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Annual Update in Intensive Care and Emergency Medicine 2019

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Contents

Abbreviations

AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CRRT	Continuous renal replacement therapy
CT	Computed tomography
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalogram
GFR	Glomerular filtration rate
ICU	Intensive care unit
IL	Interleukin
LPS	Lipopolysaccharide
MAP	Mean arterial pressure
NO	Nitric oxide
NOS	Nitric oxide synthase
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
PPV	Pulse pressure variation
RBC	Red blood cell
RCT	Randomized controlled trial
ROS	Reactive oxygen species
RRT	Renal replacement therapy
RV	Right ventricular
$ScvO_2$	Central venous oxygen saturation
SvO_2	Mixed venous oxygen saturation
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced lung injury

Part I

Precision Medicine

Precision Medicine in the Intensive Care Unit: Identifying Opportunities and Overcoming Barriers

1

T. L. Palmieri and N. K. Tran

1.1 Introduction

Is precision medicine really precise? Precision in medicine can only be achieved with precision diagnostics. Unfortunately, barriers, such as access to clean electronic medical data, accurate and precise laboratory tests, and a propensity to over simplify complex pathophysiology, hinder this transformation to achieve the 'four Ps' of precision medicine: Personalized, Preventive, Predictive, and Participatory.

The rapid evolution of intensive care medicine has resulted in advancements for integration of technology with disease pathophysiology. The result: improved therapeutics and reduced patient mortality and morbidity. However, current medical practice is predicated on the Cnidarian School of Medicine, a three-tiered approach consisting of: (1) patient evaluation and disease diagnosis; (2) comparison and matching to a similar patient population via databases or data sets; and (3) initiation and monitoring of treatment [1]. As such, treatment is reactive and compartmentalized; intensivists initiate therapy for a specific organ system after disease identification. The ultimate success of treatment, however, relies on the interaction between the individual, the disease and the treatment. For example, infection is diagnosed by obtaining a sample of the infectious source, identifying an inciting organism, and choosing an antibiotic based on culture results in a petri dish. The efficacy of that treatment is dependent on the patient, the organism, the therapy, and the interaction among the three. Current paradigms tend to underestimate the variability and complexity of the system.

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The four pillars of precision medicine allow healthcare to be proactive and predictive, enabling clinicians to address the patient-disease-therapy triad by developing targeted patient and disease-specific therapies [2]. Initial precision medicine endeavors focused on oncology, an arena in which genetic biomarkers transformed therapeutic interventions [3]. Molecular oncology has created a better understanding of malignancies and identified exploitable targets, such as human epidermal growth factor receptor 2 (HER2), for therapy. However, application in intensive care, which represents a significant health burden, has been far slower. This is due to multiple factors, including the complex nature of critical illness in an intensive care unit (ICU), poor characterization of patient populations (generalized definitions), lack of informatics that integrate physiologic data with laboratory and genetic data, timeliness of usable data analysis, and appropriate clinical trial platforms that can capture discreet patient populations [4]. However, the ICU, housing patients with the greatest severity of illness, also has the greatest opportunity for benefit for improving both patient survival and quality of life while also containing cost. The purpose of this chapter is to present a framework for application of precision medicine in the ICU and introduce potential current challenges and future areas of conflict that may arise.

1.2 Definitions

Clarity in definitions is essential to any discussion of medical treatment paradigms. Perhaps the greatest example is the definition of the 'critically ill' patient by the United States (US) Food and Drug Administration (FDA)—it does not exist! How can a disease be studied or targeted if it is not well defined? Further exacerbating the challenges faced by intensivists in defining the 'critically ill' population is the variation of the definition between institutions. In 2015, US hospitals were faced with a dilemma involving the intended use of point-of-care blood glucose monitoring systems. At the time, no blood glucose monitoring device was approved by the FDA for use in critically ill patients, and point-of-care glucose monitoring in these patients was considered off label use. Due to the lack of a definition of critical illness, hospitals were stymied in trying to conform to the regulations and risked citation by regulatory agencies including the Centers for Medicare and Medicaid Services (CMS).

Another definition challenge has been the transformation of the term individualized medicine, to personalized medicine, to now, precision medicine. Although personalized medicine has many overlapping features with precision medicine, personalized medicine and precision medicine are distinct concepts. The concept of personalized medicine, introduced in the early 2000s, was partially developed in response to the completion of the human genome project. As such, personalized medicine emphasizes specific analyses for unique treatments for each individual patient [5]. Essentially, the personalized medicine model is an N-of-1: individuals receive customized treatment designed specifically for them. Precision medicine, on the other hand, is characterized by tailoring medical treatment to patient

characteristics, i.e., classifying individuals into subpopulations with different susceptibilities, disease biology and/or prognosis, or response to treatment. Hence, the model is 1-of-N [6]. Accurate identification of subgroups, likely by genomic, metabolomic, proteomic, and immunologic data, will be essential for the success of the precision medicine model.

Due to the complexity of critical care and the multifaceted nature of the ICU environment, it is important to distinguish populations based on prognosis versus prediction. Prognostic patient selection involves the selection of patients with a greater chance of a disease-related event, such as mortality, whereas predictive selection involves selection of patients more likely to respond to an intervention based on biological mechanisms associated with a disease [7]. Prognostic precision medicine examples predominate in sepsis [8]. Predictive precision medicine is advancing rapidly with the advent of pharmacogenomics, allowing for the more targeted use of antibiotics in sepsis [9]. Both forms will be needed in the ICU setting. The most logical approach is to first define patient subpopulations followed by the use of targeted therapies designed for that population.

1.3 Diagnosis

One of the more exciting aspects of precision medicine in the ICU is its potential to identify subgroups with similar disease states or outcomes based on biomarkers. A range of critical illnesses are defined by syndromes or clinical signs which may or may not be caused by a single underlying disease, including acute respiratory syndrome (ARDS), sepsis, acute kidney injury (AKI) and delirium [10]. Sepsis trials, in particular, have suffered from this syndromic issue. Unfortunately, although biomarkers have been proposed to define a host of clinical conditions ranging from sepsis [11] to AKI [12], all have lacked the specificity necessary to define study populations.

Additional challenges with diagnosis include significant variation within laboratory testing methodology. Modern medicine has often taken for granted what is being tested. For example, a serum lactate cut-off of 2 or 4 mmol/L has often been used as part of sepsis protocols. However, the lack of standardization of lactate as a test is an underappreciated limitation. Ridenour et al. reported that many lactate tests differ significantly as values approach 4 mmol/L [13].

Even cardiac troponin (cTn), a very common biomarker of myocardial injury, is not standardized. Differences between cTnI and cTnT are well known, but, the reference materials (National Institute of Standards and Technology Standard Reference Material 2921) for manufacturers are native cTn-ICT ternary complexes [14]. However, biologically, cTn could exist as dimers, trimers, and monomers—each with a different epitope targeted by various assays. Thus, cTnI between different manufacturers are different as illustrated by their 99th percentile cut offs. In summary, to achieve precision medicine, we must also achieve precision laboratory testing. Table 1.1 shows the intrinsic differences between different common critical care tests based on the assay used to perform the test.

Table 1.1 Variation between common critical care tests

Purpose	Biomarker (standard)	Manufacturer	Platform	Format	Methodology	Challenges
Cardiac injury	Troponin I (SRM 2921)	Abbott	Architect	Mainframe	Chemiluminescent immunoassay	Biologically released troponin can be monomeric, dimeric, and/or trimeric with differing epitopes detected by each immunoassay. Different troponin I assays cannot be compared, nor can I against T assays [15, 16]
		Beckman Coulter	DxI	Mainframe	Chemiluminescent immunoassay	
		Siemens	Centaur	Mainframe	Chemiluminescent immunoassay	
	Troponin T (SRM 2921)	Roche Diagnostics	Elecsys	Mainframe	Electro-chemiluminescent immunoassay	
Coagulation	PT/INR (multiple, recombinant or rabbit thromboplastin)	Abbott	i-STAT	POCT	Electrochemical	Multiple standards exist for PT/INR tests. Some assays use rabbit thromboplastin, others use recombinant human thromboplastin. Recent reformulations resulted in significant differences between POCT and lab [17]
		Instrumentation Laboratories	ACL TOPS	Mainframe	Spectrophotometric	
		Roche Diagnostics	CoaguChek XS	POCT	Electrochemical	
Glycemic control	Glucose (SRM 965b, IDMS)	Abbott	i-STAT	POCT	Enzymatic (GO)	Previous studies show statistically significant differences across POCT and laboratory platforms using paired specimens despite efforts to standardize [18]
		Beckman Coulter	DxC	Mainframe	Enzymatic (GO)	
			AU	Mainframe	Enzymatic (HK)	
		Nova Biomedical	StatSensor	POCT	Enzymatic (GO)	
		Radiometer	ABL90	POCT	Enzymatic (GO)	
		Roche Diagnostics	c702	Mainframe	Enzymatic (HK)	
		Siemens	epoc	POCT	Enzymatic (GO)	

Liver function	ALP, ALT, AST, GGT (None)	Abbott	Piccolo	POCT	Enzyme activity	Since 1971, it has been established that it is not feasible to determine the true accuracy of enzyme activity assays [19]
		Beckman Coulter	DxC	Mainframe	Enzyme activity	
		Roche Diagnostics	c701	Mainframe	Enzyme activity	
Perfusion	Lactate (None)	Abbott	i-STAT	POCT	Electrochemical	Lactate is not standardized, with several studies showing significant discordance as values approach 4 mmol/L and beyond [20]
		Beckman Coulter	DxC	Mainframe	Electrochemical	
		Nova Biomedical	StatStrip	POCT	Electrochemical	
		Radiometer	ABL90	POCT	Electrochemical	
		Roche Diagnostics	c702	Mainframe	Electrochemical	
		Siemens	epoc	POCT	Electrochemical	
Renal function	Creatinine (SRM 967, IDMS)	Abbott	i-STAT	POCT	Electrochemical	Although creatinine was standardized to SRM 967 by IDMS, variations in methods and the significant biological variability of the biomarker causes substantial discordance between platforms [21]
		Beckman Coulter	DxC Cartridge	Mainframe	Electrochemical	
			DxC Jaffe	Mainframe	Jaffe Reaction	
		Nova Biomedical	StatSensor	POCT	Enzymatic	
		Radiometer	ABL90	POCT	Enzymatic	
		Roche Diagnostics	c702	Mainframe	Enzymatic	
		Siemens	epoc	POCT	Enzymatic	

ALP alkaline phosphatase, *ALT* alanine transferase, *AST* aspartate aminotranasferase, *GGT* gamma glutamyl transferase, *IDMS* isotope dilution mass spectrometry, *INR* international normalized ratio, *POCT* point-of-care testing, *PT* prothrombin time, *SRM* standardized reference method, *GO* glucose oxidase, *HK* hexokinase

1.4 Treatment

Several studies have used biomarker data to identify predictive cohorts that would respond to a therapeutic intervention. For example, several groups have analyzed biomarkers in ARDS to predict responsiveness to positive end-expiratory pressure (PEEP) and fluid management [22, 23]. However, the more precise identification of subtypes may make prospective trial conduct problematic, as the number of patients eligible for a study will diminish. Trials will require a greater number of participating centers, more advanced screening methods, longer conduct times, and different trial methodologies to achieve statistical significance.

1.5 Potential Conflicts/Weaknesses

Why has the adoption of precision medicine in the ICU been slower than in oncology? Perhaps the most intuitive argument is the lack of a clear well-defined target (disease process and subpopulation). Oncologists can target a cancer molecular signature in a specific organ or system. Patients in an ICU are admitted for diverse problems ranging from sepsis to cardiac failure, traumatic or burn injury to postoperative cardiac care. As such, ICU patients often have multiple potential targets. For example, a patient admitted with a closed head injury has frequently sustained other injuries (such as hemorrhagic trauma or burns) and/or has multiple organ system dysfunction, which could lead to conflicts in treatment. Should a patient with a closed head injury and major burn be treated with massive fluid resuscitation to address the burn injury or with fluid restriction to minimize intracranial edema? Precise treatment of one disease may have no effect or may even adversely impact morbidity and mortality from another medical issue. Precision medicine may assist in formulating an answer to such questions, but the answers will be late in coming, as the precise treatment of the index injuries or diseases must occur prior to determining the best treatment for combined problems. Although clinicians have made tremendous progress in the identification of pathophysiology of illness, the understanding of the complex interplay among multiple medical issues remains elusive in many medical conditions commonly encountered in the ICU.

In addition, one therapy may alter the efficacy of another. Perhaps the best example of this occurred at the end of the twentieth century. Two landmark studies, the TRICC (Transfusion Requirements in Critical Care), which reported that stable ICU patients could be maintained at a hemoglobin of 7 g/dL as opposed to the traditional 10 g/dL [24], and Van den Berghe's intensive insulin therapy study [25], which suggested that tight glycemic control improved outcomes in critically ill patients, were published. As a result, many critically ill patients were treated with both a restrictive transfusion policy and tight glycemic control. However, clinical practice combining the two strategies had a different outcome. Tight glycemic control did not yield the benefits that were reported in the randomized trial. The subsequent NICE SUGAR study suggested harm using tight glycemic control [26]. Why? First, there was a distinct difference in the types of patients enrolled. The Van den Berghe study enrolled

a very specific subpopulation, whereas the NICE-SUGAR trial had much broader enrollment criteria. Second, and equally important, the methodology for glycemic control (i.e., point-of-care glucose testing) used by most clinicians for glucose monitoring in NICE-SUGAR differed from that used in the Van den Berghe trial (serum glucose). Unbeknownst to the NICE-SUGAR investigators at that time, point-of-care glucose monitoring overestimated serum glucose levels by as much as 20% in anemic patients, likely creating unrecognized hypoglycemia in the cohort [27]. The application of the TRICC trial restrictive transfusion policy, in which ICU patients have sustained anemia, may have influenced the outcomes for patients also treated with tight glycemic control. Independently both strategies worked. Together they did not. Is tight glycemic control beneficial? The answer will require an in-depth understanding of the metabolomics of various forms of critical illness and subsequent application of targeted strategies to address the clinical variations. The application of precision medicine to the ICU will need to carefully consider the potential conflicts inherent in treating multiple different medical issues simultaneously.

The intersection of the TRICC trial and the glycemic trial also illustrate another important concept: precision medicine in the ICU will require standardization of sample collection, storage, testing and reporting; assurance of quality and reproducibility of test results; timely reporting of clinically applicable results; and clear delineation of test results in a format that clinicians can understand and apply. Recent reports from the precision method Surgical Critical Care Initiative (SC2i) have attributed data quality as the largest hurdle to the development of a comprehensive precision medicine program [28]. Even today, clinicians are bombarded with test results that need to be integrated to treat patients. Yet key elements remain unstandardized. Lactate is but one example. Lactate is currently measured using different platforms. However, no reference method or traceable material exists for lactate, resulting in non-standardized testing [13]. This is compounded by the influence of pre-analytic factors, such as testing delays and interfering substances, which can falsely elevate lactate levels. As a result, lactate measurements may vary by as much as 1.5 mmol/L for values >2 mmol/L [29]. The use of lactate in clinical trials should carefully evaluate the platforms used as well as the timing of sample analysis to assure comparable results between centers and platforms. Knowledge of how samples are analyzed and what they mean will be essential if precision medicine is to be ‘precise’. Standard operating procedures, use of certified clinical laboratories, specimen storage protocols and quality assurance for every step of the laboratory analytic process will need to be employed not just for clinical samples, but for metabolomics, genomics, biomarkers, and other testing methodologies.

1.6 Pharmacokinetics

One of the core principles of precision medicine is delivery of the right treatment at the right dose at the right time. Understanding pharmacokinetics, pharmacogenomics, and pharmacokinetic variability among critically ill patients will help guide appropriate medication administration in the critical care setting. Changes in

pharmacokinetics are both drug-specific and time sensitive and are often influenced by other treatment modalities. For example, hypothermia reduces phase I cytochrome P450 metabolism, thus increasing concentration of drugs (such as fentanyl, midazolam) that are metabolized using this system [30]. In contrast, the metabolic rate of severe burn patients is more than doubled, resulting in augmented renal clearance of many agents [31]. Effective dosing of antimicrobial agents as well as narcotics requires drug doses far exceeding the 'normal' standards. Drug interactions may also influence pharmacokinetics of a given agent. Concomitant administration of medications may increase, decrease or offset the effect of any given agent. This can be particularly problematic in the ICU, as patients receive multiple different agents. Critically ill burn patients, for example, receive, on average, more than 40 agents, many of which interact with each other [32]. Pharmacogenomics, which evaluates the influence of patient genomic makeup on pharmacokinetics and pharmacodynamics, will likely play a major role in future ICU precision medicine practice.

1.7 Data Collection and Analysis

Regardless of the type of patient being studied, the data acquired in precision medicine efforts will include not just patient physiologic and 'routine' laboratory analyses (such as electrolytes, blood counts) but also genomic, proteomic, metabolomic and transcriptome data; biomarkers; and data from other sources. Current electronic health records are fraught with inconsistent and inaccurate data due to both machine and human limitations. Data recording, integration, and interpretation will require quality assurance prior, during, and after data integration into a centralized data repository. New data management and analytic techniques (including machine learning) will be required to integrate the data sources and develop valid, clinically meaningful, and actionable data with which to treat patients. One of the keys to successful implementation of precision medicine in ICU patients is consistency in data acquisition, storage and reporting. This will require a level of collaboration far beyond what has occurred in medicine to date. In addition, how data are analyzed will need to be standardized. Study results can also vary depending upon how informatics is used.

Precision medicine will require fundamental changes in the conduct of clinical trials. Specific requirements will include development of trial methodologies that streamline collaboration to generate sufficient data for studies of smaller, better defined patient cohorts; additional time allotted to complete patient enrollment, and different trial platforms employing computer-based learning to maximize output from any given trial. One promising methodology, the registry-based randomized controlled trial (RRCT) uses data collected for other reasons, such as registry data, to identify appropriate targets for trial enrollment [33]. The RRCT can be used to identify patients who already meet pre-specified enrollment criteria (with their associated built-in screening, data capture and outcomes measurements), thus identifying new subjects for consent. This type of methodology is designed to optimize patient enrollment and increase collaborations among centers. In essence, the RRCT can use prognostic precision medicine to assign patients to different predictive

therapeutic options. Another potential new trial design is the platform trial, which uses response-adaptive randomization to test multiple treatments in a pre-specified patient group. The system uses Bayesian analysis to identify effective treatments for specific patient subgroups [34]. Ineffective treatments are eventually discarded, as are patient groups that do not benefit from a given treatment. Essentially, the platform trial system is an example of computer learning applied to clinical trials.

1.8 The Future

The key to successful implementation of precision medicine in the ICU is collaboration. Different disease processes are in different stages of precision medicine development, particularly with respect to subgroup identification and delineation. For example, oncology has identified subgroups based on genomic markers; sepsis uses broad-based physiologic definitions; trauma and burn patients are categorized on the basis of injury characteristics. Each has unique cohort identification requirements and will require a different strategy to develop meaningful subgroup analysis. Informed groups consisting of clinicians, biostatisticians, basic scientists, epidemiologists and pharmacologists need to gather for the major disease processes to delineate the current state of the disease process, identify the key steps needed to identify subpopulations for prognostic marker testing, and map out the initial course to define prognostic markers. Concurrently, biomarker development at both the bench and clinical level should continue to validate subgroup selection and study conduct for the given subgroup, as biomarker development requires time for development, testing and implementation.

Just as disease states need to be defined, so do data capture and processing. Consistent and coherent data analysis will rely heavily on the development of a universal critical care ontology that can accommodate specialty-specific topics so that data gathered are all based on the same foundation [35]. Currently different hospitals use different electronic health records, each with a unique structure. Harnessing the power of the electronic health record to gather physiologic data requires either all programs to use the same data capture system (unlikely) or the development of algorithm-based programs that can extract common data elements from multiple different data sources and collate data into a consistent, analyzable database. These data will then need to be combined with biomarker data, including genomic, metabolomic and proteomic data. Database development teams consisting of informaticists, biostatisticians, scientists and clinicians will need to unite to complete this challenging process, which will be essential to the development of precision medicine.

1.9 Conclusion

The vision for precision medicine in the ICU has been articulated. The goal is visible on the horizon. However, the road leading to the vision is unpaved, the ground is rocky, the path crooked and the construction team has not yet been assembled.

Success will depend on collaboration, strategic resource utilization, funding availability, flexibility and patience. New technologies and trial designs will need to be created. Collaborations will need to be extended. The traditional medical paradigm will need to change. The ICU team has the dedication and capability necessary to complete the journey. We just need to take the first step.

References

1. Sugeir S, Naylor S. Critical care and personalized or precision medicine: who needs whom? J Crit Care. 2018;43:401–5.
2. Naylor S. What's in a name? The evolution of "P-medicine". J Precision Med. 2015;2:15–29.
3. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–5.
4. Vincent J. The coming era of precision medicine for intensive care. Crit Care. 2017;21(Suppl 3):314.
5. Redekop WK, Madsi D. The faces of personalized medicine: a framework for understanding its meaning and scope. Value Health. 2013;16:S4–9.
6. Zhang XD. Precision medicine, personalized medicine, omics, and big data: concepts and relationships. J Pharmacogenomics Pharmacoproteomics. 2015;6:e14.
7. Wong HR. Intensive care medicine in 2050: precision medicine. Intensive Care Med. 2017;43:1507–9.
8. Langley RJ, Tsalik EL, van Velkinburgh JC, et al. An integrated clinic-metabolomic model improves prediction of death in sepsis. Sci Transl Med. 2013;5:195ra95.
9. Aung AK, Haas DW, Hulgan T, Phillips EJ. Pharmacogenomics of antimicrobial agents. Pharmacogenomics. 2014;15:1903–30.
10. Sweeney TE, Khatri P. Generalizable biomarkers in critical care: toward precision medicine. Crit Care Med. 2017;45:934–9.
11. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care. 2010;14:R15.
12. McMahon BA, Koyner JL. Risk stratification for acute kidney injury: are biomarkers enough? Adv Chronic Kidney Dis. 2016;23:167–78.
13. Ridenour RV, Gada RP, Brost BC, Karon BS. Comparison of lactate values between point-of-care and central laboratory analyzers. Am J Clin Pathol. 2007;128:168–71.
14. Apple FS. Counterpoint: standardization of cardiac troponin I assays will not occur in my lifetime. Clin Chem. 2011;58:169–71.
15. Christenson RH, Bunk DM, Schimmel H, et al. Point; Put simply, standardization of cardiac troponin I is complicated. Clin Chem. 2012;58:165–8.
16. Gaze DC, Collinson PO. Multiple molecular forms of circulating cardiac troponin: analytical and clinical significance. Ann Clin Biochem. 2008;45:349–55.
17. Kost GJ, Tran NK, Louie RF, et al. Assessing the performance of handheld glucose testing for critical care. Diabetes Technol Ther. 2008;10:445–51.
18. Moss DW, Baron DN, Walker PG, et al. Standardization of clinical enzyme assays. J Clin Pathol. 1971;24:740–3.
19. Pieroini L, Bargnoux AS, Cristl JP, et al. Did creatinine standardization give benefits to the evaluation of glomerular filtration rate. EJIFCC. 2017;28:251–7.
20. Poller L. International normalized ratios (INR): the first 20 years. J Thromb Haemost. 2004;2:849–60.
21. Tolan NV, Wockenfus AM, Koch CD, et al. Analytical performance of three whole blood point-of-care lactate devices compared to plasma lactate comparison methods sand a flow-injection mass spectrometry method. Clin Biochem. 2017;50:168–73.
22. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomized controlled trial. Lancet Respir Med. 2014;2:611–20.

23. Famous KR, Delucchi K, Ware LB, et al. ARDS subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med. 2016;195:331–8.
24. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340:409–17.
25. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
26. Investigators TNICE-SUGARS. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
27. Ceriotti F, Kaczmarek E, Guerra E, et al. Comparative performance assessment of point-of-care testing devices for measuring glucose and ketones at the patient bedside. J Diabetes Sci Technol. 2015;9:268–77.
28. Belard A, Buchman T, Dente CJ, Potter BK, Kirk A, Elster E. The Uniformed Services University's Surgical critical Care Initiative (SC2I): bringing precision medicine to the critically ill. Mil Med. 2018;183:487–95.
29. Lima K, Caynak R, Tran NK. Lactate monitoring for severe sepsis and septic shock: are all lactate measurements the same? Crit Care Med. 2016;44:443.
30. Empey PE, Miller TM, Philbrick AH, et al. Mild hypothermia decreases fentanyl and midazolam steady-state clearance in a rat model of cardiac arrest. Crit Care Med. 2012;40:1221–8.
31. Udy AA, Roberts JA, Lipman J, Blot S. The effects of major burn related pathophysiological changes on the pharmacokinetics and pharmacodynamics of drug use: an appraisal utilizing antibiotics. Adv Drug Deliv Rev. 2017;123:65–74.
32. Godwin Z, Lima K, Greenhalgh D, Palmieri T, Sen S, Tran NK. A retrospective analysis of clinical laboratory interferences caused by frequently administered medications in burn patients. J Burn Care Res. 2016;37:10–7.
33. Lauer MS, D'Agostina RB. The randomized registry trial-the next disruptive technology in clinical research? N Engl J Med. 2013;369:1579–81.
34. Maslove DM, Lamontagne F, Marshall JC, Heyland KD. A path to precision in the ICU. Crit Care. 2017;21:79–88.
35. Noy NF, Shah NH, Whetzel PL, et al. BioPortal: ontologies and integrated data resources at the click of a mouse. Nucleic Acids Res. 2009;37:170–3.

Precision Delivery in Critical Care: Balancing Prediction and Personalization

2

V. X. Liu and H. C. Prescott

2.1 Introduction

Recent developments in healthcare data availability, advanced analytic algorithms, and high-performance computing have produced incredible enthusiasm about a new age of data-driven healthcare [1–8]. When it comes to clinical care specifically, 'precision delivery' is an emerging term to describe the "routine use of patients' electronic health record (EHR) data to predict risk and personalize care to substantially improve value" (Table 2.1) [7, 9, 10]. While clinical risk prediction tools have a long history in critical care, novel machine learning applications can offer improved predictive performance by maximally leveraging large-scale, complex EHR and other data [5]. Perhaps, even more importantly, these approaches may help overcome the problem of heterogeneity, which is routinely noted to be a hallmark of critical illness as well as a major barrier to improved treatment [11–13]. In this chapter, we discuss the overarching concept of 'precision delivery', the important balance between clinical risk prediction and personalization, and the future challenges and applications of data-driven critical care delivery.

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Table 2.1 Key domains and concepts underlying the potential of precision delivery in critical care

Key domains	Concepts
Electronic health record (EHR) data	Granular EHR data are becoming increasingly ubiquitous in healthcare and these data can now be used routinely to inform data-driven approaches to clinical care delivery
Risk prediction	Machine learning algorithms can facilitate the use of complex, multi-faceted EHR data to improve the performance and capability of risk prediction models across many adverse outcomes of interest
Personalization	Machine learning can also be used to identify underlying subgroups within a heterogeneous cohort of at-risk patients allowing for treatments to be maximally targeted towards responsive subgroups
Improved value	When embedded within well-defined clinical pathways and delivered at the right moment, targeted care can improve outcomes while also reducing unnecessary resource utilization across large populations of patients

2.2 A Changing Landscape: The Fourth Industrial Revolution

In God we trust; all others must bring data. (frequently attributed to W. Edwards Deming)

Klaus Schwab, the founder of the World Economic Forum, notes that we are in the midst of a rapid societal upheaval driven by technological advances that are evolving at an exponential, rather than linear, scale [14, 15]. Prior industrial revolutions were marked by incredible achievements yielding the steam engine, the light bulb, the telephone, the internal combustion engine, the personal computer, and the internet. Today, the Fourth Industrial Revolution is heralded by advances in data availability, mobile computing, machine learning and artificial intelligence, robotics and autonomous vehicles, energy innovation, and nano- and bio-technology. Given the pace and complexity of change driven by these technological advances, it remains unclear how this revolution will impact societies and individuals. However, we are already bearing witness to rapid disruptions of existing industries and norms driven by expanded uses of data to risk stratify individuals and tailor actions to suit their needs.

Familiar examples of these disruptions outside of healthcare include the Amazon recommender system which uses item-based collaborative filtering algorithms when a customer is preparing to purchase a specific item to identify other 'related' items that are likely to be of interest [16]. This and other innovations have already altered the landscape of consumer purchases. Similar systems are also in place at Netflix, whose suite of algorithms seek to deliver the 'Netflix experience' by combining prediction and recommender systems that leverage personal interests, prior viewed content, and temporal trends in activity [17]. This approach has allowed Netflix to target content development to highly-specific subgroups and vastly increase the viewable or 'effective' size of their library even within narrow genres. Similar algorithmic approaches are used in applications like advertisement targeting software to surface the most relevant marketing content based on prediction algorithms using background browsing data.

2.3 Precision Delivery in Healthcare

In healthcare today, precision delivery describes a similar process for leveraging data-driven predictive approaches to improve the value of clinical care [9]. Rapid expansions in the availability of health data driven primarily through the increasing ubiquity of EHRs and other key emerging data sources (e.g., sensors, -omics), along with advances in machine learning algorithms have improved the performance and capability of contemporary risk stratification models. Machine learning algorithms can rapidly sift through voluminous and complex data to find clinically-relevant risk strata by applying computationally-intensive statistical modeling at scale [18, 19]. These risk models can then be used to improve the personalization of patient care by identifying patient subgroups in whom specific interventions can have the maximum impact, or those in whom specific interventions are unlikely to offer any benefit. Precision delivery is based on using this prediction-personalization approach, deployed at precisely the right moment in clinical treatment, to drive improved clinical outcomes [10]. At the same time, given the rapid rise in healthcare expenditures in the United States and in many other nations, the hope is that the precision delivery model can control or even reduce healthcare costs through improved patient targeting.

2.4 Critical Care: A Risk-Based Specialty

It is important to note that risk prognostication is not a new concept in medicine and has long been used to identify patient groups who might benefit from specific, targeted interventions [20]. Indeed, one could argue that the field of critical care arose as a byproduct of risk prognostication: a system in which patients with key observable criteria portending a high risk of imminent death (e.g., vital signs, traumatic injury, organ failure) were identified and triaged to a setting of increased monitoring and clinician staffing [21].

Given this history, it comes as no surprise then that the field of critical care has also been a leader in the development of clinical risk stratification models [22–24]. Highly robust mortality models developed decades ago, prior to the routine use of personal computers, continue to be widely used today. For example, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, published in 1985 and based on 12 routine physiologic measurements [25], remains a common risk stratification system used even for contemporary, high-profile randomized controlled trials. Similarly, the Sepsis-related/Sequential Organ Failure Assessment (SOFA) score from 1996 [26, 27], continues to play a key role in severity of illness assessment as well as in the definition of sepsis [28].

2.5 Novel Capabilities with Improved Data and Computation

Critical care already has a robust history of risk prognostication, but recent innovations in data and computation provide several new opportunities (Table 2.2). First, the breadth of data available for incorporation into prediction algorithms has

Table 2.2 Potential capabilities available through improved platforms for data collection, analysis, and computation

Domain	Improvements
Electronic health record (EHR) data	Increasing routine collection of health data within the EHR fosters a vastly increased breadth of data available for incorporation into clinical risk prediction models. In general, models developed with expanded data have shown improved predictive performance
Variable subset selection or dimensionality reduction	With a vastly increased set of variables, or 'feature space', the risk of identifying random associations increases. Machine learning algorithms can be used to statistically identify the most relevant variables to a specific problem of interest
Non-parametric modeling	Traditional risk prediction algorithms largely depended on linear modeling, which places potential limitations on interactions between complex data elements. Improved computation platforms allow for more flexible modeling approaches to maximally leverage EHR data. However, they may also decrease the interpretability of prediction models
Real-time predictive modeling	As greater numbers of risk prediction models are incorporated within EHR systems, the incremental costs of additional calculations are small (when compared with the costs of manual calculation). This allows for multiple models to be calculated for each patient, as well as multiple time points for model updating (e.g., every minute, hour, or day).
User-friendly systems	Alarm fatigue and distractions already plague clinicians working in high-acuity settings. By tuning model parameters at the development and deployment stages, models can be embedded within clinical workflows to enhance, rather than distract, clinical care

expanded tremendously, owing to the transition from pen and paper recording of data into automated EHR-based data collection. Thus, while simpler hand-calculated models continue to be calculated and used even in modern EHR systems (e.g., the Model for End-Stage Liver Disease [MELD] score), most newer prediction models now incorporate a considerably larger set of variables or 'features'. In general, these models show improved predictive capability, at least when measured by standard quantitative performance metrics like test error rates, area under the receiver operating characteristic (AUC) curves, or positive predictive values [1, 2, 5].

However, the expansion of variables available for model inclusion, or the 'feature space', brings with it new challenges related to finding robust data signals within the noise. This is an area in which machine learning excels, because algorithms can be used to empirically identify the most relevant subset of variables in a model (i.e., dimensionality reduction) as well as to apply non-parametric modeling approaches to complex data that account for non-linear relationships between variables [18, 19]. For example, gradient boosted trees, which iteratively combine many individual weaker decision trees based on random subsets of data to improve classification, have shown robust performance across many different types of clinical risk prediction challenges.

This use of machine learning algorithms does not come without cost. Computationally-intensive platforms are often needed to implement advanced modeling strategies, particularly in large databases. However, the cost of these platforms has decreased tremendously while their availability has also increased rapidly, largely

offsetting these concerns in all but the most complex scenarios. There is also an important trade-off between the ease of model development or scoring and the ability to interpret and apply the risk predictions themselves [19]. While some methods, like decision tree-based models, offer moderate degrees of intelligibility (i.e., the ability to understand which variables are driving predictions), others, like the deep learning neural networks recently used by Google [29], are considerably more challenging to interpret. Traditional linear models, including logistic regression, have generally shown weaker predictive performance in recent comparisons but offer the advantage of allowing for high degrees of intelligibility and potentially easier technical implementation. In some cases, extensions of linear models, like penalized logistic regression models—designed to identify the subset of variables which maximally contribute to prediction—have shown similar performance to other non-parametric approaches [18].

In addition to the advantages afforded by an expanded universe of potential variables and more flexible modeling approaches, the widespread uptake of EHRs and mobile computing has facilitated the deployment of real-time risk scoring and display without requiring significant additional manual effort. Thus, the incremental operating costs associated with using an EHR-based system to simultaneously calculate and display 100 risk models compared with only a single model may be relatively modest. This would certainly not be the case for individuals who might have to manually calculate and record 100 risk scores for each patient every hour.

This flexibility offers further opportunities to deploy risk models that are more user-centric and aligned with the so-called "5 rights of clinical decision support" [30]: providing the right information, to the right people, in the right format, through the right channels, and at the right time. Given that all clinicians, and in particular those operating in high-acuity environments like the intensive care unit (ICU), are already vulnerable to alarm fatigue and distractions, few would be excited about using an EHR system that simultaneously displayed 100 risk scores for each patient [31]. Instead, a more sustainable approach would be to allow risk prediction scoring to occur silently in the background, with specific alerts only surfacing when a key alert threshold has been crossed or users actively seek out the information. A car dashboard offers a familiar example outside of healthcare of a data display that has remained remarkably focused over many decades, despite the tremendous increase in the number of onboard computers constantly surveilling specific automotive functions.

2.6 Current Risk Prediction Applications in Critical Care

As described above, critical care already has numerous models designed to predict hospital mortality [22, 23]. Recent machine learning-based models incorporate a variety of newer elements including variable transformations, time-series data, and unstructured data from clinical documentation (Table 2.3). While these have contributed to some improvement in predictive performance, in many cases, the incremental gains have been modest and of uncertain benefit for clinical practice [32–34]. The capabilities available through natural language processing (NLP), a field that leverages computational approaches for understanding text-based, unstructured

Table 2.3 Balancing prediction and personalization in precision delivery by leveraging supervised and unsupervised machine learning approaches

	Prediction	Personalization
Goal	Precisely quantify the risk of experiencing an adverse outcome, while minimizing the false-positive rate associated with a given risk alert threshold	Identify subgroups of patients from a diverse at-risk group who would respond to specific targeted treatments
Machine learning approach	Supervised learning approaches fit a set of model variables to a pre-defined outcome of interest	Unsupervised learning approaches surface latent subgroups based on identifying underlying patterns and associations
Examples	ICU mortality Early warning scores Sepsis 'sniffers'	Subgroups responsive to statin therapy in acute respiratory distress syndrome; steroids in pediatric septic shock

documents like clinical notes or pathology reports, are now in wide use outside healthcare. However, the advantages of NLP in predictive models for patients who already have 'high-density' structured data available during hospitalization (i.e., frequent physiologic, laboratory, and treatment data) remain unclear [35].

Another active area of risk prediction relevant to critical care includes risk models designed to identify ward patients with a high likelihood of imminent deterioration [36, 37]. Again, many simpler scores (e.g., the Modified Early Warning Score [MEWS]; National Early Warning Score [NEWS]) have already seen widespread use within routine clinical workflows. Broadly speaking, more advanced scores (e.g., Advance Alert Monitor [AAM]; electronic Cardiac Arrest Risk Triage [eCART]; Rothman Index) demonstrate modest to moderate levels of improvement compared to existing models [38–42]. Where they are likely to excel is in their ability to reduce the number of false positives that trigger the need for clinical workup when compared to simpler models. Given the clinical burden imposed by the need to workup false positive alerts to find a single 'true positive' case, favorable reductions in the 'workup-to-detection ratio' or the 'number needed to screen' could have considerable downstream benefits on clinician sustainability and uptake.

Other areas of active focus include risk prediction models designed to accelerate the identification, triage or treatment of sepsis patients [43–50]. Although several reports suggest that use of risk prediction models has contributed to large reductions in sepsis-related mortality, it is unclear whether the described benefits actually accrue from the quantitative risk stratification (i.e., the relative improvement in the discrimination and performance of the model itself versus other screening criteria) or from the increased attention to sepsis and the clinical workflow alignment that becomes essential when an alerting system is turned on (i.e., the creation of a team-based standardized process for screening, identification, treatment, escalation and hand-off). Even prior to the advent of real-time predictive models, similar reductions in sepsis adverse outcomes were previously reported as part of system-wide quality improvement efforts.

In addition to these focus areas, a growing number of models are targeted towards increasingly prominent problems facing patients with acute and critical illness including the development of brain dysfunction or delirium [51–54], acute kidney injury (AKI) or organ failure [55–63], respiratory failure or acute respiratory distress syndrome (ARDS) [60–63], extended length of stay and post-ICU sequelae of severe illness [33, 64–66], and specific infectious types or complications (e.g., *Clostridium difficile*) [66–69]. Over the coming years, we will almost certainly see extensive growth in the development, reporting and testing of numerous predictive models incorporating EHR data with machine learning techniques to predict non-mortality outcomes.

2.7 Heterogeneity: The Hallmark of Severe and Critical Illness

Given the fundamental role that risk stratification has played in the birth and growth of the critical care specialty, the field is naturally suited to develop and deploy diverse risk models. However, while implementing broad risk prognostication tools to trigger protocolized care approaches has improved outcomes, our ability to further improve outcomes is pushing up against substantial limitations [11, 13]. In particular, the failures of numerous randomized controlled trials intended to identify novel pharmaceutical treatments for key ICU conditions like sepsis and ARDS has been particularly vexing.

There has been growing recognition that underlying heterogeneity in critical care patients represents a major barrier to the identification of specific treatments that can be targeted to responsive subgroups. Thus, while intense focus is currently placed on developing risk prediction models (i.e., a scale that quantifies each patient's risk for some adverse outcome like mortality, readmission, unexpected ICU transfer or chronic critical illness), the emerging frontier must focus on risk personalization models (i.e., models which predict the likelihood that a patient subgroup will respond to a specific therapy). To contextualize this concept within the framework of precision delivery, much more attention now needs to be shifted to the latter half of the prediction-personalization paradigm.

2.8 Unsupervised Machine Learning Approaches and Personalization

Fortunately, this is another area in which machine learning has shown excellent promise [18]. The development of standard risk prediction models focuses on using supervised learning methods in which model input variables are fit to a known outcome variable in a training dataset and then subsequently to a test dataset. However, to uncover potentially actionable subgroups within a high-risk cohort, unsupervised learning approaches—in which input variables are known but there is no