Review

Biological Psychiatry: GOS

From Computation to Clinic

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ABSTRACT

Theory-driven and data-driven computational approaches to psychiatry have enormous potential for elucidating mechanism of disease and providing translational linkages between basic science findings and the clinic. These approaches have already demonstrated utility in providing clinically relevant understanding, primarily via back translation from clinic to computation, revealing how specific disorders or symptoms map onto specific computational processes. Nonetheless, forward translation, from computation to clinic, remains rare. In addition, consensus regarding specific barriers to forward translation—and on the best strategies to overcome these barriers—is limited. This perspective review brings together expert basic and computationally trained researchers and clinicians to 1) identify challenges specific to preclinical model systems and clinical translation of computational models of cognition and affect, and 2) discuss practical approaches to overcoming these challenges. In doing so, we highlight recent evidence for the ability of computational approaches to predict treatment responses in psychiatric disorders and discuss considerations for maximizing the clinical relevance of such models (e.g., via longitudinal testing) and the likelihood of stakeholder adoption (e.g., via cost-effectiveness analyses).

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Translation of research findings into clinical settings to solve clinical problems is a primary challenge of modern psychiatry (1). This requires a coordinated effort between at least 3 constituencies: basic research ("bench"), clinical research ("bedside"), and the community ("stakeholders") (2). Within this framework, clinical insights and experience motivate novel basic research, while novel basic research motivates novel therapeutic approaches.

Computational psychiatry aims to use advances in computational cognitive neuroscience and machine learning to improve knowledge about mental health conditions and their treatment (3) and, as such, is an intrinsically translational field. However, the direction of translation so far has mostly been one-directional: from clinic to computation. Computational approaches have been deployed in many ways to shed light on the cognitive and neurobiological structure of established psychiatric descriptions and classifications, but rarely to discover novel descriptions or create new interventions. Closing this translational loop by bringing these insights back into the clinic encounters numerous challenges, many of which are faced by the broader neuroscience field in general (3). However, promising avenues for overcoming these challenges are now emerging using theory-driven, data-driven, and hybrid approaches. Here, we suggest new directions for research in this area, discuss challenges, and propose solutions to maximize translation from computation to clinic.

FROM THE BOTTOM UP: TOWARD ALGORITHMIC DEVELOPMENT OF NOVEL THERAPIES

Computational models find theoretical appeal in their ability to help bridge levels of abstraction when describing a neural system's function, i.e., from the implementation level to the algorithmic level to the computational level (4). The implementational level describes how the neural system is set up [e.g., which neurons encode rewards or punishments, and how are they connected to other neurons (5)]. The algorithmic level describes, in mathematical terms, the way in which the input (e.g., experience with rewards and/or punishments) is transformed to an output (e.g., conditioned responding or instrumental behavior), as in reinforcement learning (6). The computational level describes what the system is seeking to achieve (e.g., obtaining nutrition or avoiding harm).

As noted previously, this framework may be particularly well suited to understanding and refining existing psychiatric interventions (7). Many of the medical interventions at a clinician's disposal have been discovered, at least in part, as a result of serendipity and may therefore lack a full-fledged mechanistic theory to account for their efficacy. A well-known example in psychiatry is the case of antipsychotic medications for schizophrenia: their proposed mechanism of action during initial development is different from what we now know (8). It was subsequently hypothesized that their pharmacological action was largely dependent on their affinity for dopamine receptors (9). Models of dopamine that bridge implementation (i.e., dopamine neurons in the midbrain and their projection to the striatum and prefrontal cortex), algorithm (e.g., the temporal difference learning model), and computation (e.g., delusional beliefs, hallucinations, and/or apathy) are valuable for understanding and optimizing pharmacological interventions for schizophrenia (10–14) but were largely developed post hoc, after the initial demonstration of the efficacy of antipsychotic medications.

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However, this type of analysis implies that there may be potential for therapies to be developed and optimized at the algorithmic level alone, by focusing exclusively on the mathematical form of the psychological process that is thought to be dysfunctional in the disorder (Figure 1). We assume that a dysfunctional psychological process that is causally related to a given symptom can be described by an algorithm, which is built from a set of parameters that correspond to the core components of the process. By selectively altering algorithmic parameters or altering system inputs (e.g., providing more information) via clinical intervention, it is assumed that this will change the dysfunctional process in a way specified by the algorithm and ultimately result in an improvement of the clinical condition (7). An area in which such principles have already been adopted is within the reinforcer pathology framework for understanding substance use disorders (15). For example, substance users show a greater preference for immediate over delayed rewards (15), which can be described by algorithmic delay-discounting models (16). Behavioral manipulations [e.g., of episodic future thinking or working memory (17,18)], which reduce the discounting of future rewards, can also reduce drug consumption and thus represent a causal pathway for modulating drug intake and a possible avenue for treatment. A related example is the effect of cost on demand: demand for cigarettes can be affected by their price, so increasing cost per cigarette suppresses demand (19). Algorithmic models of demand [e.g., (20)] might be applied to determine the level of tobacco taxation that optimally suppresses demand and increases revenue (21) or evaluate contingency management therapies, i.e., monetary reinforcement of successful abstinence (22–25) and have the advantage of providing a highly translational approach to this problem (26).

One somewhat slippery aspect of developing descriptions at the algorithmic level is that in the brain, it is entirely possible that there are many algorithmic levels—computational procedures operating at different levels of description in the nervous system. In using algorithmic similarities to understand or treat behavioral or mental dysfunction, there are several reasons why this may be a moving target: first, there may be different levels of representation in the brain currently unknown to us; second, the processing at any level is always changing due to learning and adaptation; and third, there is also algorithmic degeneracy, in which the brain might concurrently implement different algorithms whose computational objective is similar (27), and which may provide the capacity for compensation in the case of functional disruption (28).

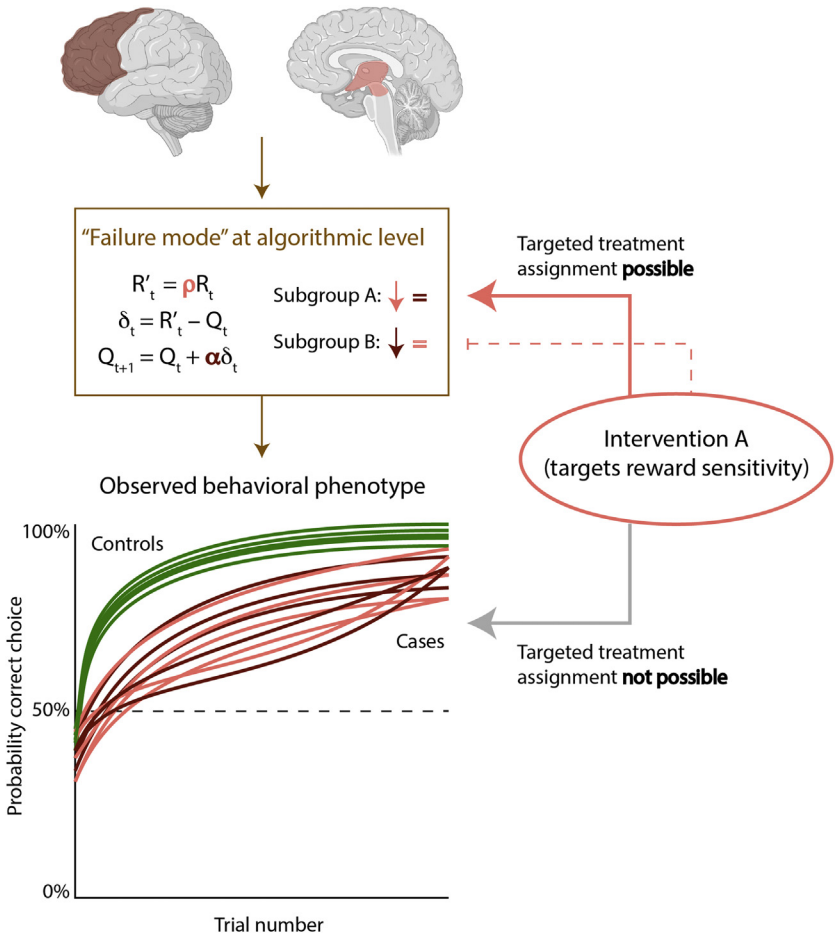

Figure 1. Theoretical example of how a potential therapy can be developed and optimized by considering the algorithmic process that gives rise to a particular symptom or behavioral phenotype, in this case, a reward learning deficit. Slowed learning (observed behavioral phenotype) can be caused by a number of upstream differences in the reinforcement learning algorithm connecting disordered neurobiology to behavior such as reduced reward sensitivity or reduced learning rate. Selectively altering algorithmic parameters, for example, reward sensitivity in a subgroup in which reward sensitivity is the cause of the learning deficit, can change learning in a targeted way, increasing therapeutic efficacy. This type of targeted treatment assignment is not possible by considering the observed phenotype alone.

Nevertheless, the computational characteristics of psychiatric patients that are reflected in their symptoms may provide key constraints in the search for their algorithmic underpinnings. These constraints might reveal the dimensionality of the algorithmic repertoire—the number and form of the latent subprocesses that might be most important in determining pathological behavior. Overall, a broader view may be needed to determine the susceptibility of a particular algorithm to a given intervention in the context of an individual's capacity for adaptation and/or compensation.

The algorithmic level also remains an essential component of other types of translational research, namely, the use of model organisms. It provides a convenient currency for identifying functional similarities and differences across species, which is crucial for valid modeling of psychiatric symptoms using experimental animals (29). For example, the identification of similarities and differences between corticostriatal functional connectivity across species (30,31), when taken in isolation, can provide only limited insight into behavior. Here, analysis at the algorithmic level provides crucial complementary information. One possibility is that the same algorithm is represented in the same way using different networks across species, so different species might show a redundant representation of the same algorithm. Alternatively, homologous circuits might implement the same algorithm(s), while nonhomologous circuits would implement different algorithms. This would open the potential for degeneracy and/or genuine behavioral differences across species.

PSYCHOMETRIC CONSIDERATIONS

A key challenge in moving computational psychiatry research toward forward computation to clinic translation is establishing the psychometric characteristics of both parametric estimates from computational models and model-derived estimates of brain activity (32). Test-retest reliability is a primary challenge of task-related functional magnetic resonance imaging studies (33), with some work finding very low test-retest reliability (34,35). However, reliability may be higher in some brain regions and under some conditions, e.g., within regions robustly engaged by the task; when collecting larger amounts of data (36–39); or when focusing on alternative metrics such as functional connectivity (39) and multivariate patterns (40).

While there is an emerging literature on the reliability of parameter estimates derived from computational models, findings thus far have been very mixed (41–44), and few systematic studies of factors that might influence test-retest reliability across different populations exist. There is also an emerging literature on the reliability of computational model–based estimates of brain activation (45,46). However, more work is needed in this domain, including a systematic examination of best practices for optimizing reliability and the conditions under which acceptable reliability is obtained. Further, it is important to acknowledge that psychometric characteristics are not an inherent property of a task or a model but are also dependent on the sample being examined (47).

Another key challenge is making predictions about individuals rather than inferences about group-level differences in parameter estimates or brain activity. Most studies using theory-driven computational modeling approaches to examine either behavior or brain activation focus on group-level differences or correlations with symptom dimensions (48–54). However, for computational psychiatry approaches to be useful for clinical application, we will need to be able to make inferences about specific individuals and to monitor longitudinal changes across time within an individual or group during treatment. Longitudinal designs raise a series of critical measurement issues, requiring not just stability of effects observable at the group level (and potentially indicative of generalizable mechanisms) but also reliability at the individual level to allow the quantification of meaningful variations in the mechanisms (33,55,56). The extension of computational psychiatry approaches to individual level prediction and longitudinal within-person change is just in its infancy, but it is a critical pathway forward to realizing the goals of computation to clinic translation (3,57–59) (see also Beyond Case Control: Capturing Dynamic Processes Via Longitudinal Computational Assessment).

Given the lack of knowledge about basic pathophysiology underlying psychiatric disorders, determining what functions as the gold standard for determining validity is a matter of consensus among subject-matter experts. While patient self-report will in some cases be the appropriate gold standard, this may not be universally true. Medically, one example of this is the instance of referred pain: A patient may self-report left arm pain that, on examination, turns out to be caused by pain and muscle damage elsewhere, such as would be the case in a heart attack. In this instance, it is not the case that self-report is unreliable or incorrect, it is simply that it alone is not sufficient to adequately diagnose the underlying pathology. In psychiatry, DSM diagnosis is also often considered as a gold standard metric for determining validity in psychiatry (i.e., does this computational parameter have sensitivity and specificity for a given disorder). However, as has been highlighted previously, this too may be problematic, because a single diagnostic label may result from highly heterogeneous biological and computational causes.

TRANSDIAGNOSTIC AND PRECLINICAL CONSIDERATIONS

In disease models from medicine, a biological process needs to be measurably related to the indices of illness, and treatment needs to alter it, thereby improving symptoms of the illness. However, psychiatric illnesses are likely not of such a kind (58); with complex compensatory processes, any symptom or associated behavioral manifestation could arise from multiple and distinct underlying causes, or the same underlying cause could lead and contribute to multiple symptoms (60). Indeed, computational, cognitive, and learning processes have been associated with specific symptom complexes (29,61–65), and emerging evidence indicates that engaging such specific and potentially transdiagnostic markers may have clinical efficacy (66–68). Nevertheless, recent work has also raised questions about whether, for instance, behavioral findings can be informative about self-reported measures of illness (69).

Transdiagnostic, dimensional approaches, such as the popular Research Domain Criteria (60), may be critical for integrating scientific findings across basic, preclinical, and clinical domains [for additional discussion see (70)]. However,

one predominant concern given the complexity of behavior is knowing what processes we are capturing. Consider anhedonia, the inability to experience pleasure, a construct listed within the Research Domain Criteria framework as a behavioral unit of analysis reflective of negative valence systems (71). In psychiatry, anhedonia is most commonly known as a core criterion for major depressive disorder, but it is also present across other psychiatric diagnoses, e.g., addiction (72,73). In humans, anhedonia involves markedly diminished interest or pleasure in all, or almost all, activities (74). This includes the inability to take interest in topics or hobbies that an individual previously found engaging and a general lack of motivation surrounding the pursuit of pleasures (e.g., food, sex). In rodents, anhedonia is often recognized as a decrease in reward-seeking actions or reward consumption and classically assessed with tests of self-stimulation or sucrose preference, respectively (75). We, of course, cannot equate a rat's preference for a sucrose solution with the paralyzing anhedonia that characterizes major depressive disorder. We can, however, parse such behavior into component parts to determine whether the behavior observed is reflective of deficits in pleasure, motivation, or even learning (76–78), all of which can be carefully parameterized with models of demand and value updating. Computational approaches, including deep phenotyping [e.g., (79)], provide an opportunity to uncover the parallel processes that go awry in animal models and contribute to psychiatric symptomatology in humans (80–84). It is nonetheless critical to note that the accuracy and utility of computational models will ultimately be dependent on the precision of the phenotyping itself (85).

Another important consideration is disease heterogeneity. For example, if individual variation is readily apparent in a given behavioral paradigm in rodents, should we expect to see such behavioral variability between human subjects on a comparable task [e.g., (80,86,87)]? If this variability is apparent in humans, how do we determine whether it is reflective of the same underlying processes captured in the rodent model? One recently proposed framework for considering this is that of computational validity (29), or the computational similarity between information processing demands underlying parallel tasks across species (29). Importantly, similar questions may apply to transdiagnostic human research, e.g., are the biological and cognitive substrates of anhedonia in fact shared across diagnoses? In addition, it is important to note that some computational processes (e.g., variables indexing reinforcement learning) may not consistently generalize across different contexts and thus may, in fact, be reflective of specific behaviors under study rather than a shared latent psychological construct (88). While we cannot offer concrete answers to these emerging questions at present, we urge researchers to think deeply about such questions and, in turn, the approaches they are using both between- and within-species to advance our knowledge pertaining to translational clinical neuroscience.

BEYOND CASE CONTROL: CAPTURING DYNAMIC PROCESSES VIA LONGITUDINAL COMPUTATIONAL ASSESSMENT

Clinically orientated neuroscience research has largely depended on cross-sectional designs, often comparing a group of individuals with a given condition or disorder to a group of control participants. Yet, these studies are not optimized for individual-level prediction or for the study of what are ultimately highly dynamic conditions, with varying symptom triggers between individuals. Moreover, cross-sectional markers do not necessarily hold information about longitudinal change relevant for intervention and therapy. Thus, to reach its clinical potential, future work will need to embrace the dynamic processes inherent to psychiatric symptoms and disorders by explicitly examining intraindividual longitudinal change in computational parameters and developing task paradigms and analytic methods specifically designed to capture these dynamics (59,85,89). As a practical example, recent work has demonstrated that intraindividual changes in computational parameters, in this case a measure of ambiguity tolerance, precede returns to opioid use among individuals in treatment (58).

Naturalistic changes in clinical symptoms can suggest potential novel treatment targets (90), and studies examining treatments or interventions have the potential to shape clinical decision making. For instance, recent successes include the application of computational approaches to decision making (54,58,91) and imaging (92–94) in predicting treatment response and course in depression and substance use disorders. Although a single time-point measurement may be sufficient for diagnostic classification, and in some cases for treatment selection, other clinically relevant outcomes such as longer-term prognosis and determining if a current treatment is sufficiently working for an individual, will require denser sampling of behavior and neural function. In fact, it can be argued that most clinical decisions require continuously (re)assessing the person in time. This is most evident in managing rapidly changing clinical phenomena, such as suicidal behavior, manic/depressive episodes, and relapse to drug use, all of which require ongoing treatment modification. Even diagnosis and treatment selection can be improved upon by longitudinal data (95). A move toward person-centered computational psychiatry research is needed not only for enhancing the potential for clinical translation but also for basic research. To elucidate the mechanisms of disease, computational psychiatry efforts need to be geared more accurately toward evaluating which are the most clinically relevant (and thus most defining) algorithmic parameters and at which timescale.

The shift toward dynamic assessment can also facilitate building computational cognitive neuroscience into the development of just-in-time adaptive interventions, which are increasing in use (96–100). The idea to study patient behavior longitudinally has been embraced in recent years with the increased availability of cost-effective and remote data collection tools (e.g., http://www.thegreatbrainexperiment.com; https://brainexplorer.net/; https://www.neureka.ie/) or, more directly, using ecologic momentary assessments (101–104), but only recently has increased emphasis been placed on acquiring similarly densely sampled neural measurements (105–109), and this work has overwhelmingly focused on the monitoring of healthy states. The neural dynamics of changing clinical phenomena remain largely unknown (59). Using computational approaches to understand these neural dynamics can help bridge between changes in

computations inferred from behavior and variation in symptom expression.

Given the heterogeneity and complexity of clinical phenomena, these longitudinal behavioral and neural dynamics should aim to capture multidimensional computational mechanisms (110). Prior work shows that conceptually distinct computational markers, such as those that describe people's preferences for risk and delay and their propensity to learn in a model-free versus model-based way, define distinct diagnostic categories (111,112), symptom domains (62,113–115), and clinically relevant outcomes (58,93,94). Further, even conceptually related markers, such as preferences for known risk and unknown or ambiguous risk, can be differentially predictive of the same clinical outcome (58). Thus, focusing on just a few behavioral and neural variables at a time could preclude more detailed computational consideration of related processes and heterogeneous clinical profiles. A longitudinal and multidimensional examination, a type of dynamic neurocomputational fingerprinting approach (89), may therefore provide a more complete understanding of mental illness and aid in developing better tailored and timed interventions at an individual level or, perhaps more immediately, at the group level via patient stratification.

THE FINAL FRONTIER: CLINICAL CHALLENGES TO IMPLEMENTATION

The final hurdles for effective translation from computation to clinic are of course those directly pertaining to implementation and subsequent treatment development and selection: how can we develop a pragmatic framework that would enable the development of computationally informed tests in psychiatry for different mental health conditions?

The types of outcomes under consideration for a test are highly variable based on time frame, level of observation (e.g., symptoms vs. biological process), and interventions available. A screening test would be useful to identify individuals at risk for the disorder or who have a not-yet-clinically manifest disorder (116,117). A diagnostic test would provide evidence for the presence of a particular disease or help arbitrate between diseases with similar manifestations (118). A prognostic test would provide patients and providers with information regarding degree of recovery, severity of residual symptoms, occurrence of associated complications, or likelihood of a disease-free interval (119,120). Finally, a treatment-specific test would help to guide which type of intervention is most likely going to be associated with a positive outcome for a particular individual. Within a computational framework, this means that one will need to explicitly consider how risk, diagnoses, recurrence, or recovery translate to model parameters that can give insights to the mechanistic aspect of the disorder as well as pragmatically be as robust and reliable as clinical tests.

Another pragmatic consideration is to determine who benefits from the test. A test would provide a patient with information that can be used to adjust activities, treatment selection, and adherence and integrate individual experiences into an explanatory disease model. The provider benefits from a test by having a more precise disease model, selecting disease-specific interventions, based on the underlying algorithmic disruption, and focusing attention on monitoring disease-specific outcomes. From a payer perspective, tests—even if not sufficiently sensitive or specific for individual cases—can aid in deployment of resources to a particular intervention or disease or other operational decisions. Finally, a public health specialist can use tests to determine the need for population-based resource allocation to reduce disease impact.

Test characteristics will have different implications for each of these stakeholders. An important challenge is to translate computational models to stakeholders such that they become both understood and actionable. Specifically, using a reinforcement model framework, the notion of different learning rates for gains or losses as critical parameters for mood disorders may require experts to reframe these measures in terms of past history considered when taking rewards or losses into account. However, an actionable test alone may also prove useful (e.g., an aggregate risk calculator approach, which is used to trigger adjustment of a well-validated treatment). Moreover, the net benefit of a computationally informed test needs to be expressed in numbers that are meaningful to stakeholders (Figures 2 and 3). For example, the number of recurrences of a depressive episode that could be prevented with a positive test may be useful for a public health specialist, whereas the likelihood of a particular patient experiencing a depressive episode within the next 6 months may be more useful for a clinician.

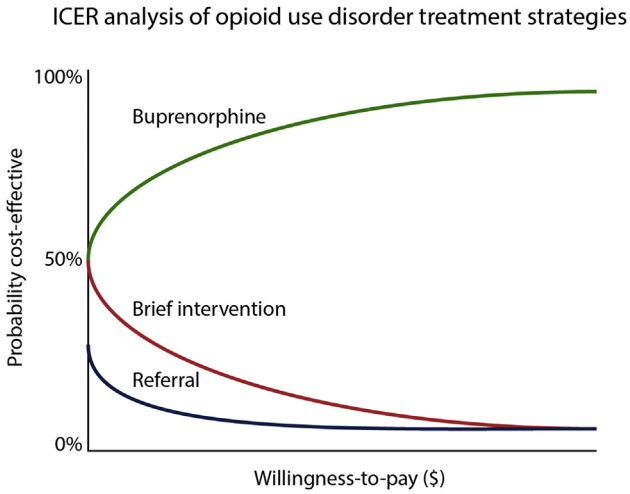

Figure 2. Incremental cost-effectiveness ratio (ICER) analysis. ICER analysis is a method of associating an economic value to the cost of conducting the test that can quantitatively estimate the effect that a test-based assignment can have on treatment. ICER is based on the incremental costs per unit of effect of the intervention and calculated as the difference in the sum of specific direct and indirect costs divided by the inverted difference in effect score [e.g., (125)]. In the example shown, the probability of a cost-effective clinically meaningful response to different clinical actions are plotted against the stakeholders' willingness to pay. Willingness to pay increases with buprenorphine given the high evidence base for its utility in treating opioid use disorder. In contrast, willingness to pay decreases for nonevidence based (e.g., brief intervention) and nontreatment (i.e., referral to alternate source) actions.

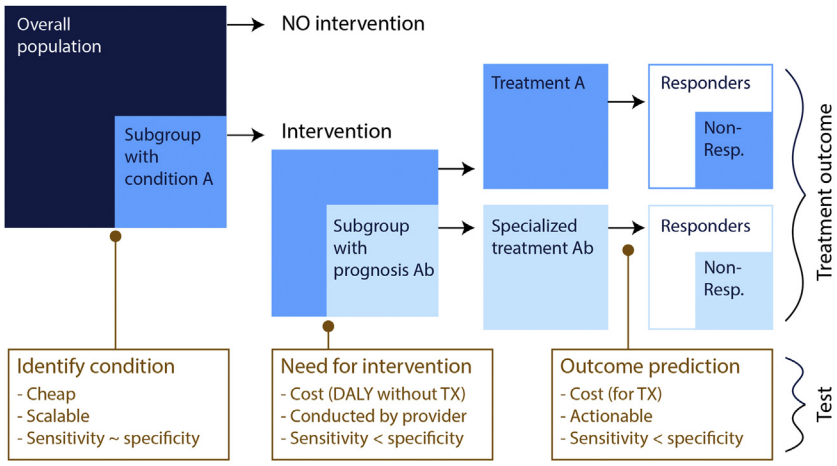

Figure 3. Schematic diagram of computational testing steps for determining clinical treatment. Conceptual overview of computational testing steps for determining clinical treatment within the specific context of tests focused on screening, treatment selection, and prognosis. However, these approaches can be readily extended to include diagnostic tests if there are differential actionables associated with a particular diagnosis. The size of the boxes and the subgroups are meant to indicate the scale of the base rate or pre- and posttest probability. DALY, disability-adjusted life years; Non-Resp., nonresponder; TX, treatment.

A test cannot be separated from the setting in which it is administered. Even with a point prevalence of 1 in 5 individuals having a mental health condition (121), a test with a positive likelihood ratio of 4 to 1 (i.e., the chance that a person with a disease will have a positive test over a person that does not have the disease but will test positive) and a negative likelihood ratio of 2 to 5 (i.e., the chance that a person who does have a disease will test negative over the chance that a person who does not have the disease will test negative) would result in as many false positive as true positive cases. In other words, as many individuals would be identified as having the condition who in fact do not have it as would be identified as truly having the disease. Thus, test characteristics, i.e., specificity and sensitivity, are very much population-specific and may not hold for the population at hand. For example, assuming that the overall goal of a low-cost intervention is (at a minimum) harm reduction, a test with high sensitivity and low specificity might be acceptable for determining the need for an intervention, such as initiation of methadone for opioid use, but might not be optimal for predicting termination of methadone treatment. In both cases, the goal is relapse and overdose prevention; however, maximizing sensitivity for methadone initiation is most likely to minimize overdose risk, whereas maximizing specificity for methadone cessation is most likely to minimize overdose risk (1). Within this context, a test with low sensitivity but high specificity might be acceptable for prediction of treatment cessation but not for prediction of treatment initiation (1). It is equally important to note that a test evaluated in the general population may behave very differently in a clinical population of a provider. Thus, the population in which a computational model is developed and tested is also essential to consider.

Tests are frequently evaluated by their statistical characteristics, which some have called the single most problematic misrepresentation of the utility of a test (119). Sensitivity and specificity do not provide sufficient information to judge the utility of a test because they do not consider the base rate of the disease (or the pretest probability, in Bayesian terms). Positive and negative likelihood ratios can readily be used to compute posttest probabilities, which provide an intuitive notion of the certainty a test can provide. Nevertheless, even these numbers are insufficient to readily assess the test utility for 2 reasons. First, there are pragmatic aspects of a test that are not reflected in these numbers. As mentioned above, the base rate of the disease in the population tested is one aspect, but more importantly, does the test involve an individual assessment by a trained provider, is it dependent on its implementation, and/or does the test itself alter the disease state in the individual or change behavior subsequently? These issues are particularly relevant for mental health conditions. Second, what are the interventions associated with a positive or negative test, and how do costs, intensity of intervention, and probability of successful or unsuccessful outcome change because of the test result? In summary, a test is merely a step embedded in a chain of evaluations and interventions aimed to improve patient outcome and needs to be evaluated as such.

These ideas might be integrated with potential for in silico simulation for the development and optimization of treatments at the algorithmic level (see From the Bottom Up: Toward Algorithmic Development of Novel Therapies). Specifically, algorithmic models of psychiatric dysfunction could be used to simulate clinical status and predicted clinical course if the mathematical form of these can be estimated. Presumably, at first, initial tests of symptoms (e.g., self-report diagnosis) may provide a somewhat uncertain indication of a patient's clinical course, but further evaluation and tests may provide more accuracy and, in particular, favor one model over another (i.e., provide more accurate differential diagnosis). Monitoring the model predictions could be conducted with further testing during treatment, and predictions of the model could be refined further. Typically, it would be expected that a single model be selected with high likelihood, and this would describe the clinical course with high accuracy. In practice, however, there might be multiple plausible models that will describe a participant's symptoms, and these might be difficult to differentiate with available tests. Treatments that might cause harm under one plausible scenario might be avoided, while the probability of different scenarios might be used for weighting the utility of tests or treatments in light of information about costs and benefits. Further testing should eventually disambiguate the different models according to the precision of their predictions, and oversight by a physician will be

particularly important in cases where model error is particularly high (for example, a manic episode elicited by an antidepressant medication during treatment). Overall, this system might be implemented computationally as a mixture of experts approach (122,123), in which different models can be gracefully integrated to provide unique predictions across different domains (e.g., across uniquely specified disorders) or compete to describe a given domain. This framework could provide weighting for probabilities of different scenarios, as well as utilities for potential harms, costs, and clinical benefits. The physician is also represented within this system, both as a provider of information (e.g., through the diagnosis) and also as an independent expert with their own biases (124), but who might exert more control if the model predictions are associated with risk or are inaccurate. The computational researchers who derived the test are also inherently represented within this system; thus, for maximal translation from computation to clinic (as opposed to vice versa), even basic computational research must also weigh the above considerations.

CONCLUSIONS

Effective forward translation from computation to clinic remains elusive, yet it may be enabled by careful consideration of mechanisms at an algorithmic level, psychometric standardization, recent developments in longitudinal phenotyping and other theory-driven computational approaches, and careful, realistic evaluation of a test's efficacy within a specific real-world clinical context.

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