UC San Diego
UC San Diego Previously Published Works

Title

An Individualized Risk Calculator for Research in Prodromal Psychosis

Permalink

Journal

American Journal of Psychiatry, 173(10)

ISSN

0002-953X

Authors

Cannon, Tyrone D
Yu, Changhong
Addington, Jean
et al.

Publication Date

2016-10-01

DOI

10.1176/appi.ajp.2016.15070890

Peer reviewed

An Individualized Risk Calculator for Research in Prodromal Psychosis

Tyrone D. Cannon, PhD[1,2], **Changhong Yu, MS**[3], **Jean Addington, PhD**[4], **Carrie E. Bearden, PhD**[5], **Kristin S. Cadenhead, MD**[6], **Barbara A. Cornblatt, PhD**[7], **Robert Heinssen, PhD**[8], **Clark D. Jeffries, PhD**[9], **Daniel H. Mathalon, PhD, MD**[10], **Thomas H. McGlashan, MD**[2], **Diana O. Perkins, MD, MPH**[11], **Larry J. Seidman, PhD**[12], **Ming T. Tsuang, MD, PhD**[13], **Elaine F. Walker, PhD**[14], **Scott W. Woods, MD**[2], and **Michael Kattan, PhD**[3]

[1]Department of Psychology, Yale University, New Haven CT

[2]Department of Psychiatry, Yale University, New Haven CT

[3]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH

[4]Hotchkiss Brain Institute, Department of Psychiatry University of Calgary, Alberta, Canada

[5]Departments of Psychiatry and Biobehavioral Sciences and Psychology, UCLA, Los Angeles CA

[6]Department of Psychiatry, UCSD, San Diego CA

[7]Department of Psychiatry, Zucker Hillside Hospital, Long Island NY

[8]National Institute of Mental Health

[9]Renaissance Computing Institute, University of North Carolina, Chapel Hill NC

[10]Department of Psychiatry, UCSF, San Francisco CA

[11]Department of Psychiatry, University of North Carolina, Chapel Hill

[12]Department of Psychiatry, Harvard Medical School at Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston MA

[13]Center for Behavioral Genomics, Department of Psychiatry; Institute of Genomic Medicine, UCSD, La Jolla CA

[14]Departments of Psychology and Psychiatry, Emory University, Atlanta GA

Abstract

Objective—About 20–35% of individuals aged 12–30 years who meet criteria for a prodromal risk syndrome convert to psychosis within two years. However, this estimate ignores the fact that clinical high-risk (CHR) cases vary considerably in risk. Here we sought to create a risk calculator that can ascertain the probability of conversion to psychosis in individual patients based on

Address correspondence and reprint requests to: Tyrone D. Cannon, PhD, Department of Psychology, Yale University, P.O. Box 208205, 2 Hillhouse Avenue, New Haven, CT 06520; tyrone.cannon@yale.edu.

Author Manuscript

profiles of risk indicators. The high risk category predicted by this calculator can inform research criteria going forward.

Method—Subjects were 596 CHR participants from the second phase of the North American Prodrome Longitudinal Study (NAPLS 2) who were followed up to the time of conversion to psychosis or last contact (up to 2 years). Our scope was limited to predictors supported by prior studies and readily obtainable in general clinical settings. Time-to-event regression was used to build a multivariate model predicting conversion, with internal validation using 1000 bootstrap resamples.

Results—The 2-year probability of conversion to psychosis in this sample was 16%. Higher levels of unusual thought content and suspiciousness, greater decline in social functioning, lower verbal learning and memory performance, slower speed of processing, and younger age at baseline each contributed to individual risk for psychosis, while stressful life events, traumas, and family history of schizophrenia were not significant predictors. The multivariate model achieved a Concordance index of 0.71, and was validated in an independent external dataset. The results are instantiated in a web-based risk prediction tool envisioned to be most useful in research protocols involving the psychosis prodrome.

Conclusions—A risk calculator comparable in accuracy to those for cardiovascular disease and cancer is available to predict individualized conversion risks in newly ascertained CHR cases. Given that the risk calculator can only be validly applied for patients who screen positive on the Structured Clinical Interview for Psychosis Risk Syndromes, which requires training to administer, it's most immediate uses will be in research on psychosis risk factors and in research driven clinical (prevention) trials.

Introduction

Given limitations of current treatments for schizophrenia, with most patients showing substantial deficits in social and occupational functioning throughout life, there is considerable interest in developing preventive approaches to psychotic disorders (1). Ascertainment of individuals at greatest risk is crucial to these efforts. For the majority of patients, onset of fully psychotic symptoms is preceded by the emergence of subtler changes in belief, thought, and perception that appear to represent attenuated forms of delusions, formal thought disorder, and hallucinations, respectively. Among individuals aged 12 to 35 years with a recent onset of such symptoms (termed clinical high-risk or CHR cases), approximately 20–35% develop fully psychotic symptoms over a 2-year period, an incidence rate that is over 100 times larger than in the same age band in the general population (2). Further, it appears that the CHR criteria are sensitive to an imminent risk for onset, as most of the conversions occur during the first year following ascertainment, with a decelerating conversion rate thereafter (3).

Although CHR criteria have been validated as sensitive to conversion risk in epidemiological studies, their utility in individual decision-making is currently limited, given that two-thirds to four-fifths of cases ascertained by these methods do not convert to psychosis within a 2-year time frame. A number of studies have examined combinations of clinical and demographic variables to determine whether prediction of psychosis can be enhanced

beyond the 20–35% risk associated with CHR status (4). Multivariate algorithms requiring particular combinations of symptoms and demographic factors achieve relatively high positive predictive values and specificity (e.g., in the 50–70% range), but low sensitivity (e.g., in the 10–30% range) (3). There is consistency among studies in showing (unsurprisingly) that greater severity of the psychosis-risk symptoms at baseline is the best predictor of conversion; nevertheless, the most predictive multivariate profiles vary across studies (4). Although it should be noted that few studies have attempted direct replication of each other's risk algorithms, this pattern suggests heterogeneity among profiles of clinical and demographic risk indicators among those who convert.

To maximize clinical utility, we require an approach that can be applied to scale the risk in an individual patient during their initial clinical contact. Such individualized risk calculation is possible when a large dataset on a reference population is available from which risks can be calculated based on one or more predictor variables. Well-performing risk calculators have been developed in numerous somatic disease contexts, including cardiovascular disease and cancer (5–9), where they provide a rationale for clinicians to pursue more or less invasive intervention strategies, based on the level of risk implied by an individual's profile across a set of risk factors. They also inform patients and their family members to help make complex treatment decisions.

Here we present such an individualized risk calculator for psychosis, using data from the second phase of the North American Prodrome Longitudinal Study (NAPLS 2). Predictors were chosen *a priori* based on a review of the prior literature on psychosis risk prediction in CHR samples, blindly with respect to the empirical relationships between any of the nominated variables and psychosis outcome within the NAPLS 2 dataset. We limited our scope to clinical, cognitive, and demographic measures that are readily obtainable in standard clinical settings. Using time-to-event proportional hazards regression, a risk calculator was generated that calculates risk according to an individual subject's values on the included variables. We evaluated the performance of the risk calculator using the Concordance index (a measure of overall accuracy, analogous to area under the receiver operating characteristic curve or AUC) and assessed the relative importance of each of the included predictor variables.

Methods

Subjects and Clinical Characterization

The study protocol and consent form were reviewed and approved by the Institutional Review Boards at each of the 8 data collection sites (UCLA, Emory, Beth Israel Deaconess Medical Center, Zucker Hillside Hospital, UNC, UCSD, Calgary, Yale). We have previously reported on the methods for evaluation of subjects and data collection (10). Participants were evaluated using the Structured Interview for Psychosis-risk Syndromes (SIPS) (11) and the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV) (12) by trained interviewers who met high reliability standards (ICCs=0.92–0.96) (10). Potential participants who had ever met DSM-IV criteria for a psychotic disorder or with histories of substance dependence, neurological disorder, or estimated IQ < 70 were excluded. Participants met SIPS criteria (13) for the presence of one

or more CHR syndromes: attenuated psychotic symptoms syndrome; brief intermittent psychotic symptom syndrome; and/or familial risk and deterioration syndrome.

Follow-up clinical evaluations were scheduled every 6 months following study entry through 2 years. Conversion to psychosis was determined by the SIPS criteria that are designed to operationalize the threshold of delusional ideation or hallucination severity required for a DSM-IV (14) psychotic disorder diagnosis. Participants were followed up to the time of conversion to psychosis or the last contact (up to 2 years), the dates for which were recorded, permitting calculation of length of time in the study until conversion or censoring (loss to follow-up).

A total of 743 SIPS-criteria meeting CHR cases were enrolled in NAPLS 2 from 2008 – 2013. For the present report, we excluded subjects who dropped from the study before any clinical follow-up was conducted (N=147). The final study cohort consisted of 596 CHR participants with at least one follow-up evaluation.

Selection of Predictor Variables

To meet the objective of developing a practical tool for risk prediction, our focus was on demographic, clinical, neurocognitive and functioning measures that are easily administered in general clinical settings. The maximum number of predictors was limited *a priori* to 8 to ensure that there were at minimum 10 converters per predictor in the model, which helps to mitigate model instability due to over-fitting. We avoided including terms for the interactions among the predictors for this same reason. The NAPLS 2 dataset itself was not used to select predictors; doing so would have invalidated the logic of using the underlying data to inform prediction for new cases (i.e., the predictive logic would then be circular). Rather, we evaluated the available published literature on psychosis prediction in CHR samples. Our selection of indicators was based on empirical links to psychosis prediction in two or more prior studies of CHR cases; there was no attempt to select predictors based on a theoretical model of causes of psychosis or clinical knowledge or intuition. Based on this process, the following 8 variables were chosen for inclusion:

Age at ascertainment was included to help account for variation in age at onset of psychosis (15) and in processes that undergo developmental modification during the age range of our sample (16–18). Greater severity of SIPS items P1 and P2 (Unusual Thought Content and Suspiciousness) are strongly predictive of psychosis in CHR samples (3, 4). Given that the meaning of gradations below the prodromal threshold are likely different from those at or above this threshold, these items were modified such that all levels in the non-prodromal range (0–2 on the original scale) were redefined as 0, levels in the prodromal range (3–5 on original scale) were redefined as 1–3, and psychotic intensity (6 on original scale) was redefined as 4, and summed together. A number of studies have found that slower processing speed and lower verbal learning and memory functioning are predictive of psychosis (19, 20) and in meta-analyses, have among the largest effect sizes amongst converters to psychosis (21). These constructs were represented by scores on the BACS Symbol-Coding Test (22) and the Hopkins Verbal Learning Test-Revised (HVLT-R; sum of trials 1–3) (23), respectively. Many CHR cases who convert to psychosis show a pronounced decline in social functioning in the year prior to ascertainment (24), measured here using the Global

Scale of Functioning-Social (GFS-S) (25). Stressful life events, along with childhood traumas, have been shown to be predictive of psychosis in prior studies of CHR samples (26). To represent the former, we aggregated 31 life events designated as negative and potentially relevant to subjects aged 12–35 years from the Research Interview Life Events Scale (RILES) (27), and for the latter, we used the Childhood Trauma and Abuse Scale (CTAS) (28). Family history of psychotic disorder in a first-degree relative is by itself not a robust predictor of psychosis in studies of CHR samples (3, 4), but was nevertheless included as it elevates ones' risk by almost 10-fold compared with the general population (29).

Statistical methods

Risk calculators have been developed to assist health care professionals for a variety of illnesses (5–9) (see http://www.lerner.ccf.org/qhs/risk_calculator/ for examples). Calculators are able to derive a risk prediction for a particular person from a given set of indicators by querying a multivariate model based on a large sample of similar cases. Through imputation, calculators can accommodate incomplete information on the panel of risk indicators; however, they become more powerful, with a tighter range of certainty, the more complete the information available on a given case.

We built a multivariate proportional hazards (PH) model to predict the likelihood of conversion to psychosis based on each participant's demographic, cognitive, and clinical characteristics, as defined above. We tested restricted cubic splines in relation to continuous variables; as none were significant, no adjustments were made. As shown in Table 1, there were no (or minimal) missing data for age, symptom severity, family history, and social functioning. Cognitive test data were missing on fewer than 4% of cases, and data regarding stressful life events and/or traumas were missing in 12–14% of cases. In order to reduce selection bias and maximize the sample size, missing predictors were multiply imputed with the multivariate imputation by chained equations (MICE) method before the multivariate regression.

The statistical model was internally validated using 1000 bootstrap resamples, where the discrimination and calibration performance were evaluated. Harrell's C-index was used to quantify the discrimination ability for separating converters and non-converters, which is analogous to the AUC, with a range of 0.5 (no discrimination) to 1 (perfect discrimination), but tailored for censored data (30). A plot of the model-predicted probabilities versus the observed outcomes was used to assess calibration performance.

All statistical analyses and graphics were conducted using the open source software R version 3.0.1 (R Core Team, 2013) including the rms and Hmisc packages.

Results

The baseline patient characteristics are summarized in Table 1. There were no significant differences between those who were and were not followed up clinically on any of the predictor variables. Of the 596 participants with follow-up data available, 84 converted to psychosis within two years. The mean age of the sample was 18.5 years. Among converters,

the mean time from baseline to conversion was 7.3 months, and among non-converters, the mean follow-up time from baseline to the last contact was 19.1 months. A total of 280 cases were followed up at 24 months without converting, and the remaining "non-converters" were lost to follow-up at various points between 6 and 24-months.

The 2-year probability of conversion to psychosis was 0.16 (95%CI 0.13, 0.19). Figure 1 provides frequency distributions of predicted risks in the sample overall and among converters. Converters are identified at a higher rate than the sample base-rate beginning at a predicted risk of .20 or higher. The output of the multivariate PH model is shown in Table 2. Prodromal symptom severity (P1P2), decline in social functioning, and verbal learning and memory (HVLT-R scores) were significant predictors, with non-significant trends for age at baseline and speed of processing (Symbol-Coding score) (p's < 0.10), though all of these variables were significant in univariate analyses (p's < 0.01). Stressful life events, traumas, and family history of schizophrenia were not significant predictors in univariate or multivariate analyses.

Table 2 provides additional diagnostics of the performance of individual predictor variables. Predictors associated with the largest decreases in the C-index when removed from the model were P1P2, decline in global social functioning, HVLT-R score, and Symbol-Coding score. Predictors associated with the largest increases in the C-index (i.e., above that of the base model that included only P1P2) were Symbol-Coding score, HVLT-R score, decline in social functioning, and age. Family history of psychosis, stressful life events, and traumas did not alter the C-index by more than one-half of one percent when added to or deleted from the model.

Based on the bootstrap internal validation, the multivariate model achieved a C-index of 0.71. As shown in Figure 2, the calibration plot revealed a high degree of consistency between observed probabilities and model-predicted probabilities of conversion to psychosis within the range of 0.0–0.4, within which 95% of the cases fell (mean = 0.18, SD = 0.11; median = 0.16). Table 3 gives statistics for prediction of actual conversion to psychosis across several thresholds of model-predicted risk. There is a trade-off between the positive predictive value (PPV; proportion of cases at the threshold of predicted risk who actually converted) versus sensitivity (proportion of actual converters who had predicted risks at that threshold). PPV is maximal (48.4%) at a threshold of 0.4 or higher of model-predicted risk, but only 17.9% of converters have model-predicted risks at this threshold. Conversely, at a model-predicted risk of 0.2 or higher, PPV is 28.1%, but with a sensitivity of 66.7%.

An on-line version of the risk calculator was built to facilitate numeric calculation of the predicted probability of conversion to psychosis (http://riskcalc.org:3838/napls/).

Discussion

The goal of this study was to develop a practical tool for the individualized prediction of psychosis in CHR cases. A well-performing risk calculator was generated from the NAPLS 2 cohort using a small number of demographic (age, family history of psychosis), clinical (unusual thought content and suspiciousness), neurocognitive (speed of processing, verbal

learning and memory), and psychosocial (traumas, stressful life events, decline in social functioning) predictor variables. The overall model achieved a C-index of 0.71, which is in the range of those of established calculators currently in use for cardiovascular disease and cancer recurrence risk, with C-indices of 0.58 to 0.81 (5–9).

The risk calculator generates a number representing the probability of transition to psychosis given a particular profile of input variables. Technically, this is an observed likelihood of conversion within the NAPLS 2 cohort itself, but this framework uses the logic of predictive inference to extend that observed likelihood based on past cases to the predicted probability for a newly ascertained case with the same profile. This logic rests on the assumption that the new case is ascertained from the same population and in a manner similar as those in NAPLS 2.

In particular, given that this risk calculator assumes a SIPS-based diagnosis of a prodromal risk syndrome as a starting point, the risk prediction tool would not be usable if such a risk syndrome has not been diagnosed. The risk calculator also assumes particular pathways to ascertainment, in that CHR cases in NAPLS are distressed and treatment seeking. This tool would thus be most useful to clinicians with training in psychosis risk detection using the SIPS (which, in addition to risk status, ascertains severity of unusual thought content and suspiciousness and family history of psychosis), who could then use the calculator for patients who have screened positive for a prodromal risk syndrome. Critically, risk determinations should be communicated to clients by trained clinicians, who can help clients understand the meaning of the risk estimates (i.e., calibrated to the sample from which they were generated) and provide commensurate treatment recommendations. Note that, within the context of NAPLS 2, with a mean±SD predicted risk of 0.18±0.11, predicted risks of .3 or higher are relatively rare (12.4% prevalence among those meeting CHR criteria) and potent (39.2% PPV). Proper training in the administration and scoring of the other measures included in the risk calculator (i.e., Symbol-Coding, HVLT-R, GSF-S, RILES, CTAS) is also required.

A key advantage of the risk calculator is that it inherently accommodates heterogeneity in profiles of risk factors among CHR cases. Examining configurations that vary across the significant predictors – greater prodromal symptom severity, lower verbal learning and memory, slower speed of processing, greater decline social functioning, and younger age – reveals that a number of separate permutations yield predicted conversion risks of 0.3 or higher. Stressful life events, traumas and family history of schizophrenia have a negligible impact on their own or in combinations with other variables in prediction of psychosis, but did occur more frequently among CHR individuals compared to healthy controls. Perhaps these variables are more significant for determining presence of a CHR syndrome and thus are not as sensitive to outcomes within a group all of whom have a CHR syndrome.

The most crucial test of robustness of a statistical model is validation on an independent, external dataset. In a companion paper (31), Carrión et al. perform such a replication test of the NAPLS 2 risk calculator in an independent sample from the Early Detection, Intervention, and Prevention of Psychosis Program (EDIPPP) that included 176 CHR cases diagnosed using the SIPS and followed clinically to monitor conversion. Only the stress and

trauma variables – found to be negligible in predicting conversion here – were not collected and were therefore omitted from the replication testing. The remaining 6 NAPLS 2 risk factors yielded a highly significant time-to-event proportional hazards regression model predicting conversion in the EDIPPP sample (p<0.003), with a C-index of 0.79, which is even somewhat better than in the NAPLS 2 sample (0.71). The predictive model was well calibrated, and the NAPLS 2 calculator provided a reasonable estimation of psychosis risk when considering the risk prediction generated by the validation model and the actual observed outcomes. In addition, when applied to the external EDIPPP sample, the NAPLS 2 calculator showed sensitivity and specificity values comparable to those found in the NAPLS 2 sample across different levels of model predicted risk (i.e., as in Table 3) (31).

There is also some degree of convergence with previous studies reporting multivariate models, but which used their own samples for variable selection (i.e., model optimization) and did not present a web-based tool for extending individualized risk estimation to future patients (3, 24, 32). For example, a recent report (24) using a smaller (N=92) and non-overlapping sample of CHR cases from one of the NAPLS sites developed a classifier that included three of predictors included in the NAPLS 2 risk calculator (suspiciousness, verbal memory deficits, and decline in social functioning). Note that the sample in that study was over 5 times smaller, used a more restricted age range (12–20), and was not ascertained using SIPS criteria, factors that make risk classifications based on it much less generalizable than that of the NAPLS 2 risk calculator.

The most immediate uses of the risk calculator are likely to be in the selection of individual subjects for participation in clinical (prevention) trials, given the desire to avoid exposing cases with lower transition risks to the potential adverse consequences of any interventions and given the potential to evaluate whether interventions differ in effectiveness based on initial risk levels and/or profiles across predictors. In terms of clinical practice outside the context of a prevention trial, at this point the most likely use is for the clinician to be able to communicate to the patient and family a scaling of risk that could help to recruit their cooperation with a monitoring and/or intervention plan.

A current limitation of the psychosis risk calculator is that risk estimates are not bounded by a confidence interval, making it unclear how well the single value output as a conversion risk represents the individual's actual likelihood of conversion. This issue is particularly problematic for computed risks of 0.5 or higher, for which there is sparse representation within the NAPLS 2 dataset and for which calibration of the risk calculator could consequently not be adequately tested. Nevertheless, the use of confidence intervals is not likely to be of value in discussing risks with individual patients and their families, as the general concept of a confidence interval relates to likelihoods under future sampling rather than to an individual case, and the calculated risk is the best estimate for that individual (33).

Because the replication study (EDIPPP) included several community behavioral health centers and inter-governmental managed mental health organizations, the risk calculator appears to be generalizable beyond academic medical centers, at least within the United States health care system. The degree to which the risk calculator generalizes to other health care system models (e.g., socialized) remains an open question.

In addition to testing the calculator's performance in independent datasets, future work could determine whether other variables, including biological tests, can improve prediction over and above the set of clinical, demographic and cognitive measures evaluated here. Some promising leads on the use of biological assays to predict psychosis among CHR cases have emerged using empirically-based discovery approaches, including machine learning algorithms for gray matter variations in structural brain images (34) and so-called "greedy" regression algorithms for proteomic/metabolic plasma parameters (35). Future studies employing discovery oriented model-optimization methods, with parallel, independent samples, are needed to better inform future versions of this and other risk calculators. However, it is still critical to note that the data used in any risk calculator could not be the same as used in the model optimization phase; as noted above, doing so would invalidate the risk predictions for new cases.

Given that in approximately one-third of CHR cases, the symptoms that determined their initial risk status remit within 6- to 12-months of ascertainment (36, 37), it should be possible to develop a complementary tool to predict a new case's likelihood of remission from a CHR syndrome. Such an estimate would not necessarily be merely the inverse of the conversion risk, as different predictors may be relevant.

It is also possible that risk calculators could eventually be used to select clients for different treatment regimens or reclassify risk following completion of a particular intervention. At this stage, the knowledge base for doing so is quite limited, as only a small number of controlled prevention trials in CHR cases have appeared. Collectively, the results support the view that any targeted intervention, whether biological or psychological in approach, is associated with better outcomes than less targeted control conditions (38). Results of two small trials with antipsychotic drugs do not support a prophylactic effect on conversion risk beyond the period of active treatment (39, 40). In general, the use of such medicines in individuals who are below the threshold of full psychosis is not recommended. Intriguing results have been obtained in an initial trial of omega-3 fatty acid supplementation (41); this finding awaits confirmation by independent studies. Psychosocial interventions such as cognitive behavior therapy and family-focused psychoeducation may be beneficial in deflecting the course of illness severity and chronicity (42, 43); however, it remains unclear whether such approaches can prevent onset of illness. Future intervention studies are encouraged to use the risk calculator at end-stage analysis to determine whether treatment efficacy is moderated by initial risk level or profile.

Ultimately, the degree of risk estimated by the risk calculator may be useful for weighing the cost-benefit ratios of various treatment options that emerge from clinical intervention research in the CHR population. Treatments associated with greater risks to the patient (e.g., medication side effects) or greater costs to healthcare delivery systems (e.g., resource and time intensive psychotherapeutic inventions) may best be reserved for those with higher-than-median levels of predicted risk (i.e., 0.16), while cost-effective treatments with benign side effect profiles may be the best option for those whose predicted risk for psychosis is in the lower range.

Like a person at risk for cardiovascular disease or cancer, an individual with a prodromal risk syndrome is more interested in receiving information pertinent to his or her personal risk profile than information about the population at large. Publication of this risk calculator is intended to assist clinicians in providing such personalized risk estimates. It is of course possible for an untrained individual to access these tools and approximate their scores on the set of risk variables. If, in so doing, a high predicted risk of conversion was generated, this could lead to significant personal distress. To mitigate this possibility, we have built in a decision-tree for the on-line calculator that requires confirmation of an interview-based SIPS diagnosis of a prodromal risk syndrome and confirmation that the ratings and test scores were obtained by a professional; if either one of these verifications are missing, the decision tree opts out of making a prediction. The risk for loss of privacy or stigmatization based on access of the prediction tool by untrained users is also mitigated for these reasons.

In summary, a well-performing risk calculator for psychosis is available for application to new patients who meet criteria for a psychosis risk syndrome. Challenges to be addressed in the next phase of research include incorporating biological assays into the risk calculations, extending the analysis to predict likelihood of remission, extending the framework to calculate reductions in risk based on particular interventions and investigating how patients and family members feel about and use this information.

Acknowledgments

References

1. Insel TR. The arrival of preemptive psychiatry. Early intervention in psychiatry. 2007; 1:5–6. [PubMed: 21352102]

2. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of general psychiatry. 2012; 69:220–229. [PubMed: 22393215]

3. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. ArchGenPsychiatry. 2008; 65:28–37.

4. Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkotter J, McGuire P, Yung A. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA psychiatry. 2013; 70:107–120. [PubMed: 23165428]

5. Kattan MW, Yu C, Stephenson AJ, Sartor O, Tombal B. Clinicians versus nomogram: predicting future technetium-99m bone scan positivity in patients with rising prostate-specific antigen after radical prostatectomy for prostate cancer. Urology. 2013; 81:956–961. [PubMed: 23375915]

6. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999; 100:1043–1049. [PubMed: 10477528]

7. Pfeiffer RM, Park Y, Kreimer AR, Lacey JV Jr, Pee D, Greenlee RT, Buys SS, Hollenbeck A, Rosner B, Gail MH, Hartge P. Risk prediction for breast, endometrial, and ovarian cancer in white

women aged 50 y or older: derivation and validation from population-based cohort studies. PLoS medicine. 2013; 10:e1001492. [PubMed: 23935463]

8. Ross PL, Gerigk C, Gonen M, Yossepowitch O, Cagiannos I, Sogani PC, Scardino PT, Kattan MW. Comparisons of nomograms and urologists' predictions in prostate cancer. Seminars in urologic oncology. 2002; 20:82–88. [PubMed: 12012293]

9. Specht MC, Kattan MW, Gonen M, Fey J, Van Zee KJ. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. Annals of surgical oncology. 2005; 12:654–659. [PubMed: 16021535]

10. Addington J, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Addington JA, Cannon TD. North American Prodrome Longitudinal Study (NAPLS 2): overview and recruitment. Schizophrenia research. 2012; 142:77–82. [PubMed: 23043872]

11. McGlashan, TH.; Walsh, BC.; Woods, SW. The Psychosis–Risk Syndrome: Handbook for Diagnosis and Follow-up. Oxford: Oxford University Press; 2010.

12. First, M.; Spitzer, RL.; Gibbon, M.; Williams, B.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.

13. Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. The American journal of psychiatry. 2002; 159:863–865. [PubMed: 11986145]

14. Association AP. Diagnostic and Statistical Manual of Mental Disorders. 5. Washington, D.C: American Psychiatric Association Press; 2013.

15. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. Archives of general psychiatry. 2006; 63:250–258. [PubMed: 16520429]

16. Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R. North American Prodrome Longitudinal Study C. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biological psychiatry. 2015; 77:147–157. [PubMed: 25034946]

17. McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Archives of general psychiatry. 2000; 57:637–648. [PubMed: 10891034]

18. Walker EF, Walder DJ, Reynolds F. Developmental changes in cortisol secretion in normal and at-risk youth. Development and psychopathology. 2001; 13:721–732. [PubMed: 11523856]

19. Riecher-Rossler A, Pflueger MO, Aston J, Borgwardt SJ, Brewer WJ, Gschwandtner U, Stieglitz RD. Efficacy of using cognitive status in predicting psychosis: a 7–year follow-up. Biological psychiatry. 2009; 66:1023–1030. [PubMed: 19733837]

20. Seidman LJ, Giuliano AJ, Meyer EC, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Tsuang MT, Walker EF, Woods SW, Bearden CE, Christensen BK, Hawkins K, Heaton R, Keefe RS, Heinssen R, Cornblatt BA. North American Prodrome Longitudinal Study G. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Archives of general psychiatry. 2010; 67:578–588. [PubMed: 20530007]

21. Giuliano AJ, Li H, Mesholam-Gately RI, Sorenson SM, Woodberry KA, Seidman LJ. Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. Current pharmaceutical design. 2012; 18:399–415. [PubMed: 22239571]

22. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophrenia research. 2004; 68:283–297. [PubMed: 15099610]

23. Brandt, J.; Benedict, RHB. Hopkins Verbal Learning Test-Revised (HVLT-R). Odessa, FL: Psychological Assessment Resources, Inc; 1998.

24. Cornblatt BA, Carrion RE, Auther A, McLaughlin D, Olsen RH, John M, Correll CU. Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. The American journal of psychiatry. 2015 appiajp201513121686.

25. Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophrenia bulletin. 2007; 33:688–702. [PubMed: 17440198]

26. Holtzman CW, Shapiro DI, Trotman HD, Walker EF. Stress and the prodromal phase of psychosis. Current pharmaceutical design. 2012; 18:527–533. [PubMed: 22239584]

27. Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP. Exemplification of a method for scaling life events: the Peri Life Events Scale. Journal of health and social behavior. 1978; 19:205–229. [PubMed: 681735]

28. Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, de Graaf R, van Os J. Childhood abuse as a risk factor for psychotic experiences. Acta psychiatrica Scandinavica. 2004; 109:38–45. [PubMed: 14674957]

29. Sullivan PF. The genetics of schizophrenia. PLoS medicine. 2005; 2:e212. [PubMed: 16033310]

30. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Statistics in medicine. 2011; 30:1105–1117. [PubMed: 21484848]

31. Carrion RE, Cornblatt B, Burton CZ, Tso IF, Auther A, Adelsheim S, Carter CS, Calkins R, Sale T, Taylor SF, McFarlane WR. Personalized prediction of psychosis: External validation of the NAPLS 2 Psychosis Risk Calculator with the EDIPPP project. Under review.

32. Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkotter J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. Archives of general psychiatry. 2010; 67:241–251. [PubMed: 20194824]

33. Kattan MW. Doc, what are my chances? A conversation about prognostic uncertainty. European urology. 2011; 59:224. [PubMed: 21071135]

34. Koutsouleris N, Riecher-Rossler A, Meisenzahl EM, Smieskova R, Studerus E, Kambeitz-Ilankovic L, von Saldern S, Cabral C, Reiser M, Falkai P, Borgwardt S. Detecting the Psychosis Prodrome Across High-risk Populations Using Neuroanatomical Biomarkers. Schizophrenia bulletin. 2014

35. Perkins DO, Jeffries CD, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Mathalon DH, McGlashan TH, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R. Towards a Psychosis Risk Blood Diagnostic for Persons Experiencing High-Risk Symptoms: Preliminary Results From the NAPLS Project. Schizophrenia bulletin. 2014

36. Addington J, Cornblatt BA, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R. At clinical high risk for psychosis: outcome for nonconverters. The American journal of psychiatry. 2011; 168:800–805. [PubMed: 21498462]

37. Schlosser DA, Jacobson S, Chen Q, Sugar CA, Niendam TA, Li G, Bearden CE, Cannon TD. Recovery from an at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. Schizophrenia bulletin. 2012; 38:1225–1233. [PubMed: 21825282]

38. van der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, McGorry P, Cuijpers P. Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12 month and longer-term follow-ups. Schizophrenia research. 2013; 149:56–62. [PubMed: 23870806]

39. McGorry PD, Yung AR, Phillips LJ, Yuen HP, Francey S, Cosgrave EM, Germano D, Bravin J, McDonald T, Blair A, Adlard S, Jackson H. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Archives of general psychiatry. 2002; 59:921–928. [PubMed: 12365879]

40. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, Hawkins KA, Hoffman RE, Preda A, Epstein I, Addington D, Lindborg S, Trzaskoma Q, Tohen M, Breier A. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. The American journal of psychiatry. 2006; 163:790–799. [PubMed: 16648318]

41. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Archives of general psychiatry. 2010; 67:146–154. [PubMed: 20124114]

42. Miklowitz DJ, O'Brien MP, Schlosser DA, Addington J, Candan KA, Marshall C, Domingues I, Walsh BC, Zinberg JL, De Silva SD, Friedman-Yakoobian M, Cannon TD. Family-focused treatment for adolescents and young adults at high risk for psychosis: results of a randomized trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2014; 53:848–858. [PubMed: 25062592]

43. Stafford MR, Jackson H, Mayo-Wilson E, Morrison AP, Kendall T. Early interventions to prevent psychosis: systematic review and meta-analysis. Bmj. 2013; 346:f185. [PubMed: 23335473]
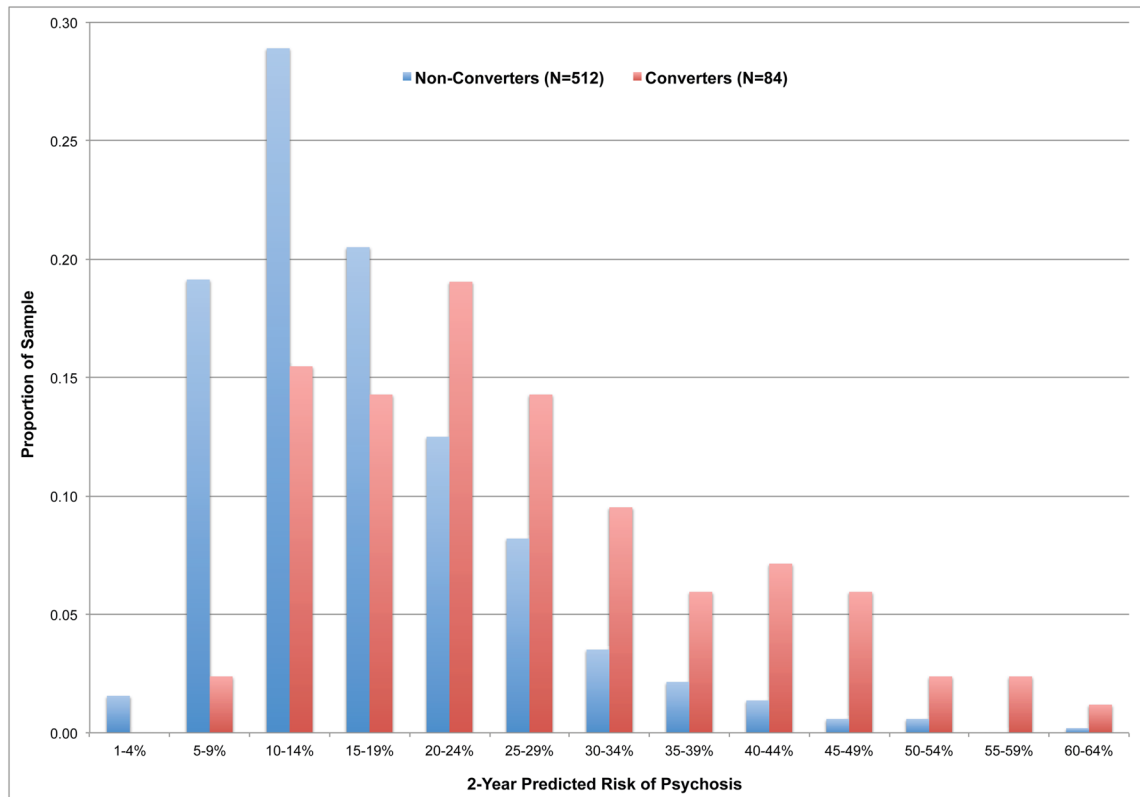
Figure 1.
Frequency distributions of predicted risks in the sample overall (blue) and among converters separately (red). Beginning at a predicted risk of .20 or higher, converters are occur at a higher rate than the sample base rate in each successive risk class.
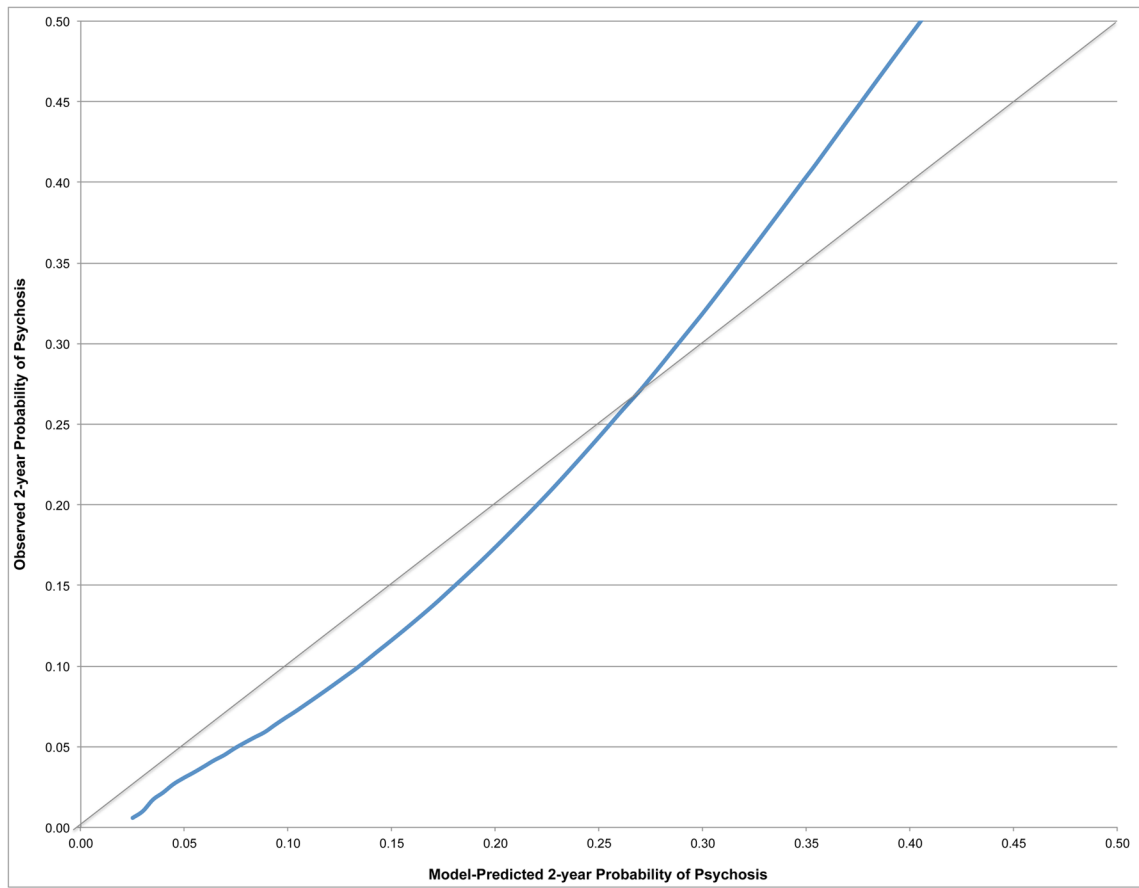
Figure 2.
Calibration plot of the accuracy of model-predicted probability in relation to observed probability of psychosis. The observed probability was estimated using proportional hazard regression evaluating the predicted 2-year probabilities in relation to the observed conversion events, taking into account time to conversion or censoring. The over-fitting bias for the estimated observed probability was corrected using 1000 bootstrap resamples. The plot shows excellent calibration across predicted probabilities of 0.0 – 0.4, corresponding to 95% of the NAPLS 2 sample. Predicted probabilities above 0.4 are too sparsely represented to permit adequate calibration testing.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Characteristics of CHR subjects who were and were not followed up in NAPLS 2.

Variable, Mean (SD)	Followed (N=596)	Not Followed (N=147)	Statistics	N Missing (%)[a]
Age	18.5 (4.3)	18.8 (4.2)	t=−0.88, p=0.38	0 (0.0)
Modified SIPS P1+P2[b]	2.6 (1.6)	2.6 (1.6)	t=0.07, p=0.94	0 (0.0)
Digit Symbol raw score correct	56.8 (13.1)	57.9 (11.6)	t=−0.81, p=0.42	22 (3.7)
HVLT Trials 1–3 summed	25.6 (5.2)	25.1 (5.4)	t=0.85, p=0.39	21 (3.5)
Stressful Life Events	10.5 (5.5)	10.0 (5.6)	t=0.90, p=0.37	69 (11.6)
Variable, N (%)				
Family History of Psychosis	96 (16.1)	18 (12.2)	X^2=1.38, p=0.24	2 (0.0)
Decline in Functioning > 0	270 (45.4)	75 (53.5)	X^2=3.05, p=0.08	1 (0.0)
Traumas > 1	289 (56.2)	48 (48.5)	X^2=2.00, p=0.16	82 (13.7)
Males	344 (57.7)	77 (52.4)	X^2=1.36, p=0.24	0 (0.0)

[a]Among those followed. Missing values were multiply imputed with the multivariate imputation by chained equations (MICE) method prior to use in prediction analyses.

[b]Modified such that all levels in the non-prodromal range (0–2 on original scale) now defined as 0, levels in the prodromal range (3–5 on original scale) now defined as 1–3, and psychotic intensity (6 on original scale) now defined as 4.

Table 2

Statistics for individual predictor variables in the multivariate Cox proportional hazards regression analysis of conversion to psychosis.

| Predictor | Multivariate Model | | | C-index[a] | |
	Hazard Ratio	95% CI	p	Decrement if removed	Increase if added
Modified SIPS P1+P2	2.1	1.6 – 2.7	<0.001	0.092	N/A[b]
Decline in social functioning	1.3	1.1 – 1.5	0.01	0.014	0.015
HVLT Trials 1–3 summed	0.8	0.6 – 0.9	0.05	0.007	0.029
Digit Symbol raw score correct	0.8	0.5 – 1.1	0.10	0.006	0.033
Age	0.7	0.5 – 1.1	0.09	0.004	0.012
Stressful Life Events	1.2	0.9 – 1.6	0.21	0.001	−0.004
Family History of Psychosis	1.2	0.7 – 2.1	0.55	0.000	0.001
Traumas	1.0	0.8 – 1.3	0.99	−0.004	0.002

[a] Harrell's C-index (equivalent to the area under the receiver operating characteristic curve or AUC) was used to quantify the discrimination ability for separating converters and non-converters. The C-index for the overall model was .714.

[b] The base model included only the modified SIPS P1+P2 scores; the C-index for the base model was 0.666.

Table 3

Prediction statistics for conversion to psychosis across various levels of model-predicted risk.

Individual's Predicted Risk is:	Base rate of Predicted Risk Class	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
0.05 to 1.00	97.5	14.3	93.3	98.8	2.7
0.10 to 1.00	78.9	16.8	96.0	94.1	23.6
0.15 to 1.00	52.9	21.6	94.3	81.0	51.8
0.20 to 1.00	33.4	28.1	93.0	66.7	72.1
0.25 to 1.00	20.6	32.5	90.7	47.6	83.8
0.30 to 1.00	12.4	39.2	89.5	34.5	91.2
0.35 to 1.00	8.1	41.7	88.3	23.8	94.5
0.40 to 1.00	5.2	48.4	87.8	17.9	96.9
0.45 to 1.00	3.5	47.6	87.1	11.9	97.9
0.50 to 1.00	2.0	41.7	86.5	6.0	98.6
0.55 to 1.00	1.2	28.6	86.1	2.4	99.0
0.60 to 1.00	1.0	16.7	85.9	1.2	99.0