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PRECISION MEDICINE IN PSYCHIATRY (S KENNEDY, SECTION EDITOR)

Precision Medicine and Suicide: an Opportunity for Digital Health

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Abstract

Purpose of Review A better understanding of suicide phenomena is needed, and precision medicine is a promising approach toward this aim. In this manuscript, we review recent advances in the field, with particular focus on the role of digital health.

Recent Findings Technological advances such as smartphone-based ecological momentary assessment and passive collection of information from sensors provide a detailed description of suicidal behavior and thoughts. Further, we review more traditional approaches in the field of genetics.

Summary We first highlight the need for precision medicine in suicidology. Then, in light of recent and promising research, we examine the role of smartphone-based information collection using explicit (active) and implicit (passive) means to construct a digital phenotype, which should be integrated with genetic and epigenetic data to develop tailored therapeutic and preventive approaches for suicide.

Keywords Suicide · Attempted suicide · Precision medicine · Mobile health · Big data · Ecological momentary assessment

Introduction

Suicide is arguably one of the most complex phenomena in the field of psychiatry. Despite being prioritized in research agendas [1], suicide continues to rank among the top ten preventable causes of death worldwide [2]. In fact, in several different countries over the past 50 years, suicide rates have remained stable or have even increased [3, 4].

After years of scientific research, many risk factors for suicide have been identified. Unfortunately, however, none has been found to be useful for predicting suicide or suicide attempts in clinical settings [5–7]. One recent meta-analysis highlighted how the capacity of known risk factors to predict suicide or suicide attempts in follow-up studies has not improved 50 years of research [8•]. The authors further point out how previous research has paid scant attention to the interaction between risk factors or short-term risk [8•]. In addition, classic risk factors tend not to change over time and have limited usefulness in short-term risk prediction of suicide [9, 10].

In light of these disappointing results, many researchers currently advocate for a change in the conceptualization of suicide risk and stress the need for new approaches. Some proposals include a strategy in which machine learning–based algorithms identify those at risk [8•], while others underscore the role of new technologies [11•], and shift from predict suicide based on risk stratification to focusing on the individual patient [12]. This is, in fact, a challenging scenario in which precision medicine may play a crucial role.

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This article provides an overview of precision medicine applied to suicide risk monitoring, focusing on the role of innovative technological approaches, especially to the extent that precision medicine and e-health go hand-in-hand. Furthermore, findings that point to the need to integrate genetic information and data from technological sources are also discussed.

Precision Medicine and Why Precision Medicine Is Necessary in Suicidology

In contemporary medicine, most treatments are designed for the "average patient," in a kind of "one-size-fits-all" procedure [13] (Fig. 1). Precision medicine, formerly known as personalized medicine, focuses on tailoring efficient preventive and therapeutic approaches to the unique characteristics of each patient [14]. To achieve this, precision medicine must integrate different sources of input, i.e., genetic and epigenetic data, clinical symptomatology, biomarkers, and environmental and lifestyle factors [15]. This scenario has led to a gap between the ability to collect and store huge amounts of data and the capacity to interrogate these data in a way that is useful for the "average clinician." As a result, an integrative approach that encompasses the fields of medicine, biology, engineering, and bioinformatics is crucial [16•].

Precision medicine ranges in scope from the description of large, homogeneous groups to N-of-1 trials, in which an expansive set of data is collected for one single person as frequently as possible [17]. In the end, precision medicine is to return to the Hippocratic aphorism of "there are no illnesses but people with illnesses" as the clinician knows so well.

In psychiatry, clinicians and researchers constantly question the validity of diagnoses [18], and many psychiatric disorders are heterogeneous syndromes rather than specific diseases, thus making them important targets for precision medicine [19]. That is of special importance for suicide, which, in addition to being heterogeneous, is a transdiagnostic phenomenon [20, 21].

With diagnoses based on symptom clustering, such as those used in the ICD and DSM, psychiatry may never reach the degree of specificity now emerging in other fields of medicine [22•]. To address this limitation, the National Institute of Mental Health's Research Domain Criteria (RDoC) [23], created in 2011, have become an alternative to current diagnostic systems [22, 24]. As Torous, Onnela, and Keshavan pointed out, connected devices (e.g., smartphones, wearables) can capture distinct units of analysis of the NIMH's RDoC framework [24]; this vast amount of data, these digital footprints [25], which define a digital phenotype [24], should be used to complement the other sources for precision medicine. Given the nearly ubiquitous ownership of mobile phones among the world population [26], technology is set to become ever more important in precision medicine (Fig. 2).

Specialists in suicidology have advocated for the introduction of precision medicine to improve prevention at the individual level [2] and in the short term [27•]. Currently, risk factors are often assessed at a single given moment [11]. Precision medicine could provide us strategies that facilitate the collection of repeated measures over time, which could be harnessed to assess, and consequently prevent risk in the short term or even in real time [20]. As Bernanke, Stanley, and Oquendo recently argued, suicidal behavior may be the final pathway for many different pathological processes [28], but empirical evidence is still needed to confirm this. Therefore, precision medicine is required in suicidology to better describe the phenomenon and to improve preventive approaches.

Precision Medicine and m-Mental Health: Collection and Analyses of Environmental Information

Technology and its application to health (e-health and m-health) play a key role in characterizing the individual phenotype that precision medicine requires. Here, ecological momentary assessment (EMA) is of special interest. EMA enables participants to be assessed in real-world settings and in real time, allowing researchers and clinicians to collect a high number of repeated observations over time, even multiple times a day, in the context of the immediate and real environment of the patient, just in the moment when the event is happening [29]. EMA is not new, and traditionally, assessments looking to gather the same data used paper-and-pencil questionnaires repeated over time; more recently digital devices such as personal digital assistants (PDAs) have replaced manual means [30, 31]. Using PDAs, Husky et al. described environmental and behavioral factors associated with suicidal ideation in patients post-discharge following hospitalization for a suicide attempt [31]. Technological advances and the ubiquity of smartphones, which are owned by 3 billion people

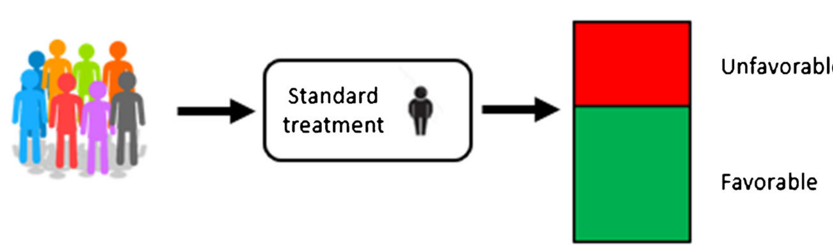

Fig. 1 Traditional medicine

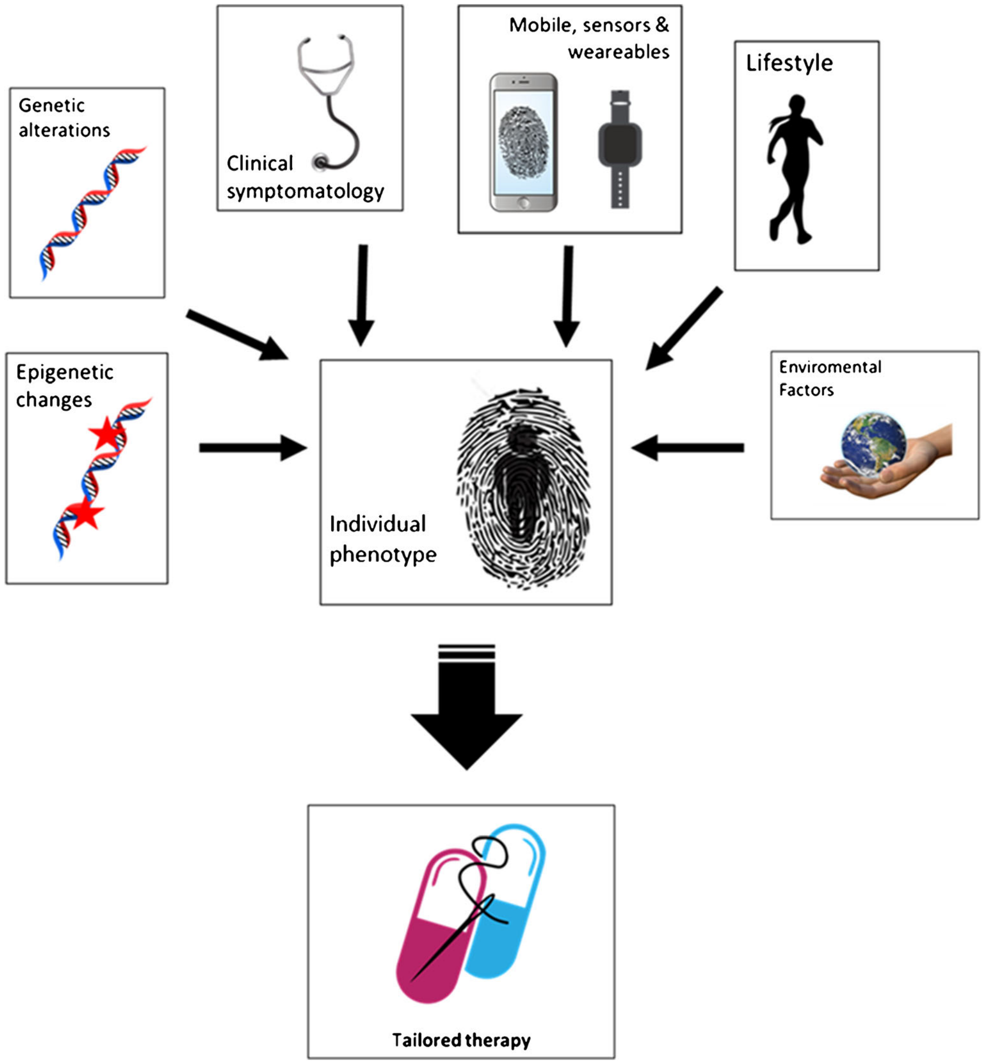

Fig. 2 Precision medicine

worldwide, [26] create an opportunity for EMA to be integrated in patient assessment, doing so in a natural and non-intrusive manner. Using mobile devices, questionnaires on the precise current status of patients can be explicitly administered, providing dynamic monitorization of feelings, stressful situations, and much more [32]. Furthermore, smartphone sensors allow researchers to collect data such as movement and location, app use, phone calls, use of social networks, or actigraphy information, which acts as a proxy for someone's physical and social activity or even sleep patterns. All this is done in a much less intrusive way, making these measures a sort of "implicit EMA" [33]. The combination of both sources of information, that is, explicit (active) and implicit (passive) EMA, yields an impressive quantity of valuable information to characterize people's behavior and develop the individual's digital phenotype [34].

After a period of underuse [35], EMA has proved to be a useful and, more importantly, safe instrument in suicide monitoring by repeatedly assessing suicidal thoughts with no negative impact on patients or increase in suicidal behavior itself [36, 37]. Moreover, technology is changing the clinician-patient relationship, and it now seems that "people are more honest with their phones than with their doctors" [38]. Indeed, evidence supports that people are more likely to reveal sensitive information such as traumatic events, substance use, or suicidal thoughts in online or smartphone-based questionnaires than in face-to-face interviews [39–41]. Furthermore, people with suicidal behavior seem to take well to EMA tools. In a recent project, we studied the profile of users of our own e-health ecosystem (www.memind.net) before they began using it. In a sample of almost 14,000 psychiatric outpatients, those who decided to use the tool were more likely to report suicidal thoughts and/or behaviors [42].

In 2013, a smartphone-based study of 36 patients with psychosis found that the instability of depression triggered thoughts of self-injury, whereas self-injurious thoughts predicted more stable depression [43]. In the last 2 years, six studies by three different research groups have provided relevant new findings about the nature and short-term predictors of suicidal thoughts and behavior using smartphone-based EMA [27•, 44•, 45•, 46•, 47•, 48•] (Table 1)

Table 1 Summary of 2017–2018 smartphone-based EMA studies on suicidal thoughts and behavior

Authors	Sample	Duration and frequency of assessment	EMA measures	Main findings
Kleiman et al., [27•]	Adults who had attempted suicide in the previous year ($n = 54$) Adult psychiatric inpatients admitted for suicide risk ($n = 36$)	28 days 4 assessments/day + event-contingent monitoring Length of hospital stay 4 assessments/day	**Suicidal ideation,** scored from 0 to 4: - The desire to die by suicide: "How intense is your desire to kill yourself right now?" - The intention to die by suicide: "How strong is your intention to kill yourself right now?" - The ability to resist the urge to die by suicide: "How strong is your ability to resist the urge to kill yourself right now?"	Great fluctuation in suicidal ideation over time Risk factors for suicidal ideation (hopelessness, burdensomeness, and loneliness) also varied over a few hours and correlated with suicidal ideation but did not predict short-term change in suicidal ideation
Kleiman et al., [44•]	Adults who attempted suicide at least once in the previous year ($n = 43$)	28 days 4 assessments/day + event-contingent monitoring	**Affect labels:** "Hopeless," "Burdensome" (not in sample 2), and "Lonely", scored from 0 to 4	Decrease in negative affect and an increase in positive affect when participants went from a period of experiencing suicidal thoughts to a period where they had no suicidal thoughts
Kleiman et al., [45•]	Adults with a history of suicide attempts over the previous year ($n = 51$) Inpatients with recent suicidal ideation or attempts ($n = 32$)	28 days 4 assessments/day Length of hospital stay 4 assessments/day	**Suicidal ideation** (SI), cored from 0 to 4: - The desire to die by suicide: "How intense is your desire to kill yourself right now?" - The intention to die by suicide: "How strong is your intention to kill yourself right now?" - The ability to resist the urge to die by suicide: "How strong is your ability to resist the urge to kill yourself right now?"	Five different phenotypes of suicidal thinking according to the intensity and variability of suicidal thoughts. Participants whose profile was characterized by more severe and persistent suicidal thoughts were most likely to have made a recent suicide attempt.
Hallensleben et al., [46•]	Inpatients with unipolar depression or current or lifetime suicidal ideation ($n = 20$)	6 days 10 assessments/day	Six constructs measured with 2 items, each one using a 5-point Likert scale: **Passive suicidal ideation (SI):** "Life is not worth living for me" and "There are more reasons to die than to live for me" **Active SI**: "I think about taking my life" and "I want to die" **Perceived burdensomeness (PB):** "I feel useless" and "…like a burden for others" **Thwarted belongingness (TB):** "I feel lonely" and "… like I do not belong" **Hopelessness:** "My future seems dark to me" and "I might as well give up because there is nothing I can do about making things better for myself" **Depression:** "I feel sad", "…downhearted"	Suicidal ideation was dynamic and followed a wide array of trajectories.
Hallensleben et al., [48•]	Inpatients with unipolar depression or current or lifetime suicidal ideation ($n = 74$)			Hopelessness and PB predicted passive SI and hopelessness; PB and the interaction PBxTB predicted active SI
Czyz et al., [47•]	Adolescents studied post-discharge after admission for suicide attempt and/or suicidal ideation ($n = 34$)	28 days 1 assessment/day (Survey was sent in an SMS containing a URL)	Two questions on suicide from a 32-item questionnaire: Suicidal ideation: "At any point in the last 24 h did you have any thoughts of killing yourself?" Suicidal behavior: "At any point in the last 24 h did you try to kill yourself or make yourself not alive anymore?" (If the answer was YES, participants were asked to indicate time intervals corresponding to all the times in the 24-h period they experienced suicidal thoughts and/or attempted suicide)	Survey adherence was 69% and decreased each week. In the month post-discharge, more teens reported suicidal thoughts using daily surveys compared to the end of the study Frequency and duration of suicidal ideation varied over time.

Although early data suggested suicidal ideation to be episodic, more recent findings show this is only one subtype of suicidal thoughts [49]. EMA data are beginning to produce evidence supporting the hypothesis that there are different profiles underlying suicide phenomena [28], and Kleiman et al. found five different patterns for suicidal thoughts according to their intensity and variability: low intensity and low variability, low intensity and moderate variability, moderate intensity and high variability, high intensity and low variability, and high intensity and high variability [44•].

The utility of smartphones does not rely solely on repeated prompts in the real-world environment, but also on the ability to implicitly capture information from multiple smartphone sensors, wearables, or social networks. Although this use has been widely discussed in terms of theory [50], this technology is just starting to be used in mental health, as Reinertsen and Clifford reported recently [51•]. Various research groups, including ours, have developed smartphone apps capable to collect sensors and data use information, that is, Automated Monitoring of Symptom Severity (AMoSS) [52], Purple Robot [53], Beiwe [54], or eB2 [33, 55]. The latter, used by our group, is an Android and iOS app which passively collects information on actigraphy data, global positioning system (GPS) location, Google location, app usage, phone calls and message logs, nearby Wi-Fi and Bluetooth devices, and inertial measurement unit signals [33, 55].

To date, information from smartphone's sensors has been used to characterize stress and anxiety, depression, bipolar disorder, schizophrenia, and post-traumatic stress disorder [51], but no work has specifically studied suicidal behavior. However, a study of violent thoughts and behavior by Ben-Zeev et al. is of special interest for suicidology, as the authors of the study combined explicit and implicit EMA in 27 inpatients at high risk for violence over 1 week; patients had to self-report thoughts and behaviors, including suicide ideation, whereas smartphone sensors captured their activity and location. Regarding suicidal ideation, the authors found it to be associated with violent ideation and with physical aggression toward an individual or individuals [56].

These technological advances of explicit and implicit EMA together with the use of data mining, neural networks, or machine learning methods may be used to generate valid information applicable for precision medicine [57, 58•]. In fact, in a recent study, our group developed sequential models based on neural networks for predicting suicidal ideation identified by clinicians in routine follow-up visits. The difficulty arises in modeling from two sources of asynchronous, length-variable, and randomly sampled sequences, such as electronic health records (completed by clinicians) and EMA (completed by patients in between medical appointments) [59].

Combining Genetic and Smartphone and Sensors Information for a Personalized Phenotype

The next and most challenging step is to combine EMA-based information and genetic and epigenetic findings in a meaningful way. Already complex, this endeavor is further complicated by the fact that there are a great many genes and genomic processes that can confer risk for suicidality, though none has been clearly established [60, 61].

Current research on the neurobiology of suicide supports a role for dysregulation in the serotoninergic and hypothalamic-pituitary-adrenal axis stress response system in suicide vulnerability, with a clear role played by epigenetic processes such as altered cortisol and glutamate pathways [62]. These processes are influenced by external psychological and social factors, which means that in the modeling of suicide risk, external environmental factors must necessarily be taken into account [63]. This highlights how the integration of EMA and genes may help clarify the complex interaction of multiple factors at play in the risk of suicide. As O'Connor and Portzky have very recently stated, "No single discipline can address the complex challenge of understanding risk, as suicide is the end product of a complex interplay of neurobiological, psychological, and social processes" [64].

To date, no research has integrated neurobiological and EMA information in the study of suicidal thoughts and behavior, but a compelling work by Niculescu et al. has approached it [65•]. The authors tested the ability of "universal blood biomarkers" to predict suicidal ideation and hospitalization in homogeneous groups (high anxiety, low mood, combined, and non-affective (psychotic)), depicted with a smartphone app assessment. They found phenotypic measures apps scores were better predictors than the blood biomarkers, although their combination showed synergy. Although this assessment is not EMA, as one single measure was taken, it may lay the groundwork for the integration of EMA and genetics. As an example from Alzheimer research, the Emory Healthy Aging Study aims to assess risk factors via health questionnaires, smartphones, and wearable devices, seeking to deeply phenotype a subpopulation every few years by profiling genetics, cardiovascular physiology, blood and spinal fluid biomarkers, and brain and retinal imaging [66]. These kinds of initiatives are also necessary in suicidology.

Concerns and Limitations to the Current State of Research

Firstly, and likely the most important issue, patients' privacy and confidentiality must be upheld while simultaneously ensuring their safety if suicidal risk is detected, taking into account personal autonomy [67]. Regarding data privacy, it depends on the specific apps. For example, in our MEmind encrypted volumes, which have a unique 256-bit key, the keys are protected by a key management infrastructure, which implemented strong logical and physical security controls to prevent unauthorized access. Data and associated keys were encrypted using the industry-standard AES-256 algorithm [42] and eB2 hash to anonymize phone numbers, email addresses, Bluetooth, and Wi-Fi media access control addresses using the SHA-1 algorithm, and the location and personal data were transformed using a non-invertible hash function [33].

Secondly, technological assessment as described here must be easily transferable to real-world clinical practice. In recent studies, patients have been compensated for their participation [27•, 44•, 45•, 46•, 47•, 48•], so studies under real conditions are required. Moreover, some research has been done in inpatient settings [27•, 44•, 46•, 48•], whereas the interest of EMA lies in being used in real environments. Of note, one limitation stems from the fact that there is evidence that EMA compliance decreases substantially after 1 to 2 weeks of assessment [68].

Thirdly, appropriate processing of these novel digital data is crucial, as Barnett et al. concluded [58]. Beyond being able to collect impressive amounts of data, if a proper analysis is not conducted, generalization and comparison of results between studies are going to be difficult.

Finally, future efforts should be made to integrate genetic and environmental factors. Moreover, clinical trials addressing the efficacy of EMA technologies in suicide research are warranted.

Conclusion

While the worldwide impact of suicidal behavior remains stable despite research efforts, precision medicine is emerging as a promising tool in suicidology. Precision medicine cannot be understood without the role of technological advances, which are already useful as a basis for digital phenotyping in suicide as well in other areas of medicine. The next challenge is to integrate genetic and epigenetic information. Furthermore, the collection and analysis of these "big data" must be refined before transferring this methodology to clinical settings. This will only be possible with a collaborative approach between clinicians, traditional researchers, bioinformatics specialists, and data analysts and, most importantly, with patient engagement and participation.

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Compliance with Ethical Standards

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Silverman MM, Pirkis JE, Pearson JL, Sherrill JT. Reflections on expert recommendations for US research priorities in suicide prevention. Am J Prevent Med. 2014;47:S97–S101.
2. Saxena S, Krug EG, Chestnov O, World Health Organization, editors. Preventing suicide: a global imperative. Geneva: World Health Organization; 2014.
3. Lee L, Roser M, Ortiz-Ospina E. Suicide [Internet]. Our World in Data. 2018 [cited 2018 Dec 9]. Available from: https://ourworldindata.org/suicide
4. Products - Data Briefs - Number 241 - April 2016 [Internet]. [cited 2017 Dec 14]. Available from: https://www.cdc.gov/nchs/products/databriefs/db241.htm
5. Large M, Sharma S, Cannon E, Ryan C, Nielssen O. Risk factors for suicide within a year of discharge from psychiatric hospital: a systematic meta-analysis. Aust N Z J Psychiatry. 2011;45:619–28.
6. Large M, Smith G, Sharma S, Nielssen O, Singh SP. Systematic review and meta-analysis of the clinical factors associated with the suicide of psychiatric in-patients. Acta Psychiatr Scand. 2011;124:18–29.
7. Chan MKY, Bhatti H, Meader N, Stockton S, Evans J, O'Connor RC, et al. Predicting suicide following self-harm: systematic review of risk factors and risk scales. Br J Psychiatry. 2016;209:277–83.
8.• Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, Huang X, et al. Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research. Psychological Bulletin. 2017;143:187–232 **This meta-analysis critically reviews 50 years of research in suicide factor risk study.**
9. Schaffer A, Isometsä ET, Azorin J-M, Cassidy F, Goldstein T, Rihmer Z, et al. A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: part II of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Aust N Z J Psychiatry. 2015;49:1006–20.

10. Glenn CR, Nock MK. Improving the short-term prediction of suicidal behavior. Am J Prev Med. 2014;47:S176–80.
11.• Torous J, Larsen ME, Depp C, Cosco TD, Barnett I, Nock MK, et al. Smartphones, sensors, and machine learning to advance real-time prediction and interventions for suicide prevention: a review of current progress and next steps. Curr Psychiatry Rep. 2018;20:51. **This paper is a revision of technological advances in suicide assessment and prevention.**
12. Mulder R, Newton-Howes G, Coid JW. The futility of risk prediction in psychiatry. Br J Psychiatry. 2016;209:271–2.
13. Reference GH. What is the precision medicine initiative? [Internet]. Genetics Home Reference. [cited 2018 Dec 16]. Available from: https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative
14. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease [Internet]. Washington (DC): National Academies Press (US); 2011 [cited 2018 Dec 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK91503/
15. Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. BMC Med. 2013;11:132.
16.• Beckmann JS, Lew D. Reconciling evidence-based medicine and precision medicine in the era of big data: challenges and opportunities. Genome Medicine. 2016;8:134. **This paper focuses on the importance of a collaborative approach in precision medicine.**
17. Schork NJ. Personalized medicine: time for one-person trials. Nature News. 2015;520:609.
18. Lilienfeld SO, Treadway MT. Clashing diagnostic approaches: DSM-ICD versus RDoC. Annu Rev Clin Psychol. 2016;12:435–63.
19. Fraguas D, Díaz-Caneja CM, State MW, O'Donovan MC, Gur RE, Arango C. Mental disorders of known aetiology and precision medicine in psychiatry: a promising but neglected alliance. Psychol Med. 2017;47:193–7.
20. Oquendo MA, Baca-García E, Mann JJ, Giner J. Issues for DSM-V: suicidal behavior as a separate diagnosis on a separate axis. Am J Psychiatry. 2008;165:1383–4.
21. Oquendo MA, Baca-Garcia E. Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. World Psychiatry. 2014;13:128–30.
22.• Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am J Psychiatry. 2014;171:395–7. **This paper proposes RDoC as a valid approach to precision medicine in psychiatry.**
23. NIMH Research Domain Criteria (RDoC) [Internet]. [cited 2018 Dec 8]. Available from: https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml
24. Torous J, Onnela J-P, Keshavan M. New dimensions and new tools to realize the potential of RDoC: digital phenotyping via smartphones and connected devices. Translational Psychiatry. 2017;7.
25. Bidargaddi N, Musiat P, Makinen V-P, Ermes M, Schrader G, Licinio J. Digital footprints: facilitating large-scale environmental psychiatric research in naturalistic settings through data from everyday technologies. Mol Psychiatry. 2017;22:164–9.
26. Poushter J. Smartphone ownership and Internet usage continues to climb in emerging economies [Internet]. Pew Research Center's Global Attitudes Project. 2016 [cited 2018 May 27]. Available from: http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/
27.• Kleiman EM, Turner BJ, Fedor S, Beale EE, Huffman JC, Nock MK. Examination of real-time fluctuations in suicidal ideation and its risk factors: results from two ecological momentary assessment studies. J Abnorm Psychol. 2017;126:726–38 **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**
28. Bernanke JA, Stanley BH, Oquendo MA. Toward fine-grained phenotyping of suicidal behavior: the role of suicidal subtypes. Molecular Psychiatry. 2017;22:1080–1.
29. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annual Review of Clinical Psychology. 2008;4:1–32.
30. Csikszentmihalyi M, Larson R. Validity and reliability of the experience-sampling method. J Nerv Ment Dis. 1987;175:526–36.
31. Husky M, Swendsen J, Ionita A, Jaussent I, Genty C, Courtet P. Predictors of daily life suicidal ideation in adults recently discharged after a serious suicide attempt: a pilot study. Psychiatry Res. 2017;256:79–84.
32. van Os J, Verhagen S, Marsman A, Peeters F, Bak M, Marcelis M, et al. The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. Depress Anxiety. 2017;34:481–93.
33. Berrouiguet S, Ramírez D, Barrigón ML, Moreno-Muñoz P, Camacho RC, Baca-García E, et al. Combining continuous smartphone native sensors data capture and unsupervised data mining techniques for behavioral changes detection: a case series of the Evidence-Based Behavior (eB2) Study. JMIR mHealth and uHealth. 2018;6:e197.
34. Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA. 2017;318:1215.
35. Davidson CL, Anestis MD, Gutierrez PM. Ecological momentary assessment is a neglected methodology in suicidology. Arch Suicide Res. 2016:1–11.
36. Husky M, Olié E, Guillaume S, Genty C, Swendsen J, Courtet P. Feasibility and validity of ecological momentary assessment in the investigation of suicide risk. Psychiatry Research. 2014;220:564–70.
37. Law MK, Furr RM, Arnold EM, Mneimne M, Jaquett C, Fleeson W. Does assessing suicidality frequently and repeatedly cause harm? A randomized control study. Psychol Assess. 2015;27:1171–81.
38. We're more honest with our phones than with our doctors. The New York Times [Internet]. 2016 Mar 23 [cited 2016 Apr 21]; Available from: http://www.nytimes.com/interactive/2016/03/26/magazine/100000004288446.embedded.html
39. Barak A. Emotional support and suicide prevention through the Internet: a field project report. Computers in Human Behavior. 2007;23:971–84.
40. Bennett GG, Glasgow RE. The delivery of public health interventions via the Internet: actualizing their potential. Annual Review of Public Health. 2009;30:273–92.
41. Torous J, Staples P, Shanahan M, Lin C, Peck P, Keshavan M, et al. Utilizing a personal smartphone custom app to assess the Patient Health Questionnaire-9 (PHQ-9) depressive symptoms in patients with major depressive disorder. JMIR Ment Health. 2015;2:e8.
42. Barrigón ML, Berrouiguet S, Carballo JJ, Bonal-Giménez C, Fernández-Navarro P, Pfang B, et al. User profiles of an electronic mental health tool for ecological momentary assessment: MEmind. Int J Methods Psychiatr Res. 2017;26.
43. Palmier-Claus JE, Ainsworth J, Machin M, Dunn G, Barkus E, Barrowclough C, et al. Affective instability prior to and after thoughts about self-injury in individuals with and at-risk of psychosis: a mobile phone based study. Arch Suicide Res. 2013;17:275–87.
44.• Kleiman EM, Turner BJ, Fedor S, Beale EE, Picard RW, Huffman JC, et al. Digital phenotyping of suicidal thoughts. Depress Anxiety. 2018;35:601–8. **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**
45.• Kleiman EM, Coppersmith DDL, Millner AJ, Franz PJ, Fox KR, Nock MK. Are suicidal thoughts reinforcing? A preliminary real-time monitoring study on the potential affect regulation function of

suicidal thinking. J Affect Disord. 2018;232:122–6. **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**

46.• Hallensleben N, Spangenberg L, Forkmann T, Rath D, Hegerl U, Kersting A, et al. Investigating the dynamics of suicidal ideation. Crisis. 2018;39:65–9. **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**

47.• Czyz EK, King CA, Nahum-Shani I. Ecological assessment of daily suicidal thoughts and attempts among suicidal teens after psychiatric hospitalization: lessons about feasibility and acceptability. Psychiatry Res. 2018;267:566–74. **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**

48.• Hallensleben N, Glaesmer H, Forkmann T, Rath D, Strauss M, Kersting A, et al. Predicting suicidal ideation by interpersonal variables, hopelessness and depression in real-time. An ecological momentary assessment study in psychiatric inpatients with depression. Eur Psychiatry. 2018;56:43–50. **This is one of the six recent studies using smartphone-based EMA in the study of suicide.**

49.• Kleiman EM, Nock MK. Real-time assessment of suicidal thoughts and behaviors. Current Opinion in Psychology. 2018;22:33–7. **This paper is a revision of technological advances in suicide assessment.**

50. Torous J, Onnela J-P, Keshavan M. New dimensions and new tools to realize the potential of RDoC: digital phenotyping via smartphones and connected devices. Transl Psychiatry. 2017;7:e1053.

51.• Reinertsen E, Clifford GD. A review of physiological and behavioral monitoring with digital sensors for neuropsychiatric illnesses. Physiol Meas. 2018;39:05TR01. **This is a comprehensive review of recent studies using sensors for monitoring neuropsychiatric illnesses.**

52. Palmius N, Tsanas A, Saunders KEA, Bilderbeck AC, Geddes JR, Goodwin GM, et al. Detecting bipolar depression from geographic location data. IEEE Trans Biomed Eng. 2017;64:1761–71.

53. Schueller SM, Begale M, Penedo FJ, Mohr DC. Purple: a modular system for developing and deploying behavioral intervention technologies. J Med Internet Res. 2014;16:e181.

54. Torous J, Kiang MV, Lorme J, Onnela J-P. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Mental Health. 2016;3:e16.

55. Evidence-Based Behavior [Internet]. Evidence-based behavior. [cited 2018 Dec 22]. Available from: https://eb2.tech/

56. Ben-Zeev D, Scherer EA, Brian RM, Mistler LA, Campbell AT, Wang R. Use of multimodal technology to identify digital correlates of violence among inpatients with serious mental illness: a pilot study. Psychiatr Serv. 2017;68:1088–92.

57. Wang F, Chen C. On data processing required to derive mobility patterns from passively-generated mobile phone data. Transportation Research Part C: Emerging Technologies. 2018;87:58–74.

58.• Barnett I, Torous J, Staples P, Keshavan M, Onnela J-P. Beyond smartphones and sensors: choosing appropriate statistical methods for the analysis of longitudinal data. J Am Med Inform Assoc. 2018;25:1669–74. **Here, authors highlight the importance of data analyses.**

59. Peis-Aznarte I, Olmos PM. Vera-Varela C. Barrigón ML: Courtet P, Baca-Garcia E, et al. Deep sequential models for suicidal ideation from multiple source data. Enviado para publicación; 2018.

60. Oquendo MA, Sullivan GM, Sudol K, Baca-Garcia E, Stanley BH, Sublette ME, et al. Toward a biosignature for suicide. AJP. 2014;171:1259–77.

61. Turecki G. The molecular bases of the suicidal brain. Nat Rev Neurosci. 2014;15:802–16.

62. Lutz P-E, Mechawar N, Turecki G. Neuropathology of suicide: recent findings and future directions. Mol Psychiatry. 2017;22:1395–412.

63. Turecki G, Brent DA. Suicide and suicidal behaviour. The Lancet. 2016;387:1227–39.

64. O'Connor RC, Portzky G. Looking to the future: a synthesis of new developments and challenges in suicide research and prevention. Front Psychol [Internet]. 2018 [cited 2018 Dec 22];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2018.02139/full

65.• Niculescu AB, Le-Niculescu H, Levey DF, Phalen PL, Dainton HL, Roseberry K, et al. Precision medicine for suicidality: from universality to subtypes and personalization. Molecular Psychiatry. 2017;22:1250–73 **This paper provides an approach to precision medicine in suicide from genetics.**

66. The Emory Healthy Aging Study | Emory University [Internet]. Emory | Healthy Aging Study. [cited 2018 Dec 23]. Available from: https://healthyaging.emory.edu/

67. McKernan LC, Clayton EW, Walsh CG. Protecting life while preserving liberty: ethical recommendations for suicide prevention with artificial intelligence. Front Psychiatry [Internet]. 2018 [cited 2018 Dec 23];9. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00650/full

68. Broderick JE, Schwartz JE, Shiffman S, Hufford MR, Stone AA. Signaling does not adequately improve diary compliance. Ann Behav Med. 2003;26:139–48.