The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/152300

Please be advised that this information was generated on 2018-02-03 and may be subject to change.
How GPs value guidelines applied to patients with multimorbidity: a qualitative study

Hilde Luijks, Peter Lucassen, Chris van Weel, Maartje Loeffen, Antoine Lagro-Janssen, Tjard Schermer

ABSTRACT

Objectives: To explore and describe the value general practitioner (GPs) attribute to medical guidelines when they are applied to patients with multimorbidity, and to describe which benefits GPs experience from guideline adherence in these patients. Also, we aimed to identify limitations from guideline adherence in patients with multimorbidity, as perceived by GPs, and to describe their empirical solutions to manage these obstacles.

Design: Focus group study with purposive sampling of participants. Focus groups were guided by an experienced moderator who used an interview guide. Interviews were transcribed verbatim. Data analysis was performed by two researchers using the constant comparison analysis technique and field notes were used in the analysis. Data collection proceeded until saturation was reached.

Setting: Primary care, eastern part of The Netherlands.

Participants: Dutch GPs, heterogeneous in age, sex and academic involvement.

Results: 25 GPs participated in five focus groups. GPs valued the guidance that guidelines provide, but experienced shortcomings when they were applied to patients with multimorbidity. Taking these patients’ personal circumstances into account was regarded as important, but it was impeded by a consistent focus on guideline adherence. Preventative measures were considered less appropriate in (elderly) patients with multimorbidity. Moreover, the applicability of guidelines in patients with multimorbidity was questioned. GPs’ extensive practical experience with managing multimorbidity resulted in several empirical solutions, for example, using their ‘common sense’ to respond to the perceived shortcomings.

Conclusions: GPs applying guidelines for patients with multimorbidity integrate patient-specific factors in their medical decisions, aiming for patient-centred solutions. Such integration of clinical experience and best evidence is required to practise evidence-based medicine. More flexibility in pay-for-performance systems is needed to facilitate this integration. Several improvements in guideline reporting are necessary to enhance the applicability of guidelines in patients with multimorbidity.

INTRODUCTION

Multimorbidity, the existence of multiple chronic conditions within a particular patient, is very common. It has a substantial impact on healthcare utilisation and costs and on patient outcomes, putting great demands on global healthcare. The care of patients with multimorbidity is complex, requiring coordinated care, management of chronic diseases and medication, which may be challenging for practitioners having only short consultations available.

Evidence-based medicine and guidelines have improved the quality of healthcare through better diagnostic and therapeutic treatment decisions. However, their application can be problematic when a patient has more than one disease, as guidelines are generally written for single diseases, with limited suitability for multimorbidity. A focus on single disease guidelines brings the risk of ‘siloing of care’ for patients with multimorbidity. National Institute for Health and Care Excellence is preparing a guideline on...
the clinical assessment and management of multimorbidity.\textsuperscript{15} The wide spectrum of multimorbidity is a practical limitation to develop guidelines for disease combinations. However, guidance in how to combine or prioritise guideline recommendations or when to stop recommended treatments could improve the care of patients with multimorbidity, but is missing in current guidelines.\textsuperscript{14} \textsuperscript{16} \textsuperscript{17}

Given the high prevalence of multimorbidity, all clinicians may struggle with guideline application in patients with multimorbidity. However, generalists who provide care to patients with any disease type without prioritising one disease over another beforehand may specifically have well-formulated ideas on this issue. It is to be expected that general practitioners (GPs) would have extensive experience in managing multimorbidity despite a gap in evidence-based guidance, and have developed practical solutions to deal with this gap. Many papers investigating practitioners’ experiences with multimorbidity management, however, had a focus on the challenges they faced in the care of patients with multimorbidity, and not on their experiences with or solutions for handling guidelines in these patients.\textsuperscript{18}

In The Netherlands, the Dutch College of General Practitioners (DCGP, Nederlands Huisartsen Genootschap (NHG)) has produced evidence-based guidelines covering 70–80\% of the conditions presented in primary care. GPs play a leading role in the development and critical appraisal of these guidelines, of which 92 are currently available, and of which approximately one-third concern (potentially) chronic conditions.\textsuperscript{19} DCGP guidelines cover diseases, symptoms and risk factors, and are established in a team composed of GPs, both with and without specific expertise concerning the topic, and representatives of other professional groups. Dutch GPs receive capitation payment, as well as a limited additional payment for the management of chronic diseases such as diabetes and chronic obstructive pulmonary disease when quality indicators are met. The DCGP’s guidelines are a main source of reference of diagnostic and therapeutic quality indicators.

Our objective was to explore and describe the value GPs attribute to medical guidelines when they are applied to patients with multimorbidity, and to describe which benefits GPs experience from guideline adherence in these patients. Also, we aimed to identify limitations from guideline adherence in patients with multimorbidity, as perceived by GPs, and to describe their empirical solutions to manage these obstacles.

We found that their main aim was to apply a patient-centred approach.\textsuperscript{20} It was anticipated that the role of guidelines as a potential facilitator or barrier of the care delivery to patients with multimorbidity might be mentioned. In the iterative qualitative process, in which data collection and analysis alternate, the insight grew that discussions on the role of guidelines, applied to patients with multimorbidity, provided important information meriting deeper exploration on itself. This resulted in formulating the current, additional research question: exploring the value GPs attribute to guidelines for multimorbidity. This topic came up spontaneously in the first focus groups and it was probed in the following group interviews if it did not arise spontaneously again. The original interview guide was not altered. When the role of guidelines had not yet been discussed spontaneously after discussing which factors were perceived as impeding factors in the management of multimorbidity, participants were asked if they perceived guidelines as an impeding or facilitating factor in this respect. A separate qualitative analysis was performed on the same qualitative data considering the current research question. In a purposive sampling strategy, GPs from the academic network of the Radboud University Medical Center and from the personal network of the research team members were invited to participate, ‘to gain more insight into GPs’ experiences with the care for patients with multimorbidity’. They were contacted by mail and telephone. The location of their practices covered a 40-mile area around the city Nijmegen, in the eastern part of The Netherlands. Heterogeneity in characteristics such as age, sex, academic involvement and urbanisation was ensured. After having conducted four focus groups, in all of which at least one GP with an academic affiliation (GP trainer or researcher) participated, we decided to organise a fifth focus group with only non-academic GPs, since we anticipated that an academic affiliation might influence their ideas regarding the initial question and the current research question. All GPs consented to participate. Anonymity and confidentiality were ensured. According to Dutch legislation, interviewing healthcare professionals regarding their professional beliefs does not need approval of an external ethics committee. Participants were offered a gift voucher and compensation of travel expenses in appreciation of their efforts.

The focus groups were held between September 2010 and March 2011 and took place at the Radboud University Medical Center. One focus group was conducted in the practice of a research team member since this resulted in a shorter travel distance for the participating GPs. Twenty-five GPs participated in 5 focus groups, each group containing 4–6 participants. Table 1 shows their characteristics. Some participating GPs knew the moderator, the observer or other participating GPs in their focus group, whereas others did not.

Focus groups can be regarded as appropriate qualitative methods, since the group process may help to
explore and clarify views of participants, and facilitates different forms of communication, which could help in generating new insights.21

Focus group interviews and data collection
A GP senior researcher with extensive experience in qualitative research moderated the focus groups, using an interview guide (available from the authors on request). One researcher observed all group interviews and paid special attention to non-verbal communication. The observer’s field notes were used during analysis, for example, to identify non-verbally expressed (dis)agreement with other comments. The interviews were audio-taped and transcribed verbatim by a medical student.

Analysis
The constant comparative analysis technique was applied by two researchers to analyse the data for the current aims.22 Disagreement was resolved by discussion or consultation with other researchers. The transcripts were read intensively. Open coding was first applied to conceptualise the data. This was followed by axial coding, where codes were clustered, side issues were distinguished from essentials and initial concepts were checked against newly collected data. Selective coding was applied in the final analysis stage to integrate data after initial fragmentation. Invalidating examples were sought. Data collection proceeded until saturation was reached concerning the current research question, which was the case after the fifth focus group. At this stage, no new insights were gained regarding GPs’ evaluation of guidelines applied to patients with multimorbidity. ATLAS.ti (V7, Berlin, Germany) supported the analysis. Citations illustrating important points discussed needed translation, which was performed by a native English speaker translator familiar with qualitative research in healthcare. In this way, potential loss of refinement in translated citations was reduced as much as possible.

RESULTS
Overview of the results
GPs commented on the value of guidelines they perceived when applied to patients with multimorbidity, and on benefits from guideline adherence. They also described potential limitations from guideline adherence in these patients, which have led to several empirical solutions to counteract these. A point-by-point description of these discussed items is outlined below.

Value of guidelines applied to patients with multimorbidity
GPs valued evidence-based guidelines in general, and felt that their wide implementation had brought clear improvements to the quality of general practice. They especially perceived guidelines as useful in the case of younger, relatively healthy patients, particularly if they suffered just from the disease described in the guideline. Most GPs followed guidelines also for the younger and ‘healthier’ patients with multimorbidity, particularly if their multiple diseases had similar therapeutic approaches. In these cases of multimorbidity, guidelines provided guidance to medical decision-making, for example, prescription of medication (A-B). Online supplemental file 1 shows all quotations.

Reduction of patients’ perceived symptoms (pain, shortness of breath) was an important reason for GPs to adhere to guidelines in patients with multimorbidity (C, D).

Guideline adherence also helped in working transparently, enabling comparison and quality control between GPs. GPs did express a need for guidelines despite the difficulties in translating these into the practical care for patients with multimorbidity (E, F). GPs stated that it would be unrealistic that guidelines should specify for any possible disease combinations, but would feel better supported in the care for patients with multimorbidity when guidelines gave more details for diagnostic, treatment and management priorities.

Limitations from guideline adherence in patients with multimorbidity
Limited usefulness of guideline adherence in multimorbidity
There was agreement that guidelines were less useful for elderly patients and ‘complex cases’ of multimorbidity. GPs commented that guidelines were essentially not

<table>
<thead>
<tr>
<th>Sex</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (72)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (28)</td>
</tr>
</tbody>
</table>

Practice type

| Single† | 4 (16) |
| Duo or group | 21 (84) |

Urbanisation

| Rural area | 2 (8) |
| Urbanised rural area | 16 (64) |
| Urban area | 7 (28) |

GP trainer‡

| At present | 11 (44) |
| In the past | 1 (4) |
| Never | 13 (52) |

Researcher

| Yes | 5 (20) |
| No | 20 (80) |

Mean age, years (range) 50 (31–63)

Mean experience as GP, years (range) 20 (2–36)

*Sex, age, practice type and urbanisation were similarly distributed among participants in our sample as compared to the Dutch professional group of GPs.24
†Count of GPs settled solitary in a practice, that is, without employment of or professional collaboration with other GPs.
‡Trainer at the Nijmegen residency training programme, a qualification needed to supervise a GP trainee.
designed for these complex patients (G, H) and felt that in these cases implementation was not as straightforward as in younger patients (I).

A component of this limitation of guidelines was the issue of ‘prevention’. GPs felt that adherence to guideline-recommended preventative measures was less appropriate in the case of older patients with multimorbidity and patients with a limited life expectancy. This was more pronounced if these measures were accompanied by side effects. They also questioned whether similar benefits could be expected from preventative measures as for younger or healthier patients. When GPs felt less convinced of the advantages of prevention, they would put less emphasis on this topic in the consultation. A sense of acceptance of limited therapeutic or preventative benefits was expressed if it concerned older patients. (J-N).

Guideline adherence conflicts with a patient-centred approach

Despite the need for guidelines, GPs often saw good reasons to ignore guideline recommendations in individual circumstances or to omit treatments in patients with multimorbidity. Consistent guideline adherence was perceived as an impediment to deliver individualised, patient-centred healthcare to patients with multimorbidity, which emerged as GPs’ major objective in their care (described in detail in our previous paper20). This came forward in their inclusion of patients’ preferences and circumstances in their management decisions, even when this meant ignoring guideline recommendations (O). Some GPs expressed this explicitly while many agreed with such comments.

It was considered impossible to exhaustively grasp the complexity within guidelines that inevitably comes along with multimorbidity (P).

A perceived risk of working too much ‘guideline-driven’ is that items addressed in the guidelines will be automatically prioritised over patients’ other important health problems (Q).

Concerns about the applicability of guidelines in multimorbidity

Scepticism was articulated on the applicability of evidence-based guidelines in patients with multimorbidity. Concerns were expressed that patients included in research and their specific circumstances are not comparable to patients with multimorbidity. Guideline recommendations following research results are not simply generalisable to patients with multimorbidity (R, S).

Also, GPs commented that combining therapeutic regimens, originating from evidence-based guidelines written for single diseases, does not lead to an evidence-based combination for patients with multimorbidity. Guidelines can be conflicting, and often it is unclear how they relate to one another, which impedes using several guidelines for one particular patient (T, U).

Empirical solutions

The disadvantages GPs perceived from guideline application to patients with multimorbidity resulted in several practical solutions, enabling them to provide continuous healthcare to these patients. This paragraph summarises the empirical solutions mentioned.

From their experience, GPs expressed a need to rely on their ‘common sense’—a source of ‘knowledge’ that may complement the limitations of guideline application in multimorbidity. This implied making patient-centred decisions, accounting for the personal circumstances of patients with multimorbidity (V). However, relying on one’s ‘common sense’ only was not considered acceptable anymore in the current era. Guideline adherence and applying ‘common sense’ needed to be in balance (W).

One GP described that an authorised guideline is not the only source providing support to GPs in the difficult decisions they need to make in patients with multimorbidity. He suggested that regular refresher courses on complex topics could provide more knowledge and insight leading to guidance in a different way (X).

Additionally, improvements could be made in guideline reporting, to increase their value for patients with multimorbidity. A GP proposed having a ranking of importance made in recommended (preventative) measures for patients with multimorbidity, considering the seriousness of adverse results if they are not adhered to (Y). The same GP proposed, with agreement of the other GPs in his group, that guidelines should more explicitly comment on their external validity (Z). This could provide support to GPs not to adhere to guidelines for specified reasons or in specific situations—creating valid reasons to make patient-centred decisions by applying their ‘common sense’.

Another GP tried to explain to his patients the evidence underlying guideline recommendations. In a conversation on how to translate guidelines into personal treatment choices, he let these well-informed patients’ opinions influence decisions on whether or not to start new treatments—again coming to a patient-centred solution (AA).

Finally, permission to exclude patients with multimorbidity from regular pay-for-performance systems could reduce the burden of imposed but inappropriate guideline adherence, and improve the quality of care delivered to patients with multimorbidity (BB, CC). In those focus groups where the issue of pay-for-performance was discussed, GPs agreed that guideline-derived incentives for patients with multimorbidity were undesirable and inappropriate (DD).

DISCUSSION

Summary

In this paper, we explored and described how GPs value evidence-based guideline application in patients with multimorbidity, that is, patients in whom they had
several potential guidelines to follow at the same time. GPs treasure the availability of guidelines in general, but at the same time expressed that guidelines do not cover the requirements needed to deliver complex care to patients with multimorbidity. They do not give sufficient opportunities to provide the desired individualised approach in multimorbidity, which may be considered as more important than adherence to the guidelines. Recommendations from single disease guidelines are not simply generalisable to patients with multimorbidity. When GPs apply guidelines for patients with multimorbidity, they incorporate patients’ specific circumstances. Guideline-supported care to patients with multimorbidity can therefore be regarded as a good illustration of the use of the core values of primary care.23 This paper provides a new insight that, from their practical experience with patients with multimorbidity, GPs apply empirical solutions, such as balancing guideline recommendations with their ‘common sense’ and a patient-centred approach, to counteract guidelines’ pitfalls.

**Strengths and limitations**

This study was performed by applying robust qualitative methods. Focus groups were guided by an experienced moderator with familiarity with the subject discussed. Participating GPs had been invited using a purposive sampling strategy. It is possible that GPs with a special interest in complex care, such as care for patients with multimorbidity, were more inclined to attend a focus group session than GPs without such an interest. This might have increased the vivacity of discussions, but participants were not selected on this criterion. Data collection proceeded until saturation was reached. The entire analysis was performed by two researchers, using the constant comparative analysis technique, which is an appropriate technique in qualitative research if new theory is to be generated.

Focus group discussions were held in Dutch and in the context of Dutch healthcare, thus providing views of participating Dutch GPs. The results do not allow generalisations to the primary care context in general. However, the resemblance of our GP sample to the Dutch professional GP group21 does increase the transferability of our findings.22 GPs in countries with a healthcare system comparable to that in The Netherlands may experience similar problems from guideline application in patients with multimorbidity, and their practical answers to such puzzles might show similarities to the empirical solutions described in the current study. Future research should elaborate this. Some time span existed between data collection and the writing of this paper, because it had not been planned originally to produce a separate paper specifically focusing on the role of guidelines applied to patients with multimorbidity. In the mean time, the number of new publications on this theme was limited. It seems unlikely that this ‘publication delay’ influenced our findings significantly. The role attributed to comorbidity in new (Dutch) primary care guidelines was not obviously different than before our data collection.

Our research question produced new insight into a research field without much preceding literature. This originality provides the major strength of our work.

Fitting the iterative nature of qualitative research, the idea to analyse the data regarding the current research question arose gradually. Although this theme was an explicit subject of discussions, participants were not made aware of it as an additional research question beforehand. Had this been the case, participants might have been overthinking the specific issue of guideline application in patients with multimorbidity consciously, which could have resulted in the expression of beliefs that remained unrevealed now. We find it unlikely that with such a scenario participants would have expressed clearly deviant ideas from the ideas they expressed here. However, it is not possible to establish if and to what extent our results would have been expanded or altered were this research question announced explicitly.

On most of the subjects discussed, we found no obvious difference between beliefs expressed by GPs with different characteristics, with two exceptions. Discussions on the applicability of guidelines in multimorbidity, and about the empirical solutions applied to overcome the guidelines’ disadvantages, were mainly brought up by GPs with an academic affiliation. GPs without academic involvement did not express opposing views but accepted these beliefs and agreed with them in general. As a consequence, we conclude that there were no contrasting beliefs between ‘academic’ and ‘non-academic’ GPs, but that academic GPs were better able to articulate the tensions between patient-centred and guideline-directed care. This might be caused by a greater familiarity of researchers with the way guidelines are realised, and GP trainers’ custom to reflect on their own practice as they do in the GP residency programme, which makes them ‘trained’ in expressing their beliefs. This may have helped in gaining valuable insights from these participants.

It came as some surprise that the collaboration with specialists did not feature strongly in the discussions. This may be due to the structure of this study, focused on the role of guidelines, and the fact that GPs in The Netherlands identify strongly with the DCGP guidelines as ‘their own’.29 Our previous study, describing GPs’ considerations and main aims in multimorbidity management, did include GPs’ views on cooperation with specialists.29

**Comparison with the existing literature**

The findings of this study help to reflect on the adequacy of ‘guideline-based’ modern medicine from the GP perspective. Evidence-based guidelines are perceived as useful in general, but several shortcomings are experienced in patients with multimorbidity. Important problems arise from discrepancies between recommendations based on single-disease guidelines, and that what is perceived by GPs as serving a particular patient with

---

multimorbidity best. From a patient-centred work style, GPs try to achieve shared decision-making; they individualise treatments and may deliberately omit specific treatments. In the setting of a continuous clinical relationship, knowing the context of the patient informs intuitive judgements.26 This ‘knowing of the particular’ is at the heart of general practice, but may be seen as contrasting with the principles of biomedical science, where it is explained what patients have in common and ignores where they differ.27 However, the practice of evidence-based medicine requires integration of individual clinical experience with the best available external clinical evidence: good doctors need to rely on both.26–30 This integration is exactly what was expressed by our participating GPs as an empirical solution to deal with the discrepancy between guideline adherence and providing optimal care in patients with multimorbidity.

To the best of our knowledge, no previous papers specifically analysed the value of guidelines for patients with multimorbidity as it is perceived by practitioners who use them in clinical practice. A few previous papers describing how GPs deal with multimorbidity reported briefly on the value of medical guidelines in this respect. Qualitative data have been synthesised by Sinnott et al.18 concluding that mixed feelings exist on the clinical utility of guidelines.

Some previous studies demonstrated guidelines’ limited suitability in patients with multimorbidity: they showed that the frequency and consistency of recommendations accounting for patients’ comorbidity are low, and that they provide limited guidance in making treatment priorities.10–12 These constraints, which were identified in literature reviews and on merely theoretic grounds, have now been exemplified by our qualitative data.

Two original studies, focusing on GPs’ perspectives on care for older patients with multimorbidity, produced results that show similarities to our findings. Fried et al described variable beliefs regarding benefits and harms of guideline-directed care among their participants. Those who expressed concerns did so regarding the limited external validity, and the adverse events that may be caused by applying multiple guidelines. Additionally, guidelines’ target outcomes may not be more relevant for patients with multimorbidity.31 In a Dutch focus group study exploring ‘GPs’ feelings on deprescribing medication’, participants also distinguished medication prescribed for symptomatic conditions and preventative medication. They experienced a lack of information regarding risks and benefits of preventative medication in patients with multimorbidity, and felt compelled to prescribe by the present guideline.32

The difficulties experienced in practice by our participating GPs led to suggestions of how to make evidence-based guidelines more viable in patients with multimorbidity—a necessary step, since guidelines are indispensable in the current era, as was confirmed by the participants. Other papers describing barriers made some similar suggestions, for example, accounting for the patient’s context,10 30 31 33 focusing on generic instead of disease-specific outcomes,34 35 providing guidance in prioritising guideline recommendations16 17 32 and improving the external validity of clinical trials and guideline recommendations.16 36 In addition, it has been recommended to include more elderly people and patients with comorbidity in future studies,16 17 and to apply more cross-referencing between existing guidelines, in order to enhance guidelines’ usefulness in patients with multimorbidity.17 An innovative possibility is to apply the concept of ‘pay-off time’, predicting if a patient with limited life expectancy is likely to benefit from adherence to a particular guideline, by calculating the minimum time until its cumulative benefits exceed its cumulative harms.37 These suggestions all address very well the guidelines’ limitations mentioned by our participants.

‘Complexity theory’ has been used to implement interventions in the primary care setting, and yielded sustained effects in individualising the structure and processes of care towards individual values.38 39 This reflects the challenges GPs reported in our study to address the needs of patients. Since their approach worked in different participating practices, this would make ‘complexity theory’ a valuable approach to incorporate in the organisation culture of care of patients with multiple health problems.

Reformulating ‘quality of care’ in patients with multimorbidity and adapting pay-for-performance systems accordingly is a merely practical need to better address multimorbidity. It challenges current systems in which payment is based on adherence to guideline-based recommendations. This suggestion, raised by participants in our study, finds support in the literature.31 40 A new proposal from this study is to make more use of post-academic trainings focused on multimorbidity. This reduces the need to rely on guidelines only as a resource providing guidance in difficult treatment decisions.

**Implications for research and/or practice**

To conclude, inconsiderate adherence to guidelines is undesirable in the care of patients with multimorbidity, and would come at the risk of losing ‘the art of medicine’. Nevertheless, evidence-based guidelines are indispensable components of modern medicine. Several suggestions have now been summarised on how to improve the applicability of guidelines in patients with multimorbidity, for example, increasing and better reporting of the external validity in future research, and prioritising guideline recommendations. Patient-centred care provision demands adjusting professional tasks to a specific patient’s needs. This requires practitioners’ autonomy to deviate from guideline recommendations when appropriate, without negative financial consequences, especially in the case of multimorbidity. Facilitating such flexibility could help to accomplish the provision of patient-centred care to patients with multimorbidity, a much needed and desired pursuit by patients as well as GPs.
Acknowledgements The authors would like to thank all participating GPs for their contribution, and Kelly Vellinga-Chan for the translation of the quotations.

Contributors HL, TS, CoV, AL-J and PL conceived and designed the study. HL and PL acquired the data. PL moderated the focus groups. HL and ML analysed the data, with contributions from PL, AL-J, CoV and TS. HL drafted the manuscript. PL, CoV, ML, AL-J and TS revised the manuscript critically for important intellectual content. All the authors had full access to all data of the study, and are accountable for the accuracy and integrity of the presented work. They also approved the final version of the manuscript for publication. HL is the guarantor.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests HL received a research grant from SBOH, Foundation for General Practice Residency Training in The Netherlands.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The interview guide is available from the first author on request.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES