Precision Medicine for Suicide Prevention:

It's Time to Take the Next Step

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Although suicide remains a worldwide public health crisis,[1] important advances have been made. Health care system-wide prevention strategies focused on risk identification and linkage to treatment are showing promise.[2,3] Randomized controlled trials (RCTs) point to multiple treatment options[4] that can be offered to individuals identified as high risk. However, there is no single path leading to death by suicide,[5] and treatment response is heterogeneous. Risk and protective factors, predictors, and moderators of outcome configure uniquely within individuals, a fact that is readily recognized by clinicians but not accounted for in outcomes focused on group-level averages.

The field can build on the availability of multiple evidence-based treatments for suicide prevention by moving toward a precision medicine approach to suicide prevention. Such an approach considers the person, their circumstances and underlying biology, treatment delivery context, and the static and dynamic conditions that contribute to the individual's risk for suicide. It marks a shift toward individual-level factors, in combination, that inform heterogeneous treatment effects, rather than group-level average effects.[6] Treatments recommended for high-risk individuals[4] often reduce risk for future suicide attempts by approximately half. Within this average, however, some individuals respond favorably, others experience some benefit, and still others do not benefit at all. If an individual has experienced only limited benefit from one treatment, they might receive greater benefit from a different approach. Precision suicide prevention seeks to address this by matching individuals to the most appropriate and beneficial treatment.

Treatment-matching is increasingly possible with recent advances in predictive modeling of treatment outcomes. Whereas earlier prediction studies typically used traditional statistical approaches and relatively few predictors, newer approaches often leverage machine learning to combine large numbers of predictors to identify individuals who are especially likely to benefit from a specific treatment. This work has been growing in psychiatry[7] and is beginning in suicide prevention. A secondary analysis of a recent suicide prevention psychotherapy RCT found that a machine learning–based, treatment-matching algorithm would have improved suicidal ideation outcomes by 13.6%.[8] Using a similar framework, we reanalyzed RCT data evaluating a suicide prevention mindfulness treatment and found that suicidal event rates were lowest among individuals assigned to the treatment arm predicted to be their "optimal treatment."[9] Although prospective trials will need to test these estimates, these predictive analytic applications represent actionable opportunities for existing, recent, and future suicide prevention RCTs to advance precision treatment-matching in suicide prevention.

Other actionable opportunities involve leveraging electronic health record (EHR) data to study suicide prevention strategies that are widely implemented within large health care systems. EHRs provide larger sample sizes for more stable prediction models, though they lack the randomization, standardized protocols, and assessment characteristics of RCTs.[10] A recent EHR analysis developed a treatment-matching algorithm for psychiatric hospitalization and found that some Veterans at risk for suicide benefited from hospitalization, but others did not.[11] Decisions to hospitalize based on the treatment-matching algorithm were estimated to reduce suicide attempts by 16%. In a follow-up EHR study, a similar framework was applied for predicting individual response to psychotherapy versus antidepressant medication.[12] It concluded that assigning treatments based on the algorithm could potentially reduce suicide attempts, suicide deaths, psychiatric hospitalizations, and emergency department visits by 7.7%, which can be substantial when scaled within a large health care system.

There have also been advances in the identification of novel predictors of suicide, including candidate predictors from biological and neurobiological domains (eg, genetics, inflammatory markers, neurocircuitry), to social determinants

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and geospatial factors.[13–16] Their utility to guide suicide prevention treatment selection is at an early stage of development, but promising studies are emerging.[17] One recent treatment-matching study found that two neurocognitive markers previously linked to suicide risk[13] were top outcome predictors.[9] These variables will likely be most useful for predicting suicide when combined with other factors, especially across domains.[7,17] Such multimodal integration remains challenging[18] but is one of the capacities for which machine learning methods hold promise.[7]

Challenges

Although the growing number of suicide prevention RCTs offer actionable opportunities to apply these precision treatment selection analyses, such efforts face two primary challenges. Most existing RCTs have sample sizes that are too small for developing stable prediction models.[10] Additionally, model accuracy across contexts needs to be established with external validation, but these efforts are rare and have proved challenging.[19] Suicide prevention RCTs also face natural limits on the predictor data that can be collected, such that they are not cost-prohibitive or overly burdensome to participants. Unfortunately, if common data elements are not evaluated across RCTs, comparative predictions between treatments and external validation become much more challenging. Therefore, there will be a need to prioritize among the numerous predictors and novel markers of suicide so that those that are most predictive, feasible, and cost-effective are made available across datasets.

Toward Solutions

To surmount these challenges, one proposed strategy involves iterating between EHR and RCT precision medicine analytics so that each approach informs the other.[10] RCTs remain the gold standard for determining efficacy and effectiveness of treatments, even within a precision medicine approach. However, large RCTs powered for precision medicine goals are expensive and difficult to implement. EHR analytics on suicide prevention treatments will help generate more stable algorithms that can later be tested in smaller, prospectively designed RCTs that would provide strong treatment-matching evidence if confirmed. This combined approach can also enhance RCT efficiency for selecting treatments, targets, or predictors of treatment response.[10] A similar iteration between RCTs allows for comparative treatment predictions, external validation, and prioritization of novel markers.

This research strategy will require considerable coordination among researchers, health care systems, clinicians, patient-level stakeholders, and research funding agencies. Learning Health Care Systems (LHSs) provide a well-suited infrastructure for this level of coordination. LHSs form a collaborative community of multiple stakeholders that work toward the goal of researching health care system innovations and integrating them into clinical care.[20] Research and health care data are applied in iterative cycles to evaluate, implement, and reevaluate continuous improvement. LHSs have had successes in suicide prevention,[21] and their infrastructure can be extended to support suicide prevention treatment-matching. This effort has begun at the Veterans Health Administration (VHA)[22] with a Suicide Prevention Learning Community focused on enhancing access to VHA administrative and clinical datasets to aid precision medicine approaches. Based on our early experience, we propose the following recommendations:

1. As done with evaluations of previous work,[11,12] apply predictive analytics to study widely implemented suicide prevention practices (eg, safety planning,[23] caring contacts[24]) within large health care systems that can be the subject of key treatment-matching questions. Who benefits most from which strategy, when, and in what context?
2. Form working groups with diverse expertise to develop proposed common data elements and increase data harmonization. Gather feedback from diverse stakeholders, ranging from clinicians and researchers, on novel predictors to prioritize for wider use. Informatics input on dataset interoperability will also be critical. In one example, one LHS gathered feedback from their network to develop common data elements and interoperability practices for studying early psychosis.[25]
3. Curate suicide prevention database resources to reduce duplications that are inefficient and result in inconsistencies that limit data harmonization. Data resources should span the domains of EHR and RCTs and include specialized data obtained from natural language processing and geographically based social determinants of health.[11] Similar to the Alzheimer's Disease Neuroimaging Initiative,[26] collect and bank biological and other novel data (eg, blood, saliva, neurocognitive), utilizing common protocols. Develop data governance to increase and manage researcher data access to these resources.
4. Develop a precision medicine clinical trial network and integrate it within the LHS model. A clinical trial network offers the capacity for well-powered trials, prospective evaluation of precision medicine treatment-matching algorithms, and a coordination framework to implement use of common data elements, novel markers, curated data resources, and predictive analytics across trials. While the issues to solve for precision

suicide prevention are unique, successes in other clinical trial networks illustrate the value of a coordinated RCT strategy.[27]

5. Finally, increase precision medicine-oriented implementation science, using collaborative approaches involving key stakeholders, especially providers and patients. Continuous assessment will be needed on ethical and legal considerations around clinical decision-making, patient-centeredness, treatment choice, and provision of assessment data.[28] These issues will likely need to be considered alongside concerns about opaqueness of machine learning–based clinical decision tools.[7]

The core principles of LHSs illustrate many of the building blocks that will be needed for a coordinated effort toward precision treatment-matching for suicide prevention. Capitalizing on opportunities for predictive analytics and building this methodological infrastructure can advance our state of suicide prevention care.

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