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Mission – Innovation

Telematics, eHealth and High-Definition Medicine in Patient-Centered Acute Medicine

Claudia Spies, Gunnar Lachmann and Maria Heinrich (Eds.)

Deutsche Akademie der Naturforscher Leopoldina –
Nationale Akademie der Wissenschaften, Halle (Saale) 2021

Wissenschaftliche Verlagsgesellschaft Stuttgart

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Director Ephemeridum der Akademie

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Mission – Innovation

Telematics, eHealth and High-Definition Medicine in Patient-Centered Acute Medicine

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Editors:

Claudia Spies (Berlin)
Member of the Leopoldina

Gunnar Lachmann (Berlin)

Maria Heinrich (Berlin)

**Deutsche Akademie der Naturforscher Leopoldina –
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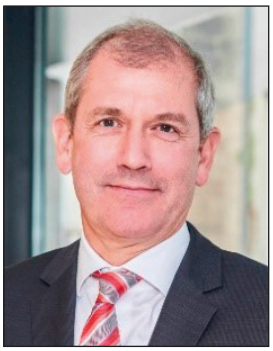
Welcome

(Deputy Chairman – Section Surgery, Orthopedics and Anaesthesiology of the Leopoldina)

Jens Scholz ML (Kiel)

CEO
of the University Hospital Schleswig-Holstein



Dear members and friends of the Leopoldina,

Welcome to the "Mission – Innovation" symposium!

There can be no cutting-edge medicine without science. Medical personalization and translation is only achievable through high-end research, for which we require not only quality data, but also an ability to interlink the two across sectors. Scientists are at the heart of these challenges, and they are expected to deliver solutions to the public and politicians alike.

With the "Mission - Innovation" Symposium, researchers with outstanding quality standards are gathered to discuss the central issues of our time, driving the debate about digitization in an independent, interdisciplinary and evidence-based manner. They provide insights for framework development, where Big Data, data science, high-definition medicine and digital health not only become viable, but also available, applicable and safe for the common good.

Intervention is one of the main tasks of the National Academy of Sciences Leopoldina. That is why "Mission - Innovation" focuses on the patient perspective, as well as legal, economic and data protection issues – aware that an all-in-all, comprehensive approach would be needed to transform the diversified isolated solutions of the medical branch, particularly in terms of digitalization. In order to enforce our medical imperative – for the benefit of the patients – a close cooperation among stakeholders is necessary. Here, it becomes crucial to synchronize the given speed with the appropriate accuracy and communication. The renowned panels stand neither for simplification nor for the preservation of vested rights; rather, they stand for the credible reasoning that follows the strict criteria of well-founded, orderly and secure knowledge.

There is an urgency to employ innovative technologies across sectors to address clinical, ethical and technical concerns. "Mission – Innovation" responds to this need so that innovation can take hold of an advanced and legally secure health care system. Another goal is to provide protection for patients, relatives, employees and organizational systems, in order to create intelligent links supporting large amounts of data through increasingly powerful IT systems, and integrate scientific data in a secure and appropriate manner.

Let us draw a more dynamic and holistic picture of each patient's health and hoist a more efficient healthcare system. After all, our system does not become more expensive through investments in innovation, but rather through an inadequate treatment of patients. In the end, we must ask ourselves, "What is our health worth?"

I congratulate the organizers on opening a discussion on digitalization in medicine and wish all of us (who may eventually become patients ourselves) that "Mission – Innovation" will become a "Mission: Possible".

Prof. Dr. Jens Scholz ML
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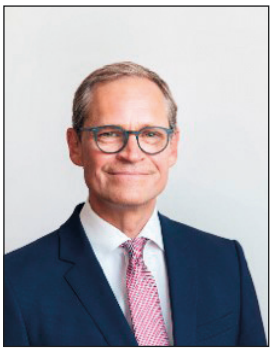
Welcome



Michael Müller (Berlin)

Governing Mayor of Berlin

Welcome to Berlin for the Leopoldina-Symposium: “Mission – Innovation”!

Central to the conference will be an interdisciplinary discussion of future-oriented medical fields such as telematics, e-health, and high-definition medicine. The question here is how new, innovative technologies can be used to benefit patients and what clinical, technological, and ethical challenges physicians and patients will face in the years to come.

I am delighted that leading experts in the field are gathering here in Berlin to discuss new insights and practical experience associated with these vital issues.

Given its many renowned research and clinical institutions and its highly regarded medical schools, the health care capital Berlin offers you an ideal setting for a successful symposium, and I am confident that you will feel at home here.

On that note, I would like to wish you a productive meeting and, for our visitors, a very pleasant stay in Germany’s capital city. I hope this symposium will be a source of fresh inspiration for all of you. My sincere thanks go to the Leopoldina – Academy of the Sciences and the Department of Anesthesia of Charité-Universitätsmedizin Berlin for making Berlin the venue of this very important gathering.

Michael Müller
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Welcome

Helge Braun MdB (Berlin)

Head
of the Federal Chancellery and Federal Minister for special tasks

A key focus of the Federal Government during this legislative period is the digitalization of the healthcare system. "Digital Health" holds enormous potential for the improvement of healthcare, and affects the entire value chain of medicine – from the research, development and approval of digital innovations, to their implementation in approaches for prevention, diagnostics, treatment or rehabilitation. Digital technologies will change individual therapy options and case management, but will also affect individual job profiles, forms of cooperation, business models, processes, and the relationship between healthcare professionals and patients.

In the digital age, the access, availability, portability and responsible use of data are key resources for social participation and scientific progress.

Combined with an interoperable, cross-sectoral digital infrastructure, special opportunities arise in regards to health data. For example, when anonymized data from routine clinical care are made available for research, powerful algorithms can analyze relationships among a multitude of such data, deriving new knowledge about the prevention, diagnosis and therapy of diseases.

An important impetus is being provided at the national level, including digital supply law, the medical informatics initiative, and AI and data strategies.

The user perspective is essential for a successful digital transformation in healthcare. Telematics, eHealth and precision medicine applications must be just as compatible with the technical affinity of the individual as with their sovereignty over personal data. For this, the foundations have already been laid – starting in 2021, each individual in Germany will be entitled to an electronic patient record. Additionally, a stepwise-access concept will be implemented, allowing for the customized release of content files.

This year, the Federal Government will provide answers to central questions regarding this digital transformation, including possible structures for voluntary data donation, or for

A video of the welcome address can be viewed online:

data-sharing obligations based on Germany's (and the rest of Europe's) high data protection standards.

There is still a lot of work to do, especially with regards to the view of the German E.U. Presidency, which pledges to develop a European vision for the data age together with our partners.

With this in mind, I wish all participants a lively, interdisciplinary exchange, rife with new insights for their practical work.

Prof. Dr. Helge Braun MdB
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Welcome

Erik Bodendieck (Dresden)

President
of the State Chamber of Physicians of Saxony

Image Credit: (c) SLÄK/fotografisch

Dear Ladies and Gentlemen,

Digitalization is infiltrating our everyday life at a breakneck pace, and medicine is in the middle of a digital revolution. These circumstances certainly provide many opportunities, but they also include risks that must be carefully considered. The progress of digital technologies is allowing for increasingly more precise and efficient diagnosis and treatment approaches across sectors.

At the same time, a myriad of clinical, social, ethical and legal issues are arising. How can the evaluation of extensive data collections ("Big Data") be reconciled with data protection and data security? What effects does High-Definition Medicine have on the Solidarity Principle? How can patient safety be guaranteed in the face of a staggering abundance of digital health applications? How must we adapt the medical curriculum and role of the physician to meet this digital transformation?

Wherever the answers might lead us, the well-being of our fellow humans remain the guiding light in these ever-changing surroundings.

These principles are echoed in the title of this year's Leopoldina-Symposium: "Mission – Innovation". Digital innovation is both a mission and a mandate - not only for medicine, but for society as a whole. Accordingly, an interdisciplinary dialogue with experts and scientists from several fields awaits you.

I wish all participants an exciting and stimulating event!

Erik Bodendieck
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Welcome

Heyo K. Kroemer ML (Berlin)

Chief Executive Officer
Charité – Universitätsmedizin Berlin

Dear Ladies and Gentlemen,

For centuries, healthcare systems have generated a large variety of patient data, ever increasing on a day-to-day basis. However, it is only during the last decades, with the progress in information technology, that it has been possible to analyze and process such large amounts of data.

The attainment of digital health data makes it possible to research medical-scientific questions faster and more efficiently than ever before, allowing us to question and optimize our conventional approaches. In the form of guidelines or quality indicators, evidence-based insights from these massive datasets find their way into acute medicine.

This data is also employed in precision medicine, where it is utilized in the development of complex, patient-specific therapy methods. This enhances the personalization and efficiency of care, and greatly expands access to medical expertise, especially in rural regions.

It is the duty of medical universities to pave the way for cutting-edge research and innovations, steering their development toward a benefit-oriented and personalized healthcare. The associated shift in knowledge requires constant support from digital innovations, and a continuous change in processes. The targeted and effective use of digital structures not only paves the way for the advancement and exchange of knowledge, but also for the quick incorporation of innovations into the healthcare setting. This is the only way to improve clinical and scientific research in a lasting manner and for the benefit of patients.

Today's symposium features not only examples of innovative applications in precision medicine, but also the ethical and legal challenges that accompany them. I am pleased that a large number of first-class speakers from science and politics are represented at this sym-

A video of the welcome address can be viewed online:

posium, so that together we may take a step toward the future of medicine. I wish you two exciting days of innovative lectures and stimulating discussions.

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Welcome

Gernot Marx (Aachen)

Representative DGAI and German Society for Telemedicine

Dear Ladies and Gentlemen,

The German healthcare system is constantly confronted with many challenges. This includes weak medical care structure in rural areas, an increasing shortage of physicians, and an aging population. Telemedical structures can help to solve these problems, as they allow for the 24/7 provision of expert knowledge in underserved regions, improving the quality of treatment in a sustainable and cost-effective manner. The greatest benefit from these developments, however, belongs to our patients, as digitalization enables them access to high quality, holistic, and personalized treatment.

Large amounts of patient data are collected daily in anesthesiology departments. The use of digital technologies to process and link these data enables physicians to identify possible risks and predict complications at an early stage. Of course, the physician remains in charge of treatment decision at all times. The digital applications serve as a support system, providing an optimal basis for decision-making by evaluating all individual patient data and presenting results quickly and clearly.

In the field of anesthesia, tele-consultations offer the possibility to provide immediate specialist supervision – from preoperative risk evaluation to post-anesthesiologic care.

Digitization also has enormous potential in intensive care medicine. Through telemedical support, an improvement in outcomes can already be seen. The best example is the large innovation fund project, TELnet@NRW. Through the cross-sector, digital health network of TELnet@NRW, teams of experienced specialist doctors and senior physicians, as well as intensive care staff from the university hospitals in Aachen and Münster are available to consult with cooperating physicians from the outpatient and inpatient sector.

To facilitate the transfer of such telemedical models to regular care, the Permanent Telemedicine Commission of the German Society for Anesthesia and Intensive Care Medicine

A video of the welcome address can be viewed online:

(DGAI) and the German Society for Telemedicine (DG Telemed) propose minimum methodological requirements for telemedical applications, thus ensuring a constant quality of care.

A future application is the virtual hospital. The virtual hospital is a digital platform that pools expertise from specialists nationwide. This bundling is intended to promote communication between physicians and access to specialist expertise. Ultimately, this approach will pave the way for an advanced healthcare structure that allows for the electronic exchange of treatment-relevant patient data and video consultations. This will enable patients to receive necessary treatments in an individualized, local and quality-oriented fashion. The pilot phase for this is scheduled to start in the spring of 2020.

Kind regards,

Prof. Dr. Gernot Marx, FRCA
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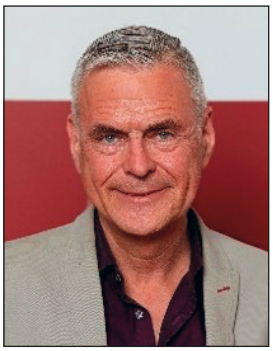
Welcome

Uwe Janssens

Past-President*
of the German Interdisciplinary Association for
Intensive Care and Emergency Medicine (DIVI e. V.)



The German Academy of Sciences Leopoldina reviews and addresses key scientific issues that are of prospective significance to society, and operates independently of political and economic objectives.

The upcoming symposium "Telematics and eHealth in Patient-Centered Acute Medicine", chaired by Professor Claudia Spies (Charité – Universitätsmedizin Berlin), will cover a broad range of relevant topics, with a focus on critical and emergency care medicine. High profile keynote speakers will provide deep insights into the rapidly changing environment of science, technology and innovation.

Telemedical support may play an important role in the near future, helping to overcome deficiencies in healthcare structures and optimize patient care. Despite dealing with complex issues, such as "high-definition medicine", "individualized medicine" and sociopolitical dimensions, the symposium does not lose sight of the critically ill patient. Improving care in the next decades implies that all measures should focus and enhance a patient-centered, personalized care approach. In light of the drastic increase in age of the population and rate of associated impairments, combined with the current and future shortages in medical and nursing care, all efforts should be undertaken to avoid further strain to the healthcare system and secure an adequate provision of care. This is certainly one of the key challenges in the near future.

* At the time of the symposium President of the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI e. V.)

A video of the welcome address can be viewed online:

The German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI e. V.) congratulates the organizers of the Leopoldina-Symposium on an excellent program and wishes all participants an exciting and fruitful experience.

Prof. Dr. Uwe Janssens
Chefarzt Klinik für Innere Medizin und Internistische Intensivmedizin Past Präsident der DIVI
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Welcome

Claudia Spies (Berlin)

Head
of Department of Anesthesiology and Operative Intensive Care Medicine
Campus Charité Mitte and Campus Virchow Klinikum
Charité – Universitätsmedizin Berlin

Dear Ladies and Gentlemen, Dear Colleagues,

It is my pleasure to welcome you to the Leopoldina Symposium 2020 "Mission – Innovation". Over the next two days, we will engage in broad discussions on innovations, digital technologies and their implementation in the acute medical setting.

Digital transformation is an urgent social challenge. Central issues include the reliable collection, processing, and interpretation of health-related data, as well as approaches to safeguard them in an increasingly interconnected world.

In order to apply data-driven scientific findings into acute medicine (i.e. to implement "machine-learning" or "deep medicine") we must critically discuss and evaluate the role of digital support systems, along with settings, conditions and its context of use.

The focus is on informed patients and their relatives, their wishes and their expectations. In order to successfully implement available innovations, such as telemedicine or robotics, organizational and system context-related interfaces must be designed and the proficiency of the staff is required to be developed accordingly.

To allow "digital advanced clinical decision support systems" (ACDSS) to become available to the parties involved in real time, digital and technical innovations must be systematically intertwined with medical specialization, with due regard to all aspects of data protection and data security. Although this goal can only be achieved by overcoming intersectoral boundaries and seeing ourselves as a multi-professional team, the creation of secure digital spaces to protect patients and respect their needs remains a prerequisite. Digital platforms for health data are required as a basis for individualized medicine, for which the development and provision of open source (not proprietary!) interfaces is essential. It is crucial that patients manage their data themselves, and incorporate their "biomarkers" on a voluntary basis. At the same time, this data must be both secure and retrievable (i.e. immediately available in acute cases) if the patient wishes so.

A video of the welcome address can be viewed online:

The aim of our symposium is to deliberate the possibilities and challenges of digital transformation in acute medicine, and harmonize our efforts for the benefit of our patients. At this Leopoldina-Symposium, we will discuss how digital transformation in medicine can succeed.

My special thanks go to the Leopoldina –National Academy of Sciences, as the patron of this symposium. I also extend my gratitude to the professional societies – the German Society for Anaesthesiology and Intensive Care Medicine (DGAI), the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI), the European Society of Intensive Care Medicine (ESICM), and the German Society of Telemedicine (DGTelemed). In addition, I would like to thank our industry partners for their support and participation.

Lastly, I would like to thank you, dear attendees, for contributing to the event by sharing your work, your perspectives, your visions and your solutions for a better tomorrow. May scientific discourse provide inspiration and insight to us all in the coming days, making this symposium a success by allowing us to create new and better ways to care for our patients.

Sincerely,

Prof. Dr. Claudia Spies ML
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Telematics and eHealth in Patient-Centered Acute Medicine

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The Mission of Innovation

Maria Heinrich (Berlin), Rudolf Mörgeli (Berlin),
Gunnar Lachmann (Berlin), Claudia Spies ML (Berlin)

Summary

This article provides a brief overview of the relevance, objectives and content of the *Nova Acta Leopoldina* "Mission – Innovation: Telematics, eHealth and High-Definition Medicine in Patient-Centered Acute Medicine".

Zusammenfassung

Dieser Beitrag gibt einen kurzen Überblick über die Relevanz, die Ziele und den Inhalt der *Nova Acta Leopoldina* "Mission – Innovation: Telematik, eHealth und High Definition Medicine in der patientenzentrierten Akutmedizin".

For centuries, knowledge in the natural sciences has been developed based on principles of observation, measurement and analysis. Each of these steps has been subject to constant technological progress, which now allows scientific, data-driven approaches to find their way into the clinical routine (Blei and Smyth 2017, Charitos et al. 2018). Through the application of new technologies and modern data processing with artificial intelligence (AI) capabilities, patient-centered innovations can flourish. Moving forward, patient-centered care must remain the focus of our efforts – digital applications do not fulfil an end in themselves.

The Nova Acta Leopoldina "Mission – Innovation: Telematics, eHealth and High-Definition Medicine in Patient-Centered Acute Medicine" presents the critical analyses of international experts on the innovative technologies and their integration into acute medicine. The *Nova Acta Leopoldina* focuses not only on the application of technical components and structures ("tool view"), but also on the incorporation of knowledge in the appropriate environment and context ("ensemble view"). To this effect, we deal with the interdisciplinary and multi-professional possibilities, identify challenges, and consider our responsibilities in guiding innovative approaches in the acute medicine setting, ensuring that it is duly applied for the benefit of the patient.

The tool view focuses on telematics and e-health, which form the foundations for cross-sectoral networks. Information and communication technologies are summarized under eHealth (*Bundesministerium für Gesundheit* 2019), which enables telemedicine and telemonitoring (among others). Meanwhile, telematics deals with the computerized evaluation of telecommunications (Vosshoff et al. 2015).

The symposium trailer can be viewed online:

Currently, eHealth and telematics are the focus of numerous innovation projects supported by the Innovation Fund. From 2016 to 2019, the Innovation Fund distributed approximately 300 million euros per year, which were made available by the Federal Government through the Federal Joint Committee (G-BA) to promote projects that "qualitatively develop the provision of statutory health insurance in Germany" (*Gemeinsamer Bundesausschuss Innovationsausschuss* 2018). The funding announcement on new forms of health care selected the thematic field "Telemedical cooperation networks of inpatient and outpatient facilities to improve medical care", highlighting the relevance of the application of telematics and eHealth (*Gemeinsamer Bundesausschuss Innovationsausschuss* 2018).

With a focus on the patient perspective, the *Nova Acta Leopoldina* will discuss projects of the Innovation Fund that deal with telematics and e-health in acute medicine. The "Enhanced Recovery after Intensive Care" (ERIC) project intents to avoid long-term consequences of intensive care treatment, such as "post-intensive care syndromes" (PICS) and long-term ventilation, by providing telemedical support. The *TelNet@NRW* Project aims to improve the quality of treatment by establishing telemedical applications across sectors, especially in the fields of intensive care and infectiology. The "Acute Neurological Care in Northeast Germany with Telemedical Support" (ANNOTeM) Project uses telemedicine to assemble interdisciplinary teams for standardized emergency diagnostics in acute neurological cases.

It must be noted that each innovative measure must be planned, implemented and evaluated in a system-related, organizational and individual context (see Fig. 1).

In a system-related context, for example, intersectoral networking, data protection provisions and interprofessional cooperation among physicians, nurses, therapists, patients, and relatives are decisive preconditions for the conduction of therapy-related measures, such as shared decision-making processes or follow-up visits. In the organizational context, it is crucial to consider how well-informed patients and team members are, as well as how knowledge management, competence-based treatment and training are contucted. Moreover, each measure must be considered in the individual context, as each patient has a different baseline. Pre-existing conditions, vulnerability, complications and factors such as social, mental and psychological support have a significant impact.

Accordingly, political, legal and socio-economic framework conditions related to the application of e-Health and telematics are discussed by experts. Aspects such as data protection, knowledge management and the removal of intersectoral barriers are highlighted.

The ensemble view focuses on High-Definition Medicine (Torkamani et al. 2017). This requires viewing *disease* as a deviation from a patient-specific baseline, and the potential for personalized prevention and treatment approaches. This not only includes data collection, but also the handling and understanding of individual health-related data, which is crucial in acute medicine.

Similarly, each consideration must regard system-related, organizational and individual contexts (Fig. 1). Increasing amounts of information can be gathered through the advancement and dissemination of technologies, including DNA sequencing, imaging, monitoring of physiological and environmental parameters, and behavioral tracking (individual context). Key prerequisites are health data platforms, electronic medical records and advanced clinical decision-support systems in the organizational context, as well as remote facilities, interoperability and data availability in the system-related context. In this way, it is possible to evaluate data responsibility and introduce the generated knowledge into medical processes.

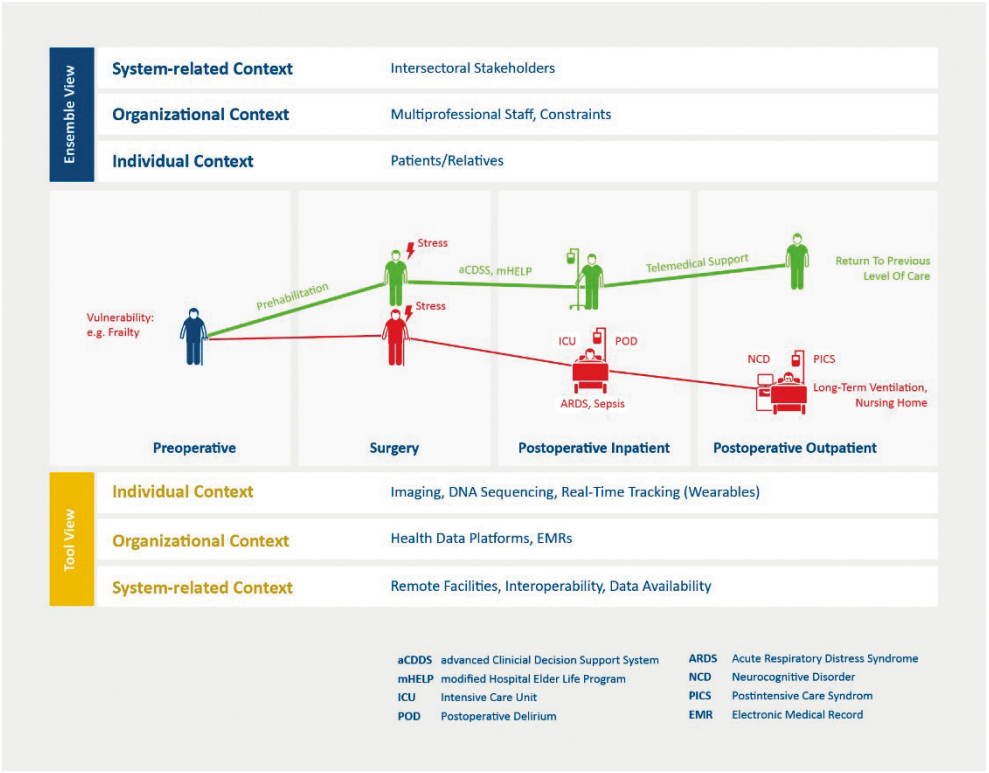

Fig. 1 Observed trajectories of patients in the acute medicine setting, depicting individual, organizational and system-related key factors in tool view and ensemble view.

The Nova Acta Leopoldina addresses the requirements for the successful application of digital support structures, such as data availability, interoperability, data integration and automation. Approaches involving "Machine Learning" and "Deep Learning" are discussed, underlining that the generated information must be managed responsibly and made available for the control of medical processes.

The focus remains on patients and their relatives, their wishes and their expectations: patient-centered factors (such as delirium, cognition, pain, frailty and relevant biomarkers) and changes following "acute on chronic" care are discussed. Based on these premises, specific health factors can be identified for each person, paving the way for the development of individual strategies for the prevention and treatment of diseases (Fig. 1). Ultimately, this will allow for the creation of a far superior healthcare system – one that is devoted to minimizing disease and suffering, and promoting long-term health throughout our society.

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The Patient's Perspective

Claudia Denke (Berlin)

It is the aim of the Leopoldina Symposium "Mission-Innovation" to discuss interdisciplinary possibilities, challenges and responsibilities of telematic, eHealth and High Definition Medicine, as well as the resulting innovation potential in acute medicine so that we can apply it for the benefit of patients.

In order to be able to evaluate the potential and the benefits for our patients, it is crucial to engage with the patient perspective.

As an example, critical illness and intensive care tend to be unexpected or sudden events for the majority of patients. Thus, the stay in the ICU would be a distressing time for them. Patients interviewed about psychological stressors most frequently reported a fear of dying, uncertainty about the future and recovery, lack of control and privacy, difficulties in communication, helplessness, feelings of bewilderment, depersonalization, and loneliness. Moreover, there are emotional stressors, for example, submission to caregivers and family concerns. Patients felt isolated from their families, friends, and the outside world, as well as abandonment and lack of information. In many interviews, the patients have initially no memories of the ICU. Fragmentary memories of ICU often recur during interviews and follow-up investigations. About half of the patients describe confusion between dream and reality, or temporal and spatial disorientation. Frightening nightmares and hallucinations were the most common recollection, and were associated with more memories of pain, fear and panic.

However, patients also link the treatment of critical illness with positive experiences. These are mainly related with support from their health care team and family. Efforts of the nursing staff to provide the patient with mental – as well as physical – care were perceived by patients. Many patients felt that they were placed in good hands, and they described having the impression that they had been well cared for and supported. The majority of patients had the impression that their dignity was maintained and that they were treated with respect. Additionally, the needs and well-being of the patients in the ICU are perceived and assessed very differently by patients and health care providers.

A video of the presentation can be viewed online:

Against this background, in this session it is in our best interest to talk with patients who have survived intensive care, and their relatives. The mission of innovation can only be successful if we take into account the experiences of our patients and incorporate them into the process.

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German Innovation Fund Projects – Key Results

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The Challenges of Intensive Care Medicine

Björn Weiss (Berlin), Claudia Spies ML (Berlin) and the *ERIC*[1] S*tudy Group*

Summary

Over the last decades, the number of ICU admissions in Germany has steadily increased. Simultaneously, patients are more likely to survive their critical illness, but survivors of critical illness frequently face functional impairments regarding their cognitive function, mental health, mobility and health-related quality of life, summarized as "Post-Intensive Care Syndrome (PICS)". For clinicians, it is imperative to ensure the highest quality of ICU care and utilize evidence-based measures to mitigate those detrimental patient outcomes. In Germany, the DIVI has issued evidence-based "German Quality Indicators of Intensive Care" (QIs), which reflect current best practice in critical care. Their application can help reduce PICS burden. The ERIC-care-program at *Charité – Universitätsmedizin* Berlin utilizes telemedicine to enhance adherence to these QIs in hospitals of the Berlin metropolitan area. The newly established tele-ICU at Campus Virchow-Klinikum, which has high-quality audio-visual equipment and is staffed with experienced intensivists and nurses, provides daily, multiprofessional and QI-centered medical rounds for eleven centers with ICUs in the region. For a comprehensive evaluation, the ERIC-care-program is designed as a multicentre, pragmatic, cluster-randomized controlled trial with an open cohort stepped-wedge design with continuous recruitment. As such, it investigates the clinical effectiveness of a telemedical intervention in the ICU to improve the adherence to the DIVI QIs and is funded by the Innovation Committee of the Federal Joint Committee (01NVF16011). The ERIC-care-program aims to deliver highest quality of care to ICU patients, no matter where they are admitted.

1 Enhanced Recovery after Intensive Care (ERIC):
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A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

A video illustrating a Telemedical QI round can be viewed online:

Zusammenfassung

In den letzten Jahrzehnten ist die Zahl der Intensiveinweisungen in Deutschland stetig gestiegen. Gleichzeitig erhöht sich die Wahrscheinlichkeit, dass Patienten ihre kritische Erkrankung überleben. Überlebende kritischer Erkrankungen erfahren jedoch häufig eine funktionelle Beeinträchtigung hinsichtlich ihrer kognitiven Funktionen, psychischen Gesundheit, Mobilität und gesundheitsbezogenen Lebensqualität, welche unter dem Begriff *Post-Intensive Care Syndrom* (PICS) zusammengefasst werden. Für Kliniker ist es zwingend erforderlich, die höchste Qualität der Intensivpflege anzubieten und evidenzbasierte Maßnahmen zu nutzen, um diese nachteiligen Patientenergebnisse abzumildern. In Deutschland hat die DIVI evidenzbasierte „Qualitätsindikatoren der Intensivmedizin" (QIs) herausgegeben, die die aktuell bewährte Praxis in der Intensivmedizin reflektieren. Ihre Anwendung kann helfen, die gesundheitliche Belastung von PICS zu reduzieren. Das ERIC-Programm an der Charité – Universitätsmedizin Berlin nutzt die Telemedizin, um eine bessere Einhaltung dieser QIs in Krankenhäusern der Metropolregion Berlin zu ermöglichen. Die neu eingerichtete Tele-Intensivstation am Campus Virchow-Klinikum verfügt über eine hochwertige audiovisuelle Ausstattung und ist mit erfahrenen Intensivmedizinern und Pflegekräften besetzt. Sie bietet elf regionalen Gesundheitszentren mit Intensivstationen tägliche multiprofessionelle und QI-zentrierte Visiten. Um das ERIC-Programm umfassend zu evaluieren, wurde eine multizentrische, pragmatische, cluster-randomisierte kontrollierte Studie mit offenen Kohorten, *Stepped-Wedge-Design* und kontinuierlicher Patientenrekrutierung konzipiert. Als solches untersucht sie die klinische Wirksamkeit einer telemedizinischen Intervention auf Intensivstationen, um die Einhaltung der DIVI-QIs zu verbessern. Sie wird vom Innovationsausschuss des Gemeinsamen Bundesausschusses gefördert (01NVF16011). Das ERIC-Programm zielt darauf ab, Patienten auf der Intensivstation höchste Versorgungsqualität zu bieten, egal wo sie aufgenommen werden.

Over 2,1 million people are admitted to a German intensive care unit each year. According to a June 2020 report from the German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI), there are 31,569 intensive care beds in Germany, located at more than 1,200 sites. As such, Germany has one of the largest intensive care treatment capacities in the world (Wunsch et al. 2008).

With more beds and increased chances for survival due to advanced technologies, the number of critical-care survivors has significantly increased in the last 20 years and imposes effects on the German healthcare sector, exceeding the inpatient-sector (Stevenson et al. 2014). The fragmentation of the health care system and the lack of networking between the inpatient and outpatient sectors in Germany results in poor follow-up treatment of patients. However, these follow ups are needed:
Studies revealed that survivors of intensive care show a characteristic pattern of secondary diseases. Regardless of the reason for admission to the intensive care unit, these affect critical functional domains: the musculoskeletal system, cognition and mental health. As the observed trajectory is typical, the consequences of intensive care have been labelled "Post-Intensive Care Syndrome", or PICS (Elliot et al. 2014). It is especially concerning that many of these are not simply temportary impairments temporary, but persist.

Forty percent of these patients suffer from measurable cognitive impairment after discharge. The majority of these are still detectable after one year (Pandharipande et al. 2013). The severity ranges from impairments comparable to traumatic brain injury up to mild-moderate Alzheimer's dementia. Studies on ARDS-survivors revealed that even five years after having survived ARDS, the median distance walked in 6 minutes was three quarters of the distance in a matched control population – despite having a comparable muscle mass on examination, patients still perceived weakness and experienced limited possibility of physical activity (Herridge et al. 2003, Herridge et al. 2011). This "ICU-acquired weakness" (ICUAW) is another major cause for post-intensive care burden (Herridge et al. 2014).

Finally, mental health is frequently affected in the form of depression and anxiety (Jackson et al. 2014). The utilization of psychopharmaceuticals is significantly higher than in

matched population-based controls (Wunsch et al. 2014). All of these impairments result in increased healthcare utilization, care-dependency, a lower health-related quality of life and an increased risk of long-term mortality.

The most serious challenge facing Germany is the increasing population of chronically critically ill patients, especially those patients who experience a permanent dependence on mechanical ventilation.

As there is no standardized care-setting for these patients after the acute phase of illness. These patients can be found in various care situations, including acute-care hospitals, rehabilitation facilities and nursing homes (Peñuelas et al. 2011). Nelson and colleagues report that these patients utilize a significant proportion health-care resources, and the DRG-groups are among the most heavily weighted in the system (Nelson et al. 2010). Especially in the German context, this results in a significant risk for PICS in patients (Brummel et al. 2017), especially with Germany's high provision and utilization of critical care, where the demographic development results in vulnerable groups (e.g. frail patients). In summary, it seems essential to keep the risk for patients as low as possible and to ensure adequate care.

Evidence-Based Measures

In the context of PICS and chronic critical illness, evidence-based strategies should be used to enhance recovery and mitigate the burden for ICU survivors. Bundles of measures include the management of delirium (Luetz et al. 2016), the preference of no-or-light sedation (Balzer et al 2015, Shehabi et al. 2012), the conduction of spontaneous breathing trials (Girard et al. 2008) and weaning programs, as well as the rational use of antibiotics, early physiotherapy (Schaller et al. 2016) and adequate medical information for families. Often, evidence-based guidelines exist for these domains, but implementation rates are low. Training strategies like special educational programs show a heterogenous effectivity in implementation (Carrothers et al. 2013). The delay caused by a training program, which may reach up to 5 years, is to be considered particularly critical. A European survey conducted by Luetz and colleagues, for example, showed that only 27% of a one-day ICU-population received delirium-monitoring with a validated instrument, even though guidelines with this recommendation were available since 2005 and updated in 2010 (Luetz et al. 2010). Therefore, the first step seems to find a way to adequately monitor the critical evidence. In Germany, the DIVI has summarized evidence-based quality indicators for intensive care treatment as the "German Quality Indicators of Intensive Care" (QIs), with the first version established in 2010 (Braun et al. 2010, Kumpf et al. 2017). QIs build a framework for structural- and process-quality to adequately use healthcare resources. The QIs can be used to develop a multi-professional medical round to ensure that quality is high and the patient receives evidence based care. The operationalization of QIs to a daily, structured medical round was the first step in the ERIC care-program.

From Structured QI-Round to Telemedicine

Telemedicine in critical care is not a new phenomenon and has become an integral part of critical care, especially in care settings with reduced access to human resources, such as in-

tensive-care specialists. Tele-ICUs typically consist of a telemedical hub and remote sites that are equipped with carts or robots to establish an audio-video connection. In addition, electronic-health-care data (EMR-data) are shared to various degrees, and depending on the tele-ICU model used. There is evidence that telemedicine in intensive care reduces ICU mortality and lengths of stay in the ICU, and is able to increase quality of care. However, there has been no approach to show whether an improvement to care by reducing long-term consequences is able to be achieved through increased standardization and implementation of evidence-based medicine by a specialist round, along a given set of quality indicators.

The ERIC-care-program fills this gap by providing structured rounds in a network of ICUs ensuring that DIVI-QIs are monitored at the bedside.

The ERIC Telemedical Round

The tele-ICU was established at the Charité-Universitätsmedizin in Berlin and it is equipped with three workstations. It is staffed seven days a week. An analogously qualified on-call service was established for use during the day and the night, by an experienced ICU specialist consultant. In the Berlin metropolitan area there are approximately 150,000 ICU admissions per year. Eleven centers with ICUs have been connected to the tele-ICU during the project.

Participating remote ICUs receive a fixed appointment time slot per day. Outside this slot there is a 24/7 on-call availability. The rounds are conducted in a tandem-team consisting of an ICU specialist and a specialised nurse. Directly before the round, a call is made to the remote ICU to discuss who will be rounded and with whom the round will take place. After the intensive care unit has positioned the cart and released the connection setup, an end-to-end encrypted connection is established. The camera is now controlled by the Tele-ICU team and a structured QI-round follows. During the round, medical questions of a more general nature are typically discussed as a part of the QI-round ("Daily multi-professional visit with documentation of daily goals"). The duration of a visit is usually about 15 –20 minutes. This means that approximately 30 rounds per day are possible at one workstation. Important factors for the acceptance of the visits are staff continuity, proper time management and regularity, as well as the interdisciplinary and multi-professional character. Transparency is also an essential factor – especially when different opinions on diagnostic or therapeutic decisions arise. In the event of disagreements, it is helpful to have a professional, standardized procedure, supported by a joint incident management system. This could, for example, allow case conferences across different clinics.

ERIC – A New Form of Care

In order to enable a comprehensive evaluation, the ERIC Care Program has been incorporated in the format of a clinical trial. ERIC is a multicentre, pragmatic, cluster-randomized controlled trial with an open cohort stepped-wedge design with continuous recruitment.
It aims to demonstrate the clinical effectiveness of a telemedical intervention in the ICU to improve the adherence to standard-quality indicators. The trial received funding from the German Innovation Fund ('New Forms of Care') coordinated by the Innovation Committee of the Federal Joint Committee (ERIC, 01NVF16011).

Fig. 1 Robot Vita – a self-driving robot that allows remote-site consultations at the patient's bedside.

In addition, all patients receive a structured 3- and 6-month follow-up to assess for PICS and CCI in cooperation with the general practitioner of the patient – this can be considered the second pillar of ERIC. Secondary outcome measures include the mental health condition, neurocognitive function, the physical function, organ-dysfunction, HRQoL, all-cause mortality and lengths of utilization of different healthcare facilities, including ICU, hospital and rehabilitation.

Redefining Quality of Critical Care

Quality of care is one of the most important aspects of healthcare-provision in the future. The WHO defines quality of care as being "*the extent to which health care services provided to individuals and patient populations improve desired health outcomes. In order to achieve this, health care must be safe, effective, timely, efficient, equitable and people-centred.*" (*World Health Organization* 2018, Lohr 1990).

The ERIC-care program strictly follows these rules. It increases safety by granting access to tertiary health care in community hospitals' effectiveness by adhering to evidence-based standards, as well as being timely, efficient, equitable and patient-centred. ERIC considers the very important aspect of value-based-healthcare with a clear focus on quality of care.

It also counteracts the fragmentation of the health care system and uses new networks to create quality structures that can ultimately guarantee financially viable patient care at the highest level.

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Summary

Germany's socio-demographic challenges are reflected in a growing discrepancy between the supply and demand for medical services: the demand is constantly growing but meets limited and insufficient human resources. Taking these obstacles into account, telemedicine is a possible solution to face the sociodemographic challenges of the 21st century. Telemedicine offers innovative approaches to achieve long-term quality in healthcare.

On the basis of the TELnet@NRW best-practice project, the requirements and potentials of tele-intensive care medicine were demonstrated, and then implemented in practice. TELnet@NRW shows that telemedical procedures improve the interdisciplinary exchange and thus increase quality and efficiency in health care. These care optimizations lead to increased quality of life for patients and ensure medical expertise also in remote areas at the same time. With the nationwide establishment of telemedical applications, new structures are being created in our healthcare system, which will enable a more efficient use of existing resources. TELnet@NRW was funded with €19.5 million from February 2017 to January 2020. Experts of the Aachen and Münster university hospitals, together with 17 cooperating hospitals and two physician networks, conducted daily expert teleconsultations. In order to improve evidence-based care, availability is provided 24/7, 365 days per year, accompanied by regular training for doctors and nursing staff. Communication takes place via a highly encrypted audio-video conference system and a certified data-exchange platform *FallAkte Plus*. The aim of TELnet@NRW was to establish a cross-sector telemedical network as a new digital form of care. A more than 150,000 patients were included in TELnet@NRW. With TELnet@NRW, we have taken a major step towards a sustainable healthcare system that allows us to provide patients with top quality health care close to their homes.

Zusammenfassung

Die soziodemographischen Herausforderungen in Deutschland spiegeln sich in einer wachsenden Diskrepanz zwischen Nachfrage und Angebot medizinischer Leistungen wider. Der steigenden Nachfrage steht eine begrenzte und unzureichende personelle Ressource gegenüber. Unter Berücksichtigung dieser Hindernisse ist die Telemedizin eine mögliche Option, den soziodemographischen Herausforderungen des 21. Jahrhunderts mit innovativen Ansätzen zur langfristigen Qualitätssicherung und -verbesserung zu begegnen.

Anhand des Best-Practice-Projekts TELnet@NRW werden die Anforderungen und Potenziale in der Tele-Intensivmedizin aufgezeigt und praktisch umgesetzt. TELnet@NRW zeigt, dass telemedizinische Verfahren den interdisziplinären Austausch verbessern und dadurch eine Steigerung von Qualität und Effizienz in der Gesundheitsver-

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sorgung hervorrufen. Diese System- und Versorgungsoptimierungen führen zu einem Anstieg an Lebensqualität bei den Patientinnen und Patienten und sichern zugleich die medizinische Expertise in der Fläche. Mit der flächendeckenden Etablierung von telemedizinischen Anwendungen werden neue Strukturen im Gesundheitswesen geschaffen, die eine effizientere Nutzung der vorhandenen Ressourcen ermöglichen. TELnet@NRW wurde in dem Zeitraum von Februar 2017 bis Januar 2020 mit einer Summe von ca. 20 Mio. € gefördert. Die Experten der beiden Universitätskliniken Aachen und Münster führen gemeinsam mit den 17 Kooperationskrankenhäusern und zwei Ärztenetzen tagtäglich Televisiten und -konsile durch. Eine 24/7/365 Verfügbarkeit, begleitet von regelmäßigen Schulungen für Ärzte und Pflegepersonal, die auf eine Verbesserung der evidenzbasierten Versorgung abzielen, wurde bereitgestellt. Die Kommunikation erfolgte über ein hochverschlüsseltes Audio-Video-Konferenzsystem und die zertifizierte Datenaustauschplattform *FallAkte Plus*. Ziel von TELnet@NRW ist der Aufbau eines sektorenübergreifenden telemedizinischen Netzwerks als neue digitale Versorgungsform. Insgesamt wurden mehr als 150.000 Patienten in TELnet@NRW eingeschlossen. Mit TELnet@NRW konnte ein großer Schritt in Richtung zukunftssicherer Gesundheitsversorgung gemacht werden und das heißt für uns, den Patientinnen und Patienten eine qualitativ hochwertige Spitzenversorgung in Wohnortnähe zu ermöglichen.

Introduction

Compared to other fields, the German healthcare system is characterized by its dynamics. Due to demographic changes, changing living conditions in society and medical-technical progress, the system has to be adapted continuously. Against the background of an ageing society with increasing multimorbidity and rising demand for long-term care with simultaneous staff shortages, the design of modern, future-proof healthcare appears more important than ever (Schrappe und Pfaff 2016).

One particular challenge will be to ensure high-quality and comprehensive health care in the future by taking into account the increasing shortage of doctors and nurses. With the help of telemedical network structures, expert knowledge can be made available in underserved regions independent of time and place, i.e. a sustainable and cost-effective improvement in the quality of treatment is generated. Numerous international studies and German-wide projects have shown positive results in the care of seriously ill patients, especially in the fields of tele-emergency medicine and tele-intensive care medicine (Marx et al. 2015). By using telemedicine, modern and up-to-date care network structures can be created, providing a needs-based, local and quality-oriented treatment option by addressing structural care deficits. In this context, telemedicine is understood as the structured cooperation and networking of different service providers using digital information and communication technologies. Innovative telemedical network structures enable the provision of expert knowledge from different specialist areas independent of location and time. Especially in the field of anesthesiology, large amounts of patient data are collected and processed daily. By simultaneously evaluating data, digital technologies assist the physician in recognizing possible risks earlier and consequently predicting complications at an early stage. Despite these outstanding technologies, the final decision-making authority stays with the physician on site. Hence, digital applications only serve as a support system and provide the physician with an optimal basis for decision making. In the field of anesthesia, tele-consultations offer the possibility of specialist medical supervision from preoperative risk evaluation to post-anesthesiologic care, tailored to the patient's needs and without delay. Digitization also holds enormous potential in intensive care medicine showing that telemedical support is associated with a significant improvement in outcomes (Deisz et al. 2016). An outstanding example is the large Innovation fond project TELnet@NRW. Via the cross-sectoral, digital health network of TELnet@NRW, teams of experienced specialists and senior physicians as well as intensive care nurses from

the university hospitals in Aachen and Muenster support cooperating physicians from the outpatient and inpatient sectors by expert teleconsultations. In order to facilitate the transfer of telemedical models into standard care, the Standing Commission on Telemedicine of the German Society for Anaesthesia and Intensive Care Medicine (DGAI) and the German Society for Telemedicine (DG Telemed) propose methodological requirements for telemedical applications to ensure a constant quality of care. Scientific projects can be supported within the framework of the Innovation fond, which has an annual funding volume of € 300 million. The projects enable new cross-sectoral care structures to be tested in practice on a defined patient population and reliable findings on real patient benefits to be gained.

Background and Objectives

Ensuring high-quality healthcare regardless of place of residence is one of the most fundamental goals in the German healthcare system – now and especially in the future. It is particularly important that every citizen receives the best possible care in the vicinity of his or her own place of residence or stay, even in the case of complex medical problems. TELnet@NRW, which is supported by the Innovation Fund, established a cross-sectoral telemedical network as a new digital form of care. With a funding amount of € 19.5 million between February 2017 and January 2020, TELnet@NRW achieved comprehensive and measurable improvement of treatment and process quality as well as an increase in efficiency in the care of relevant patient groups in the fields of infectiology and intensive care medicine (*Universitätsklinikum Aachen* 2020). More than two million intensive care patients and an estimated 700,000 deaths per year due to bacterial resistance reflect the enormous potential of these two areas, demonstrating the immense importance for research (O'Neill 2016). On the one hand, the increasing development of resistance by bacteria represents a constantly growing threat to patients, and thus enormously restricts the treatment options of physicians. On the other hand, sepsis is the most frequent cause of morbidity and mortality in most intensive care units worldwide, and the third most frequent cause of death in Germany (Deisz et al. 2016). These facts are not only devastating for medical care, but at a cost of billions of Euros, also burden the healthcare industry.

In order to minimize this problem, it is necessary to implement optimal guideline-based treatments in the outpatient and inpatient sectors. For this purpose, medical professional associations, like the German Society for Infectiology (DGI), have referred to the guideline "Strategy for the safety of rational antibiotic use in hospitals" and "Choosing Wisely". Taking the clinical picture of sepsis as the third most frequent cause of death in Germany into account, a guideline-compliant treatment within a few hours is indispensable as it reduces mortality by 25 %. TELnet@NRW addressed these deficits in care and established a cross-sectoral telemedical network that measurably improved the management of infectious diseases and sepsis (Marx et al. 2015). The participating hospitals and medical practices have the opportunity to contact and exchange information via digital applications with intensive care and infectiology experts from two university hospitals 24 hours a day, 365 days per year. The antibiotic treatment in the inpatient and outpatient sectors are optimized by means of treatment in accordance with guidelines. Taking above-mentioned aspects into account, TELnet@NRW used telemedicine to overcome the numerous challenges in the healthcare system to ensure local healthcare. Several factors have been identified as success factors, including better adherence to guideline-based therapy through expert teleconsultations.

Study Design and Evaluation

TELnet@NRW is a multi-center, stepped-wedge cluster randomized trial conducted at two University Hospitals in North Rhine-Westphalia (Aachen and Muenster), 17 hospitals and 103 outpatient physicians associated with two physician networks. In a randomized stepped-wedge study design, the participating hospitals and physicians represented the different clusters. Thus, randomization was not carried out at patient level. Accordingly, the effect of the intervention on the entire patient collective is evaluated. The intervention, i.e. the expert teleconsultations, was rolled out randomly and with a time lag ("steps") to the individual clusters (outpatient physicians and hospitals). Every hospital or practice is initially in the control phase, in which no intervention takes place, before entering the intervention phase itself (*Universitätsklinikum Aachen* 2020).

After ethical approval and written informed consent, patients aged ≥18 were included in the project by the participating hospitals and private practices. Excluded were underaged minors or pregnant patients, patients with an advanced treatment guideline that limits life-saving treatment, and patients who did not formally consent to participate in the study (*Universitätsklinikum Aachen* 2020). For the evaluation of vaccine rates, we also included children at the outpatient physician practices. Patients with a focus on infectious disease treatment in the outpatient sector and sepsis in the inpatient sector were included. After inclusion in the study, patients were visited by daily expert teleconsultations on site upon request by experts from the University Hospitals Aachen and Muenster, thus they received medical treatment with bundled expertise. Availability is provided 24 hours per day, 365 days per year, accompanied by training for doctors and nursing staff, aimed at improving evidence-based care. In this way, additional and highly specialized medical expertise and competence was made available at the required location in a needs-based and cost-efficient manner. Communication took place via a highly *encrypted audio-video conference system and the certified data exchange platform FallAkte Plus*. The primary outcome measure adhered to the 10-DGI recommendations "Smart decisions in infectiology". ICU and sepsis mortality, ICU length of stay (LOS) and adherence to the 3-hour and 6-hour sepsis bundles were measured as secondary outcomes. At the end of the recruitment phase, over 150,000 patients were included in the TELnet@NRW study (*Universitätsklinikum Aachen* 2020). The evaluation was based on primary data as well as billing data from the associations of panel physicians in North Rhine-Westphalia. Initial results of the evaluation have shown that telemedical provision of expert knowledge in correlation with the ten decision criteria of the Society for Infectiology has significant positive cross-sectoral effect on the quality of treatment. In particular, improvements in the treatment of sepsis have a significant impact on the survival probability of patients.

IT Infrastructure

The basis for the implementation of a telemedical network is a secure video communication link with a fast and protected data exchange between the involved institutions. In productive operation, all mobile devices (like computers, monitors, cameras or mobile ICU devices) are brought to the patient, so that the physician and the experts on both sides can exchange information about the individual patient via a teleconsultation. X-ray images and other findings can also be exchanged via this system. The connection is established via a highly secured data line.

During the project period of TELnet@NRW, several types of data were collected, i.e. administrative data, arising during the treatment in the hospital as well as data from new documentation processes. Data from the documentation forms of the consultations and CRFs for scoring are evaluated and processed while using various statistical procedures and taking data protection aspects into account. The data are transmitted, pseudonymized, encrypted and archived in a legally secure manner to protect it from unauthorized access. The results are evaluated and published anonymously, so that individual data cannot be assigned to specific hospitals or practices. In order to ensure a high quality of data collection, all specialists are trained in documentation procedures. Furthermore, documentation assistants are made available to hospitals and plausibility checks are carried out. In practice, the secure video communication link ensures fast and protected data exchange as well as communication independent of time and location. Via a secure data line and a highly encrypted audio-video conferencing system, the two university hospitals can exchange information with the cooperating hospitals and doctors' practices around the clock. The focus here is on the *FallAkte Plus* of Healthcare IT Solutions, a TÜV-tested electronic collaboration platform for secure doctor-to-doctor communication with certified data protection, which enables medical cooperation in the treatment of joint patients across institutional and sector boundaries (*Healthcare IT Solutions* 2020). Data collected via the *FallAkte Plus* are selectively opened and made available in a secure manner to co-treatment partners. Even if the data is stored centrally, data protection has the highest priority and sensitive handling is guaranteed at all times.

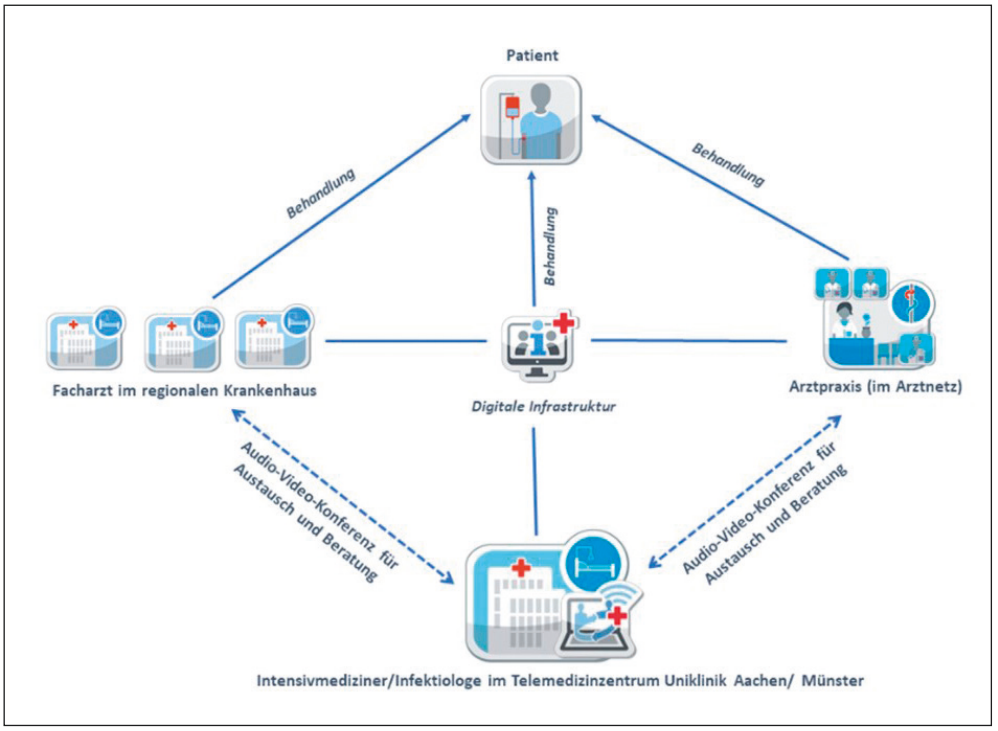

Fig.1 Functionality of TELnet@NRW (Universitätsklinikum Aachen 2020)

Conclusion and Outlook

Over the past three years, TELnet@NRW has managed to establish a large and successfully functioning, cross-sectoral telemedical network for intensive care medicine and infectiology. This success is owed to a strong team from the two model regions Aachen and Muenster as well as many project and network partners. With more than 150,000 patients included and over 10,000 ICU patients telemedically cared for, the project has far exceeded the expectations of those responsible, making it the largest telemedical study in Europe. The first evaluation results also underline the success of the project supported by the Innovation Fond. Based on the cross-sectoral telemedical cooperation between the various hospitals and university clinics, a significant increase in the quality of treatment was observed in the care of patients in intensive care and infectiology. This increase was measured by the Choosing-Wiseley recommendation of the German Society for Infectiology (DGI). The improvements in sepsis treatment were also particularly striking. It was found that expert teleconsultations increase the probability that patients are treated according to the Choosing-Wiseley recommendations of the DGI. For the inpatient sector, further analyses are to be carried out and the effectiveness and importance of cross-sectoral telemedical networks in care should be made clear. TELnet@NRW has shown that new digital healthcare structures enable a measurable improvement in care close to home. Act jointly. Treat competently.

Based on the positive experiences of TELnet@NRW, the Virtual Hospital in North Rhine-Westphalia was established in March 2020. With the Virtual Hospital, the state government wants to bring highly specialized expert knowledge to the area. Current figures show that the Virtual Hospital meets a high demand with almost 200 COVID-19 patients telemedically cared for by the University Hospital Aachen and Muenster.

The next step will be the development of a state-wide, digitally supported medical network to ensure local and quality-oriented medical treatment. By this, expertise of the top medical centers is equally and nationwide made available via telemedical networks. Indication-related expertise of physicians from seven university hospitals will be made available to hospitals and general practitioners in NRW. In the future, cross-sector, digitally supported cooperation in the field of indication-based medicine is intended to achieve long-term optimized patient care close to home.

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Effects of a TeleNeurology Assisted Multi-Layered Network for Acute Neurological Emergencies in North-East Germany: Intervention Components, Evaluation and Early Results

Heinrich Audebert (Berlin)

Background

Diagnosis and treatment of acute neurological emergencies require neurological expertise and are time-sensitive with better prognosis the earlier effective treatment can be started. The lack of neurological expertise in underserved regions poses a major barrier for state-of-the-art care for patients with acute neurological emergencies, and leads to disparities in provision of health care.

Aims

The main objective of ANNOTeM (Acute Neurological care in North-East Germany with TeleMedical support) is to establish effective and sustainable structures for evidence-based treatments for and beyond stroke, and improve acute neurological care in rural regions.

Methods

A "hub-and-spoke" network structure was implemented between three academic neuro-centres ("hubs") and rural hospitals ("spokes") caring for acute neurological emergencies. The network structure includes the implementation of (1) dedicated units for patients with acute

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neurological diseases (Neuro-acute Units), (2) standardized operating procedures in all network hospitals, (3) a 24/7 TeleNeurology service, (4) a multi-professional training scheme and (5) a quality management system. Data from three health insurance companies involved in the project as well as data from the quality assurance program are being collected and assessed in order to evaluate the network effects.

Discussion

So far, there are no studies investigating the effects of telemedicine-supported networks on treatment of acute neurological emergencies beyond stroke. Our study investigates whether this approach leads to a reduction of death, first-time need of outpatient nursing or home care. In addition, a health economic analysis will be performed to evaluate cost-effectiveness.

Trial registration

German Clinical Trials Register DRKS00013067

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Using Telemedicine to Support Newborn Emergencies

Jennifer L. Fang (Rochester, MN, USA)

Summary

Neonates who require advanced resuscitation, especially those born prematurely, are at greater risk of mortality and morbidity when delivered in hospitals without a Neonatal Intensive Care Unit. Teleneonatology programs, which allow remote neonatologists to connect with rural hospital providers via real-time, audio-video telemedicine, may facilitate improved quality of care and patient safety for these neonates while achieving high levels of provider satisfaction. A retrospective, matched cohort study demonstrated that teleneonatology significantly improves the quality of resuscitation for neonates born in community hospitals who subsequently require admission to the NICU. Neonates who received a teleneonatology consult were more likely to undergo appropriate monitoring of their temperature, glucose and blood gas during the resuscitation. When considering the impact on patient safety, implementation of teleneonatology has resulted in a substantial reduction in birth injury settlement cases across a community hospital health system. Although teleneonatology is a new health care delivery method in the resuscitation suite, both community hospital providers and remote neonatologists report a very high level of program satisfaction. During the resuscitation, the team is able to effectively collaborate and communicate via telemedicine. Teleneonatology is emerging as an effective method to improve the value of care provided to at-risk outborn neonates.

Zusammenfassung

Neugeborene – insbesondere Frühgeborene - die eine intensive Wiederbelebung benötigen, haben ein höheres Mortalität- und Morbiditätsrisiko, wenn sie in Krankenhäusern ohne neonatalogische Intensivstation entbunden werden. Teleneonatologie-Programme ermöglichen, dass Neonatologen sich aus der Ferne über Audio-Video-Telemedizin in Echtzeit mit ländlichen Krankenhäusern in Verbindung setzten können. Dabei verbessert sich die Qualität der Versorgung und die Patientensicherheit für diese Neugeborenen und ein hohes Maß an Zufriedenheit wird bei den Gesundheitsversorgern erreicht. Eine retrospektive, gematchte Kohortenstudie zeigte, dass die Qualität der Wiederbelebung von Neugeborenen, die in kommunalen Krankenhäusern geboren wurden und anschließend auf die neonatalogische Intensivstation aufgenommen werden müssen, durch die Teleneonatologie deutlich verbessert werden konnte. Neugeborene, die eine teleneonatologische Betreuung erhielten, bekamen während der Reanimation eher eine angemessene Überwachung von Temperatur, Glukosespiegel und Blutgaswerten. In Bezug auf die Auswirkungen auf die Patientensicherheit hat die Einführung der Teleneonatologie zu einem erheblichen Rückgang der Geburtsschadenregulierungsverfahren in kommunalen Krankenhäusern geführt. Obwohl die Teleneonatologie eine neue Methode der Gesundheitsfürsorge auf der Wiederbelebungsstation darstellt, berichten sowohl die kommunalen Krankenhäuser als

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auch die aus der Ferne arbeitende Neonatologen von einem sehr hohen Maß an Zufriedenheit mit dem Programm. Während der Reanimation ist das Team in der Lage, effektiv zusammenzuarbeiten und über die Telemedizin zu kommunizieren. Die Teleneonatologie entwickelt sich zu einer wirksamen Methode, um die Gesundheitsversorgung von gefährdeten Neugeborenen, die anschließend transportiert werden müssen, zu verbessern.

Introduction

Approximately 10% of newborns will require breathing assistance after delivery, and one in 1,000 will require extensive resuscitation after birth (Perlman and Risser 1995, Wyckoff et al. 2015). The goal of regionalized perinatal care is to deliver at-risk neonates in hospitals that can provide risk-appropriate care; however that is not always possible due to geographic, economic, social or other barriers. Neonates that require advanced resuscitation, especially those born prematurely, are at greater risk of mortality when delivered at hospitals with lower levels of neonatal care (Lasswell et al. 2010). In addition, these at-risk outborn neonates are at increased risk of serious morbidity, including higher rates of intraventricular hemorrhage and necrotizing enterocolitis in preterm infants (Fang et al. 2019).

These outcome disparities may be attributable to knowledge and procedural skill decay experienced by local care teams due to the infrequency of advanced neonatal resuscitation in community hospitals. Neonatal resuscitation skills have been shown to sharply decline just two to three months after training (Patel et al. 2012). In rural hospitals, providers may perform bag mask ventilation – one of the most critical steps in neonatal resuscitation – only one to three times per year (Jukkala and Henly 2009). With advanced neonatal resuscitation occurring infrequently in the community hospital setting, additional strategies are needed to support local care teams during these neonatal emergencies.

The development and advancement of telemedicine has enabled innovative healthcare delivery models across a spectrum of care. Neonatologists at Mayo Clinic (Rochester, MN, USA) utilize a synchronous audio-video telemedicine platform to provide virtual consultations (termed teleneonatology) to 19 community hospitals in a two-state region. During the teleneonatology consult, the remote neonatologist can visually assess the neonate and guide the local care team through the resuscitation, which may include positive pressure ventilation, advanced airway placement, and umbilical catheter placement (Fang et al. 2016, Fig. 1). Herein we will describe the value of teleneonatology as measured by its impact on the quality of neonatal resuscitation, patient safety and provider experience.

Methods

The *Mayo Clinic Teleneonatology Program* was established in March 2013. The Mayo Clinic (Rochester, MN) has a 32-bed Level IV Regional Neonatal Intensive Care Unit (NICU) and a 24-bed Level III NICU where approximately 50% of neonates are outborn (admitted from an outside hospital). The neonatologists who staff the NICUs provide the teleneonatology consults to participating community hospitals. Nineteen hospitals receive teleneonatology services in their family birth centres and/or emergency departments. Community hospital staffing models vary by site and may include family medicine physicians, pediatricians, and/or advance practice providers who are on-site or take call from clinic or home. The value of teleneonatology has been evaluated by measuring quality, safety, and provider experience.

Fig. 1 Remote neonatologist connecting with a care team via telemedicine during a simulated neonatal resuscitation.

In a retrospective cohort study, the quality of resuscitation was assessed for neonates delivered in community hospitals who were subsequently admitted to the Mayo Clinic NICU (Fang et al. 2018). Forty-seven neonates who received a teleneonatology consult during their resuscitation at the birth hospital were compared to 45 controls who did not receive a consult. Controls were matched on gestational age, admission diagnosis, sex, and level of neonatal care in the birth hospital. Demographic, perinatal and neonatal data were abstracted from the electronic medical record. A two-person expert panel blinded to the intervention reviewed patient characteristics and resuscitation data for each patient and assigned a "resuscitation quality rating" using a 1–10 descriptive rating scale (1=poor; 10=excellent). The resuscitation quality rating served as the primary outcome for the study and was analyzed as both a continuous measure and as a dichotomous measure using categories of 1–4 versus 5–10 (a rating of ≥5 was assigned if abnormal parameters normalized during the resuscitation). Paired comparisons between groups were evaluated using the Wilcoxon signed rank test for continuous measures and the McNemar's test for dichotomous measures.

Patient safety was measured by monitoring settled birth injury cases in the participating community hospitals before and after implementation of teleneonatology. The days between settled birth injury cases were plotted on a t-chart. This included a ten-year retrospective baseline period between January 2003 and March 2013. After teleneonatology implementation began in March 2013, settled birth injury cases were plotted on the t-chart prospectively.

Between September 2014 and April 2019, provider experience was evaluated using electronic surveys sent to both the community hospital providers and the consulting neonatologists. The survey was sent after each teleneonatology consult and included questions about

the clinical case, technology performance, overall user satisfaction, teamwork, and communication using a 1 to 5 Likert scale (1=strongly disagree; 5=strongly agree). Results were reported as percent of respondents who agreed (4=agree and 5=strongly agree) with the survey statement.

Results

Teleneonatology significantly improved the quality of newborn resuscitation in community hospitals (Tab. 1). The median resuscitation quality rating was 7 for the teleneonatology group and 4 for the control group (median difference=1, P=0.02). Fifty-five percent (26/47) of patients in the teleneonatology group had a rating of 5-10 compared to 30 % (14/47) of the matched controls (P=0.02). Neonates who received a teleneonatology consult were significantly more likely to undergo measurement of temperature, glucose, and blood gas.

Teleneonatology also enhanced patient safety as measured by the frequency of settled birth injury cases before and after program implementation. In the ten years prior to teleneonatology, the median time between settled birth injury cases in the community hospitals was 254 days (range 8–1232 days). Since program implementation, there have been zero settled birth injury cases in the participating community hospitals – making it more than 2800 days (>7 years 8 months) since the last settled case.

Tab. 1 Comparison of the resuscitation quality rating and individual resuscitation metrics in the 47 matched pairs.

	Teleneonatology Group (n=47)	**Control Group (n=47)**	**P value†**
Resuscitation quality rating, median (IQR)	7 (3, 8)	4 (3, 5)	0.002
Resuscitations with a quality rating ≥5, n (%)	26 (55)	14 (30)	0.02
Resuscitation quality metrics			
Temperature measured, n (%)	37 (79)	26 (55)	0.02
Serum glucose measured, n (%)	44 (94)	38 (81)	0.03
Blood gas measured, n (%)	23 (49)	13 (28)	0.008
Temperature, glucose, and blood gas measured during the resuscitation, n (%)	20 (43)	10 (21)	0.008

†Paired comparisons between the matched pairs were conducted using the Wilcoxon signed rank test for continuous measures and the McNemar's test for dichotomous measures unless noted otherwise.

Over a 4.5 year period (09/2014 – 04/2019), a total of 367 electronic surveys were completed by teleneonatology users, including 123 surveys by community hospital providers and 244 surveys by consulting neonatologists. Ninety-nine percent of community hospital providers (119/120) would use teleneonatology again and recommend its use to their colleagues. In addition, 98 – 100 % agreed that the neonatologist worked collaboratively with their team (121/123), asked appropriate questions and sought information from their team (121/121), and provided brief, clear and specific information (118/120). The consulting neonatologists also reported a favorable experience. Ninety-two percent of neonatologists (224/244) felt like they were a member of the resuscitation team. Ninety-seven percent of consulting neonatologists (237/244) rated the local care team's sharing of information as good or excellent, and 87 % (213/244) agreed that they had a shared mental model with the local care team.

Discussion

There is a need in rural hospitals to assist providers with complex neonatal resuscitations that exceed what they are prepared to manage. In the current healthcare delivery model, these at-risk neonates are experiencing poorer health outcomes (Lasswell et al. 2010, Phibbs et al 2007, Jensen and Lorch 2015). With the use of synchronous, audio-video telemedicine, neonatologists can leverage their expertise to better support rural hospital providers and diminish outcome disparities.

In this report, we describe the impact teleneonatology has on the value of care provided to at-risk outborn neonates, including quality of care, patient safety, and provider experience. For neonates who require transfer to a NICU after delivery in a community hospital, teleneonatology significantly improves the quality of their initial resuscitation. Complex resuscitations require the care team to recall, prioritize and perform many critical, time-sensitive tasks (Thomas et al. 2006, Katheria et al. 2016). Effectively managing advanced resuscitations can be challenging for community hospital care teams as staffing, resources, and resuscitation experience may be limited. However, with the use of teleneonatology, the remote neonatologist can effectively guide community providers through the resuscitation and ensure essential process steps are completed. When a remote neonatologist is present during complex resuscitations, at-risk outborn neonates are more likely to have their temperature, glucose and blood gas measured. Performance of these tasks ensures the neonate is appropriately monitored for hypothermia, hypoglycemia, and suboptimal ventilation which can increase the risk of neonatal mortality and morbidity (Miller et al. 2011, Lucas et al. 1988, Kaiser et al. 2006). With their additional leadership and management, remote neonatologists may improve the quality of care by enhancing team behaviors and performance.

Increased adherence to the standard of care also enhances patient safety, as evidenced by fewer settled birth injury cases following teleneonatology implementation. Birth injury, including the most common claim of hypoxic-ischemic encephalopathy (HIE; Donn et al. 2014), can have serious short- and long-term impacts for the patient and family. In fact, 45–50 % of neonates with moderate to severe HIE will die or have moderate to severe disability (Shankaran et al. 2005, Azzopardi et al. 2009, Jacobs et al. 2011). Teleneonatology may reduce the frequency of birth injury cases because the remote neonatologist can facilitate prompt initiation of resuscitation, effective ventilation during the resuscitation, and the appropriateness of continued resuscitation. Poor compliance with these resuscitation steps has been linked to severe cases of neonatal asphyxia (Berglund et al. 2008). From a health system perspective, the reduction of birth injury cases after teleneonatology implementation also has pecuniary implications. In the United States between 1985 and 2008, the average indemnity for neonatal brain injury cases was $524,047 (Donn et al. 2014). In addition, many of the top medical malpractice verdicts, often for tens of millions of dollars, were birth injury cases (Donn et al. 2014, Fanaroff 2012). For neonates requiring advanced resuscitation, teleneonatology enhances patient safety as measured by reduced frequency of birth injury cases and secondarily results in cost avoidance for the health system.

Teleneonatology represents an innovative care delivery model for neonatal resuscitation in community hospitals. Both rural providers and consulting neonatologists have widely accepted and supported teleneonatology. In our program, community providers have been very satisfied with teleneonatology and report a high degree of collaboration and teamwork with the remote neonatologist. High levels of provider satisfaction and service utilization can be

achieved by providing appropriate staff education and training, designing effective clinical workflows, ensuring supportive team communication, and using reliable, easy-to-use technology (Fang et al. 2018). The remote neonatologists also report positive experiences with teleneonatology consultations. Through the synchronous audio-video connection they are able to collaborate effectively with the community hospital providers and serve as a member of the resuscitation team. For neonatologists to gain comfort in remote resuscitation and perform well, they should receive training on the clinical workflow, the telemedicine technology, and effective communication via telemedicine. When thoughtfully designed, implemented and supported, team member satisfaction with teleneonatology can be very high.

Conclusion

Outcome disparities for neonates requiring advanced resuscitation in rural hospitals drove the need for a new approach to care delivery using telemedicine. Teleneonatology allows remote neonatologists to effectively collaborate with community hospital providers when a neonate requires resuscitation or critical care. Teleneonatology improves the quality of neonatal resuscitation and the performance of many important process steps. Patient safety is also enhanced with teleneonatology as the remote neonatologist can guide the resuscitation in accordance with the standard of care. While teleneonatology is an innovative care delivery model in the resuscitation suite, very high levels of program satisfaction can be achieved for both rural hospital providers and the consulting neonatologists. Future studies should evaluate the impact of teleneonatology on short- and long-term neonatal health outcomes as well as the cost-effectiveness of teleneonatology networks.

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Social Policy Dimensions

NAL-conference Nr. *423*, 67 (2021) doi:10.26164/leopoldina_10_00376

Political Perspective: What Changes are Needed?

Kurt Biedenkopf (Dresden)

The speed of digital developments is tremendous, and intelligent machines will soon become capable of improving themselves. However, it is crucial that artificial intelligence never overpower the human mind. We must carefully supervise the development of artificial intelligence and critically regard the implications of their use before they surpass our control.

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A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

NAL-conference Nr. *423*, 69–75 (2021) doi:10.26164/leopoldina_10_00377

AWMF: Is the Transformation of Evidence through Digitalization Possible?

Ina B. Kopp (Marburg)

Summary

The digital transformation promises disruptive developments to improve medical knowledge management and medical care. Digital transformation as a future development and the exponentially growing applications in this context must, however, prove their benefit for patients and citizens and, to this end, be integrated into the principle of evidence-based medicine. Medical science is called upon to take a leading role in shaping the digital transformation and develop concepts for its evaluation. In this context, the idea of a "Digital Trustworthy Evidence Ecosystem" is being promoted internationally. The core of this idea is interoperability as a prerequisite for the accelerated transfer and critical evaluation of medical knowledge on the basis of uniform and publicly accessible data models, terminologies and interfaces. However, the digital transformation in the healthcare system also requires a consideration of changes at the societal level with regard to medical knowledge management and a changed role of patients and citizens as owners of their health data and partners in shared decision-making. In this context, the AWMF pursues a comprehensive project on the digitalization of quality-assured guideline knowledge as a partial aspect of the overall idea of the "Digital trustworthy Evidence Ecosystem".

Zusammenfassung

Die digitale Transformation verspricht bahnbrechende Entwicklungen zur Verbesserung des medizinischen Wissensmanagements und der medizinischen Versorgung. Die digitale Transformation als zukünftige Entwicklung und die in diesem Zusammenhang exponentiell wachsenden Anwendungen müssen jedoch ihren Nutzen für Patienten und Bürger unter Beweis stellen und zu diesem Zweck in das Prinzip der evidenzbasierten Medizin integriert werden. Die Medizinwissenschaft wird aufgefordert, die digitale Transformation federführend mitzugestalten und Konzepte für ihre Bewertung zu entwickeln. In diesem Zusammenhang wird das Konzept eines „digitalen vertrauenswürdigen Beweissystems" (Digital Trustworthy Evidence Ecosystem) international gefördert. Im Mittelpunkt dieser Idee ist die Interoperabilität als Voraussetzung für den beschleunigten Transfer und die kritische Bewertung medizinischen Wissens auf der Grundlage einheitlicher und öffentlich zugänglicher Datenmodelle, Terminologien und Schnittstellen. Der digitale Wandel im Gesundheitswesen erfordert jedoch auch eine Berücksichtigung der Veränderungen auf gesellschaftlicher Ebene im Hinblick auf das medizinische Wissensmanagement und eine veränderte Rolle der Patienten und Bürger als Eigentümer ihrer Gesundheitsdaten und Partner bei der gemeinsamen Entscheidungsfindung. In diesem Zusammenhang befasst sich die AWMF in einem umfassenden Projekt mit der Digitalisierung von qualitätsgesichertem Richtlinienwissen als Teilaspekt der Gesamtidee des „digitalen vertrauenswürdigen Beweissystems".

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Challenges to Evidence-based Healthcare in the Digital Age

The rise of the age has been postulated almost 50 years ago (Bell 1973). Since then, digital transformation has gradually but profoundly changed social and normative structures (Abrams and Vasiljevic 2014, Sablonnière 2017). Examples are found in:

- the economy – relying on information rather than goods and on agile product development rather than traditional prototyping and testing (Minderhoud and Fraser 2005),
- communication – relying on electronic or online solutions rather than individual face-to face meetings or phone calls (French 2012), with an increasing role of social media (Clement 2020),
- information technology – relying on services and solutions rather than products like platforms (*PricewaterhouseCoopers* 2017),
- social services – relying on the internet of things and telecare rather than traditional, personal encounters (*Eurofound* 2020),
- healthcare – relying on outcomes rather than interventions, emphasizing prevention and self-management (*PricewaterhouseCoopers* 2017, *European Commission* 2019).

In the field of healthcare, protagonists of digital transformation now promise nothing less than a new era for the whole health ecosystem – driven by individualised medicine, artificial intelligence and robotics ("New Health", *PricewaterhouseCoopers* 2017). Notably, multiple digital health applications currently mushroom unchecked or despite a lack of evidence.

Digital transformation in health care must be contextualised with the above-mentioned changes on the societal level and other well-known challenges to healthcare systems in the 21st century (*PricewterhouseCoopers* 2017, *Association of the Scientific Medical Societies in Germany* 2018):

- ageing population and escalating demand from long-term, chronic disease and multimorbidity,
- rising costs and limited resources (money, workforce specialists),
- hospital-centric systems deal with serious, acute episodes but are not fit to deal with chronic complex conditions for the longer term,
- conflicts between business management requirements and evidence-based, patient-centered care ("Economisation"),
- lack of cross-sectoral planning of health care and evidence base for defining resp. structural requirements.

Digital transformation in health care meets the willingness of citizens and patients to actively manage their health and wellbeing (Wicks et al. 2016). In this context,

- health data (from apps or electronic health records) need to be owned by the individual patient/citizen,
- the availability of individual health data will enrich the evidence base for Health Technology Assessments, Clinical Practice Guidelines, Health Services Research and Public Health,

– access to these data for secondary use is not to be regarded as a given but as a voluntary donation by the owner,
– individual health data will be available via streaming (through the donators)- rather than documentation (through medical professionals),
– citizens and patients will seek and use trustworthy information electronically.

Inevitably, digital transformation in health care must be integrated into the principle of Evidence based Medicine to protect professionals from exaggerated claims and to avoid potential harm to citizens and patients (Thielscher and Antes 2019). In order to evaluate the impact of digital transformation, a broad perspective should be taken. This requires attainment of the broad health system goals: quality, accessibility, efficiency and equity as objectives against which to judge new digital health services. These goals are unaltered by the process of digitalization (*European Commission* 2019). Evaluation must also consider the balance of benefit and harm. Potential harm in the era of digital transformation in health care has been well addressed as information overload (Bastian et al. 2010), research waste (Glasziou et al. 2014) and fake science alongside predatory publishing (Beall 2012).

Therefore, the scientific community must embrace the opportunities of digital transformation and take on a leadership role to design its implementation and evaluation. In this context, national and international collaboration is key – we need to get away from the idea to develop individual solutions and head off to a culture of sharing information and setting international standards. Role models are global agreements on standards in telecommunication and navigation.

To achieve this, policy makers will need advice from the scientific community to drive digital transformation in health care and the scientific community will need decisions from policy makers and legislation to establish a digital transformation that meets scientific requirements in healthcare as well as societal needs (Kunnamo 2020).

Solution: Transformation of Trustworthy Evidence through Digitalization

Medical science is called upon to take a leading role in shaping the digital transformation and develop concepts for its evaluation. In this context, the idea of a "Digital Trustworthy Evidence Ecosystem" is being promoted internationally (Mavergames 2017, Boutron 2020, Fig. 1). The vision of this idea is to optimally use digital technology with regard to evidence generation, synthesis, dissemination, implementation and re-evaluation. A prerequisite to achieve this is connecting people: clinical experts in the field of primary research, systematic reviews, clinical practice guidelines and quality improvement on the one hand and technical experts on the other.

Currently, activities of these players are largely siloed, information flow is inefficient on the national and international level and the initiatives of pharmaceutic and medical product industry must be put under scientific scrutiny.

Therefore, science-driven action plans, supported by national governments are needed.

Example: the AWMF-Project Digitalization of Guideline Knowledge

Clinical Practice Guidelines are an important element of the digital, trustworthy evidence ecosystem. They serve as decision aids in clinical practice and as tools convey knowledge to phy-

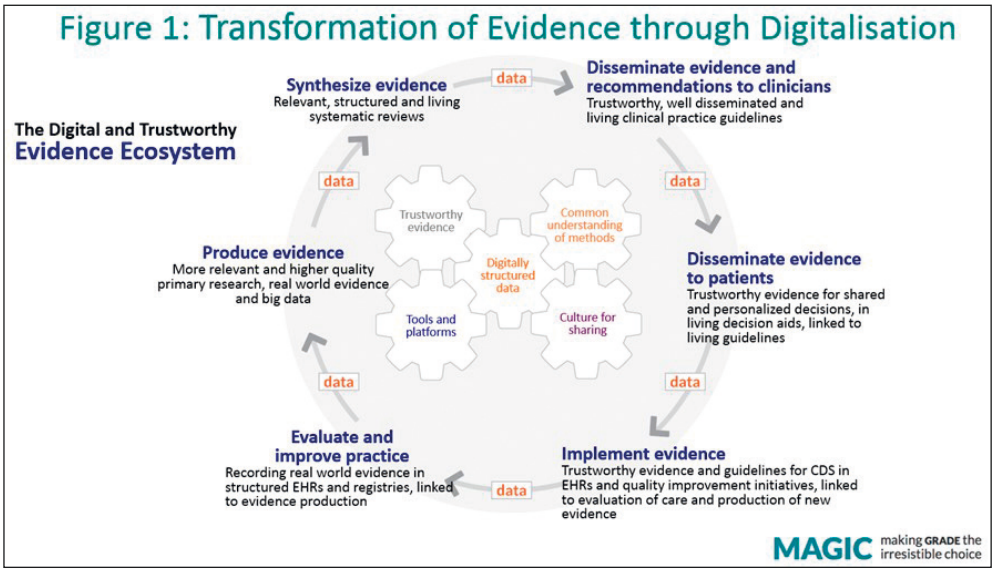

Fig. 1 Transformation of evidence through digitalization. MAGIC Evidence Ecosystem Foundation 2020. Available: http://magicproject.org/

sicians, members of other healthcare professions and patients with the aim to facilitate shared decision making and to achieve better health outcomes. To achieve these goals, Clinical Practice Guidelines need to be systematically developed, administered, implemented and evaluated ("Life Cycle" of guidelines, Fig. 2). Currently, all steps in this process are mainly managed by using traditional information processing programs. Guidelines are published as huge pdf or word documents – not fit to provide quick answers to specific questions in the clinical encounter.

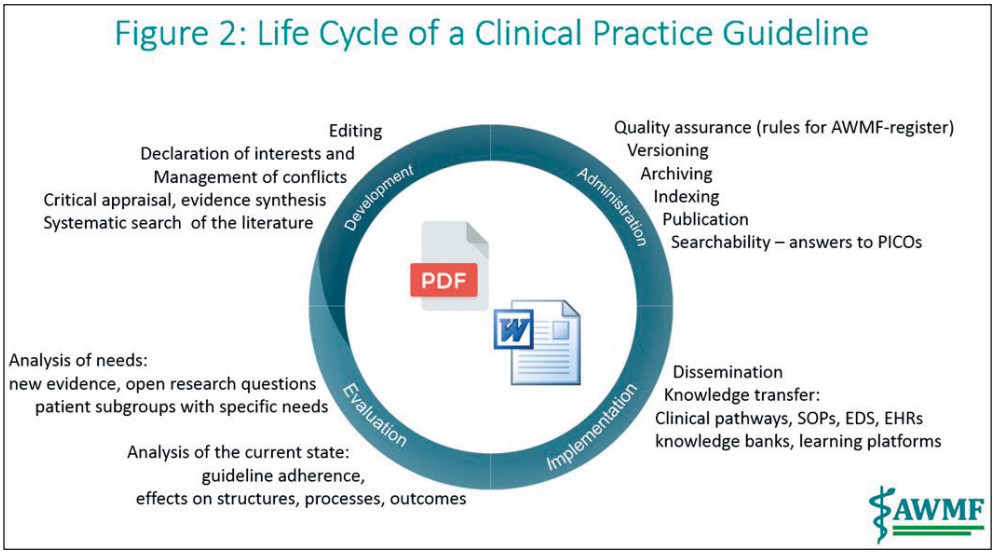

Fig. 2 Life cycle of a clinical practice guideline. AWMF 2018. Available: https://www.awmf.org/fileadmin/user_upload/Die_AWMF/Delegiertenkonferenz/DK-2018-11/TOP_12_20181110_AWMF-Delkonf_Kopp.pdf

Multiple digital applications are available aiming to improve this. However, the way forward is a more substantial, disruptive change: a global agreement on and open access to:

– a data model for guidelines,
– terminologies (semantic standards),
– interoperability (application programming interfaces).

In this context, the Association of Scientific Medical Societies in Germany (AWMF) has launched a comprehensive project to promote digitalisation of guideline knowledge (Fig. 3 and 4).

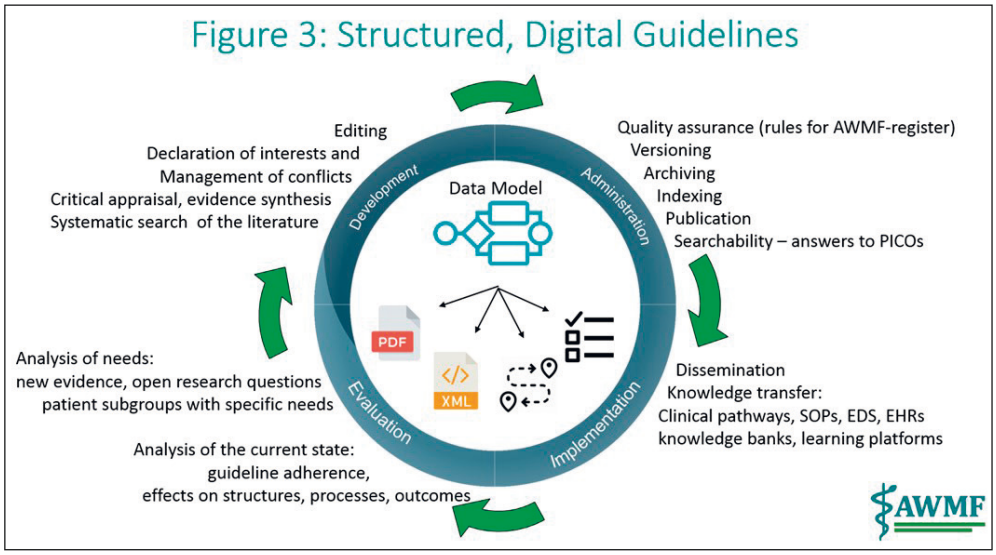

Fig. 3 Structured, digital guidelines. AWMF 2018. Available: https://www.awmf.org/fileadmin/user_upload/Die_AWMF/Delegiertenkonferenz/DK-2018-11/TOP_12_20181110_AWMF-Delkonf_Kopp.pdf

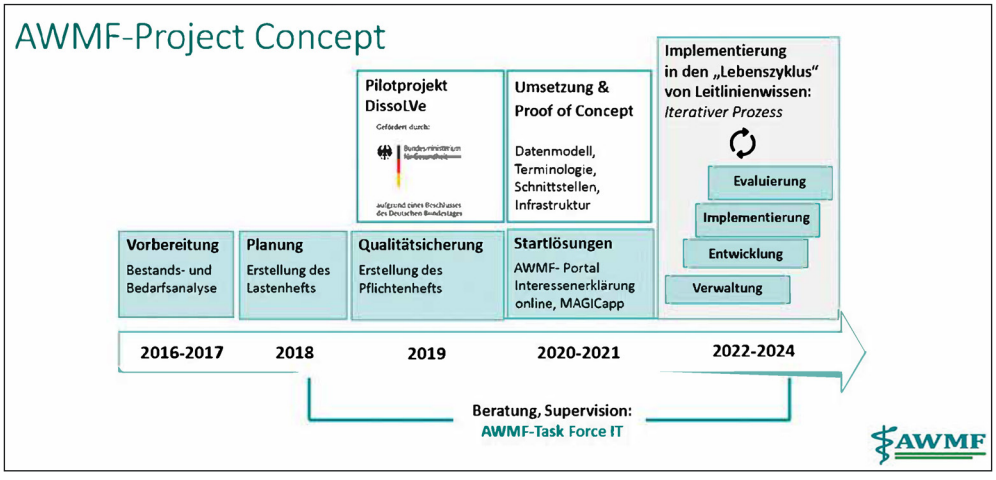

Fig. 4 AWMF-Project concept. AWMF 2019. Available: https://www.awmf.org/fileadmin/user_upload/Die_AWMF/Delegiertenkonferenz/DK-2019-11/TOP_10_20191109_AWMF-DelKonf_Digitalisierung_Kopp.pdf

Conclusion and Way Forward

Transformation of evidence through digitalization is necessary, possible and feasible. It promises perspectives for improving medical knowledge management, participatory, individualised decision-making and thus improving medical care. However, this transformation must be embedded into a scientifically sound framework of implementation and evaluation to avoid potential harm. Therefore, digital applications must be scrutinised according to the principles of Evidence Based Medicine. In Addition, Evaluations should take into account the perspective of societal changes in the digital age. As way forward, a National Action Plan is recommended to:

- design and implement a digital, trustworthy evidence ecosystem- emphasizing the role of clinical practice guidelines,
- invest in further research reg. the impact of digital transformation,
- rigorous implementation of international standards to gurantee interoperability (like FHIR, EbMonFHIR, Snomed CT, Loinc).
- address barriers and facilitators on the human side of the interface,
- improve digital literacy of professionals, citizens and patients.

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Knowledge Management for Precision Medicine

Ulf Leser (Berlin)

Summary

Medical decision-making is based on numerous types of knowledge about patients, diseases, pharmacology and the effects of interventions. Due in particular to advances in the molecular life sciences, the basis of this knowledge is growing faster than ever. At the same time, the extremely high dimensionality of molecular data makes the derivation of robust findings from limited sample numbers difficult, leading to a flood of publications with weak empirical evidence. This, in turn, challenges clinicians in their need to quickly find the most relevant facts for a given case. Modern computer-based technologies for extracting, aggregating and organizing knowledge, ranging from ontologies for structured knowledge codification to text mining algorithms for automatic extraction of findings and machine-learning based medical decision support, are expected to help cope with this challenge. Using precision oncology as an example for personalized medicine, this paper discusses recent advances in the (semi-) automatic extraction of clinically relevant findings from textual sources, their organization in knowledge bases, and their usage in medical decision support systems. We also describe requirements to accelerate the development of such technologies in Germany, especially when it comes to highly important medical documentation.

Zusammenfassung

Medizinische Entscheidungen beruhen auf einer Vielfalt an Wissen über Patienten, Krankheiten, Pharmakologie und den Auswirkungen von Behandlungen. Insbesondere durch die Fortschritte in den molekularen Biowissenschaften wächst die Wissensbasis schneller denn je. Gleichzeitig erschwert die extrem hohe Dimensionalität molekularer Daten die Ableitung robuster Erkenntnisse aus begrenzten Fallzahlen, was zu einer Fülle an Publikationen mit schwacher empirischer Evidenz führt. Dies wiederum fordert Mediziner heraus, schnell die relevantesten Fakten für einen bestimmten Patientenfall zu finden. Moderne computergestützte Technologien zur Gewinnung, Zusammenlegung und Organisation von Wissen sollen helfen, diese Herausforderung zu bewältigen. Diese Technologien reichen von Ontologien für eine strukturierte Wissenskodifizierung über Text-Mining-Algorithmen zur automatischen Gewinnung von Ergebnissen bis hin zu maschinellem Lernen für die Unterstützung von medizinischer Entscheidungsfindung. Anhand der Präzisionsonkologie als Beispiel der personalisierten Medizin zeigt dieser Beitrag die jüngsten Fortschritte bei der (halb-)automatischen Gewinnung klinisch relevanter Ergebnisse aus Textquellen, die Organisation dieser Ergebnisse in Wissensdatenbanken und ihre Verwendung als Unterstützungssysteme bei der medizinische Entscheidungsfindung. Darüber hinaus stellen wir die Voraussetzungen für eine beschleunigte Entwicklung solcher Technologien in Deutschland dar, insbesondere wenn es sich dabei um äußerst wichtige medizinische Unterlagen handelt.

A video of the presentation can be viewed online:

Introduction

Medicine is and has always been a knowledge-intensive science. When judging upon a patient's case, clinicians need to consider an intimidating amount of knowledge, including the detailed characterization of the patient, her history and family background, knowledge on disease etiology and phenotypes, the impact of possible (and approved) interventions, issues regarding the patient's quality of life and suitability of measures etc. The recent advances in the molecular life sciences have contributed another level of detail, making available information on thousands of genes, their function and interplay, and known implications of their inherited or acquired mutations on disease progression. Keeping pace with this enormous flood of information is a serious challenge for current medicine (Hey and Kesselheim 2016).

Molecular technologies produce measurements of the state of different molecules in a sample, such as the genome or transcriptome of a biopsy of a patient. Large studies, both preclinical and clinical, are required to condense such data into context-specific information, such as the overexpression of a certain gene under certain circumstances, and, eventually, into clinically relevant knowledge, such as the suitability of a treatment in a disease state as measured by a certain gene signature. The primary way of communicating such knowledge is natural language text – in the form of scientific publications, textbooks, clinical guidelines, case reports, medical documentation, discharge summaries etc. Given a clinical decision that needs to go beyond standard procedures, clinicians must search the most relevant texts, extract the relevant facts by reading, and assess their importance for the given case using personal experience and by comparing to results reported in other texts.

However, as the amount of potentially relevant published text is growing at an exponential scale[1], performing this step in a comprehensive manner becomes more and more difficult given the tense time constraints found in practice. The question arises how computer technology can help practitioners to find relevant information faster.

Extracting and Organizing Knowledge from Scientific Articles

Research in the (semi-)automatic extraction of facts from natural language text, summarized under the term "text mining", has seen on enormous growth over the last decades. In medicine, text mining can, for instance, be used to find relevant articles faster (Ševa et al. 2019), to automatically prepare digests of large text collections (Wei et al. 2019), or to support the creation of expert-curated knowledge bases (Lever et al. 2019). In the following, we describe applications of text mining in the field of precision oncology, before we give a short account on the current state of the art.

An important branch of current oncological research is concerned with the impact of somatic variations on disease formation, progression, therapy, and outcome (Gagan and Van Allen 2015). A famous example with approved therapeutic implications are EGFR mutations in colon and lung cancer (Seshacharyulu et al. 2012). A range of similar but not yet broadly confirmed relationships between individual mutations and certain drugs are currently studied in clinical practice (Lamping et al. 2020). The basis of these findings are numerous international trials investigating the associations between genomic features and

1 See, for instance, PubMed growth statistics at https://www.nlm.nih.gov/bsd/stats/cit_added.html

diseases. Therapeutic decisions are increasingly dependent on access to comprehensive knowledge bases that extract and organize large collections of such associations in the form of Variant Information Systems (VIS, Starlinger et al. 2018), a process illustrated in Fig. 1.

Biomedical Text Mining (BTM) can speed up and improve the creation and maintenance of such VIS considerably. To this end, typical BTM workflows process very large text collections (e.g. all PubMed abstracts) to find putatively relevant findings, which are subsequently aggregated into oncological knowledge and presented to experts for inclusion in a VIS. The three main steps in such workflows are (1) Named Entity Recognition (Habibi et al. 2017) concerned with finding textual mentions of genomic variants, genes, cancer types, drugs etc., (2) Named Entity Normalization (Leaman and Lu 2016) which assigns discovered mentions to unique biological entities, such as standardized gene and drug names, and (3) Relationship Extraction (Weber et al. 2020) for identifying the semantic relationships between those entities, such as the association of a mutation to a drug or of a drug to a cancer type.

Recent progress in these fields has been significant, boosting extraction accuracies for many cases into the 80% – 95% range. Extraction at that quality applied over large text collections can bring an enormous help for clinical practice. However, it is also important to keep in mind that BTM is not yet at a state where human judgement of extracted findings would be superfluous. For instance, a BTM process as described above would not be able to differentiate between the values of a mutation-drug association resulting from a large clinical trial, one found in single case report, or one found by in-vitro experiments with a small number of cancer cell lines. Further research on such problems is necessary, for instance to cope with conflicting results from different studies or to adequately consider the strength of empirical evidences.

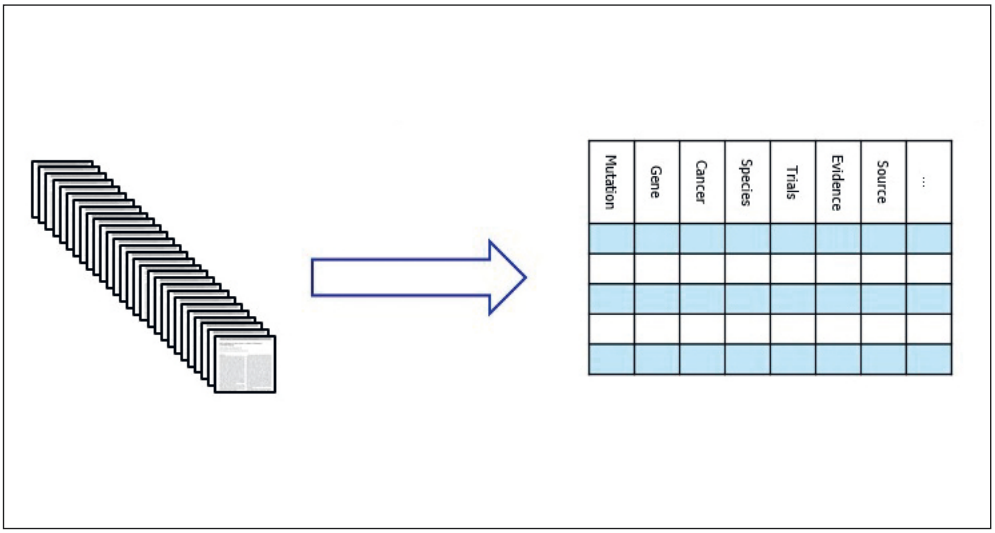

Fig. 1 Information on the role of mutations in specific types of cancer must be extracted from the literature and put into structured format for consideration in clinical decision support.

Supporting Medical Decision-Making

The most important application of BTM in clinical oncology is the support of therapeutic decisions in cases outside the guidelines, which often are taken by Molecular Tumor Boards (MTB). The preparation of individual patients for MTB meetings currently takes up to several hours, which are spent in searching publication databases, querying VIS, reading papers and database entries, judging upon the strength of the underlying evidences, and preparing an integrated report as basis for a rational decision. Several projects are ongoing to support this process by BTM to reduce preparation times and to improve the quality of decisions by making more relevant information available faster[2]. For instance, we recently performed a study comparing the content of five large curated variant-level knowledge bases for precision oncology, showing that using at least three of them significantly improves the recall of a search compared to using any single one (Pallarz et al. 2019). A similar analysis is described in (Perera-Bel et al. 2018), which also presents a software for generating integrated reports given the mutation signature of a patient. (Wagner et al. 2020) present a graphical user interface for intuitive browsing expert-curated information from multiple VIS.

Extracting Knowledge from Medical Reports in Germany

Access to comprehensive, integrated VIS can offer substantial support for clinical decision-making when the individual genome of a patient is to be taken into account. However, they inherently provide only a very narrow view on patients, i.e., their mutational signatures. Evidently, the utility of decision support systems could be improved considerably when also other patient information would be integrated, such as demographic information, family history, previous treatments, or clinical markers. Several clinics in Germany currently are building up clinical data warehouses (CDW) to provide such data fast and at high quality, but still very often it is available only in the form of medical reports[3]. It is thus a natural idea to develop BTM solutions also for medical text, as a complement to BTM on scientific text.

However, the situation in BTM on German medical text is much worse than for English (Starlinger et al. 2016). The main reason is that all state-of-the-art methods for BTM are based on machine learning and must be trained on large, language- and domain-specific annotated text collections, also called Gold Standard Corpora (GSC). Over the last two decades, the international research community has created dozens of such GSC for various tasks for English scientific texts, and large corpora also are freely available for English medical text (Johnson et al. 2016). However, currently not a single such GSC exists for German medical text (Hahn et al. 2018). This not only means that the best current BTM algorithms are not usable, but also that different methods cannot be compared to each other in a systematic manner.[4] Many English GSC have been created in the course of international BTM competitions, which boosted the performance of methods enormously. Such competitions are also emerging

2 See, for instance, the BMBF initiative id:SEM: https://www.gesundheitsforschung-bmbf.de/de/i-dsem-integrative-datensemantik-in-der-systemmedizin-3367.php

3 Note that any CDW faces the problem of integrating the Millions of treatments that were handled prior to building the system – which are available only in textual form.

4 Several companies offer solutions for German medical BTM, but the quality of their tools cannot be compared in an unbiased manner due to the lack of German GSC.

for other western languages, like French or Spanish, but none for German. This also hinders the development of other important applications of BTM on medial reports, such as systems for automatically quality controlling medical accounting systems, e.g. DRG codes, or quality assurance of treatments by controlling compliance to predefined clinical pathways.

There are multiple reasons for this situation (Starlinger et al. 2016). Undoubtedly, the most important one is data protection regulations. Medical reports, in principle, can be shared publically after complete anonymization. However, there exists no common understanding or clear guidelines what a "complete anonymization" of a medical report implies, and different data protection authorities in different federal states and different organizations tend to communicate very different points-of-view on this subject (Dierks and Rossnagel 2020). This creates a situation in which none of the actors dares to share such data, which severely hinders research progress in German BTM.

Conclusions

Biomedical text mining and knowledge management has great potential to improve medical treatments. The potential is the larger, the more precise characterizations of patients and treatments are available and actually taken into account i.e., in precision medicine. While research in obtaining such information semi-automatically from English texts is well developed, our abilities to analyse German medical text are still very limited. German clinics currently trail far behind in their means to exploit the wealth of medical knowledge buried in their EHR systems, so to change this situation it is of utmost importance to define safe and reliable ways of exchanging carefully selected, carefully anonymized, and carefully annotated medical text corpora. The availability of such corpora would quickly lead to the free availability of high-quality BTM tools, especially because it would open the door for the large German communities of Computational Linguistics and Artificial Intelligence to work on such problems.

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Data Protection as a Challenge

Christian Dierks (Berlin)

In the ideal world of patient-centered acute medicine, all personal health data is available at the point of care and the diagnostic and therapeutic decisions are based on a complete data base. However, in the ideal world of data protection, this is the only and scarce moment of data availability and nobody else has access to these data. It is this dichotomy of paradigms that characterises the first challenge of data protection in medicine. Availability is the antinomy to protection, and these two goals need to be reconciled by a clear data privacy structure and technical and organizational measures.

The second challenge is the heterogeneous legal framework for medical research in Germany. Despite the ubiquity of the GDPR, we still have regional data protection laws, hospital laws and the legal framework of the two big German churches governing the preconditions of research with patient data in a disturbing variety. This has become a major burden (not only) to multi-center studies and requires legislative action on the German federal and state level. A data protection space for medical research on an EU-level would be the next logical and essential step towards enabling EU-wide research and quality control.

Thirdly, and most importantly, we need to define a new role for the patient in healthcare data processing. As the number of data sources rise, and data processing evolves to the cardinal basis of decision making, the responsibility for personalized health data is the key aspect of quality in medical care. And yet, there is no outright responsibility defined in our legal framework. There can be no doubt that this role needs to be filled by the patients (respectively the citizen or consumer) themselves: from cradle to grave they are the only constant in a continuously changing setting, and they are the ones who will have the most to benefit from having a complete and well-curated set of data. Therefore, society and legislator need to pave the way for a patient-centric, patient-driven framework of medical data processing. This should encompass opportunities for patient education, secure data storage and processing as well as the option of delegation to trusted third parties.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Scientists, society and legislators need to align to encounter these challenges with a systematic approach to unlock the enormous potential of available but undeployed data resources.

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How to Pay for it? The Challenge of Scaling-Up and Financing Innovative Services (with a Focus on Telemedical Services)

Reinhard Busse (Berlin)

The Innovation Fund was created to ensure a qualitative advancement of the statutory health insurance (SHI) scheme. Although the provision of grants to projects to test innovative services limited in time and scale (often within one region and limited to one sickness fund selectively contracting providers) is a necessary step, it is not enough to secure the overarching goal of advancing SHI care in general, which requires scaling-up of effective and cost-effective innovations to other regions and sickness funds.

One area which needs particular attention are tele-medical projects, as they are not only testing new organizational forms of providing services but need equipment, and thus investment costs, to do so – on both sides of the service, i.e. at the side of the institution providing the tele-medical services, and on the side of the recipient, be it another provider institution or patients directly.

Opportunities and challenges for the scaling-up of Innovation Fund-sponsored (tele-medical) projects into coverage as part of the standard benefit basket are not only securing enough participants during the project phase and using an evaluation methodology suited to such interventions (which is not the topic here) but especially in the financial gap that is inherent in the funding conditions, and which is aggravated in the case of tele-medical projects.

In the example given in the Figure, inclusion of patients, and thus payment for the innovative form of care was financed under a selective contract under paragraph 140 of the fifth German social code book (SGB V) until the end of March 2020, while the project period will last another 9 months for evaluation. The time for evaluation is mainly due to the fact that the last data point will be collected 6 months after the end of the financing. During this first phase of the funding gap, the effectiveness of the innovative form of care is not yet established. Subsequently, the consortium has another 6 months to prepare the final project report. On this

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

basis, the projects are then assessed by the Innovation Committee, which in turn has 3 months to take the decision.

In the event of a positive recommendation for inclusion into the standard benefit package, the decision should also specify which self-governing body or other institution is responsible for this. If the Federal Joint Committee (G-BA) is deemed to have jurisdiction here, the G-BA must "decide on a regulation for inclusion in standard care" within a period of 12 months (paragraph 92b of the fifth German social code book in the modification introduced in 2019, *German Bundestag* 2019a). There is currently no time perspective on the competence of other institutions. In this period, successful projects have already been positively evaluated, thus constituting a second phase of the funding gap (Fig. 1).

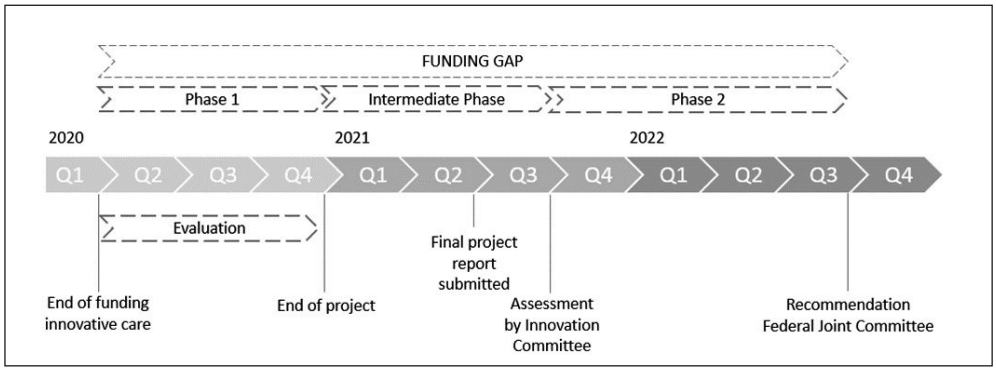

Fig. 1 Phases of funding gap after the completion of successful Innovation Fund projects.

For the example project in question, this would mean a funding gap of up to 30 months, although a decision by the G-BA is not yet equivalent to the actual remuneration. Such a funding gap will almost certainly mean the death of the innovative form of health service provision as it is not just about having a break in providing services (which might already be difficult enough) – but the infrastructure can no longer be supported, especially if it is based on renting agreements or maintenance contracts for purchased equipment.

We therefore propose a two-phase approach to address this problem. In phase 1, the period following completion of patient treatment within the project and during the evaluation and subsequent writing of the report, the positive effect on outcomes and/or cost-effectiveness is still unclear. Accordingly, the gap in remuneration in this phase should be restricted to the project setting and could be covered by an extension of the selective contract with the participating sickness funds. If the project had recruited successfully, it would qualify for financial resources set aside by the Innovation Committee to partially reimburse sickness funds for their expenses upon request.

Phase 2 takes place after completion of a project report – and assuming a positive evaluation result. Here, although the effect of the new pathway has already been determined, it is often not yet considered a "generally recognized standard in medicine". A sensible option at this stage would be a remuneration system similar to the New Examination and Treatment Methods (NUB) regulation within the hospital sector. In contrast to that (where each qualifying hospital has to negotiate with the sickness funds about actually being eligible reimburse-

ment as well as the amount), however, the healthcare provider would be "automatically" qualified to continue to deliver the services as in the project, while all sickness funds would have the choice of opting in. According to the NUB procedures, the service providers would submit a cost calculation for the additional costs. Unlike NUB costs, which only arise at the institution providing the new method, this calculation needs to take costs arising on both sides, i.e. for the "providing" as well as the "receiving" institution, with the reimbursement potentially also divided.

Phase 3 is the time following the decision for an introduction of the service(s) into standard care, i.e. for all regions and sickness funds, as foreseen by law to be done by the Federal Joint Committee. For this, suitable remuneration instruments will have to be (further) developed in many cases to enable the transfer of positively evaluated projects, or project elements, to SHI-wide standard care. These might include, per example, additional payments (in German *Zusatzentgelt*) on top of the DRG-based payment based on complex OPS codes (i.e. procedure codes based on a certain procedure which requires a certain set of both professionals as well as services) with corresponding requirements for processes and structures in the sense of minimum requirements, or the definition of centers which would be qualified to act as the provider of tele-medical services. No matter which exact reimbursement method is chosen, the division of the fee between "providing" and "receiving" institution provides an additional challenge unique for tele-medical services.

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Consolidation of Innovation Funds – Dream or Reality?

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Round Table Discussion

Christina Berndt (Munich)

Participants of the Round Table in alphabetical order:

Prof. Dr. Kurt Biedenkopf, former Prime Minister of the Free State of Saxony
Prof. Dr. Reinhard Busse, Professor of Management in the Healthcare Sector at the Faculty of Economics and Management of the Technische Universität Berlin
Dr. Jörg Caumanns, Head of the Competence Center "E-HEALTH – Platforms and Solutions for Connected Health" at the Fraunhofer Institute for Open Communication Systems (FOKUS)
Prof. Dr. Christian Dierks, Professor for Health System Research at the Charité Universitätsmedizin Berlin and founder of the law firm Dierks+Company
Prof. Dr. Martin Gersch, Professor of Business Administration, Freie Universität Berlin
Dr. Ursula Marschall, Head of the Department of Medicine and Health Services Research at Barmer Ersatzkasse
Prof. Dr. Claudia Spies, Director of the Clinic for Anesthesiology and Operative Intensive Care Medicine (CCM, CVK), Charité – Universitätsmedizin Berlin

Summary

Since 2016, the Innovation Fund has been supporting projects that aim to advance the integrated care of patients. The round table, "Perpetuation of the Innovation Fund – Dream or Reality", dealt with the question of how desirable a permanent installation of the Innovation Fund is and how the initiators of funded projects can securely implement their work in clinical practice following the funding phase. The panel agreed that, despite the relative rigidity of the German healthcare system, it is the interdisciplinary cooperation within the Innovation Fund projects that enables real innovations to flourish. However, the lengthy period between the evaluation of a project and a decision regarding its continuation or implementation in practice remains a challenge. The panel identified and discussed further factors that promote and inhibit innovations.

Zusammenfassung

Seit 2016 unterstützt der Innovationsfonds Projekte, die die integrierte Patientenversorgung vorantreiben. Die Diskussionsrunde „Fortbestand des Innovationsfonds – Traum oder Wirklichkeit" beschäftigte sich mit der Frage, wie wünschenswert eine dauerhafte Etablierung des Innovationsfonds ist und wie die Initiatoren der geförderten Projekte nach der Förderphase die Umsetzung ihrer Arbeit in die klinische Praxis sicherstellen können. Das Expertenpanel war sich einig, dass, trotz der relativen Unnachgiebigkeit des deutschen Gesundheitssystems, die interdisziplinäre Zusammenarbeit bei den Projekten des Innovationsfonds die treibende Kraft hinter den wahren Innovationen ist. Die lange Zeitspanne zwischen der Auswertung eines Projekts und der Entscheidung über seine Weiterführung oder Umsetzung in die Praxis bleibt jedoch eine Herausforderung. Das Panel identifizierte und debattierte weitere Faktoren, die Innovationen fördern und hemmen.

A video of the round table discussion can be viewed online:

The Innovation Fund has existed in Germany since 2016. It is a health policy instrument to promote the integrated care of patients and the necessary research for health-care development. Between 2016 and 2019, the Innovation Fund has annually awarded 300 million euros to innovative, cross-sectoral research projects on health care. This will be continued in 2020 with 200 million euros to be distributed annually. The aim is to ensure that the successfully evaluated projects are permanently transferred to the health care system. The round table dealt with the question of how desirable a permanent installation of the Innovation Fund is and how the initiators of funded projects can secure the implementation of their work into clinical practice following the funding phase.

The round table agreed that the Innovation Fund has successfully promoted innovative projects and provides a tremendous driving force for health care research and improvement of patient care, so that a perpetuation of the project would be greatly desirable. "No one doubt that the Innovation Fund is a good idea," said Reinhard Busse. He added that such a funding instrument was needed in order to generate new ideas, particularly in the cumbersome and rigid German health care system. In particular, inter-sectoral research in cooperation with health insurance companies and service providers are helpful to facilitate an eventual transfer into clinical practice. "We must now ensure that the knowledge generated through research remains usable for the patients," said Claudia Spies. The networking among different disciplines is of fundamental importance. In the ERIC project ("Enhanced Recovery after Intensive Care"), for example, which aims to reduce the long-term consequences of intensive care treatment, a central goal is to bundle the knowledge base of several disciplines into an eHealth platform. This should allow tele-visits to take place daily, in which the participating doctors and nurses can communicate with each other via video, regardless of location. "Only if we place our project in a networking context will it be useful for all patients," says Spies.

Nevertheless, the panel also saw problems with the continuity of the Innovation Fund. Kurt Biedenkopf warned that innovations always involve opportunities and risks, and that neither one nor the other could be completely controlled by legislation. Christian Dierks criticized the fact that the restrictions imposed in the name of data protection were sometimes too great. In Germany, he said, there were too many data protectionists and drawn-out negotiations, which often rendered innovations impossible. Ursula Marschall wished for more political support, so that individual health insurance company projects would not remain isolated, but have the possibility to be extended to other health insurance companies. According to Marschall, the interest of other insurers could be increased by shifting the debate away from costs and towards quality. The ERIC project has already taken this path.

"A lot of preliminary work has been done here", said Marschall, "a consensus was reached in the professional associations that this approach is sensible".

However, there is usually a long gap between the conclusion of an Innovation Fund project and further financing – often, 2.5 years go by before a decision is made. Reinhard Busse said that some projects can hardly bridge this period, perishing long before a decision can be reached on their continuation. In fact, not all Innovation Fund projects can be continued, said Ursula Marschall. Barmer alone currently supports 60 such projects, some of which are duplicated in terms of content.

Claudia Spies said it would make sense to combine projects with similar focuses. "It's not a matter of competition, but of cooperation. All these projects attempted to improve the treatment and needs of patients. These cannot be achieved by remaining rigidly compartmentalized."

According to Busse, other aspects of the healthcare system also require modernization. In the ERIC project, for example, we see the dilemma. The aim of the project is to shorten the duration of mechanical ventilation, which is unquestionably beneficial for the patients. However, achieving this goal leads to a financial loss for the clinics, as the duration of mechanical ventilation is a key factor in determining the compensation amount.

"The hospitals that get patients off the ventilator earlier through ERIC are doubly penalized," says Busse. It would be sensible to use the money for the planned telemedical consultation for further patient care, but the remuneration system must make this possible. Ursula Marschall confirmed that there are economic disincentives in the system, "which produce imbalances that certainly hinder improvement."

However, a renewal of the health care system is very difficult, explained transformation researcher Martin Gersch, "Many stakeholders hold different parts of the system. This leads to the fact that a change may have advantages for one stakeholder, but there are always others under the impression that they are losing something."

Jörg Caumanns suggested that in the future, decisions about therapies should be made similarly to decisions currently made regarding the use of health apps. Here, patients can request a special permission, if licensed. However, he said that the elimination of the G-BA, as has been done with health apps in accordance with the Digital Healthcare Act, will hardly be possible in the entire system.

This would not be necessarily sensible, either, said Marschall and Busse. "In this case, many decisions would certainly be faster, but we would certainly not be any happier with it," said Busse. "The main advantage of G-BA decisions is that stakeholders who can set their own rules are more likely to stick to them."

Nevertheless, Christian Dierks said that decisions on innovation projects were often problematic. The system is a black box. There is no transparency. No one can really understand the criteria according to which Innovation Fund money was allocated; nor were there any legal recourses against a rejection.

Conclusion

From the panel's point of view, there is a clear answer to the question of whether the Innovation Fund should be continued: the concept itself can be considered as a success, but bureaucratic obstacles make it difficult to successfully implement the projects in practice. Here, hurdles caused by data protection and power structures of stakeholders in the German healthcare system must be removed and, above all, the speed of decisions must be increased.

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High Definition Medicine in Patient-Centered Acute Medicine

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Data, Data Science and Artificial Intelligence in Medicine

Ramin Yahyapour (Göttingen)

Summary

Due to the rapid development of sensor technologies, vital data can be recorded on a completely new scale with high temporal resolution even over long periods of time. This applies both to the clinical care context, but also to all other areas of daily life. As these amounts of data were historically difficult to manage, the technological evolution in information technology and computer science now offers new possibilities. Big data and artificial intelligence are increasingly finding a wide application in life sciences. The effects on medical care and research are not fully foreseeable as of today. As the necessary algorithms and infrastructures are more easily accessible, their use in a wide variety of areas becomes easier. Technological advances in information technology will, for the foreseeable future, continue to follow a slightly weaker form of Moore's law. This evolves the miniaturization of IT accompanied by an increase in cost efficiency and performance. Taking these developments into account, an estimation can be made of the extent to which medical data can be recorded and analyzed at affordable costs. From this follows the creation of a qualitatively ever better personal digital twin, whose 24/7 monitoring of health data allows completely new possibilities regarding the detection and prediction of abnormalities. In addition to the individual perspective, this provides new possibilities for research to carry out analysis on a new scale based on large populations. Various projects are already working on the exchange, merging and analysis of clinical care data for research. The development of common data formats, semantic interoperability and data protection-compliant consent procedures are essential steps. However, these developments also have to be considered in relation to ethical, social and economic issues. It requires a joint effort by different disciplines and stakeholders to leverage the potential of these technologies.

Zusammenfassung

Durch die rasante Entwicklung von Sensortechnologien können Vitaldaten in einem völlig neuen Maßstab mit hoher zeitlicher Auflösung auch über lange Zeiträume hinweg erfasst werden. Dies gilt sowohl in der klinischen Versorgung als auch in allen anderen Bereichen des Alltags. Früher waren diese Datenmengen kaum handhabbar. Nun bieten Entwicklungen in der Informationstechnologie und Informatik neue Möglichkeiten. Große Datenmengen und die künstliche Intelligenz finden zunehmend eine breite Anwendung in den Biowissenschaften. Die Auswirkungen auf die medizinische Versorgung und Forschung sind bis heute nicht vollständig absehbar. Da die notwendigen Algorithmen und Infrastrukturen leichter zugänglich sind, wird ihr Einsatz in den verschiedensten

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Bereichen erleichtert. Die technologischen Fortschritte in der Informationstechnologie folgen auf absehbare Zeit weiterhin dem Mooreschen Gesetz in abgeschwächter Form. Damit wird die Miniaturisierung von IT weiterentwickelt, begleitet von einer Steigerung der Kosteneffizienz und der Leistungsfähigkeit. Unter Berücksichtigung dieser Entwicklungen lässt sich abschätzen, in welchem Umfang medizinische Daten zu erschwinglichen Kosten erfasst und analysiert werden können. Daraus folgt die Erzeugung eines qualitativ immer besseren, persönlichen digitalen Zwillings, dessen Rund-um-die-Uhr Überwachung von Gesundheitsdaten völlig neue Möglichkeiten zur Erkennung und Prognose von Anomalien ermöglicht. Neben der individuellen Perspektive bietet es der Forschung neue Möglichkeiten, Analyse in einem neuen Maßstab auf Basis großer Bevölkerungsgruppen durchzuführen. Verschiedene Projekte befassen sich bereits mit dem Austausch, der Zusammenführung und der Analyse von klinischen Versorgungsdaten für Forschungszwecke. Wesentliche Fortschritte werden durch die Entwicklung gemeinsamer Datenformate, der semantischen Interoperabilität und datenschutzkonformen Einwilligungsverfahren gemacht. Bei diesen Entwicklungen müssen jedoch auch ethische, soziale und wirtschaftliche Fragen in Betracht gezogen werden. Die Ausnutzung dieser Technologie erfordert gemeinsame Anstrengungen verschiedener Disziplinen und Interessengruppen.

Introduction

Digitalization and artificial intelligence (AI) are considered game changers for our society, arguably with similar impact on the different aspects of our life as the industrial revolution. Algorithms are becoming capable of performing tasks that were not conceivable some years ago, mastering challenges that only humans were able to perform until now. The underlying theory, though, is not new and mainly technical advancements in hardware technology led to the rather late breakthrough of machine learning and neural network. Often subsumed under the term artificial intelligence, we see the rise of a large amount of new application areas that see transformational change by these technologies. The impact to our society, our work, life and economy are not yet understood, but it is obvious that a growing number of traditional processes are likely to disappear and to be replaced by automation.

Naturally, this change is also perceivable in medicine, not only in research but also regarding its application in healthcare. There is a stream of publications showing the high potential of the application of AI. There are many areas in medicine which benefit from machine learning and AI. The list is extensive and only a small selection is presented here. Typically,

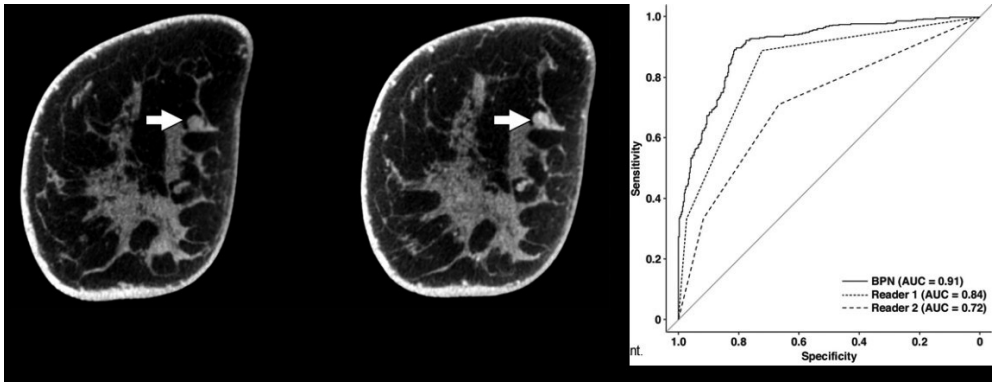

Fig. 1 Deep Machine Learning: overall tendency to outperform readers in correct discrimination of benign vs. malignant lesions in breast CT (Uhlig et al. 2018).

examples are given in areas with benefit from automatic analysis of images or texts. Solutions for analyzing medical images in radiology, see Fig. 1 (Uhlig et al. 2018), or pathology (Sarwar et al. 2019) are obviously application areas in which we see scientific projects but also first commercial solutions to offer decision support solutions (Walczak 2018). Similarly, data allows phenome-wide association studies (PheWAS) by combining information from electronic health records, biobanks, and genomics (McCarty et al. 2011). In this context, machine learning can help in identifying recurring patterns or deriving recommendation in diagnosis or treatment of individual patients.

Background

The term "artificial intelligence" is not well defined and often misleading. The discussion whether or to what extent algorithms can be considered intelligent is not very relevant for most scenarios. At the core of most AI applications are neural networks, a model already known from the first half of the last century. The design of a computer with an artificial neural networks and backpropagation for learning has been proposed by Marvin Minsky in 1951 (Minsky 1952). Despite the large interest in the concept, the approach did not gain traction and did not find its way into real applications at that time. Until the beginning of the 2000s, neural networks and artificial intelligence were considered impractical for most relevant use cases. The renaissance occurred with further advancements in computing capabilities and multi-layered structures for instance with convolutional layers. Success in pattern recognition and more cost-effective computing hardware allowed speech or image recognition on a level comparable to humans. These algorithms are based on learning methods necessary to train a neural network. Starting from a given training data set, these algorithms adjust their configuration automatically. Thus, machine learning (ML) is a more specific term for classifying a certain type of AI. Especially, the ability to learn from large data sets and neural networks with many layers have led to the success of deep machine learning (DML).

Common traditional machine learning methods are: (1) *Supervised Learning*, which requires labeled data and knowledge of earlier decisions; (2) *Unsupervised Learning*, which is often used if no labeled data exists and which requires typically large data sets to learn from; (3) *Reinforcement Learning*, which follows a trial-and-error approach, often combined with simulation models to improve the speed of learning.

Successful research in this field requires:

(1.) *Data resources*: Often access to data suitable for ML is not readily available and a precious resource. Depending on the considered problem, a large amount of data is required and ideally needs to be well annotated so that algorithms can use this information as a baseline for comparison. Knowledge on the quality of the data, as well as the syntactic and semantic understanding are crucial challenges for an ML project.

(2.) *Hardware infrastructure*: Learning from large amounts of data is a compute intensive task, which requires large-scale compute resources like GPU or HPC clusters. The capability to consume and process large amounts of data is technically challenging. The application of an already trained neural network at a later stage is usually less demanding.

(3.) *Software tools*: Most projects benefit from access to available software solutions to help in implementing data analysis pipelines and creating neural networks.
(4.) *Data Scientists*: Experts with knowledge about the selection of the right methods and tools to create meaningful results are required. There are, in particular, many further aspects beyond the actual data analysis, which need to be covered for successful projects.

Technological Requirements

A major driver for the rapid proliferation of machine learning is the ongoing technological advancement in computer technologies. While traditional computers have been optimized for scalar operations, current general purposed graphic (GPU) accelerators provide exceptional compute power for vector operations. As machine learning is often based on tensor or matrix operations, such applications benefit from GPU-based computer systems. The ability to learn from huge datasets requires such large-scale computing systems (Bengio 2009).

The necessary investment and operational cost for such systems are high and often result in multi-million Euro yearly budgets. For medical research it is generally neither feasible nor sensible from an economic perspective to build such large-scale computing and data infrastructures from scratch on their premise.

Fortunately, Germany has a comparatively well-established infrastructure of high-performance computing systems, which also offers GPU-clusters to researchers (Fig. 1). There are several compute centers that provide access to such resources on a national or regional level. This is a valid alternative for many large compute- and data-intensive projects. However, medical and healthcare applications currently only make for a small fraction of the overall workload on this infrastructure. This might be caused by special requirements on data protection or by a missing awareness of existing offers. Here, a closer collaboration between medical researchers, data scientists, and infrastructure experts is needed stay scientifically competitive.

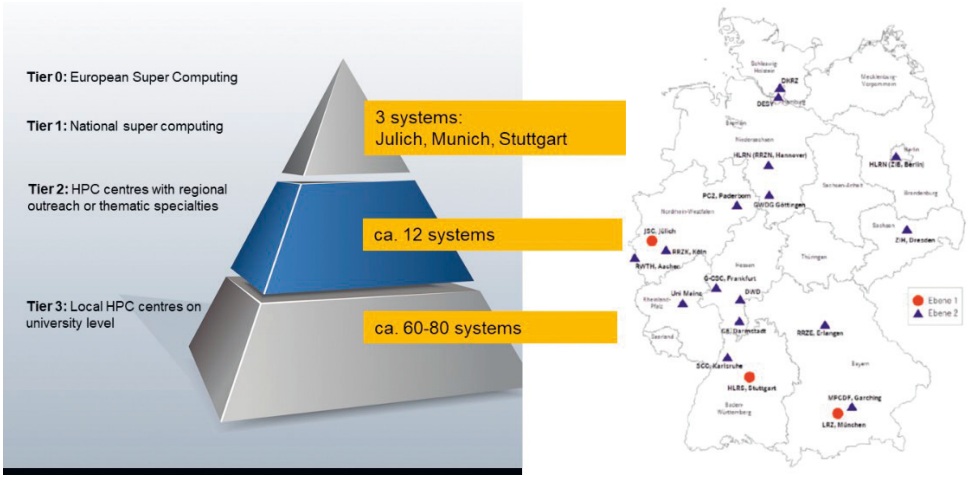

Fig. 2 German ecosystem for high-performance computing (*Gauß-Allianz e. V.* 2016).

Future compute systems will see more specialized hardware optimized for machine learning. For instance, there are already new chip designs for tensor processing units (TPU). Tensor operations are at the core of machine learning and inference. It is noteworthy that as of today such designs have been created exclusively by and for large cloud providers like Google. Such processors are currently not readily available for sale to the general public, but only as services through the cloud infrastructure of these companies. This poses a tangible risk that certain applications and research might only be possible ivy service acquisition, and thus outside our public research infrastructures. The implication on maintaining long-term sovereignty are therefore not clear.

It must to be differentiated that the learning from large data sets typically requires demanding infrastructure. However, the application of existing, already trained networks on given data items is much less complex. That means introducing and applying AI in healthcare has quite different requirements in comparison to the actual research on AI for medicine and healthcare.

Access to Data

One of the most valuable resources is the access to large datasets that can be used for learning and training. The quality of the data contained in such sets is a crucial topic, as it requires a good understanding on how data has been collected and how reliable the derived information is (*German Council for Scientific Information Infrastructures* 2020). It is often beneficial or essential to have labelled or curated data, where classifications are available that can be used for learning and comparing the quality. Especially supervised learning strategies require access to such information.

Medical research often lacks access to suitable sets of data. One reason for this is that learning requires larger datasets than those which are usually gathered through typical medical studies. There is a huge potential to use data from clinical settings that resides for instance in the electronic medical record. It was and is challenging to use such data for various reasons including the often difficult obtainment of an educated consent of a patient or the fulfilment of data quality requirements e.g. in the EMR domain.

Interoperability on a syntactic and also sematic level is needed if data from different sources is combined. As machine learning requires sufficient data, it is essential for some clinical cases like rare diseases to have a combination of and exchange between different data sources. There are many ongoing activities to establish national and international standards to achieve interoperability in the medical domain. Germany currently has the medical informatics initiative (MII) in which many academic medical centers collaborate in four consortia to establish an interoperable network for medical data within and between the consortia (Semler et al. 2018). The participants establish medical integration centers at the different sites to facilitate data exchange for research.

Challenges of Machine Learning

A rich and powerful ecosystem of free, open-source software frameworks for data management, machine learning, and analysis already exists. Tools are readily available and do not

require significant investments from scientists or research projects before usage. This makes the entry to the field easy leading to many scientific activities. While the potential of machine learning is very high and we will continue to see more applications, it is becoming clear that there are also many areas where the current approaches will reach their limits. Unfortunately, we see an increasing number of publications which are not sufficiently critical with the methods or results. This leads to unreliable and non-reproducible results. Thus, it is important to have a very good understanding of data and methods to assure that the results will hold up to scientific scrutiny.

A crucial problem of machine learning and AI is that errors and limits are often difficult to predict. The careless selection of learning data sets, misunderstanding of the data or wrong parameterization can induce various forms of bias or issues of overfitting. Results may not be reliable in new or slightly different scenarios. The robustness of such machine learning approaches is therefore an important research topic. It requires deep understanding of and experience in data science to assure good and reliable solutions.

Thus, training and education in data science are highly relevant, calling for new skill sets and new professions that need to be established. This fact is already being accounted for as new training programs and curricula are being introduced in the area of data science. But to be effective, domain-specific knowledge is also required (e.g. in medicine or biology) to be able to work successful in multi-disciplinary teams on AI projects. The German council on research infrastructures (RfII) provided an analysis on new digital competencies to address such needs (*German Council for Scientific Information Infrastructures* 2019).

It is increasingly challenging to completely assess the implications of data analysis and the long-term use of data. In addition, the use of artificial intelligence especially in medical settings often poses difficult questions on data privacy and individual consent. On the one hand, the assumption of "informed" consent will be difficult to maintain if taken seriously. On the other hand, major innovation is based on the availability of large data sets. There are difficult societal and ethical questions that are not yet answered. There are countries which have arguably lower priorities on protecting individual rights and thus leverage the ability to faster adopt and innovate in this field. However, it is also obvious that progress through this kind of digitalization will not be slowed in general by such discussions.

It is perceivable that major data pools, AI infrastructures, and corresponding skill and competence centers are created by large international companies. Notably, the majority of these cloud and Internet companies are not located in the European Union. There is a non-negligible probability that certain research and consequently the resulting innovations into products might only be possible at such companies in the future.

Many AI applications suffer from the so-called "black box" approach, which implies that certain algorithms and trained neural networks are not known. It is sometimes surprising for a human how and when algorithms fail on certain tasks. As such methods are not infallible, it needs to be understood who is liable for such errors. Especially in the medical field, misinterpretations can lead to significant consequences. It is commendable that organizations like NIH push for "explainable artificial intelligence" which can offer a better understanding on the limitations of a method (Fellous et al. 2019).

Conclusion

The potential of adopting methods from the domain of artificial intelligence like machine or deep learning to medical tools and applications is very high. We are currently still experiencing the early phase of adoption. However, it needs to be distinguished whether AI-based solutions are merely applied by adopting commercial products in healthcare, or whether individual research and development is sought in this area by academia. The requirements vary significantly depending on which scenario is considered. For maintaining international competitiveness in this scientific domain, academia needs access to data, infrastructure, tools and experts in data science. A positive factor in this context is that the access to essential tools and methods is easy and not a dominant cost-factor. More difficult is the access to data sets and infrastructure needed to train algorithms. Unfortunately, in comparison to other research areas, the medical field is non well prepared to organize such large data sets, establish or use the necessary infrastructures and attract a sufficient number of data scientists. It thus needs a major collaborative and interdisciplinary effort to bring different stakeholders together to address these issues and stay competitive in the field of AI in medicine.

Significant efforts are required by clinicians and medical centers to improve data quality and adopt standards for data interoperability. This needs to be complemented by training and raising awareness on the relevance of data, but it also requires sufficient financial support. Furthermore, we need better exchange and federation of data from different clinical settings to get larger data sets. Beyond data from a well-defined clinical setting, we need strategies to integrate data from individually collected through lifestyle and fitness devices who reach higher quality standards over time. They allow for large long-term longitudinal data beyond case-based data from patients.

Successful research in this area also needs to answer the often challenging questions related to privacy, ethics, and liability. Although academia has the duty to discuss such questions and provide guidance, it is also essential to continue the societal dialogue related to these topics and trigger political decision making whenever necessary.

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Connected Healthcare – How Does it Benefit the Patient?

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Remote Monitoring Technologies and Barriers of Implementation in Critical Care

Felix Balzer (Berlin)

Summary

In critical care, the monitoring of patients' physiological parameters has significantly improved patient safety by alarming staff when one such parameter deviates from the norm. However, such devices are usually bound to a certain setting (e.g. stationary bedside monitoring in the ICU) and furthermore do not take the multitude of electronically available patient data into account. As a consequence, patient monitoring often lags behind its potentials as a result of recent advances in clinical data science.

To promote a rapid and sustainable implementation of digital health solutions in the ICU, user-derived findings shall play a key role in the design of novel devices. For a digital transformation in health care, increasing the trust and awareness of ICU staff in digital health technology may be an essential prerequisite for implementing high-definition medicine in routine clinical practice.

Zusammenfassung

In der Intensivpflege hat die Überwachung der physiologischen Parameter der Patienten die Patientensicherheit erheblich verbessert, weil das Personal alarmiert wird, sobald solche Parameter vom Normalbereich abweichen. Solche Überwachungsgeräte sind jedoch in der Regel an bestimmte Einstellungen gebunden (z. B. stationäre bettseitige Patientenüberwachung auf der Intensivstation) und berücksichtigen zudem nicht die Vielzahl der elektronisch verfügbaren Patientendaten. Damit bleibt die Patientenüberwachung trotz der jüngsten Fortschritte der klinischen Datenwissenschaft oft auf der Strecke.

Um eine rasche und nachhaltige Implementierung digitaler Gesundheitslösungen auf der Intensivstation zu fördern, werden die von Anwendern gewonnenen Erkenntnisse eine Schlüsselrolle bei der Entwicklung neuartiger Geräte spielen. Für die digitale Transformation im Gesundheitswesen und die Implementierung von „High-Definition Medicine" in den klinischen Alltag ist eine Erhöhung des Vertrauens und der Sensibilität für die digitale Gesundheitstechnologie bei der Belegschaft der Intensivstation eine wichtige Voraussetzung.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Introduction

Dr. Eric Topol, author of the book "Deep Medicine", once referred to remote monitoring as the "next big thing" when it comes to developments in artificial intelligence (AI) and mobile technology. At the core of this statement is a change in our understanding of healthcare delivery. The more remote patient monitoring is able to become, the more we need to think about of adapting our practises in routine care.

In the past, high dependency units in hospitals were more or less the only places that allowed for monitoring of patient parameters in a high timely matter. With the developments in technology that we have witnessed, patient monitoring will play a much greater role in other parts of hospital, but also beyond hospital barriers at patients' homes. In the last decade, the number of mobile devices connected to the Internet has doubled every five years, leading to approximately 50 billion devices today (Topol et al. 2015). It has been estimated that there will be almost seven connected devices per individual in the near future. Part of the exponential growth of the "Internet of Things" comprises sensors, which are increasingly embedded into smartphones and wearable devices. It is not just about the hypercompression of transistors into integrated circuits; it is the remarkable decline in cost.

Right now, it is expected that more than 90 % of all individuals in the world older than 6 years will have a mobile phone by the end of this year. On the one hand, there is the potential availability of large amount data of real-time data, on the other hand are two main barriers, one of which is the restriction due to technical barriers. Interoperability, for instance, plays a major role in this context, and similar challenges have been addressed by other contributors of this Leopoldina-Symposium. In this paper, the often neglected challenge of staff acceptance will be addressed. Though the true impact of remote patient monitoring will be found beyond high dependency units, the intensive care unit may serve as a well suited starting point for the question of staff acceptance due to the important role of monitoring technologies for staff.

Remote Patient Monitoring and Critical Care

In critical care, the combination of telemedicine and data science have led to the implementation of mobile devices such as tablets or even entire tele-intensive care units (tele-ICUs) in patient care. In particular, this technology allows the provision of high quality care by non-specialised healthcare personnel who is supervised and supported by a remote intensivist physician (Goedken et al. 2017). The availability of highly sensitive, specific and at the same time less invasive measurement of vital parameters are thought to increase patient safety, though there still is gap with respect to sufficient evidence (Noah et al. 2017). On the ICU, visualization techniques and clinical decision support systems (CDSS) on an as-needed basis have been found to support clinicians and (e.g. reduce reaction time, time to diagnosis, etc.) (Michard 2016, Gozal et al. 2018).

Challenges

Sociotechnical factors play a major role for the success of implementing novel technology in healthcare (Anderson 2007). Generally speaking, implementation barriers of digital health

applications into routine care can be clustered in the following categories: poor usability, limited knowledge and awareness as well as lack of resources (Ross et al. 2016).

In a recent study from our institution, we identified specific barriers and proposed strategies to overcome certain particularities that are frequently seen in this context (Poncette et al. 2019a, Poncette et al. 2019b). First, leadership involvement and identification with the proposed new technology has found to be vital for a successful implementation. Special attention has to be paid to the group of users, i.e. members of the ICU staff, not only during the phase of development and implementation, but also during conceptualisation. Individual user needs may also differ with respect to the ICU's characteristics (e.g. general vs. specialised care, university vs. rural hospital, etc.). Assignment of a "local champion" has proven to be effective. One member of staff, or one member per stakeholder group, should be appointed as implementation leader with dedicated protected time for making him or herself familiar with the responsibilities and roles with the team (Anderson 2007). This person should make use of adequate means of communications. For instance, if emails are not frequently used for informing staff members about work related news, there is a high chance for slow diffusion of information and potential misunderstandings. In contrast, a small number of in-person meetings with a well-respected agenda and predetermined roles for all participants could be a better alternative to mostly asynchronous communication.

Beyond the "local champion", full support and involvement of key stakeholders is required for fostering successful implementation of new technology on the ICU. A common understanding of all staff members regarding the expected outcomes and goals of the implementation project is essential. Strategies to involve key stakeholders might include the following: (1) Finding out the motivations and interests of key stakeholders, (2) Involving key stakeholders early in the conceptualization phase, (3) Making key stakeholders identify with the proposed project, (4) Explaining new technology taking into account their motivations and interests, (5) Inspiring key stakeholders of the proposed new technology, (6) Explaining key stakeholder roles and responsibilities.

Administrative barriers should be targeted at the earliest moment. Special attention needs to be paid to data privacy related matters and obtaining approval by local authorities (e.g. the hospital data protection officers). Though the introduction of the European General Data Protection Regulation (GDPR) dates back to May 2018, there still is a great need to expertise and guidance regarding the implementation of novel technologies that involve the processing of patient data. With an ever-rising number of interconnected and intersectoral health systems, there is an unprecedented need for an information technology infrastructure that meets these requirements.

Finally yet importantly, hospitals might consider offering trainings in digital health to their staff through expert workshops, simulations or e-learning, also to get them acquainted with current developments in digital health in order to enhance digital literacy. Another method en vogue is the hackathon concept, which may also be used as an instrument of recruiting technologically savvy healthcare professionals.

Conclusion

Monitoring technologies are prominent examples of the ongoing digital transformation process in healthcare. Digital Health not only achieves a translation from analog-to-digital pro-

cesses, but also induces new processes. This refers in particular to the fact that healthcare professionals will have to consider more and more resources for their decision, as for instance recommendations by remotely located specialists from a telemedical unit or artificial intelligence systems. Thus, new responsibilities and roles in ICU structure are expected to change as a result of digital transformation.

Implementing novel technologies in critical care setting require a thorough assessment of the possible barriers and a diligent planning of how to overcome those. However, not only technological advancements are necessary for improving patient care through digitalisation. Sociotechnical factors are key, and measures as for instance the early involvement and continuous training of the end-user may be crucial of the success of an implementation project.

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Interoperability

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Interoperability

Digital data are anticipated to transform medicine. However, most of today's medical data lack interoperability: data is often hidden in isolated databases, incompatible systems and proprietary software, which makes it difficult to exchange, analyze and interpret. This slows down medical progress, as technologies that rely on these data (artificial intelligence, big data or mobile applications) cannot be used to their full potential.

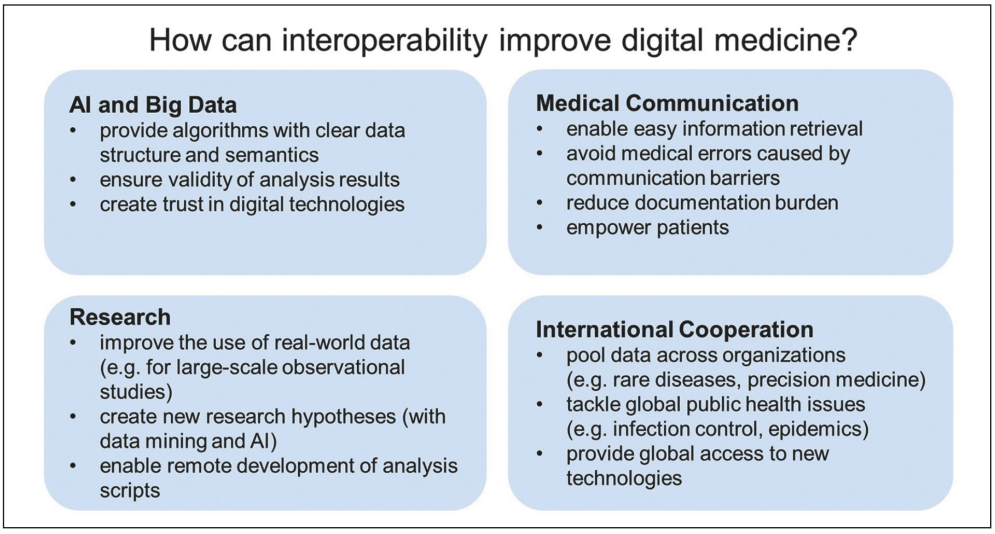

Fig. 1 Areas in which interoperability can improve digital medicine: AI and big data, medical communication, research and international cooperation.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

In this presentation, we discuss how interoperable health data can help to realize the full potential of electronic health records (EHRs), wearables, AI and big data to improve the communication of medical information, make medical research more efficient and foster international cooperation. As interoperability requires the collaborative efforts of healthcare professionals, researchers, IT experts, data engineers, and politicians, it is important to make interoperability a prominent topic in medicine and healthcare.

Eventually, efforts to improve interoperability will pay huge dividends. With international standards and medical terminologies, interoperability can pave the way for an interconnected digital health infrastructure that overcomes barriers between individuals, organizations and countries. This will make it possible to turn digital medical data into meaningful information and improve the health and well-being of patients worldwide.

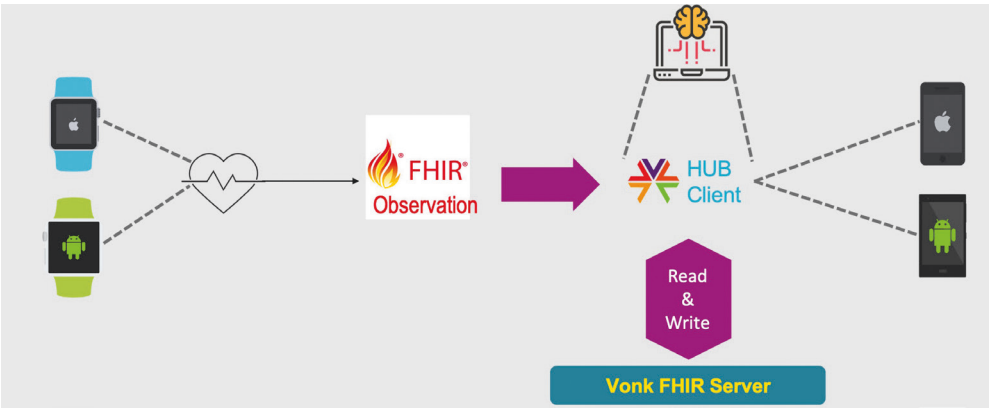

Fig. 2 Example of an interoperable health infrastructure integrating sensor data from wearables via HL7 FHIR.

Fast Healthcare Interoperability Resources (FHIR), an international standard for exchanging digital health data, is increasingly used in health information technology. FHIR promises to facilitate the use of electronic health records of EHRs, enable mobile technologies and make health data accessible to large-scale analytics.

Conclusion

Higher evidence, global collaboration, improved reporting, and data sharing with FAIR principles are the grand challenges of modern medicine.

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Automation in Healthcare – Increasing Efficiency and Improving Patient Care

Basil Matta (Cambridge, UK)

Summary

Automation, where control systems and information technologies are used to reduce the need for human work, is not a new concept. In industry, repetitive manual tasks performed by machines with minimal human input have improved efficiency and reduced errors. Although we often complain about automation and how the "human" touch is lost, as consumers we have also come to expect a high level of automation to ease the ever increasing demands of life.

Despite being well embedded for years in many industries, automation in healthcare has lagged behind, used mainly for billing and procurement. This has been driven by the lack of suitable technologies, the ingrained attitude that "every patient is different and machines cannot replace doctors and nurses", as well as a lack of evidence that they improve patient outcomes.

However, the spiraling cost of healthcare, the aging population, and a shortage of trained healthcare professionals have heightened interest in healthcare automation. Put simply, there are not enough caregivers to continuously monitor and deliver care to an increasingly complex, growing, and aging population. Although the primary aim of automation has been a reduction in cost and staff, it is becoming increasingly obvious that automation can also improve patient outcome and experience through standardization, connectivity, seamless transfer of data, and accessibility of information.

Despite all of the perceived benefits of automation, it is important that we openly talk about the concerns of preserving the value of human interaction and focus on where automation does not replace skilled healthcare professionals, but instead helps to eliminate tasks that require little cognitive function and improve workflows and efficiencies, thereby empowering doctors, nurses, the patient and family to focus on the patient's health with reliable data to support them.

Zusammenfassung

Automatisierung, bei der Steuerungssysteme und Informationstechnologien eingesetzt werden, um den Bedarf an menschlicher Arbeitskraft zu verringern, ist kein neues Konzept. In der Industrie wurde die Effizienz verbessert und Fehler reduziert indem wiederholende manuelle Aufgaben von Maschinen mit minimalem menschlichem Einsatz ausgeführt werden. Obwohl wir uns oft über die Automatisierung beklagen und lamentieren, dass die „menschliche" Komponente verloren geht, erwarten wir als Verbraucher ein hohes Maß an Automatisierung, um die stetig steigenden Anforderungen des Lebens zu bewältigen.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Trotz ihrer jahrelangen, festen Verankerung in vielen Branchen, hinkt die Automatisierung im Gesundheitswesen hinterher. Hier wird sie hauptsächlich für die Rechnungsstellung und Beschaffung eingesetzt. Grund dafür sind ein Mangel an geeigneten Technologien, die tief verwurzelte Einstellung, dass „jeder Patient einzigartig ist und Maschinen Ärzte und Krankenpfleger nicht ersetzen können“ sowie fehlende Indizien, dass dadurch die Behandlungsergebnisse verbessert werden.

Nichtsdestotrotz steigt das Interesse an einer Automatisierung im Gesundheitswesen aufgrund der explodierenden Kosten, der alternden Bevölkerung und des Mangels an gut ausgebildeten Arbeitskräften. Vereinfacht ausgedrückt: es gibt nicht genügend Pflegekräfte, um eine zunehmend komplexe, wachsende und alternde Bevölkerung kontinuierlich zu betreuen und zu versorgen. Obwohl das Hauptziel der Automatisierung eine Reduzierung von Kosten und Arbeitskräften ist, wird es immer offensichtlicher, dass die Automatisierung durch Standardisierung, Konnektivität, nahtlosen Datentransfer und Zugänglichkeit von Informationen auch die Behandlungsergebnisse und die Versorgung der Patienten verbessern kann.

Trotz der vermeintlichen Vorteile der Automatisierung ist es wichtig, dass wir offen über eine Wertigkeitsbewahrung der menschlichen Interaktion reden. Der Fokus soll nicht auf dem Ersetzen von medizinischen Fachkräften liegen, sondern auf der Abschaffung von Aufgaben, die nur wenig kognitive Fähigkeiten erfordern. Dies führt zu einer Verbesserung der Arbeitsabläufe und der Effizienz, damit Ärzte, Krankenpfleger, Patienten und ihre Angehörigen sich auf die Gesundheit des Patienten mithilfe von zuverlässigen Daten konzentrieren können.

Lecture Synopsis

Repetitive manual tasks are reduced by the use of information technology. Machines with minimal human input can improve efficiency and reduce errors. Although we often complain about automation and how the “human touch” is lost, as consumers we have come to expect a high level of automation to ease the ever-increasing demands of life. It is hard to imagine life without self-check-in at airports, cash machines, Apple Pay, Amazon and Uber!

Despite being well-embedded in many industries for years, automation in healthcare has lagged behind, with its use mainly reserved for billing, procurement and replacing “paper-based” systems with paperless electronic patient records. This has been mainly due to lack of suitable technologies, the ingrained attitudes that “every patient is different, and machines cannot replace doctors and nurses”, the lack of hard evidence that automation improves patient outcomes, and the perceived cost of implementation.

Over the past several years, interest in automation has increased, driven initially and mainly by the spiralling cost of healthcare and ageing population, the shortage of trained healthcare professionals, many of whom are leaving because of stress and dissatisfaction (> 50 % of doctor report burnout, and ~ 60 % would not recommend medicine as a career), and the drive to improve safety by reducing human error. In most countries, there are not enough carers to continuously monitor and deliver care to an increasingly complex, growing, and ageing population, at an affordable cost, with minimal number of human errors. It is becoming increasingly evident that automation, often used for cost and staff reduction, can also improve patient outcomes and experience (through standardisation, quality control, connectivity, data transfer, and accessibility of information).

In a report for the Taxpayers’ Alliance regarding automation, the Rt. Honourable Matt Hancock M.P., Secretary of State for Health and Social Care in the UK, highlights the value of time released for NHS staff through improved productivity is approximately ~ £ 12.5 bn/year, with a further ~ £ 5.9 bn annually saving in the social care sector, bringing the combined potential annual savings to £ 18.5 bn by 2030 – almost 15 % of the annual NHS budget. These annual savings could be achieved with £ 1.1 bn in pathology costs, £ 0.55 bn in end of life care, £100 m savings on surgical procedures and £ 75 m on medications. In a speech delivered

earlier this year, Mr Hancock raised technology higher on the agenda by highlighting the importance of leadership driving digital transformation, backed by a recognised team, not just the IT department, but the need for it to be clinically led to have a chance of success. He summarised that "Better tech is not a 'nice to have' but vital to have for the NHS."

Healthcare professionals aim is to make patients better. However, new therapies are not the only way. We must first do no harm! Doctors and nurses often make decisions based on imperfect, inaccurate out of date information, leading to patient harm. This has been recently highlighted by Panagioti et al., who found in a sample of over 7000 medical records that 1 in every 20 patients (6 %) are exposed to preventable medical errors, with 12 % of those leading to serious harm or death.

The wealth and complexity of data available now makes analysing different changes in multiple patients difficult. Artificial Intelligence based on deep learning-based early warning system has been shown to be a better predictor of deterioration of patients in a general ward than conventional methods. Kyung-Jae Cho et al. (2020) highlighted the potential and effectiveness of AI in a rapid response system, which when combined with automated clinical data recorded in electronic health records, was useful in identifying deteriorating patients and help daily decision making. In a similar theme, AI and Machine Learning Algorithms have been shown to improve outcome in patients with sepsis, reducing length of hospital stay and in-hospital mortality.

However, for AI to fulfill its promise in improving health, at least three key challenges need to be addressed; the data must be available and reliable, information obtained via AI must get into the hands of the right providers as in the wrong hands, even the best tools can be ineffective or harmful, and the health systems where AI is going to be applied must have the regulatory capacity to oversee and manage the rapid changes. The absence of well-curated, high-fidelity, reliable and clinically applicable data sets is a challenge that can hinder proper application of AI. Autonomous systems, in which important decision making has devolved from humans to machines, can have major failures with very serious consequences if they are fed incorrect or unreliable information. The recent Boeing MAX airplane crashes, when faulty autonomous machine-driven decisions overrode the actions of highly trained pilots is a sobering example.

Similarly, the ability to better predict the deteriorating patient has been shown to reduce admission to intensive care. In a landmark study published in *Anesthesiology* in 2010, researchers found that continuously monitoring adult patients on a post-surgical floor at Dartmouth-Hitchcock Medical Center using Patient SafetyNet with Masimo bedside devices resulted in a 65 % reduction of rapid response team activations and a 48 % reduction in transfers back to the ICU (Taenzer et al. 2010). Following the initial implementation and positive results in one post-surgical orthopedic unit, Patient SafetyNet with Masimo bedside devices was expanded to cover more than 200 inpatient beds in all medical and surgical units. In subsequent articles published in the *Anesthesia Patient Safety Foundation Newsletter* in 2012 and *The Joint Commission Journal on Quality and Patient Safety* in 2016, researchers reported that Patient SafetyNet enabled the facility, over a five-year period, to achieve their goal of zero preventable deaths or brain damage due to opioids (Taenzer and Blike 2012), and over a ten-year period (McGrath 2018) maintain a 50 % reduction in unplanned transfers to ICU and 60 % reduction in rescue events after implementation of the system, despite increases in patient acuity and occupancy (McGrath et al. 2016). As a result of the Patient SafetyNet implementation, Dartmouth-Hitchcock Medical Center saved $ 1.48 million annually, showing

that implementing Masimo SET® and Patient SafetyNet to more safely monitor post-surgical patients can also have a significant impact on a hospital's bottom line by increasing ICU bed availability and reducing the costs associated with emergency rescue events.

In October 2014, Cambridge University Hospitals replaced all paper-based patient records with the Electronic Patient Record, EPIC. Despite more than two years of preparation, EPIC encountered some problems when going live, with widespread local and national media criticisms, many described the system as a £ 200 m EPIC failure. However, the organization persisted in implementation, driving change and supporting staff so that by 2015, only a year later, the system has become indispensable to staff and patients alike, generating significant improvements in care and significant saving, and rated as EMRAM level 6 by HIMSS. (The HIMSS Analytics Electronic Medical Record Adoption Model (EMRAM) incorporates methodology and algorithms to automatically score hospitals around the world relative to their Electronic Medical Records (EMR) capabilities. This eight-stage (0-7) model measures the adoption and utilization of electronic medical record (EMR) functions).

Adoption of Electronic Patient Record system such as EPIC should not be considered a mere replacement of a paper-based patient record. By optimising and adopting best practice workflows, significant benefits can be realised in patient outcomes, patient experience, staff experience and financially. EPIC adoption in Cambridge University Hospitals has resulted in – £ 470,000 saving due to paperless processes in medical records, £ 750,000 additional income from improved coding, and saved 20 WTE Staff as a result of Pathway automation. The introduction of the in-house electronic sepsis alert and workflow alerts has improved care of patient with sepsis, with 70 % increase in patients receiving antibiotics for sepsis within 1 hour of ED arrival, 50 % increase in adult inpatients receiving antibiotics within 60 minutes of the sepsis alert triggering. At least 64 lives saved from sepsis in the past year (2018-19), 42 % reduction in sepsis mortality Trust-wide compared to 2015 sepsis data.

In our Neurosciences Critical Care Unit, and in common with over 150 other units worldwide, we have been using an in-house software ICM+ to collect and analyse haemodynamic signals in patients who have suffered traumatic brain injury. By continuously relating changes in ICP to blood pressure, an autoregulatory index is derived which indicates the state of cerebral autoregulation, an important determinant of outcome. By using a modified algorithm, we are able to determine the cerebral perfusion pressure which provides best cerebral autoregulation, defined as Optimal CPP. Optimal CPP is determined for each patient, providing "individualised" care and not "one size fits all" approach to CPP management. Trials are now underway to determine the effect on long term outcome (https://cppopt.org/).

However, despite all of the perceived benefits of automation, it is important we talk openly about the concerns of preserving the value of human interaction. Automation's main objective should not be replacing skilled healthcare professionals, but helping eliminate tasks that require little cognitive function thus improving workflows and efficiencies, empowering doctors, nurses, the patient and family to focus on the patient's health with reliable data to support them.

In summary, the spiralling cost of healthcare and ageing population, the shortage of trained healthcare professionals, and the drive to improve safety by reducing human error are clear indicators that technology has to play a vital part in the future of healthcare delivery. By understanding how automation can be used to reduce the burden of tasks that require little human input, significant benefits can be realised in terms of reduced errors, efficiency, outcomes and reduced costs. We must adopt technologies for what they are able to provide and not discard them for what we perceive to be their shortcomings.

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Toward a Digital Triage Platform for the German Healthcare System

Dominik Graf von Stillfried (Berlin)

Summary

While Germany's healthcare system seems to have abundant resources compared to other countries, it also has a very high level of utilization (OECD 2019). Due to a high degree of patient choice, a lack of coordination has frequently been diagnosed, in particular with respect to the rising use of emergency care (*Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen* 2018). This critique peaked in legislation trying to curb the use of emergency care by non-urgent patients. While the legislative process has not yet been finalized, a unified demand management system was implemented by the Associations of Statutory Health Insurance Physicians as of January 1, 2020. This comprised a telephone-triage system based on software supported decision making on the urgency of need and the appropriate level of care, and a telephone appointment service. The triage software named *Strukturierte medizinische Ersteinschätzung in Deutschland* (SmED) is based on a Swiss development which has been adapted for implementation in Germany. By way of a progress report, initial experiences with its implementation are being reported and options for further development are being explored. Early data suggests that 3 out of 4 patients are being directed to the ambulatory sector, while more than half of those require attention within 24 hours. To increase availability of the service and to address the increasing share of patients who begin their contact with the health system digitally, implementation of a self-triage version of the software is being prepared for 2020. While an evaluation of the software and its implementation is still underway, it is obvious that it will only foster effective demand management if patients and practices perceive this as a benefit.

Zusammenfassung

Im Vergleich zu anderen Ländern scheint das deutsche Gesundheitssystem zwar über reichliche Ressourcen zu verfügen, ist aber auch sehr stark ausgelastet (OECD 2019). Weil Patienten eine hohe Wahlmöglichkeit haben, verzeichnet sich häufig ein Mangel an Koordination, insbesondere im Hinblick auf die steigende Inanspruchnahme der Notfallversorgung (*Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen* 2018). Diese Kritik gipfelte in einer Gesetzgebung, die versucht, die Inanspruchnahme der Notfallversorgung durch Patienten, die keine Notversorgung benötigen, einzuschränken. Obwohl das Gesetzgebungsverfahren noch nicht abgeschlossen ist, haben die Kassenärztlichen Vereinigungen zum 1. Januar 2020 ein einheitliches System zur Nachfragesteuerung eingeführt. Dies besteht aus einem telefonischen Termindienst sowie einem telefonischen Triage-System, das mithilfe einer Software die Entscheidungsfindung auf der Grundlage der Dringlichkeit und des angemessenen Niveaus der Versorgung unterstützt. Die Triage-Software mit dem Namen *Strukturierte medizinische Ersteinschätzung in Deutschland* (SmED) beruht auf einer

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Schweizer Entwicklung, die für eine Implementierung in Deutschland angepasst wurde. In einem Zwischenbericht wird über erste Erfahrungen bei der Umsetzung berichtet und Optionen für die weitere Entwicklung ausgelotet. Erste Daten deuten darauf hin, dass 3 von 4 Patienten in die ambulante Behandlung geleitet werden, wobei mehr als die Hälfte dieser Patienten innerhalb von 24 Stunden behandelt werden müssen. Im Jahr 2020 wird die Implementierung einer Selbsttriage-Version der Software vorbereitet, damit diese Dienstleistung öfters zur Verfügung steht und die steigende Anzahl von Patienten, deren Kontakt mit dem Gesundheitssystem digital beginnt, angesprochen wird. Obwohl die Bewertung und Implementierung der Software noch im vollen Gange sind, wird ein effektives Nachfragemanagement nur dann erreicht werden, wenn Patienten und Arztpraxen dies als Vorteil wahrnehmen.

Defining the Problem: Who Manages Access to Acute Care Facilities in Germany?

Up to the COVID-19-outbreak the health policy debate in Germany was dominated by planned legislation to reform acute and emergency care in search of a remedy for a seamingly ever increasing utilization of prehospital emergency services and emergency departments which to a large extent was considered inadequate. Literature suggests that telephone and digital triage and appointment systems can contribute to more rational utilization if such services are run well and have been optimally embedded in the healthcare system (van den Heede and van den Voorde 2016, Semigran et al. 2015, Zhao et al. 2017). Diverting inappropriate utilization of emergency care is necessary given that present utilization of emergency departments of about 20 million cases annually, half of which are being treated on an out-patient basis, is easily dwarfed by potential utilization which has been estimated to reach approximately 200 million acute cases annually out of 600 million cases presently treated in the ambulatory care sector by office-based physicians (*Zentralinstitut für die kassenärztliche Versorgung* 2019).

Digital media have become a major source of information on health issues; approximately half of the population uses them prior to contacting a physician (Marstedt 2017). Scanning app stores and websites in January 2020, we identified at least 21 providers active in Germany offering to help with finding suitable physician practices and appointments, partly combined with features of telemedicine such as teleconsultations, symptom checking, disease diaries and transmission of medical data. Prior to the pandemic only a limited number of patients and physician practices, however, were taking part in digital appointment systems combined with features of self-triaging or telemedicine. Also, while many symptoms might hint at potentially serious diseases there is a lack of differentiated advice regarding the degree of urgency of medical treatment and the adequate point of care (Lupton and Jutel 2015, Chambers et al. 2019). If digitization leads more and more patients to question whether they should contact their GP first, we would argue that there needs to be a digital equivalent to the first assessment and further guidance which primary care delivers in the analog world.

What has been Done: Development of a German Telephone Triage System

Prompted by the debate about crowding of emergency care by non-urgent cases the Central Research Institute for Abulatory Care in Germany (Zi) commissioned a study 2016 to survey instruments of demand management. This resulted in set criteria which a technical solution to manage patients' acute needs for care should fulfill (Herrmann et al. 2017). This could be narrowed down to 4 criteria:

– highly sensitive detection of potentially avoidable threats to health with high urgency of treatment (red flags),

– specific direction of patients to an adequate point of care,
– based on a systematic structure or algorithms to support delegation to non-physician staff,
– easy documentation and generation of patients summaries.

Given that all existing telephone triage systems would require adaption prior to implementation in Germany in December 2017 a decision was made to base the German demand management system on the Swiss Medical Assessment System (SMASS). Zi joined a cooperation with the Swiss in4medicine AG and the German aQua-Institut to develop Strukturierte medizinische Ersteinschätzung in Deutschland (SmED) as software which supports trained healthcare workers (nurses, practice-assistants, paramedics) during telephone triage (Stillfried et al. 2019, Stillfried 2019).

SmED contains roughly 900 sets of questions with defined options for answers which are centered on 87 main health problems derived from the ICPC-2 coding system for primary care. Based on an ongoing review of medical literature and expert consensus the questions and answers are organized in a static neural network which suggests next questions depending on the answers given so far. Among other views SmED offers a hierarchical list of questions highlighting questions which would lead to most urgent treatment recommendations and/or highest levels of care. By automated runs through this hierarchical view Zi has identified more than 48 million pathways through SmED which are reduced to 9 endpoints shown in table 1. While SMASS also contains other endpoints such as selfcare, SmED always leads to some form of physician contact reflecting a cultural difference which may later be reconsidered. In 2017 a consortium around aQua-Institut (a private research institute in Göttingen) won a 3-year grant by the government-sponsored Innovationsfonds to evaluate SmED (*Gemeinsamer Bundesausschuss Innovationsausschuss* 2020).

Tab. 1 SmED – 9 Endpoints

	Prehospital emergency service	**Emergency department**	**Physician appointment / out-of-hours service**	**Teleconsultation with a physician**
Emergency	X	X		
Immediate medical treatment		X	X	
Medical treatment within 24h		X	X	X
Medical treatment not urgent (>24 Stunden)			X	X

Where we are at Present: Implementation of a unified Demand Management Program in Germany

In Germany, the 17 Associations of Statutory Health Insurance Physicians (Kassenärztliche Vereinigungen) represent office-based physicians in the collective bargaining system with the health insurance funds and hold quasi-governmental authorities in organizing universal access to ambulatory care in their geographic jurisdictions. Legislation enacted in May 2019 (*Bundesministerium für Gesundheit* 2020) required the Associations of Statutory Health Insurance Physicians to implement a unified telephone triage systems as of January 1, 2020, for all patients calling in on the central service number 116 117 with acute health problems. Based on the result of the triage patients need to be directed to an adequate point of care within the timeframe of the respective urgency-level. Fifteen Regions are using SmED to support their medically quali-

fied call-center staff. Implementation has been interrupted by the COViD-19-outbreak. In 2019 roughly 9 million patients used this service number which amounts to 13 % of all statutorily insured patients. Daily calls more than tripled during the pandemic. Early data showing the distribution of SmED recommendations in January 2020 are presented in Table 2.

Tab. 2 Early results

SmED Recommendations Urgency	Type of care	**Prehospital emergency service**	**Emergency department**	**Physician appointment out-of-hours service**	**Teleconsultation**	∑
Emergency		0,6 %	0,9 %			**1,5 %**
Immediate			22,9 %	11,1 %		**34,0 %**
Within 24h			0,1 %	31,6 %	5,5 %	**37,2 %**
Not within 24h				2,3 %	24,8 %	**27,1 %**
∑		**0,6 %**	**23,9 %**	**45,0 %**	**30,4 %**	

N = 85,000 Assessments, analysis by Zi, January 10, 2020, data: November 29, 2019

Altogether, prior to the pandemic about 75 % of all SmED-recommendations would require an appointment or out-of-hours contact in a physician practice or a teleconsultation. More than half of those contacts were recommended either within 24 hours or shorter. This requires a considerable effort on behalf of the ambulatory care system and could over time revolutionize the way patients approach healthcare. Emergencies are a rare event in this context. In table 2 they are underrepresented and amount to approximately 3 % of all calls. When SmED was used to triage emergencies dyspnea was recorded for 77 % of these cases, chest pain (9 %), temperature (9 %) and coughing (8 %) were also frequent. Combinations of symptoms are possible. Contrary, those patients who received a recommendation for ambulatory care most frequently recorded nausea (15 %), abdominal pain (12 %), back pain (12 %) and temperature (10 %).

Looking Ahead: Toward a Digital Demand Management Platform

Potentially, SmED could be implemented in four different settings as displayed in table 3. Presently, more experience needs to be generated with its routine implementation as a tool supporting health professionals which perform telephone triage. The pandemic, however, demonstrated how fast this professional service could be clogged up by sudden intense demand. To improve accessibility of the service for patients Zi pushes ahead with two developments: a) using natural language processing AI to automate the telephone dialogue with the patient until a recommendation is reached which could still be communicated by a health professional, b) implementing SmED as digital self-triage via chatbot with ensuing option to find a suitable practice and immediately make an appointment if appropriate. Both developments are scheduled to be launched at least in pilot versions still in 2020. The chatbot version might also be given to patients in waiting areas of emergency departments or practices to help collect anamnestic information and to prioritize appointments and is presently tested in a clinical trial in Switzerland (Meer 2019).

SmED might also help to manage demand in the realm of emergency care: Prehospital emergency services increasingly record deployments to patients whose demands appear to

Tab. 3 SmED – Areas of application

At point of care	**SmED deployment**	
	Supporting health professionals	**Patient-led self-triage**
Patient not present	Telephone triage	Online / app
Patient present	Prehospital emergency service / triage point of ed / clinic	Waiting area of ed / clinic

be non-urgent to ambulance teams on site (*Sachverständigenrat zur Begutachtung der Entwicklung im Gesundheitswesen* 2018). Therefore, in various regions pilot implementations of SmED on mobile devices are underway to support ambulance teams in their decision making not to deliver patients automatically to an emergency department but, if appropriate, to designated practices which will be able to handle their health problem. Given new findings that clinical triage systems may not be suited to support demand management by redirecting non-urgent patients to GP practices (Slagman et al. 2019) Zi works with emergency departments to evaluate the use of SmED as a filter for non-urgent patients. Finally, SmED could help support prioritizing appointments in GP-practices. The benefit of using a unified demand management system in all of these cases would be that it might be that access to increasing scarce medical resources will no longer be determined by patients' choice of first contact but by a structured assessment of the acute health problem.

To achieve this SmED needs to be embedded in processes which effectively improve patients' experience and the provision of care. Given that patients have no financial incentives to access the healthcare system in cases of acute need via telephone triage or digital self-triage demand management can effectively work only by acceptance. This involves a change in culture on the side of patients as well as in practices and in emergency care institutions. Implementing a digital platform for demand management will therefore be a long process which well exceeds development and deployment of the triage software.

Postscriptum

Please note the following update on Tab 2: In 2020 roughly 813,000 SmED telephone assessments were executed with SmED. The average duration per assessment was 154 seconds. The percentage of recommendations for time to treat (urgency level) was: emergency 2.9, immediate 38.2, within 24 hours 31.7, not within 24 hours 20.3, without recommendation 6.9. The recommendations for type of care were distributed as follows (in percent): emergency service 1.3, emergency department 22.1, office-based physician 46.7, teleconsultation 20.1, selfcare (only COVID-19) 2.4, no recommendation 6.9.

As a consequence of the COVID-19-pandemic all projects designed to implement versions of SmED for the mobile use in prehospital emergency services and for digital self-triage had been postponed for action in 2021. In May 2021 an SmED-version to be used at the triage desk in hospitals and out-of-hours practices will be available as a medical product. It will, however, be available only for research purposes and clinical testing at first. A clinical study is scheduled to begin in May 2021 at the emergency departments of Charité and the University Hospital of Leipzig.

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Visual Exploration and Analytics of Disease Maps with the MINERVA Platform

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Summary

Disease maps are knowledge repositories that support the discovery process of molecular mechanisms of human diseases by elucidating complex cross-talks of multiple relevant pathways. At the core of disease maps are diagrams that are constructed following the standards of systems biology. These diagrams can be used for exploration and visual analytics but requires a proper set of tools. The MINERVA Platform is a web server developed for the visual analysis of molecular interaction diagrams, especially disease maps. We discuss different aspects of discovery processes in disease maps, including their reproducibility. We illustrate them with examples using the MINERVA Platform. Extensive exploration is enabled through interactive browsing, the visualization of protein structures and multi-omics datasets, and integration with databases of drug, chemical or miRNA targets. The platform offers a contextualized view of omics datasets, including genetic variants, improving their interpretation. Reproducible and customizable analytics is attainable via dedicated API and plugins, allowing the establishment of entire visualization workflows. In summary, the MINERVA Platform supports exploration and visual analysis of complex disease maps by offering dedicated, built-in functionalities, but also by flexible data interfaces.

Zusammenfassung

Disease Maps sind Wissensspeicher, die den Erkenntnisprozess der molekularen Mechanismen menschlicher Krankheiten unterstützen, indem sie komplexe Querverbindungen zwischen mehreren relevanten Signalwegen aufdecken. Der Kern von *Disease Maps* sind Diagramme, die nach systembiologischen Standards konstruiert sind. Diese Diagramme können zur Exploration und zur visuellen Analyse verwendet werden, erfordern aber ein geeignetes Set von Werkzeugen. Die MINERVA-Plattform ist ein Webserver, der für die visuelle Analyse von molekularen Interaktionsdiagrammen, insbesondere von Krankheitsdiagrammen entwickelt wurde. Wir diskutieren verschiedene Aspekte von Entdeckungsprozessen in Krankheitskarten, einschließlich ihrer Reproduzierbarkeit und veranschaulichen sie mit Beispielen unter Verwendung der MINERVA Plattform. Eine umfangreiche Visualisierung ermöglicht die Darstellung von Proteinstrukturen und *Multi-omics*-Datensätzen, und die Integration mit Datenbanken von Medikamenten, Chemikalien oder *miRNA-Targets*. Die Plattform bietet eine kontextualisierte Ansicht von *Omics*-Datensätzen, einschließlich genetischer Varianten, und verbessert so deren Interpretation. Reproduzierbare und anpassbare Analytikverfahren können über dedizierte API's und *Plugins* angesprochen werden, was die Erstellung ganzer Visualisierungs-Workflows ermöglicht. Zusammenfassend lässt sich sagen, dass die MINERVA Plattform die Exploration und visuelle Analyse komplexer Krankheitskarten unterstützt, indem sie dedizierte, eingebaute Funktionalitäten bereitstellt, aber auch durch flexible Datenschnittstellen erweitert werden kann.

Introduction

Systems medicine aims to formulate informed hypotheses about molecular mechanisms of diseases using complex prior knowledge and large-scale omics datasets. Disease maps (Mazein et al. 2018) support this process by organizing prior knowledge of relevant disease

mechanisms into a diagrammatic, standardized representation. These diagrams are as complex as the processes they represent, so to fully benefit from them, they require web-based, interactive exploration, data analytics and integration into bigger bio-computational workflows. Unlike pathway databases like Reactome (Jassal et al. 2019) or KEGG (Kanehisa et al. 2017), disease maps are a decentralized, platform-independent effort. Their diagrams are drawn in systems-biology-oriented editors like CellDesigner (Kitano et al. 2005), creating custom versions of relevant pathways. Importantly, integration with bio-computational databases, visual data analytics and computational biology workflows are needed to increase the impact of disease maps on the discovery in systems biomedicine.

The MINERVA Platform (Gawron et al. 2016) is a web server for visual exploration and analytics of disease maps. It features a rich exploration interface with drug targets search, allowing on-the-fly visualization of omics datasets and display of protein structures. These features are coupled with an extensive API, and an architecture supporting plugins, and conversion between major systems biology standards.

We will discuss the architecture of the MINERVA Platform, its visual exploration functionalities related to exploration of disease maps, including search for drug targets, visualization of protein structures and omics data. Finally, we will demonstrate how MINERVA can become a building block of bigger visualization workflows and serve for layout-preserving conversion of systems biology formats. All functionalities and workflows are illustrated with examples using the Parkinson's disease map, available at pdmap.uni.lu (Fujita et al. 2014). An extensive documentation and examples of use of the MINERVA Platform are available at minerva-web.lcsb.uni.lu.

The Architecture of the MINERVA Platform

The architecture of MINERVA platform is illustrated in Fig. 1. A structured model is transformed, annotated and stored in the database together with the optional information, including layout, glyphs and pre-defined data overlays. The content is visualized on-line and can be arranged into sophisticated diagrams, with illustrative overview images and hierarchically organized content. Visualization of protein structures (Hoksza et al. 2018) and genetic information (Vanderkam et al. 2016), or display of drug (Gaulton et al. 2017, Wishart et al. 2018), chemical (Davis et al. 2019) and miRNA (Chou et al. 2018) targets are provided via integrated external resources.

The MINERVA Platform imports and exports the three main, layout-supporting, systems biology formats: CellDesigner SBML, SBML with layout and render, and SBGN Process Description. The conversion between these formats is possible, as diagrams uploaded in one format can be also exported to the two other formats (Hoksza et al. 2020). Uploaded diagrams can be automatically annotated and verified by the MINERVA Platform, which reduces the time necessary to create rich, high-quality diagrams representing complex mechanisms of disease, and improves the utility of disease maps.

MINERVA API (Hoksza et al. 2019) offers a programmatic control of disease and maps hosted on MINERVA. Exploration of content can be implemented to search across the entire disease map and its submaps for key molecules with a given expression profile and drugs targeting them. Interactions of disease maps in MINERVA can be directly transformed into network representation and combined with network analysis approaches (Glaab and Schnei-

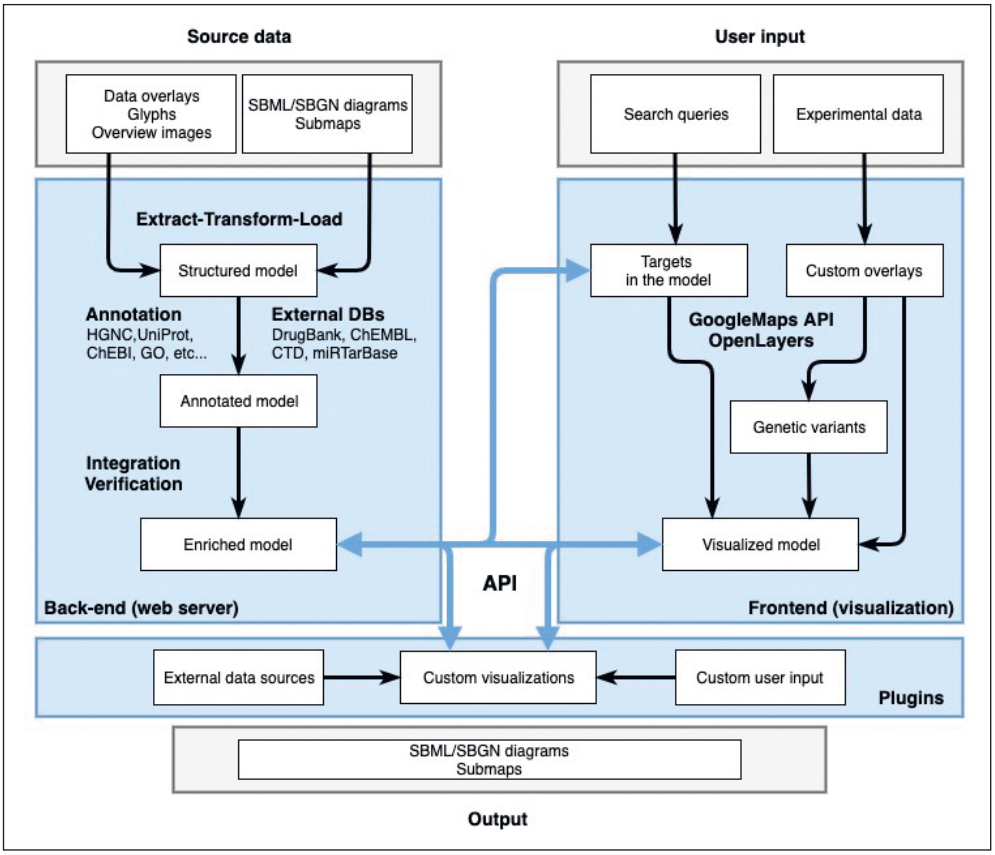

Fig. 1 MINERVA architecture diagram, adapted from (Gawron et al. 2016) and updated to include new features. The back-end server handles input diagrams, its annotation and integration with predefined graphical content. The front-end displays the content using either Google Maps or OpenLayers APIs, while datasets, including genetic variant data and protein structures, are shown on top of them. The web server handles search queries and visualizes their results. Finally, content can be exported either as a systems biology diagram (.xml file) or as an image (.png or .pdf). All communication between the front-end and the backend is handled by a dedicated API, and the plugin architecture enables users to develop customized visualizations.

der 2012, Ignac et al. 2014). Altogether, the API allows for automated and reproducible exploration of disease maps, as most of the manual exploration tasks and workflows can be performed with API calls.

An important feature of MINERVA architecture is the possibility of running user-provided plugins (Hoksza et al. 2019). MINERVA plugins are JavaScript snippets using a dedicated Plugins API giving flexibility in designing and running custom analytics and visualization. Plugins are integrated directly in the MINERVA front-end and can interact with the displayed content. Users can design their own visualizations and link external data sources without changing the core source code.

Visual Exploration of Disease Maps

Disease maps are diagrams representing a conceptual and contextualized model of a given disease, combining signaling pathways, metabolic reactions or macromolecular interactions. Visualization of such diagrams helps to illustrate the known landscape and highlight important cross-talks.

The MINERVA Platform allows for an easy lookup of molecules with names matching a given text, which are then marked as pins in maps and subordinate maps. This search may result in multiple instances of the same molecule, when it appears in multiple contexts. This allows enumeration of relevant pathways and compartments. Search for multiple terms visualizes areas, where the molecules of interest can interact. Finally, users can search the contents of disease maps for literature supporting molecular interactions. They can either search using a PubMed identifier to directly highlight annotated interactions, or they can go to a dedicated view summarizing all literature in a given disease map. In both cases, this allows for a quick check if a paper of interest is already represented in the map (Fig. 2).

Visual exploration of molecular interaction networks may benefit from the display of the structural properties of a given protein. To this end, the MINERVA Platform integrates the MolArt tool (Hoksza et al. 2018). MolArt combines protein sequence and structure visual-

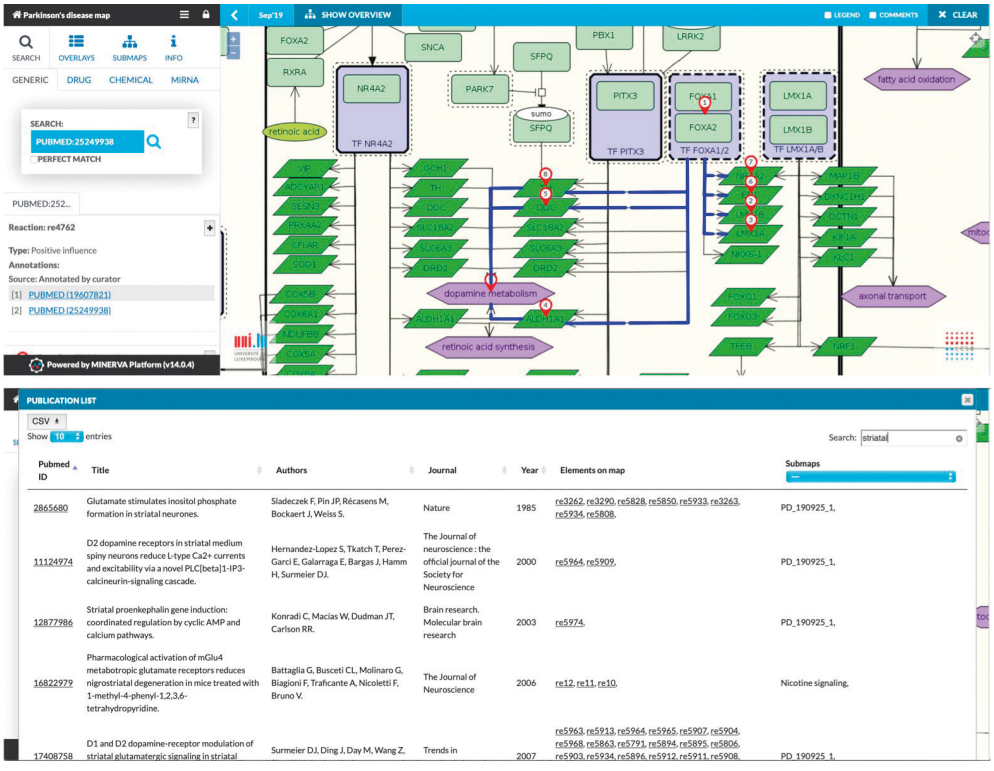

Fig. 2 Literature search in MINERVA Platform. Top: Search by PubMed ID reveals interactions annotated with this ID. Bottom: Literature annotating the disease map can be narrowed down by a keyword in the title or author's name, here by the term 'striatal'.

ization and annotation, giving the user the possibility of easy navigation through structurally important components, as illustrated in Fig. 3. MolArt in MINERVA Platform uses UniProt identifiers in the annotation of diagram elements to retrieve the corresponding structures. Because of this, even structures that have no PDB entry (Burley et al. 2017), can be visualized using predictions from SWISS-MODEL repository (Waterhouse et al. 2018). Known disease-related variants are mapped on the sequence and the structure, indicating areas they may affect. For novel information about the possible effects of amino-acid modifications, MolArt uses data from PredictProtein (Yachdav et al. 2014).

Disease-related mechanisms may relate to known modifying molecules, like drugs, chemicals or microRNAs. With the growing number of available knowledge and databases, diagrams may benefit from cross-linking to such resources. The MINERVA Platform implements interfaces to four major interaction databases: (i) DrugBank (Wishart et al. 2018) and ChEMBL (Gaulton et al. 2017) for drug targets; (ii) Comparative Toxicogenomic Database (Davis et al. 2019) for disease-focused chemical-gene interactions; and (iii) miRTarBase (Chou et al. 2018) for miRNA-gene interactions. Using a particular search functionality causes MINERVA to retrieve relevant targets from the corresponding databases and display them on the disease map. Wherever applicable, supporting literature is provided as well. A reverse search is also possible, and the user can query available drugs, chemicals and miRNAs targeting a selected element.

Fig. 3 Visualization of protein structures in MINERVA with MolArt. Top: right click on a protein reveals contextual menu, marked in red, to run MolArt for the corresponding UniProd ID. Bottom: MolArt is run within MINERVA for the selected protein.

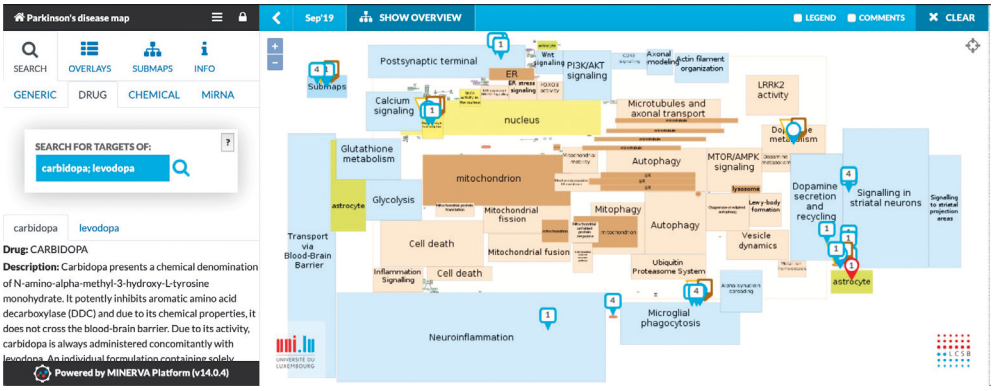

Fig. 4 Drug target search in MINERVA. Targets of carbidopa and levodopa are simultaneously shown in the Parkinson's disease map.

Investigation of disease mechanisms is often supported by omics datasets, describing molecular profiles of the relevant tissues or cells. These omics datasets are usually both complex – they describe multiple molecules at once – and noisy. Moreover, the usual omics analysis provides a list of molecules significantly associated with the disease, but without direct relation to the molecular mechanisms or pathways they may affect. The MINERVA Platform visualizes omics datasets as graphical overlays on top of the molecular interaction diagrams (Fig. 5). For each displayed dataset, relative level of the molecule level is shown, allowing a direct visual interpretation and contrasting of datasets representing different conditions. To show genetic variants, MINERVA integrates the genome browser *pileup.js* (Vanderkam et al. 2016). Each gene with variants is highlighted and their popup windows will feature a genome browser with indicated variants. Protein-coding variants can be annotated with their corresponding amino-acid positions, showing them in MolArt view in MINERVA to show these variants.

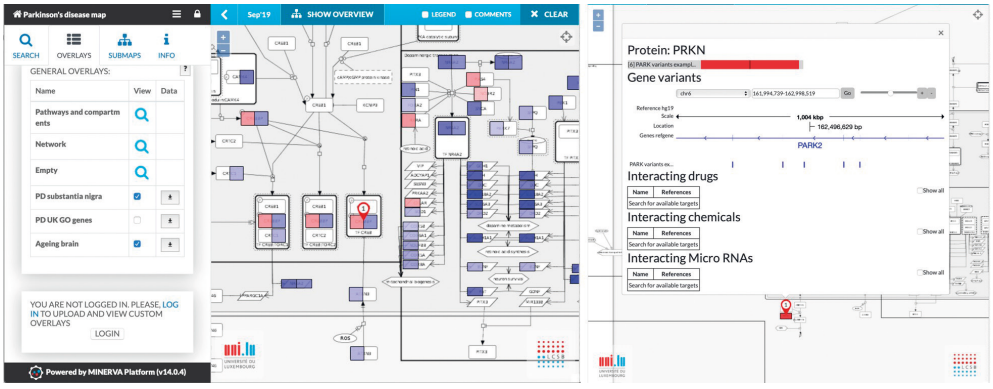

Fig. 5 Visualization of data overlays in MINERVA. Left: two transcriptomics data sets displayed simultaneously show different expression pattern for CREBP. Right: Integrated genome browser pileup.js displays genetic variants for PRKN.

Advanced Visualization with Plugins

Custom visualization workflows can be implemented using the plugin architecture. It allows running user-provided JavaScript code using dedicated API calls (Hoksza et al. 2019). Such an approach offers flexibility in expanding visualization and data linking capabilities of the platform, as illustrated using existing and available plugins. These plugins are available in the PD map (pdmap.uni.lu), and the figures below use this disease map as a use case.

An alternative visualization of diagram content is implemented in a plugin for tree-based exploration.[1] For a selected element in the diagram, the plugin summarizes their nearest neighbors as a tree that can be traversed, with each step revealing the neighbors of the next selected elements, indicating the directionality and the type of the neighbors. The traversal path is simultaneously visualized in the original diagram (Fig. 6).

Another example is a plugin performing Gene Set Enrichment Analysis[2] (GSEA) (Irizarry et al. 2009). It utilizes the hierarchical organization of diagrams in MINERVA into subordinate maps and pathways. The plugin calculates the enrichment of elements in a given disease map highlighted by a given overlay (see Section above). Enriched subordinate maps and pathways are highlighted on the disease map diagram.

A cross-link is also possible between the content of a given map and external databases or datasets, as illustrated by a plugin for disease-related variants.[3] It allows lookup of a disease name in Proteins API (Nightingale et al. 2017) and Open Targets Platform (Carvalho-Silva et al. 2019) to fetch a list of known variants, and visualize its results on a disease map. With this a user can ask if a given disease map may be affected by variants specific for other disorders.

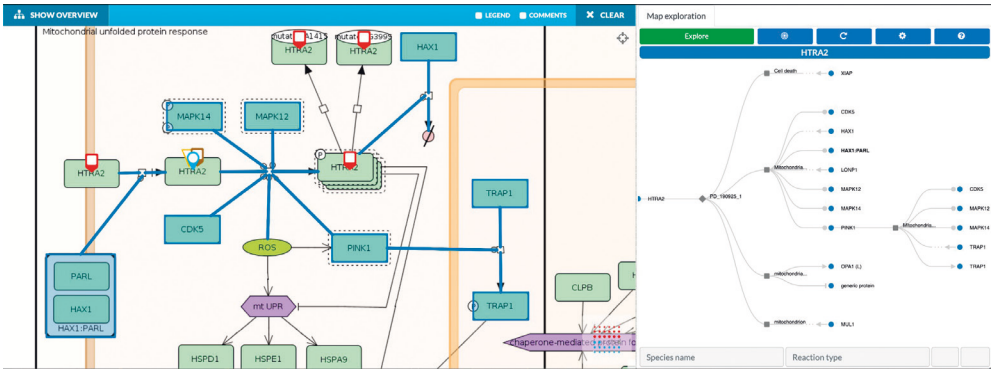

Fig. 6 Tree-based exploration plugin in MINERVA. Tree-based exploration plugin visualizes neighbors of the start-ing element as a tree and allows to traverse the tree expanding it stepwise. Here, exploration starts for HTRA2 and reveals molecules from PINK1, next step of exploration.

1 Code and documentation available at https://git-r3lab.uni.lu/minerva/plugins/exploration
2 Code and documentation available at https://git-r3lab.uni.lu/minerva/plugins/GSEA
3 Code and documentation available at https://git-r3lab.uni.lu/minerva/plugins/disease-associations

Conclusion

Disease maps are an important resource supporting research on disease mechanisms (Mazein et al. 2018, Ostaszewski et al. 2019). The MINERVA Platform enables their comprehensive exploration and interpretation, including highly dimensional and often noisy omics datasets. One of the foremost functionalities is the rich interface for visual exploration of layout and annotations in often large and complex maps, allowing to drill down to the fine-grained details of molecular mechanisms. Omics datasets can be visualized in the disease maps as multi-colored data overlays, also on the level of genetic variants. Together with the integrated search for drug, chemical and miRNA targets, users can cross-check disease maps content from the perspective of disease-modifying molecule or environmental factors. In summary, MINERVA superimposes multiple layers of knowledge and data, highlighting areas, interactions and elements of importance, greatly improving the process of discovery in the area of molecular mechanisms of disease.

Importantly, this process of discovery can be largely automated into reproducible procedures using the extensive API. Queries for the contents of disease maps, including types, parameters and annotations can be embedded into larger workflows, or used by other bio-computational services. Similarly, searches for molecule targets or analyses of omics data overlays can be performed systematically and automatically for the entire disease map. This way, even complex manual tasks can be expressed as a series of API calls which, when scripted, transform a process of visual exploration into a repeatable routine. Finally, MINERVA plugins combine the visual capabilities of the platform and the procedural automation of the API, empowering the user community to write their own visualizations (Hoksza et al. 2019).

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Translational Genomics for Rare Disease

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Summary

Next-generation sequencing technologies have revolutionized our ability to assess genetic variation across the genome of patients in a variety of clinical contexts. However, interpreting the clinical relevance of variation is now the major bottleneck for implementation of genomic health care in rare disease, cancer, and precision medicine settings. Although terminologies exist to describe clinical data, standard formats for capturing clinical data about individuals have not existed, which hinders data exchange and limits the ability to perform analyses. The Human Phenotype Ontology was initially developed in 2008 to provide a standard ontology for the analysis of clinical phenotype data with a focus in medical genetics and rare disease (RD). It has grown to become the de facto international standard for RD phenotype analysis. The emerging Phenopacket standard of the Global Alliance for Genomics and Health provides a structural for capturing and computing over detailed descriptions of individual patients and is being developed to enable standardized phenotypic data exchange in medical and scientific settings.

Zusammenfassung

Sequenzierungstechnologien der nächsten Generation verändern grundlegend unsere Fähigkeit, genetische Variationen im gesamten Patientengenom in einer Vielzahl von klinischen Kontexten zu erkennen. Die Interpretation der klinischen Relevanz von Variationen ist heute der größte Engpassfaktor in der Einführung der genomischen Gesundheitsversorgung bei seltenen Erkrankungen, Krebs und der Präzisionsmedizin. Obwohl es Terminologien zur Beschreibung klinischer Daten gibt, existierte bisher keine Standardisierung bei der Erfassung klinischer Daten über einzelne Patienten. Dadurch wird der Datenaustausch erschwert und die Durchführung von Analysen eingeschränkt. Die *Human Phenotype Ontology* wurde 2008 entwickelt, um eine Standardontologie für die Analyse von klinischen Phänotypdaten mit Fokus auf medizinische Genetik und seltene Erkrankungen (SE) bereitzustellen. Sie hat sich zum internationalen De-facto-Standard für die Phänotypanalyse von SE entwickelt. Der im Entstehen begriffene Phenopacket-Standard der *Global Alliance for Genomics and Health* bietet ein Gerüst für die Erfassung und Berechnung überdetaillierter Beschreibungen einzelner Patienten und wird weiterentwickelt, um einen standardisierten phänotypischen Datenaustausch im medizinischen und wissenschaftlichen Bereich zu ermöglichen.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Understanding genomic variation is the key to precision medicine; however, despite the ease of sequencing, clinical interpretation in the context of genomics is still challenging. Clinicians face long lists of candidate diseases, genes, and countless variants of unknown significance. Indeed, the efficiency and affordability of sequencing has shifted the bottleneck to interpretation; however, interpretation requires robust information about the typical phenotypic presentation of diseases. However, this vital phenotype reference data is often missing, poorly structured (e.g., free text), non-interoperable, or is recorded in various locations using disparate terminologies or free text (e.g., within Electronic Health Records, EHRs).

Diagnostic Challenges of Rare Disease

Unambiguous, computable descriptions of disease phenotypes are critical for robust differential diagnosis and clinical care, especially for rare and genetic diseases. Diagnosis of genetic diseases is often problematic, either because the disease is rare or because of lack of access to expert diagnosticians and/or hospitals. Roughly 25 % of rare disease (RD) patients go 5 – 30 years without a diagnosis, and 40 % of initial diagnoses are wrong. It remains extremely challenging to even retrieve information about RDs computationally. An estimated 80 % of RDs have a genetic component (*Rare Disease UK*), but diagnostic success rates using genomic sequence data are still low (25 – 50 %) (Clark et al. 2018). At least 10,000 RDs have been described in the literature (Haendel et al. 2019). Although individually rare, cumulatively, RDs may affect about 5 % of the population (Nguengang Wakap et al. 2020).

Human Phenotype Ontology

To improve the diagnostic yield for RDs, we developed the Human Phenotype Ontology (HPO). The HPO is a comprehensive bio-computational resource for the analysis of human diseases and phenotypes, offering a computational bridge between genome biology and clinical medicine, and is used across the globe for analysis and exchange of phenotype data in RD (human-phenotype-ontology.org, Robinson et al. 2008, Köhler et al. 2014, Köhler et al. 2017). The HPO is the clinical flagship of the Monarch Initiative (monarchinitiative.org), a much larger network of knowledge about disease biology. Monarch embeds the HPO into a semantically unified framework of knowledge on diseases, genes, phenotypes, and model organisms with over 50,000,000 items of knowledge (Mungall et al. 2017). The HPO has become the *de facto* standard for RD phenotype analysis, having been adopted by projects such as the 100,000 Genomes Project, SOLVE-RD, the NIH Undiagnosed Diseases Program, the NIH Undiagnosed Diseases Network, the Global Alliance for Genomics and Health (GA4GH), and many others (Köhler et al. 2018). International groups are translating the labels, synonyms and textual definitions of the HPO into 10 languages: French, Spanish, Italian, German, Dutch, Portuguese, Turkish, Japanese, Russian, and Chinese. In addition, a plain language translation of the HPO was created to facilitate patient involvement in research and improve patient understanding of medical terminology (Vasilevsky et al. 2018). The HPO is therefore an important standard for clinical diagnostics and RD patient empowerment.

Our group has developed HPO-based software for genomic diagnostics called Exomiser/Genomiser (Robinson et al. 2014, Smedley et al. 2015, Smedley et al. 2016) that is widely

used by projects such as the NIH Undiagnosed Diseases Program (Bone et al. 2016, Gall et al. 2017) and Genomics England's 100,000 Genomes project (Davies 2017). Exomiser leverages the HPO to 'compute over' clinical phenotype data. The ontological structure of the HPO allows fuzzy, specificity-weighted phenotype matching of sets of HPO terms observed in the person being sequenced (Köhler et al. 2009, Bauer et al. 2012, Schulz et al. 2009). Additionally, the underlying logical definitions enable HPO terms to be integrated with numerous other resources, such as model organism data (Robinson and Webber 2014). Exomiser then combined this phenotypic analysis with an assessment of the predicted pathogenicity of variants to derive the final ranking of candidate genes.

Data Exchange Challenges in RD

There are a number of formats for describing, exchanging, and computationally analyzing genotype information, such as VCF and BAM. In contrast, standard formats for specifying the observable characteristics of disease (e.g., symptoms) have not existed. The lack of a standard format across health care providers and research organizations hinders communication and limits the ability to perform analyses.

Phenopackets

The Phenopacket Schema represents an open standard for sharing disease and phenotype information to improve our ability to understand, diagnose, and treat both rare and common diseases. A phenopacket links detailed phenotype descriptions with disease, patient, and genetic information, enabling clinicians, biologists, and disease and drug researchers to build more


```
{
 "type": {
  "id": "HP:0011463",
  "label": "Macroscopic hematuria"
 },
 "modifiers": [{
  "id": "HP:0031796",
  "label": "Recurrent"
 }],
 "ageOfOnset": {
  "age": "P14Y"
 }
}
```


Fig. 1 Representative element of a phenopacket. This element specifies that recurrent macroscopic hematuria with onset at age 14 years was observed.

complete models of disease. The standard is designed to encourage wide adoption and synergy between the people, organizations and systems that comprise the joint effort to address human disease and biological understanding. The Phenopacket schema is being developed by a team within the Global Alliance of Genomics and Health (Lead developer: Julius O. B. Jacobsen, Queen Mary University of London).

A phenopacket contains a set of mandatory and optional fields to share information about a patient or participant's phenotype, such as clinical diagnosis, age of onset, results from lab tests, and disease severity. If available, a phenopacket can link to a separate file containing a patient's genetic sequence. Fig. 1 displays an element within a phenopacket that is being used to specify a phenotypic abnormality.

Phenopackets are expected to standardize phenotypic data exchange within the medical and scientific settings. This will allow phenotypic data to flow between clinics, databases, clinical labs, journals, and patient registries in ways currently only feasible for more quantifiable data, like sequence data. The phenopacket schema is freely available (Jacobsen et al. 2019) and was confirmed as a GA4GH standard in October 2019.

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fMRI Imaging and Neurocognitive Performance

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Summary

From its inception, medical imaging has been a step in the right direction towards individualized medicine. The brain is the human organ that has benefited tremendously from advances in medical imaging especially with the discovery of functional MRI (fMRI). fMRI has been widely used by cognitive neuroscientists to map brain mechanisms underpinning complex human functions such as literacy, motivated behavior and social cognition. Recently, fMRI has started to play a role in clinical practice. In terms of individualized medicine, fMRI has found application in pre-surgical planning to map eloquent areas, pre-symptomatic diagnosis and more recently drug development. We use fMRI to understand traumatic brain injury (TBI) processes and recovery from TBI. Since TBI is a complicated disease, personalized approaches are a necessity and lead to cost-effectiveness. We provide empirical examples, as well as future plans of how task-based and resting-state fMRI, in combination with neurocognitive testing, can help us to prognosticate outcomes and better understand drug action following treatment.

Zusammenfassung

Von Anfang an war die medizinische Bildgebung ein Schritt in die richtige Richtung für die individualisierte Medizin. Das menschliche Gehirn hat am meisten von den Fortschritten der medizinischen Bildgebung – insbesondere von der Entdeckung der funktionellen MRT (fMRT) – profitiert. fMRI wird von kognitiven Neurowissenschaftlern weithin genutzt, um Hirnmechanismen abzubilden, die hinter komplexen menschlichen Funktionen wie Lesen und Schreiben, motiviertem Verhalten und sozialer Kognition stehen. Seit kurzem spielt die fMRI auch in der klinischen Praxis eine Rolle. Im Hinblick auf die individualisierte Medizin findet die fMRT Anwendung in der präoperativen Planung bei der Abbildung von eloquenten Hirnarealen, bei präsymptomatischen Diagnosen und in jüngerer Zeit auch bei der Entwicklung von Medikamenten. Wir setzen fMRI ein, um die Prozesse des Schädel-Hirn-Traumas (SHT) und die Genesungsschritte vom SHT zu verstehen. Da es sich bei dem SHT um eine komplizierte Krankheit handelt, sind personalisierte Ansätze notwendig, welche wiederum zu einer Kosteneffizienz führen. Wir stellen empirische Beispiele sowie Zukunftspläne vor, die darstellen, wie aufgabenbasierte und Ruhezustand fMRT in Kombination mit neurokognitiven Tests uns helfen können, Behandlungsergebnisse zu prognostizieren, die Wirkung von Medikamenten nach der Behandlung besser zu verstehen und festzustellen, ob Patienten mit Bewusstseinsstörungen zu verdeckten Reaktionen fähig sind.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Introduction

Personalised or individualised medicine has a core purpose: to tailor treatment to the individual's needs. This ambitious but fundamental goal cannot be attained without reaching a sufficient level of detail in our understanding of disease processes. Medical imaging techniques, whether X-rays, CT, PET, SPECT or MRI bring us closer to personalised medicine by making visible parts of the body we cannot see without surgical intervention and hence augment our understanding of disease processes. Our understanding of one human organ in particular, the brain, has benefited enormously from advances in medical imaging. Where CT imaging initially imaged the structure of the brain, PET and SPECT imaging were used to illuminate functional aspects of the brain. Presently, state of the art brain imaging, whether structural or functional, almost always involves MRI, although both PET and CT maintain prominent roles in human brain imaging.

Functional MRI

Functional MRI (fMRI) is a relatively new development in the field of MRI technology. fMRI allows the rapid acquisition of whole brain 3D images and following a substantial amount of pre-processing and statistical modelling, allows us to visualise which parts of the brain respond to specific stimulation. The fMRI signal, also known as the BOLD (blood-oxygen-level-dependent) signal depends on the oxygenated blood that activated neurons are supplied with, and allows us to visualise the relative degree of activation in different parts of the brain (Stamatakis et al. 2017). Specifically, task-based fMRI is used to identify brain regions that increase their signal in response to stimulus presentation (e.g. visual, auditory, sensory). One advantage of task fMRI is that it allows the collection of behavioural data such as response accuracy and reaction times concurrently with neuroimaging data. Behavioural data can inform the interpretation of neuroimaging data and the combination of the two can lead to more effective diagnoses and treatments. Such data allows the subdivision of large group of patients with similar symptomatology into smaller groups and therefore allows for more tailored diagnoses and prognoses.

fMRI served initially as a tool to confirm findings from years of neuropsychological research and later to extend them. As such, fMRI has played a major role in cognitive neuroscience for over twenty years allowing neuroscientists to localise brain function in a spatially rigorous manner. More recently, fMRI has started to play a role in clinical settings and by consequence in individualised medicine. Examples are in pre-surgical planning to map eloquent areas (Nadkarni et al. 2014), pre-symptomatic diagnosis and more recently drug testing.

Despite the discussed advantages of task-based fMRI, the collection of resting state fMRI (rs-fMRI) has become popular in clinical settings. During rs-fMRI, participants lie quietly inside the MRI scanner with eyes either closed or open (from about 5 minutes to a few hours) but do not engage with any stimulus presentation and therefore this approach is especially useful among clinical populations or elderly patients who cannot perform cognitive tasks or get tired easily. Using this method, a number of large-scale brain networks comprising primary somatosensory and associative brain regions have been identified (Beckmann et al. 2005), with findings indicating that the functional state of these networks can be computed and used not only to differentiate disease states (Whitfield-Gabrieli et al. 2012) but also to establish the efficacy of pharmacological interventions (Guldenmund et al. 2012).

Resting state fMRI has become widely used in this context, especially when it comes to understanding psychiatric and neurodegenerative brain diseases. While behavioural data cannot be collected simultaneously with resting state fMRI, it is good practise to collect such data if possible, before or after MRI scanning. The combination of the two allows more precise personalisation of treatment as well as assessment of the effectiveness of treatment.

fMRI in Traumatic Brain Injury

Our research in the area of Traumatic Brain Injury (TBI) employs fMRI as a tool to track disease progression and recovery processes. Internationally, there are an estimated 50 million TBI cases each year (Feigin et al. 2013) and it is an increasing worldwide problem due to increasing road traffic accidents and an active ageing population with higher fall risk (Maas et al. 2017). fMRI research in TBI can help to accelerate the discovery of early prognostic markers. Moreover, it can help the development of targeted therapeutic interventions especially where rehabilitation potential is greatest for the individual. To comprehend disease and recovery processes in TBI we employ a three-pronged approach: a) We investigate the value of fMRI in predicting outcome in patients with TBI, b) we assess benefits from pharmacologically treating individuals with TBI with long-term cognitive deficits and finally c) we evaluate dysfunction and study individualised therapeutic interventions in patients who survived TBI but suffer from disorders of consciousness (DOC).

fMRI in Predicting Outcome Following Traumatic Brain Injury

To assess the usefulness of fMRI in predicting outcome in patients with TBI we utilise a uniquely large longitudinal rs-fMRI dataset which was contemporaneously acquired with clinical outcome data and behavioural measurements. The data comes from CENTER-TBI (www.center-tbi.eu), a European project that aims to improve the care for patients with TBI. Previous studies, mainly due to small sample sizes and limited follow-ups, have not managed to sufficiently explain how changes in rs-fMRI derived metrics underpin TBI progression and recovery. Our goal is to relate rs-fMRI derived indices and their changes over time to clinical and cognitive outcome measures. fMRI derived measures will include basic functional connectivity indices, which track relationships in fluctuations in activity between different brain regions, as well as measures of integration and entropy which we have used successfully in our studies of disorders of consciousness (Luppi et al. 2019). The broader goal is to combine functional connectivity (FC) based metrics to characterise disease progression. Our approach is unique in that we plan to build mathematical models to prognosticate outcomes in individual patients and will also determine which rs-fMRI biomarkers can be used to fine-tune individualised therapeutic interventions.

fMRI in Assessing Pharmacological Interventions Following Traumatic Brain Injury

An increasing number of patients with acute traumatic brain injury survive with good neurological outcomes. However, a large proportion of TBI survivors suffer from neuropsychological se-

quelae such as loss of memory and personality changes. The neural bases of these changes have traditionally been investigated using neuropsychological testing, structural imaging and/or PET imaging. This research partially explained the mechanisms and outcome of brain injury, however patients who perform poorly on neuropsychological assessments may have apparently normal structural MRI scans (Ruff et al. 1994). fMRI can disambiguate this phenomenon by revealing the functional mechanisms underlying neurocognitive deficits on a patient by patient basis. Understanding those mechanisms increases the chances of discovering candidate drugs likely to improve the full range of cognitive/behavioural functional impairments following TBI. An example of this is the study we carried out to investigate the neural correlates of working memory improvement following the administration of methylphenidate (Manktelow et al. 2017).

We found that the effects of methylphenidate on working memory performance were not uniform across patients. Specifically, patients in the mid-range of cognitive performance (when on placebo) benefited mostly from methylphenidate. Personalised fMRI scanning allowed us to establish that functional enhancement was mediated by cerebellar-cortical functional connectivity suggesting that methylphenidate may be enabling residual functionality in patients with relevant residual structural underpinnings. Patients with the worst performance (when on placebo) benefited the least from methylphenidate, possibly because structural connectivity in these patients is so severely compromised that neurochemical enhancement cannot deliver any benefit. Neurocognitive and fMRI data in this example were imperative for the stratification of patients for treatment with methylphenidate and enabled progression to individualised medicine (Manktelow et al. 2017).

fMRI in Disorders of Consciousness

Patients with DOC have severe neuropathology with damage to neural systems underlying awareness and wakefulness (Giacino et al. 2014). Accurate diagnosis at the bedside is complicated because their behaviour can fluctuate and may therefore be dependent on the time of observation. fMRI biomarkers can aid the diagnosis and prognosis of patients with DOC on an individual basis and are therefore essential. Early research in this field showed that a subset of patients can covertly respond to commands while in the scanner by imagining they are playing tennis (Owen et al. 2006) or imagining they are walking around their house (Monti et al. 2010). However, not every hospital has the facility to carry out stimulus based fMRI experiments. To assess level of residual functionality in individuals who survived TBI but suffer from disorders of consciousness we are focusing our efforts on developing a rs-fMRI based, machine learning classifier. To this end, we are investigating whether deep learning algorithms may discriminate patients with covert response capacity. Preliminary testing, is currently attaining an accuracy of 85% in distinguishing individuals with capacity for covert responses. These results show that it is possible to distinguish between individual DOC patients who are able or unable to respond to a volitional task using rs-fMRI and demonstrate the technique's potential for individualised clinical use.

fMRI in Personalising Pharmacological Intervention in Disorder of Consciousness

Considering the great variety of neurochemical systems involved in normal arousal mechanisms, it is evident that precise mapping of these will not only improve our understanding of

conscious processing but may also inform individualised treatment in disorders of consciousness, where pharmacological arousal agents produce inconsistent responses (Whyte and Myers 2009, Giacino et al. 2012). Accordingly, the precise delineation of ascending arousal network subcomponents through rs-fMRI may lead to distinct prognostic and therapeutic implications (Brown et al. 2010). To this end, we characterise brainstem nuclei connectivity signatures for consciousness in individuals by comparing healthy awake volunteers to a cohort of DOC patients. Hence, by observing how certain transmitter systems change their connectivity in chronic DOC we further our understanding of what macroscopic alterations in individual patients may lead to impaired consciousness. This account of brainstem functional connectivity changes, in combination with preclinical findings, inform drug development. Preliminary rs-fMRI results from this endeavour point to the importance of dopamine signalling in maintaining consciousness. These data are congruent with data from animal studies, such as the one by Palmiter and colleagues (Palmiter et al. 2011) who observed that dopamine-deficient mice were behaviourally unconscious until dopaminergic signalling was retrovirally reactivated.

Conclusion

We have discussed the significant role that fMRI can play in individualised medicine. Activity and connectivity profiles derived from task-based fMRI, together with neurocognitive findings can provide detailed insights into an individual's responsiveness to drugs. When patients with disorders of consciousness cannot produce overt responses, machine learning algorithms may be trained on rs-fMRI connectivity profiles to evaluate their capacity for producing responses. Furthermore, in patients with disorders of consciousness, personalised connectomes of brainstem nuclei could inform treatment options and assist the monitoring of treatment effects.

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Bioinformatic Prediction and Therapy Optimization by Artificial Intelligence in Hypotension

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Summary

Intraoperative hypotension (IOH) is a relevant complication of general anesthesia, representing a major challenge for anesthesiologic management. Depending on the definition of IOH, it occurs in up to 81 % of non-cardiac surgery and is associated with complications, including myocardial infarction, acute kidney injury, and an increased 30-day-mortality. In order to detect and treat these hemodynamic alterations, advanced hemodynamic monitoring combined with a treatment algorithm can be used. It seems likely that reducing the frequency, depth and duration of IOH will reduce organ injury. Recently a hypotension prediction index (HPI) algorithm has been developed that analyzes big data from two different data sources: (1) a retrospective cohort used for training, consisting of 1,334 patient records and (2) a prospective, local hospital cohort (204 patients) used for external validation. The algorithm uses a large set of features calculated from the high-fidelity arterial pressure waveform to predict an upcoming hypotensive event. Receiver-operating characteristic curve analysis evaluated the algorithm's success in predicting hypotension, defined as mean arterial pressure below 65 mmHg. This machine-learning algorithm is able to identify IOH 15 minutes before it occurs, promising a new approach to avoiding perioperative complications.

Zusammenfassung

Die intraoperative Hypotonie (IOH) ist eine relevante Komplikation der Allgemeinanästhesie und stellt eine große Herausforderung für das anästhesiologische Management dar. Je nach Definition der IOH tritt sie bei bis zu 81 % der nicht-herzchirurgischen Eingriffe auf und ist mit Komplikationen wie Myokardinfarkt, akuter Nierenverletzung und erhöhter 30-Tage-Mortalität verbunden. Um diese hämodynamischen Veränderungen zu erkennen und zu behandeln, kann eine fortschrittliche hämodynamische Überwachung in Kombination mit einem Behandlungsalgorithmus eingesetzt werden. Eine Verringerung der Organschädigung ist durch eine Reduzierung der Häufigkeit, Tiefe und Dauer der IOH wahrscheinlich. Vor kurzem wurde ein Algorithmus für den Hypotonie-Vorhersage-Index entwickelt, der große Datenmengen aus zwei verschiedenen Datenquellen analysiert: (1) eine retrospektive Kohorte, die aus 1.334 Patientenakten besteht und für Trainingszwecke verwendet wird und (2) eine prospektive Kohorte eines örtlichen Krankenhauses (204 Patienten), die für die externe Validierung verwendet wird. Der Algorithmus nutzt einen großen Satz von Merkmalen, die aus der High-Fidelity Wellenform des arteriellen Drucks berechnet werden, um ein bevorstehendes hypotensives Ereignis vorherzusagen. Eine ROC-Kurvenanalyse bewertete den Erfolg des Algorithmus

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bei der Prognose einer Hypotonie, definiert als mittlerer arterieller Druck unter 65 mmHg. Dieser selbstlernende Algorithmus ist in der Lage, die IOH 15 Minuten vor ihrem Auftreten zu identifizieren, was einen neuen Ansatz zur Vermeidung perioperativer Komplikationen verspricht.

Mean arterial pressure (MAP) is the inflow pressure in most organ systems and together with organ-specific outflow pressure the main determinant of organ perfusion pressure (Saugel et al. 2019). Profound hypotension is common in patients undergoing surgery and in critically ill conditions and can result in tissue hypoperfusion and subsequent organ damage. Blood flow autoregulation provides some protection against hypotension-induced hypoperfusion for the brain and heart but perfusion of other organ systems such as splanchnic organs with practically no blood flow autoregulation such as the stomach, gut, liver, and pancreas most exclusively depends on blood pressure (Meng et al. 2019). Therefore, intermittent or continuous blood pressure monitoring using invasive or non-invasive measurement methods is standard of care in perioperative and intensive care medicine to ensure patient safety and optimize perfusion pressure (Saugel et al. 2019).

Despite constant development of recommendations, guidelines and improved monitoring devices, intraoperative hypotension (IOH) remains a relevant complication of general anaesthesia and a major challenge for anaesthesiological management. Risk factors for intraoperative hypotension include emergency surgery, age, pre-induction hypotension, neuraxial blocks, male sex, and American Society of Anesthesiologists class IV (Südfeld et al. 2017). Depending on the definition of IOH, it occurs in up to 81 % of non-cardiac surgery and is associated with perioperative complications, including myocardial infarction, acute kidney injury, and an increased 30-day-mortality (van Waes et al. 2016). It appears to be the cumulative time spent in hypotension that increases the risk of harm to patients (Davies et al. 2020). This has important implications as even relatively short episodes of hypotension that are treated immediately can reach accumulated hypotension time associated with increased injury rates during (prolonged) surgery. Schneck and colleagues revealed that a surgical patient collective undergoing total hip arthroplasty had mean hypotensive episodes of 5 (2–6) per hour relating to a total of 6 % (2–12) of the total anaesthesia time (Schneck et al. 2019). One reason for these relatively high numbers is that hypotension often occurs unexpectedly, and clinicians are forced to react when the hypotension has already occurred. Many parameters that can be measured – even using extended hemodynamic monitoring – such as mean arterial pressure, stroke volume, stroke volume variation or pulse pressure cannot predict hypotension sufficiently (Davies et al. 2020). Underlining the relevance of IOH, Monk and colleagues noted that 1-year-mortality is raised by 3.6 % for every minute the systolic arterial blood pressure remains below 80 mmHg (Monk et al. 2015). IOH mainly occurs due to three patho-physiological dysregulations: hypovolemia and consecutively decreased cardiac output, myocardial depression and low systemic vascular resistance (Davies et al. 2020). In order to detect and treat these haemodynamic alterations, advanced haemodynamic monitoring combined with a treatment algorithm can be used. It seems likely that reducing the frequency, depth, and duration of IOH will reduce organ injury. Currently, clinicians respond to blood pressure trends and treat hypotension as necessary when it occurs. It would be a major improvement to move from this reactive to a more proactive treatment, knowing in advance when a patient is going to be hypotensive and thus avoiding IOH altogether.

Hatib and co-workers recently developed an algorithm for real-time prediction of hypotension, the so-called "hypotension prediction index" (HPI), (Hatib et al. 2018). It uses machine-learning models based on the continuous analysis of a large number of hemodynamic features extracted from the arterial blood pressure waveform. The hypotension prediction index is a unit less number that ranges from 0 to 100 (Fig. 1). The higher the number, the higher is the probability that hypotension will occur in the near future and the shorter is the time for its occurrence. The HPI algorithm was developed by analyzing big data from 3,022 individual and 2,603,125 combinatorial features from two different data sources: (1) a retrospective cohort, used for training, consisting of 1,334 patients' records with 545,959 min of arterial waveform recording and 25,461 episodes of hypotension; and (2) a prospective, local hospital cohort used for external validation, consisting of 204 patients' records with 33,236 min of arterial waveform recording and 1,923 episodes of hypotension. The algorithm relates a large set of features calculated from the high-fidelity arterial pressure waveform to the prediction of an upcoming hypotensive event. Receiver-operating characteristic curve analysis evaluated the algorithm's success in predicting hypotension, defined as mean arterial pressure below 65 mmHg for ≥1 minute.

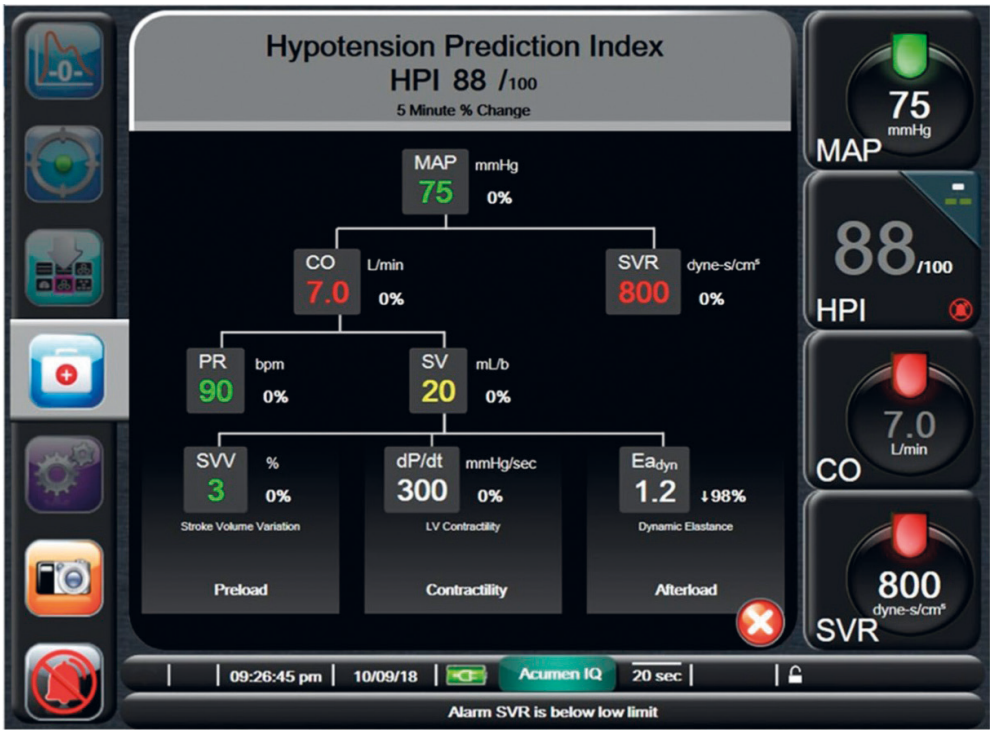

Fig. 1 Advanced hemodynamic monitoring. This secondary screen shows global haemodynamic parameters mean arterial pressure (MAP), cardiac output (CO) and systemic vascular resistance (SVR). Moreover, it divides further parameters according to the treatment option into Preload: pulse rate (PR) and stroke volume variation (SVV), Contractility: stroke volume (SV) and rate of contractility (dP/dt) as well as Afterload: dynamic elastance (Ea_{dyn}). Taken from Maheshwari et al. 2019.

In a validation trial Davies and co-workers investigated the diagnostic ability of the HPI algorithm to predict intraoperative hypotension (defines as MAP ≤ 65 mmHg for > 1 min) in comparison to other routinely collected hemodynamic variables during the perioperative period. In this retrospective study, they analyzed 292,025 perioperative data points collected with the EV1000 monitoring system containing the HPI software in 255 patients having major surgery (major abdominal, vascular, or off-pump coronary artery bypass surgery). Using a ROC analysis, the performance of the change in mean arterial pressure to predict hypotension, as well as absolute values of mean arterial pressure, cardiac output, stroke volume, pulse pressure, heart rate, stroke volume variation, pulse pressure variation, and systemic vascular resistance were evaluated. The HPI algorithm reliably predicted a hypotensive event up to 15 min before its occurrence, and the predictive capabilities of the HPI were superior (AUC 0.879, 95 % confidence interval 0.879 to 0.880; sensitivity 81 %; specificity 81 %) to all other static hemodynamic variables or their dynamic changes (Fig. 2).

In their above-mentioned single centre feasibility randomised blinded prospective interventional trial evaluating the incidence and duration of IOH, Schneck and colleagues also used the HPI system in their high-risk patient collective (Schneck et al 2019). They found a significant reduction of intraoperative hypotension in the HPI group compared to the control group (HPI 48 %, vs. control 87.5 %). Perioperative quantity of IOH was significantly reduced in the interventional group (HPI: 0 hypotension episodes/h vs. control: 5/h. Same ob-

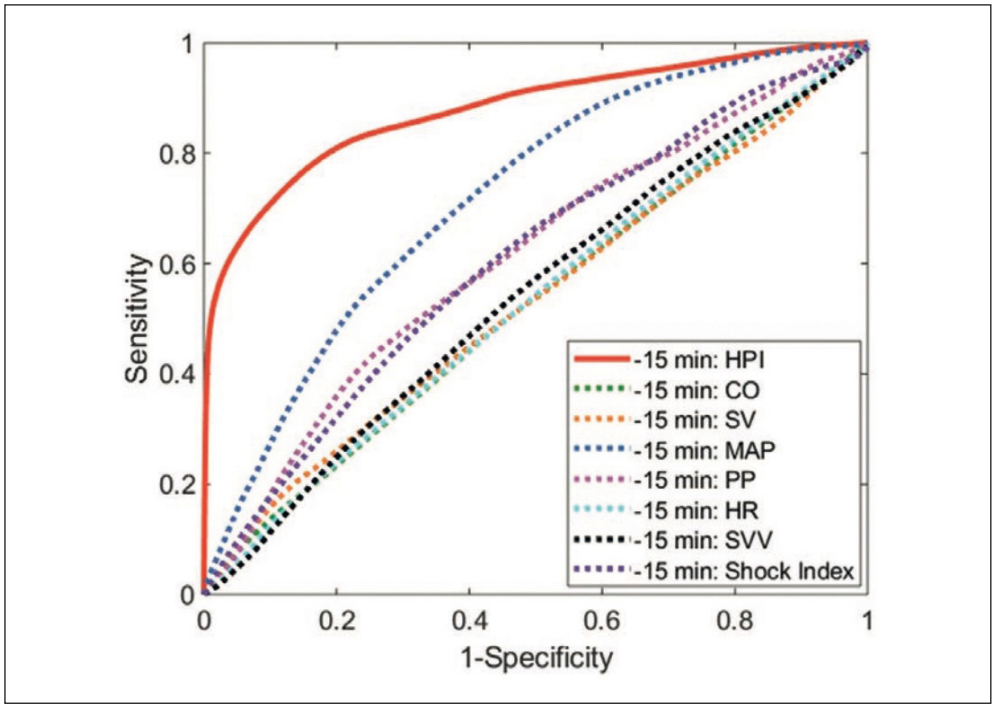

Fig. 2 Receiver operating characteristic curves for HPI (hypotension prediction index), CO (cardiac output), SV (stroke volume), MAP (mean arterial pressure), PP (pulse pressure), HR (heart rate), SVV (stroke volume variation) and shock index for prediction of hypotension 15 min before the event. Taken from Davies et al. 2020.

servations were identified for absolute (HPI: 0 (0–140) s vs. control: 640 (195–1315) s) and relative duration of hypotensive episodes (minutes MAP ≤ 65 mmHg in % of total anaesthesia time; HPI: 0 (0–1) vs. control: 6 (2–12)).

Maheshwari and colleagues evaluated the HPI in a setting with non-invasive blood pressure monitoring, using a finger blood pressure monitor (ClearSight) in patients undergoing moderate-to-high-risk surgery (Maheshwari et al. 2020). The algorithm predicted hypotension (defined as mean arterial pressure below 65 mmHg) 5 min in advance, with a sensitivity of 0.86 and specificity 0.86. At 10 min, the sensitivity was 0.83 and the specificity was 0.83 and at 15 min, the sensitivity and specificity were both 0.75. The positive predictive value of the algorithm prediction at an Index threshold of 85 was 0.83. A HPI of 80–89 provided a median of 6 minutes warning before hypotension occurred. Therefore, the HPI, which was developed and validated with invasive arterial waveforms, predicts IOH reasonably well from non-invasive estimates of the arterial waveform as well.

In summary, the Hypotension Prediction Index (HPI) provides real time and continuous prediction of impending hypotension before its occurrence and has superior predictive ability than the commonly measured perioperative hemodynamic variables. As the HPI increases, so does the actual event rate, and the time to hypotension decreases. Future work is necessary to show if avoiding intraoperative hypotension using the HPI can reduce postoperative complications and improve patient outcome.

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AI-Supported Individual Risk Prediction of Post-operative Cognitive Disorders

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Summary

Postoperative cognitive impairment following surgical interventions frequently occurs in elderly patients (10–50 %). An individual pre-operative risk prediction with subsequent treatment adaptation is currently not possible. This constitutes a serious unmet medical need with consequences for patients, their relatives and the society at large (socioeconomic impact).

Postoperative cognitive impairment is debilitating, frequent and costly. It is characterized by acute post-operative delirium (POD) and frequently followed by chronic post-operative cognitive dysfunction (POCD). With ~7.1 million surgical in-patient procedures per year in Germany, POD occurs in 350,000 to 1.75 million elderly patients per year. For these patients, the consequences can be serious: e.g. a prolonged hospital stay including in intensive care units (ICUs), the inability to participate in rehab programs, or transfer to a nursing home. Economic costs for our aging society are dramatic: ~ US$ 150 billion per year in the US (~ €30 billion per year in Germany). Costs of POCD for insurers in Germany have been recently calculated by us (~ €1.6 billion per year) (Weber 2021).

Our novel app offers a solution to this unmet need. Its risk prediction algorithm was validated in our EU-funded BioCog study. It supports the pre-operative decision-making process when considering surgery, e.g. whether or not to conduct surgery, perform conservative treatment, or adapt pre-, peri-operative treatment. Once available for clinical care, the patient and society will benefit from the app: a reduction in POD/POCD incidences by 50 % (conservative expert opinion) in order to improve the patient's health and quality of life. At the same time, German health care insurers will save more than 1 billion EUR/year and ICU resource utilization will be lowered in times of an otherwise increased need for ICUs (e.g., during the COVID-19 epidemic).

Zusammenfassung

Postoperative kognitive Beeinträchtigungen nach chirurgischen Eingriffen treten häufig bei älteren Patienten auf (10 – 50 %). Eine individuelle präoperative Risikovorhersage mit anschließender Therapieanpassung ist derzeit nicht möglich. Dies stellt einen ersthaften ungedeckten medizinischen Bedarf mit Folgen für die Patienten, ihre Angehörigen und die gesamte Gesellschaft (sozioökonomische Auswirkungen) dar.

Postoperative kognitive Beeinträchtigungen sind hinderlich, häufig und kostspielig. Sie sind durch ein akutes postoperatives Delir (POD) gekennzeichnet. Häufig folgt eine chronische postoperative kognitive Dysfunktion (POCD). Bei ~ 7,1 Millionen stationären chirurgischen Eingriffen pro Jahr in Deutschland tritt POD bei 350.000 bis

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1,75 Millionen älteren Patienten pro Jahr auf. Dies kann schwerwiegende Folgen für diese Patienten haben: z. B. ein verlängerter Krankenhausaufenthalt – auch auf der Intensivstation, die Unterbindung einer Reha-Teilnahme oder eine Verlegung ins Pflegeheim. Die wirtschaftlichen Kosten für unsere alternde Gesellschaft sind dramatisch: ~ 150 Milliarden US$ pro Jahr in den USA (~30 Milliarden EUR pro Jahr in Deutschland). Die Kosten der POCD für Versicherungsgesellschaften wurden von uns auf ~1,6 Milliarden EUR berechnet (Weber 2021).

Unsere neuartige App mit Risikovorhersage-Algorithmus wurde in unserer von der EU finanzierten BioCog-Studie validiert. Die App bietet eine Lösung für diesen ungedeckten Bedarf. Sie unterstützt den präoperativen Entscheidungsprozess, wenn ein chirurgischer Eingriff in Betracht gezogen wird z. B., ob eine Operation, eine konservative Behandlung oder eine Anpassung der prä- bzw. perioperativen Behandlung bevorzugt wird. Sobald sie für die klinische Versorgung zur Verfügung steht, profitieren Patienten und die Gesellschaft von der App. Erwartet wird eine Reduzierung der POD/POCD-Inzidenz um 50 % (konservative Meinung der Experten) zur Verbesserung der Gesundheit und Lebensqualität der Patienten. Gleichzeitig sparen die deutschen Krankenversicherungen mehr als 1 Mrd. EUR/Jahr und die Ressourcenauslastung der Intensivstationen wird in Zeiten eines ansonsten erhöhten Bedarfs an Intensivstationen (z. B. während der COVID-19-Epidemie) reduziert.

Postoperative cognitive impairment is characterized by disturbed cognition incl. memory deficits, inattention, disorientation, hallucinations, sleep disorders etc. An acute phase (post-operative delirium (POD)) is frequently followed by more chronic postoperative cognitive dysfunction (POCD). Together, the economic costs are in the range of US$ 150 billion per year (USA) or €30 billion per year (Germany). Only recently, this global unmet problem increasingly gained media attention. Unfortunately, the underlying pathophysiological and molecular conditions are hardly understood and no systematic studies with sufficient statistical power have been conducted that allow an individual risk prediction in clinical practice. A possible solution to this problem is it to develop an expert system, which allows a pre-operative risk prediction for clinical decision-making. However, this requires a structured big databank with a large number of patients, deep phenotyping/-omics, a modern algorithm for pattern recognition and a diagnostic application software (app) for professional users (physicians). Therefore, we have conducted a large European study (Biomarker development for postoperative cognitive impairment in the elderly (BioCog)) (Winterer et al. 2018) during the past few years with a total funding of 10 million Euro (www.biocog.eu).
In total, 7,727 surgical patients were screened and 1,135 patients were enrolled in the study at the Charité Berlin and the *University Hospital* Utrecht. All patients were at least 65 years old with no history of neuropsychiatric disorders and an expected duration of surgery of >1 hour. A large variety of data were collected pre- and postoperatively up to two year after surgery. In addition to the patient history and extensive clinical assessments, we conducted neuropsychological tests, neuroimaging investigations, and obtained blood for 70+ blood markers and genomewide investigations (DNA, mRNA, miRNA). A paper, presenting the major results of the BioCog project has been submitted for publication (Winterer, submitted May 2021).

In order to develop the diagnostic prediction app, we pursued a modular approach defining five different domains: clinical, neuropsych, laboratory, neuroimaging and -omics. At present, we have successfully implemented the risk prediction algorithm based on clinical and neuropsychological parameters. The assessment of the probability of risk occurrence is based on a set of non-redundant predictors (risk criteria). We have now developed a Minimal Valuable Product (MVP) with an algorithm based on clinical and neuropsychological paramters. We employed a training-test set strategy providing a pre-operative estimate on the POD likelihood in an individual patient. With the MVP alone, a validated AUC of 79.1 % (70.7 – 87.5 %) is achieved with 6 parameters (modules 3-5 for optimization in progress). The test is implemented as an App using mobile devices. Front end: 1. medical history data are entered

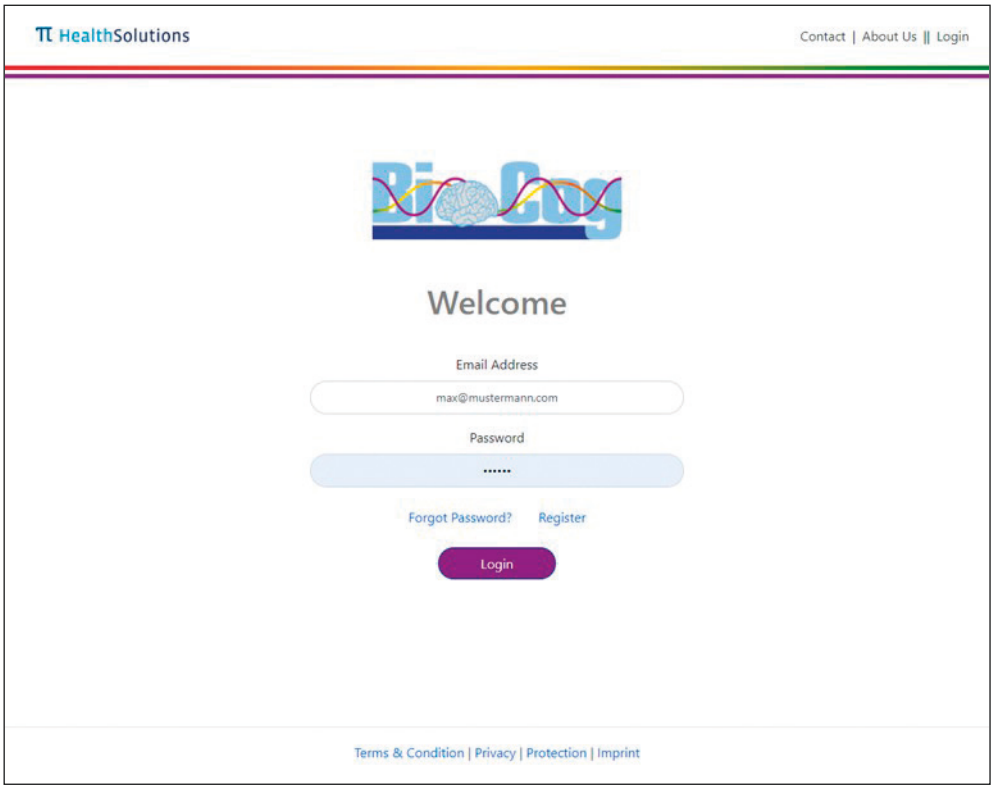

Fig. 1 BioCog Prediction App for preoperative risk assessment of postoperative cognitive dysfunction.

in a question mask by medical professionals (< 5min). 2. a self-guided, newly developed electronic cognitive test is conducted by the patient (<10 min). Data are transferred to backend, risk is calculated and displayed by frontend within milliseconds. The BioCog app (Fig. 1) is currently in the beta test phase and can be rolled out in the next few months. With this setup, we are at least 3 – 4 years ahead compared to any other competitor group worldwide.

Based on the risk estimate an informed decision can be made as part of the overall treatment strategy plan whether a surgery should be conducted or not or adapted if possible. Example: painful hip arthritis, which severely impairs mobility, is common among elderly patients. Hip replacement is the treatment of choice. Regular intake of analgetic drugs albeit with potential side effects (e.g., gastritis) is also possible. After surgery and prolonged hospital incl. intensive care unit (ICU) stay, the cognitively impaired patient may not be able to participate in a rehab program and is transferred to a nursing home. In a high-risk patient, our app would recommend not to conduct surgery to avoid harm to the patient and costs for the health care system. Accordingly, potential stakeholders are: patients (improved health, life quality), physicians (informed decision-making in clinical care, potential source of income when using the app depending on local health care system regulations), hospitals (improved patient care, shorter in-patient stay offers a competitive advantage), insurers: higher earnings (less expenses for surgeries, post-operative in-patient care, rehab), Pharma Industry: drug

development (patient stratification), society as a whole: less expenses, time expenditure, effort and emotional burden for family members (many women quit their job to support their afflicted relatives in daily life!)

Economic savings (example): POD results in delayed hospital discharge by 7.4 days (cost increase ~7000 EUR per case) (Zywiel 2015) and reducing POD incidence by 50% (using our BioCog app) cuts the number of POD cases by 175,000 – 875,000 per year in Germany. Cost savings for health care insurers in Germany: 1,225,000,000 – 6,125,000,000 Euro per year.

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Patient-Centered Risk Reduction – Which Patient Does it Help?

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Postoperative Delirium and Cognitive Trajectories

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Summary

Postoperative Delirium (POD) is a frequent and serious complication after surgery. Depending on predisposing and precipitating factors, the incidence ranges between 10 – 50 %. POD is associated with loss of autonomy, increased morbidity and mortality and long-term neurocognitive disorders (NCD) in approximately 5 – 10 % of the POD patients.

This article will focus on mechanisms involved in the development of POD and NCD, such as inflammation, toxicity, hypoxia/perfusion deficit and metabolism. Innovation Fund projects, such as "Prehabilitation of Frail Elderly Patients Prior to Elective Surgery (PRÄP-GO)" and the quality contract for "Prevention of Postoperative Delirium in the care of Elderly Patients" will be discussed. A focus will be placed on pathomechanisms and the prevention of risk factors while employing patient-centered principles.

Zusammenfassung

Das postoperative Delir (POD) ist eine häufige und schwerwiegende Komplikation nach einer Operation. Je nach prädisponierenden und auslösenden Faktoren liegt die Inzidenz zwischen 10 – 50 %. Bei etwa 5 – 10 % der Patienten wird POD mit einem Verlust der Autonomie, erhöhter Morbidität und Letalität, sowie langfristigen neurokognitiven Störungen (NCD) verbunden.

Dieser Beitrag befasst sich mit den Mechanismen, die an der Entwicklung von POD und NCD beteiligt sind, wie z. B. Entzündungen, Toxizität, Hypoxie/Perfusionsdefizit und Metabolismus. Projekte des Innovationsfonds, wie die „Prähabilitation von älteren Patienten mit Gebrechlichkeitssyndrom vor elektiven Operationen (PRÄP-GO)" und der Qualitätsvertrag zur „Prävention des postoperativen Delirs in der Versorgung älterer Patienten", werden diskutiert. Ein Schwerpunkt liegt auf Pathomechanismen und der Prävention von Risikofaktoren unter Anwendung patienten-zentrierter Prinzipien.

Postoperative delirium (POD) and cognitive dysfunctions are serious complications after surgery, affecting up to 45 million patients worldwide. Delirium is defined by the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria of the American Psy-

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chiatric Association for neurocognitive disorders (*American Psychiatric Association* 2013) as an acute and sudden change in the mental state, characterized by fluctuating levels of attention, consciousness and cognition, which is not caused by preexisting neurocognitive disorders. POD is associated with an increased length of hospitalization (Radtke et al. 2010), impairment of functional status (Liang et al. 2014), as well as short-term and long-term increase in mortality (Aldecoa et al. 2017, Witlox et al. 2010). In addition, POD is associated with the development of long-term postoperative neurocognitive disorders (NCD) (Daiello et al. 2019, Inouye et al. 2016, Sprung et al. 2017). In 2018, recommendations for the nomenclature of cognitive changes associated with anesthesia and surgery were published, as there was no previously uniform and established definition (Evered et al. 2018). Also here, the DSM-5 criteria were followed in the definition of NCD (*American Psychiatric Association* 2013). A distinction was made between mild and major NCD: mild NCD comprises a concern for the individual, informant or clinician and a modest cognitive decline, which does not interfere with independence, i.e. activities of daily living; major NCD comprises a concern and a significant cognitive decline that interferes with independence (Evered et al. 2018). Furthermore, different entities could be defined according to the timing of their occurrence: an emergence delirium or a POD occurs immediately after the operation, delayed neurocognitive recovery occurs ≤ 30 days post-surgery, postoperative mild or major NCD occur > 30 days up to one year post-surgery, and mild or major NCD occur one year post-surgery (Evered et al. 2018). In a retrospective observational study, we found the incidence of NCD to be at 8.5% in POD patients 3 months after surgery (Knaak et al. 2020). Importantly, also patients' functional status is affected by POD as demonstrated by Saczynski et al. (Saczynski et al. 2012). The authors found postoperative functional decline to be more pronounced in POD than in non-POD patients after 6 months along with reduced cognition out to 1 year postoperatively.

The tremendous burden caused by POD and NCD to patients and relatives has a sustained effect on quality of life and autonomy. In an analysis of the treatment preferences of patients with limited life expectancy, it could be shown that 88.8% of the participants would forgo treatment (resulting in death from the underlying disease) if the outcome was survival with severe cognitive impairment (Fried et al. 2002). This strongly underlines, from the patient's perspective, that POD and NCD must be considered in everyday clinical practice. This unified nomenclature was a decisive step, standardizing the language, increasing the comparability of research results, and enabling diagnosis and coding of NCD.

For the prevention and therapy of POD and NCD, the implementation of intersectoral, multiprofessional and interdisciplinary holistic approaches is indispensable. An immediate prerequisite is the understanding that each patient has a unique risk constellation and must therefore be treated individually. One major reason is that the incidence of delirium depends on predisposing (e.g., age, cognitive impairment, comorbidity, or impaired functional status) and precipitating risk factors (e.g., major surgery, cardiac surgery, or Intensive Care Unit (ICU)-stay) (Inouye and Charpentier 1996, Aldecoa et al. 2017). Therefore, incidences vary between 10 and 50% depending on the risk profile (Aldecoa et al. 2017). In addition, pathogenesis is very complex and multifactorial. The leading hypotheses on the etiology of delirium involve neuroinflammation, ageing, neurotransmitter dysregulation, oxidative stress, neuroendocrine dysregulation, network disconnectivity and sleep/melatonin dysregulation (Maldonado 2013).

Surgery, injuries and systemic infections induce an immune response, activating an inflammation cascade of proinflammatory cytokines (Maldonado 2013). Once extended to the central nervous system, neuroinflammation is maintained by the activation of microglia cells

(which can be restricted by a cholinergic inhibition) (van Gool et al. 2010). This can lead to neuronal and synaptic dysfunction, which in turn leads to behavioral and cognitive disorders, such as POD or, over the long-term, NCD.

The cholinergic pathway was investigated in a prospective randomized controlled double-blinded two-armed phase IV trial – PHYDELIO (EudraCT number: 2008-007237-47). We investigated the association between a perioperative physostigmine administration and the development of POD and NCD (Spies et al. 2021). Here, it was shown that the targeted use of physostigmine, an acetylcholinesterase inhibitor, did not reduce POD and NCD but influenced the survival of patients six months after surgery. In the prospective multicenter observational study – CESARO, we investigated the relevance of peripheral cholinesterase activity (ChE) on POD in adult surgical patients (Müller et al. 2019). We could show a significantly higher Acetyl ChE (AChE) activity in patients with POD compared with patients without POD, both preoperatively and postoperatively. This suggests that higher levels of AChE can result from upregulation, increasing provision of substrates for ACh synthesis and ensuring cholinergic neurotransmission. Interestingly, we did not see this effect in patients over 70 years of age, which could be a sign of non-existenting counter regulation.

Other inflammatory markers include "toll-like receptors, cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α, as well as S100 Ca^{2+} binding proteins and oxidative stress pathways" (Subramaniyan and Terrando 2019). Furthermore, we could show in a secondary subgroup analysis of the parallel group randomized controlled trial – SuDoCo, that preoperative levels of the C-reactive protein (CRP) were independently associated with POD but not with NCD three months after surgery (Knaak et al. 2019). These markers can interfere the blood-brain barrier by, e.g. endothelial dysfunction (Maldonado 2013).

In addition, neuronal aging processes increase the vulnerability of the brain to stressors, so that age-related changes in brain metabolism, such as continuous neuronal degradation, neurotransmitter imbalances, microcirculation disorders and modulations in the intracellular signal transduction system, promote neurodegeneration and impair compensatory mechanisms (Maldonado 2013). For this reason, elderly patients are particularly susceptible to developing POD and NCD.

Systemic metabolic disturbances, such as the metabolic syndrome, can also affect cognition. In a prospective multicenter observational study which aims to establish biomarker panels for risk and clinical outcome prediction of POD and NCD – BioCog (ClinicalTrials.gov: NCT02265263) – we could identify low high-density lipoprotein (HDL-C) as an independent risk factor for cognitive impairment in older age (Feinkohl et al. 2019). In addition, we could show in a cross-sectional analysis, an association between obesity in older people and cognitive impairment independently of co-morbid hypertension or diabetes (Feinkohl et al. 2018). Furthermore, we found that intraoperative hyperglycemia was independently associated with POD (Windmann et al. 2019), while diabetes was associated with postoperative NCD (Lachmann et al. 2018). However, we did not see such an association between cerebral microbleeds (also known to reflect metabolic disturbances) and POD or NCD (Lachmann et al. 2019).

Especially in the perioperative context, special attention must be given to oxidative stress e.g. due to hypoperfusion or hypoxia. In 2010, we were able to demonstrate that duration of preoperative fluid fasting is a risk factor for POD, for the first time (Radtke et al. 2010). In addition, there is evidence, that a preoperative hemoglobin level of < 11.1 g/dL is associated with POD (Kijima et al. 2020). In the CESARO study, we furthermore could show, that an acute postoperative anaemia (by excluding patients with preoperative anaemia) is associ-

ated with development of POD (Kunz et al. 2020). This underlines the need to implement risk-adapted prevention measures in the field of hypoxia/perfusion deficit.

Fueling the complexity of these conditions is the fact that these hypotheses are by no means contradictory, but have an additive or even synergistic effect. This also leads to the development of different phenotypes of the delirium (e.g., hypoxic/perfusion, inflammatory/septic, and sedative-associated, i.e. toxic, metabolic) (Girard et al. 2018). In a prospective cohort study aimed to investigate the association between phenotypes of delirium and long-term cognitive outcomes, it was observed that sedative-associated delirium is as common as other phenotypes and causes similar sustained cognitive damage (Girard et al. 2018). This is particularly important as there is an evidence-based recommendation to avoid excessive sedation of patients (*DAS-Taskforce* 2015 et al. 2015). Another key recommendation that takes into account the neurotoxicity of anesthetics is the strict monitoring of the depth of anesthesia (Aldecoa et al. 2017). In the BioCog study, we could show for example, that preoperative cognitive impairment is associated with absolute intraoperative frontal α-Band Power of the electroencephalogram (EEG) but not with baseline α-Band Power (Koch et al. 2019). This underlines the importance of implementing guideline recommendations to prevent adverse outcomes in our patients.

One of the most important measures in the adequate treatment of POD is to screen regularly for the condition. In 2017, the European Society of Anaesthesiology published the evidence-based and consensus-based guideline on postoperative delirium (Aldecoa et al. 2017). POD screening is recommended in all patients, starting in the recovery room and once per shift up to the fifth postoperative day, using a validated delirium score. Furthermore, in order to initiate risk-adapted prevention measures, it is recommended to evaluate preoperative risk factors for POD. Unfortunately, these evidence-based measures are not sufficiently implemented. A survey showed that 73 % of patients in intensive care units were still not regularly monitored with a validated score (Luetz et al. 2014, *DAS-Taskforce* 2015 et al. 2015).

To fill these gaps in implementation, the Institute for Quality and Transparency in Health Care (IQTIG) launched the quality contract for "Prevention of Postoperative Delirium in the care of Elderly Patients". This program provides incentives in connection with higher quality requirements, improving the current standards of care in which too little delirium prevention is practiced, insufficient screening is carried out, and patients are often discharged into nursing care facilities. The goal is to provide patients with an evidence-based risk assessment, regular delirium screening and adequate delirium therapy. Only in this way, the serious consequences associated with delirium can be prevented.

An important risk factor for POD is frailty, which underlines the fact that every patient needs individualized treatment. Frailty describes a multidimensional geriatric syndrome and is characterized by the loss of physiological reserves, so that the focus is on biological rather than chronological age. Fried's description of "phenotypic frailty" is the most widely cited characterization of the syndrome (Fried et al. 2001). This phenotype includes five domains: shrinking, weakness, exhaustion, slow gait speed and low physical activity level. Frailty results in increased vulnerability to stressors and a reduction in compensatory mechanisms. For this reason, frailty is associated with increased risk of in-hospital postoperative complications, discharge to care facilities and loss of independence (Birkelbach et al. 2019).

To address this problem and to improve the quality of treatment in this vulnerable patient collective, the innovation fund project "Prehabilitation of Frail Elderly Patients Prior to Elective Surgery (PRÄP-GO)" was initiated, funded by the Federal Joint Committee (G-BA). The aim of the project is to establish and employ a suitable preoperative case-care management system to

maintain or improve the independence of surgical patients with signs of frailty syndrome after an operation and to improve postoperative quality of life and to reduce institutionalization rates. Besides the routine frailty screening of elderly patients, an interdisciplinary shared decision-making conference and prehabilitation measures are the main features of this project. These measures are crucial to ensure that the needs and expectations of each patient are considered individually.

Although the pathomechanisms of POD and NCD are complex, annotated structured data and algorithms to counteract POD and NCD can be integrated in a manner that allows machine-learning, and on the long-term data-driven science to balance between the risk to develop POD and NCD and to schedule surgery after reducing the relevant risks for the individual patient. That can be performed by pre-habilitation as well as by risk-based clinical pathways in the hospital and after discharge from the hospital. Most important for the vulnerable patient is an intersectoral, interdisciplinary, multiprofessional holistic approach.

In summary, the overall goal is to transfer the strategies of high-definition medicine to the areas of POD and NCD (Torkamani et al. 2017). Using comprehensive individual risk assessment (including frailty) before surgery, we will be able to define the personal risk profile for our patients. Through the consistent implementation of guideline recommendations and an individual decision-making process, it will be possible to practice high-definition prevention. The consideration of multifactorial pathogenesis and the application of recommended tools and individual treatment algorithms will make high precision treatment possible. And finally yet importantly, after the application of evidence-based medicine and adherence to standards, the direct use of the data of interest "enables a continuously improving, learning healthcare system, whose" data-integrated knowledge and data-driven science can help preserve the health of an individual (Mikalsen et al. 2017, Torkamani et al. 2017).

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Light Therapy for Prevention of ICU Delirium

Alawi Luetz (Berlin)

Delirium is the most frequent psychiatric syndrome in the Intensive Care Unit (ICU). This form of acute brain dysfunction predicts higher mortality rates and is associated with long-term cognitive impairment after ICU discharge (Ely et al. 2004, Pandharipande et al. 2013). Therefore, delirium prevention bundles have become an integral part of guideline recommendations. Clinical trials investigating pharmacological strategies to combat ICU delirium have failed to demonstrate results in terms of improved patient outcomes. Hence, the focus has moved towards non-pharmacological approaches.

Sleep disruption is one of the leading clinical manifestations of circadian dysthymia and an essential driver of further disarray in peripheral clocks (Wright et al. 2013). Downstream effects of sleep disruption include the mitigation of an effective immune defence (Lange et al. 2010) which puts critically ill patients at high risk for worse outcome. ICU patients are especially susceptible to harmful effects of sleep deprivation, as their mental and physical capacity to withstand it are inherently low. Disturbances in the sleep-wake circle are almost always seen in delirious ICU patients (Figueroa-Ramos et al. 2009) supporting emerging evidence that ICU delirium is a clinical manifestation of circadian dysrhythmia (Fig. 1). New data indicate that chronodisruption in critically ill is not only present as a clinical symptom but is evident on a molecular level as well. Gene expression analysis in 11 neurosurgical patients with subarachnoid or intracerebral haemorrhage or traumatic brain injury revealed complete disappearance of clock gene rhythmicity after one week of ICU treatment (Diaz et al. 2019). In conclusion, one may hypothesize that despite the disease or injury, the ICU environment itself substantially contributed to the alteration of the molecular machinery of the circadian system. There are a number of environmental factors that contribute to the alteration of the circadian system, including high sound pressure levels, bedside interventions during night and inadequate lighting conditions.

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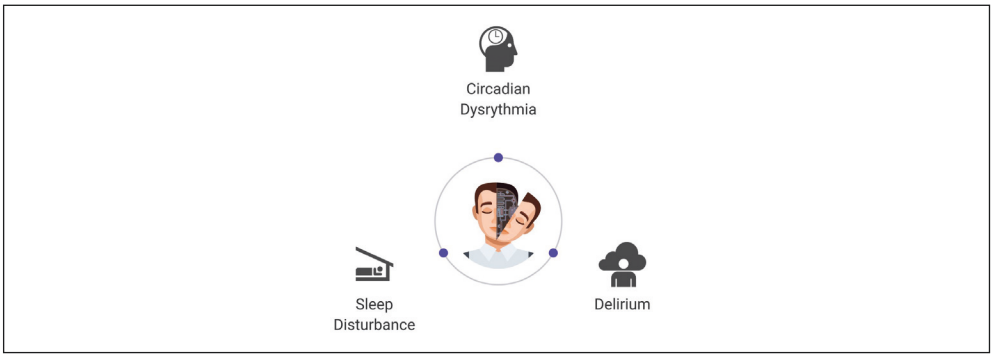

Fig. 1 The loss of "chronofitness": Delirium and sleep disturbance as a result of circadian dysrhythmia in intensive care unit patients (Figure by A. Luetz).

Light is the most critical external regulating factor of the circadian clock. The circadian clock itself is located in the suprachiasmatic nucleus (SNC) which is part of the anterior part of the hypothalamus. As such, the SCN plays an essential role in regulating the sleep-wake cycle, cognition, and brain metabolite clearance (Hastings et al. 2018). One major factor influencing suprachiasmatic nucleus activity is the influx of blue light reaching melanopsin photoreceptor cells in the retina, leading to suppression of melatonin secretion. Conversely, a decrease in the amount of blue light entering the eye decreases SCN activity and triggers increased release of melatonin (Nakagawa et al. 1992, Sack and Lewy 2001) 8; 9).

Melatonin supplementation is known to improve sleep quality in healthy persons and non-critically ill patients (Brzezinski et al. 2005). However, the effects of melatonin and melatonin receptor agonists on sleep quality and outcome of critically ill patients have been inconsistent (Ibrahim et al. 2006, Bourne et al. 2008). Studies on melatonin release in critically ill patients observed that patients exhibited either constantly high or low melatonin levels. Constantly high melatonin levels are especially prevalent in delirious patients with high severity of illness (Shigeta et al. 2001). As abnormally high melatonin levels were found in many critically ill patients, it was reasoned that suppression of melatonin levels could lead to improved sleep architecture and quality.

Current recommendations for the design of ICU rooms include sufficient amounts of natural as well as artificial light, in an attempt to improve patient's well-being and staff workflow (Thompson et al. 2012). Experimental data suggest that environments with an abundance of natural light offer beneficial immunomodulatory effects, as compared to environments with restricted light influx (Alibhai et al. 2014). Wunsch and colleagues analyzed the influence of ICU room windows in patients with traumatic brain injury. The presence of windows in the ICU rooms was viewed as a surrogate for the amount of natural light reaching the patients. In their cohort, the presence of windows in ICU rooms did not have any effect on patient outcomes (Wunsch et al. 2011). However, a major problem when interpreting the findings of Wunsch is that there are not quantifiable data on the level of light actually reaching the patient's retina and, by extension, the photoreceptor cells. It is important to know that the illuminance level is distance-dependent. As the distance from the window increases, the illuminance decreases exponentially to levels that do not have the potential for melatonin suppression (Bullough et al. 1996). Deep sedation levels in critically ill patients are another

confounder that must be taken into consideration when interpreting data from light studies in the ICU population. The eyes of the patient need to be open to make lighting interventions effective.

In consequence of the poor controllability and effectiveness of natural light sources in the ICU, technical solutions using artificial light therapy are coming into focus. So far, bright-light therapy alone has not been extensively studied in critically ill patients but was shown to improve delirium in geriatric patients (Chong et al. 2013) and post-surgical cohorts (Ono et al. 2011). A recent randomized-controlled trial using a dynamic light application in 734 ICU patients failed to prove a significant reduction in the cumulative incidence of delirium (Simons et al. 2016). Consequently, no comprehensive data is supporting the use of bright-light therapy in the critically ill.

Within an interdisciplinary project, we developed a new ICU room concept which aims to reduce delirium and cognitive trajectories in the critically ill. Beside interventions aimed at noise reduction, workflow optimisation and infection control, it comprises a newly developed light ceiling that enables clinicians to apply patient individualised light therapy. Each bed is equipped with an individual light-ceiling, extending from above the patient's head down to the patient's feet, covering an area of up to 6 x 2.4 m. Two layers of light-emitting diodes (LEDs) make up the lighting device. The first layer consists of red, green, and blue (RGB) LEDs. The second layer comprises 3,456 white-light LEDs over an area of 1.8 m · 2.4 m. The second white-light-emitting layer allows the clinician to apply individualized dynamic-light therapy for circadian entrainment. The first experimental study (Luetz et al. 2016) compared photometric parameters between the lighting equipment used in the study by Simons and colleagues (fluorescent tubes) (Simons et al. 2016) and Charité's new light-ceiling. The study results unveiled that only the large LED-based ceiling provided adequate illuminance and E_c levels for mmS without entering the area of absolute glare.

In 2013 we finished the renovation of 2 double ICU rooms that includes most of the outlined room features including the new light ceiling. The preliminary results of a first observational cohort study revealed that the incidence of ICU delirium was significantly lower among patients treated in the modified rooms (46 %) compared with patients treated in the standard rooms (76 %) (Luetz et al. 2018). However, as the study refers to a bundle of multimodal study interventions, the observed clinical benefit for patients might not be solely attributable

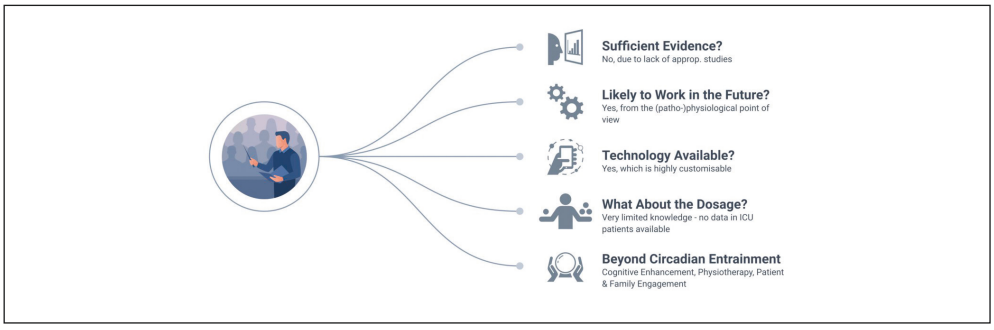

Fig. 2 Key messages regarding the application of light therapy for prevention of intensive care unit delirium (Figure by A. Luetz).

to the described light intervention. The analysis of additional data might allow an estimation about which of the room interventions contributed to this clinical effect.

Due to the lack of appropriate studies, there is currently no sufficient evidence to support the use of light therapy for prevention of delirium in the critically ill patient. More importantly, there is no data regarding the dosage of light needed to provoke certain clinical effects in ICU patients. However, because we now have the adequate technical equipment available for use in the ICU, future studies will answer these open questions. Moreover, it will open up the field for light therapy in the critically ill patient beyond circadian entrainment (Fig. 2).

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A Look into the Future of Pain Control

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Summary

Pain signaling and modulatory mechanisms change following physio-pathological events, for example the two major types of pain: neuropathic and inflammatory pain. Very different chemical events and ion channel changes underlie these pains at the peripheral level, so treatments have to differ. Lower back pain and cancer pain can be one or the other or a combination of these different mechanisms, called mixed pains. The final pain experience is a combination of all these peripheral and central events; however, within the central nervous system, the pain controlling systems are more common so that therapies acting on central modulation can span a range of pain conditions (Bannister et al. 2017). Linking the brain back to the spinal cord are descending controls and noradrenaline in these pathways is a key inhibitory transmitter in pain control. Descending controls run from the brain to the spinal cord and can be gauged in patients – the balance between excitations and facilitations shift to the latter in persistent pain states, reinforcing pain transmission (Bannister and Dickenson 2016). Understanding mechanisms for pain enhancement and modulation can help to explain these altered pain states in patients and will lead to better and more appropriate treatments for particular patients. It is clear that one size does not fit all – precision medicine is needed. With potential new drugs and precision medicine, the future looks bright.

Zusammenfassung

Schmerzsignalisierung und Modulationsmechanismen ändern sich nach physiopathologischen Ereignissen wie z. B. bei neuropathischen Schmerzen und Entzündungsschmerzen – zwei der Hauptschmerzarten. Diese Schmerzen sind auf sehr unterschiedliche chemische Ereignisse bzw. Ionenkanalveränderungen auf peripherer Ebene zurückzuführen und erfordern dadurch unterschiedliche Behandlungsansätze. Schmerzen im unteren Rückenbereich und Krebsschmerzen sind das eine oder das andere oder sogar eine Kombination beider Mechanismen – so genannte Mischschmerzen. Das eigentliche Schmerzerlebnis ist eine Kombination aus all diesen peripheren und zentralen Ereignissen, aber innerhalb des Zentralnervensystems sind die Schmerzkontrollsysteme häufiger, so dass Therapien, die auf eine zentrale Modulation der Schmerzen basieren, eine Reihe von Schmerzzuständen abdecken können (Bannister et al. 2017). Absteigende Kontrollmechanismen verbinden das Gehirn mit dem Rückenmark. In diesen Bahnen ist Noradrenalin bei der Schmerzkontrolle ein wichtiger inhibitorischer Transmitter. Die absteigenden Kontrollmechanismen verlaufen vom Gehirn zum Rückenmark und können bei Patienten gemessen werden – die Bilanz zwischen Anregungen und Erleichterungen verschiebt sich bei anhaltenden Schmerzzuständen zu letzteren, wodurch die Schmerzübertragung verstärkt wird (Bannister und Dickenson 2016). Das Verständnis der Mechanismen zur Schmerzverstärkung und -modulation kann helfen, diese veränderten Schmerzzustände bei Patienten zu erklären

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A video of the discussion can be viewed online:

und wird zu besseren und angemesseneren Behandlungen bei bestimmten Patienten führen. Es ist klar, dass es keine Einheitsgröße gibt – Präzisionsmedizin ist hier gefragt. Mit potenziellen neuen Medikamenten und der Präzisionsmedizin sieht die Zukunft aber rosig aus.

The final pain experience is built up from a number of changes in sensory and affective systems that are often first driven by peripheral mechanisms but then involved transmission and modulation by spinal cord and brain events. I will discuss how forward and backward translation from the bench to the bedside is key to better pain control by better understanding these mechanisms of pain. Aimed at the periphery, I will give examples of blocking Nerve Growth factor as a target for control of osteoarthritis and low back pain, the success of anti-CGRP antibodies for migraine, the potential of topical agents and the challenge of novel sodium channel blockers for all pain states. However, likely not all patients – the idea of varying sensory phenotypes of patients that reflect different mechanisms could form the basis for prediction of those patients who will benefit from a particular agent. There is already evidence for sub groups of patients responding to a drug for neuropathic pain. At central sites, excitingly, the efficacy of drugs that work on descending monoamine controls can be predicted in patients by sensory testing based on preclinical science and this sort of approach will be the future of pain control. Using patient sensory profiles, who will respond to a particular drug, may start to be predictable.

A large number of preclinical studies have shown that Nerve Growth Factor (NGF) is released in damaged tissue. The factor derives from a number of non-neuronal cells and binds to its receptor, TrkA, found on many pain sensing peripheral fibers but particularly those innervating deep tissues such as bone and muscle. Thus, it is especially relevant to pains such as those from surgery, trauma, osteoarthritis (OA) and low back pain (LBP). NGF has indirect effects on pain via Mast cell activation and autonomic effects and induces a state of hyperalgesia when injected into subjects. Another component to this pronociceptive profile is its uptake and transport to the cell body of the fibers in the dorsal root ganglion after receptor binding. Here, genomic effects arise with a switching on of genes for pain mediators and ion channels. Thus, NGF becomes a key target and the approach used to modulate this mediator was monoclonal antibodies delivering high specificity and a long duration of action and no centrally mediated side-effects due to the molecules not crossing the blood brain barrier (Hefti 2020). The drugs have been highly effective in patients with OA and LBP but all trials have recognised a group of patients at risk of premature joint replacement (Schnitzer et al. 2019). Mitigation of this adverse effect will be needed before blocking NGF becomes a clinical reality.

Another antibody approach that has been successful is in migraine where the peripheral mediator has been the peptide, calcitonin gene related peptide (CGRP). A big advantage in this field where a migraine is triggered when an altered central nervous system coincides with a peripheral release of the peptide has been the ability to monitor CGRP levels in blood (Akerman et al. 2017). Elevations are seen in migraine patients and the peptide acts to both dilate blood vessels and activate pain fibers. The antibodies have been raised against both CGRP and its receptor and have proven effective and well tolerated (Edvinsson et al. 2018).

Whatever the aetiology of the pain condition and whether its arises from tissue damage, nerve damage or a combination, incoming peripheral activity has to be generated by action potentials through the opening of sodium channels. Messages then arrive in the spinal cord where the information is integrated, often amplified if the peripheral drive continues and then sent upwards to the sensory and emotional areas of the brain where each individual produces their personal pain experience. Although the anti-NGF anti CGRP approaches are novel ther-

apies based on stopping pain where it starts, sodium channel modulation though drugs such as lidocaine, the basis for local or regional anaesthesia has been used extensively. The main issue with their usage is to restrict their action to the source of the pain to avoid cardiovascular and central side effects.

However, the discovery that we have 9 sodium channels and that at least three (namely, 1.7, 1.8 and 1.9) are rather selectively found in peripheral pain pathways, gave rise to the possibility of systemic yet pain selective sodium channel blockers (Dib-Hajj and Waxman 2019). Remarkably, before any drug had been developed, strong proof of concept arrived from recognition of a number of inherited pain disorders where the sodium channel proteins were abnormal leading to loss or gain of function and corresponding pain abnormalities (Dib-Hajj and Waxman 2019). This provided an impetus for the discovery of novel pain related sodium channel blockers. As these were being developed two key findings were made that points to the need for assessment of drugs for pain to consider that not all patients are the same and so may have differential responses to particular drugs. This has major implications for clinical trials. Firstly, big data from the German neuropathic pain network based on meticulous sensory testing of large numbers of patients revealed that independently of aetiology, the subjects fell into three distinctive groups. It is therefore plausible that the subgroups have different sensory phenotypes because of different underlying mechanisms (Baron et al. 2017). Since drugs for neuropathic pain act on quite different targets, then is possible that there will be a differential pharmacological sensitivity within the three groups (Bannister et al. 2020) and an explanation for why the general efficacy of drugs for neuropathic pain is not very high on a population basis (Finnerup et al. 2015).

One intriguing study has directly tested this premise (Demant et al. 2014). Using the sodium channel blocker, oxcarbazepine, patients were tested with the drug but there was no separation from placebo. However, there is a group of neuropathic pain patients who are characterized by hypersensitivity to evoked stimuli – the so-called irritable nociceptor group. Remarkably, these patients responded to the therapy. This study has huge implications for assessment of pain drugs since it suggests that a trial based simply on aetiology and the presumption that all patients are the same may fail if sensory phenotypes of subgroups are not considered (Baron et al. 2017). Many drugs may have been abandoned on this basis. And recently, a trial of a novel selective 1.7 blocker failed (McDonnell et al. 2018). There are a number of possible reasons for this failure to find an effect of a drug acting on a validated target. One is that the compound was peripherally restricted that would not allow actions on the central terminals of the pain fibers where the channel plays an important role. Secondly, patients were not selected other than having ongoing pain so that the irritable nociceptor subgroup were not studied. Finally, with the sodium channel blocker, lacosomide, sensitivity to the drug was seen predominantly in patients with a particular mutation of the channel. Others with alterations in other parts of the channel were weakly or not responsive (de Greef et al. 2019). Genetic testing of the site of the mutation will not be generally possible so the idea of patient sensory phenotypes as a basis will be more widely useful. However, neuronal recordings in pain pathways can gauge drug effects on different modalities and so guide preclinical development of pain drugs (Dickenson and Patel 2018).

A final example of the use of a pain phenotype as a predictor of efficacy comes from monitoring descending controls, pathways from deep in the limbic brain and brainstem that run to the spinal cord and modulate activity, either inhibitory or excitatory (Bannister and Dickenson 2016). It would seem counterintuitive that these pathways could be measured

if it were not for Diffuse Noxious Inhibitory Controls (DNIC). These descending controls, first described in animals, are triggered by a painful stimulus and act to inhibit spinal wide dynamic range neurons. A conditioning noxious stimulus will inhibit a test stimulus at sites distant in the body Bannister and Dickenson 2016). The human counterpart, Conditioned pain modulation (CPM), often gauged by heat on the arm versus cold pain on the foot, are reduced in many chronic pain patients, suggesting altered descending controls are key to many pain states (Yarnitsky 2015). Three crucial studies then followed. Firstly, the efficacy of the serotonin- noradrenaline reuptake inhibitor (SNRI), duloxetine, could be predicted by CPM in patients with diabetic neuropathy. Normal CPM was accompanied by low efficacy of the drug, but in those patients with weak CPM or, as in many, the second painful stimulus enhanced pain, then the drug was highly effective (Yarnitsky et al. 2012). Secondly, the mu opioid-noradrenaline reuptake blocker, tapentadol, restored CPM in a similar patient group (Niesters et al. 2014). The common link between the two drugs is the ability to increase synaptic levels of noradrenaline and soon after, preclinical studies showed that DNIC was mediated by noradrenaline acting on the spinal alpha-2 adrenoceptor (Bannister et al. 2015). Thus, two clinically effective drugs relieve pain by re-establishment of a lost descending inhibition. This is a remarkable example of the pain phenotype relating to the efficacy of analgesics. Although these studies were carried out in patients with neuropathy, a loss of DNIC/CPM is observed in patients with a wide variety of pain disorders such as musculoskeletal pain, migraine, fibromyalgia and a low CPM at the time of surgery is a risk factor for persistent post-operative pain (Yarnitsky 2015). DNIC are balanced by a descending facilitator system that is mediated by 5HT, so as the inhibitory arm decreases in persistent pain, then the excitations dominate (Bannister and Dickenson 2016, Lockwood and Dickenson 2019). In an imaging study in fibromyalgia patients, exactly this was seen (Harper et al. 2018). Thus, a maladaptive change in central modulation can lead to a diffuse pain through central descending mechanisms without peripheral nerve or tissue damage.

Overall, there have been new drugs developed, the potential for more novel agents and the better use of existing drugs. But clinical trials are the basis for the adoption of new or old agents into the clinic and we are learning that the idea of aetiology based groups ignores the fact that patients are not all the same and a drug effect on a subgroup may not be revealed by these approaches. Phenotypes represent underlying mechanisms and there is now accumulating data on using successfully these to better target pain. On this basis, being focused and precise on this basis, no matter the pain patient, will allow for the better use of old and new analgesics and may help to avoid the negative effects of a failed drug trial.

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Treating Frailty – New Opportunities

Ursula Müller-Werdan (Berlin)

Summary

Current interventions targeting physical frailty in seniors mainly comprise physical exercise – in order to enhance endurance, strength and balance – and nutritional protocols tackling sarcopenia, e.g. by supplementing additional protein. Medication review is advised in prefrail and frail individuals. These measures are widely recommended by guidelines and can be considered to be a standard therapy for frailty. Current evidence suggests that frailty may in part be reversible and preventable. Therefore, prehabilitation is suggested to slow down or reverse the occurrence of frailty. Geroscience aims at identifying pharmacological agents that counteract the aging process: metformin or senolytics are currently being tested, which in future could help combat frailty.

Beyond a mere biological explanation of frailty, the World Health Organization calls for a "Global strategy and action plan on aging and health" emphasizing the role of environmental factors which may help prevent or alleviate frailty in older individuals. Moreover, for cognitive frailty, the role of gut microbiota is being examined.

Zusammenfassung

Aktuelle Therapien der körperlichen Gebrechlichkeit bei älteren Menschen umfassen vor allem die körperliche Bewegung, um Ausdauer, Kraft und Gleichgewicht zu verbessern, und Ernährungsprotokolle zur Bekämpfung von Sarkopenie, z. B. durch die Zufuhr von zusätzlichem Eiweiß. Eine Überprüfung der Medikamente wird bei Personen mit Prä-Gebrechlichkeit und Gebrechlichkeit angeraten. Diese Maßnahmen werden anhand von Leitlinien empfohlen und können als Standardtherapie der Gebrechlichkeit betrachtet werden. Aktuelle Erkenntnisse deuten darauf hin, dass Gebrechlichkeit zum Teil reversibel und vermeidbar sein könnte. Daher wird eine Prehabilitation vorgeschlagen, um das Auftreten von Gebrechlichkeit zu verlangsamen oder umzukehren. Die Alternswissenschaft zielt darauf ab, pharmakologische Wirkstoffe zu identifizieren, die dem Alterungsprozess entgegenwirken. Derzeit werden Metformin und Senolytika getestet, die in Zukunft die Gebrechlichkeit bekämpfen könnten.

Über eine rein biologische Erklärung der Gebrechlichkeit hinaus fordert die Weltgesundheitsorganisation eine „Globale Strategie und einen Aktionsplan für Altern und Gesundheit". Diese Strategie betont die Rolle von Umweltfaktoren, die dazu beitragen können, Gebrechlichkeit bei alten Menschen zu verhindern oder zu lindern. Darüber hinaus wird für kognitive Gebrechlichkeit die Rolle der Darmflora untersucht.

A video of the presentation can be viewed online:

A video of the discussion can be viewed online:

Frailty is a condition of general weakness and rapid exhaustion – physically and psychologically commonly seen in individuals of high age. When encountering a frail person, any medical specialist or lay person may empathetically be aware of the high vulnerability and impending threat of a rapid health deterioration. However, when it comes to defining, quantifying or diagnosing frailty, medical science still resorts to the realms of phenomenology. Numerous frailty indices have been proposed, mostly referring either to the Fried criteria regarding the frailty phenotype (Fried LP et al. 2001) or to the deficit accumulation frailty index by Rockwood and co-workers (Rockwood K and Howlett SE 2018). In October 11, 2019, *The Lancet* dedicated a mini series to the topic of frailty (Hoogendijk et al. 2019, Dent et al. 2019), and in an editorial "Bringing frailty into all realms of medicine" (*The Lancet* 2019) addressed the issue of a lack of precision and standardization in frailty diagnosis and called for a more robust and high-quality trials to prevent and manage frailty.

Frailty is not inevitably associated with the aging process and is – in part – reversible, which gives rise to expectations that frailty may be prevented and treated effectively. Multimorbidity is a major determinant of whether or not an individual is prone to become frail or prefrail (Hanlon et al. 2018). On the other hand, there is a substantial regional variation as to the prevalence of prefrailty and frailty in elderly subjects, both in Europe (Santos-Eggimann et al. 2009) and globally. The "World report on ageing and health" (*World Health Organisation* 2015) impressively points out that in income-deprived neighbourhoods, both life expectancy and disability-free life expectancy were found to be lower than in in neighbourhoods that were better off.

Presently, evidence-based interventions and prevention for physical frailty comprises exercise (aerobic endurance, resistance, balance) (Kidd et al. 2019), medication review and nutritional interventions (caloric substitution, protein supplements, vitamin D) (Morley et al. 2013, Dent et al. 2019). For elderly in particular, home-based exercise programs are encouraged (Ganz and Latham 2020). While conventionally, geriatric care is given in a rehabilitative approach within an acute care setting, "prehabilitation" prior to elective surgery or health deterioration has not been established, but seems promising (Tautenhahn et al. 2020) and is currently under investigation in a large multicenter trial (*Gemeinsamer Bundesausschuss Innovationsausschuss* 2020).

Ideas in search of a pharmacological therapy refer to Metformin (Espinoza et al. 2019), Reservatrol and ACE-Inhibitors (in mice) (Bisset and Howlett 2019), gut microbiota alterations (for cognitive frailty) (Ticinesi et al. 2018) and Oxygen-ozone treatment (hypothetically) (Scassellati et al. 2020). Senolytics targeting senescent cells have shown impressive results in animal models (Xu et al. 2018).

Artificial intelligence and information technology may help cope with the complexity of the clinical syndrome of frailty (Fürstenau et al. 2019, Ambagtsheer et al. 2020). Robotic solutions give rise to hopes for a more convenient life for frail and disabled persons and caregivers (e.g., German "Pflegepraxiszentren" supported BMBF).

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Perspectives from the Industry

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Cost-Effectiveness Analysis of Landiolol, an Ultrashort-Acting Beta-Blocker, for Prevention of Postoperative Atrial Fibrillation for the German Health Care System (Amomed Pharma GmbH)

Evelyn Walter (Vienna, Austria) and Matthias Heringlake (Lübeck)

Objectives

Landiolol is an ultrashort-acting beta-blocker with high beta-1 receptor affinity, as well as less blood pressure lowering properties than other beta-blockers available for intravenous use in Germany. The present analysis aimed to determine whether perioperative treatment with landiolol in cardiac surgical patients is cost-effective under the conditions of the German Diagnosis-Related Groups health cost reimbursement system.

Design

On the basis of clinical outcome data from a meta-analysis that included 622 patients from seven randomized controlled trials, a decision model was developed to determine the cost-effectiveness of landiolol versus standard-of-care (SoC).

Setting

Hospital setting.

Participants

Hospital patients undergoing a representative mix of cardiac surgical procedures (MIX-CS) and isolated coronary artery bypass grafting (CABG).

Interventions

Landiolol versus SoC in prevention of atrial fibrillation immediately after cardiac surgery.

Results

The model benefit was expressed in a reduction of postoperative atrial fibrillation (POAF) episodes and reduced complications. The model calculated total inpatient costs over the hospital length of stay. Costs from published sources were used for the German hospital perspective. SoC was associated with POAF rates of 36.0% to 39.2% and 24.4% to 30.1 % in the MIX-CS and CABG populations, respectively. Patients with POAF had a higher morbidity and mortality. Estimated total costs for SoC patients in the MIX-CS and CABG groups were 28,792 € and 25,630 €, respectively. Landiolol reduced the incidence of POAF to 12.6% in the MIX-CS and 12.1% in the CABG groups. This was associated with a cost reduction of 2,209 € and 1,470 €.

Cost Results

Tab. 1 Cost-Effectiveness Results

Cost Components	**All surgery procedures**			
	Landiolol	**Control**	**Landiolol**	**Control**
Costs hospital stay	21,568 €	23,073 €	19,931 €	20,835 €
Costs ICU stay	3,068 €	3,370 €	2,084 €	2,255 €
Complication costs	301 €	460 €	631 €	853 €
Re-hospitalization	1,646 €	1,890 €	1,515 €	1,688 €
Total costs	**26,583 €**	**28,793 €**	**24,161 €**	**25,631 €**

Conclusions

This analysis suggests that preventing POAF with landiolol is highly cost-effective. Additional studies are needed to assess whether a comparable reduction in POAF and associated cost savings may be achieved using conventional intravenous beta-blockers or amiodarone.

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Service-oriented Device Connectivity (SDC) in the Hospital (Drägerwerk AG & Co. KGaA)

Tobias Klotz (Lübeck)

Summary

The Service-oriented Device Connectivity (SDC) standard within the family of ISO/IEEE 11073 medical technology standards is now interoperable, allowing information to be retrieved from various devices without any interference. Further SDC enables devices to be remotely operated and to generate new functionalities. SDC is also useful for the automation of hospital processes. The central component of the SDC-standard is the Basic Integrated Clinical Environment Protocol Specification (BICEPS). With this layer, devices exchange data on an application level. SDC can be connected to the existing HL7 hospital communication standard or FHIR (Fast Healthcare Interoperability Resources).

Zusammenfassung

Durch den sogenannten *Service-oriented Device Connectivity* (SDC) Standard ist die Familie ISO/IEEE 11073 der Standards für Medizingeräte nun interoperabel, so dass Informationen von verschiedenen Geräten ohne eine Interferenz abgerufen werden können. Weitere SDC ermöglicht die Fernsteuerung von Geräten und die Entwicklung neuer Funktionalitäten. SDC ist auch für die Automatisierung von Krankenhausverfahren nützlich. Die zentrale Komponente des SDC-Standards ist die Basic Integrated Clinical Environment Protocol Specification (BICEPS). In dieser Schicht tauschen Geräte Daten auf einer Anwendungsebene aus. SDC kann an die bestehenden HL7-Kommunikationsstandards der Krankenhäuser oder an FHIR (*Fast Healthcare Interoperability Resources*) angeschlossen werden.

A New Standard for Medical Technology

When it comes to Health Information Technology (HIT), the focus today is on telemedicine, the electronic patient file and smartphones. And yet, there is a quiet revolution taking place, which will see various medical devices in the OR or ICU capable of exchanging information. Networked medical technology is key to the hospitals of tomorrow, facilitating the collaboration of multidisciplinary teams, increasing the efficiency of treatment and establishing the basis for a doctor/patient partnership (Mokhtar 2017). Networked medical technology offers new fields of application and can be operated more reliably and with greater security than conventional stand-alone devices (*NCO/NITRD* 2009). It has been proven that, by using networked medical devices, patients are provided with better medical care (Scott-Kruse and Beane 2018). It is the lack of data exchange between medical devices that may be detrimental to patients (Weininger et al. 2017).

In the past, the lack of an industry standard facilitating real interoperability had hindered the unlimited exchange of information between devices. It was not possible, for example, to centrally operate several medical devices during surgery, call up analysis results or findings on the OR monitor or acknowledge alarms from ventilators remotely located in patient rooms without additional hardware.

Tobias Klotz

ISO/IEEE Standard for an Unlimited Exchange of Data

With manufacturers following their own specific protocols for the electronic data traffic generated by their medical devices and systems, the resulting solutions were less than ideal. In order to be able to connect clinical workplaces with each other, interfaces first required elaborate programming. It was generally the operator who ran the risk of an interruption or failure. Heterogeneous IT solutions also hampered security, while increasing complexity for IT administrators and the incorporation of medical technology into the hospital IT environments. This now changes with the Service-Oriented Device Connectivity (SDC) standard within the family of ISO/IEEE 11073 standards. Devices will become interoperable, allowing information to be retrieved from various devices without any interferences. With SDC, it is also possible to control devices remotely and to generate new functions. SDC has even proven useful when it comes to the automation of hospital processes.

Breaking down Barriers

The complexity of communicating between various devices, for example in an intensive care unit, can be illustrated with a simple example. In order to be able to transmit measured values from a pulse oximeter via the hospital IT network, they first need to be coded. However, every manufacturer was using their own codes. It was not possible to show the oxygen saturation values determined using a pulse oximeter on device A on the screen of device B. Only with

Fig. 1 Device interoperability creates more efficient work processes and optimizes surgical treatment. © Drägerwerk AG & Co. KGaA

SDC and the introduction of a protocol involving a standard code for the exchange of data was it possible to accordingly show the values on different device screens.
The key element of the SDC standard is the Basic Integrated Clinical Protocol Specification (BICEPS). Devices communicate on an application level with this specification, thus enabling the doctor to, for example, display the PEEP (positive end-expiratory pressure) of a ventilator on both the device screen and a remotely located vital signs monitor. Alternately, the measured value of a pulse oximeter count be shown on a patient monitor, but also on the screen of an anesthesia machine.

Connection to Existing Hospital Standards

In addition to a seamless networking between devices, SDC also builds a bridge to the HL7 hospital communication standards or FHIR (Fast Healthcare Interoperability Resources). These are primarily aimed at the real-time data processing carried out by the hospital information system (HIS) and other data infrastructures such as PACS (Picture Archiving and Communication System) or LIS (Laboratory Information System).

Advantages for both Doctor and Patient

The interoperability of medical devices in the OR and ICU has a number of advantages. The doctor can centrally access all data required for the treatment and thus always has the full picture regarding the status of the patient. Alarm management is also simpler with SDC, as device alarms can be validated, forwarded or stopped from one location if necessary. Medical devices in isolation rooms can be remotely operated under visual control from the outside with the help of SDC, which reduces the risk of nosocomial infections. Another advantage is the increased security provided by an end-to-end encryption of the data transmitted.

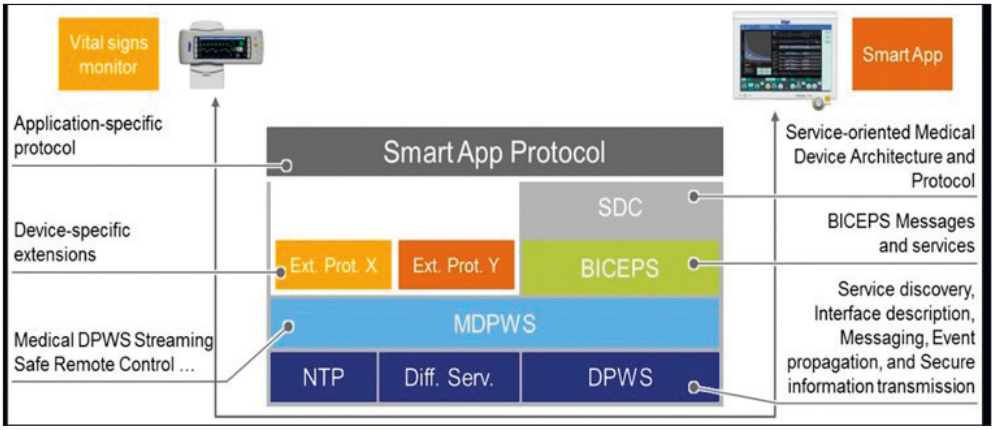

Fig. 2 SDC protocol stack (draft) for IEEE 11073 © Drägerwerk AG & Co. KGaA

How does SDC work?

The open Service-Oriented Device Connectivity (SDC) standard is based on the principle of the Service-Oriented Architecture (SOA) or – with regard to hospitals – a Service-Oriented Medical Device Architecture (SOMDA). The SOA organizes an IT system in such a way that device applications function as service providers, while also being able to communicate with each other. In the past, the system structures were monolithic. The functions were managed by a central software solution, which controlled the functions of its components and thus the tasks of the entire system.

The advantage of the SOA is that it can follow business processes far more flexibly, processes for which the system can only offer certain services or in specific combinations on request, for example. It can react to a revised request by rearranging the combination of services. A new task thus doesn't automatically mean a new IT system. An SOA could be compared with a surround-sound system, in which any speaker can be connected to any receiver, LED projector or even television, all of which are operated by remote control. This is possible because all components have standardized interfaces (Hammergren 2009).

SDC follows SOA architecture, while also having a special communication model for the exchange in such a network: the SDC protocol comprises several layers. In the very first (or lowest) layer, DPWS (Devices Profile for Web Services) forms the communication level with the Medical Devices Profile for Web Services (MDPWS) based on this. These protocol elements enable devices to provide or retrieve services in an IP(Internet Protocol)-based network. In the layers above this "transport" level, the Basic Integrated Clinical Environment Protocol Specification (BICEPS) defines the information that can be exchanged in the network, as well as device-related services within a clinical workplace in the OR, ICU or neonatology. BICEPS thus makes it possible to exchange data between devices on an application level, for example between a vital signs monitor and a device application or ventilator, thus facilitating the desired interoperability. The actual SDC standard ultimately describes how the data elements from BICEPS are connected with the transport mechanism from MDPWS, so that they can be used for communication in an SOA. On the other hand, it also manages aspects such as time synchronization or the quality of network transmission.

Fig. 3 How does SDC work?

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The Convergence of Artificial Intelligence and Telehealth (InTouch Health, Inc.)

Yulun Wang (Santa Barbara, CA, USA)

Summary

Beginning this century, telehealth has become part of the digital transformation of healthcare. The COVID-19 pandemic has shifted the delivery of healthcare from traditional means to a virtual-first strategy.

Health systems are now investing heavily in this cost-effective technology which can expand their presence, better leverage their clinical teams, and provide easier and safer access to care for patients. Because telehealth requires the transmission of a digital medium, it is also uniquely positioned to benefit from AI.

Technology has progressed to a point where telehealth is not merely a proxy for in-person care, but in certain ways can improve the care that is delivered. The combination of AI and telehealth can clearly provide specific benefits to the healthcare clinician's capabilities, as well as efficiency. New diagnostic abilities, smart recommendations, and augmented AI tools will empower physicians to perform clinical care like never before.

The path forward is to digitize and scale AI enabled telehealth throughout the patient care journey. Once AI and telehealth are embraced as a common piece of digital health technology, we will be able to continually create better, safer, and easier healthcare at a cost our society can afford.

Zusammenfassung

Zu Beginn dieses Jahrhunderts ist die Telemedizin Teil der digitalen Transformation des Gesundheitswesens geworden. Die COVID-19-Pandemie verlagert die Bereitstellung von Gesundheitsdienstleistung durch traditionelle Mittel auf eine Strategie, die eine virtuelle Versorgung bevorzugt.

Gesundheitssysteme investieren jetzt stark in diese kosteneffektive Technologie, die ihre Reichweite vergrößert. Damit können klinische Teams besser eingesetzt werden und Patienten haben einen einfacheren und sichereren Zugang zur Gesundheitsversorgung. Da die Telemedizin die Übertragung eines digitalen Mediums erfordert, ist sie auch einzigartig positioniert, um von der künstlichen Intelligenz zu profitieren.

Die Technologie ist so weit fortgeschritten, dass die Telemedizin nicht mehr nur ein Stellvertreter für die persönliche Betreuung ist, sondern in gewisser Weise die erbrachte Pflege verbessern kann. Die Kombination aus künstlicher Intelligenz und Telemedizin bietet eindeutige Vorteile für die Leistungsfähigkeit sowie die Effizienz des Mediziners. Neue diagnostische Fähigkeiten, intelligente Empfehlungen und erweiterte KI-Tools werden Ärzte in die Lage versetzen, eine klinische Versorgung wie nie zuvor anzubieten.

Der Weg nach vorn ist die Digitalisierung und Skalierung der KI-fähigen Telemedizin entlang der ganzen Kette der Patientenversorgung. Sobald die KI und Telemedizin als digitale Gesundheitstechnologie des Alltags anerkannt werden, werden wir in der Lage sein, kontinuierlich eine bessere, sicherere und einfachere Gesundheitsversorgung zu schaffen, die für die Gesellschaft erschwinglich ist.

Introduction

Virtual care has experienced a bellweather year in 2020. The COVID-19 pandemic has shifted the delivery of healthcare from traditional means to a virtual-first strategy to limit disease exposure and flatten the curve. The Centers for Disease Control and Prevention (CDC) in the US list telemedicine as a recommended solution for social distancing and disease spread mit-

Fig. 1 Operation Lindbergh

igation (*Centers for Disease Control and Prevention* 2020). Adoption of this technology and the implementation of virtual care strategies have soared over the past five months at a speed and scale that may have taken years without this sudden, urgent demand.

Although a global emergency and deadly pandemic is a tragic reason for the healthcare industry to disseminate telehealth throughout their systems, the result is a seismic shift of care delivery models for the better; and there is no going back.

I got my start in telehealth at the beginning of the 21st century with the Lindbergh Operation – the world's first telesurgery. For this procedure, surgeons in New York City used a modified ZEUS (Marescaux 2001) surgical robot to successfully remove the gallbladder from a patient laying on an operating table in Strasbourg, France (Moore 2018). After the success of that trans-Atlantic operation, it was clear that telemedicine could fundamentally alter the practice of medicine. Twenty years later, telemedicine is now finally achieving mass adoption, following the same disruption playbook that online banking used to virtualize the financial sector.

The initial hurdles – widespread adoption and acceptance – are now in the rearview mirror, and it is time to again look forward.

The Fourth Industrial Revolution

We are amid the fourth industrial revolution; a time where cloud computing and the internet is disrupting and improving every industry and market. These revolutions are cyclical and

overall beneficial. Professor Clayton Christenson of Harvard explains that innovation in any industry leads to improvements in quality and access to the service, and a drop in cost (Christensen et al. 2009).

Artificial Intelligence (AI) is now another driving force behind this revolution. Recent advances in computing hardware and availability of data at scale have led to a surge in AI capabilities, with new models and algorithms arriving at a rapid rate, that are both faster and more accurate than their predecessors. Today, AI is being applied to previously unsolved problems and offering immense value to many industries. This new technology has become ubiquitous in several industries through the inclusion of AI-enabled capabilities like voice recognition, natural language processing, and image understanding.

AI is also shaping our healthcare industry by reimagining how care can be administered. Read any article, paper, or lecture on Artificial Intelligence these days and you cannot help but notice the broad applications and impact predicted. Abuzz with words more commonly found in MBA syllabuses than research pieces – inflection point, inevitable, disruptive, automation – the future of AI seems broad in its market opportunities, yet uncertain in its future forms.

For healthcare, however, the combination of AI and telehealth can clearly provide specific benefits to the healthcare clinician's capabilities, as well as efficiency. Wherever AI is headed in medicine, it will have a profound impact on our future health; Professor Wachter of the University of California, San Francisco agrees writing, "Starting now and lasting until forever, your health and healthcare will be determined, to a remarkable and somewhat disquieting degree, by how well the technology works." (Wachter 2017).

Defining Telehealth

At its inception, telehealth was attempting to replicate the current physician experience, albeit with the doctor and patient physically apart. This process necessitated the digitization of the clinician and patient interaction. Beginning this century, telehealth has become part of the digital transformation of healthcare.

Audio/video digitalized streams transmitted over the internet to enable patients to receive care from remote clinicians has taken hold with many of the world's health systems. Health systems are now investing heavily in this cost-effective technology which can expand their presence, better leverage their clinical teams, and provide easier and safer access to care for patients. Because telehealth requires the transmission of a digital medium, it is also uniquely positioned to benefit from AI.

Telehealth is the Perfect Application for AI

Having a digital conduit between the patient and clinician enables the seamless capture of high quantities of valuable data. The data is recorded and available for easy input to train AI-based neural nets to discover patterns around workflow efficiency and drive real clinical benefits.

These programs are solving an urgent need at precisely the right time i.e. bringing remote diagnostic abilities, automation, and scale to a market struggling with supply- and demand-side challenges; a growing patient population living longer but with chronic co-morbidities; an

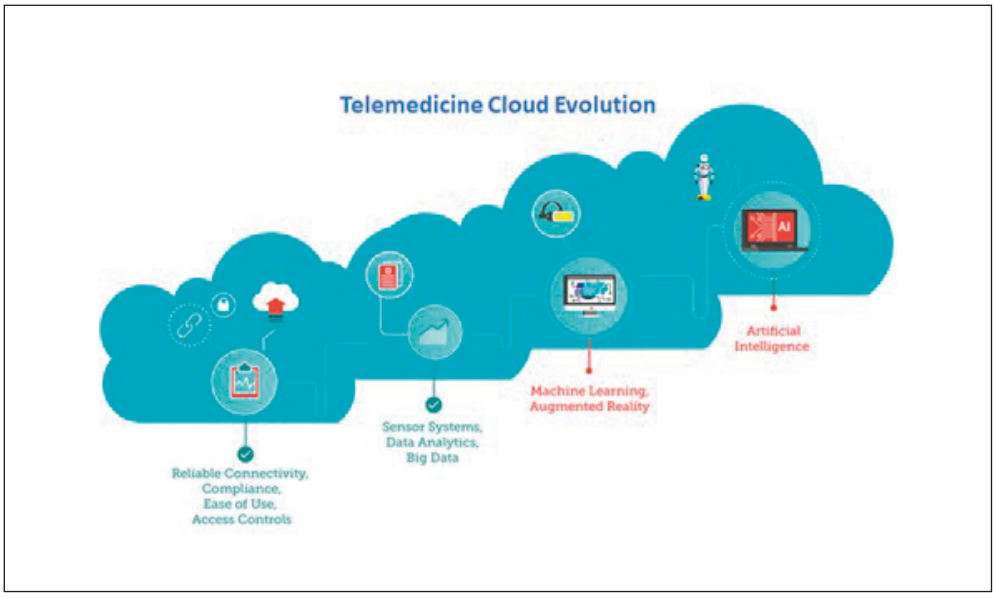

Fig. 2 Telemedicine Cloud Evolution

aging and decreasing clinical community; an increasingly complex and sub-specialization of healthcare; ballooning costs; and lack of healthcare access to treat people fairly and appropriately wherever they might reside and at times that suit their own circumstances.

Technology has progressed to a point where telehealth is not merely a proxy for in-person care, but in certain ways can improve the care that is delivered. New diagnostic abilities, smart recommendations, and augmented AI tools will empower physicians to perform clinical care like never before.

Intelligent Diagnostic Assistance and Peripheral Support

AI can be used to give clinicians uniquely powerful and non-intrusive clinical diagnostic tools. Such tools would provide the clinician with insights about their patient which are not immediately obvious, and/or offer suggestions on patient treatment options due to large databases of similar situations. The core aspects of a telehealth consult can be supercharged to improve the patient information available to clinicians in a seamless user experience.

AI-based signal processing algorithms can now be used to program cameras to read vital signs, such as heart rate, respiration rate, even patient sentiment and possibly oxygen saturation levels. In reading heart rate, for example, Al-based image processing methods can be used to detect the subtle skin tone changes of the patient's face due to the pulsating blood flow (Balakrishnan et al. 2013).

Respiration rate can be detected by slight motions of the patient's chest, too small to be easily observed by the physician. Sentiment is detected by the rapidly changing facial expressions and eye movement of the patient, or through natural language processing of a patient's

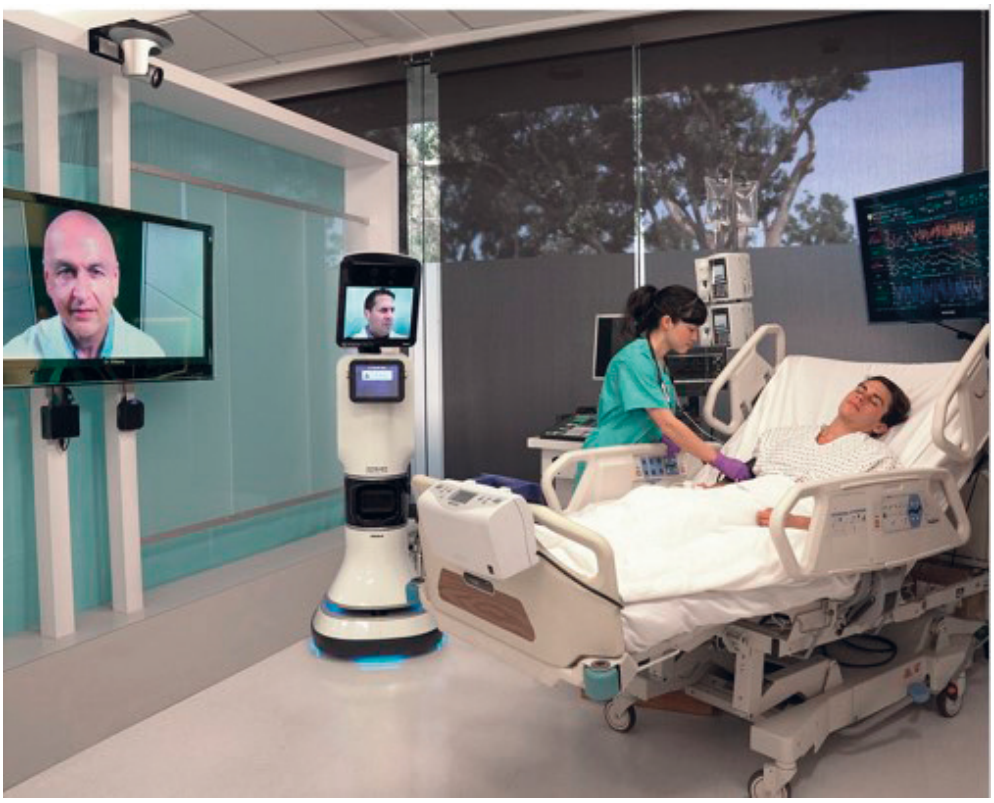

Fig 3 ICU

utterances. These biometrics can inform the clinician of valuable clinical data to help diagnose, treat, and connect with their patients.

Auto-Documentation

Clinician burn-out is continually reported as one of the biggest problems in healthcare today (Lagasse 2019). The primary reason for physician burn-out is that the documentation requirements on the physician has become time consuming, frustrating, and overwhelming. Several studies have reported that for every hour of patient care a physician provides, they spend two hours documenting the care they've delivered (Sinsky et al. 2016). This leads not only to poor job satisfaction, but also contributes greatly to our physician shortage problem.
A possible solution is to leverage telehealth and AI to automatically document and bill for the care the physician provides. Ensuring information as critical as medical documentation and billing is precise, extensive training and testing of AI is needed. However, telehealth makes this process simple.

AI training requires the creation of datasets to run through the neural net. Neural networks are typically trained through a technique known as backpropagation. This requires a large

amount of training data to optimize weights and biases in the network by assessing performance on individual training examples through a loss function.

These datasets represent audio, and possibly video, recordings of physician-patient consults for various types of clinical interactions. In telehealth, the audio recording is greatly simplified when compared to in-person audio since it is relatively easy to separate the audio tracks of the physician and patient by using the directionality of the audio channels; as the two parties are remote, each have their own assigned microphone. In-person audio, where a single microphone is placed to record the conversation of both participants, creates a much more difficult challenge.

By coupling the corresponding audio and video interactions with the resulting documentation, extensive training datasets can be gathered. With these training datasets of targeted use cases, one should be able to train a neural network to automatically create accurate documentation and billing for the physician-patient consult.

Improvements to Staffing

Labor costs is roughly 60% of a hospital's expenditure (LaPointe 2018). A significant financial drain on the healthcare system is staffing inefficiency. Telehealth allows a channel to

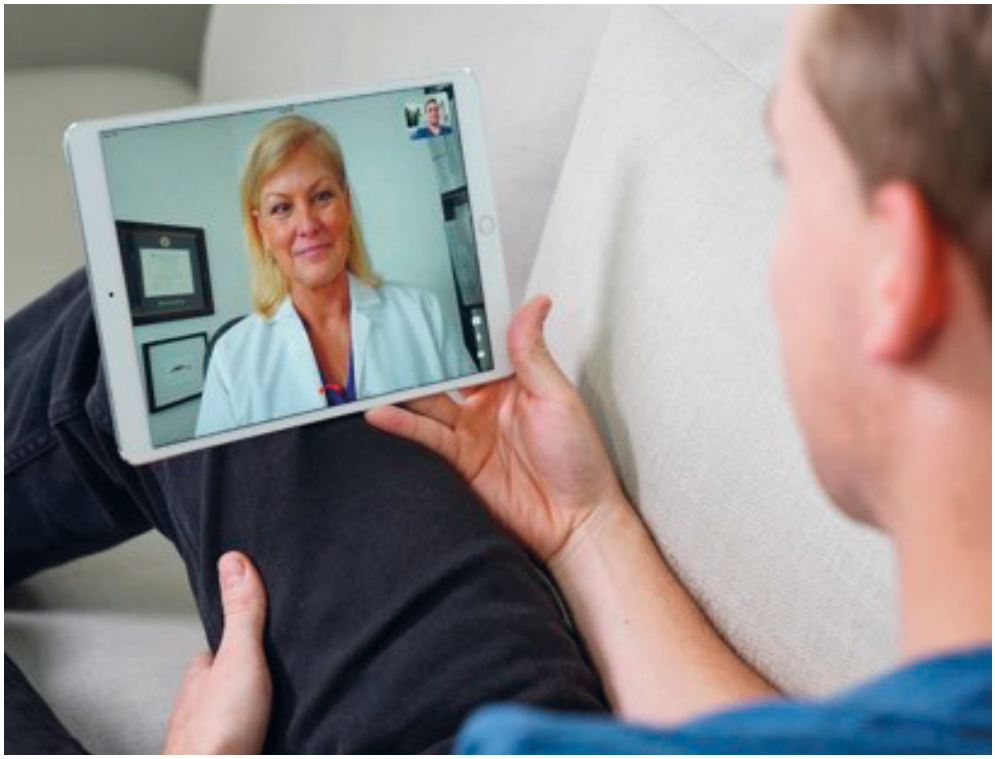

Fig. 4 Convenient Care

seamlessly automate and monitor staffing levels. Training an AI neural network on the habits and trends of patient flow patterns for a health system allows it to recommend staff level considerations to operators and administrators. This application is analogous to online shopping.

Brick and mortar retailers rely on consumers to walk into stores and leave with a purchase; but this does not represent the full extent of that shopper's interaction with the retailer. During this interaction, the shopper might try on various items, yet if they did not purchase either item, the store has no record of their interest in either accessory. Online retail does, however, capture those behaviors. AI allows retailers to curate a set of merchandise that would appeal to each individual and present this tailored list to them in future online shopping sessions.

Telehealth supports a similar paradigm. It allows clinicians to be on-call simultaneously in more locations to cover more patients than traditional means. AI can then be used to automatically detect trends such as peak activity times in healthcare facilities and propose proper staffing levels and composition at various locations and times, improving patient access and operational efficiency for the healthcare system.

Next Steps

These are only three of the many examples where AI and telehealth are converging to improve healthcare for the 21st century. Telehealth is already prevalent in a number of use cases, from stroke to a sore throat, but wide-spread adoption has lagged.

One reason for slow proliferation is the fear many clinicians have that AI would replace their functions in the care workflow. This is not the case. To truly see the benefits AI can have on healthcare, perhaps Professor Eric Topol of Scripps said it best, "The greatest opportunity offered by AI is not reducing errors or workloads, or even curing cancer: it is the opportunity to restore the precious and time-honored connection and trust – the human touch – between patients and doctors. Not only would we have more time to come together, enabling far deeper communication and compassion, but also we would be able to revamp how we select and train doctors." (Topol 2019) AI serves as an assistant to our physicians so they can do their jobs better, letting them focus on the reason they originally got into medicine: patient treatment and interaction.

The path forward is to digitize and scale AI enabled telehealth throughout the patient care journey. Once the next step in this evolution is embraced as a common piece of digital health technology – where AI and telehealth are combined – we will be able to continually create better, safer, and easier healthcare at a cost our society can afford.

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The Digital Healthcare Act in Germany: Clinical Aspects by the Example of POD and POCD – Opportunities for Patient's Risk Evaluation and for Clinical Research (Sintetica GmbH)

Wilfried Dierkes (Münster)

Summary

Germany's Digital Healthcare Act, with its planned research data centre and electronic patient records, provides opportunities for evidence-based decision making for patient procedures and therapies. With regard to postoperative diseases POD (postoperative delirium) and POCD (postoperative cognitive dysfunction), risk factors can be analysed and the monitoring of the diseases will be much easier. Analysis of non-interventional and epidemiological data will provide evidence for causal relationships with perceived risk factors, for example anaesthetic procedures (spinal anaesthesia versus general anaesthesia). The main challenges will be the standardisation of data interfaces and scores for diagnosis and monitoring. A consensus within the scientific community will be necessary. Furthermore, data protection requirements will have to be respected.

Zusammenfassung

Durch ein geplantes Forschungsdatenzentrum und eine elektronische Patientenakte bietet Deutschlands Digitale-Versorgung-Gesetz Möglichkeiten zur evidenzbasierten Entscheidungsfindung für Patientenbehandlungen und -therapien. Im Hinblick auf die postoperativen Erkrankungen POD (postoperatives Delir) und POCD (postoperative kognitive Dysfunktion) können Risikofaktoren bewertet werden und Erkrankungen viel leichter überwacht werden. Die Analyse nicht-interventioneller und epidemiologischer Daten bietet die Möglichkeit eines Nachweises kausaler Zusammenhänge mit vermeintlichen Risikofaktoren, z. B. bei Narkoseverfahren (Spinalanästhesie gegenüber Vollnarkose). Die wichtigsten Herausforderungen werden die Standardisierung von Datenschnittstellen und Wertungen sein, die bei der Diagnose und Überwachung verwendet werden. Ein Konsens der wissenschaftlichen Gemeinschaft wird notwendig sein. Darüber hinaus müssen die Anforderungen des Datenschutzes beachtet werden.

Digitalisation in Healthcare in Germany – Opportunities for Research and Therapy

In November 2019, Germany's Digital Healthcare Act was approved by the *Bundestag* and adopted by the *Bundesrat* ("Act to Improve Healthcare Provisions through Digitalisation and Innovation"; *Bundesgesundheitsministerim* 2019). One aspect of the act is an obligatory digital network for the health sector. Physicians, pharmacies (by end of September 2020) and hospitals (by 1 January 2021) are obliged to connect to a Telematics Infrastructure (TI). One aspect of the developing digital network is the possibility of research on the base of the invoicing data available to the health insurance funds. Pseudonymised data will be available in the protected space of a research data centre. Further aspect will be the possibility of healthcare providers to exchange patient's clinical data faster and more easily with open and standardised interfaces, based on international standards. This information may also be available in an electronic patient record, for which data protection provisions will be regulated in a separate law in the future.

From a clinical perspective, two aspects are of future relevance:

– *Patient centred information*: during patient's journey to different healthcare providers (general practitioner, specialist, hospital) the exchange of data gives opportunities (1) to improve the individual therapy based on better anamnestic information, for example with respect to risk factors and, (2) to improve the clinical follow up of patients.
– *Clinical research*: health insurance data and data from standardised interfaces will open opportunities for data analysis. Retrospectively, for example, risk factors may be evaluated and diagnostic and therapy strategies may be adapted accordingly.

Exemplarily, the clinical opportunities of the digitalisation of healthcare in Germany are discussed with regard to cognitive dysfunctions of patients submitted to surgery and anaesthesia in hospitals. Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are in the focus of this discussion.

From the industries perspective (of a manufacturer of medicinal products for fast track regional anaesthesia), items of special interest include the aspects of comparison of general anaesthesia versus spinal anaesthesia and the impact of duration of processes.

POD and POCD – A Challenge for an Ageing Society

A proportion of apparently previously cognitively well patients undergoing surgery and anaesthesia will develop symptoms of cognitive dysfunction afterwards. Patients may experience postoperative delirium (POD) and/or postoperative cognitive dysfunction (POCD). Depending on risk factors the incidence of POD varies within a broad range (4.0 to 53.3 %; Aldecoa et al. 2017). There is suggestion that both diseases are most marked in higher age groups (Needham et al. 2017). POCD for example increases from 36.6 % in patients aged 18-39 to 41.1 % in those aged 60 and older (Rundshagen 2014). Currently in Germany the age group of 67 years and older includes 16.2 million and will increase to 21.4 million in 2040 (*Statistisches Bundesamt* 2019). Pro-active management with respect to risk factors and prevention of POD and POCD will therefore become increasingly important.

POD is associated with several negative clinical consequences, including major postoperative complications, cognitive decline, distress, longer hospitalisation with increased costs and higher mortality (Aldecoa et al. 2017). Subsequently, patients with POD have an increased risk for the consecutive development of postoperative cognitive dysfunction (POCD). The latter is characterised by a progressive and permanent loss of cognitive abilities (Saczynski et al. 2012).

POD – Definition and Risk Factors

Postoperative delirium (POD) is an adverse postoperative complication that can occur in patients at any age. Its incidence is influenced substantially by patient-related risk factors. Elderly patients are generally thought to be at higher risk because predisposing factors accumulate and overlap with ageing (Aldecoa et al. 2017). Delirium is an acute and fluctuating alteration of mental state of reduced awareness and disturbance of attention. A diagnostic definition is given by either the current Diagnostic and Statistical Manual of Mental Disorders DSM-5 (*APA* 2013) or the current International Statistical Classification of Diseases and Related Health Problems ICD 10 (*WHO* 2016) (Table 1).

Delirium can present as hypoactive (decreased alertness, motor activity and anhedonia), as hyperactive (agitated and combative) or as mixed forms. Increased age seems to be a predisposing factor for the hypoactive form. The prognosis may be worse with hypoactive delirium, possibly due to relative under-detection by staff and consequently delayed treatment (Aldecoa et al. 2017). Table 2 gives an overview of risk factors especially for the elderly.

Tab. 1 Definitions for POD

DSM-5 (APA, 2013): Disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment).
ICD 10 (WHO, 2016): An aetiologically nonspecific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe.

Tab. 2 Predisposing risk factors for POD in the elderly (Aldecoa et al. 2017, Needham et al. 2017)

Advanced age
Cognitive impairment, dementia
Comorbidities (e.g. cardiovascular, cerebrovascular including stroke, peripheral vascular diseases, metabolic diseases including diabetes, Parkinson's disease, depression, chronic pain)
Sensorial deficits (hearing loss, visual impairment)
Malnutrition (proteins, minerals, vitamins; dehydration)
Polymedication
Impaired functional status (reduced levels of independence, abilities and socialisation)
Frailty (critically reduced functional reserves, involving multiple organ systems)
Type of surgery (e.g. major vascular/cardiac)
Unclear: regimen of anaesthesia (general vs. regional anaesthesia)

POCD – Definition and Risk Factors

No definition of postoperative cognitive dysfunction (POCD) has been widely accepted (Glumac et al. 2019). POCD may be considered as a mild neurocognitive disorder of unspecific aetiology within the confines of DSM-5, defined by a noticeable decrement in cognitive functioning that goes beyond normal changes seen in aging. POCD is generally described as a form of cognitive dysfunction that begins between seven days and one year after surgery, which is very similar to a mild cognitive impairment (MCI), which may be described by the characteristics shown in Table 3 (Needham et al. 2017). Table 4 gives an overview of predisposing risk factors.

Anaesthetic Procedure – a Risk Factor for POD and/or POCD?

Despite continuous research, the predictive effects of the regimen of anaesthesia for the development of POD and/or POCD remain unclear. Data in the literature for regional versus

Tab. 3 Definition POCD (Needham et al. 2017)

No widely accepted definition
Described as cognitive dysfunction starting seven days to one year after surgery
Characteristics of mild cognitive impairment MCI (Albert et al. 2011) – Concern regarding a change in cognition – Impairment in one or more cognitive domains – Preservation of functional independence – Absence of dementia

Tab. 4 Predisposing risk factors for POCD (Needham et al. 2017)

Increasing age
Poor education (shorter time in school education)
History of cerebrovascular disease with no residual impairment
Duration and type of surgery (cardiac, orthopaedics and vascular)
Pre-existing cognitive impairment
Poor functional status
Postoperative respiratory complications
Postoperative infections
Depth and length of anaesthesia
Unclear: regimen of anaesthesia (general vs. regional anaesthesia)

general anaesthesia are inconclusive and contradictory. Meta-analyses showed that regional anaesthesia decreases the risk of POCD, but not POD. Since accepted definition is missing and used scores are not standardised, heterogeneity of analysed POCD studies was high. Nevertheless a likelihood favouring regional anaesthesia was found in the meta-analysis (Mason et al. 2010). Similarly, in the meta-analysis for POD (Zhang et al. 2013) included studies showed great inconsistencies in definition, incidence, severity and duration of POD.
Depth of sedation seems to be a predictive factor. For spinal anaesthesia with light sedation (BIS ≥ 80) a significantly lower delirium rate (19 %) was shown compared to deeper sedation (40 %) in orthopaedic surgery (Sieber et al. 2010).

Surgical trauma is known to result in systemic inflammatory changes that can lead to POD or POCD (Sun et al. 2016, Ezhevskaya et al. 2019). Neuroaxial anaesthesia in patients undergoing lower abdominal or lower extremity surgery could reduce the risk of POD/POCD by attenuating the surgical stress response. Further promising effect of stress reduction may be expected from short acting anaesthetics resulting in fast track processes and reducing time of sensory and motor block versus longer acting products (Gebhardt et al. 2018a) or reducing time schedule versus general anaesthesia (Gebhardt et al. 2018b) with enhanced recovery. Clinical data of the prognostic effect of spinal anaesthesia with short acting anaesthetics, like chloroprocaine or hyperbaric prilocaine (*Sintetica* GmbH 2017) for the occurrence of POD and/or POCD are missing up to now and are currently under investigation (Spies et al. 2018). Analysis of structured data from digitalised patient files or invoicing data from research data centre are future promising sources of evidence.

Patient's Journey – Sharing Data for Better Decision Making

During the patient's journey through different settings of healthcare, data emerge at multiple sites. Especially for older patients it is difficult to detail their medical history at each step of the journey. In the future, it will be possible to accumulate the evidence in one major document, the electronic patient record (Fig. 1). This will give detailed insight in patient's history at every station of his/her path through healthcare system.

Data Exchange with Standardised Interfaces – Opportunities and Challenges

POD and POCD are often undetected (esp. hypoactive POD, mild to moderate forms or late POCD). Implementing routine tests and follow up will improve detection of risk factors, and therapy of these underestimated diseases. On the other hand, there will be a long way to standardise observational tools and their analysis.

Opportunities with Respect to Detection of Risks Factors and Follow up of POD/POCD

Collecting the relevant data in a centralised way in the electronic patient record will give the opportunity to include all risk factors, to take the adequate measures and to follow up the

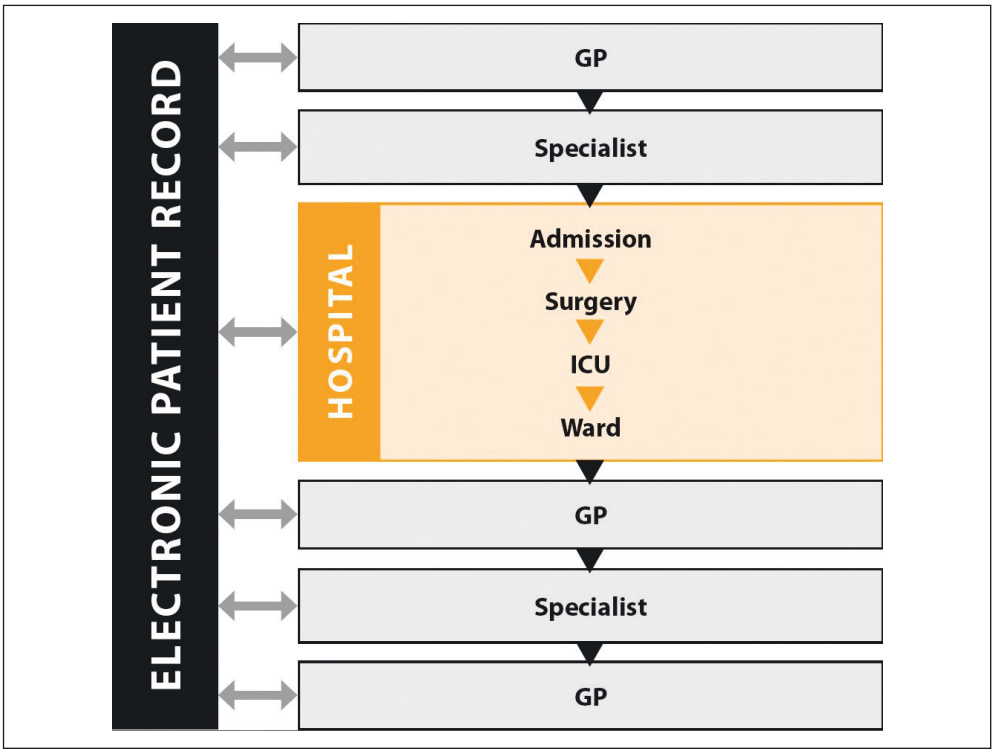

Fig. 1 Possible flow of patient's data. GP indicates general practitioner; ICU intensive care unit.

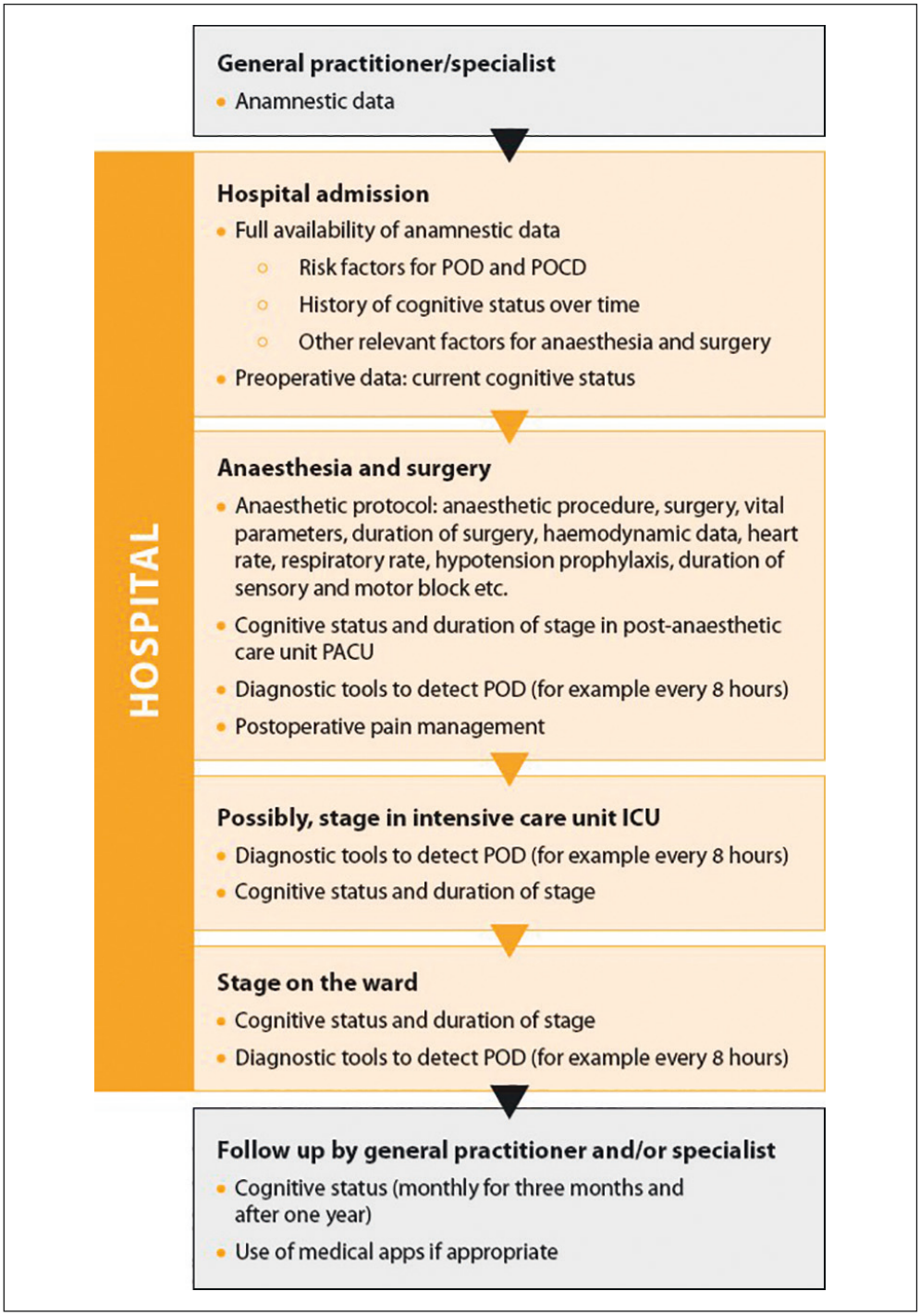

Fig. 2 Possible template for standardised data entry: example of hospital stay

patient. With a standardised template for the relevant data, further research with respect to risk factors, for example the anaesthetic procedure, will be possible. Figure 2 gives an idea of such a template for inpatients with surgery.

Challenges for Research Projects on POD/POCD with Big Data from Digitalised Healthcare

One of the major challenges will be the structured recording of information with standardised instruments. In the beginning, we can expect that physicians will fill the electronic patient record with pdf reports to comply with the TI system. By entering the data in a standardised template, patients and research can profit much more from them. First step would be to plan respective medical information objects. Such "MIO"s are planned to be edited by physician's association KBV to be part of the electronic patient's record. (First projected MIO is for example an e-version of a vaccination passport). From the researcher's perspective, standardised interfaces would be useful not only for procedures (standardised anaesthetic protocol) but also for the diagnostic tools and the follow up of course of disease for POD and POCD.

For POD, a certain standard has established with diagnoses following DSM 5 or IDC-10 and screening/monitoring with the Nursing Delirium Screening Scale (Nu-DESC) and the Confusion Assessment Method (CAM) (Aldecoa et al. 2017). It will be much more difficult to find a standard for POCD, since until now the scales for dementia are often used (like the Mini-Mental State Examination MMSE), and no common standard has been established, although some tests would be promising (like the Montreal Cognitive Assessment Tool MoCA, Addenbrookes's Cognitive Exam ACE-III or the Quick MCI Screen Qmci) (Needham et al. 2017). A common standard with annotated forms would be the optimal tool to analyse the course of disease and to analyse cohorts of patients, for example for epidemiologic or non-interventional research. Any other interface for data entry (like anaesthetic protocols) would have to fulfill similar requirements.

A further hurdle could be data protection. The planned research data platform with invoice data already causes considerable political resistance. The regulation for data protection of patient files is much more sensitive and a corresponding separate law will be complex. Data access of different stakeholders of health system remain unclear up to now. Local data networks of university hospitals, like the "Gutenberg Gesundheits-Hub" in Mainz, Germany (*Anonymous* 2019) may perhaps also be an option. Anyway, the consent of patients will be a prerequisite of the analysis of clinical data.

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Integrated Infusion Systems – More than just "smart" (Fresenius Kabi Deutschland GmbH)

Alexander Boreham (Berlin)

Summary

Infusion pumps are ubiquitous in hospitals where they supply patients with medication and parenteral nutrition. Incorrect settings or even the failure of infusion pumps can have serious consequences for the patient. For this reason, safety is always a priority in the ongoing development of infusion pumps. Although smart pumps have contributed to making patient care safer compared to conventional infusion pumps, there is still room for improvement. Continuous innovation and the development of new technologies will enable further advances in patient and user safety. In particular, the integration of infusion pumps into the IT infrastructure of hospitals offers great potential that manufacturers such as Fresenius Kabi have already started to exploit. With the Vigilant® Software Suite, Fresenius Kabi has developed a comprehensive software solution that enables the full integration of the Agilia® Connect infusion pumps into the hospital's IT infrastructure. The Vigilant® Software Suite meets the highest standards of safety and user-friendliness. This innovative solution for implementing an integrated infusion system is expected to significantly improve patient care.

Zusammenfassung

Infusionspumpen sind in Krankenhäusern allgegenwärtig, wo sie Patienten mit Medikamenten und parenteraler Ernährung versorgen. Falsche Geräteeinstellungen oder sogar der Ausfall von Infusionspumpen können schwerwiegende Folgen für den Patienten haben. Aus diesem Grund steht bei der Weiterentwicklung von Infusionspumpen die Sicherheit immer an erster Stelle. Obwohl intelligente Pumpen dazu beigetragen haben, die Patientenversorgung im Vergleich zu herkömmlichen Infusionspumpen sicherer zu machen, gibt es immer noch Raum für Verbesserungen. Kontinuierliche Innovation und die Entwicklung neuer Technologien werden weitere Fortschritte bei der Patienten- und Anwendersicherheit ermöglichen. Insbesondere die Integration von Infusionspumpen in die IT-Infrastruktur von Krankenhäusern stellt ein großes Potenzial dar, das Hersteller wie Fresenius Kabi bereits genutzt haben. Mit der Vigilant® Software Suite hat Fresenius Kabi eine umfassende Softwarelösung entwickelt, die eine vollständige Integration der Agilia® Connect Infusionspumpen in die IT-Infrastruktur des Krankenhauses ermöglicht. Die Vigilant® Software Suite erfüllt die höchsten Ansprüche an Sicherheit und Benutzerfreundlichkeit. Von dieser innovativen Lösung zur Implementierung eines integrierten Infusionssystems wird eine deutliche Verbesserung der Patientenversorgung erwartet.

Infusion Pumps in Patient Care

Infusion pumps are high-tech medical devices that deliver fluids to the patient's body in precisely controlled amounts. Compared with gravity infusion, infusion pumps offer many advantages. Very small amounts of liquid can be administered, the infusion rates precisely controlled, and the infusion solution automatically administered in well-defined intervals

when required. It is hardly possible to adhere to complex therapeutic regimes, e.g. in oncology, without infusion pumps.

Focus on Safety

Infusion pumps usually supply the patient with substances vital for survival, e.g. catecholamines, antibiotics, chemotherapeutic agents, or insulin, but also with other medication that is essential for the patient's welfare such as pain killers. Pump malfunction or erroneous programming can have grave consequences for the patient (*FDA* 2018). The safety of the infusion is therefore of paramount significance for the patient, the doctors and the nursing staff alike. In particular, the five principles – or "Five Rights" – of safe infusion administration should be observed: the right drug, dose, route, patient, and time (Vanderveen 2014).

With technological progress in infusion pump technology, the safety features have evolved, too. Earlier infusion pumps were able to give a warning when technical problems occurred such as blocked infusion tubes. In the course of the further development to so-called "smart pumps", additional safety features were added. For instance, smart pumps can warn the user when parameters outside of a prespecified range have been entered.

Smart Pumps – a First Step Towards Greater Safety

Before smart pumps were used, the error rates for infusions could be very high. A study in an intensive care unit found that 67% of infusions (285/426) were not administered without error (Husch et al. 2005). After the introduction of smart pumps, this proportion could be significantly reduced. Yet, a prospective observational study on a pediatric ward using smart pumps still found that every fourth administration did not match the prescribers' instructions (Russell et al. 2010). This shows that smart pumps alone cannot guarantee the greatest possible safety for patient and user.

How Patient Care can be Further Improved

Overcoming many of the existing fundamental obstacles to patient and user safety will require innovation and the development of new technology (Giuliano and Niemi 2016). Improvements to pump design, such as simplified operability, easier-to-read displays, and an increased pump mobility can contribute to improved user safety (Giuliano and Niemi 2016). The current Agilia® connect infusion pumps were designed by Fresenius Kabi with these safety-relevant aspects in mind (Fig. 1).

The next significant improvement in patient care will only be achieved through comprehensive integration of smart pumps with the existing IT infrastructure of hospitals (Giuliano and Niemi 2016, Vanderveen 2014). Automatic programming according to the prescriber's information reduces the risk of erroneous user input. Patient data management system (PDMS) connectivity reduces the documentation-related workload for HCP and thereby contributes to improved patient care. Data for each infusion can be monitored in real time, which makes it possible to detect critical constellations before these result in patient-relevant errors. The drug library, workflow processes and safety can be continuously optimized based on the

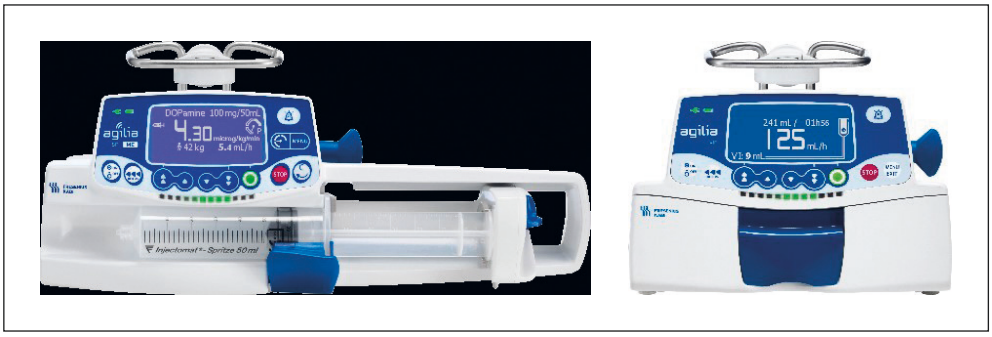

Fig. 1 Agilia® connect syringe pump (left) und volumetric infusion pump (right) with intuitive user interface, easy-to-read displays and ergonomic design.

analysis of the data collected from all infusions. IT integration of infusion pumps can ensure the "Five Rights" for the safe administration of infusions and, in addition, facilitates comprehensive documentation and enables the best possible response to critical events. However, IT integration also entails risks: Suitable, and above all safe, digital interfaces are mandatory. Hence, cyber security is a further security-relevant issue that needs to be addressed.

Integrated Infusion Systems

What was once a vision (Vanderveen 2014) is now reality: the complete integration of infusion pumps into the existing IT network of the hospital, with many advantages for users and patients. However, it is necessary to guarantee the constant availability, confidentiality and integrity of the generated and transmitted data. The Vigilant® software suite, developed by Fresenius Kabi, is a comprehensive solution for fully integrating Agilia® connect infusion pumps into the IT infrastructure of the hospital. At the same time, it meets the high requirements regarding security and user-friendliness (Fig. 2).

Definition of Standards

The drug library is a database containing the drugs in use at the hospital in which all relevant parameters for their administration are predefined. This library can be stored in the smart pump's memory and is an important tool to prevent dosing errors. As internal organization and infusion protocols can differ from hospital to hospital, the drug library must be adaptable to the specific requirements of each hospital. To ensure that such a library is well accepted and continuously updated by doctors and pharmacists, the user interface needs to be well structured and easy to navigate so that the main settings can be accessed swiftly. The maximum value of the drug library can only be realized when customizability and user-friendliness are combined. The drug library Vigilant® Master Med, which is included in the Vigilant® software suite, supports up to 19 profiles, e.g. for different wards. In addition, injection pumps and drug dosing can be individually specified for each profile. Common settings can be defined for both syringe and volumetric pumps or, alternatively, separately for each pump type.

Fig. 2 With the Vigilant® software suite, all Agilia® connect infusion pumps can be fully integrated into the hospital's IT infrastructure.

The safety configurations in Vigilant® Master Med and a global dose error reduction system (DERS) for all Agilia® connect infusion pumps significantly reduce the risk of error. For an efficient workflow, the user interface of Vigilant® Master Med is divided into 5 clearly defined sections, covering all relevant steps from database setup through to database upload.

Integration of Devices

All integrated infusion systems need an appropriately equipped control center. Here, all key processes converge, can be administered, and are integrated into the PMDS. In the Vigilant® software suite, this functionality is provided by Vigilant® Centerium. It enables the interconnection of infusion pump racks, the administration of user access rights, and connects to the digital medical records (Fig. 3).

Datasets that are sent to the infusion pumps via Centerium are downloaded onto the pump before it is turned on, ensuring that the current dataset is immediately available to the user, thereby reducing the risk of errors. During the infusion, all relevant data are sent to Centerium via Vigilant® Bridge, from where they are transmitted to the PDMS. Consequently, the digital medical records are automatically kept up to date, workflow efficiency is improved, and the hospital staff's workload is reduced. Once the infusion has been completed, the usage data is stored on the Centerium server and is available for further in-depth analysis using Vigilant® Insight. The data transfer via the interface between infusion pumps and PDMS demands high standards for data and cyber security. Data breach can only be prevented if these high standards are meet.

Fig. 3 The bidirectional communication with all parts of the hospital is brought together by the Centerium server.

Secure Data

Vigilant® Bridge enables the secure data transfer between Agilia® connect infusion pumps, Vigilant® Centerium server and the hospital's PDMS. Adhering to the HL7 (Health Level Seven) security standards, it offers comprehensive protection against unauthorized data access and data loss. Furthermore, only secure communication protocols are used (https with TLS). Fresenius Kabi is an active member of the initiative "Integrating the Healthcare Enterprise" (IHE). Thus, Vigilant® Bridge is compliant with the IHE goals for data exchange in healthcare: time saving, reliability, consistent data quality, as well as a reduction of effort and investments required for implementation.

Improvement of Patient Care

The clear assignment of an infusion to the corresponding patient and continuous monitoring of the infusion promises several benefits: improved patient safety, increased productivity through workflow optimization and reduced cost (Vanderveen 2014). Data for infusion pumps, including the time remaining, can be displayed in real time on a central screen using the Vigilant® Sentinel dashboard. Color coding provides a fast overview of device status. This facilitates the identification of changes in infusion rates and when the infusion has to be changed, and makes it possible to respond to warnings as quickly as possible. Up to 24 beds, each with up to 16 infusion pumps, can be monitored simultaneously with Vigilant® Sentinel. All relevant parameters can be displayed in the detailed view per bed/patient or pump. The workflow for changing the infusion can be optimized by using the remaining time view, which only shows those infusions with a remaining infusion time below a customizable threshold, for instance 4 hours.

Optimization of Processes

The integration of devices into infusion systems creates a multitude of datasets on infusion administration. This data offers new opportunities to further improve the workflow within the hospital and hence also patient care. This does, however, require thorough data analysis and appropriate tools for analysis. Vigilant® Insight provides a user-friendly analysis tool with which the data can be evaluated with regard to many different aspects, such as per ward, profile or drug. In addition, instances in which the drug level was exceeded can be analyzed, and infusion profiles can be created that allow for the identification of days and times with the highest alarm rates. Vigilant® Insight turns the hospital into a "learning system" and hence offers significant potential to make the hospital even more efficient in the future and in consequence to realize savings in the healthcare system.

Prevention of Pump Malfunction

Nowadays, every hospital has a great number of infusion pumps. Considering that these pumps usually administer substances vital for survival, it is evident that these pumps must not cease to function abruptly. A function failure can have severe consequences for the patient. Consequently, the routine maintenance of infusion pumps is crucial, while at the same time providing a formidable logistical challenge due to the sheer number of pumps. Integrated infusion systems offer the possibility of centrally managing all pumps. This opens up entirely new opportunities for ensuring quality control and patient safety: With Vigilant® Partner, Fresenius Kabi has developed a software tool with which all infusion pumps can be managed centrally. For instance, the date of the next maintenance can be viewed for each pump, the firmware on the pump can be upgraded, and a function test can be performed when necessary.

Conclusion

Fresenius Kabi has developed an innovative solution for the implementation of an integrated infusion system. The Vigilant® software suite combines several powerful components, each contributing to a significantly improved patient und user safety of infusion pumps and hence patient care. With the aim of continuously improving user-friendliness and patient safety, the current technology is being continually developed and expanded with new innovations.

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Scientific Symposium Abstract Winner

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1st Prize: Personalized Effects of Valve Morphology, Blood Pressure Control and Age on Aortic Wall Properties

Niky Ghorbani[1,3], Vivek Muthurangu[4], Abbas Khushnood[4], Leonid Goubergrits[1,3], Stephan Schubert[1,2,3], Sebastian Kelle[2,5,6], Felix Berger[1,2,3], Titus Kuehne[1,2,3], Marcus Kelm[1,3,7]

Objectives:
We aimed to investigate the combined effects of arterial hypertension, bicuspid aortic valve disease (BAVD) and age on the distensibility of the ascending and descending aorta in patients with aortic coarctation.

Methods:
In a two-centre study (ID: clinicaltrials.gov NCT02591940, October 30, 2015), 121 patients with aortic coarctation (age 1–71years) underwent cardiac MRI and blood pressure measurements. Cross-sectional diameters of the ascending and descending aorta were assessed to compute aortic area distensibility. Findings were compared with age-specific reference values. The study complied with the STROBE statement and reporting guidelines.

Results:
Impaired distensibility (below 5th percentile) was seen in 37 % of all coarctation patients in the ascending aorta and in 43 % in the descending aorta. BAVD (43 %) and arterial hypertension (72 %) were present across all ages. In patients above the age of 10 years distensibility impairment of the ascending aorta was predominantly associated with BAVD (OR: 3.1, 95 % CI: 1.33-7.22, p=0.009). Distensibility impairment of the descending aorta was predominantly associated with arterial hypertension (OR: 2.8, 95 % CI: 1.08-7.2, p=0.033) and was most pronounced in patients with uncontrolled hypertension despite antihypertensive treatment.

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Conclusion:
From early adolescence on, both arterial hypertension and BAVD have a major impact on aortic distensibility. Their specific effects differ in strength and localization (descending vs. ascending aorta). Moreover, adequate blood pressure control is associated with improved distensibility. These findings could contribute to the understanding of cardiovascular complications and the management of patients with aortic coarctation.

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2nd Prize: SAMS: Symptom Annotation Made Simple

Robin Steinhaus, Daniela Hombach and Dominik Seelow (Berlin)

Precision medicine needs precise phenotypes. Correctly characterizing the symptoms of rare disorders is of utmost importance to diagnose, understand and treat the disease. However, this is difficult to achieve within the clinical routine as hospital information systems are usually aimed at accounting, rather than a thorough description of the patients' phenotypes. This is especially problematic for rare genetic diseases which often do not have an ICD-10 code. In addition, it hampers clinical studies where concise information about the underlying symptoms is needed.

With SAMS (Symptom Annotation Made Simple), we offer a free and simple tool for tracking rare disease symptoms based on four widely used symptom and disease annotation databases: HPO, OMIM, Orphanet, and DIMDI Alpha-IDs. SAMS has distinct user modes for clinicians and patients. The inclusion of patients into the process helps gathering more complete information and can empower patients to better cope with their burden. SAMS features simple and intuitiveweb-based interfaces, allowing users to annotate symptoms with ease.

SAMS is developed at the BIH group for bioinformatics and translational genetics. Future versions of SAMS can readily be integrated into hospital information systems. It will also be available as apps for iOS and Android. A prototype can be accessed at: https://www.genecascade.org/sams/

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3rd Prize: Enhanced Recovery after Intensive Care (ERIC): Tele-ICU

Franziska Staerck[1], Lucas Albers[1], Moritz Adam[1], Ivo Pobering[1], Julian Herm[1], Nicolas Paul[1], Mario Menk[1], Robin Kleinwächter[1], Karin Steinecke[1], Martina Gassner[1], Enrico Dähnert[1], Andreas Edel[1], Björn Weiss[1], Claudia D. Spies[1] and the *ERIC Consortium*[2]

Background:
In Germany, more than 2.1 million patients are admitted to the intensive care unit (ICU) annually (*Federal Statistical Office* 2016). To enhance quality of care in the ICU, the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI) has issued ten evidence-based quality indicators (QIs) for acute critical care (Kumpf et al. 2017).

Aim:
To increase adherence to the QIs by implementing a QI-centered, telemedical round-and-response system.

Methods:
A telemedical hub (Tele-ICU) has been set up at Charité – Universitätsmedizin Berlin for communication and data collection with participating centers. A target study sample of 1,431 patients was enrolled in centers in Berlin and the state of Brandenburg between September 2018 and March 2020. All centers started in the control phase, where patients were treated according to standard of care, but QI adherence was monitored. After completing a blended-learning training on the QIs, centers switched to the intervention phase according to the stepped wedge, cluster-randomized trial protocol. Patients received daily, QI-centered telemedical rounding by experienced intensivists from the Tele-ICU, which also provided a telemedical 24/7 response system. Intensivists and nurses communicate via an audio-video device. As part of a case-care management, patients received two follow-up assessments to detect long-term, post-ICU impairments. ERIC received ethical approval from the ethics committee of Charité – Universitätsmedizin Berlin (EA1/006/18) as well as the ethics com-

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mittee of Brandenburg Medical School (MHB) Theodor Fontane (Z-01-20180828) and is registered at ClinicalTrials.gov (NCT03671447; 14 September 2018).

Results:
Results are expected in 2021.

Conclusion:
ERIC evaluates whether a telemedical round-and-response system can increase adherence to evidence-based QIs.

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