# Translating Scientific Opportunity Into Public Health Impact

## *A Strategic Plan for Research on Mental Illness*

*Thomas R. Insel, MD*

**Context:** Research has transformed many areas of medicine, with profound effects on morbidity and mortality. Exciting advances in neuroscience and genomics have transformed research but have not yet been translated to public health impact in psychiatry. Current treatments are necessary but not sufficient for most patients.

**Objectives:** To improve outcomes we will need to (1) identify the neural circuitry of mental disorders, (2) detect the earliest manifestations of risk or illness even before cognition or behavior appear abnormal, (3) personalize care based on individual responses, and (4) implement broader use of effective psychosocial interventions.

**Results:** To address these objectives, NIMH, working with its many stakeholders, developed a strategic plan for research. The plan calls for research that will (1) define the pathophysiology of disorders from genes to behavior, (2) map the trajectory of illness to determine when, where, and how to intervene to preempt disability, (3) develop new interventions based on a personalized approach to the diverse needs and circumstances of people with mental illnesses, and (4) strengthen the public health impact of NIMH-supported research by focusing on dissemination science and disparities in care.

**Conclusions:** The NIMH is shifting its funding priorities to close the gap between basic biological knowledge and effective mental health care, paving the way for prevention, recovery, and cure.

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NEW TOOLS IN BIOMEDICAL research have created an era of unprecedented discovery. Genomics is transforming our understanding of complex diseases, from inflammatory bowel disease to macular degeneration. Imaging has become standard for diagnosis in clinical practice, from cardiology to oncology. Biomarkers are changing our approach to the diagnosis of disease and to the administration of many medical treatments, allowing interventions to be tailored to the specific physiology of each patient. As a result, nearly 1 million cardiovascular deaths were averted last year, and cancer is increasingly being viewed as a chronic, treatable disease rather than a fatal diagnosis.[1,2] For the past decade, researchers have been anticipating how the power of genomics and imaging will yield biomarkers and new treatments for mental disorders. Despite high expectations, neither genomics nor imaging has yet impacted the diagnosis or treatment of the 45 million Americans with serious or moderate mental illness each year.[3] While we have seen profound progress in research (with molecular, cellular, and systems neuroscience revealing new, unexpected insights about the brain), the gap between the surge in basic biological knowledge and the state of mental health care in this country has not narrowed and may be getting wider.[4-6]

How will we close this gap? The National Institute of Mental Health (NIMH) has been considering new answers to this question for the past 2 years. This article begins with a summary of the current state of the field, based on several recent studies. This appraisal will strike many as harsh, but only by accepting our current needs will we be able to move forward to ensure positive outcomes in the future. Based on these current needs and new scientific opportunities, the NIMH worked with its many stakeholders to develop a strategic plan for mental health research. The plan is intended to realize the institute's mission: to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

### AN ASSESSMENT OF THE FIELD

In 1986, with the potential of the dexamethasone-suppression test as a diagnostic bio-

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marker for depression, the promise of positron emission tomography for diagnosing schizophrenia, and the advent of new generations of antidepressant and antipsychotic drugs, former NIMH Director, Herbert Pardes, MD, proclaimed: "Neuroscience is offering not only new information but startling new technologies and approaches. . . . While much in the way of clinical implications from brain research is promise, there is an expectation of great change over the next ten to twenty years."[7] Now, more than 20 years later, what promise have we realized in the diagnosis and treatment of individuals with serious mental illness? In contrast to the steadily decreasing mortality rates of cardiovascular disease, stroke, and cancer, there is no evidence for reduced morbidity or mortality from any mental illness.[2,8-10] A recent analysis of mortality in 8 states reported that individuals with serious mental illness die 13 to 32 years earlier than those without mental illness.[11] Rates of suicide have remained constant, resulting in more than 30 000 deaths per year in the United States.[12] The number of suicides is greater than the number of homicides, deaths due to AIDS, or mortality from all but 5 forms of cancer.[12] Premature deaths related to mental illness were more often due to medical comorbidity, especially cardiovascular and pulmonary disease, rather than suicide.[11] Tobacco use may be an important mediator of increased medical comorbidity in individuals with mental illness. While approximately 26% of the population will experience mental illness in a given year,[3] Lasser et al[13] estimate that 44% of cigarettes are consumed by individuals with current mental illness.

Aside from mortality, is there evidence to support that progress in psychiatry leads to reductions in morbidity or disability in people with serious mental illness? The World Health Organization Global Burden of Disease study listed mental illnesses as the leading source of disability in Americans and Canadians aged 15 to 44 years, accounting for nearly 40% of all medical disability in this age range.[14] The National Comorbidity Survey (1992) and National Comorbidity Survey Replication (2002) used face-to-face surveys to compare disability from mental disorders in nearly 10 000 households. The results demonstrate no change in the prevalence of mental illness between 1992 and 2002, but increased rates of treatment. For all classes of mental illness, rates of treatment increased from 20% to 33% during this 10-year period.[10] Curiously, despite increased treatment, there was no evidence for decreased disability. Indeed, the more recent cohort shows a loss of income that is considerably greater than all previous reports.[15] While more people are receiving treatment, fewer than half of those who are treated receive treatments for which there is any evidence base. For instance, among individuals with major depressive disorder (an illness with substantial morbidity and mortality), even though 50% receive treatment, only about 20% receive minimally adequate care.[16]

Even when appropriate care is provided, a series of NIMH-sponsored effectiveness trials (involving nearly 10 000 patients seen at 200 clinical sites, including primary care offices and community mental health centers) demonstrated the limits of current pharmacological treatment for mental illness. These trials (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE], Sequenced Treatment Alternatives to Relieve Depression [STAR*D], and Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD]) have been the subject of many articles and reviews, as they represent the largest trials in psychopharmacology not supported by the pharmaceutical industry. Accepted pharmacological treatments were studied to determine effectiveness in real-world patients with comorbid illnesses and suicidal ideation, those more typical of clinical practice compared with those selected for typical industry-sponsored efficacy trials. In aggregate, these studies reveal that current medications are far from sufficient. In CATIE, 74% of patients with chronic schizophrenia discontinued their medications within 18 months.[17] In the STAR*D trial, 31% of patients with major depressive disorder were in remission after taking a selective serotonin reuptake inhibitor for 14 weeks (no placebo control is available).[18] In the STEP-BD trial, 24% of patients with bipolar disorder experienced 8 consecutive weeks of depression remission throughout the 26-week trial, results that were no better with medication than with placebo.[19] Given that these trials used evidence-based treatments of well-documented efficacy that were administered with optimal clinical standards, the results show the significant limitations of current pharmacological interventions. This point bears emphasis. These limited outcomes, in terms of recovery and remission, are not due to suboptimal delivery of care. Instead, with optimal care using today's medications, too many people will not recover.

While psychosocial interventions have received much less marketing attention than pharmacological treatments, the results are arguably more encouraging. For people with schizophrenia, assertive community treatment, family psychoeducation, and supported employment have substantial effects on functional recovery and relapse rates.[20] Many studies have found cognitive behavior therapy to be an effective treatment for mood and anxiety disorders. However, few patients actually receive evidence-based psychosocial treatments.[21]

Given the limited improvements associated with current treatments, it is not surprising that the outcome data for serious mental illness in 2008 are disappointing. Today, mental disorders are the largest diagnostic category for those receiving disability (Supplemental Security Income and Social Security disability income) at a cost of almost $25 billion per year.[22] Of those with schizophrenia, roughly 80% remain unemployed,[23] and relatively few will marry.[24,25] Despite 5 decades of antipsychotic medication and deinstitutionalization, there is little evidence that the prospects for recovery have changed substantially in the past century. For bipolar disorder, the long-term picture is equally concerning. Sixty percent of affected individuals exhibit comorbid substance abuse dependency,[26] and 20% currently experience ideas of suicide.[27] Major depressive disorder, which one might consider more responsive to treatment, remains too often a chronic, disabling illness with 30% of patients not remitting on current therapies.[18] Typically, clinical trials for antidepressant medications that seek some improvement in symptoms rather than remission and that consider improvement after 12 weeks of treatment a success are setting a very low bar for people

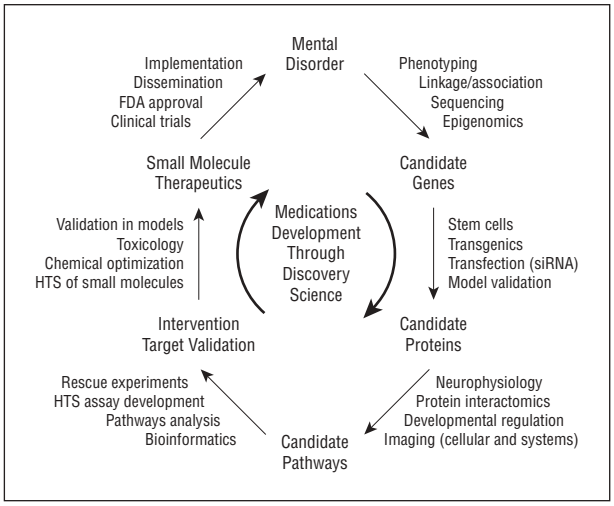


**Figure 1.** Clinical progress in mental health care requires the development of new, effective psychosocial and biomedical therapies. This figure depicts a reverse translational approach to the development of new medications based on an understanding of the molecular pathophysiology of mental disorders. FDA indicates Food and Drug Administration; HTS, high throughput screening; siRNA, small interfering RNA.

with a life-threatening disorder defined by acute suffering. Posttraumatic stress disorder, which was a primary focus for the NIMH in 1947,[28] is not less prevalent in either the clinic or the community in 2008. Recent estimates indicate that the number of posttraumatic stress disorder cases expected as a result of the current wars in Iraq and Afghanistan could exceed 300 000.[29,30] Clearly, these data on prevalence, treatment, and mortality indicate that mental illness remains an urgent, unmet public health concern.

## OPPORTUNITIES FOR PROGRESS

Despite the sobering facts of current mental health treatment and outcomes, the field of psychiatry and our patients do have reason to be hopeful. In psychiatry, we have the advantage of witnessing some notable successes in other fields of medicine, enabling the identification of some winning strategies. Herein, I will distill these to 4 opportunities that can transform our approach to mental illness.

First, we can understand mental disorders as brain disorders, that is, disorders of specific brain circuits. Neuroscience can reveal the pathophysiology of the mental disorders. Most biological research in the past 4 decades has been focused on the mechanisms of drug action, as if the cause of schizophrenia were an absence of neuroleptics. To be fair, throughout most of this period, we did not have many other options; attempting to understand the disorder by gaining knowledge of the mechanism of treatment was the best option available. Today there are new, powerful discovery tools that have already proven to be successful in many other areas of medicine. These will begin to elucidate the pathophysiology of schizophrenia, mood, and anxiety disorders just as they have given us transforming insights about diabetes, heart disease, and cancer.

Genomic investigation offers a unique opportunity for understanding the pathophysiology of mental disorders. Most mental disorders are more heritable than the medical disorders for which genomics has been so important.[31] In these mental disorders, genomics will be critical for defining the risk architecture, suggesting key cellular and neural pathways for pathophysiology, and identifying novel targets for intervention. It will be important to remember that genes do not code for disorders, they code for proteins, and there will be many genes involved in the categories we now define as singular disorders. The task will be to define the combinatorial code of genomic variations that alter protein expression which, in turn, affects brain development, biasing brain circuits toward disease or resilience. Just as understanding the key tyrosine kinase involved in chronic myeloid leukemia led to a cure for this once fatal disorder,[32] understanding the pathophysiology of mental disorders is our best strategy for finding targets for new generations of far more effective treatments (**Figure 1**).

Of course, mental disorders are, like most complex medical illnesses, the result of experience as well as genetic vulnerability. Recent breakthroughs allow us, for the first time, to understand how experience and biology interact at multiple levels. The emerging field of epigenetics is revealing how experience alters the expression of the genome, in the short-term providing a mechanism for learning[33] and in the long-term perhaps explaining how early stressful experiences can have enduring effects on behavior in the presence of genetic vulnerability.[34] Neuroscience research teaches us about the remarkable plasticity of brain circuits, showing that rapid reorganization takes place in the cortex in response to changing input. For the first time, we can explore not only how brain circuits are involved in mental illness, but how experiences become encoded biologically to alter thinking, perception, and behavior.[35]

Second, we can understand mental disorders as developmental brain disorders (example of schizophrenia in **Figure 2**). Currently, mental disorders are diagnosed by symptoms that emerge at a late stage, presumably years after brain systems veer from more typical development. Diagnosing schizophrenia or bipolar disorder with the emergence of psychosis may be analogous to diagnosing coronary artery disease by myocardial infarction. One of the most hopeful approaches to reducing the morbidity and mortality of serious mental illness borrows a page from the cardiology playbook. By developing biomarkers for early diagnosis, we may be able to preempt many of the most disabling aspects of our most severe mental illnesses. For example, a combination of 3 factors (genetic risk, unusual thought content, and changes in social functioning) can predict 80% of conversions to psychosis in individuals with identified prodromal syndrome.[36] The predictive power of such factors has not yet been examined in a larger population, but if the psychotic phase of this illness can be preempted with either psychosocial or medical interventions, much of the disability associated with schizophrenia may be avoided.

Third, we can begin to design a pathway to personalized treatments (**Figure 3**). The classic randomized control trial has been useful for characterizing medications, but it often fails to give patients what they want: information on what is best for their specific situation. Recent research hints at the heterogeneity of mental disorders at the level of genes and brain circuits.[37] Is it sur-

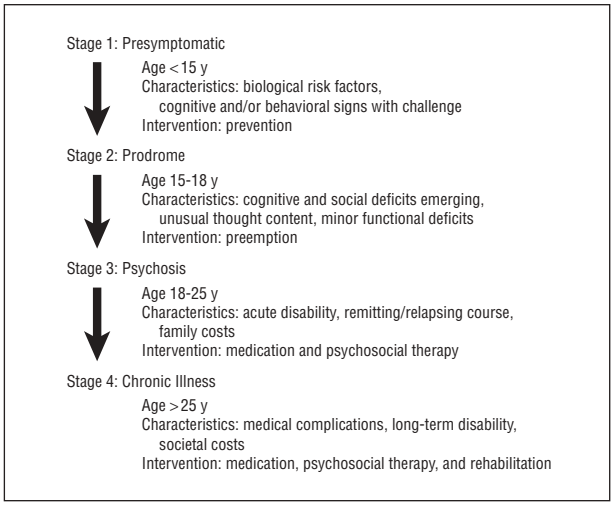


**Figure 2.** Potential neurodevelopmental stages of schizophrenia. This model presumes that psychosis is a late stage of schizophrenia. Earlier stages could be detected either by identifying biomarkers or cognitive deficits (potentially with challenge tests), analogous to the detection of early stages of coronary artery disease.

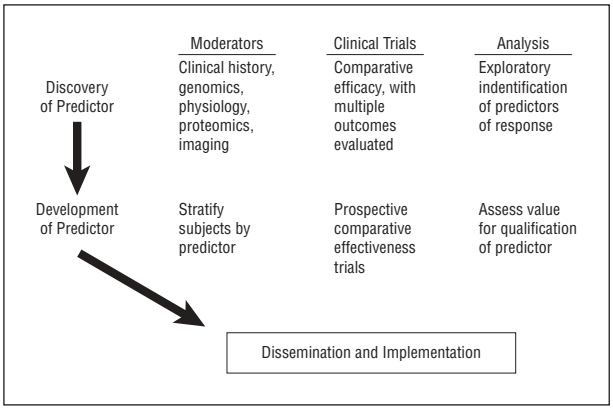


**Figure 3.** Personalized medicine will require clinical trials that assess individual patterns of response in addition to group means. Moderators are potential predictors of response that can then be tested in prospective trials. The pathway includes discovery, development, and dissemination with the ultimate goal of tailoring clinical practice to the needs of each individual.

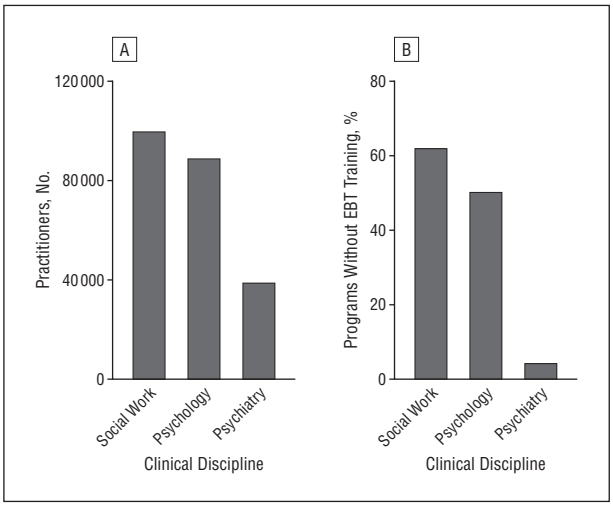


**Figure 4.** Much of the psychotherapy workforce is not trained to provide evidence-based treatments. A, The number of practitioners within mental health–related clinical disciplines in the United States.[42] B, The percentage of mental health–related clinical training programs that do not require gold standard training (both didactic and clinical supervision) in any evidence-based psychotherapies. More than 50% of psychology and social work programs do not require gold standard training in any evidence-based psychotherapies. Psychology data include both PhD and PsyD training programs.[43] EBT indicates evidence-based therapy.

prising that individual responses to treatment may vary from what is seen with group means from clinical trials? Have we fully considered that absence of a statistically significant mean effect in 500 patients could obscure a profound effect in 50? Future clinical trials will need to build in moderators of treatment response.[38] Moderators are individual characteristics associated with treatment response. They can be genetic traits, imaging results, plasma proteins, or clinical features. While their initial detection emerges from exploratory analyses, their practical value can be determined in subsequent prospective trials. One can imagine using genotype and imaging data along with clinical presentation to determine which patient with depression will respond best to cognitive behavior therapy vs medication or which medication at which dose will yield an optimal response.

Finally, we need to remember the untapped power of select psychosocial treatments. Cognitive behavior therapy is an effective treatment for many people with mood and anxiety disorders. In one remarkable example, a randomized clinical trial of individuals who recently attempted suicide demonstrated a 50% reduction in reattempts in the 18 months following treatment.[39] In the past 2 decades, many controlled studies have demonstrated the value of various psychosocial interventions for psychotic illnesses, from assertive community treatment to supported employment. Drake et al,[40] among others, has shown a 6-fold increase in employment for people with schizophrenia who were receiving supported employment, including positive outcomes 8 to 12 years following the intervention.[41] We have powerful, evidence-based psychosocial interventions, but they are not widely available and, when available, may not be supported by payers. A serious deficit exists in training for evidence-based psychosocial interventions. Manderscheid and Henderson[42] estimate that the mental health workforce may include over 500 000 professionals, spanning from psychiatrists to marriage and family therapists. How many of these therapists are trained to provide evidence-based therapy? **Figure 4** provides data from a survey of training programs by Weissman and colleagues,[43] showing that for psychologists and social workers, 2 of the largest sectors of this workforce, more than half of the training programs in 2004 required no training in a single evidence-based psychotherapy.

None of the progress we are seeing in clinical research will have the necessary impact on public health unless we can close the gap between what we know and what we apply in practice. This translational gap exists throughout medicine,[5] but the problem is more acute in psychiatry because so much of mental health care takes place outside the health care system. Individuals with serious mental illness appear in the criminal justice system, homeless shelters, emergency departments, and college counseling centers—almost everywhere except in specialized clinics and hospitals with the resources for

optimal treatment of serious brain disorders. The President's New Freedom Commission on Mental Health report[21] addressed the need for transformation of the mental health care system by reintegrating behavioral health into health care and by reorienting mental health care to become patient- and family-centered. Relative to developing a new generation of medications or finding a biomarker for the earliest stages of schizophrenia, this transformation may seem like the proverbial low-hanging fruit, yet it turns out to be an equally significant challenge. Both scientific and political efforts will be required to ensure that the fruits of research are disseminated efficiently to those who most need it, often poor, underserved, and socially isolated individuals.

## A STRATEGIC PLAN

Building on these opportunities for progress, the NIMH, working with its many stakeholders, developed 4 strategic objectives for NIMH funding. A full explanation of each objective is provided at http://www.nimh.nih.gov. The main points in brief are the following:

Objective 1. Promote discovery in the brain and behavioral sciences to fuel research on the causes of mental disorders. We need a renewed focus on discovery science, identifying the molecular and cellular candidates for normal and abnormal brain function. Genomics and epigenomics will be important pathways into the pathophysiology of mental disorders. Current technology permits reverse translation, for instance, using induced pluripotent stem cells to move from clinical genetics to basic biology.[44] A greater understanding of pathophysiology can transform diagnosis, permitting early detection and biological validation of mental disorders.

Objective 2. Chart mental illness trajectories to determine when, where, and how to intervene. If mental disorders can be understood as developmental brain disorders, we can develop critical insights into risk and resilience. Prevention can then be targeted based on individual risk as well as cultural context. If longitudinal studies can yield biomarkers for early detection, then interventions can be focused on preemption of disability, with profound public health consequences.

Objective 3. Develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses. Current treatments are necessary but not sufficient for most patients. We need a new generation of innovative clinical trials focused on personalized care, recovery, and diverse populations. Personalized care is as essential in mental illnesses as in other fields of medicine. Studies that define which treatment is best for an individual can move us beyond the trial and error approach of current interventions, allowing a tailored, more effective evidence base for care.

Objective 4. Strengthen the public health impact of NIMH-supported research. We need to improve our understanding of the factors that affect access to service, quality and cost of services, and the means by which newly discovered effective mental health interventions are disseminated and implemented. Translational research will focus not only on "bench to bedside," but also on "bedside to practice" as the institute focuses on increasing its public health impact, addressing disparities in mental health care, and reducing the burden of mental illness.

## CLOSING THE GAP

This plan aims to close the gap between basic biological knowledge and effective mental health care in the United States. Each strategic objective will serve as a guide, ensuring that basic and clinical research goals will have high applicability to developing and implementing new and effective mental disorder treatments. Implementation of this plan will include educating NIMH peer-review committees, grantees, and our various stakeholders. The NIMH is shifting its funding priorities to meet each of these objectives. For unsolicited grant applications, the strategic plan objectives will guide funding decisions by defining program priorities within those grants deemed scientifically meritorious by peer review. For research areas that are not being addressed by unsolicited grant applications, the NIMH will set aside funds for specific funding opportunity announcements that will solicit applications and ensure progress on each of these objectives.

While clinical neuroscience research offers hope for the future, the problems of millions of Americans with serious mental illness are urgent, requiring immediate attention. Unfortunately, the problems of dissemination or implementation are no less complex than understanding the intracellular signaling pathways or the language of genetic transcription. The NIMH seeks a difficult balance between supporting research with short-term policy or service implications (such as comparative effectiveness trials of current treatments) and supporting longer-term efforts for discoveries that can truly transform practice. We must do both, recognizing that the urgent problems may not be resolved simply with better access to existing treatments.

## CONCLUSIONS

Progress will only be made with a realistic assessment of the current state of affairs, an acceptance of just how serious the challenge will be, and a recognition that the task can be mastered. The challenge for those who seek to prevent and cure mental illness is awesome. In the past, we advanced via serendipitous discoveries, stumbling on treatments that helped people to get better but not well. In the future, to find effective preventions and cures, we will need a more disciplined scientific approach, based on identifying individual risk and the pathophysiology of each disorder. Successes in other areas of biomedical research give us reason to be optimistic that we will prevail, but we will need a new strategic approach that ensures bringing the best tools of genomics and neuroscience to solve the tough questions of pathophysiology of mental disorders as well as innovative behavioral science to get new, effective treatments into the hands of clinicians.

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## REFERENCES

1. Cancer survivorship–United States, 1971-2001. *MMWR Morb Mortal Wkly Rep*. 2004;53(24):526-529.
2. National Heart Lung and Blood Institute. *Morbidity and Mortality: 2007 Chartbook on Cardiovascular, Lung, and Blood Diseases*. Bethesda, MD: National Heart Lung and Blood Institute; 2007.
3. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month *DSM-IV* disorders in the National Comorbidity Survey Replication [erratum published in *Arch Gen Psychiatry*. 2005;62(7):709. Merikangas, Kathleen R added]. *Arch Gen Psychiatry*. 2005;62(6):617-627.
4. Gould TD, Manji HK. The molecular medicine revolution and psychiatry: bridging the gap between basic neuroscience research and clinical psychiatry. *J Clin Psychiatry*. 2004;65(5):598-604.
5. Woolf SH. The meaning of translational research and why it matters. *JAMA*. 2008; 299(2):211-213.
6. Sartor RB. Translational research: bridging the widening gap between basic and clinical research. *Gastroenterology*. 2003;124(5):1178.
7. Pardes H. Psychiatric researchers, current and future. *J Clin Psychopharmacol*. 1986;6(1):A13-A14.
8. National Cancer Institute. Surveillance Epidemiology and End Results, Cancer Statistics Review, 1975-2005. http://seer.cancer.gov/csr/1975_2005/sections.html. Accessed June 18, 2008.
9. Kessler RC, Berglund P, Borges G, Nock M, Wang PS. Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *JAMA*. 2005;293(20):2487-2495.
10. Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, Wang P, Wells KB, Zaslavsky AM. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515-2523.
11. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.
12. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. *Natl Vital Stat Rep*. 2008;56(10).
13. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *JAMA*. 2000; 284(20):2606-2610.
14. World Health Organization. The world health report 2002: reducing risks, promoting healthy life. Geneva, Switzerland: World Health Organization; 2002: http://www.who.int/whr/2002/en/. Accessed June 18, 2008.
15. Kessler RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, Wang PS, Zaslavsky AM. Individual and societal effects of mental disorders on earnings in the United States: results from the national comorbidity survey replication. *Am J Psychiatry*. 2008;165(6):703-711.
16. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-3105.
17. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
18. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. 2007;9(6): 449-459.
19. Thase ME. STEP-BD and bipolar depression: what have we learned? *Curr Psychiatry Rep*. 2007;9(6):497-503.
20. Pharoah F, Mari J, Rathbone J, Wong W. Family intervention for schizophrenia. *Cochrane Database Syst Rev*. 2006;(4):CD000088.
21. President's New Freedom Commission on Mental Health, Achieving the Promise: Transforming Mental Health Care in America. Final Report. DHHS publication No. SMA-03–3832. 2003. http://www.mentalhealthcommission.gov/reports/FinalReport/downloads/FinalReport.pdf. March 17, 2008.
22. Insel TR. Assessing the economic costs of serious mental illness. *Am J Psychiatry*. 2008;165(6):663-665.
23. Shean GD. Recent developments in psychosocial treatments for schizophrenic patients. *Expert Rev Neurother*. 2007;7(7):817-827.
24. Woods SW, Ziedonis DM, Sernyak MJ, Diaz E, Rosenheck RA. Characteristics of participants and nonparticipants in medication trials for treatment of schizophrenia. *Psychiatr Serv*. 2000;51(1):79-84.
25. US Census Bureau. Current population survey: marital status and living arrangements. 1998. http://www.census.gov/population/www/socdemo/ms-la.html. Accessed March 13, 2008.
26. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264(19):2511-2518.
27. Goldberg JF, Allen MH, Miklowitz DA, Bowden CL, Endick CJ, Chessick CA, Wisniewski SR, Miyahara S, Sagduyu K, Thase ME, Calabrese JR, Sachs GS. Suicidal ideation and pharmacotherapy among STEP-BD patients. *Psychiatr Serv*. 2005;56(12):1534-1540.
28. Grob GN. Creation of the National Institute of Mental Health. *Public Health Rep*. 1996;111(4):378-381.
29. Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004;351(1):13-22.
30. Tanielian TL, Jaycox L, eds. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery*. Santa Monica, CA: RAND Corporation; 2008.
31. McGuffin P, Riley B, Plomin R. Genomics and behavior: toward behavioral genomics. *Science*. 2001;291(5507):1232-1249.
32. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood*. 2005;105(7):2640-2653.
33. Levenson JM, Sweatt JD. Epigenetic mechanisms in memory formation. *Nat Rev Neurosci*. 2005;6(2):108-118.
34. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004;7(8):847-854.
35. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell*. 2007;131(2):391-404.
36. 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. *Arch Gen Psychiatry*. 2008;65(1):28-37.
37. Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Roccanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia [published online ahead of print March 27, 2008]. *Science*. 2008;320(5875):539-543.
38. Kraemer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. *JAMA*. 2006;296(10):1286-1289.
39. Brown GK, Ten Have T, Henriques GR, Xie SX, Hollander JE, Beck AT. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. *JAMA*. 2005;294(5):563-570.
40. Drake RE, McHugo GJ, Bebout RR, Becker DR, Harris M, Bond GR, Quimby E. A randomized clinical trial of supported employment for inner-city patients with severe mental disorders. *Arch Gen Psychiatry*. 1999;56(7):627-633.
41. Becker D, Whitley R, Bailey EL, Drake RE. Long-term employment trajectories among participants with severe mental illness in supported employment. *Psychiatr Serv*. 2007;58(7):922-928.
42. Manderscheid RW, Henderson MJ. *Mental Health, United States, 2002*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
43. Weissman MM, Verdeli H, Gameroff MJ, Bledsoe SE, Betts K, Mufson L, Fitterling H, Wickramaratne P. National survey of psychotherapy training in psychiatry, psychology, and social work. *Arch Gen Psychiatry*. 2006;63(8):925-934.
44. Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons [published online ahead of print July 31, 2008]. *Science*. 2008;321(5893):1218-1221.