-Diaz has been insignificant in sections recognised as problematic.

2.4.7. Sufficiency of ethical reviews

According to the investigation committee, the essential question is that if the research, conducted with serum samples taken before the start of the research, can be considered as medical research and if it, thus, requires an ethical review. According to the investigation committee, Finnish legislation on medical research is based on the Convention of the Council of Europe on Human Rights and Biomedicine. The agreement stipulates that a preliminary ethical review and an approval in advance are requirements of research on humans. In Finland, these requirements have been presented in section 3.2 of the Medical Research Act.

Gilbert has pleaded that her research was justified based on the Act of the Medical Use of Human Organs and Tissues, because the samples did not contain personal data. The investigation committee states that section 20 of the Act enables surrendering tissue samples with permission from the health care unit, but the permission does not free the researcher from the ethical review obligation. Furthermore, the committee states that the investigated study has been made with serum samples. Serum is not tissue referred to in the Act of the Medical Use of Human Organs and Tissues, which means that the Act does not apply to research reported in the Validation Paper in the first place.

The report of the investigation committee states that there have been some contradictions in relation to the definition of medical research. The legal counsel member of the investigation committee submitted a separate clarification on the definition of medical research and the scope of application of the Act of the Medical Use of Human Organs and Tissues, the Blood Service Act and the Medical Research Act. To understand the relationships between the Acts and their scopes of application requires in-depth knowledge of the legislation and used medical concepts. The legal counsel member mentioned that it has been stated, for example, in the legislative history of the Biobank Act that the use of samples taken before the start of a research would not require an ethical

review. The stand of the investigation committee is that a sample-based study is medical research and an approval of the ethics committee in compliance with the Medical Research Act, Section 17, must be applied for it. According to the investigation committee, this is an established practice in Finland.

In the previous phase of the research, the authors had informed the investigation committee that Finnish samples had been used in the study. The committee knew that Gilbert had applied for an ethical review for some studies from the KSSHP Ethics Committee. The investigation committee made an information request to KSSHP on the statement requests Gilbert had submitted in 2014–2019. In the information request, the committee justified why it should see also the confidential parts of the statement requests, in practice, the attached research plans.

KSSHP informed the investigation committee that Gilbert had made several statement requests for the same research. The names of the studies strongly alluded to the study of the Validation Paper, but because the investigation committee did not receive the research plans from KSSHP, it was not possible to confirm this conclusively. Gilbert did not hand over the research plans either. She has consistently claimed that the statement requests are not connected to the Validation Paper. The perception of the investigation committee is that Gilbert refuses to hand over the research plans because they would reveal her to have conducted medical research without an ethical review. The investigation committee concurred with KSSHP's recommendation about that the Rector as the representative of Gilbert's employer should request to see the research plans.

2.4.8. Differences between the Validation Paper and the SR Article; the suitability of earlier conclusions to the SR Article.

The investigation committee states that the Validation Paper and the SR Article are substantially based on the same research. The purpose of the Validation Paper is to develop and evaluate a test method for observing IgM and IgG antibodies. The SR Article goes a step further because its purpose is to prove a causal relationship between patients who suffer from tick-borne illnesses and polymicrobial infections. The SR Article does not anymore describe the test validation done in the Validation Paper. However, the data of the whole SR Article depends on the results of a test whose validation has been found problematic.

The investigation committee states that the problems of the test validation have been discussed in Final Report 1. The committee repeats its earlier observations and states that the deficiency of case definitions and the calculation of performance parameters as combinations instead of calculating them separately are problematic. Without the background data of patients, it cannot be known how universally the samples represented the population. Moreover, when looking at the group "healthy", the data even seems clearly doubtful.

The investigation committee states that the conclusions the authors present in the Validation Paper:

> *"Outstandingly large immune responses to other microbes and Borrelia antigens indicated the profound polymicrobial nature of tick-borne diseases."*

"Figure 3 suggested that Lyme symptomatic patients suffer from polymicrobial infections (multiple infections) where existence of a microbe may pre-dispose a patient to colonization by other microbes."

"Evidently, positive immune responses to Borrelia antigens either in an individual morphology or in combination, predisposed patients to multiple other microbes (figures 6B and 7B)"

and the claims of the SR Article referring to polymicrobial infections in patients with tick-borne diseases, such as:

"Outstandingly large immune responses to many other microbes and Borrelia signified the profound polymicrobial nature of tick-borne diseases (Fig. 4)"

"Our findings regarding the presence of polymicrobial infections at all stages of TBD further supports the causal relationship between TBD patients and polymicrobial infections (Fig. 2)"

are unfounded.

The reason for this is the lack of clear case definitions in all processed patient groups, and a selection bias in the "healthy" category.

The selection of patients and the description of the selection are not sufficient to justify the conclusions.

The investigation committee presents literary references about a conventional validation of a diagnostic test (see Final Report 2, page 12) and, in the referred instructions, identifies sections that conflict with which the conduct of the authors. These sections deal with the selection of research participants, their representativeness, and the principles of comparing new test and reference test.

2.5.Conclusions of Final Report 2

The investigation committee reminds that even though each member of the research team is responsible for observing the responsible conduct of research, Meriläinen, Franz, Croucher, Pirttinen and Quevedo-Diaz have had only a limited opportunity to understand the serious problems of sample selection and test validation. Therefore, the committee considers that the conduct of these authors has been negligent but does not meet the essential criteria of a violation of the responsible conduct of research. In addition, there is no reason to change the earlier interpretation to vindicate Oliver Hendricks.

The investigation committee considers to have proven that Gilbert and Garg carried main responsibility for the project. According to the committee, they are guilty of

- research misconduct, in more detail, falsification

- disregard for the responsible conduct of research, in more detail, reporting research results and methods in a careless manner, resulting in misleading claims

- other irresponsible practices, in more detail, misleading the general public by publicly presenting deceptive or distorted information concerning one's own research results or the scientific importance or applicability of those results.

The investigation committee reminds that a research misconduct must be deliberate. According to the understanding of the investigation committee, it is still improbable that the conduct of Gilbert and Garg would have been unintentional. However, if the Rector would end up to find no deliberateness, Gilbert and Garg can be considered to be guilty of disregard for the responsible conduct of research and other irresponsible practices.

2.6.Rector's hearing of the parties

After receiving the investigation committee's Final Report 2, the Rector gave the parties an opportunity to be heard. Croucher and Franz were not heard for the Validation Paper and Final Report 1, because they did not participate in the writing of the Validation Paper or the research resulting in it. A response was requested first from Gilbert and after that from other authors. The parties were requested to comment if they had anything to add to the evidence presented in the final report and if they agreed with the investigation committee on the definitions of RCR violations.

2.6.1. Gilbert

Gilbert disputed to be guilty of an RCR violation. She considered to have used operating methods acknowledged by the science community and methods that have been widely used in other peer-reviewed studies. According to Gilbert's view, it is not wrong to use methods that differ from the methods possibly used by others. Gilbert remarked that the earlier response had also referred to a publication whose author is one of the members of the investigation committee. The publication has used the same methods as she has used in the Validation Paper.

Gilbert repeatedly noted that the investigation committee has been biased and unskilful, has operated inappropriately, and has purposefully misled the investigation.

Gilbert denied the committee's view about that it would be an established practice to require an ethical review for a sample-based study. As for the ethical review, Gilbert stated that otherwise than what is mentioned in the final report, she requested a statement from KSSHP twice, in 2016 and 2017. Only one of the statements was negative and the other conditional. Gilbert also mentioned in her statement that she tried to clarify what kind of permits or preliminary reviews was required, or if they were required at all, when the question was about pseudonymised serum samples. According to Gilbert's understanding, necessary permits had been acquired in the United States in connection of collecting the original samples. She clarified the matter from the KSSHP Ethics Committee (emails on 12 and 18 March 2013). The matter was also inquired from the PSSHP Ethics Committee and TUKIJA, whose interpretation was that, based on Finnish law, no ethical review is required because the samples are from a serum bank, they were collected in the United States and they had a positive ethical review statement from the Penn State Hershey College of Medicine. In addition, it was not even possible to request a statement after the start of the research. Gilbert was instructed to

contact the Valvira (National Supervisory Authority for Welfare and Health) legal counsel to ensure that Valvira does not require an approval for conducting the research.

In the final report of the investigation committee, the committee concluded that the titles of the study's statement requests suggest that the requests were connected to the Validation Paper and the SR Article, in which case the study would have been conducted against KSSHP's negative decision in 2017. According to Gilbert, the study had been completed already in 2016. However, she does not detail in which study she refers to here. According to Gilbert, the statement requests and the investigated papers are not connected to each other. According to her statement, Gilbert has not submitted her research plans to the investigation committee because she does not trust they would be kept confidential. Instead, Gilbert told she will submit the research plans to TENK, which then would be able to notice that the investigation committee was wrong. According to Gilbert, Garg participated in the writing of the statement requests.

The final report stated that the raw data of completed tests had not been submitted and that the data has been falsified. According to Gilbert, raw data is never included in the reference material purchased for the validation of test kits. According to Gilbert, this demonstrates the investigation committee's lack of competence in the standards of this type of research.

The final report states that the selection and description of patients in the Validation Paper do not justify the presented results. According to Gilbert, the editors of different publications and numerous researchers have a different opinion.

In her statement, Gilbert criticises that the conclusion of the final report is that only Gilbert and Garg have been found guilty of an RCR violation and the other authors of negligence. She also criticises that the results of the investigation should be submitted for information to the institutions of other authors. Here she refers to a section of TENK's RCR guidelines, which says that sanction for a violation must be in just proportion to the severity of the violation.

Gilbert criticises emphatically the sections of the final report that define where the investigation results should be submitted.

Gilbert insists that the Rector must find all authors not guilty of RCR violations and decide on possible consequences related to an unfounded RCR notification.

Gilbert also notifies that they will make an appeal if any negative consequences will result to them from the Rector's decision. According to her, the investigation committee has not been fair and unbiased, and information related to the investigation has not been distributed equally to all participants. The matter has not been dealt with in a competent and prompt manner. Because of deficiencies in the investigation, also principles in compliance with the European Code of Conduct for Research Integrity have been breached.

2.6.2. Croucher

Croucher stated that he supported Gilbert's team in the SR Article in statistical analyses and helped to edit the article and its tables, but did not participate in the laboratory work, analysis, the acquisition of an ethical review, and the collection of data. He stated that, in his opinion, the RCR

investigation does not concern the statistical methods of the SR Article. He did not consider to have operated negligently. Instead, he found the claim insulting.

2.6.3. Franz

Franz stated that he did not participate in the Validation Paper and did not know about it before the contact of the investigation committee. Therefore, he was not aware of any ethical problems in research conducted by the Gilbert's team. Instead, Franz described to have participated as a student in an assistive role in the preparations of the SR Article. He told he had relied on that the experienced principal investigator had acquired necessary permits and knew how to conduct research appropriately. Franz told that he had a conception that it would not be possible to publish the article in the Scientific Reports journal if it had problems with permits or research methods. He told his contribution to be tests, the making of a literary review and proofreading. Franz requested to consider that it should have been possible to trust the principal investigators (referring to Garg and Gilbert) and that Gilbert and Garg should have told him about the RCR investigation of the Validation Paper when asking him to join. In his decision, the Rector should pay attention to the protection of persons who were not aware of the problems and were drawn into writing the SR Article.

2.6.4. Garg

Garg's key argument was that the investigation committee's work is not based on scientific research but opinions. According to Garg, the final reports of the investigation committee do not include references to scientific articles, decrees or regulations. According to him, the work of Gilbert's research team is based on peer reviews, has got a lot of citations, and the articles have been downloaded and shared a lot in social media. According to Garg, their research results have endured the test of time and general opinion. According to Garg, the question is about a conflict between schools of thought, and the investigation committee has not been able to scientifically prove that there would be anything unethical in the research of Gilbert's team. He pleads with the Rector to demand the investigation committee to provide references to scientific sources in order to support their views on acceptable and non-acceptable methods.

Garg considered to have been able to prove undoubtedly that the methods he has used are not against the responsible conduct of research. In addition, he emphasised that he has not dealt with the statement requests to KSSHP. He states that the consequences of the investigation are very detrimental to his career and the reputation of the university.

In addition to the statement, Garg also submitted the same attachments as in the response to the investigation committee.

2.6.5. Meriläinen

Meriläinen appealed to that the investigation committee has not provided scientific evidence in its final reports but has presented personal opinions without proper evidence or citations to scientific articles. She referred to that the SR Article has gone through a peer review. Meriläinen considers

that other authors than Garg and Gilbert have not dealt with the alleged RCR violations. She did not agree with the investigation committee's assessment that Garg and Gilbert would be guilty of an RCR violation because the committee has not provided convincing evidence on the matter. Meriläinen considers that the recommended consequences do not follow the European Code of Conduct for Research Integrity and the TENK guidelines on that the violation must be in just proportion to the severity of the violation. In Final Report 2, Meriläinen, Franz, Croucher, Pirttinen and Quevedo-Diaz are found guilty of negligence but not an RCR violation. However, the end result of the investigation is planned to be sent to such parties that this would harm the authors. She considered that, with the wide publication of the report, the investigation committee intents to punish also the researchers who have been found innocent. Meriläinen remarks that the European Code of Conduct for Research Integrity requires that if suspects are found not guilty of an RCR violation, appropriate corrective means must be taken. Meriläinen remarked that she has not signed the Validation Paper or the SR Article as an employee of the University of Helsinki. At the end, Meriläinen criticises that Final Report 2 was sent first to Gilbert.

2.6.6. Pirttinen

In her response, Pirttinen told to have participated in the writing of the article only in the "Materials and methods" section for the ELISA technology. She does not consider to be guilty of negligence because she had performed her duties according to given instructions. Pirttinen had joined the Gilbert's research team as a master's student and writer of a master's thesis and did not question authorities. According to Pirttinen, she had been assured that everything was in order with the permits. She explains to have left the Gilbert's team when the Validation Paper was still in progress. Pirttinen considers that it would be unfair to report about the investigation to all parties mentioned in the report because it has already been discovered that all of the authors are not guilty of an RCR violation. If this is done, it should be specified very clearly who are guilty of an RCR violation and who are not.

2.6.7. Reimer

Reimer stated that he fully agrees with the conclusions presented in Final Report 2.

2.7. Rector's additional questions to the investigation committee

When considering the decision, the Rector noticed that the investigation committee had not justified all of its views meticulously. The deficiencies related especially to the common response of the authors, which was submitted both to the investigation committee and the Rector in the preparation phase of Final Report 2. In Final Report 2, the committee had noted the content of the response on the title level but had not actually commented on the claims the authors presented for their defence. The committee was asked 12 additional questions.

The investigation committee stated that they have nothing in itself against the reference tests the authors have listed in their response. Instead, the ambiguity of case definitions and the erroneous calculation of performance parameters are problematic, and the authors' conduct does not match

the basic principles or international guidelines to which the authors refer in order to support the conduct of their research.

The investigation committee admits that detailed patient data are often missing in similar studies. However, basic data that are crucial for the examined topic must be provided. The authors' research lacks all necessary information about the origin on the samples and if an exposure to ticks was possible in the first place.

In its answers, the investigation committee clarifies the difference between a comparison of two tests (analytical test validation) and a subsequent assessment of the test's clinical performance. In the Validation Paper, the question has been about the first phase, that is, the comparison of tests. The comparison of tests requires that each tested variable is assessed separately with a new test and the result is compared to an existing test or an international gold standard test. The investigation committee emphasises that, for example, the IgG test results must be compared to the IgG test results of both tests (the new test and a test known to be functional). Conclusions on the functionality of the test must be made one variable at a time. You cannot take the immunity response indicated by a random test as a reference point. An analytical test validation must be completed before it is possible to move to research settings in which it is possible to assess the combined clinical performance of analytically validated tests. Also here, the investigation committee describes unambiguously that the instructions, to which the authors refer to support their conduct, do not support the calculation of combined performance parameters in an analytical test validation.

In its answers, the investigation committee also justified in detail and with references why serology is not suitable for finding opportunistic CMV and EBV infections even though the authors claim so.

The investigation committee refutes the authors' claim that the methods used by the authors are approved by the science community. The methods that are not supported by the presented source references or that are not genuine scientific disputes are the following:

- Unknown origin of specimens so that their representativeness could be assessed

- Incorrect manner to calculate the test performance (as presented in the final report, table 1)

- The authors' inability to prove why the data seem to have a strong selection bias or why some of the seroprevalence figures are exceptional.

The specification provided by the investigation committee also includes a more detailed analysis where the authors have acted against the guidelines to which they refer.

As a conclusion, the investigation committee stated that the source references presented by the authors do not support the way their research was conducted. Answering the additional questions does not give a reason to change the conclusions presented earlier in the final reports.

3. REASONING OF THE RECTOR'S DECISION

The investigation has been long-lasting, it has had multiple steps, and the content matter has been demanding. However, based on the two final reports, the submitted responses and the specification requested from the investigation committee, it is possible to make conclusions. The reasoning is

presented topic-specifically.

3.1. Author-specific assessment

In Final Report 1, the investigation committee presented as its conclusion that all the authors were guilty of an RCR violation. This conclusion was based on the basic assumption that all authors of an article are responsible for its content, which is true as such. At this stage, the investigation committee was asked to supplement the investigation and evaluate the share of each author separately. The request was supported by the TENK guidelines, which require a reasoned assessment concerning the nature of the violation as well as a reasoned assessment concerning the severity of the violation and its frequency of occurrence.

Upon the request of the Rector, the investigation committee thoroughly compared the participation of each author and noted that only Leona Gilbert and Kunal Garg had overall responsibility and understanding on the implementation of the research. The Rector has no reason to doubt the analysis of each author's participation presented by the investigation committee in Final Report 2, pages 8–9. It was not possible for other authors to clarify the problematic parts of the research and they did not have all the data at hand. Ole Franz, who joined the team only for the SR Article, has expressly told that he was not even informed of the initiated RCR process. The Rector sees that in these circumstances the conduct of other authors than Garg and Gilbert cannot be considered negligent.

3.2. Occurrence of an RCR violation

The authors have, especially in their common response, aimed to present counterarguments in order to support their conduct on the basis of various guidelines and standards within the discipline. The authors have also argued that the standpoint of the investigation committee is based on mere opinions and cannot be justified scientifically and with references. The authors have also pleaded to that the SR Article is peer-reviewed.

However, already in Final Report 2 the investigation committee has itemised the guidelines and specific parts whose violations Garg and Gilbert are guilty of.[5] The committee has further specified the content of guidelines in relation to the authors' conduct by answering additional questions submitted by the Rector. Garg and Gilbert's view that the investigation committee's standpoint would be based only on opinions without scientific evidence is not correct. The investigation committee has been able to itemise and explain reasons for their standpoint and refute the counterarguments of Garg and Gilbert.

Especially after the supplementary answers of the investigation committee, it is clear that the source references presented by the authors do not support their conduct. The investigation committee's clarification on the differences between the comparison of tests (analytical test validation) and the assessment of the test's clinical performance, which takes place after the test comparison, has been

[5] Final report 2 s. 12-13.

especially demonstrative. The investigation committee has also unanimously noted that the proceedings of the authors have not been recognised by the science community and that there cannot be genuine conflicting interpretations or scientific debate on the erroneousness (see itemisation in section 2.7).

It is true that the SR Article is peer-reviewed. However, peer reviews are not infallible. It must be noted that the SR Article is based on the Validation Paper. In this case, probably some background assumptions (the most crucial being the earlier deficient test comparison / analytical test validation) have been left unopened in the peer review, which may explain why the SR Article has passed the peer review. Passing a peer review in itself is not a sufficient justification to overrule the RCR allegation. Instead, the matter must be solved based on the investigation committee's thorough investigation. The committee has also pointed out claims that lack scientific reasoning in the SR Article.

The Rector considers it to be proven that Gilbert and Garg are guilty of an RCR violation as presented in Final Report 2.

3.3. Nature of the conduct of Gilbert and Garg

At the beginning of the investigation, the target was the Validation Paper, which was published only on the company's website. Apparently the Validation Paper was available for a few months. However, it had been noticed at least by an Ålandian researcher and a Danish researcher. The latter contacted Hendricks after considering the content of the Validation Paper problematic. At the end of the first phase of the investigation, Garg, Gilbert, et al., had published a new article based on the Validation Paper.

When assessing the nature of the conduct of Gilbert and Garg, it is noteworthy that they continued to process further the material under a suspected RCR violation and published a new article during the investigation process. The investigation committee has expressed an assessment that the errors in the conduct of Garg and Gilbert cannot be made accidentally. It must also be remembered that Oliver Hendricks had informed Garg about the erroneous processing of SPA cohort already in 2015. In addition, Hendricks had, before the publication of the SR Article, notified Gilbert about that the earlier Validation Paper and the new manuscript based on the Validation Paper, suffered from a selection bias. Regardless of Hendricks's remark and the ongoing RCR investigation, Garg and Gilbert knowingly continued their activities and published the SR Article. Especially when considering Gilbert's long experience, she should have understood that she needs to fully correct the reported deficiencies and, if necessary, carry out the research again. Changes made to the SR Article have not been sufficient to remove the fundamental problems of Garg's and Gilbert's conduct.

Throughout the investigation, Gilbert and Garg have presented a plenty of source material and bibliographical references. The investigation committee noted already at an early stage of the investigation that bibliographical references presented at that point were not decisive for the key issue. At the end of the investigation, the investigation committee has been able to prove that the discipline-specific guidelines and other studies in the field of expertise, presented by Gilbert and Garg as their defence, do not in fact support the way Gilbert and Garg conducted the research. The Rector's conception is that the submitting of an abundance of claims and references that seem superficially justifies but which, after an overall assessment of the content, prove to be unfounded

and irrelevant alludes to an attempt to take the investigation committee's and Rector's focus away from the main point. It is not plausible that the researchers would sincerely interpret the internal guidelines of their discipline this erroneously or that they would fail to assess when other researchers' conduct is comparable with their own conduct and when not. For the abovementioned reasons, the conduct of Garg and Gilbert must be considered intentional and to fulfil the essential elements of research misconduct.

3.4. Ethical review and research permits

The situation of an ethical review required for a sample-based study is still unclear. The investigation committee's clear view is that a sample-based study requires a preliminary ethical review. The committee has concluded that the research permit granted by the owner of samples collected earlier substitutes the consent of research subjects, but not an ethical review of an ethics committee. On the other hand, the university's Legal Services consulted with KSSHP, PSSHP and TUKIJA and ended up to an answer that no ethical review is needed. In this respect, the conduct of Gilbert and Garg cannot be criticised. Instead, the matter clearly requires national discussion and harmonisation of practices.

A separate issue is that it has not been possible in the investigation proper to reliably clarify the connection between the discussed research and the statement requests submitted by Gilbert to KSSHP. According to the Rector's conception, the KSSHP Ethics Committee has the best understanding to interpret the matter.

3.5. Impartiality and duration of the investigation

The authors have presented views that the investigation has not been performed impartially and promptly. Impartial and simultaneous informing of the parties has been complicated by numerous confidentiality claims presented in the matter, concerning also the handing of gathered material to other authors. The processing of the confidentiality claims has also delayed the processing of the matter. In addition, the investigation has been prolonged because of the publication of the SR Article, because it has expanded the investigation. The Rector's conception is that the investigation committee and JYU staff have operated impartially in the solving of the matter.

4. PUBLICATION OF THE DECISION AND FURTHER ACTIONS

4.1. Reasoning

According to the RCR guidelines, the investigation committee's final report needs to contain a proposal concerning the publishing of the conclusions of the final report and possible proposals on how the consequences of the violation should be rectified. The decision must be communicated to

the person alleged of misconduct, to the instigator of the allegation as well as to the Advisory Board on Research Integrity.

Since the conclusion of the investigation is that the misconduct constitutes a violation against the responsible conduct of research, according to the TENK guidelines: "measures must be taken to publish the findings of the final report in a manner deemed appropriate by the committee and when possible, at least in the publication channel where the fraudulent research findings or results based on fraudulent means have already been published."

In its Final Report 2, the investigation committee has named the Nature Publishing Group's journal Scientific Reports, in which the SR Article was published, as the most important publication channel. According to the Rector, this procedure should be followed. The decision will be sent for information to Scientific Reports, which will decide on the publishing actions.

The RCR guidelines state the following about the informing of employers and financers: "If the person alleged of misconduct works in a research organisation other than the one in which the allegation has been handled or receives external research funding, the employer or the funding organisation must be notified of the decision." Therefore, this decision will be submitted, in addition to the University of Jyväskylä, to the organisations named in the affiliations section of the SR Article. For those found not guilty, the accompanying letter will clearly state that the person is not guilty of an RCR violation.

In the acknowledgements section of the SR Article, the following parties are named to have supported the research: Schwartz Foundation, the Finnish Innovation Funding Agency TEKES TUTL project number 774/31/2015, and the Scientific Grant Agency of Ministry of Education, Science, Research and Sport of the Slovak Republic and Slovak Academy of Sciences (project Vega 2/0139/16). Because the RCR guidelines obligate to notify also financers, these parties must be informed.

The investigation committee has noted that it will not deal with the marketing or authority permits of the Tickplex test. Nevertheless, the investigation committee has recommended the final results of the investigation to be sent for information to the Finnish Competition and Consumer Authority and Valvira (National Supervisory Authority for Welfare and Health). The Rector finds this proposal justified, so that competent authorities can evaluate if the noticed RCR violation has an effect to Tickplex. The Rector emphasises that the investigation has not assessed the scientific validation or functionality of the Tickplex test as a whole. Instead, the investigation has been targeted only to the Validation Paper and the SR Article. The investigation has not clarified other possible evidence to prove the functionality of Tickplex.

The final report will be sent for information to the KSSHP Ethics Committee. Regardless of requests, Gilbert has not submitted the research plans related to the statement requests to KSSHP. KSSHP will be requested to make a statement about its conception if Gilbert has conducted medical research against a decision of the KSSHP Ethics Committee.

Helsinki Challenge will be informed that the RCR investigation has not been targeted to the Pockit test.

A bulletin about the decision will be published on the JYU website.

4.2. List of recipients

Summary of the recipients of this decision:

Leona Gilbert
Kunal Garg

Leena Meriläinen, Marco Quevedo-Diaz, Oliver Hendricks, Heidi Pirttinen, Stephen Croucher and Ole Franz

Finnish Advisory Board on Research Integrity (TENK)

Editors of the Scientific Reports journal

Slovak Academy of Sciences / Biomedical Research Center SAS; University of Southern Denmark / Faculty of Health Sciences; Massey University, Wellington, New Zealand / School of Communication, Journalism and Marketing.

Schwartz Foundation, Business Finland, the Scientific Grant Agency of Ministry of Education, Science, Research and Sport of the Slovak Republic, and Slovak Academy of Sciences

Finnish Competition and Consumer Authority, Valvira (National Supervisory Authority for Welfare and Health)

KSSHP Ethics Committee

Organisers of the Helsinki Challenge competition (information that the RCR investigation has not been targeted to the Pockit test)

Mats Reimer

Members of the investigation committee

5. APPEALING

A party dissatisfied (the person alleged of misconduct or the instigator of the allegation) with the rector's decision, with the procedures adopted in the preliminary inquiry, in the investigation proper or with the final report, may request a statement from TENK within six months of the date of notification. The request must be reasoned and it must detail the issues for which the statement is requested. The statement must be requested no later than six months from the decision.

6. APPENDICES

Final Report 1
Final Report 2
The common response of the authors
The investigation committee´s answers to additional questions submitted by the Rector