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Schizophrenia Research and Care

Assessment of Challenges and Opportunities

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MILKEN INSTITUTE

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The Milken Institute is a nonprofit, nonpartisan think tank focused on accelerating measurable progress on the path to a meaningful life. With a focus on financial, physical, mental, and environmental health, we bring together the best ideas and innovative resourcing to develop blueprints for tackling some of our most critical global issues through the lens of what's pressing now and what's coming next.

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Foreword

While our work at the Milken Institute Science Philanthropy Accelerator for Research and Collaboration (SPARC) spans a wide range of brain and mental health conditions, from neurodegeneration to serious mental illnesses (SMIs), schizophrenia stands out within the SMI umbrella as one of the most visible and urgent challenges in public discourse. Affecting millions globally, schizophrenia remains misunderstood and under-resourced. Its impact on individuals, families, and society is profound, with consequences that ripple across health, housing, and justice systems.

People living with schizophrenia—and their loved ones—deserve better. This report, *Schizophrenia Research and Care: Assessment of Challenges and Opportunities*, reflects that commitment. It draws on insights from over 70 experts, including those with lived experience, to identify major gaps in research and care and lay the groundwork for solutions. Scientific understanding has advanced considerably in the last decade—particularly in genetics and neurobiology. Yet the gap between knowledge and practice remains wide. Treatments often miss the symptoms most tied to recovery, and care systems are fragmented and reactive.

This report is a call to action. We know what works: biologically informed approaches to schizophrenia's heterogeneity, a broader therapeutic toolbox, coordinated specialty care, and community-based supports. What's needed now is scale, access, and sustained innovation.

SPARC works at the intersection of science and philanthropy, driving increased rigor in funders to generate better science, accelerated innovation, and patient-informed approaches. We help funders understand scientific ecosystems and the problems for which their resources can solve and catalyze progress. But we don't just follow the evidence—we help direct the biomedical ecosystem toward scientific and medical solutions that move beyond discovery toward real-world impact. The schizophrenia community is ready to see real change and direct outcomes to empower those with this condition to take ownership of their lives.

A forthcoming companion publication will explore care models and access in greater depth, offering a roadmap for transforming crisis-driven systems into proactive, person-centered care for individuals diagnosed with schizophrenia. Together, these efforts reflect a strategic approach to advancing schizophrenia research and care—one that is informed, intentional, and built for impact.

Cara Altimus, PhD
Managing Director, SPARC, Milken Institute

Executive Summary

Schizophrenia—a leading cause of disability—is a serious, chronic brain disorder affecting about 24 million people worldwide. The condition features various symptoms, the most well-known being psychosis, a state of disconnection from reality characterized by hallucinations, delusions, and disorganized thought. Life expectancy for people with schizophrenia is approximately 15–20 years shorter than average due to factors including medication side effects and common comorbidities such as cardiovascular disease, substance use disorders, and depression.

When symptoms go untreated, individuals often rely heavily on emergency services during crisis and cycle among hospitalization, homelessness, and interaction with the criminal justice system. This pattern drives an estimated annual economic burden of over $300 billion in the US—a substantial sum on par with that of costly chronic diseases like diabetes. When the mental health system fails to provide adequate care, costs are pushed onto other systems, with consequences for society, caregivers, and individuals struggling with schizophrenia.

Scientific understanding of schizophrenia has advanced significantly in the past few decades, especially regarding genetics and underlying pathology. Yet critical gaps persist between scientific discovery and clinical practice. Researchers have gained considerable knowledge about biology and best practices for treatment, but objective diagnostic tests are needed, and treatment limitations are significant.

Available antipsychotics primarily address positive symptoms like hallucinations and delusions in those who respond, and medications inadequately treat symptoms, such as cognitive impairments, that most strongly correlate with functional recovery. This treatment gap leads to significant unmet need—only around 20 percent of diagnosed individuals achieve functional recovery. As social problems associated with unmanaged symptoms accumulate, individuals disengage from their communities, limiting their recovery trajectories. Yet treatment paradigms continue to prioritize reducing positive symptoms over addressing the problems that most impact functional outcomes.

Despite the substantial economic burden and unmet clinical need, schizophrenia research remains underfunded compared to conditions of similar impact. Much of the federal research investment has focused on genetics, yielding insights into underlying mechanisms, yet translation into improved treatments lags. Private funding also does not match the levels seen for other conditions where philanthropic capital helps fill critical gaps—due in part to persistent stigma that affects advocacy efforts. Funding misalignment extends beyond the scale of investment to limited areas of focus. Investments are not consistently directed toward what matters most to individuals with lived experience, nor do they always target research with near-term therapeutic potential.

Key Opportunities to Advance Schizophrenia Research and Care

This report synthesizes an extensive literature review and insights from over 70 experts across diverse specialties and backgrounds, including those with lived experience, to identify strategic opportunities for philanthropic impact. Understanding the underlying biology and current treatment landscape was necessary to find strategic solutions to advance research, treatment, care delivery, and access. This work revealed interconnected challenges and opportunities across five important areas that impact schizophrenia care: research priorities, clinical treatment, models of care, social context, and systemic barriers.

Research priorities: Decades of biological research have revealed key mechanisms underlying schizophrenia. But this research has not yet translated into improved treatments or better evidence-based care. Implementation science is one way to narrow the delay, which can be as long as 15–20 years, from research evidence to practice. Philanthropic support can fund studies to identify essential elements of effective interventions, support data aggregation across programs, and advance emerging technologies like digital biomarkers and artificial intelligence (AI) applications for diagnosis and monitoring.

Clinical treatment: Current pharmaceutical options manage psychotic symptoms, leaving other debilitating symptoms unaddressed. Key support opportunities include developing biomarkers and precision medicine approaches to enable personalized treatment selection, advancing novel therapeutics to address all symptom domains, and increasing access to underutilized evidence-based treatments, such as clozapine and long-acting injectable medications.

Models of care: The current care system is fragmented in ways that worsen disparities and limit effectiveness. Coordinated specialty care demonstrates strong evidence for early intervention, but accessibility is an issue. Capacity constraints, long waitlists, geographic disparities, and insurance barriers limit access to care. Strategic investments could expand access to evidence-based care models and develop programs to ease transitions between levels of care. A companion publication will further explore models and accessibility of care because the care landscape is complex.

Social context: Schizophrenia is among the most stigmatized medical conditions and occurs within a broader context that shapes treatment, care, and recovery outcomes. Investment opportunities may include developing and implementing effective interventions to reduce stigma, supporting family education and peer support programs, and promoting community integration and belonging.

Systemic barriers: Issues affecting people with schizophrenia intersect with multiple systems, including health care, criminal justice, and housing. Some aspects require policy change to spur reform. Insurance reimbursement models remain largely misaligned with the complexity of SMI treatment, and infrastructure and workforce shortages create long waitlists for specialized care. Investment opportunities include supporting crisis intervention programs—which reduces criminalization of mental illness—and developing long-term supportive housing solutions that are foundational to effective treatment.

Despite persistent challenges, there is reason for optimism. Momentum for change has been building over the last decade, driven by the success of federal investments, including a National Institutes of Health (NIH) study that demonstrated the effectiveness of coordinated specialty care (CSC) and the model's subsequent expansion to all 50 states. The field has established clear evidence for what works in early intervention and is poised for breakthroughs in precision medicine.

Philanthropy can accelerate progress across multiple dimensions of schizophrenia research and care. Philanthropic investment can help transform fragmented, crisis-driven care into an integrated system, which can proactively support individuals with schizophrenia and their families. Given the variety of opportunities across research, care delivery, and systems change, there are meaningful ways for philanthropic capital of all sizes and interests to contribute to advancement. At this crossroads, there is hope for change—at the systems level and for individuals who can thrive with proper treatment and support.

Clinical Presentation and Epidemiology

Schizophrenia is a chronic brain disorder characterized by episodes of psychosis, including disorganized thinking and disturbances in perception and behavior (Hurley 2022) (see **Box 1**). The condition is complex and involves symptoms across three primary domains: **positive** (e.g., hallucinations, delusions), **negative** (e.g., flat affect, diminished emotion, social withdrawal), and **cognitive** (e.g., deficits in attention and working memory). Symptom presentation is highly heterogeneous and overlaps with other mental illnesses and medical conditions, complicating diagnosis and treatment. Schizophrenia is an SMI and a leading cause of disability worldwide, but with appropriate treatment, people with schizophrenia can live full lives. Functional recovery, including maintaining rewarding relationships and engaging in meaningful work, is possible.

According to the World Health Organization (WHO), the **prevalence** of schizophrenia is approximately 0.5 percent in the adult population, affecting 24 million people worldwide (WHO 2022) (see **Box 2**). Though estimates of prevalence in the US typically vary from 0.25 to 0.64 percent (NIMH 2023), a recent report found the lifetime history of schizophrenia spectrum disorders could be as high as 1.8 percent of US adults (Ringeisen et al. 2023).

Box 1: Psychosis vs. Schizophrenia

Psychosis is a mental state characterized by a loss of contact with reality. Symptoms can include hallucinations (seeing, hearing, or feeling things that aren't there), delusions (fixed false beliefs), and disorganized thinking or speech.

Psychosis is a symptom that can occur in many conditions—including schizophrenia, bipolar disorder, severe depression, substance use, medical illnesses, or medication side effects.

Schizophrenia is a psychotic spectrum disorder. It is one specific mental health condition with psychotic symptoms. Psychotic, also called positive, symptoms are one of three core symptom domains in schizophrenia.

Symptom Domains of Schizophrenia

Positive symptoms include altered perceptions and thoughts, such as hallucinations and delusions.

Negative symptoms involve reduced expression and social engagement, such as flat affect, diminished emotion, and social withdrawal.

Cognitive symptoms affect thinking processes, including deficits in processing speed, attention, and working memory.

Onset of illness is typically in the late teens and early 20s, with women averaging a later onset than men. The age of onset in women is bimodal, with one peak in the 20s–30s and a second during perimenopause (Li, Zhou, and Yi 2022). Several studies note that the **incidence** of schizophrenia is higher for men than women (a ratio of 1.4 men:1 woman) (Aleman, Kahn, and Selten 2003; Li, Zhou, and Yi 2022; McGrath et al. 2004). However, the overall prevalence may be similar for men and women across the lifespan for several reasons, including the variable age of onset and different recovery rates. Research also emphasizes clinical characteristics more common in men, potentially leading to underdiagnosis of women who present with different symptom patterns and obscuring epidemiological patterns.

Box 2: Epidemiology—Prevalence vs. Incidence

Incidence is the number of new cases of a disease during a specific time period, such as one year.

Prevalence is the proportion of existing cases in a population at a given time.

Debilitating symptoms experienced by those living with schizophrenia are associated with significant premature mortality. People with schizophrenia have a greater than 3.5-fold increased mortality rate compared to the general population (Olfson et al. 2015), and life expectancy is approximately 15–20 years lower than average (Hjorthøj et al. 2017; Correll et al. 2022; Olfson et al. 2015).

Several factors could help explain premature mortality among people with schizophrenia. Comorbidities, such as cardiovascular illness, diabetes, metabolic illness, infectious disease, and liver disease, are common and worsened by side effects from medication or lifestyle. Schizophrenia is often comorbid with substance use disorders and other psychiatric conditions, including depression and suicidality. One study found 76 percent of Medicaid enrollees with SMI have at least one comorbid chronic condition, such as heart disease, diabetes, or substance use disorder (Saunders et al. 2025). In parallel, some hypotheses about premature mortality also implicate accelerated aging and genetic factors.

Risk Factors

Causes and risk factors of schizophrenia are not fully understood, though genetic factors and social or environmental stressors are thought to play a role.

Family history: Family history is a known risk factor for schizophrenia. Having parents with SMI confers increased risk for a range of psychiatric disorders, including psychosis and schizophrenia (Rasic et al. 2014; Thakkar et al. 2023). Heritability estimates for schizophrenia are as high as 80 percent, but the genetic factors contributing to this risk are not well understood due to schizophrenia's complex genetics (Sullivan, Kendler, and Neale 2003; Hilker et al. 2018) (see section "Scientific Background").

Nongenetic factors, such as social and environmental stressors: A number of nongenetic factors confer increased risk for schizophrenia, including social inequality, social isolation, trauma, and childhood adversity (e.g., abuse, neglect, parental death) (Stilo and Murray 2019; Thakkar et al. 2023). These risk sources may disproportionately impact vulnerable populations, such as migrants who experience chronic stress, discrimination, and social isolation and have a documented higher risk of psychosis (Stilo and Murray 2019). Nongenetic risk factors for schizophrenia start as early as the prenatal period (Davies et al. 2020). Factors such as low parental age (e.g., maternal age <20), parental psychopathology, maternal infections, maternal hypertension, complications during pregnancy or delivery, famine or nutritional deficits during pregnancy, and low birth weight are associated with increased risk (Davies et al. 2020).

Cannabis use: Substance use, specifically cannabis use, is associated with increased risk of psychosis and schizophrenia (Twohey, Ivory, and Kessler 2024; Hjorthøj et al. 2023; Marconi et al. 2016; Stilo and Murray 2019). Earlier lifetime use, longer duration of use, and higher tetrahydrocannabinol (THC) potency all increase the risk of psychosis and psychosis spectrum disorders like schizophrenia (Bearden 2025). There is evidence that other substances, such as alcohol or amphetamines, may be associated with increased risk for psychosis (Stilo and Murray 2019).

Societal Cost

According to recent estimates, the economic burden of schizophrenia is approximately $300 billion in the US, though estimates of economic burden, and indirect costs in particular, vary widely. This estimate includes direct costs of health care and indirect costs of unemployment, caregiving, and loss of human capital (Kadakia et al. 2022; Schizophrenia & Psychosis Action Alliance [S&PAA] 2021). The category of indirect costs represents a substantial financial burden, as direct costs of health care only account for approximately one-fifth of this total (Kadakia et al. 2022; S&PAA 2021).

Despite a high economic burden and significant need, an estimated two-thirds of individuals with psychosis worldwide—and 40 percent in high-income countries—do not receive specialized care for mental illness (WHO 2022; Jaeschke et al. 2021). When the mental health system fails to provide adequate care, costs are pushed onto other systems, leading to higher societal costs and worse outcomes for those with schizophrenia.

For example, individuals with schizophrenia experience increased reliance on emergency services, increased interaction with the criminal justice system, and high rates of homelessness and demand for associated services. Individuals with schizophrenia also face significant stigma and tend to suffer from social isolation, which undermines their access to community support and reinforces barriers to seeking care.

The intersection of schizophrenia with criminal justice, housing instability, medical rights, and human rights requires coordinated action to address unmet needs. Research suggests that investing in quality mental health care reduces burden and increases participation in the labor market (Counts et al. 2025).

Journey from Early Symptoms to Diagnosis and Treatment

Each individual's lived experience with schizophrenia is unique. Yet highlighting common stages helps uncover shared barriers to accessing effective, high-quality care. An initial stage of early symptom presentation is followed by diagnosis and long-term treatment, but each of these stages can be prolonged as diagnosis and treatment are often delayed due to complexities presented by the illness and the care system. The following sections provide an overview of these stages to ground the later discussion in lived experience and an understanding of common barriers to effective care.

Early Symptom Presentation

Recognizing Early Signs

Early symptoms of schizophrenia can be difficult to identify, and individuals may have prepsychotic or subthreshold symptoms before receiving a diagnosis of schizophrenia. The condition has subtle or soft signs, such as flat affect, slower movement, difficulty with eye contact, nervousness, difficulty concentrating, social withdrawal, or psychotic-like experiences. It may be difficult to distinguish these subthreshold symptoms from typical adolescent behavior, as the symptoms can be subtle and coincide with normal life transitions.

Families and friends are often the first to identify the need for care, especially because many individuals may not recognize their own symptoms. Studies estimate that at least 50 percent of individuals with schizophrenia experience a symptom called **anosognosia**, or lack of insight, meaning that they do not recognize themselves as having a mental illness (Rose and Harvey 2024; Treatment Advocacy Center, n.d.; Buckley et al. 2007; Lehrer and Lorenz 2014). Anosognosia is a core neuropsychiatric feature of schizophrenia and can impede diagnosis and treatment (Lehrer and Lorenz 2014).

Individuals who are symptomatic for anosognosia often do not recognize a need for care and have higher rates of treatment nonadherence (Silver and Sinclair Hancq 2023). Handling this lack of insight can be especially painful and challenging for family and caregivers to navigate and help their loved ones. This symptom can appear early and persist throughout the lifespan, presenting challenges for seeking care and adhering to treatment.

Clinical High-Risk Populations

Sometimes only recognizable in retrospect, the stage before diagnosis is called the prodromal or premorbid phase. As more emphasis is placed on the importance of early intervention, the concept of a **clinical high risk** (CHR) state has developed to describe individuals at elevated risk of developing psychosis. CHR refers to people experiencing subthreshold symptoms that do not meet full diagnostic criteria and who are at elevated risk of developing psychosis.

According to experts, the CHR population is typically aged 12–30, though sometimes the range is as wide as 9 to over 35 (Salazar de Pablo et al. January 2021). Approximately one in four individuals at CHR go on to develop psychosis over a period of three years (Salazar de Pablo et al. July 2021). The majority do not go on to develop psychosis, though they may be at risk for other psychiatric conditions, including mood or substance use disorders.

CHR is evaluated using structured interview assessments that look for early warning signs or milder versions of psychotic symptoms (Woods et al. 2014). It is not well understood who within the CHR population will go on to develop psychosis or schizophrenia, though researchers are working to identify biomarkers that could improve clinical prediction. While some CHR programs exist to provide early intervention and support, issues like insurance barriers, limited geographic availability, and capacity constraints limit access. Experts note that many programs struggle with basic operating costs as they are often underfunded and understaffed.

First Episode Psychosis and Schizophrenia Diagnosis

Challenges in Receiving an Accurate Diagnosis

Receiving a diagnosis of schizophrenia can be a long and fraught process. Diagnosis is complicated by the heterogeneity of symptoms and the variety of presentations of the illness. Due to lack of objective biomarkers, laboratory tests, genetic tests, or scans, health-care providers must rely on clinical judgment and subjective measures. This subjectivity drives wide variation in diagnosis and treatment.

Unfortunately, individuals often do not receive care until emergency services are necessary, which increases the likelihood of placement in intensive inpatient facilities or forensic state hospitals, straining the facilities' capacity. It is common for emergency responders, such as police and emergency department personnel, to become involved during initial episodes of psychosis. This first interaction with mental health care can cause trauma that disincentivizes ongoing engagement in care for people with schizophrenia and often occurs outside of specialty centers. Receiving an accurate diagnosis is thus further complicated because those without specialized training may provide an initial diagnosis.

First Episode Psychosis Populations

Ideally, individuals experiencing initial symptoms of psychosis are quickly referred to specialty care, such as an early-intervention program. The field often uses the term **first episode psychosis** (FEP) to refer to the experience of psychotic symptoms with an onset within the past two to five years (Lundin et al. 2024). Rather than referring only to the individual's initial psychotic episode, FEP is defined by the duration relative to the onset of symptoms (Lundin et al. 2024) (see **Box 3**). As a result, FEP populations are heterogeneous, complicating diagnosis.

Box 3: Definition of First Episode Psychosis

First episode psychosis is often used to refer to the recent onset of psychotic symptoms within the past two to five years. The term refers to a period of early onset of symptoms that encompasses an individual's initial psychotic episode and the phase of early illness.

One recent study found that approximately 53 percent of the FEP population goes on to develop a schizophrenia spectrum disorder—one of a group of conditions characterized by psychotic symptoms that affect how a person thinks, feels, and behaves (Inchausti et al. 2023)—while others receive diagnoses of affective psychoses or other psychotic disorders (Whitty et al. 2005; Inchausti et al. 2023; Gale-Grant et al. 2021). Other research has shown that schizophrenia is the most consistent diagnosis over time among the FEP population (Fusar-Poli et al. 2016; Whitty et al. 2005; Gale-Grant et al. 2021; Palomar-Ciria et al. 2019), and the most common shift from initial diagnosis is toward a diagnosis of schizophrenia (Fusar-Poli et al. 2016).

Duration of Untreated Psychosis

Early psychosis is a critical time for intervention, with evidence suggesting that shortening the time between the symptom onset and treatment initiation predicts better overall outcomes (Penttilä et al. 2014). Fragmented systems mean that individuals and caregivers often struggle to find and access effective care, with peer support and advocacy organizations trying to fill the gaps. The **duration of untreated psychosis** (DUP) is the time between the first presentation of psychosis and treatment. Higher DUP is associated with worse outcomes (Penttilä et al. 2014), highlighting the importance of early intervention. In the US, psychosis often goes untreated for months or more, with a median DUP of 74 weeks and a wide range (Kane et al. 2015), highlighting a critical gap in care.

Barriers to Care

Ideally, individuals experiencing initial psychotic symptoms would receive rapid referral to specialty early-intervention programs. In reality, many who need and qualify for this care cannot access it. Limited availability of specialty services, insufficient geographic coverage, and restrictive eligibility criteria create significant barriers to treatment. Peer support and advocacy organizations attempt to bridge these gaps, but systemic challenges persist.

Long-Term Treatment and Symptom Management

Schizophrenia is a chronic condition that requires integrated care across the lifespan to achieve and maintain recovery, but the available treatments and care options often fall short. Many individuals do not receive sufficient support to manage symptoms, even though early intervention during CHR and FEP phases can positively impact the trajectory of illness.

Treatment Limitations

Antipsychotic medications are the first line of pharmaceutical treatment for individuals with schizophrenia. However, these medications primarily address positive symptoms (e.g., hallucinations, delusions). Negative symptoms and cognitive deficits, which most strongly correlate with functional outcomes, remain unaddressed. Furthermore, these medications are far from ideal, especially when taken chronically. They are often accompanied by significant side effects, most notably cardiometabolic complications that impair physical health and shorten lifespan. Many individuals are on complex medication regimens to address the considerable side effects, which can further deteriorate health and cognition, creating a vicious cycle (see section "Clinical Treatment").

In addition to treatment limitations, some people do not respond to the currently available treatments. Approximately one-third of diagnosed individuals meet criteria for **treatment-resistant schizophrenia** (TRS), defined as a failure to respond to two or more medications taken with sufficient dose and adherence (Potkin et al. 2020; Demjaha et al. 2017; Lally et al. 2016; Meltzer 1997; Nucifora et al. 2018).

Access and Provider Challenges

Treatments are limited, and individuals and their caregivers face many challenges in finding and accessing effective, ongoing care. It can be difficult to find providers and treatment programs that specialize in schizophrenia. Access is limited and highly disparate, depending on factors like geography, cost, and insurance coverage.

In navigating systems of care, individuals and caregivers face many common barriers and challenges to finding and accessing effective treatment.

Recovery and Relapse

For most, schizophrenia is a chronic illness that requires ongoing treatment and symptom management. Once psychotic symptoms are stabilized, many individuals still struggle with functional disability and social isolation (Valencia et al. 2015; Jääskeläinen et al. 2013; Hansen et al. 2023). Over time, many people who initially respond to treatment experience relapse, requiring periods of intensive care to adjust treatments and restabilize. The challenge of relapse is worsened by significant gaps in the care system, including a shortage of beds in inpatient or forensic facilities that results in individuals not receiving care or sufficient duration of care (Warburton 2024).

Insufficient support during transitions from intensive care programs can leave individuals prone to relapse. They face homelessness and cycle in and out of the criminal justice system. Although effective treatment and care are possible, recurrent institutionalization is an alarmingly common experience in the US (Warburton and Stahl 2020; Warburton 2024).

Despite the formidable obstacles presented by schizophrenia, approximately 20 percent of patients achieve functional recovery, which could include maintaining relationships, having jobs, and completing school (Valencia et al. 2015; Jääskeläinen et al. 2013; Hansen et al. 2023). Recovery estimates vary widely, with some higher figures resulting from defining recovery as merely symptom remission rather than full functional recovery.

Summary of Barriers Across the Stages of Care

The journey from early symptoms through diagnosis to long-term treatment reveals a health-care system struggling to meet the complex needs of individuals with schizophrenia. Barriers span every stage—from delayed recognition of early symptoms and prolonged diagnostic processes to inadequate treatment options and fragmented long-term care (**Figure 1**). Addressing schizophrenia care requires comprehensive, multipronged approaches that tackle the clinical complexities of the condition and the systemic barriers to effective care.

Figure 1: Stages of Symptom Presentation, Diagnosis, and Treatment

Early Symptom Presentation and Clinical High Risk (CHR)	First Episode Psychosis (FEP) and Schizophrenia Diagnosis	Long-Term Treatment and Symptom Management
Early signs of schizophrenia include changes in behavior and subthreshold psychotic symptoms, often appearing during adolescence. Some individuals may be designated as CHR; not everyone in CHR develops psychosis or schizophrenia.	The onset of positive symptoms, such as hallucinations, characterize the early psychosis phase, usually appearing in late teens to early 20s; may include diagnosis of schizophrenia. Some individuals enter FEP programs; not all develop schizophrenia.	Most individuals with schizophrenia require ongoing, integrated care throughout the lifespan. The intensity of care needed varies by person, and the level of support an individual needs can fluctuate.
Major Gaps and Barriers		
• Nonspecific early symptoms are hard to recognize; lack of screening tools and biomarkers hinders early detection • CHR programs have limited availability and geographic coverage, often with long wait times and other access gaps • Lack of training for early recognition and support among families, primary care providers, first responders, etc.	• Early symptoms of psychosis go unrecognized; psychosis goes untreated for months to years • Delays in diagnosis due to symptom overlap with other conditions, lack of diagnostic tests, or lack of insight into one's illness • Few programs available locally, long waitlists, difficult to navigate • Individuals often enter care system through emergency services rather than dedicated early-intervention programs	• Limited medication options, especially for cognitive and negative symptoms • Side effects and lack of integrated support contribute to medication noncompliance and relapse • Limited access to psychosocial treatments, stable housing, and sustained social support needed for functional recovery • Many cycle through emergency services and criminal justice system due to reliance on crisis care

Source: Milken Institute (2025)

Scientific Background

It is unsurprising that underlying biological mechanisms of schizophrenia are complicated, as its symptom presentation is complex and heterogeneous. Questions remain, yet studies across the areas of pharmacology, genetics, and neurobiology, along with analysis of neuroimaging data and postmortem tissue, have revealed much about the pathology of schizophrenia and a wealth of information about underlying biological signatures.

Biological changes are observed from the molecular level to the broader brain structure level, and understanding these underpinnings can help contextualize the current state of clinical treatment and opportunities to advance care. This section provides a high-level overview of key features of the neurobiology and genetics of schizophrenia.

Neurobiology

Schizophrenia involves complex neurobiological changes that span multiple levels of brain organization. Research reveals disruptions from molecular neurotransmitter systems to brain cells to large-scale brain networks, with these changes manifesting as the characteristic structural changes, such as a loss of gray matter, observed in individuals with the disorder.

Neurotransmitter Dysregulation

Dopamine, a neurotransmitter involved in reward and motor control, has long been central to hypotheses about schizophrenia mechanisms, in part because of historical happenstance—the discovery that the first antipsychotics affected dopamine regulation. As a result, the field focused on dopamine-blocking approaches before understanding the pathophysiology and role of dopamine in schizophrenia. Recent research implicates other neurotransmitters and pathways—most notably, glutamate (Coyle 2024).

Schizophrenia likely involves complex changes across multiple neurotransmitter pathways, unlocking new avenues for potential therapeutic intervention. Emerging evidence suggests that dopamine dysregulation may be a consequence of neural circuit imbalances in brain regions like the hippocampus, challenging the view that dopamine dysregulation is the primary driver of dysfunction. This evolving understanding indicates that targeting alternative mechanisms, such as glutamatergic signaling or hippocampal dysfunction, may offer more comprehensive therapeutic benefits than traditional dopamine-focused approaches.

Cellular Changes in Neurons and Glia

Schizophrenia is associated with cellular changes in multiple cell types in the brain. One of the most consistently observed findings in neurons is a reduced number and density of dendritic spines across several brain regions (Glausier and Lewis 2013; Moyer, Shelton, and Sweet 2015). Dendritic spines, the sites of synapses on neurons, play a key role in neural plasticity, a core process for learning, memory, and other brain functions.

Other brain cells called **glia** also exhibit cellular abnormalities. **Microglia**, glial cells that support brain maintenance and neuroimmune function, may be a key link between genetics, immune dysfunction, and schizophrenia risk (Hartmann et al. 2024). Some genetic variants associated with schizophrenia implicate neuroimmune activity and microglial activation (Koskuvi et al. 2024). Alongside genetic risk, stress is a key dimension in the etiology of the disease. Neuroimmune abnormalities may leave the brain more susceptible to stress, potentially leading to a cycle of dysfunction.

Emerging evidence points to overactive microglial processes as drivers of a characteristic loss of gray matter in the brain, supported by related genetic findings and cytokine biomarkers (Hartmann et al. 2024; Koskuvi et al. 2024; Laskaris et al. 2016; Zhuo et al. 2023). Interestingly, neuroinflammatory dysfunction links schizophrenia and neurodevelopmental disorders—such as autism spectrum disorders, which also have a neuroinflammatory phenotype.

Emerging evidence also suggests a role for metabolic **redox biology** in microglial function in schizophrenia (Chouinard et al. 2025; Dwir et al. 2023; Murray et al. 2021). Redox biology describes chemical reactions critical to cellular functions that involve chemical processes called reduction or oxidation. An imbalance between these reactions indicates metabolic dysregulation and increases cellular stress. These processes are closely intertwined with immune mechanisms and microglia activation.

In addition to microglia, other glial cells are implicated in pathology, with evidence of **oligodendrocyte** abnormalities and **astrocyte** dysfunction in schizophrenia (Bernstein et al. 2015; Dietz, Goldman, and Nedergaard 2020; Bernstein et al. 2025). Having fewer oligodendrocytes reduces the insulation around nerve fibers, contributing to connectivity deficits among neurons and between brain regions (Bernstein et al. 2025). Connectivity changes could contribute to symptoms across the schizophrenia spectrum, especially cognitive symptoms.

Brain Circuitry and Structural Changes

Cellular abnormalities can aggregate into disruptions of brain circuits and anatomy. The **hippocampus** has emerged as a key brain region where hyperactivity and dysrhythmia, or disrupted timing of neural activity, could drive symptoms across all three symptom domains of schizophrenia (Schobel et al. 2009). A loss of **parvalbumin interneurons** in the hippocampus, likely due to stress, appears critical to the pathology of schizophrenia.

Parvalbumin interneurons are neurons that help maintain the balance between excitation and inhibition in neural circuits, which is essential for coordinated neural activity or brainwaves. When this balance is disrupted, it leads to abnormal brainwaves, which can be detected by measuring brain activity. Because the hippocampus is implicated across symptom domains, the region may be a compelling therapeutic target. Restoring dysfunctional hippocampal circuitry may help address all three symptom classes, unlike dopamine blockers that treat only positive symptoms.

At the macroscopic level, individuals with schizophrenia exhibit characteristic structural changes, including gray matter loss, enlarged ventricles, and decreased white matter integrity, which are indicative of cell death and worsen as the disease progresses. Major brain regions such as the hippocampus and the amygdala are typically reduced in size. Changes in gray matter, such as **cortical thinning**, can be detected early in the progression of the disorder. Recent neuroimaging studies detected rapid gray matter loss and accelerated cortical thinning in specific regions before full psychosis onset. This accelerated cortical thinning is predictive of conversion to psychosis in a CHR cohort (Collins et al. 2023).

Further understanding these morphological changes may help define symptom presentation and could be used to help diagnose and predict the clinical trajectory of schizophrenia. The further development of a clinical signature may help support early diagnosis because these changes emerge early. Treatments that better target mechanisms that drive morphological changes may be effective in addressing negative and cognitive symptoms.

Genetics

Schizophrenia is highly heritable. In fact, the largest twin study estimated the heritability of schizophrenia to be nearly 80 percent (Hilker et al. 2018). However, after decades of research, researchers still struggle to explain this high heritability, revealing the complexity of schizophrenia's genetic architecture. Unlike single-gene disorders that follow simple inheritance patterns, schizophrenia is highly polygenic, meaning it results from many genes that each have small effects.

Recent years have seen significant advancements in understanding the genetics of schizophrenia, and many notable genetic variants have been identified. Genetics studies have identified numerous copy number variants—sections of DNA that are duplicated, deleted, or modified (Henriksen et al. 2017; Legge et al. 2021; Merikangas et al. 2022; Owen et al. 2023; Trifu et al. 2020).

For example, one variant called the 22q11.2 deletion is associated with 20–25 times increased risk of developing schizophrenia (Bassett and Chow 2008). The variant is rare, however, affecting only approximately 1 percent of schizophrenia cases (Bassett and Chow 2008). At a population level, more common variants involve the major histocompatibility complex locus, which is involved in immune function (McGrath et al. 2004; Sekar et al. 2016). These variants implicate a protein called complement component 4A (C4A), affecting synaptic pruning, which could partially explain the reduction in synapses associated with schizophrenia (Sekar et al. 2016).

Because schizophrenia involves many genes with small effect sizes, researchers have turned increasingly to polygenic risk scores, which calculate an individual's risk of developing a complex disease by combining information across many genes. According to a 2021 review, polygenic risk scores account for approximately 7.7 percent of variance in schizophrenia-control status (Legge et al. 2021). This is a modest effect size, but within the range that is seen for polygenic risk scores in clinical psychology—approximately 3–15 percent (Bogdan, Baranger, and Agrawal 2018).

Experts still believe that genetic markers are promising tools to understand the risks and mechanisms of schizophrenia onset, but these markers have shown limited predictive power to date. Even though many genes have been implicated in schizophrenia, this information has not translated into diagnostic tests, specific pharmaceutical interventions, or changes in clinical treatment—and may not for some time.

Scientific Research: Assessment and Opportunities for Progress

Despite progress in understanding the neurobiology of schizophrenia, significant gaps remain between scientific discovery and clinical implementation. Researchers have identified key biological mechanisms underlying pathology, but these advances have not yet translated into transformative treatments for those who need them. The challenge is to bridge the gap between scientific discovery and clinical practice.

Current Scientific Research Priorities

Decades of research into the biology of schizophrenia have revealed various biological features that characterize the disorder, including rare genetic variants, neurotransmitter dysregulation, and cellular dysfunction (see section "Scientific Background"). Understanding of the biological mechanisms underlying schizophrenia is still growing and evolving, which will further inform therapeutic development (see section "Clinical Treatment"). Several research areas remain underexplored and represent opportunities for further investment.

Open areas of interest include the mechanisms of negative and cognitive symptoms, stress and resilience mechanisms, and the role of the gut-brain axis in disease pathology. Also underexplored are sex differences in clinical presentation and underlying biology. Researchers are actively studying the interconnected biological mechanisms of comorbidities like cardiometabolic dysfunction and related conditions, such as neurodevelopmental disorders and substance use disorders.

Beyond these areas of study, there is a significant need for research and development of new treatments that reduce side effects and address the full spectrum of schizophrenia symptoms (see section "Clinical Treatment"). While knowledge about the neurobiology and characterization of schizophrenia has grown, translating this information into clinical utility remains a challenge for the field.

Disease Heterogeneity and Precision Medicine

Given the various neurobiological changes observed and symptoms experienced, schizophrenia likely represents multiple biological pathways converging on similar clinical presentations. This complexity requires a more sophisticated understanding of underlying neurobiology to develop targeted treatments and precision medicine approaches. A long-term vision of schizophrenia care includes developing and integrating biomarkers with genetic profiling to enable customized treatment approaches for each individual.

Many experts are excited about the potential of combining genetic markers with other biomarkers to predict individual trajectories and personalize treatments, clinical protocols, and intensity of care. Developing the necessary biomarkers to realize this possibility is a current opportunity (see section "Clinical Treatment"). The Foundation for the National Institutes of Health (FNIH) leads a key effort in this area—the Accelerating Medicines Partnership® (AMP®) program.

The AMP program is a public-private partnership with government, industry, and nonprofit partners. AMP Schizophrenia (AMP SCZ) began in 2020 to address unmet needs for people with schizophrenia (AMP SCZ 2022). The first phase of the research collaboration focused on validating biomarkers in the CHR population and developing the research infrastructure to support therapeutic development (FNIH, n.d.). Results from the AMP SCZ collaboration are forthcoming and may provide significant advances for biomarker development (Nelson et al. 2025; Addington et al. 2025).

Current research priorities include connecting underlying biological changes to symptom profiles, treatment responses, and functional outcomes. Understanding disease heterogeneity and possible subtypes at the biological level—such as schizophrenia with perimenopausal onset as a distinct subtype from earlier onset—is an important step. Characterizing possible subtypes may help clinicians predict an individual's treatment response based on underlying biology.

Advanced Study Design, Data Aggregation, and Measurement

Innovation in study design and data aggregation could significantly advance schizophrenia research. The field of psychiatry could look to other medical specialties, such as oncology, to inform the development of, adoption of, and adherence to standardized measurements and personalized treatment protocols. There are key opportunities to improve standardized measurement and methodology.

Stratification based on genetic or biomarker profiling for clinical trials is one promising approach to advance more targeted drug development. Depending on the biomarkers a given patient displays, this approach could make it easier to predict which drugs may be effective.

Another avenue to explore is improving clinical trial design. Platform trials, which randomize patients to multiple treatments simultaneously, could be a useful model for more efficient drug development. They have proven valuable in oncology and neurodegenerative disease research, and they also helped accelerate testing of COVID-19 therapeutics (Burki 2023).

Across research domains, scientists emphasize the need for larger cohort studies and more longitudinal data. Individual programs are typically too small to generate meaningful data on trajectories and longitudinal outcomes, making data aggregation across programs an important way to accelerate discovery. There is a pronounced need for data aggregation in order to examine long-term outcomes of interventions, where demonstrating such outcomes is challenging but essential for advancing treatment approaches.

For instance, short-term CSC outcomes and CHR early-intervention outcomes appear strong, but some evidence suggests that effects taper off over time. The reasons for this decline remain unclear, though some suggest that the two– to three-year program duration is insufficient or that the lack of follow-on care options may be to blame. Answering this question requires longitudinal data, which are limited, because many studies were not designed with long-term outcomes in mind, and these studies are hard to fund due to short grant cycles and a high administrative burden of long-term enrollment.

While more longitudinal data are collected, researchers can leverage existing large data sets. For example, genetics data are available through the Psychiatric Genomics Consortium, which has a schizophrenia working group, and the NIH *All of Us* Research Program (Barr, Bigdeli, and Meyers 2022; Trubetskoy et al. 2022).

The Enhancing Neuro Imaging Genetics through Meta Analysis Consortium is an international network of investigators that brings together data from genomics and neuroimaging, with many working groups, including schizophrenia and other psychiatric conditions (Thompson et al. 2014). Finally, studies like the Adolescent Brain Cognitive Development (ABCD) Study® or the HEALthy Brain and Child Development (HBCD) Study have large sample sizes with longitudinal data. While not specifically designed for schizophrenia research, these studies can be useful for examining early indicators of illness (Karcher and Barch 2021).

Emerging Technology and Innovation

There is enthusiasm around emerging trends in digital tools and AI applications, including natural language processing, digital phenotyping, and AI-based provider training tools. Speech and voice analysis may provide scalable diagnostic and monitoring tools (see section “Clinical Treatment”). Digital tools show promise across multiple user groups, including diagnosed individuals, caregivers, and providers.

Digital tools enable self-management approaches that align with the movement toward recovery, which emphasizes building individual capacity, agency, and autonomy in care. However, experts emphasize that human support remains essential even for sophisticated tech-enabled approaches. Tools and apps designed for diagnosed individuals need to account for their abilities, preferences, and levels of access to technology. Further, technology-enabled approaches face additional implementation and scaling challenges because, unlike for pharmaceuticals, there is no well-established path for bringing digital health tools to market.

Opportunities to Advance Schizophrenia Research

With strategic investment, unique research opportunities can start to close the gap between scientific discovery and clinical impact by advancing the understanding of schizophrenia and developing transformative treatments. Our assessment of the landscape reveals key opportunities for advancing schizophrenia research that are summarized in **Table 1**. These opportunities are complementary strategies to accelerate progress by leveraging existing research infrastructure and knowledge, focusing attention and investment to lead to breakthroughs, and addressing fundamental knowledge gaps.

Alongside these opportunities, researchers have voiced concerns about funding instability and potential industry withdrawal from psychiatry research. This instability creates uncertainty about the sustainability of current research efforts and the ability to pursue the comprehensive, longitudinal studies needed to advance the field. This is a key moment for philanthropy to support critical research efforts. With strategic investment focused on these priority areas, philanthropy can help accelerate the development of transformative treatments and improve outcomes for individuals with schizophrenia.

Table 1: Opportunities to Advance Schizophrenia Research

Category		
Established but Underutilized	**Promising but Underdeveloped**	**Fundamental Gaps and Needs**
Definition		
Impact of established intervention or approach could be amplified	Impact could grow with additional attention, evidence, or investment	New developments would help address unmet needs
List of Opportunities		
• Existing large data sets, with the potential for targeted add-on studies • Increasing use of high-quality research probes and standardized assays	• Promising research into novel therapies across pharmaceutical, psychosocial, and neuromodulatory approaches • Biomarkers and precision medicine • Stratification based on biomarker profiling for clinical trials • Innovative clinical trial designs, such as platform trials	• Data aggregation across small programs and longitudinal outcomes

Source: Milken Institute (2025)

Clinical Treatment: Assessment and Opportunities for Progress

Available antipsychotic medications can manage positive symptoms like delusions and hallucinations, but they inadequately address the negative and cognitive symptoms known to most impact functional recovery for individuals. This section will discuss diagnostic methods, treatment approaches, and pharmacological and nonpharmacological approaches and highlight opportunities for advancing schizophrenia diagnosis and treatment.

Diagnosis of Schizophrenia

Schizophrenia diagnosis relies on clinical observation and symptom assessment according to criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Current diagnostic methods lack objective measures such as biomarkers, laboratory tests, or genetic markers, making diagnosis challenging and prone to inaccuracy. This underscores the need for more accurate, objective diagnostic tools.

Current Practice

Schizophrenia is a clinical diagnosis made via observation and assessment of characteristic symptoms. According to the DSM-5, a diagnosis of schizophrenia requires the presence of two (or more) of a core set of symptoms, including delusions, hallucinations, and disorganized speech. Grossly disorganized or catatonic behavior and avolition or diminished emotional expression, referred to as negative symptoms, may also be present. For a diagnosis to be made, each symptom must be present for a significant portion of time during a one-month period and cause impairment in one or more major areas of functioning, such as work, interpersonal relations, or self-care (Substance Abuse and Mental Health Services Administration [SAMHSA] 2016; Hurley 2022). The DSM-5 discontinued the subtype classifications (e.g., paranoid, disorganized, catatonic, undifferentiated, residual) used historically (SAMHSA 2016).

In addition to relying on DSM criteria, current diagnostic methods typically incorporate a subjective clinical interview assessment and mental status exam. The Structured Clinical Interview for DSM-5 (SCID-5) is a semi-structured interview guide used to make diagnoses according to the DSM-5. Most providers also use diagnostic checklists and tools (see **Box 4**) (Kumari et al. 2017). While these tools may appear more efficient, they can oversimplify the process and miss important clinical nuances.

Box 4: Examples of Diagnostic Assessment Tools

- Positive and Negative Syndrome Scale (PANSS)
- Scale for the Assessment of Negative Symptoms (SANS)
- Scale for the Assessment of Positive Symptoms (SAPS)
- Clinical Global Impression-Schizophrenia (CGI-SCH)
- Brief Psychiatric Rating Scale (BPRS)
- Calgary Depression Scale for Schizophrenia
- Negative Symptoms Assessment-16 (NSA-16)
- Newer assessment tools include Clinical Assessment Interview for Negative Symptoms (CAINS) and the Brief Negative Symptoms Scale (BNSS)

Diagnostic Limitations and Challenges

Schizophrenia diagnosis is complicated because symptom presentation can be varied, subtle, or nonspecific, which can lead to misdiagnosis as one of several conditions (see **Box 5**) (Griswold, Regno, and Berger 2015; Frankenburg 2024; Wong, Cunningham, and Puder 2019).

Diagnosis is further complicated because schizophrenia can manifest at a time in adolescence or early adulthood when it is difficult to distinguish between pathological symptoms and normal development. This is particularly an issue during early adolescence and makes early diagnosis (and research during this life stage) more difficult.

One of the biggest challenges in the diagnosis of schizophrenia is a lack of objective tools and measures—such as brain scans, laboratory tests, biomarkers, or genetic tests. In the diagnostic process, laboratory tests are only used to rule out other causes of symptoms (e.g., medical conditions, tumors, metabolic disorders, infection). Genetics and genomics studies have identified many genes that confer risk; however, none is a definitive marker for schizophrenia, and many genetic risk factors overlap with other conditions, such as autism.

Box 5: Common Misdiagnoses for Schizophrenia

- **Other psychiatric disorders**, such as bipolar disorder, major depressive disorder with psychotic features (also called psychotic depression), or delusional disorder
- Certain **personality disorders**, including schizotypal, schizoid, or paranoid personality disorders
- **Substance-induced psychosis**
- Psychosis resulting from **medical conditions**, such as neurological conditions (e.g., epilepsy, brain tumors or lesions), metabolic illnesses (e.g., Wilson disease), or infectious diseases (e.g., HIV, syphilis)

A lack of screening tools and training for primary care providers, social workers, teachers, and others, who often make the initial assessment, can also affect diagnosis. Lack of time, training, and other resources can impede diagnosis in clinical settings, notably in community mental health centers, where providers have limited time and resources. This is particularly problematic because appropriate, effective treatment depends on having an accurate diagnosis.

Importantly, stigma and fear can contribute to patient or caregiver hesitancy around seeking help or having conversations about potential symptoms, ultimately resulting in delays in diagnosis and treatment. To improve diagnosis, priorities include developing objective diagnostic measures and biomarkers; creating sensitive and accurate screening tools; and enhancing training for providers, teachers, first responders, social workers, and others.

In the absence of objective biomarkers, diagnosis remains heavily dependent on clinical judgment.

Treatment of Schizophrenia

The therapeutic landscape for schizophrenia centers on antipsychotic medications that primarily target positive symptoms while leaving negative and cognitive symptoms largely unaddressed. Two key pharmaceutical advances—long-acting injectable (LAI) formulations and clozapine—remain underutilized. Promising nonpharmacological approaches face implementation challenges. To support functional recovery, there is a critical need to support integrated treatment options that address all symptom domains.

Pharmacological Treatments

The current pharmaceutical arsenal for treating schizophrenia is geared toward antipsychotics, first introduced in the 1950s, which can effectively manage positive symptoms like delusions and hallucinations in those who respond. Antipsychotics fall into two main categories: **typical antipsychotics** (first-generation), such as haloperidol, chlorpromazine, and fluphenazine; and **atypical antipsychotics** (second-generation), including olanzapine, risperidone, quetiapine, aripiprazole, and clozapine. Typical antipsychotics primarily work by blocking dopamine receptors, while atypical antipsychotics have more complex mechanisms of action involving other neurotransmitters.

While often effective for positive symptoms, antipsychotics do not adequately address negative or cognitive symptoms. Other pharmaceutical options targeting negative or cognitive symptoms are lacking (McCutcheon, Keefe, and McGuire 2023). In addition, antipsychotic medications can cause severe side effects and cardiometabolic comorbidities, including metabolic abnormalities, cardiovascular complications, diabetes, and weight gain. These drugs also affect reward centers in the brain, altering motivation and reward processing. Many people do not like taking antipsychotics due to side effects on their health and mindset, contributing to adherence issues.

Long-Acting Injectable Antipsychotics

Medication nonadherence is not unique to schizophrenia—patients across many chronic conditions often stop taking medications within months of leaving treatment programs (Lieslehto et al. 2022). To help address this issue, some antipsychotics are available in an injectable formulation that releases medication slowly into the body over weeks to months. These **long-acting injectables** (LAIs) ensure sustained medication levels in the body between infrequent doses, without the need to take a daily pill; this can be critical for managing symptoms and preventing relapse (Milz et al. 2023). The benefits are important to diagnosed individuals; one study surveyed people about their treatment preferences and found that 77 percent preferred LAIs to daily oral pills (Blackwood et al. 2020).

Real-world evidence supports superior adherence rates for LAIs over oral antipsychotics (Milz et al. 2023; Lian et al. 2022; Blackwood et al. 2020). Despite improving adherence, however, LAIs remain underutilized, with relatively low prescription rates compared to the high rates of nonadherence among people with schizophrenia. Administrative barriers likely play a role—prescribers frequently cite that LAI insurance authorization is cumbersome and that payers often require that other approaches fail before LAIs are reimbursed.

Drawbacks of LAIs include the fact that that injections must be administered by a health-care provider rather than at home, and any dangerous side effects may be difficult to control because the medication remains in the body longer than it does after taking a pill. Individuals sometimes have negative perceptions of or are hesitant around needles, so providers may need training to help take advantage of the benefits of LAIs. Many advocacy groups encourage increasing the use of LAIs via education programs for diagnosed individuals and prescribers and promote the development of more convenient delivery methods for long-acting treatments, such as implantable drug-delivery systems.

Clozapine

Unique among antipsychotic medications, **clozapine** is classified as an atypical antipsychotic and primarily targets psychosis (i.e., positive symptoms). Despite decades of study, the mechanism of action for clozapine is not fully understood, though there have been several hypotheses ranging from pharmacokinetics to the involvement of multiple neurotransmitter mechanisms (Morrison, Jauhar, and Young 2025; Nucifora et al. 2017; de Bartolomeis et al. 2022).

A 2021 meta-review found that clozapine has superior effects on positive, negative, and overall symptoms as well as relapse rates in schizophrenia compared to first-generation antipsychotics or to a pooled group of first- and second-generation antipsychotics (Wagner et al. 2021). Despite this demonstrated efficacy, access to clozapine is limited due in part to concern about side effects, including neutropenia and agranulocytosis, which require regular blood test monitoring. Other side effects include increased risk of pneumonia, seizures, cardiac disease, constipation, metabolic abnormalities, and weight gain.

Even with these risks, clozapine is indicated for TRS and for patients with a high risk of suicide or aggressive behavior (Wagner et al. 2021). Clozapine is the only Food and Drug Administration (FDA)-approved treatment for TRS, which is defined as schizophrenia with a lack of response to at least two antipsychotic regimens that were adequately adhered to. Estimates of the incidence of TRS vary but are commonly cited as about 30 percent of individuals with schizophrenia (Meltzer 1997; Siskind et al. 2022; Potkin et al. 2020; Nucifora et al. 2018; Lally et al. 2016), yet only about 5 percent of schizophrenia patients are prescribed clozapine in the US (Torrey and Lieberman 2024; Torrey et al. 2015; Siskind, Siskind, and Kisely 2017).

Despite its effectiveness, clozapine is underprescribed, in part due to concern about side effects and the burdensome process of prescribing.

Most experts agree that clozapine is underutilized in the US. Notably, it is prescribed far less in the US relative to other countries, such as Australia, where prescription rates are 20 percent within the schizophrenia population (Torrey and Lieberman 2024). Aside from safety concerns, several factors contribute to clozapine underutilization. Administrative burden and ongoing blood-testing requirements create barriers to prescribing, and lack of training on dosing, implementation, and patient communication adds to provider hesitancy.

The absence of incentives to prescribe clozapine and uncertainty around optimal treatment protocols and response rates may further limit utilization. In early 2025, the FDA eliminated its clozapine Risk Evaluation and Mitigation Strategy (REMS), a program that had mandated strict administrative requirements for prescribing the drug. Despite eliminating the REMS restriction, experts expect that clozapine will continue to be underutilized without implementation strategies to address other persistent barriers.

For individuals who respond to the treatment, clozapine can be life-changing, and advocacy groups such as Team Daniel, CURESZ, and The Angry Moms are working to expand access, as diagnosed individuals often struggle to find clozapine providers. In addition to increased utilization, these groups and others suggest that clozapine should constitute an earlier line of treatment, rather than being reserved for use after multiple other drugs fail, especially for individuals at high risk of self-harm or suicide.

Despite the positive impact of clozapine for many patients, an estimated 40 percent of people with TRS fail to respond to clozapine, indicating that this segment of 12–20 percent of people with schizophrenia will be designated ultra-resistant to treatment (Siskind, Siskind, and Kisely 2017). This finding highlights the need for additional treatment options with fewer side effects and improved delivery mechanisms.

Nonpharmacological Approaches

Medication is one component of schizophrenia treatment. Individuals can also benefit from incorporating nonpharmacological techniques and psychosocial treatments. Psychosocial approaches can help individuals navigate symptoms that are not well managed by medication, better supporting their functional recovery. Some promising or underutilized approaches follow.

Neuromodulation techniques: The following techniques alter neural activity, typically through targeted stimulation of key brain regions. Researchers are investigating various approaches for schizophrenia, but protocols are still under development, and their use is not widespread.

- **Electroconvulsive therapy** (ECT) administers controlled electrical currents and is effective for severe depression. For schizophrenia, ECT has been used to augment pharmacological treatment. While ECT has been used in the treatment of psychiatric disorders for over 80 years, several newer neuromodulatory techniques are under development that could provide safer and more effective options, especially for individuals with TRS.
- **Transcranial magnetic stimulation** (TMS), a noninvasive approach, uses magnetic pulses to provide targeted stimulation to specific areas of the brain. According to experts, TMS has potential, warranting further investigation, but it has not yet shown clear efficacy for schizophrenia treatment.
- **Transcranial direct current stimulation** (tDCS) is noninvasive and uses weak electrical current to modulate neuronal excitability; it has shown some promising results in schizophrenia (e.g., Schwippel et al. 2025).
- **Focused ultrasound** (FUS) is another noninvasive technique that relies on concentrated ultrasound and has potential as a neuromodulatory approach. FUS is accessible and relatively inexpensive, but many variables can affect its treatment delivery and efficacy, and treatment paradigms have not yet been optimized for schizophrenia (Zhai et al. 2023; Qi et al. 2025; Brinker et al. 2025).

Psychotherapy: Including various forms of talk therapy, psychotherapy can be helpful as part of schizophrenia treatment. One evidence-based intervention is a particular adaptation of cognitive behavioral therapy (CBT) called CBT for psychosis (CBTp) (McDonagh et al. 2017; Turner et al. 2020). CBTp has been shown to address symptoms and improve functioning in people with schizophrenia spectrum disorders. Despite strong evidence of effectiveness, CBTp is underutilized in the US (Kopelovich et al. 2022).

Cognitive remediation therapy: This distinct behavioral training intervention focuses on improving functional outcomes through brain training exercises that target cognitive deficits most strongly correlated with functioning, such as sensory processing, verbal learning, working memory, and processing speed. Despite its effectiveness for addressing cognitive deficits, this type of training is not widely available outside of academic centers (Fisher et al. 2023). Implementation is resource-intensive, and providers generally cannot reimburse for these therapies, disincentivizing adoption.

Motivation-focused interventions: These interventions have potential for addressing symptoms of schizophrenia, particularly deficits in social motivation. Because motivational deficits correlate strongly with functioning and can be a key barrier to community integration and recovery, motivation is an important target of intervention. A combination of a technique known as motivational interviewing with CBT has shown promise for improving motivational deficits (Reddy et al. 2023). Technological tools are also emerging as an effective approach, as demonstrated in a recent study using a phone-based app featuring goal-setting, remote coaching, and social network functions to enhance motivation (Schlosser et al. 2018).

Social skills training and community building: Critical to recovery, social cognition is linked to intrinsic reward systems, and training has been shown to improve self-ratings of motivated behavior. Social cognition exercises (e.g., eye gaze detection, facial emotion matching, and face matching) can be part of comprehensive cognitive training, and social cognition and social skills training should be part of a comprehensive treatment approach. Peer support programs can also play a crucial role in care and recovery.

Supported employment and education services are also important for functional recovery, helping individuals reintegrate into society through work, school, and volunteer opportunities. However, these services are often not billable, and access is limited.

Challenges of Treatment and Functional Recovery

Patient response to medications is highly variable and unpredictable. Without biomarkers or predictive tools to aid in treatment selection, it typically takes trial and error to refine complex medication regimens. Arguably, the principal challenge facing clinical treatment of schizophrenia is improving functional recovery rates—fewer than 20 percent of diagnosed individuals achieve functional recovery despite available antipsychotics. In large part, this outcome occurs because complications arising from negative or cognitive symptoms can impede functional recovery more so than positive symptoms that can be managed with medication.

Treatment should be recovery-oriented. True recovery goes beyond symptom management to support individuals in living full lives.

As social problems associated with unmanaged symptoms accumulate, individuals disengage from their communities, making it harder to return and limiting their recovery trajectories. Despite these challenges stemming from negative and cognitive symptoms, typical treatment paradigms prioritize reducing positive symptoms rather than addressing the symptoms that most impact functional outcomes.

Contrary to stigma and bias, individuals with schizophrenia can complete school, build careers, form rewarding relationships, and lead meaningful, fulfilling lives. Yet many people, including providers, do not recognize this functional potential, which can hinder treatment and recovery for diagnosed individuals. To achieve functional recovery, treatment should combine integrated pharmaceutical

and nonpharmaceutical therapeutic modalities that address all symptoms. Recovery-oriented services should prioritize incorporating meaningful social engagement, employment support, and independent living skills over managing symptoms alone. Recovery should empower individuals to take ownership of their care and emphasize building individual capacity, agency, and autonomy.

Opportunities to Advance Clinical Treatment

Development of Biomarkers to Improve Diagnosis, Treatment Prediction, and Monitoring

Given the challenges and limitations of current approaches to diagnosis, researchers are trying to develop biomarkers and objective measures for diagnosis and monitoring. In addition to improving diagnostic accuracy, biomarkers are of particular interest for precision psychiatry, where they can be used to predict and monitor treatment response. Various approaches are under development.

Genetics-based biomarkers: Many genetic markers related to diverse pathophysiological cascades and processes have been identified. Genetics could help illuminate subtypes of schizophrenia and eventually culminate in genetic profiles associated with customized treatment plans. However, because the genetics of schizophrenia are complex, genetic markers would likely be most impactful when coupled with other factors or biomarkers.

Neuroimaging signatures: Neuroimaging, via technologies like functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) imaging, is of interest for measuring brain activity and structure. Imaging biomarkers have shown promise for stratifying CHR populations. Electroencephalography (EEG) signatures are of particular interest as translational biomarkers that can measure patterns across research and clinical contexts, offering a window into neurocircuitry-level dysfunction and neuroanatomical changes characteristic of the pathology of psychosis spectrum disorders.

EEG offers candidate biomarkers for predicting conversion to psychosis in CHR individuals and is associated with functional outcomes after cognitive training (Light et al. 2020; Clayson et al. 2021; Mathalon et al. 2025). EEG technology is more accessible than expensive neuroimaging approaches like fMRI or PET (Lee and Kim 2022). Experts are enthusiastic about using EEG biomarkers to stratify patients for more targeted treatment and to more objectively measure treatment effects in clinical trials. Furthermore, repeated longitudinal collection of neuroimaging data may help to define clinical trajectories according to structural changes, thus improving clinical prediction capabilities.

Circulating molecular biomarkers: Researchers are also investigating cytokine biomarkers, or markers of peripheral inflammation, as indicators of neuroimmune functioning. Such factors could be collected in a blood sample, though researchers are also assessing the presence of molecular biomarkers within other biosamples, such as saliva, stool, or cerebrospinal fluid.

Digital or behavioral markers: With the advent of advanced wearable devices and the associated availability of big data analytics, interest is also growing in biomarkers based on continuously collected activity data. Individual-level behavior changes, such as sleep patterns or activity levels, can be tracked digitally and provide early indicators for detecting relapse. Digital analysis of voice and speech patterns is also promising. Research indicates that natural language processing can be used to detect thought disorder (Tang et al. 2021), and classification models can differentiate with high accuracy between individuals with schizophrenia and control participants based on speech and voice features (Huang et al. 2025; Berardi et al. 2023).

Development of New Therapeutic Options

One of the most exciting developments in the therapeutic landscape for schizophrenia was the approval of **Cobenfy** (formerly KarXT) by the FDA in September 2024. Cobenfy is an antipsychotic that targets the acetylcholine, rather than dopaminergic, neurotransmitter system. This new treatment option is the only antipsychotic medication with a novel mechanism of action in decades. Cobenfy could also be an important innovation because it is associated with lower cardiometabolic side effects compared to other antipsychotics. Reduced cardiometabolic side effects could improve cognitive and negative symptoms. While many are excited about its potential, the full impact of this new medication is not yet known.

Several other novel therapeutic targets and mechanisms of action are under investigation. Modulators of muscarinic acetylcholine receptors are of particular interest, given the efficacy of Cobenfy on the acetylcholine system. Some hope that modified compounds could provide similar efficacy with fewer side effects than the available options cause. Regulating the function of the neurotransmitter glutamate is also of interest, especially in hippocampal circuitry, which could drive symptom improvement across all three symptom domains of schizophrenia. Although previous efforts to target the glutamatergic system failed in clinical trials, some experts believe that improved compounds merit continued investigation.

Other promising targets include central nervous system kinases, a type of enzyme in neurons that plays a key role in signal transduction. Compounds targeting these proteins could address positive symptoms, negative symptoms, and cognitive deficits simultaneously. Researchers are also investigating mechanisms that target mitochondrial function, neuroinflammation, and plasticity, among other cellular functions, to identify potential novel targets.

In addition, there is interest in strategies that could target cross-diagnostic symptoms like fatigue, cognitive dysfunction, or impairment in social motivation (Begni, Marchesin, and Riva 2025). Combination strategies that pair existing therapeutic agents to boost efficacy or reduce side effects represent a near-term opportunity. For example, GLP-1 agonists like semaglutide can be paired with antipsychotic medications to minimize common cardiometabolic side effects caused by antipsychotic effects on the brain and body's signals of satiety (Siskind et al. 2025).

Finally, other ongoing efforts aim to improve current compounds to reduce side effects or improve administration. For instance, although clozapine is considered the gold standard for TRS, a version with lower side effects, easier administration, or a longer-acting formulation would have many benefits. **Table 2** summarizes opportunities to advance clinical treatment for schizophrenia.

Table 2: Opportunities to Advance Clinical Treatment

Category		
Established but Underutilized	**Promising but Underdeveloped**	**Fundamental Gaps and Needs**
Definition		
Impact of established intervention or approach could be amplified	Impact could grow with additional attention, evidence, or investment	New developments would help address unmet needs
List of Opportunities		

• Interventions with strong evidence but underutilization or limited access:
  • Clozapine
  • LAIs
  • Cognitive remediation therapy
	• Ability of Cobenfy to address negative and cognitive symptoms
	• Metabolic interventions
	• Interventions for improving motivation deficits
	• Neuromodulation techniques like ECT, TMS, or FUS
	• Personalized, multimodal therapeutic approaches
	• Improved implementation strategies focusing on evidence-based treatment
		• Biomarkers and objective diagnostic tools
		• Novel drug targets with new mechanisms of action
		• Novel treatments with fewer side effects or improved delivery mechanisms
		• Treatments for negative and cognitive symptoms

Source: Milken Institute (2025)

Models of Care: Assessment and Opportunities for Progress

The landscape of schizophrenia care comprises a plethora of diverse models to address dynamic care needs across individuals and throughout the lifespan. Significant gaps exist in accessing early-intervention programs and finding evidence-based treatment options along the continuum of care. The care delivery landscape is complex and merits in-depth analysis. This section gives a high-level overview and previews a forthcoming analysis and companion publication focused on models and accessibility of schizophrenia care.

Coordinated Specialty Care

CSC is a care framework that uses a team-based approach comprising psychotherapy, family support and education, medication management, employment and education support services, and case management. CSC has been rigorously tested for treating FEP. The American Psychiatric Association recommends that patients experiencing FEP receive treatment in a CSC program. As of 2014, CSC had been widely implemented across Australia, the UK, Scandinavia, and Canada (Heinssen, Goldstein, and Azrin 2014).

The CSC model NAVIGATE is a comprehensive program designed to provide early and effective treatment to individuals within FEP. The program includes medication management, individual resiliency training, family education, supported employment, and education. NAVIGATE was tested in the US through Recovery After an Initial Schizophrenia Episode (RAISE)—a study funded by the National Institute of Mental Health (NIMH)—and found to be more effective than typical care. This research led to the expansion of CSC programs nationwide (SAMHSA, n.d.).

A subsequent NIMH-funded effort called Early Psychosis Intervention Network (EPINET) includes more than 100 clinics with CSC teams organized across eight regional hubs (EPINET, n.d.). These clinics are connected in a learning health system—a model in which data from clinical care are analyzed to improve future care in a feedback loop between care and research.

Despite the effectiveness of the CSC model and efforts to expand insurance coverage of and access to this model of care, CSC programs have limitations, including limited capacity, long waitlists, and insurance barriers. These programs enroll individuals across various psychotic disorders, not only schizophrenia. Moreover, the duration of enrollment is capped at one to three

years for most programs, but many individuals with schizophrenia require longer-term care. When patients transition out of FEP programs, they typically enter general outpatient psychiatry, receiving a level of care that may not be sufficient. Many health-care providers emphasize the need for better step-down care, gradually reducing the level of service intensity to transition out of CSC, though care needs vary considerably among individuals.

The Broader Care Landscape

Beyond early-intervention programs, the care landscape includes multiple models and approaches for addressing different needs. There is wide variation in these models, which typically serve a broader population of people with SMI and substance use disorders. This brief overview makes clear that this is a complicated, nuanced system for individuals and caregivers to navigate.

Inpatient psychiatric care and forensic systems: Representing the most intensive end of the care spectrum, these systems typically serve individuals in acute crisis or those in the criminal justice system. However, these settings reflect crisis-driven responses, not optimal care pathways. A significant gap remains in having robust, high-quality care options along the continuum of need.

Residential and intensive care models: Providing wraparound support for individuals who need more than outpatient care but less than inpatient hospitalization, these programs provide integrated treatment for a population with various mental health conditions. Services are often restricted to those with private insurance and are typically intended for short-term care on the scale of months.

Community-based treatment: These approaches focus on community integration and incorporate peer support. One example of this type of treatment is Assertive Community Treatment (ACT). ACT teams provide multidisciplinary services for people with SMI, with 24/7 availability. Typically, they serve people with more established illness. The **clubhouse model** leverages community as therapy, providing dignified spaces that empower members through connection and belonging. Examples of clubhouses include Fountain House in New York and Magnolia Clubhouse in Ohio.

Specialty treatment clinics and traditional outpatient care: These less-intensive options focus on treatment and symptom management. Emerging telehealth and digital interventions offer additional opportunities and, given that virtual options are likely insufficient on their own, could supplement these other models.

Opportunities to Improve Access to High-Quality Care

The current US system to provide care for schizophrenia and other SMIs is fundamentally fragmented in ways that worsen disparities and limit impact. Such gaps represent key opportunities for innovation and investment to improve effectiveness and access to high-quality schizophrenia care.

Insufficient care options across the care continuum: As noted, while CSC programs are evidence-based and highly effective, they offer a limited duration of enrollment. When this period of CSC eligibility has elapsed or individuals age out of programs, they can struggle with the transition to traditional outpatient care. Even well-resourced CSC programs struggle to connect individuals to appropriate follow-on treatment. In general, diagnosed individuals face challenges during transitions between levels of care. The lack of connectivity between these systems and different levels of care exacerbates problems and leaves people prone to relapse.

Underserved populations: Specialized FEP programs serve only a subset of diagnosed individuals for several reasons. Some programs exclude people with comorbid intellectual disabilities or those who use cannabis. FEP programs are inherently limited in their scope—patients must be within early onset and often have age restrictions. These restrictions typically have upper limits of ages 25–30 that exclude individuals with later onset, who are disproportionately women. As a result, there is concern that the system is overly focused on early intervention at the expense of serving the adult population and those with established illness. The needs of people who do not match the persistent stereotype of a schizophrenia patient as a young, white male are commonly underserved. For example, Black individuals with schizophrenia often end up criminalized rather than receiving care. In addition, CSC programs are geared toward younger people, leaving many older adults underserved.

Access and geographic disparities: Care deserts—areas with limited or no access to specialized health-care services—are especially common in rural and underserved communities, exacerbating health disparities in treatment. These care deserts compound workforce shortages and long waitlists, limiting access to quality care. It is challenging to sustain specialized programs in less populated regions, and community mental health centers struggle with low provider pay, high staff turnover, and difficulty hiring qualified staff. Insurance coverage gaps and a lack of awareness among individuals and caregivers also limit access.

Implementation science opportunities: Implementation science is well positioned to advance the field. There is a substantial 15–20-year delay from research evidence to practice, with large implementation gaps between research findings and clinical practice. Implementation science studies could help address known gaps, such as in the underutilization of clozapine. One specific opportunity is to conduct deconstructing studies (also called dismantling studies) that aim to identify the essential elements of effective care models and other interventions.

This information would facilitate adaptations of approaches like CSC to other contexts while maintaining core fidelity. Programs can then prioritize the most important elements and avoid overinvesting in nonessential components. Deconstructing studies are challenging and expensive but essential for scaling programs efficiently. Without knowing their core elements, it is challenging to implement interventions like CSC with new populations or settings while maintaining fidelity. Supporting grants in implementation science or learning health systems approaches would help address these needs.

Opportunities to address these gaps and improve access to high-quality care for schizophrenia are summarized in **Table 3**. The complexity of these challenges also requires a comprehensive examination of care models and the system of care delivery. A forthcoming analysis will explore potential solutions to meet these needs in more depth, examining alternative examples, innovative approaches, implementation strategies, and opportunities to improve schizophrenia care.

Table 3: Opportunities to Improve Access to High-Quality Schizophrenia Care

Category		
Established but Underutilized	**Promising but Underdeveloped**	**Fundamental Gaps and Needs**
Definition		
Impact of established intervention or approach could be amplified	Impact could grow with additional attention, evidence, or investment	New developments would help address unmet needs
List of Opportunities		

• Access is varied and limited, even for models with a strong evidence base, such as:
  • CSC and FEP programs
  • ACT teams
  • Clubhouse models
	• Technology-mediated approaches, likely to supplement other models of support
	• Some standards of care have been established, but implementation of best practices is inconsistent in clinical practice
	• Educational tools and support systems to help individuals reach the right level of care at the right time
		• Connection across care systems and levels of care
		• Care options across the continuum of need
		• Care approaches that extend across the lifespan
		• Step-down programs and follow-on care options after more intensive care programs
		• Deconstructing studies to understand essential elements of effective interventions

Source: Milken Institute (2025)

Social Context: Assessment and Opportunities for Progress

Aside from research and clinical treatment, social context also shapes care, recovery, and quality of life for individuals living with schizophrenia. Misconceptions among various parties, including first responders, providers, teachers, and caregivers, create obstacles for diagnosed individuals who are seeking care and support in leading full, meaningful lives. These social barriers can compound clinical challenges, exacerbating social isolation, demands on caregivers, and negative outcomes for individuals.

Stigma and Lack of Public Awareness

Schizophrenia remains among the most stigmatized medical conditions. The public tends to immediately associate schizophrenia with damaging, incorrect stereotypes—mistakenly viewing individuals as dangerous, unpredictable, or violent—even though individuals with schizophrenia are more likely to be victims of violence than to perpetrate violence. Misconceptions about schizophrenia have evolved over time, but many have been persistent.

Table 4 contrasts the reality with some common misconceptions that continue to reinforce stigma. Stigma negatively impacts all aspects of patient care, from ignoring early signs to a hesitancy to seek care to a lack of acceptance that contributes to treatment noncompliance and drives social isolation. Parents' shame about a child's potential symptoms can also exacerbate treatment challenges, such as disincentivizing or delaying seeking help and treatment.

Table 4: Correcting Common Misconceptions About Schizophrenia

Common Misconception	Reality
People with schizophrenia can never recover and are permanently disabled. Stabilizing symptoms of psychosis is sufficient and as good as it gets.	With effective treatment and support, individuals with schizophrenia can hold jobs, maintain relationships, live independently, and lead full lives.
Schizophrenia is an emotional disturbance.	Schizophrenia is a serious brain disorder reflecting neurobiological changes.
Schizophrenia is associated with violence, danger, and unpredictability.	Individuals with schizophrenia are more likely to be victims of violence than to perpetrate violence.
People with schizophrenia have multiple or split personalities.* *Note that *split personality disorder* is an outdated term for dissociative identity disorder (DID).	Schizophrenia symptoms can include delusions and hallucinations. Schizophrenia and DID are distinct diagnoses.
Everyone with schizophrenia experiences the same standard set of symptoms.	Schizophrenia is a unique experience for each person. The condition presents with various symptoms.
Schizophrenia is genetic, and family history tells the whole story.	Schizophrenia is highly heritable, but there are other risk factors, such as stress.

Source: Milken Institute (2025)

Individuals experiencing symptoms or a diagnosis are often affected by self-stigma, or internalizing bias and prejudice against oneself. Self-stigma can limit the impact of early-intervention services and treatment. Self-stigma can occur even when individuals don't personally believe negative stereotypes. Simply being aware that others hold these beliefs can trigger harmful behaviors like avoiding disclosure to friends or employers. Moreover, structural stigma, including employment discrimination, housing barriers, and involuntary hospitalization, remains especially harmful and is often perpetuated by sensational coverage or portrayals in the media.

Compared to other neurological conditions or diseases, stigma also leads to a disadvantage for schizophrenia advocacy and fundraising. Whereas other conditions have highly visible public figures who raise awareness and resources for medical conditions, schizophrenia does not, and donors often choose to remain anonymous due to stigma and a reasonable desire to protect loved ones from any public association with mental illness. This lack of visible advocacy may also affect investment, as it is difficult to attract high-profile donors or public campaigns, which have increased funding for other diseases.

Organizations like CureSZ (CureSZ, n.d.) and the Schizophrenia & Psychosis Action Alliance (S&PAA) (S&PAA, n.d.) are among the few nonprofit organizations dedicated specifically to schizophrenia spectrum disorders, with efforts in advocacy, education, peer support, and research.

Effective stigma reduction requires a multipronged intervention that combines education to increase awareness with interpersonal contact using specific narrative structures (Yang et al. 2021). CHR and FEP programs assume that symptom reduction automatically addresses stigma, but substantial stigma persists. Adding anti-stigma interventions within these programs would be a tangible next step.

Cannabis Legalization and Recognition of Risk

Cannabis use presents a documented increased risk of psychosis and psychotic disorders. Evidence supports a dose-response relationship between cannabis use and psychosis risk, whereby earlier onset of use, longer or more frequent duration of use, and higher THC potency all confer increased risk (Bearden 2025). Use is of particular concern during important windows of brain development under the age of 25.

Moreover, the levels of THC—the major psychotropic component of cannabis—are much higher in modern products, increasing over 300 percent since 1995, according to data from the National Center for Natural Products Research (National Institute on Drug Abuse [NIDA] 2024). Higher potency is associated with an elevated risk of cannabis-induced psychosis and may contribute to treatment-resistant psychosis in young people. The risks are especially notable as access to highly potent products has increased alongside the legalization and commercialization of cannabis.

Despite documented evidence that cannabis is a major modifiable risk factor for psychosis and schizophrenia, the underlying biology is poorly understood. Mechanistic research into cannabis-induced psychosis is needed, which could then support therapeutic development targeted for cannabis-induced psychosis. In the meantime, education is needed so that young people and parents are aware of the risks, symptoms to watch for, and how to seek help if needed.

Social Connection and Belonging

Social connection and belonging are key to recovery, but individuals with schizophrenia are prone to experiencing social isolation. Schizophrenia is associated with a lack of social motivation and underestimating the value of social rewards (Catalano and Green 2023; Lee et al. 2019). **Social anhedonia**, a lack of interest in or motivation for social interaction, may be a key barrier to seeking care and to community integration (Catalano and Green 2023); however, connection and belonging are understudied.

Understanding of social connection interventions is limited, despite being consistently identified by those with lived experience as core to recovery. Clubhouse models offer a useful counterexample of leveraging community as a therapeutic modality. Members often arrive with extrinsic motivations, such as a need for a job or housing. Through community engagement, members develop an intrinsic sense of value that persists beyond meeting those immediate needs. More research is needed to build on these examples and clarify the effects of specific interventions and best practices to promote social integration and belonging.

Unmet Support Needs of Family Members and Caregivers

Schizophrenia is associated with a particularly high burden on family members and caregivers. In caring for their loved ones, family members and caregivers face challenges that vary from finding and accessing treatment to barriers in acquiring sufficient insurance coverage for care. They must contend with complex care and legal systems, usually with no one to help orient or guide them, to find appropriate care on behalf of their loved ones and support their lifelong care needs.

Intensifying these issues, care system failures push the caregiving burden onto families, who become unpaid caregivers and often develop their own mental health challenges with stress, depression, and anxiety. Diagnosed individuals also have a wide variation in the degree of family support available, which may contribute to health disparities for groups who are already at a systemic disadvantage.

One barrier that family members are often ill-equipped to manage is resistance from their loved one, who may have schizophrenia and not recognize the need for treatment. This lack of insight into one's condition, or anosognosia (see section "Journey from Early Symptoms to Diagnosis and Treatment"), is a core neurobiological symptom of schizophrenia that hinders engagement with treatment. Family communication patterns, especially in negotiating this complicated symptom, can impact clinical outcomes. Evidence-based communication strategies can help family members in these situations. The LEAP method, for example, teaches families to normalize emotions and avoid confrontational approaches to improve engagement (LEAP Institute, n.d.).

Given all these factors, it is important to recognize the needs of family members and caregivers alongside those of patients. Community-based advocacy organizations fill critical gaps in family support and system navigation while providing forums to engage in peer support with other families. Organizations like S&PAA, Team Daniel, CureSZ, and Arizona Mad Moms provide mentors, educational materials, and other resources to support families, but they need resources to keep up with the high demand for family support.

Opportunities to Address Social Context Challenges

Social context challenges—stigma and misconceptions, cannabis risks, social isolation, and caregiver burden—represent significant barriers to recovery and important opportunities for strategic intervention. Addressing these challenges requires coordinated effort to improve training, provide education, build community, and support families and caregivers. **Table 5** summarizes key opportunities to amplify existing resources, strengthen social support, and increase awareness in the schizophrenia community.

Table 5: Opportunities to Increase Awareness and Strengthen Social Support

Category		
Established but Underutilized	**Promising but Underdeveloped**	**Fundamental Gaps and Needs**
Definition		
Impact of established intervention or approach could be amplified	Impact could grow with additional attention, evidence, or investment	New developments would help address unmet needs
List of Opportunities		
• Family education and support programs • Training in effective communication strategies for family, caregivers, first responders, and more	• Peer support for families and caregivers • Interventions to improve community integration and belonging • Adding anti-stigma interventions within FEP/CSC programs	• Broad education campaigns focusing on stigma reduction • Campaigns to raise awareness of cannabis use as a risk factor • Interventions to address social motivation deficits

Source: Milken Institute (2025)

Systemic Barriers: Assessment and Opportunities for Progress

Systemic barriers across the US health-care system significantly impede access to high-quality schizophrenia care. These barriers operate at multiple levels, from insurance reimbursement structures that are often misaligned with the complexity of SMI treatment to infrastructure and workforce shortages that create long waitlists for specialized care. Structural challenges, such as a lack of stable housing and overreliance on the criminal justice system, further compound access issues. Addressing these interconnected barriers requires policy reform and coordination across systems, including health care, criminal justice, and housing.

Insurance Reimbursement and Payment Barriers

One of the biggest barriers to improving schizophrenia care in the US is the insurance and reimbursement landscape, which impacts everyone from diagnosed individuals and caregivers to providers. The US system is primarily built around a fee-for-service model in which providers are paid per service regardless of clinical outcomes or other factors. The current paradigm does not account for the complexity of treating SMI, such as schizophrenia, as compared to other mental health or medical conditions. For example, reimbursing based on 15-minute, fee-for-service increments is misaligned with holistic, comprehensive care. Extra work for providers, such as coordinating care or prescribing clozapine, goes unreimbursed, discouraging best practices.

Lack of Insurance Coverage

In addition to this misalignment, insurance often does not cover evidence-based practices. There is little to no coverage for nonpharmaceutical treatment modalities, family support, or care coordination. Providers often cannot bill for supported employment services, cognitive training, or motivation enhancement apps, so delivering therapies like social and cognitive training typically relies on research grant support. Even when services are reimbursable, rates are highly variable and often inadequately low, further challenging care delivery.

Need for Improved Payment Models

There is a need for payment models that reward quality of life and functional outcomes rather than traditional metrics, and many experts suggest that alternative models, such as value-based or capitated models, could help address current problems. However, alternative payment models can face implementation challenges, especially for areas like behavioral health, due to a relative lack of quantitative outcome metrics. In addition, mental illness diagnoses are not good predictors of resource utilization, making them difficult to incorporate into payment models. Successful implementation of alternative models will likely require flexibility and adaptation, such as flexible financial caps or quality floors, rather than rigid standards.

Medicaid Billing Challenges

Of Medicaid enrollees in the US, 10 percent have an SMI, meaning that about one million Medicaid-enrolled adults carry a diagnosis of schizophrenia or psychotic disorder as of 2021 (Saunders et al. 2025). Medicaid, which accounts for 45 percent of inpatient mental health and substance use coverage (Counts 2025), has become the primary payer for mental health services in the US. This reality has inadvertently set up a reactive safety-net model rather than a proactive care model.

These dynamics incentivize waiting for a crisis to intervene and disincentivize investing in prevention or early intervention. Despite the Centers for Medicaid and Medicare Services (CMS) adding billing codes for services like FEP programs, existing codes are underutilized, likely due to a combination of provider hesitance and implementation gaps. The Kennedy Forum is one organization working to address these gaps, starting with an implementation study to understand the issues and pilot test cases to improve adoption.

Lack of Mental Health Parity

Compounding these payment issues, reimbursement disparities between medical care and mental health care have long been documented for both Medicaid and private insurance alike (Zhu et al. 2023; Mark and Parish 2024). Recent data show that average office visit reimbursement is more than 30 percent higher for medical and surgical physicians than for behavioral health clinicians (Mark and Parish 2024).

The 2008 Mental Health Parity and Addiction Equity Act requires equal insurance coverage for mental health and substance use disorders versus medical and surgical benefits, but violations are common and often go unaddressed (The Kennedy Forum, n.d.) For example, insurers sometimes require more treatment failures for behavioral interventions than for medical ones before approving a more expensive treatment option. Disincentives such as lower reimbursement rates and high administrative burden lead a significant portion of providers to opt out of insurance networks (Bishop et al. 2014; Donohue, Goetz, and Song 2024). These factors also reduce compensation, exacerbating workforce shortages by potentially disincentivizing careers in mental health compared to other medical specialties.

Provider Shortages and Infrastructure Limitations

Individuals often face long waitlists for care—a result of limited capacity and a shortage of specialized providers. In particular, a lack of diverse providers affects engagement among racially and ethnically diverse individuals.

Several factors contribute to workforce shortages. Working with a population struggling with SMI can take an emotional and mental toll on providers. These challenges, combined with insufficient support for clinicians and complications like administrative and insurance barriers, lead to high provider turnover and burnout. In addition, medical schools and residency programs lack standardized training on specialized, evidence-based practices for schizophrenia treatment, leaving providers without adequate training. A more expansive workforce could include an increased reliance on nurse practitioners, psychologists, physician assistants, and general practitioners, who could provide specialized care with sufficient training.

Aside from provider shortages, infrastructure and capacity constraints, specifically the shortage of inpatient psychiatric beds, limit access to care. Due in part to the Medicaid exclusion rule, which limits federal funding for psychiatric beds, estimates indicate only 22–28 psychiatric beds per 100,000 persons in the US population (Lindenfeld et al. 2025; La et al. 2015).

This number amounts to less than half the number of beds in similar countries or the number recommended to meet the needs of those in the US with SMI and requiring inpatient treatment (Mundt et al. 2022). Furthermore, there are significant geographic disparities across the US with limited specialized facilities beyond major medical centers. Insufficient infrastructure generates pressure to release individuals from treatment, sometimes prematurely. This pressure can lead to revolving-door situations in which individuals cycle in and out of facilities and can increase involvement of emergency services or criminal justice.

The Criminal Justice System and Structural Barriers to Care

Individuals with schizophrenia and SMI face circumstances ripe for overreliance on police and the criminal justice system, which is sometimes described as the de facto mental health system. Rates of joblessness and homelessness are higher within the SMI population, and crisis situations often involve law enforcement or other emergency responders. Throughout US history, trends have shifted between favoring institutionalization and favoring deinstitutionalization. The current era leans toward the latter, and a lack of community support means that incarceration can take the place of appropriate treatment and care.

Crisis intervention team (CIT) programs are one approach to handling this issue, in which police teams are trained to manage mental health crises. CIT programs are promising, but the training is variable and inconsistent.

Alternatively, community responder models seek to shift away from police involvement by dispatching mobile crisis teams for nonviolent mental health situations. In recent years, mobile crisis teams spread throughout the country, as SAMHSA identified these units as an important element of crisis response (SAMHSA 2020). Approximately 40 percent of US counties have at least one mobile crisis team (Burns et al. 2024). For example, Denver's Support Team Assisted Response program launched in 2020 and has rapidly scaled, demonstrating a reduction in criminal offenses, improved outcomes for those in mental health crisis, and cost effectiveness (Dee and Pyne 2022; NLC, n.d.).

Criminalizing mental illness intersects with structural barriers, such as the lack of reliable transportation or stable housing, that affect health-care access overall. One study found that two-thirds of forensic hospital admissions were experiencing homelessness at the time of arrest, and nearly half received no mental health services in the six months before arrest (Warburton 2024).

The lack of safe, stable housing drives breakdowns in the system of care, adding to the cycle between homelessness, hospitalization, and incarceration. Housing is integral to effective schizophrenia treatment and recovery. Further, age exacerbates these challenges, and few programs exist to help the older SMI population. Providing comprehensive care requires addressing gaps in housing support and developing permanent supportive housing solutions.

Opportunities to Address Systemic Barriers to Care

A supportive policy landscape would increase access to existing care solutions across many of the areas discussed in this report. Specific policy needs differ across the federal context and various states in the US, but strategic investment in policy reform and implementation could truly move the needle on access to quality care for individuals living with schizophrenia across the US. **Table 6** summarizes opportunities to address systemic barriers, including policy reform.

Articulating economic arguments for mental health care is essential for advancing policy objectives, particularly when it comes to interventions with longer time horizons. Mental health interventions yield generalizable economic benefits across conditions (Counts et al. 2025), giving them a high return on investment. If the Congressional Budget Office were to routinely account for long-term mental health impacts in economic modeling, bills addressing mental health would show cost savings via health-care utilization savings, labor productivity gains, and tax revenue increases. Incorporating economic benefits from mental health gains could make these bills more politically viable. An increased focus on collecting outcome data would also support policy evaluation.

Specific policy changes could also increase capacity and access, according to experts. The Medicaid exclusion rule for mental health care remains a significant barrier to care for SMI because it limits funding for infrastructure, perpetuating the reliance on emergency services. After successful

advocacy, CMS has developed some Medicaid billing codes for services such as CSC, but adoption and utilization of these codes have been limited. To facilitate implementation, rates and standards need to be set across states, highlighting a need for state-level technical assistance for rate development and billing infrastructure.

The schizophrenia community may also benefit from identifying points of common ground with other conditions, which could bring more attention and investment to common issues. One such issue is the need for long-term supportive housing, which is foundational to effective treatment for conditions across SMI and substance use disorders.

Table 6: Opportunities to Address Systemic Barriers to Care

Category		
Established but Underutilized	**Promising but Underdeveloped**	**Fundamental Gaps and Needs**
Definition		
Impact of established intervention or approach could be amplified	Impact could grow with additional attention, evidence, or investment	New developments would help address unmet needs
List of Opportunities		
• Crisis intervention training programs and teams • Community responder models for crisis response • Case management programs and support	• Capitated or value-based payment models	• Lack of state hospital beds and limited infrastructure • Long-term supportive housing options

Source: Milken Institute (2025)

Funding and Investment Landscape

This section reviews funding trends in schizophrenia research and care, examining investments across public and private funders. Methods can be found in the Appendix.

Overview of Schizophrenia Funding

The largest funder of schizophrenia research in the US is the federal government—specifically, the NIH. Within the NIH, the NIMH represents the largest portion of funding, averaging about $300 million per year. However, this funding level has been in decline, lacks specificity for schizophrenia, and focuses on relatively few research categories.

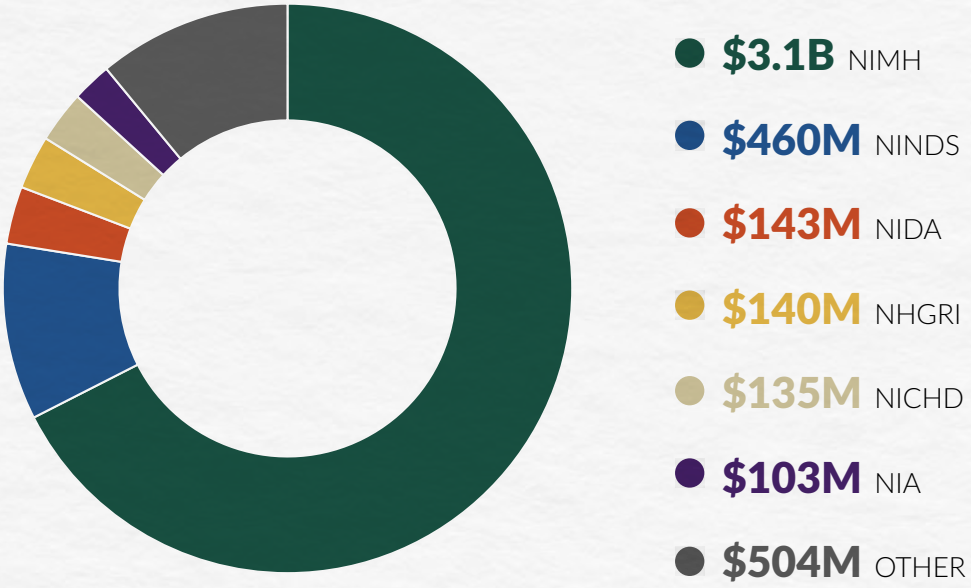
For schizophrenia care, Medicaid serves as the primary payer for mental health services, and SAMHSA plays a key role in supporting care innovation, pilot programs, and technical assistance. Although SAMHSA funding has increased over the last decade, the annual budget is relatively small compared to other programs within the Department of Health and Human Services (HHS), and SAMHSA spending on mental health is considerably less than that for substance abuse treatment and prevention.

In addition to federal funding sources, many private foundations and organizations fund biomedical and psychiatric research. However, relatively few private funders specifically focus on schizophrenia. The schizophrenia field would benefit from focused support and coordinated, specific efforts across both private and public funding.

Federal Funding for Schizophrenia Research

HHS is the single largest funder of schizophrenia research in the US, with the NIH specifically responsible for allocating most research funds. Outside of HHS, other federal entities, such as the Department of Veterans Affairs Office of Research & Development, also provide research support for schizophrenia (Veterans Affairs, n.d.).

Figure 2: NIH Funding for Schizophrenia by IC, 2015–2024

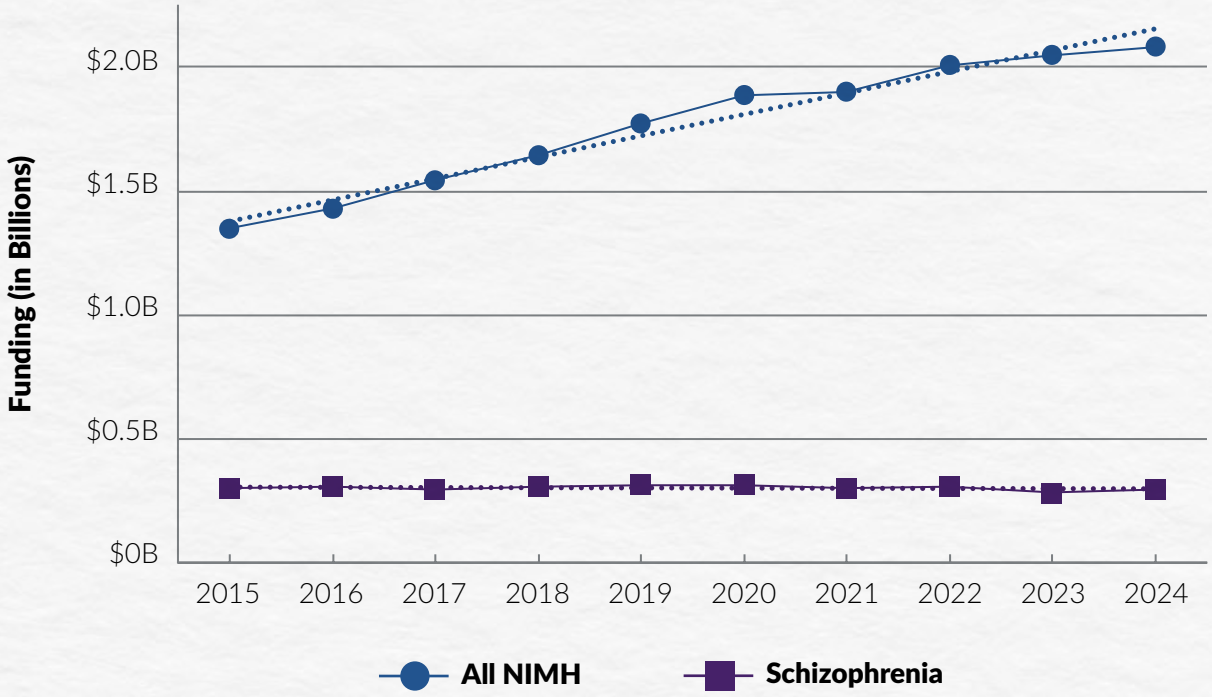


Notes: Institutes or centers (ICs) listed at threshold over $100 million over the 10-year period. NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NIDA = National Institute on Drug Abuse; NICHD = Eunice Kennedy Shriver National Institute of Child Health and Human Development; NHGRI = National Human Genome Research Institute; NIA = National Institute on Aging
Source: Milken Institute analysis of funding from NIH RePORTER (2025)

Between 2015 and 2024, NIH funding related to schizophrenia research totaled approximately $4.5 billion, based on the NIH RePORTER database (see the Appendix for more detailed methods). Within the NIH's institutes or centers (ICs), the NIMH is the single largest funder, accounting for approximately two-thirds of total NIH investment in schizophrenia research (**Figure 2**). Several other ICs have contributed over $100 million from 2015 to 2024; these include the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse (NIDA), the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Human Genome Research Institute (NHGRI), and the National Institute on Aging.

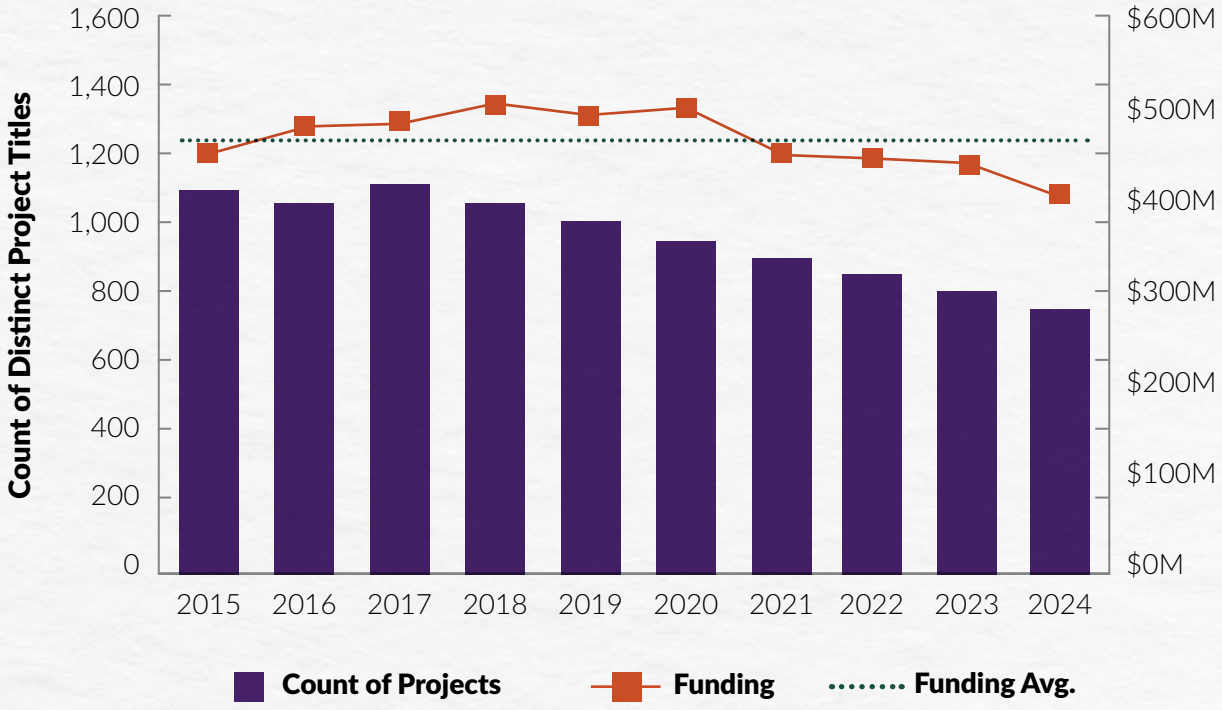
In the context of growing NIMH budgets over the last decade, NIMH annual support for schizophrenia has remained stagnant (**Figure 3**). Because NIMH funding overall increased over the same period, this suggests that gains in the NIMH budget have been directed toward other conditions and priorities. Considering the total NIH investment in schizophrenia beyond NIMH, both the number of active projects and the total funding related to schizophrenia have decreased over the 10-year period (**Figure 4**). Total NIH schizophrenia funding fell to $403 million in 2024, about $50 million lower than the 10-year average.

Figure 3: NIMH Overall Budget vs. NIMH Schizophrenia Research Funding, 2015–2024



Source: Milken Institute analysis of funding from NIH RePORTER (2025)

Figure 4: Total NIH Research Funding for Schizophrenia Compared to the Number of Active Projects



Note: Dashed line marks the NIH annual funding average of $456 million toward schizophrenia-related research.
Source: Milken Institute analysis of funding from NIH RePORTER (2025)

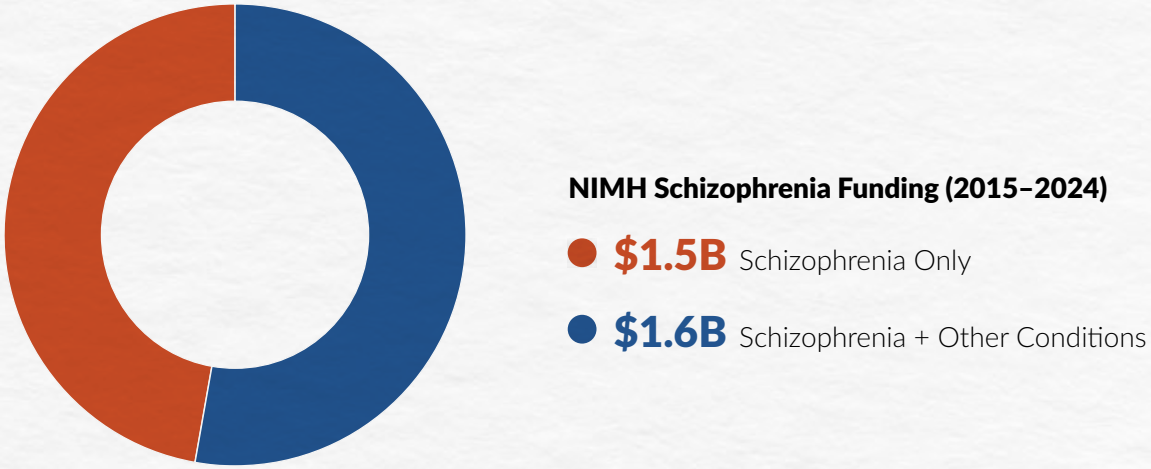
NIH Funding for Schizophrenia Supports Broad Research Areas with Limited Disease-Specific Focus

Much of the spending related to schizophrenia research appears to be nonspecific. Using a narrower definition of schizophrenia-specific funding, such as data from the NIH Research, Condition, and Disease Categories (RCDC) system, indicates that, on average, $251 million was targeted toward schizophrenia from 2015 to 2024 (see Appendix for more detailed methods). This amounts to about 55 percent of the total NIH funding related to schizophrenia.

Examining the number of projects with the term "schizophrenia" in the title is another indicator of whether a project has schizophrenia as a top focus. A minority of projects in the readout from the RePORTER database have schizophrenia in the title, and the percentage is trending down from nearly 25 percent in 2015 to less than 18 percent in 2024. Together, these measures suggest that while NIH funding for schizophrenia may be related to the disorder or associated research infrastructure, many of the projects appear to have a different focus and may not primarily investigate mechanisms of disease or develop clinical advancements.

Funding for psychiatric conditions tends to have a broad lens rather than focusing on one specific disorder or disease, as shown in a similar analysis of bipolar disorder funding (Pham and Altimus 2021). Within the list of NIH spending categories that co-label grants for schizophrenia with other disorders, the highest frequencies of overlap are bipolar disorder, depression, autism, anxiety disorders, major depressive disorder, Alzheimer's disease, and post-traumatic stress disorder. Approximately half of the funding for schizophrenia from the RePORTER database is cross-diagnostic in nature, meaning that it has a more general focus on two or more psychiatric conditions (**Figure 5**). This finding further underscores the fact that, although there has been a substantial investment in schizophrenia research, much of the funding is nonspecific.

Figure 5: Proportion of Cross-Diagnostic Funding

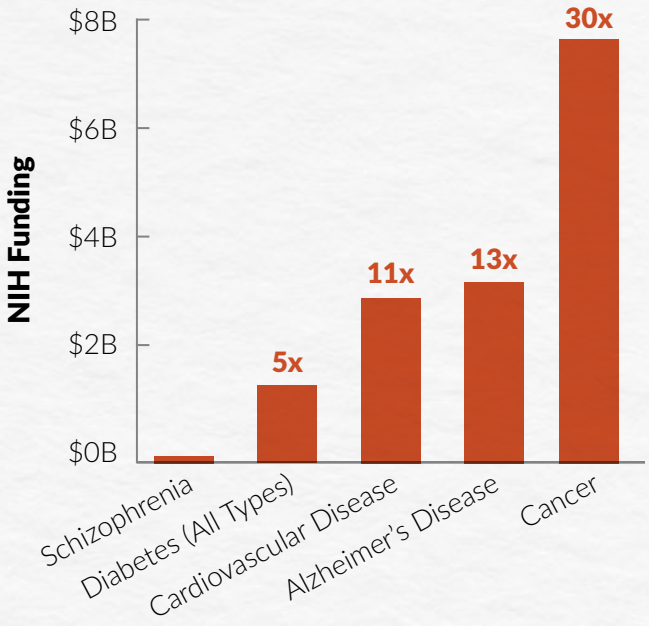


Note: This analysis looked at overlap with bipolar disorder, depression, autism, anxiety disorders, major depressive disorder, Alzheimer's disease, and post-traumatic stress disorder at the level of project title, project abstract, or spending category.
Source: Milken Institute analysis of funding from NIH RePORTER (2025)

Schizophrenia Is Underfunded Relative to Its High Economic Burden

The NIH has invested substantially in schizophrenia research, surpassing its investment in other psychiatric conditions, such as bipolar disorder (Pham and Altimus 2021). However, it is essential to consider this total in the context of the needs of the field. Notably, recent estimates suggest schizophrenia's annual economic burden is over $300 billion (S&PAA 2021; Kadakia et al. 2022). As noted previously, reducing this strain requires better care outcomes, which depend on the development of better treatments and clinical care tools. Such advancements are only possible with significant and targeted research funding.

Figure 6: Comparison of Research Funding for Conditions with Comparable Economic Burden



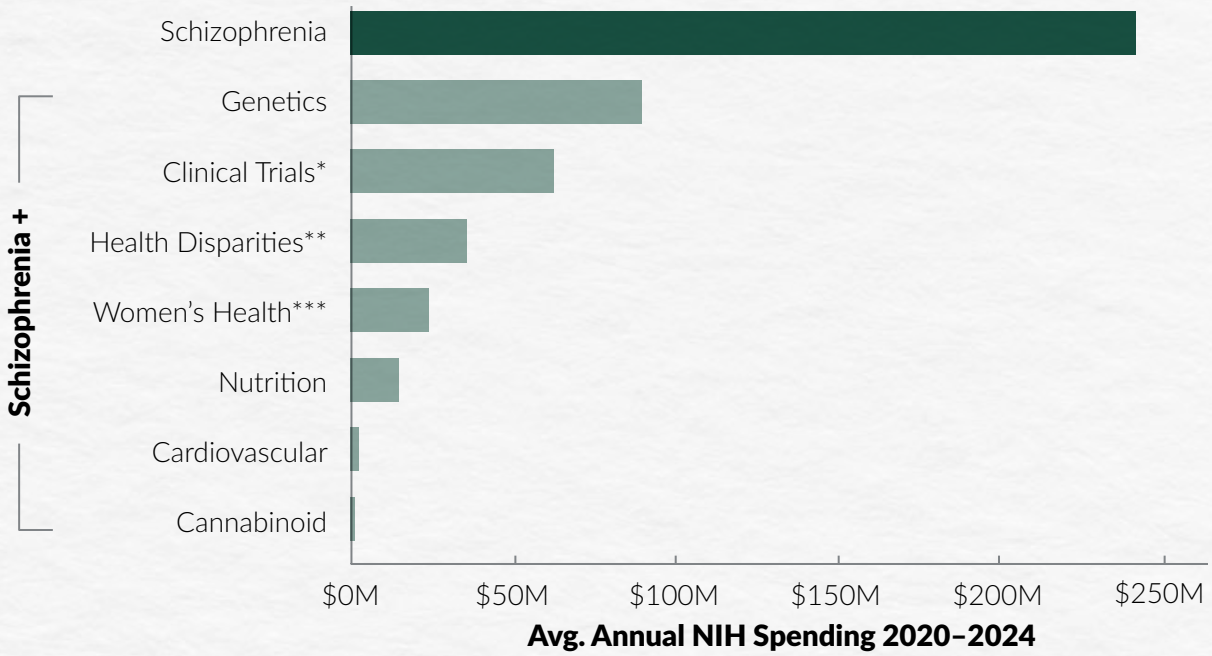
Source: Milken Institute analysis from NIH RCDC (2025)

Even though the estimated economic burden of schizophrenia is on par with conditions such as cancer and diabetes, funding for schizophrenia research is 5–30 times less (**Figure 6**). This discrepancy underscores an underinvestment in schizophrenia relative to economic impact and is in line with broader trends regarding underinvestment in psychiatric conditions relative to their economic impact (Dawes et al. 2024). Unlike chronic conditions affecting primarily older adults, the onset of schizophrenia occurs as early as adolescence, meaning that a substantial burden on individuals and families is often experienced over decades. The current level of funding does not reflect the reality of a major chronic illness with sustained high costs.

NIH Schizophrenia Funding Priorities Show Mismatch with Clinical Need

NIH funding for schizophrenia varies in focus, with much of the investment focused on genetics research and, recently, increased support for clinical trials (**Figure 7**). This section explores these spending categories, as described in **Box 6**, and the extent to which research support aligns with major challenges identified in the field.

Figure 7: NIH Funding for Schizophrenia by Spending Category



*Notes: *Full category name is Clinical Trials and Supportive Activities; **Renamed in 2023 as Health Disparities and Racial or Ethnic Minority Health Research, includes Health Disparities Research and Racial and Ethnic Minority Health Research; *** Listed as Women's Health from 2020–2023 and Women's Health Research from 2024 to present. This analysis examined the level of funding relative to the category of Schizophrenia over the last five years, 2020–2024, due to changing category titles.*
Source: Milken Institute analysis of funding from NIH RePORTER, using RCDC spending categories (2025)

Box 6: Research, Condition, and Disease Categories

The RCDC system was created in 2009 to promote transparency in NIH spending and standardize reporting. It uses a text-mining method to identify the relevant categories for each funded project. This means that the text of a project must include core concepts that are relevant to a category in order for it to be identified. The projects included in the current assessment had, on average, eight spending categories, though some had greater than 20.

Though the unbiased approach of categorization has clear benefits over using the investigator-defined project terms, which often include topics that are not directly relevant, there are drawbacks. The list of categories is limited, and there are topics excluded that would be of interest to measure, such as cognition or drug development. Further, categories vary widely in specificity, and they can change over time. For example, *psychosis* was added in 2024, and reporting in that category is not available for prior years.

Despite limitations, the RCDC system can be useful in estimating funding for a specific topic and identifying trends over time.

Genetics Research in Schizophrenia Has Been Comparatively Well-Funded

The category of Genetics averaged over $80 million in funding per year between 2020 and 2024—approximately one-third of total NIH funding in the Schizophrenia category. This is likely a conservative estimate, as the NIH has supported large-scale sequencing and genomics efforts through NHGRI. Many of these programs, such as the Centers for Common Disease Genomics, have supported work in the genetics of psychiatric illness, though they are not categorized under Schizophrenia (e.g., NIH Center for Common Disease Genetics, n.d.).

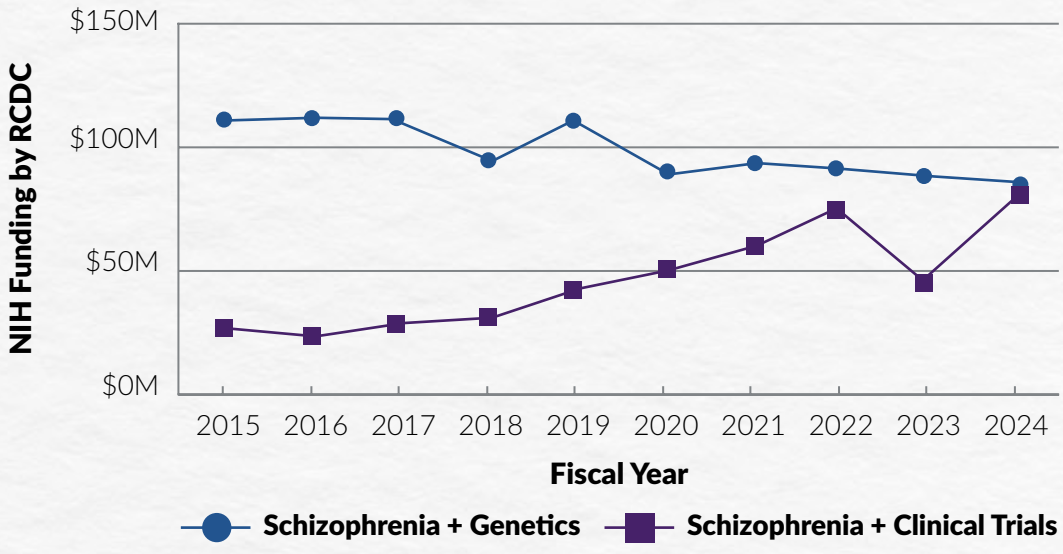
As noted previously, despite the high heritability of schizophrenia, the genetic risk factors are not fully understood. While many genetic risk factors have been identified, the relatively high investment in genetics research has not yet translated into major clinical advances, such as new biomarkers or therapeutics. Nevertheless, many experts remain optimistic that meaningful progress in precision medicine is on the horizon, especially with advances in machine learning models and technologies to support analysis of big genomics data sets.

Support for Clinical Trials Is Trending Upward

Though NIH funding for genetics research still constitutes a substantial portion of schizophrenia research support, it has declined over the past decade. Conversely, funding within the spending category of Clinical Trials and Supportive Activities has increased (**Figure 8**), accounting for almost the same portion as Genetics in 2024.

Despite this increase, experts note that NIH funding for clinical trials remains insufficient compared to funding needs. Researchers shared that NIH funding for clinical trials is focused on identifying the mechanism of action of a drug rather than testing efficacy. There is also a noted lack of head-to-head trials that directly compare two or more treatments. Funding for the Comparative Effectiveness Research category averaged $8 million over the last decade, compared to $45 million for Clinical Trials and Supportive Activities.

Figure 8: Funding Under the Schizophrenia RCDC That Is Co-labeled with Genetics or Clinical Trials



Source: Milken Institute analysis of funding from NIH RCDC (2025)

Research on Sub-populations Receives Moderate Spending

As noted previously, some subpopulations of people with schizophrenia experience unique challenges. The Health Disparities Research category describes research that is focused on populations who face barriers to achieving health or experience a disproportionate impact of a disease. This category, combined with Racial and Ethnic Minority Health Research, received an average of about $30 million per year between 2020 and 2025, which is 13 percent of the Schizophrenia category.

Not covered within these categories is the subpopulation of women with schizophrenia, who have a different pattern of disease onset and often have a different symptom presentation than men. In 2020, the RCDC system started tracking Women's Health Research as a distinct category, and, since then, an average of $17.5 million per year—only 7 percent—has been spent within the Schizophrenia category. These funding levels are in the middle of the range across major spending categories for schizophrenia research. That said, research on the most affected populations and key subgroups is essential in developing more personalized treatment and care options.

Schizophrenia Research in Cardiovascular Health, Nutrition, and Cannabinoids Receives Minimal NIH Funding Support

Many spending categories represented less than 2 percent of NIH funding in the Schizophrenia category, or under $5 million per year. One such category is Cardiovascular, which averaged less than $3 million per year from 2020 to 2024. Individuals with schizophrenia have a high rate of comorbid cardiovascular disease, which contributes to a 15- to 20-year reduction in life expectancy. Many experts noted that the clinical care landscape does not adequately address cardiovascular comorbidities, and many common pharmaceutical treatments for schizophrenia can worsen cardiovascular and metabolic health. Despite these known complications, little funding for schizophrenia has a cardiovascular focus.

Other categories with little funding are Nutrition and Cannabinoid Research, which involve factors that can contribute to the development and clinical trajectory of schizophrenia. Nutrition impacts schizophrenia on many levels: Poor maternal nutrition is a risk factor for the illness, many pharmaceutical treatments have weight-related side effects, and metabolic interventions are a potential avenue for new treatment development. Cannabinoids are a class of compounds that include THC, the active ingredient in cannabis, the use of which is a major risk factor for schizophrenia. Research in these areas of lifestyle-based impacts on schizophrenia is much-needed and is arguably underfunded within the current NIH budget.

NIH Support for Coordinated Large Research Efforts

In addition to funding individual schizophrenia-focused research projects, the NIH provided support for large initiatives that coordinated research across multiple sites. These initiatives have primarily targeted understanding or intervening during the early stages of schizophrenia.

In 2008, the NIMH launched RAISE, an initiative that investigated the impact of CSC during early psychosis. Funding from this program supported $25 million in research across 34 clinics in 21 states. The RAISE study demonstrated the importance of early intervention and led to the recommendation of CSCs as the standard of care during the first episode of psychosis by the American Psychiatric Association (Keepers et al. 2020). To expand on the findings from RAISE, NIMH established EPINET in 2019. EPINET is a learning health system centered on improving care in early psychosis through the implementation of evidence-based practices.

EPINET consists of eight regional scientific hubs that are connected to CSC programs and supported by a National Data Coordinating Center, as well as funding for EPINET research grants. More than $40 million has been awarded across multiple sites over five years, and the NIMH announced an intended commitment of an additional $9.5 million in 2024 for EPINET sites. However, experts have said that funding for this next phase is in question, raising concerns about sustaining the research infrastructure and analyzing the data collected via EPINET.

The **Accelerating Medicines Partnership Schizophrenia** (AMP SCZ) is another major research effort, with funding from the NIH and others. AMP SCZ is a public-private partnership focused on predicting clinical outcomes and creating a platform to develop new treatments for schizophrenia. AMP SCZ focuses on the CHR population and aims to discover biomarkers that can be used to better define individuals within the CHR group who will go on to develop psychosis or schizophrenia.

This program relies on a large clinical cohort, involving a multisite, coordinated effort. Launched in 2020, AMP SCZ is managed by the FNIH, with a majority of funding from NIMH. They have a reported five-year budget of $117.7 million in NIH funding and supplemental funding from private sources across biopharmaceutical and nonprofit organizations. Its potential impacts are yet to be realized, though researchers are hopeful about the potential of the large data set being collected.

These initiatives represent innovative models of collaborative research that are especially important because many experts in the field have noted a need for more standardized, longitudinal data sets. These efforts not only support the improvement of clinical care but also provide outcomes data that help influence public policy and advocacy programs. Though some of the impacts of these programs have yet to be seen, there is a clear power in research that is coordinated across multiple sites with shared goals and missions.

Federal Support for Clinical Care

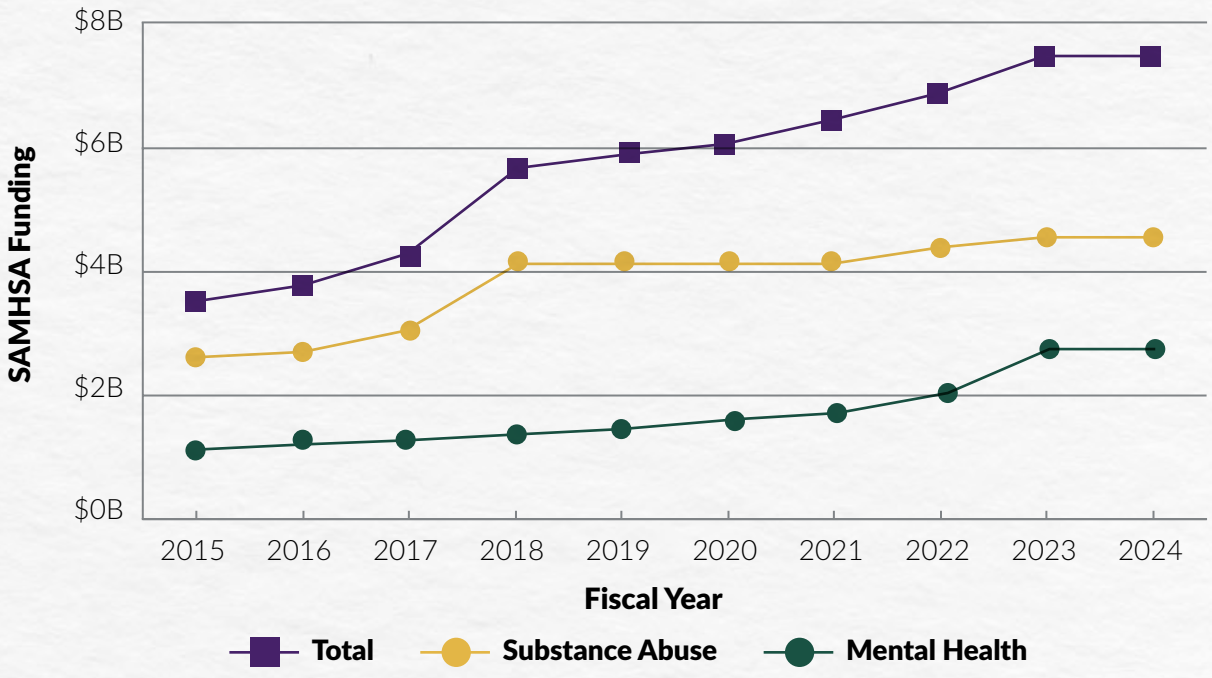
Looking beyond research into the care landscape, federal funding for schizophrenia care comes primarily from Medicaid, which is the largest payer for mental health services in the US (Counts 2025). Medicaid's role is significant, spending over $58 billion in 2019 for mental health care, with schizophrenia as one of the major conditions covered. Approximately one million Medicaid-enrolled adults had a diagnosis of schizophrenia or psychotic disorder in 2021, and the program covers 26 percent of adults with any mental illness (Saunders et al. 2025). Analyzing the specific Medicaid contribution for schizophrenia care is difficult given the program's complex structure and highly variable implementations across states.

SAMHSA is an agency of HHS that supports initiatives intended to improve behavioral health in the US. A significant portion of its budget is specifically used to help individuals with SMI, including people with schizophrenia. Its programs target many of the gaps outlined throughout this report and provide funding for nationwide efforts to advance mental health care and clinical outcomes, giving insight into federal priorities and funding mechanisms to address SMI. The following sections outline the mechanisms by which SAMHSA supports mental health care and, where possible, identify specific funding for SMI. However, none of these programs are specific to schizophrenia and may not meet all of the unique challenges of the condition.

SAMHSA Funding for Substance Use Has Outpaced That for Mental Health

SAMHSA's budget has increased steadily over the past decade (**Figure 9**), though it still represents less than 1 percent of the total HHS budget. SAMHSA funding is primarily divided between efforts for mental health and substance use, covering prevention and treatment, though these conditions are commonly comorbid. Spending on substance use has typically been about twofold higher than for mental health (**Figure 9**), despite the similar—or even higher—estimated economic burden of a subset of mental health conditions (schizophrenia, bipolar, and major depressive disorder) compared to substance use disorders.

Figure 9: SAMHSA Funding for Mental Health and Substance Use Disorders



Note: Funding for Substance Abuse includes both Substance Abuse Treatment and Substance Abuse Prevention programs.
Source: Milken Institute analysis via HHS budget reports (2025)

Most of the SAMHSA Mental Health Budget Is Intended for Serious Mental Illness

Though the SAMHSA funding for mental health is not specific to schizophrenia, a substantial portion of the funding is intended to target SMI—usually about $900 million to $1.5 billion per year. This support is provided through various programs.

The largest component of funding for SMI is the Community Mental Health Services Block Grant (MHBG). These funds support state-level efforts and are deployed at the discretion of each state to support mental health services with some restrictions. They are not competitive but require that the state apply and meet minimum program requirements. A portion of this funding is earmarked for the support of early psychosis programs; in 2021, this total was over $400 million (NIMH 2023). Block grants often serve as core funding for community mental health centers, many of which operate with limited resources. As noted, mental health clinics rely on grant funding to fill in insurance gaps, and the impact of this funding is constrained by the breadth of services the grants support.

Another large effort within SAMHSA is support for Certified Community Behavioral Health Clinics (CCBHCs). These community-based clinics offer access to coordinated behavioral health services and must ensure access regardless of circumstances, including the ability to pay. This program was first tested in 2015 through demonstration programs in a subset of US states. These efforts led to the development of infrastructure and certification criteria for CCBHCs, and the program has expanded into most states.

Like block grant funding, funding for the CCBHC program has increased, growing from $100 million in 2018 to over $400 million budgeted in 2025. However, this budget is spread across all clinic sites nationwide, which now total over 500. Across all conditions treated, SAMHSA estimates that more than 800,000 individuals have received care through this program and observed a reduction in hospitalization and homelessness within the population served.

In addition to block grants, SAMHSA manages several more programs that are partially or fully dedicated to helping individuals with SMI. These are listed in **Table 7**.

Table 7: SAMHSA Initiatives and Funding

Program	Description/Purpose	Funding Estimate
Assertive Community Treatment	Provides access to comprehensive mental health care within the community, reducing reliance on hospitals and promoting recovery (see section "Models of Care")	$45M since 2018; >60 awards; supports grants of up to $678K/year over five years
Assisted Outpatient Treatment	Establishes court-supervised mental health support, which promotes adherence to treatment through mandatory engagement	$45M since 2016; >175 awards; supports grants of up to $1M/year over four years; average award of about $200K
Children's Mental Health Services (CMHS)	Supports mental health care in children to reduce SMI development and severity	About $100M–$200M per year since 2017 across all CMHS; estimated 10 percent of this budget spent on early intervention for SMI
Crisis Systems	Coordinates crisis response for people with SMI with ongoing outpatient services to mitigate demand for inpatient services	$45M since 2022 for about 60 awards to the Community Crisis Response Program; additional funding is allocated from the MHBGs
Primary and Behavioral Health Care Integration Program	Coordinates primary care services and community behavioral health services for individuals with SMI	About $300M since 2017; about 150 awards; supports grants of up to $2M/year over five years
Projects for Assistance in Transition from Homelessness	Connects homeless individuals, including those experiencing SMI, with safe and secure housing	About $65M per year since 2017
Protection and Advocacy for Individuals with Mental Illness	Provides legal advocacy services and protects the rights of individuals with SMI	About $35M–$40M per year since 2017

Source: Milken Institute analysis via SAMHSA Grants Dashboard (2025)

SAMHSA funding provides a critical level of support for mental health services in the US. However, administrators from community care centers note a lack of sustainability and insufficient budgets despite federal support. Furthermore, SAMHSA funding is inherently distributed across psychiatric conditions, which can limit the funding available to address the unique care challenges of schizophrenia. Evidence indicates that investing in programs that provide sufficient support for schizophrenia and other SMI would be cost-saving in the long run by reducing the societal economic burden (Counts et al. 2025).

Private Funding for Schizophrenia Research and Care

Several private funders also make meaningful contributions to schizophrenia research and care (see Appendix for more detailed methods of assessment). Funding from nonprofit and philanthropic foundations is a critical component of the scientific landscape and often represents a targeted focus on a specific disease area. This targeted support led to significant progress and major breakthroughs for several medical conditions (**Box 7**).

Though many philanthropic initiatives have focused on psychiatric health or support biomedical science research, relatively few programs specifically focus on schizophrenia. Further, the private support for schizophrenia is limited compared to other conditions in the context of its significant societal burden. Expanding private investment in this area has the potential to have an outsized impact, and several foundations and groups are already leading the way.

Box 7: Examples of Key Medical Breakthroughs Facilitated by Targeted Philanthropic Support

- The Michael J. Fox Foundation for Parkinson's Research: Development of a biomarker assay called α-SAA for Parkinson's disease
- Simons Foundation Autism Research Initiative: Identification of genetic risk factors in autism
- amfAR: Development of new therapeutics for HIV/AIDS
- Susan G. Komen: Development of new therapeutics and screening aids for breast cancer, including Lymphoseek
- Cystic Fibrosis Foundation: Development of transformative therapies for cystic fibrosis that improve life expectancy

Schizophrenia-Specific Organizations

Compared to other illnesses, there are relatively few organizations dedicated specifically to schizophrenia research. Those that exist tend to have cross-cutting work across the research and care space, in line with the needs of the schizophrenia community.

S&PAA is a nonprofit that specifically aims to identify and address barriers to care for individuals with schizophrenia. Its three strategic areas include (1) research, (2) education and care, and (3) advocacy and public policy. While it does not fund a competitive grant program, it internally manages research programs and collaborates with industry and scientific consortia, such as AMP SCZ.

The **Schizophrenia International Research Society** is the leading academic society for schizophrenia researchers around the world, and its primary work involves managing resources for the community, such as in-person meetings and the *Schizophrenia* research journal. It also supports research grants and travel awards that largely target researchers in lower- or middle-income countries and early-career investigators.

The **Sidney R. Baer, Jr. Foundation** is a nonprofit with the mission to have a positive impact on the field of mental health and improve the care landscape for those living with schizophrenia. Though it also funds work that supports the bipolar field, targeted attention to schizophrenia is a key founding objective and primary focus of the organization.

Major Individual Gifts for Schizophrenia and Psychiatry Research Centers

Some philanthropists have made major contributions to individual institutions to establish specialized centers or dedicated funds. Though many examples of such gifts can be found in areas of psychiatric research, two stand out for their size and impact in schizophrenia—the Lieber family and the Stanley Family Foundation.

The **Lieber family**, through the Lieber Family Foundation, Essel Foundation, and associated partners, is one of the most significant private funders to focus specifically on schizophrenia. They have been a major supporter of mental health research since 1980 and were influential in the development of the National Alliance for Research on Schizophrenia & Depression, now known as the Brain and Behavior Research Foundation (BBRF) (see "Private Funders of Psychiatric Research Grants").

They established the **Lieber Center for Schizophrenia Research** at Columbia University, which included the opening of the Lieber Recovery Clinic that offers a comprehensive care model for individuals in need of psychiatric care. In 2011, they partnered with other philanthropic families to gift $200 million to establish the **Lieber Institute for Brain Development** at Johns Hopkins University, which now houses the world's largest collection of postmortem human brains from individuals with neuropsychiatric disorders and supports a strong research program in schizophrenia.

The **Stanley Family Foundation** is a nonprofit that broadly supports initiatives in mental health and SMI. In 2014, it made a $650 million gift to the Broad Institute, which led to the establishment of the **Stanley Center for Psychiatric Research**. Much of the work at the Stanley Center focuses on genetics, though it also funds the development of new therapeutics and biomarkers. While it is not a schizophrenia-specific research center, it maintains dedicated funds and programs to focus on the illness, including the Schizophrenia Exome Meta-analysis (SCHEMA) consortium.

Private Funders of Psychiatric Research Grants

Several private organizations fund research more broadly within psychiatry. Within these organizations, schizophrenia is often one of several psychiatric conditions targeted.

BBRF, noted previously for its support from the Lieber family, is a nonprofit that funds innovative research grants in neuroscience and psychiatry. Since 1987, it has awarded $178 million to schizophrenia research, with the largest portion from Young Investigator Awards that fund promising early-career researchers. Since 2015, it has funded nearly 300 Young Investigator Awards to researchers studying schizophrenia.

One Mind is a nonprofit that has competitive research psychiatry programs and aims to transform mental health care through research funding, education programs, workplace initiatives, and engagement of individuals with lived experience. Within its programmatic work, One Mind funds the Rising Star Award, representing innovative research grants in neuroscience and psychiatry. Since 2007, seven of these awards specifically supported research in schizophrenia. It has also partnered with larger efforts, such as AMP SCZ.

Another avenue of private funding can be through pharmaceutical and biotech companies that support academic schizophrenia research through grant programs. One example is **Alkermes**, which awards competitive research grants in areas of interest, with current support in schizophrenia, bipolar disorder, and narcolepsy. For example, since 2018, it has awarded 11 Pathways Research Awards focused on schizophrenia. It also awards Medical Education Grants intended to develop resources for continuing medical education.

Aside from psychiatry-focused organizations, several foundations focused primarily on other conditions also have relevance to schizophrenia. For example, due to the high comorbidity between schizophrenia and cardiovascular disease, the **American Heart Association** has provided modest research support for schizophrenia. Similarly, because autism and schizophrenia share genetic risk factors, schizophrenia is sometimes represented in the grant portfolios of organizations targeting autism. One example is the **Simons Foundation Autism Research Initiative**.

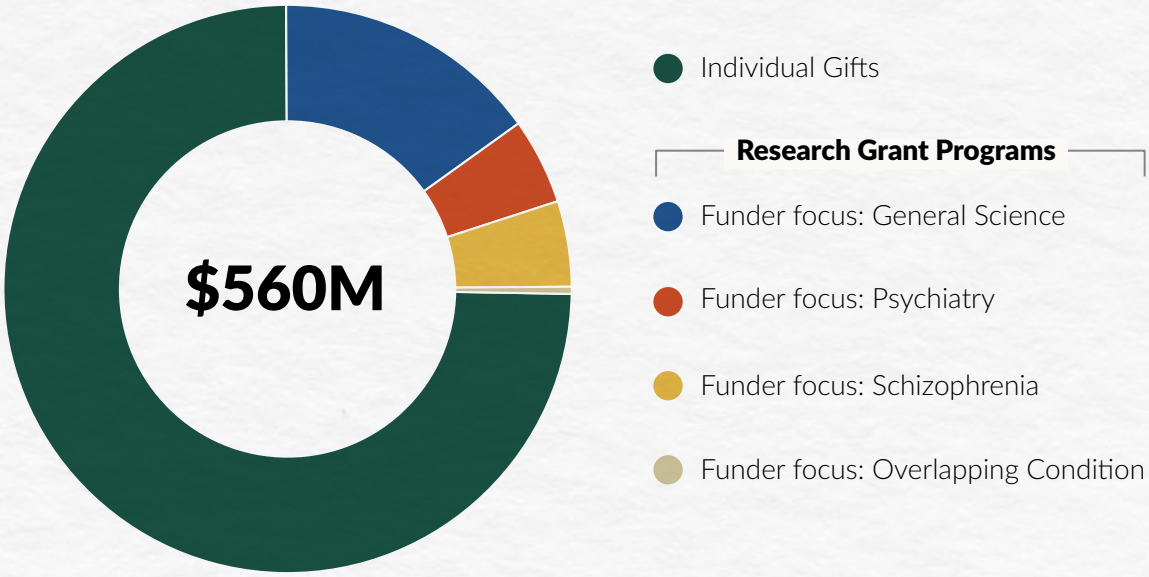
Many philanthropic foundations provide funding for multiple areas of research, rather than focusing on one disorder or field of study. The **Wellcome Trust**, a UK-based nonprofit, is a major cross-disciplinary funder of scientific research. Mental health was added as one of its priority research areas in 2020. Since then, its investment in mental health has reached nearly £250 million, or approximately $300 million USD, making it one of the foremost private funders for mental health globally. Though it has not had a specific call for schizophrenia research, it has supported three Mental Health Award programs related to psychosis and has funded schizophrenia through other award mechanisms.

Other foundations that have supported grants in schizophrenia research include the **Burroughs Wellcome Fund**, the **McKnight Foundation**, the **Doris Duke Foundation**, **The Medical Foundation**, and **The Donaghue Foundation**.

Impact and Scale of Private Support

As summarized in **Figure 10**, the schizophrenia field has received an estimated $560 million in support from nonprofit organizations, philanthropic foundations, and biopharma companies over the last decade. This funding is less than one-fifth of the $3.1 billion NIMH contribution toward schizophrenia-related research during the same period. However, the details of private funding are not as readily available, and the numbers provided here are a conservative estimate. Private funding sources excel at providing targeted support for specific conditions like schizophrenia and addressing gaps left by other funders. These programs can serve as models for how private investments can make an outsized impact.

Figure 10: Schizophrenia Funding Estimate Across Private Funding Categories



Source: Milken Institute analysis of funding information available in public records (2025)

Funding Landscape Conclusion

While at first impression there appears to be substantial funding for schizophrenia research, much of the funding is nonspecific. Moreover, the total sum does not match schizophrenia's tremendous economic burden. Given the societal costs and, more importantly, the potential to improve the lives of millions of people with schizophrenia, targeted investments could yield meaningful improvements in the schizophrenia landscape. Philanthropic support has the potential to make impactful changes in the field and can establish reliable sources of funding to specifically target schizophrenia.

Of note, there is also a clear demand for additional funds to support the development and implementation of clinical care support. Though this analysis only scratches the surface of that area of need, a forthcoming report will focus on systems of clinical care and ways in which they are supported.

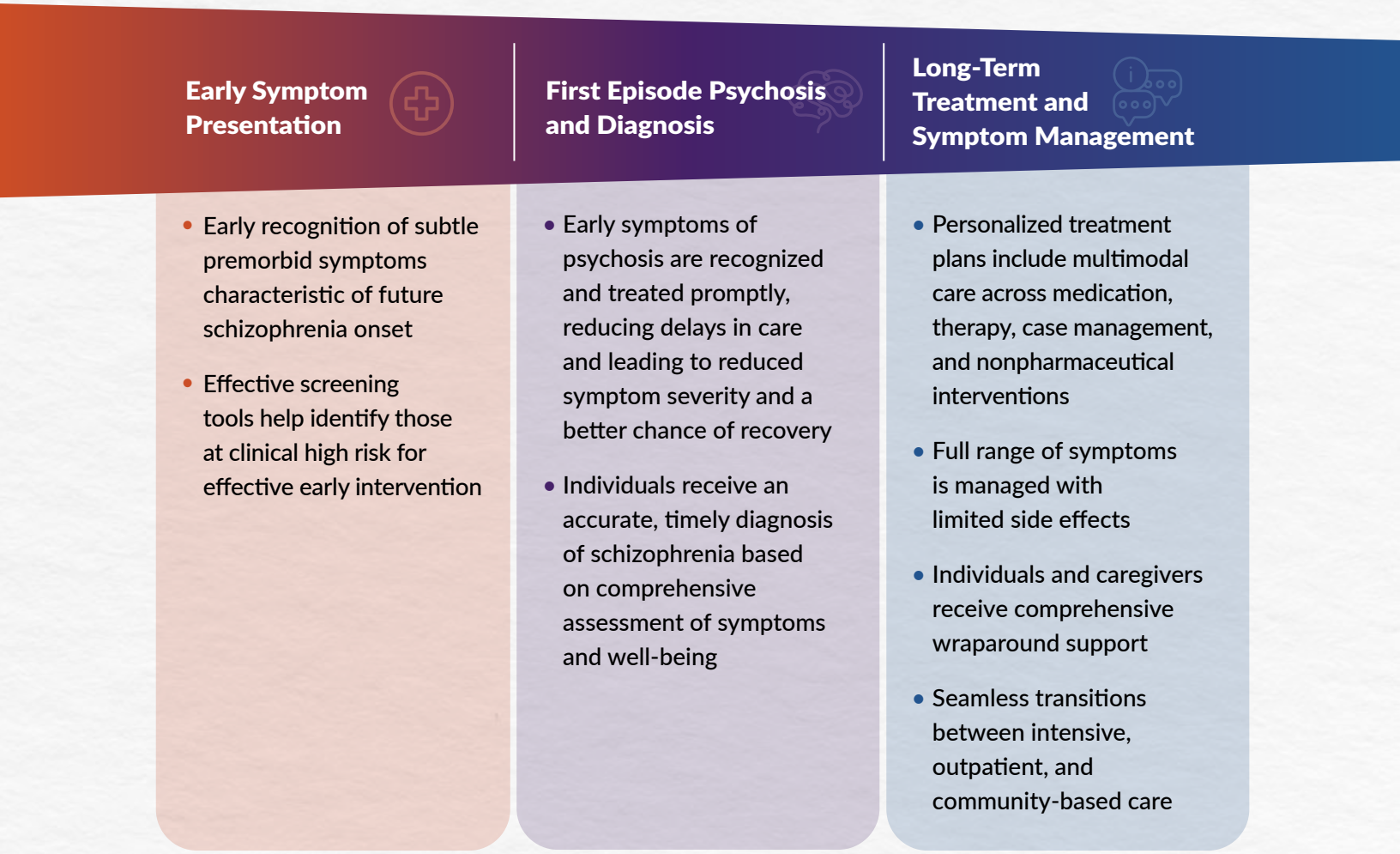
Conclusion and Next Steps

Schizophrenia is a serious brain disorder, albeit one with which people can thrive given proper treatment. This report began by detailing the many barriers that limit access to high-quality care for people with schizophrenia, from delays in diagnosis to fragmented care systems and overreliance on emergency services for treatment.

Opportunities to improve these dynamics are expansive—covering development of biomarkers and new treatment options, campaigns to increase awareness and reduce stigma, payment reform and implementation, workforce development, family navigation and peer support, and policy initiatives. Investment in these areas can start closing the gaps between best practices and the harmful experiences that many people face.

By addressing these barriers, a contrasting vision emerges: one where an individual's experience is optimized with personalized treatment, seamless care, and comprehensive support. At every stage, the optimized experience supports functional recovery with individuals with schizophrenia leading full lives (**Figure 11**).

Figure 11: Recovery-Oriented Care Across Stages of Symptom Presentation, Diagnosis, and Treatment



Source: Milken Institute (2025)

Symptom presentation: From the outset, there is an emphasis on prevention and early detection. Readily available screening tools, training, and education help families, teachers, and primary care providers recognize early signs and symptoms and address risk factors, such as cannabis use. Based on biomarker profiles, individuals at high risk could receive preventive interventions and effective early treatment if needed.

FEP and diagnosis: Everyone has immediate access to CSC when and where it is needed. Diagnosis is made rapidly and accurately based on comprehensive biomarkers (e.g., EEG signatures, neuroimaging, voice analysis) and objective diagnostic tools. Early in the journey, peer and navigation support, as well as training (e.g., LEAP communications training), are available for families and caregivers.

Mobile CITs are widely available and reduce reliance on emergency services. First responders are trained in effective methods and tools for communication and therapeutic engagement during crisis intervention to end the criminalization of people with a serious brain disorder.

Clinical treatment and symptom management: Clinical treatment consists of integrated care where individuals receive personalized treatment approaches based on their unique profile of biomarkers, symptoms, and needs—rather than by trial and error. Multimodal care integrates the most effective pharmacological and psychosocial approaches for the individual; care management teams provide coordinated psychiatric care, physical health care, cognitive remediation and other therapy, and caregiver support via colocated specialists.

Effective medications like LAIs and clozapine are accessible early in the treatment journey. Treatments address the full spectrum of an individual's positive, negative, and cognitive symptoms, as well as comorbidities, to support functional recovery. Side effects are minimal and well managed with integrated monitoring and support for physical health and cardiometabolic comorbidities.

Recovery: Sustained support for individuals and their families is accessible across the lifespan, from early intervention through aging, with appropriate levels of services tailored to different levels of need. Recovery-oriented care emphasizes functional outcomes, community integration, and support for education and employment. Everyone has access to safe, stable housing to support their recovery. Finally, indicators of relapse are detected early. If relapse predictors are detected, the individual is in contact with their care team such that effective interventions are seamless, keeping individuals on track in their recovery.

This vision may seem quite distant from the current reality—in some ways it is—but it is absolutely feasible to achieve through strategic support for research priorities, policy initiatives, and evidence-based care. More work is needed to develop objective biomarkers and personalized treatments to address the heterogeneous needs of individuals with schizophrenia. Until the potential of precision psychiatry is realized and transforms the treatment paradigm, there are known best practices to help people living with schizophrenia, and it should be a priority to ensure they have access to the highest quality care. Evidence-based care models and care delivery systems are critical to achieving this vision and thus are the focus of a forthcoming publication about possible solutions to improve care access for people with schizophrenia.

Appendix

Methods

State of the Field Landscaping Process

In 2025, the Milken Institute Science Philanthropy Accelerator for Research and Collaboration (SPARC), in partnership with several philanthropic families, undertook a landscape analysis of schizophrenia research and care. We reviewed academic literature and interviewed over 70 experts across various backgrounds and specialties—lived experience, health-care providers, research scientists, health-care and program administrators, and more. These insights shaped our analysis and assessment of key opportunities to advance schizophrenia research and care.

Funding Landscape Methods

We used primarily NIH Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) to understand federal research funding for schizophrenia. We conducted advanced searches in the NIH RePORTER database for fiscal years 2015 to 2024 for the terms "schizophrenia" or "schizoaffective" in the title or abstract. We considered including additional keywords (e.g., "psychosis") but ultimately did not because the results included many unrelated projects (e.g., where psychosis was listed as an exclusion criterion).

The total funding amount determined using this RePORTER database search resulted from a general approach that includes not only schizophrenia-specific grants but also projects in broad areas with wider scope, such as infrastructure development projects like postmortem brain tissue repositories or neuroimaging probe development. We also examined data via the NIH RCDC system, which uses a text-mining process to assess NIH spending across various categories. In the case of schizophrenia, we found that the RCDC approach aggregated a smaller subset of NIH research projects. The two databases provide complementary views into NIH research support.

We examined data in Excel, using pivot tables to analyze aspects such as the breakdown of expenditures across ICs and spending over time. For some analyses, we also determined whether specific terms (e.g., "schizophrenia," "genetic," "cardiovascular") appeared in the title, abstract, project terms, or spending categories. Total NIMH funding was exported for 2015–2024 for comparison.

To assess whether the types of NIH-funded research reflect the research needs for improving outcomes for individuals with schizophrenia, we used RCDC spending categories to identify relevant technical and scientific topics for each grant. Across all projects from 2015 to 2024, more than 150 spending categories were represented. We focused our analysis on the last five years (2020–2024) because some spending categories have changed since 2015, and funding levels have shifted, making the more current data more representative of current research priorities.

For comparison with other conditions, we used the RCDC system because keyword searches in RePORTER included too many nonspecific results, especially for chronic conditions. For assessment of overlap with other conditions, we determined whether relevant terms (e.g., "bipolar disorder," "autism," "major depressive disorder") appeared in the project title, project abstract, or spending category across all NIMH-funded schizophrenia research.

For the allocations of the SAMHSA budget across projects, we referenced the annual HHS Budgets in Brief. The SAMHSA Grants Dashboard was used to determine the total funding for individual projects and programs.

We identified sources of private funding via literature search, the Health Research Alliance Analyzer database, and conversations with experts. Funding amounts were sourced from organizations' annual reports, funding announcements, tax records, and press releases. In some cases, these are likely a conservative estimate of total giving based only on what is available through public records.

Glossary

Anosognosia: This is an inability to recognize oneself as having a mental illness.

Assertive Community Treatment (ACT) teams: These teams, with 24/7 availability, provide multidisciplinary services for people with SMI. They typically serve people with more established illness.

Astrocytes: These cells surround and support neurons; they are a subtype of glia.

Atypical antipsychotics: These medications to manage delusions and hallucinations have more complex mechanisms of action than typical antipsychotics, generally involving other neurotransmitters in addition to dopamine.

Biomarker: This is a measurable biological indicator of a disease state.

Care deserts: These areas have limited or no access to specialized health-care services and are especially common in rural and underserved communities.

Clinical high risk (CHR): CHR refers to people experiencing subthreshold symptoms that do not meet full diagnostic criteria for psychotic disorders and who are at elevated risk of developing psychosis.

Clozapine: This medication is an atypical antipsychotic that has superior effects on positive, negative, and overall symptoms as well as relapse rates in schizophrenia. The mechanism of action of clozapine is not fully understood.

Clubhouse model: This approach to care leverages community as therapy and provides dignified spaces that empower members through connection and belonging.

Cobenfy: This antipsychotic medication targets the acetylcholine neurotransmitter system via cholinergic receptors. It was approved in September 2024 and is the first new antipsychotic medication with a novel mechanism of action in decades. It is associated with lower cardiometabolic side effects compared to traditional antipsychotics and may improve cognitive and negative symptoms.

Cognitive remediation therapy: This behavioral training intervention focuses on improving functional outcomes through brain training exercises targeting cognitive deficits, such as sensory processing, verbal learning, working memory, and processing speed.

Cognitive symptoms: These symptoms are related to thinking processes, including deficits in processing speed, attention, and working memory.

Coordinated specialty care (CSC) program: This care model uses a team-based approach consisting of psychotherapy, family support and education, medication management, employment and education support services, and case management.

Cortical thinning: This is a reduction in the thickness of the cerebral cortex. Cortical thinning is a structural change characteristic of schizophrenia.

Crisis intervention team (CIT) programs: This approach involves training police teams to manage mental health crises. CIT programs are promising, but the training is variable and inconsistent.

Deconstructing studies: Also called dismantling studies, these studies identify which elements of care models are effective so they can be replicated.

Duration of untreated psychosis (DUP): DUP is the time between presentation of psychosis and receiving treatment. Higher DUP is associated with worse outcomes.

Dysrhythmia: This refers to disrupted timing of neural activity.

Electroconvulsive therapy (ECT): ECT is the administration of controlled electrical currents. For schizophrenia, ECT has most commonly been used to augment pharmacological treatment.

First episode psychosis (FEP): FEP is the first occurrence of psychotic symptoms in an individual, extending through the first two to five years of early illness. FEP refers to a period of early onset of symptoms that encompasses an individual's initial psychotic episode and the phase of early illness.

Focused ultrasound (FUS): FUS is a noninvasive neuromodulatory technique that relies on concentrated ultrasound. FUS is accessible and relatively inexpensive, but treatment paradigms have not yet been optimized for schizophrenia.

Glia: These are brain cells that support neurons. Subtypes include astrocytes, microglia, and oligodendrocytes.

Hippocampus: This part of the brain is involved in memory and spatial navigation. In schizophrenia, hippocampal abnormalities such as loss of volume, hyperactivity, and dysrhythmia could contribute to symptoms across all three symptom domains of schizophrenia.

Incidence: This refers to new cases of a disease during a specific time period, such as one year.

Long-acting injectables (LAIs): LAIs are injectable formulations that release medication slowly into the body over weeks to months, attempting to ease medication adherence challenges.

Microglia: These cells support brain maintenance and neuroimmune function; they are a subtype of glia.

Mobile crisis teams: These teams are dispatched for nonviolent mental health situations, helping to prevent negative police interactions.

Negative symptoms: These are symptoms of reduced expression and social engagement, such as flat affect, diminished emotion, and social withdrawal.

Neuromodulation techniques: These techniques involve targeted stimulation of key brain regions to alter neural activity.

Oligodendrocytes: These cells support neurons by forming a sheath that insulates nerve fibers and accelerates neural communication; they are a subtype of glia.

Parvalbumin interneurons: This is a type of neuron found in the hippocampus, the loss of which appears important to the pathology of schizophrenia.

Platform trials: These clinical trials randomize patients to multiple treatments simultaneously.

Polygenic trait: This is a characteristic resulting from many genes with small effects; schizophrenia is polygenic.

Positive symptoms: These are symptoms of altered perception and thinking, such as hallucinations and delusions.

Prevalence: This refers to the total existing cases of a condition in a population at a given time.

Prodromal/premorbid phase: These terms refer to the stage of illness before diagnosis; it is often only recognizable in retrospect.

Psychosis: This mental state is characterized by a loss of contact with reality. Symptoms can include hallucinations (seeing, hearing, or feeling things that are not there), delusions (fixed false beliefs), and disorganized thinking, speech, and behavior.

Redox biology: This is the study of the reduction and oxidation reactions that are critical to many cellular functions. An imbalance between these reactions indicates metabolic dysregulation and increases cellular stress.

Schizophrenia: This condition is a serious, chronic brain disorder typically characterized by episodes of psychosis, including disorganized thinking and disturbances in perception and behavior.

Serious mental illness (SMI): SMI is a mental disorder or condition that substantially interferes with functional capacity and major life activities and is chronic (typically lasting 12 months or longer).

Social anhedonia: This is a lack of interest in or motivation for social interaction. This symptom may be a key barrier to seeking care and to community integration.

Structural changes: These are macroscopic changes in the brain. Individuals with schizophrenia exhibit characteristic structural changes in the brain, including gray matter loss, enlarged ventricles, decreased white matter integrity, and cortical thinning.

Transcranial direct current stimulation (tDCS): tDCS is a noninvasive method using weak electrical current to modulate neuronal excitability that has some promising results for schizophrenia.

Transcranial magnetic stimulation (TMS): TMS is a noninvasive approach that uses magnetic pulses to provide targeted stimulation to specific areas of the brain. TMS has potential, but it has not yet shown clear efficacy.

Treatment-resistant schizophrenia (TRS): TRS is a case of schizophrenia that has failed to respond to two or more medications taken at sufficient doses and with adherence.

Typical (first-generation) antipsychotics: These medications to manage delusions and hallucinations primarily work by blocking dopamine receptors.

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