The opportunities and challenges of machine learning in the acute care setting for precision prevention of posttraumatic stress sequelae

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Abstract

Personalized medicine is among the most exciting innovations in recent clinical research, offering the opportunity for tailored screening and management at the individual level. Biomarker-enriched clinical trials have shown increased efficiency and informativeness in cancer research due to the selective exclusion of patients unlikely to benefit.

In acute stress situations, clinically significant decisions are often made in time-sensitive manners and providers may be pressed to make decisions based on abbreviated clinical assessments. Up to 30% of trauma survivors admitted to the Emergency Department (ED) will develop long-lasting posttraumatic stress psychopathologies. The long-term impact of those survivors with posttraumatic stress sequelae are significant, impacting both long-term psychological and physiological recovery. An accurate prognostic model of who will develop posttraumatic stress symptoms does not exist yet. Additionally, no scalable and cost-effective method that can be easily integrated into routine care exists, even though especially the acute care setting provides a critical window of opportunity for prevention in the so-called golden hours when preventive measures are most effective. In this review, we aim to discuss emerging machine learning (ML) applications that are promising for precisely risk stratification and targeted treatments in the acute care setting.

The aim of this review is to present examples of digital health innovations and to discuss the potential of these new approaches for treatment selection and prevention of posttraumatic sequelae in the acute care setting. The application of artificial intelligence-based solutions have already had great success in other areas and are rapidly approaching the field of psychological care as well. New ways of algorithm-based risk predicting, and the use of digital phenotypes provide a high potential for predicting future risk of PTSD in acute care settings and to go new steps in precision psychiatry.

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Conflicts of interest
None of the authors has any conflict of interest to declare.

Keywords

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Introduction

The Emergency Department (ED) is the frontline of the health care system, and often the earliest point of entry in the health system for patients treated for diverse and potentially life-threatening acute traumatic events. ED clinicians are tasked with delivering high-quality care while working in demanding clinical environments that may be crowded and highly stressful (Asplin et al., 2003). There are approximately 40 million ED visits annually in the U.S. after potential trauma exposure (McLean et al., 2019) leading to not just significant physical morbidity but also adverse mental health effects as 30% of ED patients exposed to trauma report moderate-to-high symptom severity of post-traumatic stress disorder (PTSD) one year after discharge (Lowe et al., 2020). The psychological sequelae of life-threatening events are not limited to the traumatic domain. Patient populations surviving acute medical emergencies are also at risk for long-term adverse psychological outcomes including patients with cardiovascular events. Acute coronary syndrome (ACS) describes a spectrum of cardiovascular diseases including acute myocardial infarction or unstable angina (Fanaroff et al., 2015). As shown in a meta-analysis of 2,383 patients they found that 1 out of 8 patients with suspected ACS develop PTSD (Edmondson et al., 2012). The development of PTSD after an ACS or stroke is associated with negative health outcomes, for instance, higher rates of recurrence of cardiovascular diseases (Musey Jr et al., 2020; Schultebraucks et al., 2020c).

It is well-known that PTSD is a particularly complex disorder with up to 636,120 different possible manifestations (Galatzer-Levy and Bryant, 2013). Numerous biological factors contribute to recent theory development of PTSD (Heim et al., 2018). Several studies have identified diverse risk factors early after the traumatic event (Galatzer-Levy et al., 2013; Galatzer-Levy et al., 2014; Galatzer-Levy et al., 2017; Karstoft et al., 2015; Papini et al., 2018; Segman et al., 2005; Shalev et al., 1998; Yehuda et al., 1998), such as biological factors (Heim et al., 2018; Hinrichs et al., 2019; Mellon et al., 2018; Michopoulos et al., 2019; Morris et al., 2016; Ressler, 2018), e.g., stress response and threat perception (Heim et al., 2018; Mellon et al., 2018; Morris et al., 2016; Ressler, 2018; Schultebraucks et al., 2019; Van Zuiden et al., 2012), psychophysiological arousal (Hinrichs et al., 2019; Shalev et al., 1998), inflammation, and immune response (Mellon et al., 2018; Michopoulos et al., 2019; Michopoulos et al., 2017), and psychosocial risk factors (Shalev et al., 2017) for PTSD. Other discussed risk factors for PTSD involve the acute care environment in which patients are treated. Recent work has found that factors of the ED environment, such as hourly ED occupancy rates have been shown to increase PTSD risk after ACS (Edmondson et al., 2014; Edmondson et al., 2013). Given the rich diversity and heterogeneity of risk factors, typically, these factors are difficult to integrate into a unified quantitative regression model due to high-dimensionality and potential multicollinearity of candidate predictors (Huys et al., 2016).

A reliable and precise predictive model is a facilitator for evidence-based treatment allocation as it will allow the timely targeted intervention (Roberts et al., 2010; Shalev and Barbano, 2019) within the "golden hours" (Carmi et al., 2016; Vermetten et al., 2014; Zohar et al., 2011) early after the traumatic events, such as an early exposure intervention in the ED hours after the traumatic event took place (Rothbaum et al., 2012; Rothbaum et al., 2014), early internet-based intervention (Mouthaan et al., 2013) and pharmacological interventions (Carmi et al., 2016; Vermetten et al., 2014; Yehuda et al., 2015). In this early phase, several critical pathogenic processes take place such as the neuroendocrine stress sensitization and manifold neurobiological alterations (Heim et al., 2018) that can become targets for early preventive interventions before the biological responses have become more permanent changes (Shalev and Barbano, 2019). In consequence, the ED provides an important window to proactively plan risk-based follow-up care for trauma survivors at an early stage, where patients are still in contact with the healthcare system.

Despite the evidence for the presence of significant psychological and physical morbidity and mortality associated with posttraumatic stress symptoms following acute medical/ traumatic events, screening is currently limited in the ED setting. Several longitudinal cohort studies identified risk factors in the ED acute care setting by using clinical screening (Lowe et al., 2020; McLean et al., 2019; van der Mei et al., 2020) only 7% of EDs nationwide regularly screen for symptoms of PTSD (Love and Zatzick, 2014). The acute care setting in the ED is characterized by a high pace and acute care demand therefore time-consuming screenings are often not feasible. Therefore, automatable computational methods that provide precise risk prediction at scale are indicated for informing prevention PTSD after traumatic events in the acute care setting. The review aims to discuss recent advancements in algorithm-based risk stratification and digital phenotyping and their benefits for precision psychiatry in the acute care setting.

Automatable methods integrated into clinical care

Machine learning (ML) approaches for data-driven exploratory analysis offers unique opportunities for knowledge discovery and predictive modeling (Schultebraucks and Galatzer-Levy, 2019). In past years, a large number of early factors immediately after trauma have been examined as candidate predictors for PTSD susceptibility and multiple independent studies have shown that early factors comprise significant predictive signals to discriminate clinically meaningful trajectories of symptom development or long-term risk (Galatzer-Levy et al., 2013; Galatzer-Levy et al., 2014; Galatzer-Levy et al., 2017; Karstoft et al., 2015; Papini et al., 2018; Segman et al., 2005; Shalev et al., 1998; Yehuda et al., 1998).

However, no clinical prediction model is yet available to be used directly in the acute care setting without additional clinical screening or diagnostic interviews in an already clinical and resource stretched setting (van der Mei et al., 2020). This lack significantly impedes the feasibility of clinical risk prediction models under conditions of ED overcrowding, large-scale emergency events, disasters, and epidemic outbreaks. The SARS-CoV-2 pandemic and future similar situations are a paradigm case illustrating the critical need to support highly

charged EDs through computational methods to identify the possible risks of long-term mental health care needs.

In response to this fact, a vital public mental health funding objective of the NIMH is to enable "practical, scalable, and sustainable mental health screening and triage, and providing interventions at scale" (Gordon and Borja, 2020). The National Institute of Mental Health (NIMH) has funded a large multi-site consortium to collect data to build generalized models of posttraumatic stress courses (McLean et al., 2019; NIMH, 2016). Similarly, military agencies are engaged in large initiatives to identify and predict risk for PTSD in soldiers deployed to warzones (Dean et al., 2019; Schultebraucks et al., 2020a; van der Wal et al., 2019). The use of ML-algorithms for the improvement of prognosis directly implemented into the ED is a new and emerging field aiming to prevent trauma-related stress pathology at first contact with the health system. Schultebraucks et al. (2020b) demonstrated that readily available data such as vital signs and lab tests abstracted from electronic medical records yield probabilistic information to discriminate patients with high non-remitting PTSD symptoms vs. patients with low symptoms (resilience). The authors recruited participants in two Level-1 Emergency Trauma Centers in the U.S. The model development sample was collected at Grady Memorial Hospital, Atlanta, Georgia (N=377), and the external validation sample was collected at Bellevue Hospital Center, New York, New York (N=221). The predictive model achieved high accuracy to discriminate PTSD trajectories of non-remitting symptoms vs. resilience using data from electronic medical records including biological markers from blood sampling along with four items from a validated stress questionnaire (discovery dataset, N=377, f1-score=0.85, AUC=0.85), and equivalent accuracy on the independent test set (Validation dataset, N=211, f1-score=0.86, AUC=0.86) (Schultebraucks et al., 2020b). These findings support the feasibility to develop and validate clinical prediction models using readily available data collected directly in the ED and show that important predictors of adverse mental health effects after trauma exposure can be used by utilizing routinely collectible data (Schultebraucks et al., 2020b). Since this algorithm is based on psychometric data of a four-item stress questionnaire it is not yet fully automated. However, it is very promising to further explore whether routinely collected data from electronic medical records alone is sufficient to predict PTSD risk with high discriminatory accuracy and there is a large-scale project funded by the National Institute of Health that promises to provide further evidence to test the potential of this research avenue (McLean et al., 2019).

This builds on a larger vision of how computational psychiatry can lead to new directions to prognosticate who is at risk at the early onset directly after the traumatic event took place when the patients are still in contact with the health care systems and follow-up care can be planned (Fig. 1). Eventually, this may open new ways for precision psychiatry at scale and directly implemented into the electronic medical system of the acute care setting. These initially promising findings will need to be extended to the broad clinical population of ED patients from routine practice and to other types of acute emergencies such as ACS or stroke to demonstrate the full potential as an automated clinical readout of posttraumatic risk.

In general, large hospital systems are currently actively working to identify novel automatable methods that can be integrated into the standard of care to improve patient

outcomes and to decrease the long-term costs to the hospital system (Horwitz et al., 2019). It is important for future research to leverage such big data in the hundreds of thousands or millions of patients who are routinely cared for in the ED so that the predictive models can develop their full potential.

Digital health

In addition to algorithm-based prediction models directly integrated directly into health systems such as large hospital EDs, new and flexible modalities to use artificial intelligence (AI) and ML offer novel opportunities to collect behavioral data and to of maladaptive stress responses. By using deep learning to integrate multi-model information from digital devices such as smartphones or smartwatches, new horizons emerged to identify transdiagnostic markers to remotely identify and monitor individuals at risk (Carmi et al., 2020). Digital phenotyping refers to new computerized methods for objectively measuring behavior and emotions via human-computer interaction or by passively extracting predictive features of facial expression, voice, and speech content using computerized processing of audio and video data in situ from wearables, smartphones, and other personal digital devices (Insel, 2017a; Onnela and Rauch, 2016). Digital phenotyping capitalizes on innovations in computational psychiatry to unlock the diagnostic and prognostic potential of digitally captured biomarkers (Fig.2). The clinical value of digital biomarkers is to enable self-monitoring of psychopathology signs and enables low threshold remote diagnostic screening that may reduce barriers to successful intervention. This facilitates efficient allocation of prevention measures and is of high relevance in circumstances of crisis such as infectious disease, pandemics, or other natural catastrophes.

There are in general two broader types of applications: (1) digital phenotyping technologies to measure behavior by using AI technology to identify and predict psychological functioning and (2) digital technology for communication and provision of clinical care, such as telehealth applications for remote patient evaluations by clinicians and clinical monitoring or automated passive clinical monitoring and intelligent algorithm-based "chatbots" (Carmi et al., 2020; Marzano et al., 2015; Vaidyam et al., 2020).

AI-based digital phenotyping is using real-world data that is rapidly evolving in volume, velocity, and veracity as sensors of wearables have become more precise and very widespread. In the area of digital phenotyping, there are in particular two types of different data sources, active (Smart Active Monitoring – SAM) and passive data sources (Continuous Passive Monitoring – CPM). Passive data include behavioral patterns that are identified through the usage of the mobile device. Examples are the use of GPS, Glonass or Galileo data to monitor behavioral activation and avoidance (Glenn and Monteith, 2014; Torous et al., 2015), to use smartphones or wearables to monitor sleep and physiological states (Onnela et al., 2018) but also to use keystroke activity, taps and swipes to passively assess cognitive functions via smartphone apps (Dagum, 2018). Active data sources include information such as facial, speech, and voice data (Insel, 2017b). Facial expressions convey important information about the emotional and mental states of a person with decades of neuropsychological research showing that emotional expression and valence contain probabilistic information of diverse forms of psychopathology (Gaebel et al., 1992; Gehricke

and Shapiro, 2000; Renneberg et al., 2005). Speech and voice are additional channels conveying probabilistic information about mental health (Cannizzaro et al., 2004; Cohn et al., 2009; France et al., 2000; Leff and Abberton, 1981). Further, digital approaches can also be used to collect detailed information by monitoring patients in their daily lives repeatedly over time, i.e., Ambulatory Assessment and Ecological Momentary Assessment (Doherty et al., 2014; Stone and Shiffman, 1994) for assessing behavioral and cognitive processes in their natural settings by using smartphone diaries or measuring physiological function, and physical behavior via accelerometers, or GPS trackers (Reichert et al., 2020; Trull and Ebner-Priemer, 2013).

Digital communication also offers the opportunity to administer clinical intervention via telehealth applications. These approaches are using AI and natural language processing to perform assessments as well as clinical interventions (Carmi et al., 2020). However, even when telehealth promises to allow broader and faster mobilization of clinical resources, it is difficult to perform complex and deep conversions. COVID-19 in particular has shown that new ways of not only risk stratification but also remote patient care must take place. However, digital health procedures such as remote cognitive behavioral therapy or "chatbots" (Marzano et al., 2015) still require broader evidence-based validation, e.g., through the use of randomized controlled trials or at least pragmatic clinical trials (Chang et al., 2020).

Digital phenotyping and digital communication might have crucial relevance for monitoring, diagnostic, and identification of behavioral patterns to allow low-threshold and timely targeted prevention strategies and optimized allocation of relevant resources and interventions (Insel, 2017a). These uprising trends are promising especially for PTSD research to identify reliable and ecologically valid signatures of stress pathology and prognostic markers of clinical functioning and to develop novel patient-oriented outcomes that complement the traditional quality of life measures by digital augmentation. Powerful open-source methodologies for face detection and speech recognition have made pre-trained neural nets available for academic research. A recent study by Schultebraucks et al. (2020e) used digital phenotypes to classify PTSD and depression in trauma survivors who were admitted to the ED after a traumatic event. A brief video-recorded semi-structured interview was used to objectively capture voice, speech, head movement, gaze, pupil dilation, and facial landmark features of emotion in trauma-survivors who were admitted to a Level 1 trauma center. The video-recording was decomposed into different modalities using separate neural nets to extract predictive information from independent verbal and non-verbal information channels. Facial recognition software was applied to identify emotional expressions and combined with deep learning-based analysis of voice prosody and speech content. Subsequently, the candidate predictive features were combined to systematically discover predictive signatures across multiple modalities spanning facial, voice, speech content along with head and eye movement. Similar to human beings that process emotional information in human interaction in an automated way using both verbal and non-verbal cues, the idea in this digital phenotyping approach is to combine multiple information channels. The aim was to define multi-model signatures extracted from free-speech video recordings that can be used as digital biomarkers in an lightweight and potentially automatble assessment. The benefit of deep learning is that a model trained on one dataset

can easily "transferred" to another dataset and the existing model can be further adapted using the information of the new data. This is called "transfer learning" (Pratt, 1993) and the key drive of the great success of deep learning for tasks such as voice or speech recognition. This form of transfer learning can overcome some of the limitations of deep learning in clinical research such as the traditional "small" sample size of high-quality clinical research data. For example, while face recognition requires large amounts of independent samples to train a deep neural net from scratch, this task can be successfully performed on publicly available data outside of the clinical research context. Once the neural net has been successfully trained to detect faces and facial expressions in a non-clinical context, it can then be transferred to a clinical sample and adapted to perform specialized tasks such as the discrimination of clinically informative signatures in facial expression.

The potential of digital phenotyping based on deep learning has been explored by using face, voice and speech content to classify PTSD and depression (Schultebraucks et al., 2020e). The same approach has also been used to explain variance in predicting cognitive functioning (Schultebraucks et al., 2020d). A big advantage of this approach is its flexibility by making use of transfer learning and the possibility to adapt existing pre-trained neural nets to specific clinical tasks.

These results show that digital phenotyping might be an alternative to clinician-administered interviews or subjective self-reports — with high potential to develop an objective, flexible, economical, and ecologically valid digital biomarker.

To identify digital biomarkers of affect and arousal that are digital proxies for depression, PTSD, or cognitive functioning is of timely relevance. The recent events of the COVID-19 pandemic have only underlined the pressing need to rethink traditional approaches and to offer new opportunities for remote diagnosis and monitoring of psychiatric disorders. A digital biomarker approach has the potential to deliver a sensitive and objective measure and therefore low-threshold prevention. In consequence, time-to-treatment may be reduced, and interventions can be targeted more precisely to individual needs. The field of psychiatry has not yet benefitted from the new methods of digital phenotyping in the same way as fields such as cancer research where it is successfully used to detect differential recovery trends after surgery (Panda et al., 2020). Early application to schizophrenia (Henson et al., 2020), bipolar disorder, substance abuse, and risk of suicide (Huckvale et al., 2019) are very promising and show that the best of precision psychiatry is yet to come as researchers will continue to leverage digital methods to unlock clinical actionable targets for prevention methods in other fields of psychiatry as well.

Challenges of the application of ML

One reason why the field of psychiatry has not yet benefitted from the new methods of digital phenotyping may be suspected in the relative complexity of clinical phenotypes in psychiatry. Advances in psychiatric classification for research are promising for digital phenotyping in psychiatry (Insel et al., 2010; Insel, 2017a). Yet, the complexity of clinical phenotypes in psychiatry, often spanning multiple levels of explanations including individual factors (e.g. genetic and biological factors, or personality traits), social factors (e.g.

environmental and cultural influences) and complex interactions thereof, comes at cost of leading to complex models that can be very demanding to interpret and comprehend.

As with all methodology used in clinical research, ML has to ensure that the results are robust and reproducible, the design is rigorously planned and the analytical approach is transparent (Nosek et al., 2018). While the flexibility of ML is a big advantage to identify novel diagnostic and prognostic information and to develop accurate and robust digital biomarkers, the associated algorithmic complexity is a significant challenge for the field. The use of open-source software can facilitate the critical appraisal of the strength and weaknesses and is important to allow the independent assessment including the examination of hidden pitfalls and sources of algorithmic biases (Obermeyer et al., 2019). However, there remain limitations of model transparency that simply reflect the mathematical sophistication required for understanding deep learning. These methods often approximate non-linear associations of multiple variables using mathematical equations whose functional form is not pre-specified beforehand but empirically discovered in a data-driven way. Where well-understood prior findings are available, e.g. empirical effect sizes of univariate linear relationships between a predictor and the outcome-of-interest, this information can be of high value to design ML models and to increase the transparency and credibility of the results, it is desirable, also for ML approaches, to make use of hypotheses that are based on clinical insights and prior knowledge. However, this is not always possible with high-dimensional data and exploratory data analysis is therefore also of high importance (Tukey, 1980). For ML, cross-validation, bootstrapping, and external validation sets must be used to ensure generalizability and replicability (Efron and Gong, 1983). Given these precautions to prevent overfitting the ML models to particularities in the data (Cawley and Talbot, 2010), the advantage of flexible ML methods can be used to study complex interactions of multiple factors that go well beyond testing univariate linear associations. Importantly, there are existing solutions aiming to better understand complex ML models, such as SHapley Additive exPlanation (Lundberg and Lee, 2017). These approaches can help to increase the confidence in ML models by approximating complex mathematical functions by simpler ones (i.e., better understandable proxy models) that are approximately correct but offer increased human interpretability. For instance, the influence of a particular variable on the predictions of a particular model can be studied post hoc by systematically changing the values of the variable and then observing the change in the model output. Using large computational power, these can be repeated for each variable and for all permutations of dropping variables from a complex model to better understand each variables unique contribution to the prediction. In clinical care, where human understanding is important for shared decision-making of patients and care providers, it will remain an important challenge for ML approaches to make use of such interpretable ML approaches (Roscher et al., 2020) so that patients can be informed on which clinical variables the predicted outcome is derived from.

Conclusion

Computational and informatics-driven approaches have previously yielded clinically actionable results in many health contexts, from improving the diagnosis of stroke (Petrone, 2017), congenital disease recognition through facial recognition (Gurovich et al., 2018), and

the more precise allocation of preventive surgery in breast cancer (Bahl et al., 2017). In the context of psychiatric and behavioral pathology, new computational and AI-based approaches are starting to translate into the field of stress pathology. The unprecedented popularity of digital devices will allow the application of these new approaches to identify novel digital and biological markers for timely and precisely targeted psychological interventions, remote monitoring, and telehealth counseling.

Especially, the acute care setting provides an important opportunity and setting for automated risk stratification and individualized treatment allocation as part of precision psychiatry. The use of algorithm-based prediction models using routinely collectible data that can be automatically abstracted from electronic medical records will bear a high clinical potential for targeted and actionable clinical insight at the point of care. This approach to computational psychiatry and medicine might lower the threshold for the implementation of precision psychiatry at scale and to make the research available to clinicians at the time when prognostic information is most relevant for planning preventive measures using a risk-based approach. Despite the pace of recent advancements, some challenges remain. In particular, secure data protection, data-sharing for research purposes under adequate privacy protection, and the fair use of available datasets need to be realized on a large scale. Clinically heterogeneous, population-based datasets need to become available more easily to continue the facilitation of research innovation in precision psychiatry. Ultimately, digital phenotyping approaches will greatly impact and improve the precision and cost of diagnostic and prognostic screening and will provide a risk-based approach to treatment selection and preventive care in psychiatry.

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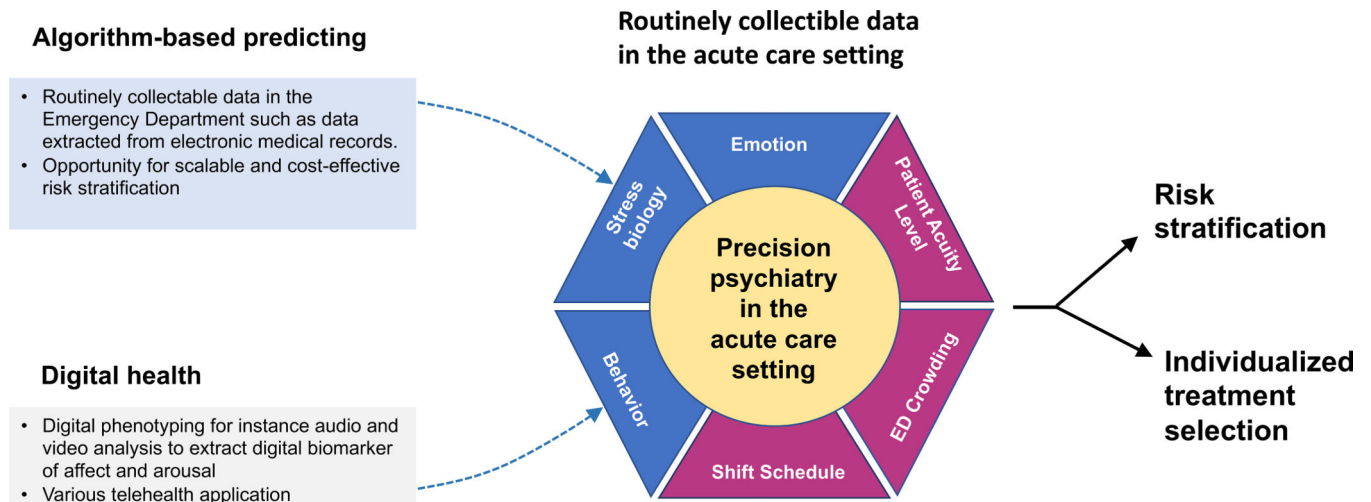
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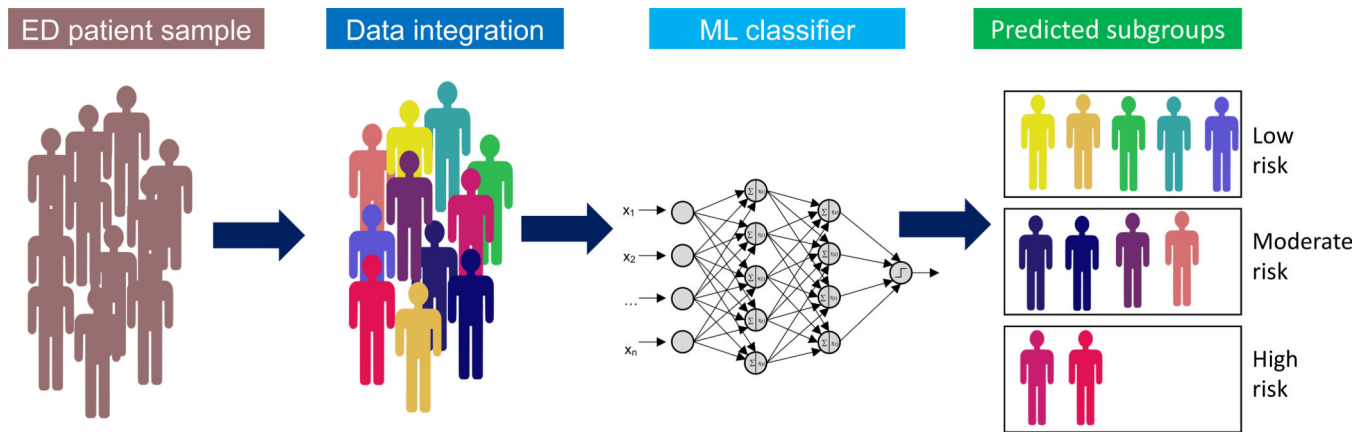
Figure 1.
Schematic depiction of the automated algorithm-based risk stratification in the ED for predicting high, moderate, and low risk patients.

Algorithm-based predicting

- Routinely collectable data in the Emergency Department such as data extracted from electronic medical records.
- Opportunity for scalable and cost-effective risk stratification

Routinely collectible data in the acute care setting

Digital health

- Digital phenotyping for instance audio and video analysis to extract digital biomarker of affect and arousal
- Various telehealth application

Emotion · Patient Acuity Level · ED Crowding · Shift Schedule · Behavior · Stress biology

Precision psychiatry in the acute care setting

Risk stratification

Individualized treatment selection

Figure 2.

Shematic picture of the conceptual model for algorithm-based prediction and digital health. Integration of routinely collectible data provides informative data about diverse domains relevant to the acute care setting encompassing behavior and emotion through digital phenotyping, markers of stress biology obtained from diagnostic blood draws in the ED and contextual information about the index event as well as the ED environment. Togehter, the integration of multiple sources of information yields promise to unlock the potential of precision psychiatry for improving risk stratification and individualized treatment selection.