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Original article

Personalized risk prediction of postoperative cognitive impairment – rationale for the EU-funded BioCog project

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ABSTRACT

Postoperative cognitive impairment is among the most common medical complications associated with surgical interventions – particularly in elderly patients. In our aging society, it is an urgent medical need to determine preoperative individual risk prediction to allow more accurate cost–benefit decisions prior to elective surgeries. So far, risk prediction is mainly based on clinical parameters. However, these parameters only give a rough estimate of the individual risk. At present, there are no molecular or neuroimaging biomarkers available to improve risk prediction and little is known about the etiology and pathophysiology of this clinical condition. In this short review, we summarize the current state of knowledge and briefly present the recently started BioCog project (Biomarker Development for Postoperative Cognitive Impairment in the Elderly), which is funded by the European Union. It is the goal of this research and development (R&D) project, which involves academic and industry partners throughout Europe, to deliver a multivariate algorithm based on clinical assessments as well as molecular and neuroimaging biomarkers to overcome the currently unsatisfying situation.

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1. Background

Dementia-associated cognitive impairments result from different, interacting medical, physiological and molecular conditions (cognitive dysfunction with multifactorial etiology). Impaired cognition can be the consequence of age-associated primary brain disorders such as neurodegenerative conditions like Alzheimer dementia (AD) and/or cerebrovascular disease, depression, secondary brain disorders due to diabetes or other metabolic disorders, (chronic) inflammation, treatment interventions (e.g. anticholinergic drugs) as well as life style factors. An understanding of the interacting pathological mechanisms of cognitive impairment requires a cross-cutting "systems medicine" approach with different medical and scientific disciplines working together as well as studying different physiological and molecular mechanisms. This includes the application of molecular biomarker and neuroimaging technologies for stratification of cohorts. Supplementing traditional hypothesis-driven approaches, big data strategies using omics-platforms and bioinformatics tools may eventually help us to disentangle the complex interplay.

Postoperative cognitive impairment is a prime example of impaired cognition due to various reasons. One can think of it as a "quasi-experimental" model condition of cognitive decline with a well-defined starting point, i.e., the time point of surgical intervention, which is mostly planned ahead of time. Postoperative cognitive impairment is among the most common medical complications associated with surgical interventions – particularly in but not limited to elderly patients. In general, postoperative cognitive impairment is divided into two stages: (1) postoperative delirium (POD) (= delirium due to another medical condition, DSM-V: 293.0) and (2) postoperative cognitive dysfunction (POCD) (= major neurocognitive disorder due to another medical condition DSM-V: 294.10). During the acute and transient POD lasting hours and days after the surgical intervention, delirium can present either as hyperactive, hypoactive or mixed subtype. In rare cases POD can even persist. The hyperactive subtype presents with agitation, delusions and disorientation, which can be easily confused with psychosis in other neuropsychiatric conditions or it presents as hypoactive subtype. The latter is easily overlooked, apathy and quiet confusion are present and it can be confounded with depression. The incidence of POD after elective, non-cardiac surgery varies between 4–54% depending on a number of sociodemographic and clinical factors including age, duration of surgical intervention among others [1]. POD is frequently followed by the more chronic POCD which tends to persist over time [2,3]. In the ISPOCD1 study, the largest study of POD/POCD to date conducted during the early 1990s with funding from the European Union, $n = 948$ non-cardiac surgical patients were studied with preoperative cognitive assessment and follow-up investigations at 3 months. Cognitive decline was measured using a composite score of memory and/or attention tasks in a neuropsychological test battery. Cognitive decline occurred in 19% with no documented prior delirium, in 32% after short delirium duration (1–2 days), in 55% after prolonged delirium [2]. In elderly patients, POCD resembles dementia due to chronic neurodegeneration and appears to accelerate the cognitive decline in prior Alzheimer dementia [4]. In a recent meta-analysis [5], an odds ratio = 12.52 [95% CI, 1.86–84.21] was reported for the association of POD and the subsequent development of dementia after 3.2 and 5.0 years of follow-up (corrected for baseline dementia, severity of illness, age). A significant association between POD and mortality was also found after a mean follow-up of 11.4 months (OR = 1.71 [95% CI, 1.27–2.30]). In aging societies such as the western industrialized nations, the socioeconomic implications of postoperative cognitive impairments are therefore profound: POD/POCD are associated with longer and more costly hospital treatment, increased mortality, and dependency on social transfer payments [2]. Thus, developing effective diagnostic tools and treatments constitutes an urgent medical need – in particular, because there are hardly any treatments available partly due to a lack of understanding of the relevant pathological mechanisms. At present, the perhaps most important question to be clarified is it to establish diagnostic algorithms for the prediction of the individual (personal) risk to develop POD/POCD following a planned (elective) surgical intervention as part of a cost–benefit analysis prior to surgery. For instance, if a patient faces a high individual risk to develop cognitive impairments after surgery (e.g. hip replacement because of osteoarthritis or hip fracture), this patient may decide not to undergo surgery because the "costs" (cognitive impairment) are simply too high. Rather, this patient may opt for conservative treatment (long-term analgesic drug treatment). However, such a cost–benefit analysis would require an accurate algorithm for the prediction of POD/POCD, which is not yet available. The scale and urgency of this problem becomes even more obvious when considering the ongoing public discussion in the UK on hip replacement surgery, which is denied to thousands each year despite National Health Service (NHS) guidelines. Part of the problem is that these guidelines are rather vague in terms of cost–benefit analysis. The question who is going to develop cognitive impairment after surgery is not even part of the guidelines although expenses for surgery are generally not covered for older patients with preexisting cognitive impairment (dementia) since it is expected that these particular patients may not be able to cope with rehabilitation afterwards. At present, we are only able to make rough predictions on who is going to experience POD. Published prediction algorithms [6,7] are mostly based on older studies and the basis for prediction in these studies mostly relies on clinical studies with limited statistical power, which did not allow to address the question on possible interactions of risk factors – a major issue when one considers the multifactorial etiology of this condition. The Harvard group provided a long list of potential POD risk factors. However, for the most part, the individual risk due these factors was not further quantified due to an insufficient database. Even so, the group was able to attach a number at least to a few risk factors. On the basis of their work it is relatively safe to say that an approximately 2–3-fold increased risk for POD is seen in patients with preoperative age (> 70 years), impaired physical function, alcohol abuse, white blood count ($> 12{,}000$ cells/mm^3), hypo-albuminemia (< 3.5 g/dL) and clinical depression while the POD risk may even be higher in patients with preexisting cognitive impairment (Mini Mental State Examination Test [MMSE] < 24) – in fact, low MMSE scores have been most frequently reported as a POD risk factor. According to this study, plasma electrolyte concentrations and type of surgery may also play a quantifiable role (aortic vs. non-cardiac). Importantly, hardly any prediction is currently possible on who is developing (persisting) POCD, which is ultimately the more serious problem for a patient due to its tendency to become chronic. Originally, it was thought that POCD following POD is most likely to occur in elderly patients with preexisting cognitive impairment or clinically undetected preexisting neuropathology [3,6]. While this might be the case in a substantial portion of surgical patients, other factors may also play a considerable role like length of postsurgical Intensive Care Unit (ICU) stay, duration of delirium which itself partly depends on the duration (and the extent) of the surgical intervention [8,9]. Unfortunately, even though we know that these factors among others are risk factors for POCD, it is unclear how this translates into the individual (personal) risk of a patient. The scale of the problem becomes increasingly obvious. The trajectory of an initial decline (delirium) and subsequent prolonged impairment of cognitive function was highlighted by a recently published clinical study of Pandharipante et al. [10] in a mixed

sample of surgical and medical ICU-patients. They reported ICU-associated (transitory) delirium in 74% out of over 800 patients. 34% and 24% of all patients with cognitive assessments at 12 months also showed similar scores like patients with moderate traumatic brain injury or patients with mild AD, respectively. Notably, the authors reported cognitive decline both for elderly patients and for a considerable number of younger adults suggesting that even with little or no prior neurodegeneration, long-term cognitive decline can develop being triggered by delirium.

2. Current state of neuroimaging and biomarker research

During the past few years, there has been a sharp increase in papers addressing the underlying pathological mechanism of POD/POCD. These studies were mostly based on relatively small samples of patients addressing selected research questions using neuroimaging and molecular biomarkers. These studies are not only interesting for a better understanding of POD/POCD but also for possible identification of putative risk predictors which may help to develop more accurate risk prediction algorithms in the future.

2.1. Neuroimaging biomarkers

In the neuroimaging field, most of the very few studies so far used structural magnetic resonance imaging (MRI). As part of the SAGES project (Successful Aging after Elective Surgery) at Harvard a prospective cohort study with 566 elective surgical elderly patients (age: >69 yrs., non-demented, modified Mini Mental State Examination score <69) was recently conducted. A subgroup of these patients ($n = 146$) was also investigated with MRI before surgery of whom $n = 32$ (22%) developed POD [11,12]. Presurgical white-matter hyperintensities (WMHs), whole brain and hippocampal volume were not significantly associated with delirium incidence or severity (unadjusted and adjusted for age, gender, vascular comorbidity, and general cognitive performance). Likewise, the same group reported no significant association of POD and cerebral flood flow as assessed with MRI (three-dimensional Arterial Spin Labeling [ASL]) – even though they reported an association with presurgical baseline cognitive performance (Hopkins Verbal Learning Test–Revised (HVLT-R) total scores) [13]. However, these negative findings are in contrast to several other albeit smaller studies which presently suggest that POD/POCD might be predicted by both (silent) vascular lesions and atrophy of cortical (prefrontal/parietal) gray- and white-matter as well as hippocampus volume [14–19]. As part of the VISIONS (VISualizing Icu SurvivOrs Neuroradiological Sequelae) study, a cohort of $n = 47$ medical and surgical ICU survivors (mean age 58 yrs., range: 48–65) with delirium was investigated. Patients with a CDR (Clinical Dementia Rating) score of 3, indicating severe preexisting dementia, were excluded from the study. The question was whether the duration of delirium during ICU stay predicts brain volumes as assessed by MRI at hospital discharge and three months later. Longer duration of delirium was significantly associated with postoperative brain atrophy, smaller (superior) frontal lobe and hippocampal volumes [17]. Importantly, in this study no baseline MRI was obtained, that is an MRI before ICU admission, so one cannot be sure whether this was cause or consequence. As part of the same project, DTI (diffusion tensor imaging) was also conducted and revealed a corresponding relationship with lower fractional anisotropy (FA) in various brain regions [18]. Intriguingly, the Sages group recently reported that presurgical diffusion tensor imaging abnormalities of the cerebellum, cingulum, corpus callosum, internal capsule, thalamus, basal forebrain, occipital, parietal and temporal lobes, including the hippocampus, are associated with delirium incidence and severity – even after further controlling for age and general cognitive performance the associations remained statistically significant [20]. The findings of the VISION study resemble in part those findings seen in cognitive decline and (early stages of) AD; at the same time these regions are well known to be involved in memory formation, working memory and attention – cognitive domains that are typically disturbed both in AD and POD/POCD.

A recent study from the Alzheimer's Disease Initiative (ADNI) explored the possible relationship between POCD and dementia. A surgical cohort ($n = 41$) with/without mild cognitive impairment (MCI) (age range: 55–90 years) was investigated before and 5–9 months post-surgery as well as a propensity matched nonsurgical control cohort ($n = 123$) [21]. Postsurgical atrophy (hippocampus, cortical gray matter) was reported in surgical patients compared to nonsurgical controls, however, postoperative cognitive decline was seen in surgical patients with prior MCI only. While the relatively small sample size and clinical heterogeneity may partly explain the unexpected lack of cognitive decline in non-MCI patients given the usually observed high incidence of POCD in elderly patients, the results also could indicate that structural brain changes might be more sensitive than cognitive measures for predicting POCD.

Taken together, the only recently reported neuroimaging findings on the ability of predicting risk for POD/POCD are currently conflicting. However, so far, only few and relatively small studies have been conducted, which were likely underpowered. On the other hand, these results also might be considered as an indication that neuroimaging parameter on its own will not be sufficient for an individual risk prediction. On the other hand, the potential of neuroimaging for the prediction of POD/POCD has not yet been fully exploited. For instance, functional neuroimaging (fMRI) and electrophysiology hardly have been used so far. In this context, it may also be of considerable interest to address the so-called functional reserve capacity of the brain which could be protective with regard to the development of POD/POCD as recently reported by us [22]. In any case, it is quite obvious that additional clinical and molecular parameters will be required for risk prediction.

2.2. Molecular biomarkers

A considerably larger number of studies, albeit all with small sample sizes, has tried to identify molecular mechanisms underlying POD/POCD as recently reviewed by us [23,24]. Most molecular studies of POD/POCD focused on blood-based markers tracking the cholinergic-anti-inflammatory pathway, some studies also explored a possible relationship between POD/POCD and metabolic syndrome – with the latter condition possible interacting with the inflammatory response [25]. As it stands right now, there is obviously an association of inflammatory markers and POD/POCD in surgical populations. However, it needs to be acknowledged at this point that these positive association findings of inflammatory markers (CRP, cytokines) with POD/POCD might reflect a bias simply because the inflammatory system was most widely studied. In fact, during the past decade, the cholinergic-anti-inflammatory pathway attracted increasing attention since systemic inflammation emerged as a significant driver of cognitive decline in the aged and vulnerable brain as recently reviewed by Cunningham and Hennesey [26]. Based on experimental studies in small animals, the key concept is that microglia, primed by neurodegenerative pathology and/or repeated (systemic) inflammatory events or chronic (systemic) inflammation, produces exaggerated responses of the central nervous system (CNS) to subsequent systemic inflammation which leads to increased cell

death, accelerated disease progression, delirium and persistent cognitive impairment. In addition, it was suggested that loss of the neuro-modulatory and anti-inflammatory influence of acetylcholine may worsen this process [27]. Epidemiological and clinical studies support the notion that systemic acute and chronic inflammation are linked to delirium and cognitive decline including POD/POCD. Cognitive impairment is well known to occur both in elderly and younger patients after acute inflammation (sepsis) and it has been suggested that sepsis may act as a major inflammatory hit and potentially increase the brain's susceptibility to neurodegenerative disease, further deterioration of cognitive ability, and risk of developing dementia in later life – in part due to disruption of blood-brain barrier (BBB). In fact, there is good evidence from numerous clinical studies for a role of chronic systemic inflammation in the development of dementia [28]. For instance, based on a >20 years long, population-based cohort study with >1000 patients, the chronic inflammatory condition arthritis was shown to be associated with the development of AD (risk ratio 2.45). The notion of systemic inflammation as a cause (or disease modifying factor) of dementia is not restricted to typical AD but it was conceptually expanded to the development of cognitive impairment following clinical conditions that occur particularly frequent in elderly subjects, i.e., cognitive impairment after surgical interventions which involve more less (low grade aseptic) systemic inflammation depending of the extend of the surgical intervention [29]. In line with this concept of POD/POCD resulting from inflammation, a critical role of the BBB disruption is suggested by experimental work. Terrando et al. [30] have studied various cohorts of mice that were tested for systemic and hippocampal inflammation, the integrity of the BBB, and cognition. They found that peripheral surgery disrupts the BBB via release of TNFα, which facilitates the migration of macrophages into the hippocampus. Macrophage-specific deletion of IκB kinase (IKK)β, a central coordinator of TNFα signalling through activation of nuclear factor (NF) κB, prevents BBB disruption and macrophage infiltration in the hippocampus following surgery. Activation of the α7 subtype of nicotinic acetylcholine receptors, an endogenous inflammation-resolving pathway, prevents TNFα-induced NF-κB activation, macrophage migration into the hippocampus, and cognitive decline following surgery. They also suggested that microglia activation in the brain by TNFα is amplified by BBB disruption.

In summary, as it stands right now both (chronic) inflammation and metabolic syndrome appear to predict POD/POCD. However, it is not yet clear whether molecular markers associated with these two clinical conditions are sufficient for an individual risk prediction preoperatively. When considered in conjunction with the reported neuroimaging findings, it is obvious that biomarker research is still at a very early stage when it comes to risk prediction of POD/POCD. Moreover, it would be highly desirable to collect cerebrospinal fluid from patients with POD/POCD to allow better comparisons on a molecular level with patients suffering from Alzheimer dementia.

3. The European BioCog project

Developing biomarker-based algorithms for risk prediction of POD/POCD is the basic idea of the EU-funded BioCog project "biomarker development for postoperative cognitive impairment in the elderly" (www.biocog.eu). In the original notion, a combined approach using clinical parameters in combination with neuroimaging and molecular biomarkers appeared to be most appropriate. The idea was that neuroimaging would allow with high sensitivity the identification of impaired brain circuits, whereas molecular biomarkers would detect specific molecular pathomechanisms such as inflammatory-cholinergic pathway, impaired glucose metabolism, early AD pathology etc. for subtyping.

In total, the BioCog consortium includes 12 partners, seven from academia and five from industry, i.e. small-to-medium-sized enterprises (SME). Among other purposes, the inclusion of industry partners makes sure that the primary objective of this project is achieved: the development of an industry-standard biomarker-based algorithm (multivariate expert system) to predict the individual (personal) risk to develop POD/POCD. It is expected that this expert system will support clinical decision-making in patient care, e.g. (1) to balance the individual POD/POCD risk against the expected overall clinical outcome of an (elective) surgical intervention, (2) to allow the design of more sophisticated and hypothesis-driven clinical studies and drug trials (translational research) in the future.

The project is divided into six work packages (WP1-WPs). In WP1 (clinical study), clinical and neuropsychological data are collected. Recruitment centers are the Departments of Anesthesiology and Intensive Care Medicine at the Charité – University Medicine Berlin (Germany) and at the University Medical Center Utrecht (Netherlands). Patient recruitment started in 11/2014 and it was completed by 04/2017. In total, $n=1150$ patients (incl. $n=100$ control subjects) were enrolled in the study (all patients with MMSE >23). Thus, the BioCog project is the largest project of its kind worldwide. The major task of WP1 is it to collect clinical/neuropsychological data of surgical patients with/without POD/POCD at various time points pre- and postoperatively (see Fig. 1). All data were collected according to standard operating procedures (SOPs) and were entered into an electronic case report form (eCRF).

In WP2 (neuroimaging study), a battery of neuroimaging data (MRI) were collected at repeated time points (see Fig. 1). The MRI protocol (3-Tesla MRI) consists of T1 weighted high resolution proton density weighted imaging of the hippocampus, T2 FLAIR weighted, T2 weighted, arterial spin labeling (ASL) perfusion weighted, diffusion tensor imaging (DTI) MRI, and resting state functional MRI (rs-fMRI) data acquisition with simultaneous EEG (electroencephalography). The major task of this work package is it to identify imaging-markers (structural, functional, vascular lesions, vascular perfusion) to predict POD/POCD. In WP3 (molecular study), blood is repeatedly collected (see Fig. 1). For POD/POCD prediction, both a hypothesis-based and data-driven (omics) approaches are pursued. Based on literature, we are investigating several inflammatory and metabolic plasma proteins/molecules including CRP, pro- and anti-inflammatory cytokines, TNF, interleukins (IL-1, IL-6, IL-8, IL-10) as well as the ability of blood leukocytes to appropriately react to an inflammatory challenge, HbA1c, anticholinergic activity, cholesterol, triglycerides, cortisol concentration [23,24]. In the omics-based approach, genomewide analyses are conducted with a custom-designed GSA Global screening array (Illumina) focusing on AD-candidate genes. In addition, we are analyzing the blood transcriptome (mRNA, miRNA) using Affymetrix Clariom S and Affymetrix miRNA Array Plates. Furthermore, collecting plasma as part of the present study will allow building a worldwide unique plasma biobank which can be used for many years to come, e.g. to apply proteomics-based strategies for identifying additional POD/POCD markers. In WP4 (bioinformatics study), multivariate prediction algorithms are developed (stepwise linear regression, machine learning algorithms, neural networks) using sophisticated data administration and analysis software packages with integration of clinical data with neuroinformatics (XNAT) and molecular data including bioinformatics approaches. In essence, a 2-step strategy is pursued using a part of the available data as training set (exploratory data set) with confirmation on the basis of the test set data (validation data set) (see Fig. 2).

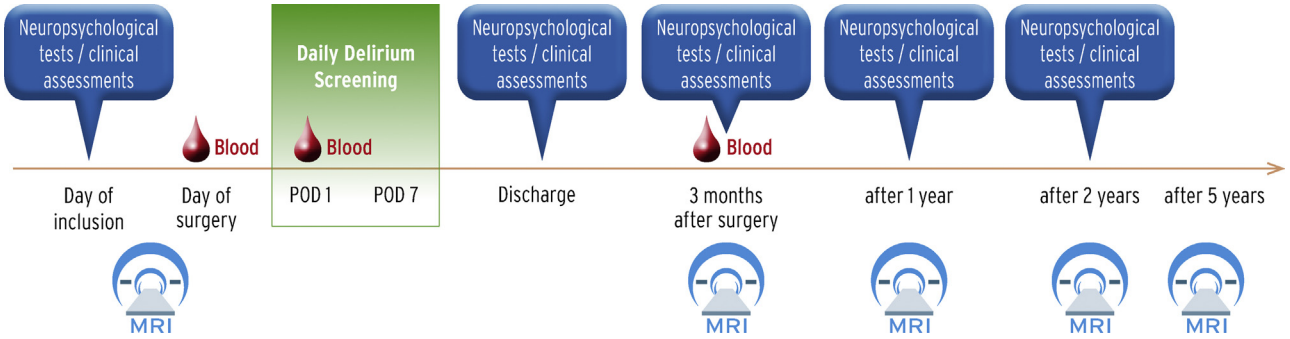

Fig. 1. Study flow chart of clinical investigations, blood collections and neuroimaging sessions (MRI).

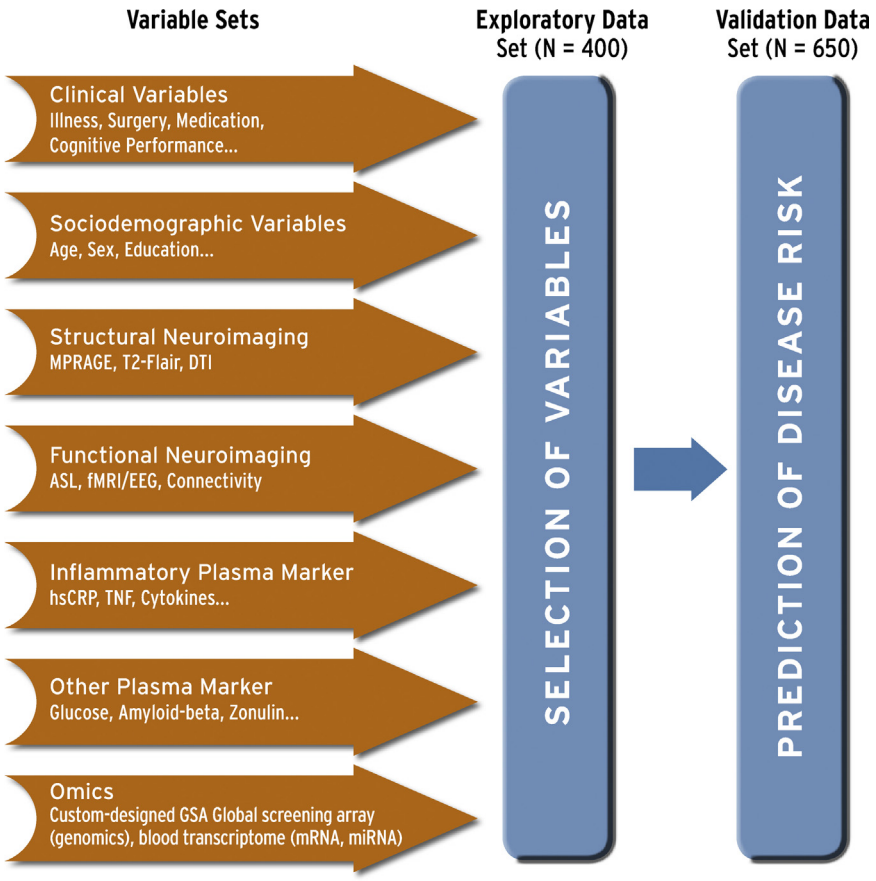

Fig. 2. Developing a multivariate prediction algorithm using various data-sets of clinical, neuroimaging and molecular parameters (left). Developing the prediction algorithm includes an exploratory and a validation step.

Project management as well as dissemination and exploitation are the tasks of WP5 and WP6. The ultimate goal of our R&D project is it to identify clinical, neuroimaging and molecular biomarker predictors for POD/POCD and to deliver a multivariate algorithm allowing individual preoperative prediction of POD/POCD risk, which eventually can be used in clinical practice and drug development.

In summary, it is obvious that the individual prediction of POD/POCD constitutes an urgent medical need in our aging society. We expect that the BioCog project is a big step forward in the development of the required prediction algorithms.

Disclosure of interest

The corresponding author Prof. Dr. Georg Winterer is also Chief Executive Officer of PharmaImage Biomarker Solutions GmbH in Berlin Germany and President of PharmaImage Biomarker Solutions Inc. in Boston, USA.

The other authors declare that they have no competing interest.

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