

Prioritizing research for patients requiring surgery in low- and middle-income countries

National Institute for Health Research Global Health Research Unit on Global Surgery*

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Background: The National Institute for Health Research Global Health Research Unit on Global Surgery is establishing research Hubs in low- and middle-income countries (LMICs). The aim of this study was for the Hubs to prioritize future research into areas of unmet clinical need for patients in LMICs requiring surgery.

Methods: A modified Delphi process was overseen by the research Hub leads and engaged LMIC clinicians, patients and expert methodologists. A four-stage iterative process was delivered to prioritize research topics. This included anonymous electronic voting, teleconference discussions and a 2-day priority-setting workshop.

Results: In stage 1, Hub leads proposed 32 topics across six domains: access to surgery, cancer, perioperative care, research methods, acute care surgery and communicable disease. In stages 2 and 3, 40 LMICs and 20 high-income countries participated in online voting, leading to identification of three priority research topics: access to surgery; outcomes of cancer surgery; and perioperative care. During stage 4, specific research plans to address each topic were developed by Hub leads at a priority-setting workshop.

Conclusion: This process identified three priority areas for future research relevant to surgery in LMICs. It was driven by front-line LMIC clinicians, patients and other stakeholders representing a diverse range of settings. The results of the prioritization exercise provide a future framework for researchers and funders.



*Co-authors of the study are listed under the heading Collaborators and in *Appendix S1* (supporting information)

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Introduction

The Lancet Commission on Global Surgery recognized surgery as an indispensable component of global health, highlighting an urgent need to increase both the volume and quality of surgical provision¹. Annual mortality from surgically treatable diseases is around 17 million², exceeding the total combined deaths caused by malaria, tuberculosis and human immunodeficiency virus (2.97 million)³. Surgery has a central role in the management of up to one-third of the burden of disease², but there is considerable global disparity in surgical provision, with 4.8 billion people, predominantly in low- and middle-income countries (LMICs), lacking access to safe, affordable surgery⁴. In addition, there is significant global variation in surgical outcomes, with adults up to three times, and children seven times more likely to die after emergency abdominal

surgery in LMICs compared with high-income countries (HICs)^{5–9}.

Participation in clinical research improves patient outcomes¹⁰, but most research is conducted in high-income settings¹¹. Given the distinct clinical needs and financial constraints in LMICs, research findings from HICs cannot always be translated directly between settings. In spite of logistical and organizational challenges, proof of principle for the feasibility of high-quality international LMIC studies is provided by the randomized CRASH-2¹² (20 211 injured patients) and CORONIS¹³ (15 935 obstetric patients) trials.

Previous research prioritization exercises have been limited to individual LMICs^{14,15}. To improve global provision for, and outcome from, surgically treated diseases, a structured process is required to select topics objectively for future large-scale international research studies.

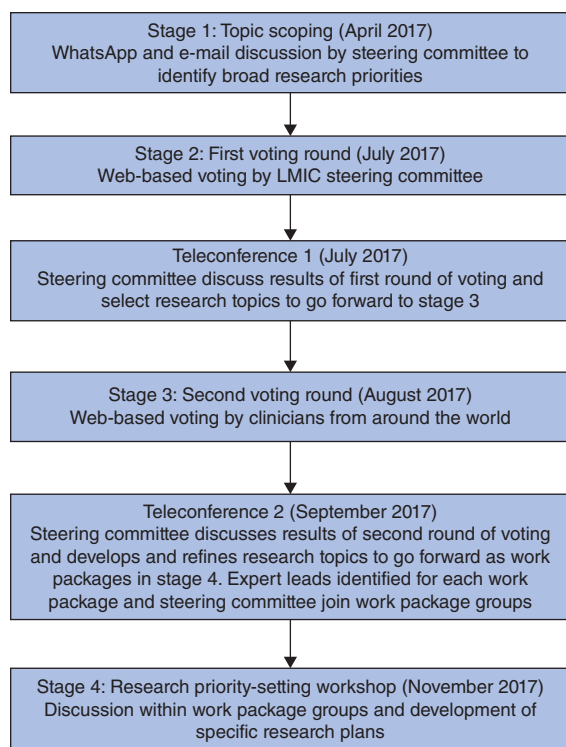


Fig. 1 Overview of four-stage Delphi process for prioritizing research for patients requiring surgery in low- and middle-income countries. LMIC, low- and middle-income country

Embedding front-line stakeholders at every stage of the process will ensure clinical relevance to both patients and healthcare systems. The aim of this study was to identify and prioritize collaboratively derived research questions that will address the areas of greatest unmet need for patients with surgical conditions in LMICs.

Methods

Network

The National Institute for Health Research (NIHR) Global Health Research Unit on Global Surgery is a partnership between the Universities of Birmingham, Edinburgh and Warwick. It is establishing funded LMIC research Hubs, led by local clinicians. Hubs and associated Spoke hospitals deliver training and clinical research, including RCTs, to identify solutions that will result in improved delivery of surgical care within LMICs.

Design

The modified Delphi method is a structured process of reaching consensus through iterative rounds of voting

followed by group feedback. This methodology is particularly appropriate to the global health setting as it enables large numbers of geographically scattered individuals to participate. Participants may represent diverse settings and areas of expertise, but, by providing each participant with an equal vote, overdominance by particular individuals or groups is prevented. Voting is anonymous, ensuring that all participants are able to contribute their genuine views, as responses are not influenced by a desire to be seen to agree with other individuals.

Starting from an initially broad range of ideas and themes, the process was planned to deliver a consensus on the highest research priorities. A four-stage consensus process was designed for this priority-setting exercise, including two rounds of voting (*Fig. 1*). To facilitate participation from across the international network, the first three stages were completed via online and teleconferencing platforms, with in-depth discussions for the fourth stage undertaken at a residential workshop. The prioritization exercise was overseen by a steering group of Hub and Spoke leads, and representatives of the NIHR Global Health Research Unit on Global Surgery, including surgeons, anaesthetists, public health physicians and methodologists with LMIC research experience.

Stage 1: topic scoping by steering group

The objective of the first stage was to identify broad research themes to be refined and prioritized in subsequent stages. Research topics representing the greatest needs in LMIC surgical practice were identified by Hub leads and the wider steering group through a structured discussion hosted on the secure mobile platform WhatsApp (Facebook, Menlo Park, California, USA) and by e-mail during April 2017. The aim was to identify a minimum of 20 specific research topics. All identified topics were categorized independently by two steering committee members into thematic domains, with any discrepancies resolved by discussion with a third colleague. To streamline voting in the next round, the steering group refined topics through discussion.

Stage 2: first voting round (LMIC steering group)

Research topics across the identified top four domains were included (through teleconference discussion by the steering group) in the first round of anonymous online voting. Hub and Spoke leads voted through a secure online survey during July 2017. Participants scored each research topic out of five points, with a score of 1 indicating lowest priority and a score of 5 indicating highest priority. Research topics were ranked based on the mean score. The results were discussed at a steering group teleconference during

July 2017, with agreement on the top scoring research topics to proceed to the next stage.

Stage 3: second voting round

To ensure broad generalizability of the prioritization exercise, surgeons and anaesthetists from around the world were invited to participate in the second round of anonymous online voting during August 2017. Invitations to participate were e-mailed to individuals who had previously participated in either of two international surgical cohort studies^{7,16}. In addition, the survey was disseminated through social media, including Twitter (San Francisco, California, USA) and Facebook. Voting was conducted through online surveys available in English, French and Spanish. Responses were invited from both LMICs and HICs, to allow comparison of results.

Participants scored each of the research topics selected in stage 2 based on criteria adapted from a previous LMIC research prioritization exercise¹⁷. These criteria were: burden – the proportion of patients undergoing surgery in LMICs who might benefit from addressing the research topic; impact – how significant potential gains would be for those patients who do benefit; implementation – likelihood of implementation of research findings into routine clinical practice.

Each criterion was scored from 1 (lowest score) to 5 (highest score). The topics selected in stage 2 were ranked separately, based on average scores derived from LMIC compared with HIC respondents, to identify common research priorities.

The steering group held a teleconference during September 2017 to review and discuss the voting results, and to select the leading three research topics for development as dedicated work packages at the planned priority-setting workshop. Steering group members each selected one work package group to lead, and prepared background material in advance of the workshop.

Stage 4: research priority-setting workshop

The research prioritization workshop was held in Johannesburg, Republic of South Africa, on 13–14 November 2017. The workshop was attended by Hub leads, invited LMIC anaesthetists and surgeons, and methodology experts. Before the workshop and during sessions, literature reviews were conducted to identify evidence gaps, and the results were fed into group discussions. Three 2-h multidisciplinary workshops were held in parallel to allow Hub leads and other stakeholders to develop specific research proposals within each work package. Each group was supported with input from methodological

experts and a patient representative. Rotation of individuals around different work packages, and regular feedback to the full group of progress within each work package, enabled ideas to be shared across workshops, with development based on iterative feedback.

Results

Stage 1: topic scoping by steering group

After initial discussions, a total of 32 different research topics were proposed. These topics were categorized into six broad domains: access to surgery, cancer care, perioperative care, research methodology, acute care surgery and communicable disease (*Fig. 2*). At this early stage it was evident that many research questions crossed multiple thematic domains. For example, topics within the methodology domain focused on how to deliver high-quality research in resource-restricted settings efficiently with limited research infrastructure. This could be incorporated into studies focusing on any of the clinical questions highlighted in the other domains. The steering group agreed a shortlist of 16 key research topics (*Table 1*) across four domains: access to surgery, acute care surgery, cancer care and perioperative care. There was insufficient support for topics from the other two domains (communicable disease and research methods) to proceed to the next stage.

Stage 2: first voting round (LMIC steering group)

The most popular topics identified were access to surgical care, emergency laparotomy, appendicectomy, and preoperative nutrition and optimization (*Table 1*). The steering committee selected eight research topics to proceed to voting in stage 3, based on the perceived feasibility of addressing these across the network. These included topics relating to perioperative care, cancer surgery, acute care surgery and access to surgery. It was agreed that the substantial crossover between the various access to surgery themes required these to be combined into one overarching access research topic.

Stage 3: second voting round

A total of 119 participants from 40 LMICs and 75 participants from 22 HICs took part in the online vote in stage 3. Just under half of respondents in both LMICs (53 of 119) and HICs (33 of 75) were trained surgeons, with the remainder being junior doctors, nurses and medical students. Similar priorities were identified among LMIC and HIC participants, with three of the top four highest-ranked research topics being identical across both groups (*Table 2*). These included postoperative ward care, improving access to surgical care from the community,

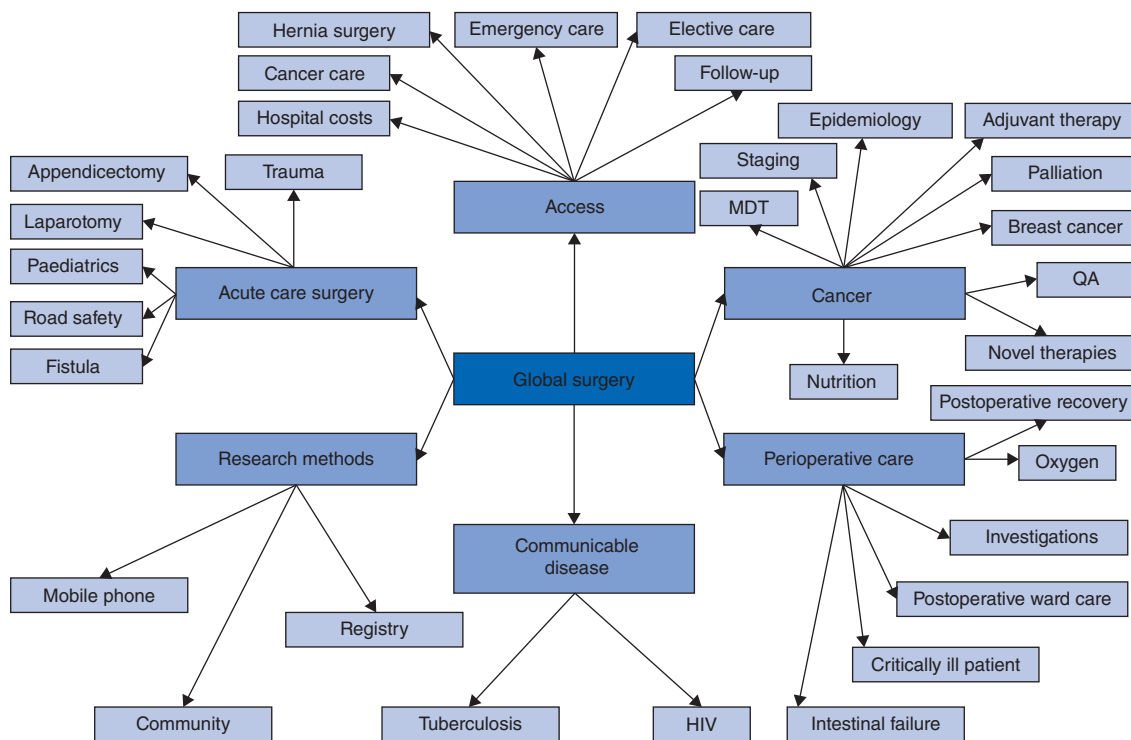


Fig. 2 Six domains and 32 research topics identified in stage 1 of the Delphi process. MDT, multidisciplinary team; QA, quality assurance; HIV, human immunodeficiency virus

Table 1 Research topics ranked on mean score from voting in stage 2 of the Delphi process

Rank*	Topic	Points
= 1	Access from the community for emergency surgery	4.6
= 1	Emergency laparotomy	4.6
3	Appendicectomy	4.4
= 4	Access from the community for elective surgery	4.2
= 4	Preoperative nutrition	4.2
= 4	Preoperative optimization	4.2
7	Access to surgical follow-up	4.0
= 8	Surgical workforce planning	3.9
= 8	Postoperative ward care	3.9
= 8	Standardizing cancer staging	3.9
= 8	Quality assurance of cancer surgery	3.9
= 8	Trauma	3.9
13	Introducing novel cancer therapies via multidisciplinary team	3.8
= 14	Care of the critically ill surgical patient	3.6
= 14	Paediatric surgery	3.6
16	Immediate postoperative oxygen therapy	3.4

*Scores range from 1 (lowest) to 5 (highest).

and emergency laparotomy. LMIC participants also ranked preoperative optimization in the top four, whereas HIC participants ranked quality assurance of cancer surgery among their top four research topics.

Following steering group discussion of the results of this vote, three broad research topics were prioritized for development into deliverable work packages at the

workshop: access to surgery from the community (voting rank 3); cancer care, including quality assurance of cancer surgery (voting rank 6) and preoperative nutrition for patients with cancer (voting rank 5); and perioperative care, including postoperative care (voting rank 1) and preoperative optimization (voting rank 2) with a focus on emergency laparotomy (voting rank 4).

Stage 4: research priority-setting workshop

The prioritization workshop was attended by 67 delegates, including Hub leads and other invited stakeholders, representing 21 countries. During the meeting, each work package reported back interim progress to the full group and received feedback, finally agreeing a series of specific research questions.

Access

Consensus objective

The objective was to improve access from the community to emergency hospital care.

Delphi research questions

What are the barriers and facilitators to accessing emergency hospital care in LMICs?

Table 2 Research topics ranked on mean total score from voting in stage 3 of the Delphi process, stratified by low- and middle-income versus high-income country responses

Low- and middle- income country respondents					High-income country respondents						
Rank	Topic	Criterion			Total	Rank	Topic	Criterion			Total
		1	2	3				1	2	3	
1	Postoperative ward care	4.3	4.1	4.0	12.4	1	Access to surgical care from the community	4.1	4.0	3.4	11.5
2	Preoperative optimization	4.0	4.0	3.9	11.9	2	Postoperative ward care	3.9	3.8	3.7	11.4
3	Access to surgical care from the community	4.0	3.9	3.5	11.4	3	Emergency laparotomy	3.8	3.7	3.7	11.2
4	Emergency laparotomy	3.9	3.7	3.8	11.4	4	Quality assurance of cancer surgery	3.6	3.8	3.4	10.8
5	Preoperative nutrition	3.7	3.7	3.6	11.0	5	Appendicectomy	3.7	3.3	3.4	10.5
6	Quality assurance of cancer surgery	3.7	3.7	3.5	10.9	6	Standardizing cancer staging	3.5	3.6	3.3	10.4
7	Appendicectomy	3.5	3.5	3.7	10.7	7	Preoperative optimization	3.5	3.5	3.3	10.2
8	Standardizing cancer staging	3.5	3.5	3.4	10.4	8	Preoperative nutrition	3.2	3.4	3.2	9.8

Research topics were scored from 1 (lowest) to 5 (highest) across three criteria: (1) burden, (2) impact and (3) implementation. Scores from the three criteria were added together to give a total score, which could range from a minimum of 3 to a maximum of 15.

What interventions aimed at improving access have been proposed and/or implemented, and how were they evaluated?

Can novel interventions aimed at improving access be identified?

Workshop discussion points

Globally, 4.8 billion people lack access to safe, affordable, and timely surgery when they need it⁴.

There is an unmet need for an additional 143 million operations per year in LMICs¹⁸. Patients who do get to hospital may be delayed due to the challenge of ensuring affordable, effective and safe means of transport from the community to hospital.

The three delays model¹⁹ is applicable to surgical patients: delay in seeking care (first delay); delay in reaching care (second delay); delay in receiving appropriate care (third delay). Surgical patients face similar physical, social, financial and cultural barriers across highly diverse settings^{20,21}.

To improve patient care, the group must move beyond simply describing barriers, and identify how interventions might be designed with the aim of improving access.

Agreed research plan

Consensus was reached that the greatest impact on patient outcomes would be achieved by improving access from the community to emergency rather than planned care. It was agreed that initial studies should focus on patients requiring hospitalization for any acute illness, as patients face similar challenges in accessing emergency treatment, regardless of their presenting complaint. Currently, there are insufficient baseline data to inform the development of novel interventions. Therefore, it was agreed that the group’s priority was to explore the scope for future interventions by conducting a series of qualitative studies,

underpinned by relevant systematic reviews. These mixed-methods projects would study patient, community and health provider perspectives on barriers and solutions to improving access.

Cancer care

Consensus objective

The objective was to establish a resource-weighted (or resource-appropriate) quality assurance framework for cancer surgery.

Delphi research questions

What are the indicator procedures that measure surgical capacity in cancer care?

What is the optimal surgery, radiology and pathology skill mix, caseload and centre distribution for cancer care in LMICs?

Will improving nutrition around the time of cancer surgery improve patient outcomes?

What is the role of the multidisciplinary team meeting in delivering cancer care in LMICs?

Can mobile phone technology be used to capture long-term outcomes following cancer surgery in LMIC settings?

Workshop discussion

Future policy-making would be informed by identifying evidence-based cancer indicators relevant across all resource settings.

Across the world, 80 per cent of patients with cancer require surgical treatment, but less than one-quarter have access to safe, affordable and timely surgery²². Data concerning the indicator procedures would allow mapping of the global provision of surgical cancer care, enabling benchmarking for individual hospitals and health systems.

Defining the optimal surgery, radiology and pathology skill mix, caseload and centre distribution for cancer care would inform the development of cancer services in LMICs.

Further research priorities should include evaluation of the role of multidisciplinary team-based cancer care, and the value of patient navigators in LMICs.

Agreed research plan

It was agreed that, to identify for service improvement and research, a global observational cohort study was needed to benchmark care pathways and outcomes in LMICs against HICs. This study would capture data on patient pathways, including availability of diagnostic and therapeutic services, short-term surgical outcomes (mortality, postoperative morbidity such as surgical-site infection, return to work), longer-term cancer-specific outcomes (disease-free survival, local recurrence, overall survival), and also patient-reported outcomes for quality-of-life and health economic evaluation. Consensus was reached to capture data initially for common cancers such as breast, colorectal and gastric cancer, before expanding to include other disease sites. It was further agreed to develop, in parallel, the feasibility of a major trial for optimizing nutrition around the time of surgery. To facilitate capture of long-term outcomes, it was considered important to begin developing innovative follow-up strategies using mobile phone technology.

Perioperative care

Consensus objective

The objective was to identify suitable perioperative interventions that can benefit patients and that are feasible to test in RCTs.

Delphi research questions

What perioperative interventions are feasible to test in LMICs, and have the potential to be affordable and sustainable in routine practice?

What evidence-based practice points should be incorporated into future LMIC perioperative trials to define baseline good practice?

Which study design is best to assess one or more perioperative interventions in LMICs?

Workshop discussion

Previous observational studies^{5,7,8} have demonstrated increased perioperative mortality in LMICs, so there is an urgent need to identify strategies to reduce perioperative mortality.

A range of outcomes are affected by variability in perioperative care, and could be targeted in future research studies (for example sepsis, surgical-site infection, kidney injury, death).

Studies including high-risk patients will be of high impact, such as those undergoing common procedures (caesarean section, emergency laparotomy, open fracture fixation). However, there was recognition that elective patients also represent an important target for improvement of perioperative care.

Interventions might span one or more of the preoperative, intraoperative and/or postoperative intervals.

Innovative and efficient research designs, including the opportunity to compare multiple interventions simultaneously, should be considered in future trial design.

Agreed research plan

As there is a good body of evidence for interventions in well resourced settings, RCTs are needed to test interventions in resource-limited settings. Complex study designs (such as multiarm multistage or factorial trials) could offer efficiency, flexibility and maximum potential impact for patients.

Potential perioperative interventions were identified during the workshop, including preoperative optimization, surgical risk scoring, optimization of perioperative oxygen therapy, perioperative infection prevention and postoperative early warning scores. Further feasibility work is needed to select interventions for future trials. Clinical practice points with a high level of supporting evidence and a subsequent lack of equipoise should be incorporated into the trial protocol to define baseline standard clinical care.

Discussion

This process has prioritized three research topics for development into major research projects: access to acute care from the community, cancer care and perioperative care. Specific research questions have been identified within each of these broad topics. The process embedded LMIC collaborators from the outset, ensuring selected topics had the greatest potential to improve surgical care in LMICs. In addition, a reproducible, structured process has been developed that engages front-line LMIC clinicians in identifying research priorities relevant to their clinical practice, and supports them to work in partnership with other key stakeholders to develop deliverable research proposals.

Several research prioritization exercises have been conducted in anaesthesia, and perioperative care and surgery. These include processes run by the James Lind Alliance²³, the American Society of Colon and Rectal Surgeons²⁴ and

the Association of Coloproctology of Great Britain and Ireland²⁵. Whereas these previous prioritization exercises focused on the needs of patients in high-income settings, the present exercise identified research topics relating to the key unmet needs of patients with surgical conditions in LMICs. For example, cancer topics were notably different from those selected in HICs. Rather than focusing on high-resource procedures, the need for quality assurance of cancer surgery and short-term outcomes was emphasized. A perioperative research prioritization exercise has been conducted previously in South Africa, although its results were country-specific¹⁴.

It was not possible to achieve representation across all LMICs in this prioritization exercise, but collaborators from across 40 LMICs were embedded throughout the process, enabling an internationally relevant research agenda to be identified that recognizes variability in infrastructure and resources. Inevitably, in this first exercise there was a disproportionate representation of participants from tertiary and academic LMIC hospitals, with fewer participants from poorly resourced rural and district hospitals. As more Spoke research centres are set up in the most poorly resourced environments, it is expected that more clinicians from these settings will participate in future exercises. As the principal aim of this exercise was to prioritize topics for international research studies, subgroup analyses were not planned, for example between low- and middle-income countries. However, both existing infrastructure and resources, and disease burdens vary greatly amongst LMICs. Future prioritization exercises should aim to capture input from a broader range of LMICs to enable priorities to be explored with greater granularity across diverse settings.

High-impact, practice-changing research requires input from multidisciplinary teams. This process has engaged stakeholders including patients, public health physicians, surgeons and anaesthetists. Participants in the exercise represented a number of surgical specialties, but the majority were general surgeons and this may have biased the results in focusing on patients with abdominal conditions. Although the exercise did not directly identify trauma, orthopaedic surgery or obstetric themes, the prioritized topics cut across all specialties.

Clinical trials generate new evidence and establish networks that can translate research findings into routine clinical practice. However, as high-quality trials are expensive and challenging to deliver, only a limited number can be run simultaneously. This study will support a wide range of researchers to target their trials to address priority issues, most likely to result in substantial improvements in surgical care across diverse LMIC settings. The

broader long list of topics identified in the earlier stages of this exercise will also be of considerable use to researchers to support the formulation of research questions relevant to patients in LMICs. It can also inform strategies for funders of global anaesthetic, perioperative and surgical research, informing the allocation of funding, and the development of sustainable research infrastructure and LMIC research leaders.

Collaborators

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.