

# Clinical research

## *A knowledge network for a dynamic taxonomy of psychiatric disease*

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*Current taxonomic approaches in medicine and psychiatry are limited in validity and utility. They do serve simple communication purposes for medical coding, teaching, and reimbursement, but they are not suited for the modern era with its rapid explosion of knowledge from the “omics” revolution. The National Academy of Sciences published a report entitled Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. The authors advocate a new taxonomy that would integrate molecular data, clinical data, and health outcomes in a dynamic, iterative fashion, bringing together research, public health, and health-care delivery with the interlinked goals of advancing our understanding of disease pathogenesis and thereby improving health. As the need for an information hub and a knowledge network with a dynamic taxonomy based on integration of clinical and research data is vital, and timely, this proposal merits consideration.*

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### Introduction

**D**isease is a fluid concept influenced by social and political attitudes and research that changes with time and in reaction to new scientific developments.<sup>1</sup> There are numerous definitions of disease, but one concrete and comprehensible definition is to consider disease as a state that places individuals at increased risk of adverse consequences.<sup>2</sup>

Linnaeus, the famous classifier, attempted a simple classification of disease that focused on fever.<sup>3</sup> This effort was the original precursor to the current standard classification of diseases and related health problems that uses the standard diagnostic tool called the *International Classification of Diseases (ICD)*, now in its 11th edition). Today, the *ICD* remains the most widely used system of classification.<sup>4</sup>

Taxonomies, in medicine, underpin medical teaching, organization, and reimbursement—they are the language of modern health care and medicine.

The current system attempts to balance the need for consistent terminology to ensure clear communica-

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# Clinical research

tion with integration of advances in knowledge. These disease classification systems are limited in their utility, information content, and usability. They are based on symptoms, physical signs, pathology, and occasionally, some laboratory and radiological findings.<sup>1</sup> A specific disease denotes the sum of abnormal features (eg, symptoms, signs, laboratory findings, etc) that have been shown in a group to differ from the standard normal features of the population in a manner that places them at risk of adverse outcome. Norms are established by studying relevant populations, divergences from the norm, and subsequent risks may or may not need formal statistics. Adverse consequences include physical morbidity, mortality, and psychological impairment, and limitations in activity.<sup>1</sup>

Current nosological systems are not designed to predict treatment or prognosis other than in a broad and unrefined fashion.<sup>1</sup> They are not adaptive in their ability to rapidly assimilate the overwhelming deluge of molecular data, treatment responses, and social environmental information.<sup>5</sup> These taxonomies are hierarchical, segmented, and linear, which leads to an artificial rigidity. It impedes characterization and linkages between and across differently labeled entities.<sup>5</sup> The introduction of molecular medicine is rapidly highlighting these limitations.

## Single gene, many diseases

First, individual mutations in genes underlie a plethora of expressions of what, on the surface, are markedly distinct diseases. Retinoblastoma, a cancer of the retina, which chiefly affects children, is caused by mutations in the *Rb* gene.<sup>6</sup> However, not all people who carry this mutation develop retinoblastoma. For instance, two siblings could inherit the same mutation of the gene from their parents, and one might be affected by the disease, while the other is not. This reflects penetrance.<sup>7</sup>

Neurofibromatosis is another disease with a similar pattern, where a mutation in neurofibromin gene can lead to the disease in some, but not others.<sup>8</sup>

## Multiple mutations in several genes with similar clinical features

The *Cancer Genome Atlas*, funded by the National Institutes of Health, shows that a specific cancer, such as breast cancer, can be caused by different mutations.

Knowledge of these mutations can, in certain instances, enable the prediction of treatment response and help identify potential new treatments. However, what is striking is that the same mutations can be involved in what, nominally and even pathologically, looked to be very different type of cancers. One of the mutations in a gene called *V-RAF Murine Sarcoma Viral Oncogene Homolog B1 (BRAF)* highlights the challenge current classification systems are facing.<sup>9</sup>

The *BRAF* mutation is linked to more than half of all melanoma cases; 7% of certain lung cancer tumors, 4% of colon cancer malignancies, and to a lesser extent, brain, bladder, head-and-neck, kidney, and ovarian cancers.<sup>10</sup> The same gene is linked to many ostensibly different types of cancers. The classification systems are clearly turning out to be less than adequate. There is, therefore, a need for more dynamic and updateable systems.

## Where are we in psychiatry?

In psychiatry, the broadly used system called the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* for psychiatric diseases is now in its 5th iteration.<sup>11</sup> The *DSM* system works for simple coding and reimbursement purposes, but is not designed to facilitate the development and integration of biomedical knowledge. An alternative approach has been the Research Domain Criteria (RDoC) system proposed and endorsed by the National Institute of Mental Health.<sup>11</sup> This multidimensional approach uses units of information beyond clinical phenotypes, such as imaging, behavior, etc. Thus, a matrix is developed with constructs that can then be related to different elements of information from imaging to genetics. The five domains with constructs include positive valence, negative valence, cognitive systems, arousal systems, and systems for social processes. These domains do not readily map to the widely used clinical constructs and also do not provide the ultimate reason to classify, which is to improve the lives of patients.<sup>12</sup>

Today, clinical constructs are nominalist in nature as they are defined by a cluster of symptoms, signs, and their course. Even though the *DSM* states that “there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder”<sup>11</sup> the plain statement listing a diagnostic concept in an official nomenclature and providing a

precise definition makes it appear concrete and distinct.

In addition, once notions are stated in such a rigid form they tend to become codified and reified without an examination of the fundamental validity. How do we check for validity?

Robins and Guze<sup>13</sup> proposed strict criteria for defining the validity of psychiatric diagnoses. They enumerated five criteria: (i) clinical description (symptoms); (ii) laboratory studies; (iii) demarcation from other disorders; (iv) follow-up studies of diagnostic stability; and (v) familial history consistent with the entity. However, almost none of the more than 300 entities in *DSM* meet these criteria. One of the requirements for symptom- and course-based identification and demarcation is to establish points of no overlap between similar syndromes. Attempts to determine natural borders even between what, on the surface, look like distinct syndromes, such as schizophrenia and bipolar disorder, often have not been successful.<sup>14</sup> The points of rarity between psychiatric diseases are not distinct. Trying to clearly separate individuals—to classify them as having a particular disease—leads to some individuals clearly falling within one group, but over time many move between groups and sometimes meet the criteria for more than one group. This leads to calling many conditions or entities simultaneously present or comorbid, which is a word that reflects the basic problem with the system. Strauss et al indicated, in a sample of first admissions to a psychiatric unit, that symptom constellations representative of the classic diagnostic groups (ie, mania, schizophrenia, neurotic depression, and psychotic depression) could be identified, but only a few patients resembled the prototype of these traditional descriptions.<sup>15</sup> Strauss et al stated that “These findings suggest that although syndromes do exist that fit traditional diagnostic categories, the vast majority of patients fall between these syndromes, having characteristics from several of them.”<sup>15</sup>

Manton et al,<sup>16</sup> Davidson et al,<sup>17</sup> and our group developed a “grade of membership” model to address this issue by assigning individuals to diagnostic categories, while explicitly recognizing fuzzy boundaries allowing individuals to be partly assigned to more than one class.

As a result of these findings Kendell,<sup>18</sup> Kendell and Gourlay,<sup>19</sup> Kendell and Gourlay,<sup>20</sup> Kendell and Brockington,<sup>21</sup> and others suggest that the concept of disease as a distinct entity in the psychiatric context is problematic.

The search for foundations of this nominally based classification will be elusive. Let’s say we find that patients with depression have an abnormal test result, say a molecular anomaly; we can use these data to attempt to develop it as a test to identify specificity, sensitivity, etc. Now, let’s say that the test is for the presence of a mutation in a gene, and that mutation links not just to depression, but to anxiety, bipolar disorder, etc. This will be construed as a nonspecific test when that mutation may be pointing to a cause for the illness. Then, a purely nominalist approach and use of the data, as a test for the nominalist disease, will be disadvantageous. It is likely to not change our practice or improve our understanding, and thus may not lead to better identification of subjects and treatments.

However, we are making progress by beginning to understand the biology and underlying cause(s) of some of these psychiatric diseases, and in many cases, just as in cancer, it is changing our underlying assumptions about the definition of some of these conditions.

## Alzheimer’s disease

Let us take Alzheimer’s disease (AD). It is the most common form of dementia. The basic criteria in the current, clinically used nosology emphasizes the age of onset, course outcome, and in some cases, the pathological and radiological criteria. However, the molecular basis of some types of AD is now delineated.

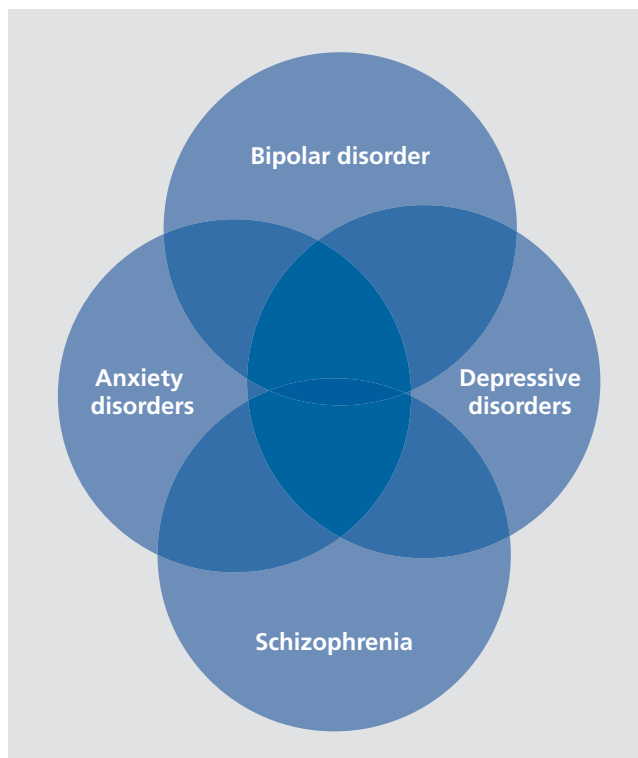
A dominant pattern of inheritance is seen in most presenile cases and accounts for about one third of all cases of AD. Four genes have been identified. Many cases of AD can be then classified based on its genetic origin (*Figure 1*). They include mutation(s) in the genes for amyloid precursor protein (*APP*),<sup>22</sup> presenilin-1 (*PSEN1*),<sup>23</sup> and presenilin-2 (*PSEN2*),<sup>24</sup> and can be associated with the apolipoprotein E\*e4 (*APOE*\**E4*) allele on chromosome 19.<sup>25</sup> Mutations in the *APP* gene have been associated with early-onset, cerebral amyloidosis of the Dutch type.<sup>26</sup> In addition, some mutations have been associated with hemorrhagic strokes, occipital calcifications, and arterial dysplasia. Individuals with *PSEN* mutations also have early-onset disease, and some have myoclonic jerks, spastic paresis, behavioral symptoms, and cerebral amyloid angiopathy.<sup>27</sup> Patients with *PSEN2* mutations also have early-onset dementia.<sup>28</sup>

The most important genetic risk for AD is *APOE*. The *APOE*\**E4* allele has been associated as a risk fac-

# Clinical research

tor for AD and cardiovascular disease. Unlike *PSEN 2* and *APP* mutations, the *APOE\*E4* allele confers a risk for both sporadic, including late-onset AD, and familial AD.<sup>25</sup> The *APOE\*E4* allele is neither necessary nor sufficient for the expression of AD, highlighting the importance of other environmental or genetic factors that, in combination with *APOE\*E4*, increase the risk of AD. OMIM (Online Inheritance in Man), an online catalogue of human genes and genetic disorders, names this form of AD as AD2.

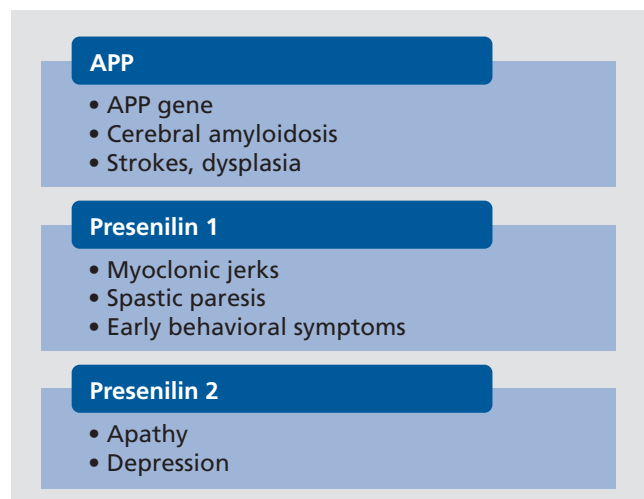
Here research has changed and defined AD by subtyping based on molecular risk. This system is not currently used, as the subtyping does not yet have clinical relevance. Nevertheless, it serves as an example of a nominalist entity now getting a biological basis and then being subtyped. In this case, the subtyping highlights clinical features that help differentiate the different diseases. So now, if one looks at AD, it can be described, or broken down, as shown in *Figure 2*. It is likely that it will be subtyped further as our knowledge increases.



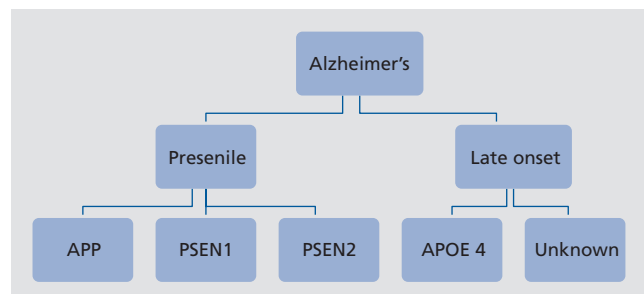
**Figure 1.** Overlap between diagnostic categories. This overlap can occur at a particular moment in time or in the same patient at different times.

## Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a relatively rare autosomal dominant disease arising from mutations in a gene called *NOTCH3* (*Figure 3*).<sup>29</sup> These mutations lead to small-vessel disease in the brain. Magnetic resonance imaging shows severe white-matter lesions and infarcts in deep white matter and subcortical regions of the brain. The disorder starts relatively young and patients usually present with migraine, depression, memory impairment, and over time, they develop strokes and dementia. It is a form of pure vascular dementia, and is an example of an inherited



**Figure 2.** Genetic causes of Alzheimer's disease with *APP*, *PSEN1*, and *PSEN2* genes. APP, amyloid precursor protein; PSEN1, presenilin-1; PSEN2, presenilin-2.



**Figure 3.** Subtypes of Alzheimer's disease with respect to *APP*, *PSEN1*, *PSEN2*, and *ApoE* genes. ApoE, apolipoprotein E; APP, amyloid precursor protein; PSEN1, presenilin-1; PSEN2, presenilin-2.

form of subcortical vascular disease.<sup>29</sup> The disease has an estimated prevalence of 4 per 100 000 adults.

As discussed regarding the field of cancer,, this is an example of mutations in a single gene leading to a range of clinical manifestations or disorders. Also, a single patient can have more than one manifestation at different times during the illness.<sup>29</sup>

### Common forms of subcortical ischemic disease

We introduced the notion of a single gene leading to a vascular disease that affects the brain by producing a plethora of “psychiatric and neurological diseases,” but this form of vascular disease is very common. Subcortical ischemic disease (SID) and its labeling give an idea of the complexity of labeling neurological and psychiatric disorders and the challenges that lie ahead. Any proposal of diagnostic criteria claiming that a psychiatric disorder is due to a medical condition, should undergo detailed scrutiny.<sup>30,31</sup> SID is very common in the elderly. The risk factors are similar to that for stroke. They include hypertension, diabetes, hyperlipidemia, and smoking. SID, just as in the case of CADASIL, can present with, and lead to, numerous manifestations (Figure 4).

As noted in a publication by Post, the German psychiatrist Gaupp described 45 elderly patients with depression secondary to arteriosclerosis. Many had apathy and sadness.<sup>32</sup> Magnetic resonance imaging (MRI) has increased the detection of subtle, but surprisingly widespread, structural brain changes in vivo. SID is a defining characteristic, just like coronary artery disease, and

an expression of the disease could include depression. Mood disturbances associated with SID may meet the full criteria for major depression, bipolar disorder, or dysthymia, but are more likely to be less severe chronic mood disturbances that are associated with subcortical ischemia. Our current diagnostic nomenclature does not capture these other disturbances. Other manifestations of SID include cognitive impairment, dementia, falls, and psychoses.

A subcategory of SID is subcortical ischemic vascular dementia; this is similar to what we have previously called MRI-defined vascular depression.<sup>33-35</sup> Does this syndrome meet the Robins and Guze definition of validity?<sup>12</sup> SID has a clinical description and can be identified through MRI,<sup>36-38</sup> can be delimited from other disorders by pathology, is not associated with familial factors for depression, and the pathological changes seen on MRI predict outcomes longitudinally.<sup>37,38</sup>

SID is more common in depressed elderly subjects than in control subjects, and even more prevalent in late-onset elderly depressed subjects.<sup>39-45</sup> These patients are, as expected, at higher risk of dying and developing dementia.<sup>46</sup> There may also be a biological specificity by anatomical location, wherein SID’s contributions to depression occur in specific regions<sup>47-48</sup> and worsening of ischemic disease is associated with poor depression outcomes.<sup>46</sup> In this context, depression is part of a continuum of neuropsychiatric conditions associated with SID.<sup>49</sup>

Only a small percentage of patients with psychiatric illness have clearly identifiable causes at this time. The vast majority have many intersecting and multiple risks that are not easily put together.

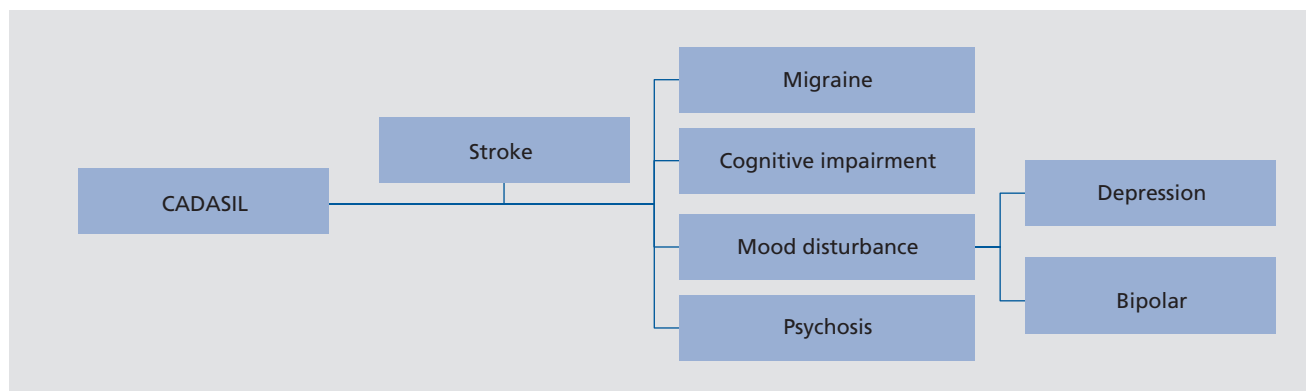


Figure 4. Clinical manifestations of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).



# Clinical research

Therefore, this brings us to the vast majority of psychiatric illnesses for which we do not have clearly identifiable causes. Even when there is a family history of illness, it is quite common that the features of the family illness are very different from each other; therefore, it is no surprise that attempts to link specific illnesses, classified in the nominalist tradition, to genetic factors have been, for the most part, unsuccessful. Recent studies are showing that even when links are observed, they cut across nominalist diagnostic categories such as autism, schizophrenia, attention deficit disorder, bipolar disorder, and major depression.

Why should neuropsychiatric illness be any different from cancers? Just as in cancer, it is likely that many genes are involved and the same gene mutation may manifest differently in patients. Some may have little or no symptoms, and others may have a whole range of symptoms that could fluctuate and evolve over time. Emerging work clearly points in this direction.

Autism is an example. In about 10% of patients, an identifiable genetic cause or chromosomal anomaly can be found.<sup>50</sup> There are many genetic diseases linked to Fragile X syndrome, tuberous sclerosis, Angelman syndrome, Down syndrome, Sanfilippo syndrome, Rett syndrome and other MECP2-related disorders, phenylketonuria, Smith-Magenis syndrome, 22q13 deletion syndrome, Cohen syndrome, adenylosuccinate lyase deficiency, and Smith-Lemli-Opitz syndrome.<sup>51</sup> Each one of these diseases has very characteristic features and manifestations, with autism being just one of them. (Figure 5).

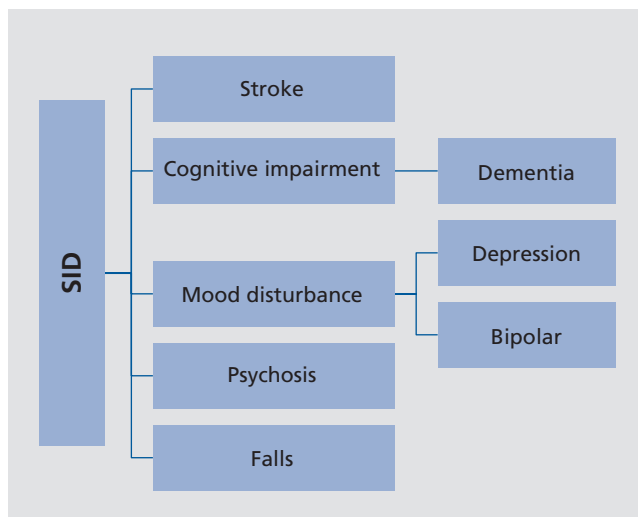


Figure 5. Clinical manifestations of subcortical ischemic disease (SID).

In addition, a whole range of genes have been implicated by genetic studies and a few are now considered to be validated by more than one study. Most of them involve the glutamate system and/or brain development. These genes, along with a multitude of rare deletions, are believed to account for about 7% of patients with autism.<sup>52</sup> Thus, just like in Alzheimer's disease, there is increased genetic dissection. Imagine the complexity for taxonomy as more of autism is dissected, and maybe as many more causes are identified, each accounting for less than 0.1% of the whole pie.

Although we have focused on genetic risk, there are many other factors external to the individual that can play a role in the development and evolution of a disease and response to treatment. In psychiatry, life stress, trauma in early childhood and social support are all well known to be critical in the development of psychiatric disorders. These are usually thought of as nonspecific risks. Another way to look at these "nonspecific risks" are to consider them as an interacting risk that leads to different manifestations of the disorder depending on the genetics and life history of the patient (Figure 6).

## The exposome

The exposome concept has major implications for psychiatry. The exposome is the sum of all factors to which an individual has been exposed which could relate to that individual's health. These include diet, lifestyle, stress, occupational exposures, and social support from conception onward.<sup>53</sup> The exposome clearly interacts with the individual and plays a role in the development of diseases. The concept of the exposome has not been widely considered in psychiatric illnesses, but it should be considered as an essential complement to the study of an individual's biology.

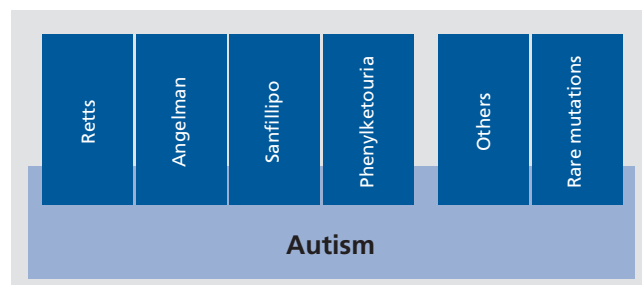
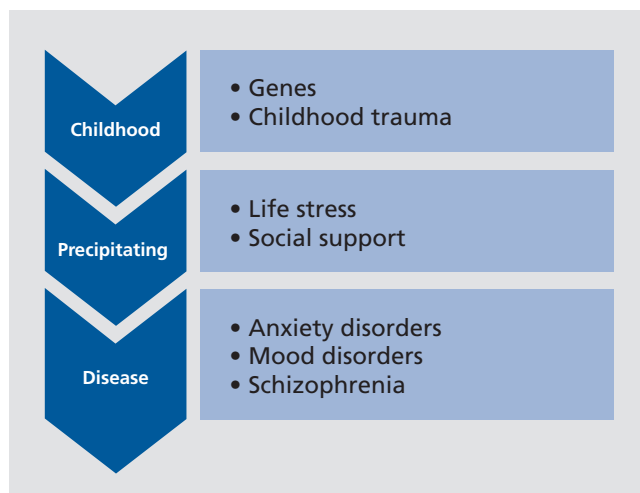


Figure 6. The many entities that can present with features of autism. Not all are shown. Note that each of them will have their own unique characteristics.

### Where do we go? Knowledge network for psychiatric taxonomy

It is clear from our description of where we currently are in psychiatric taxonomy that a static approach to classifying psychiatric disease is not of much value. A dynamic approach is needed. In a recent report, the National Academy of Sciences has advocated a knowledge network for biomedical research as a base from which to build a dynamic taxonomy of diseases.<sup>5</sup> Psychiatric research has entered, just like the rest of medicine, an inflection point where the data deluge is beginning to overwhelm our capacity to absorb, integrate, and utilize knowledge. The growth of data-intensive biology and information technology developments have generated an exciting opportunity to improve the diagnosis and management of disease by developing a knowledge network, and a new taxonomy, that integrates biological and clinical information with outcome data to improve the lives of patients.<sup>5</sup>

The compelling need is to improve the link between biology and the patient with their treatment and outcome. This will require a new mindset on the part of stakeholders, funders, clinicians, and scientists. We have more than 20 000 genes in our genome, and countless numbers of these genes will have many disease-relevant mutations, just like the genes that we already know about.<sup>5</sup> Even if only a fraction of these genes link to disease risk or treatment response, there is enormous potential to improve patient care, diagnosis, and man-

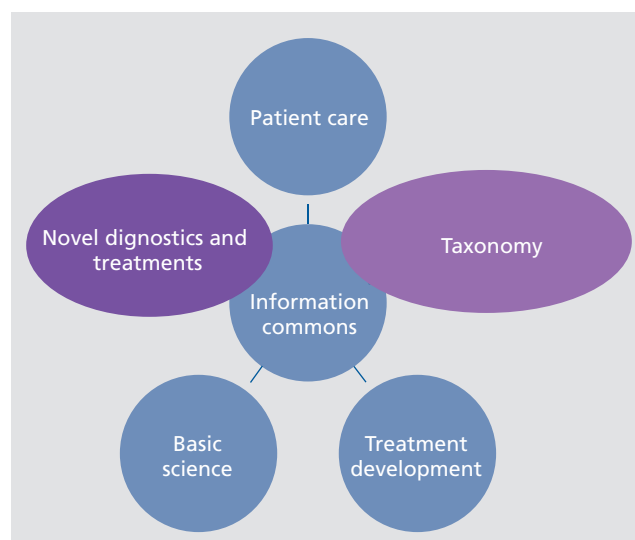


**Figure 7.** Evolution of illness from childhood, combining environment and genetic factors.

agement of disease. By integrating patient biology, their genome, microbiome, transcriptome, and metabolome with health information and outcome data a dynamic taxonomy can revolutionize health care.

The framework committee, responsible for developing a new taxonomy, came up with a scenario that entails a common, integrated information network.<sup>5</sup> At the center of the network is an Information Hub that contains up-to-date disease information on individual patients and is continuously updated by a wide set of new data emerging through the progression of routine health care. This is connected to emerging knowledge from basic and translational research, and serves three purposes: (i) generating a dynamic, adaptive taxonomic system; (ii) providing the foundation for novel diagnostic techniques, treatments; and (iii) becoming a catalyst for basic discovery. Any data that emerge, and are validated, will be integrated into the taxonomy to improve diagnosis and treatment (*Figure 7*).<sup>5</sup>

A concerted effort to develop such a knowledge framework and information hub is sorely needed. There are many barriers—ranging from handling patient-level data, privacy, and unwillingness to share—that need to be overcome in order to create a system that will enhance health care. A simple clinical information hub that has been built at Duke University, North Carolina, USA, uses anonymized data to predict patient outcomes



**Figure 8.** Overview of the vision of the integrated information network laid out by the framework committee, who were responsible for developing a new taxonomy of disease. Oval shapes are outputs, while circles are both input and outputs.

# Clinical research

to different options. Even without biological data, the system is already showing the predictive power of large data sets. The time for static taxonomy based on con-

sensus should come to an end and a dynamic system, as portrayed by the National Academy of Sciences report, should be built.<sup>5</sup> □

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### Una red de conocimiento para una taxonomía dinámica de las enfermedades psiquiátricas

Los enfoques taxonómicos actuales tanto en medicina como en psiquiatría son limitados en validez y utilidad. Ellos sirven para fines de una comunicación simple en la codificación médica, la enseñanza y el reembolso, pero no se adaptan a la era moderna con su rápida explosión del conocimiento a partir de la revolución de los "ómicos". La Academia Nacional de Ciencias publicó un informe titulado: "Hacia la Precisión en Medicina: Construyendo una Red de Conocimiento para Investigación Biomédica y una nueva Taxonomía de la Enfermedad". Los autores abogan por una nueva taxonomía que pueda integrar datos moleculares, información clínica y resultados terapéuticos de una manera dinámica y repetida, reuniendo investigación, salud pública y la prestación de cuidados de salud, con los objetivos interrelacionados de avanzar en nuestra comprensión de la patogénesis de la enfermedad y así mejorar la salud. Esta propuesta merece consideración, ya que es vital y oportuna la necesidad de un centro de información y de una red de conocimiento con una taxonomía dinámica basada en la integración de datos clínicos y de investigación.

### Un réseau de connaissance pour une taxonomie dynamique des maladies psychiatriques

Les stratégies taxonomiques actuelles en médecine et en psychiatrie sont limitées en validité et en utilité. Elles servent des objectifs simples de communication pour le codage médical, l'enseignement et le remboursement, mais ne conviennent pas à l'époque contemporaine avec son explosion rapide de connaissance issue de la révolution « omics ». L'Académie Nationale des Sciences aux États-Unis a publié un rapport intitulé « Vers une médecine de précision : Construire un réseau de connaissance pour la recherche biomédicale et une nouvelle taxonomie de la maladie. » Les auteurs prônent une nouvelle taxonomie qui intégrerait des données moléculaires, cliniques et des résultats des thérapeutiques de façon dynamique, itérative, en rassemblant la recherche, la santé publique et les prestations de soins avec des objectifs interdépendants visant à faire progresser notre compréhension de la pathogenèse de la maladie et donc à améliorer la santé. Le besoin d'un centre d'information et d'un réseau de connaissance doté d'une taxonomie dynamique fondée sur l'intégration de données cliniques et de recherche étant vital et opportun, cette suggestion mérite d'être examinée.

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