1. *Simonsen L, Higgs E, Taylor RJ, Wentworth D, Cozzi-Lepri A, Pett S, et al.* **Using Clinical Research Networks to Assess Severity of an Emerging Influenza Pandemic. Clin Infect Dis. 2018 Jul 18;67(3):341-9.**

ABSTRACT

Background: Early clinical severity assessments during the 2009 influenza A H1N1 pandemic (pH1N1) overestimated clinical severity due to selection bias and other factors. We retrospectively investigated how to use data from the International Network for Strategic Initiatives in Global HIV Trials, a global clinical influenza research network, to make more accurate case fatality ratio (CFR) estimates early in a future pandemic, an essential part of pandemic response.

Methods: We estimated the CFR of medically attended influenza (CFRMA) as the product of probability of hospitalization given confirmed outpatient influenza and the probability of death given hospitalization with confirmed influenza for the pandemic (2009-2011) and post-pandemic (2012-2015) periods. We used literature survey results on health-seeking behavior to convert that estimate to CFR among all infected persons (CFRAR).

Results: During the pandemic period, 5.0% (3.1%-6.9%) of 561 pH1N1-positive outpatients were hospitalized. Of 282 pH1N1-positive inpatients, 8.5% (5.7%-12.6%) died. CFRMA for pH1N1 was 0.4% (0.2%-0.6%) in the pandemic period 2009-2011 but declined 5-fold in young adults during the post-pandemic period compared to the level of seasonal influenza in the post-pandemic period 2012-2015. CFR for influenza-negative patients did not change over time. We estimated the 2009 pandemic CFRAR to be 0.025%, 16-fold lower than CFRMA.

Conclusions: Data from a clinical research network yielded accurate pandemic severity estimates, including increased severity among younger people. Going forward, clinical research networks with a global presence and standardized protocols would substantially aid rapid assessment of clinical severity.

Clinical trials registration: NCT01056354 and NCT01056185.

2. *Ossandon MR, Agrawal L, Bernhard EJ, Conley BA, Dey SM, Divi RL.* **Circulating Tumor DNA Assays in Clinical Cancer Research. J Natl Cancer Inst. 2018 Sep 1;110(9):929-34.**

ABSTRACT

The importance of circulating free DNA (cfDNA) in cancer clinical research was recognized in 1994 when a mutated RAS gene fragment was detected in a patient's blood sample. Up to 1% of the total circulating DNA in patients with cancer is circulating tumor DNA (ctDNA) that originates from tumor cells. As ctDNA is rapidly cleared from the blood stream and can be obtained by minimally invasive methods, it can be used as a dynamic cancer biomarker for cancer early detection, diagnosis, and treatment monitoring. Despite the potential for clinical use, few ctDNA assays have been cleared or approved by the US Food and Drug Administration. As tools for clinical and translational research, current ctDNA assays face some challenges, and more research is needed to advance use of these assays. On September 29-30, 2016, the Division of Cancer Treatment and Diagnosis at the National Cancer Institute convened a workshop entitled "Circulating Tumor DNA Assays in Clinical Cancer Research" to garner input from industry experts, academia, and government research and regulatory agencies to understand and promote the translation of ctDNA assays to clinical research, with potential to advance to use in clinical practice. This Commentary presents the topics of the workshop covered in the presentations and points made in the discussions that followed: 1) background on ctDNA, 2) potential clinical utility of ctDNA assays, 3) assay technology, 4) assay clinical and analytical validation, and 5) industry perspectives. Additional relevant information that has come to light since the workshop has been included.

3. *Bruland P, Doods J, Brix T, Dugas M, Storck M.* **Connecting healthcare and clinical research: Workflow optimizations through seamless integration of EHR, pseudonymization services and EDC systems. Int J Med Inform. 2018 Nov;119:103-8.**

ABSTRACT

Objective: In the last years, several projects promote the secondary use of routine healthcare data based on electronic health record (EHR) data. In multicenter studies, dedicated pseudonymization services are applied for unified pseudonym handling. Healthcare, clinical research and pseudonymization systems are generally disconnected. Hence, the aim of this research work is to integrate these applications and to evaluate the workflow of clinical research.

Methods: We analyzed and identified technical solutions for legislation compliant automatic pseudonym generation and for the integration into EHR as well as electronic data capture (EDC) systems. The Mainzelliste was used as pseudonymization service, which is available as open source solution and compliant with the data privacy concept in Germany. Subject of the integration was the local EHR and an in-house developed EDC system. A time and motion study was conducted to evaluate the effects on the workflow.

Results: Integration of EHR, pseudonymization service and EDC systems is technically feasible and leads to a less fragmented usage of all applications. Generated pseudonyms are obtained from the service hosted at a trusted third party and can now be used in the EDC as well as in the EHR system for direct access and re-identification. The evaluation of 90 registration iterations shows that the time for documentation has been significantly reduced in average

by 39.6 s (56.3%) from 71 ± 8 s to 31 ± 5 s per registered study patient.

Conclusions: By incorporating EHR, EDC and pseudonymization systems, it is now feasible to support multicenter studies and registers out of an integrated system landscape within a hospital. Optimizing the workflow of patient registration for clinical research allows reduction of double data entry and transcription errors as well as a seamless transition from clinical routine to research data collection.

Keywords: Data management; Electronic data capture; Health information systems; Pseudonymization; Workflow optimization.

4. *Ishigami J, Matsushita K*. **Clinical epidemiology of infectious disease among patients with chronic kidney disease. Clin Exp Nephrol. 2019 Apr;23(4):437-47.**

ABSTRACT

Infectious disease is recognized as an important complication among patients with end-stage renal disease, contributing to excess morbidity and health care costs. However, recent epidemiological studies have revealed that even mild to moderate stages of chronic kidney disease (CKD) substantially increase risk of infection. Regarding underlying mechanisms, evidence suggests various aspects of altered immune response in patients with CKD including impaired function of T cells, B cells and neutrophil. Multiple conditions surrounding CKD, such as older age, diabetes, and cardiovascular disease are important contributors in the increased susceptibility to infection in this population. In addition, several mechanisms impairing immune function have been hypothesized including accumulated uremic toxins, increased oxidative stress, endothelial dysfunction, low-grade inflammation, and mineral and bone disorders. In terms of prevention strategies, influenza and pneumococcal vaccines are most feasible and important. Nevertheless, the extent of vaccine utilization in CKD has not been well documented. In addition, antibody response to vaccination may be reduced in CKD patients, and thus a vaccine delivery strategy (e.g., dose and frequency) may need to be optimized among patients with CKD. Through this review, we demonstrate that infection is a major but underrecognized complication of CKD. As CKD is recognized as a serious public health issue, dedicated research is needed to better characterize the burden of infectious disease associated with CKD, understand the pathophysiology of infection in patients with CKD, and develop effective strategies to prevent infection and its sequela in this high risk population.

Keywords: Bloodstream infections; Chronic kidney disease; Infections; Influenza vaccination; Pneumococcal vaccination; Pneumonia; Renal failure.

5. *Shah P, Pellicori P, Kallvikbacka-Bennett A, Jufen Zhang J, Pan D, Clark AL.* **Warm water immersion in patients with chronic heart failure: a pilot study : Shah immerse: HF. Clin Res Cardiol. 2019 May;108(5):468-76.**

ABSTRACT

Background: Patients with chronic conditions, such as heart failure, swim regularly and most rehabilitation exercises are conducted in warm hydrotherapy pools. However, little is known about the acute effects of warm water immersion (WWI) on cardiac haemodynamics in patients with chronic heart failure (CHF).

Methods: Seventeen patients with CHF (NYHA I and II; mean age 67 years, 88% male, mean left ventricular ejection fraction 33%) and 10 age-matched normal subjects were immersed up to the neck in a hydrotherapy pool (33-35 °C). Cardiac haemodynamics were measured non-invasively, and echocardiography was performed at baseline, during WWI, 3 min after kicking in the supine position and after emerging.

Results: In patients with CHF, compared to baseline, WWI immediately increased stroke volume (SV, mean $\pm$ standard deviation; from 65 ± 21 to 82 ± 22 mL, $p < 0.001$), cardiac output (CO, from 4.4 ± 1.4 to 5.7 ± 1.6 L/min, $p < 0.001$) and cardiac index (CI, from 2.3 ± 0.6 to 2.9 ± 0.70 L/min/m², $p < 0.001$) with decreased systemic vascular resistance (from 1881 ± 582 to 1258 ± 332 dynes/s/cm^5, $p < 0.001$) and systolic blood pressure (132 ± 21 to 115 ± 23 mmHg, $p < 0.001$). The haemodynamic changes persisted for 15 min of WWI. In normal subjects, compared to baseline, WWI increased SV (from 68 ± 11 to 80 ± 18 mL, $p < 0.001$), CO (from 5.1 ± 1.9 to 5.7 ± 1.8 L/min, $p < 0.001$) and CI (from 2.7 ± 0.9 to 2.9 ± 1.0 L/min/m², $p < 0.001$).In patients with CHF, compared to baseline, WWI caused an increase in left atrial volume (from 57 ± 44 to 72 ± 46 mL, $p = 0.04$), without any changes in left ventricular size or function or amino terminal pro B-type natriuretic peptide.

Conclusions: In patients with CHF, WWI causes an acute increase in cardiac output and a fall in systemic vascular resistance.

Keywords: Exercise; Heart failure; Swimming; Water immersion.

6. *Ek A, Örjan Ekblom O, Hambraeus K, Åsa Cider A, Kallings LV, Börjesson M.* **Physical inactivity and smoking after myocardial infarction as predictors for readmission and survival: results from the SWEDEHEART-registry. Clin Res Cardiol. 2019 Mar;108(3):324-32.**

ABSTRACT

Background: Physical activity (PA) and smoking cessation are included in the secondary prevention guidelines after myocardial infarction (MI), but they are still underutilized. This study aims to explore how PA level and smoking status (6-10 weeks post-MI) were associated with 1-year readmission and mortality during full follow-up time, and with the cumulative 5-year mortality.

Methods: A population-based cohort of all hospitals providing MI-care in Sweden (SWEDEHEART-registry) in 2004-2014. PA was expressed as the number of exercise

sessions of ≥ 30 min in the last 7 days: 0-1 (low), 2-4 (medium) and 5-7 (high) sessions/week. Individuals were categorized as smokers, former smokers or never-smokers. The associations were analyzed by unadjusted and adjusted logistic and Cox regressions.

Results: During follow-up (M = 3.58 years), a total of 1702 deaths occurred among 30 644 individuals (14.1 cases per 1000 person-years). For medium and high PA, the hazard ratios (HRs) for mortality were 0.39 and 0.36, respectively, compared with low PA. For never-smokers, the HR was 0.45 and former smokers 0.56 compared with smokers. Compared with low PA, the odds ratios (ORs) for readmission in medium PA were 0.65 and 0.59 for CVD and non-CVD causes, respectively. For high PA, the corresponding ORs were 0.63 and 0.55. The association remained in adjusted models. There were no associations between smoking status and readmission.

Conclusions: The PA level and smoking status are strong predictors of mortality post-MI and the PA level also predicts readmission, highlighting the importance of adherence to the secondary prevention guidelines.

Keywords: Hospitalization; Myocardial ischemia; Physical activity; Survival; Tobacco.

7. *Kaspar M, Fette G, Güder G, Seidlmayer L, Ertl M, Dietrich G, et al.* **Underestimated prevalence of heart failure in hospital inpatients: a comparison of ICD codes and discharge letter information. Clin Res Cardiol. 2018 Sep;107(9):78-787.**

ABSTRACT

Background: Heart failure is the predominant cause of hospitalization and amongst the leading causes of death in Germany. However, accurate estimates of prevalence and incidence are lacking. Reported figures originating from different information sources are compromised by factors like economic reasons or documentation quality.

Methods: We implemented a clinical data warehouse that integrates various information sources (structured parameters, plain text, data extracted by natural language processing) and enables reliable approximations to the real number of heart failure patients. Performance of ICD-based diagnosis in detecting heart failure was compared across the years 2000-2015 with (a) advanced definitions based on algorithms that integrate various sources of the hospital information system, and (b) a physician-based reference standard.

Results: Applying these methods for detecting heart failure in inpatients revealed that relying on ICD codes resulted in a marked underestimation of the true prevalence of heart failure, ranging from 44% in the validation dataset to 55% (single year) and 31% (all years) in the overall analysis. Percentages changed over the years, indicating secular changes in coding practice and efficiency. Performance was markedly improved using search and permutation algorithms from the initial expert-specified query (F1 score of 81%) to the computer-optimized query (F1 score of 86%) or, alternatively, optimizing precision or sensitivity depending on the search objective.

Conclusions: Estimating prevalence of heart failure using ICD codes as the sole data source yielded unreliable results. Diagnostic accuracy was markedly improved using dedicated search algorithms. Our approach may be transferred to other hospital information systems.

Keywords: Data warehouse; Electronic health records; Heart failure; ICD coding; Information extraction.

8. *Varenhorst C, Lindholm M, Sarno G, Olivecrona G, Jensen U, Nilsson J, et al.* **Stent thrombosis rates the first year and beyond with new- and old-generation drug-eluting stents compared to bare metal stents. Clin Res Cardiol. 2018 Sep;107(9):816-23.**

ABSTRACT

Objectives: Old-generation drug-eluting coronary stents (o-DES) have despite being safe and effective been associated with an increased propensity of late stent thrombosis (ST). We evaluated ST rates in o-DES, new-generation DES (n-DES) and bare metal stents (BMS) the first year (< 1 year) and beyond 1 year (> 1 year).

Methods: We evaluated all implantations with BMS, o-DES (Cordis Cypher, Boston Scientific Taxus Liberté and Medtronic Endeavor) and n-DES in the Swedish coronary angiography and angioplasty registry (SCAAR) between 1 January 2007 and 8 January 2014 (n = 207 291). All cases of ST (n = 2 268) until 31 December 2014 were analyzed.

Results: The overall risk of ST was lower in both n-DES and o-DES compared with BMS up to 1 year (n-DES versus BMS: adjusted risk ratio (RR) 0.48 (0.41-0.58) and o-DES versus BMS: 0.56 (0.46-0.67), both p < 0.001). From 1 year after stent implantation and onward, the risk for ST was higher in o-DES compared with BMS [adjusted RR, 1.82 (1.47-2.25], p < 0.001). N-DES were associated with similar low ST rates as BMS from 1 year and onward [adjusted RR 1.21 (0.94-1.56), p = 0.135].

Conclusion: New-generation DES were associated with lower ST rates in comparison to BMS during the first-year post-stenting. After 1 year, n-DES and BMS were associated with similar ST rates.

Trial registration: This study was a retrospective observational study and as such did not require clinical trial database registration.

Keywords: Bare metal stents; Drug-eluting stents; Percutaneous coronary intervention; Stent thrombosis.

9. *Vogel D, Meyer M, Harendza S.* **Verbal and non-verbal communication skills including empathy during history taking of undergraduate medical students. BMC Med Educ. 2018 Jul 3;18(1):157.**

ABSTRACT

Background: Verbal and non-verbal aspects of communication as well as empathy are known to have an important impact on the medical encounter. The aim of the study was to analyze how well final year undergraduate medical students use skills of verbal and non-verbal communication during history-taking and whether these aspects of communication correlate with empathy and gender.

Methods: During a three steps performance assessment simulating the first day of a resident 30 medical final year students took histories of five simulated patients resulting in 150 videos of physician-patient encounters. These videos were analyzed by external rating with a newly developed observation scale for the verbal and non-verbal communication and with the validated CARE-questionnaire for empathy. One-way ANOVA, t-tests and bivariate correlations were used for statistical analyses.

Results: Female students showed significantly higher scores for verbal communication in the case of a female patient with abdominal pain ($p<0.05$), while male students started the conversations significantly more often with an open question ($p<0.05$) and interrupted the patients significantly later in two cases than female students ($p<0.05$). The number of W-questions asked by all students was significantly higher in the case of the female patient with abdominal pain ($p<0.05$) and this patient was interrupted after the beginning of the interview significantly earlier than the patients in the other four cases ($p<0.001$). Female students reached significantly higher scores for non-verbal communication in two cases ($p<0.05$) and showed significantly more empathy than male students in the case of the female patient with abdominal pain ($p<0.05$). In general, non-verbal communication correlated significantly with verbal communication and with empathy while verbal communication showed no significant correlation with empathy.

Conclusions: Undergraduate medical students display differentiated communication behavior with respect to verbal and non-verbal aspects of communication and empathy in a performance assessment and special differences could be detected between male and female students. These results suggest that explicit communication training and feedback might be necessary to raise students' awareness for the different aspects of communication and their interaction.

Keywords: CARE; Communications skills; Empathy; History taking; Undergraduate medical education.

10. *Akram A, Rizwan F, Sattar K, Hadi JIS, Meo SA*. **An approach for developing integrated undergraduate medical curriculum. Pak J Med Sci. 2018 Jul-Aug;34(4):804-10.**

ABSTRACT

Background and objectives: Medical schools are to develop integrated medical curricula because the term 'integrated curriculum' has grown up and flourished globally and it has become mandatory to align the medical education with the global concept in Pakistan. This paper aims to present a guideline to design an undergraduate integrated medical curriculum.

Methods: Various themes are used to develop integrated curriculum which are basic medical science, simulation skills, clinical science, personality development, research, entrepreneurship and pre specialization. Each theme is subdivided, termed a module and its contents primarily focus on particular aspect.

Results: Knowledge, skill and attitude, embodied in themes or modules, are planted in specific way that they have horizontal as well as vertical integration. There is no boundary of various traditional disciplines in template of five years curriculum. For example, diagnosis is a theme which carries contents from medicine, surgery, orthopedics etc.

Conclusion: The blueprint introduced in this paper would help medical educators to draft integrated medical curricula for those institutions which intend to switch their medical programs from traditional to integrated one.

Keywords: Basic sciences; Clinical science; Curriculum; Integration; Module; Undergraduate.