St. Francis of Assisi's fatal illness:

A diagnosis based on alternative forms of intelligence

St. Francis of Assisi fresco located near the entrance of the Abbey of Saint Scholastica in Subiaco, Italy. Painted March 1228–March 1229 C.E. by an unknown artist. Photo permission from the photographer, Joanne Schatzlein

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In 1226, Giovanni di Pietro di Bernardone, who would become St. Francis of Assisi, one of the most renowned and revered of all the Catholic saints, died of a mysterious illness, the cause of which has been debated throughout history. In May 2019, during the latest in an ongoing series of historical clinicopathological conferences at the University of Maryland School of Medicine, individual, artificial, and collective intelligence, respectively, were employed to diagnose St. Francis' fatal illness. The exercise generated a diagnosis supported by all three forms of intelligence and illustrated the promise and the limitations of artificial intelligence and collective intelligence in augmenting the capacity of individual clinicians to diagnose difficult cases.

Three independent assessments of St. Francis' clinical record were undertaken in diagnosing his fatal disorder—one by Sr. Joanne Schatzlein in collaboration with internist Daniel P. Sulmasy (ΑΩΑ, Weill Cornell Medical College, 1981); a second by the Isabel Differential

Diagnostic Generator; and a third by the Human Diagnosis Project's panel of international electronic consultants. In each instance, diagnoses were based on information contained in a case summary derived from Donald Spoto's 2002 biography of St. Francis.[1]

Case Summary

By the time St. Francis reached the end of his life, absolute poverty and disease had reduced his condition to that of a living corpse. He was not, however, born destitute. His family's wealth enabled him as a youth to live a hedonist's life of nightly escapades of revelry and song. However, when St. Francis was 19-years-old, his life changed radically. Captured during a battle with neighboring Perugia, he was imprisoned in a damp and polluted subterranean cell where he languished for a year in near perpetual darkness on a diet of rancid food and tainted water. When finally freed, he was so frail he could barely walk or speak. His face was drawn and sallow, and his digestion impaired. By some accounts, he was also wracked repeatedly by protracted episodes of chills and fever, which left him bedridden for a year. Eventually, he recovered much of his former strength but continued to suffer with chronic gastritis and intermittent episodes of chills and fever for the rest of his life.[2]

In the aftermath of St. Francis' imprisonment, he rejected both his family and former life as a popular and endlessly inventive wastrel. He committed himself to an existence of possessing nothing—not just less than the poorest of the poor, but, literally, nothing. He became homeless and shoeless, dirty, pale, and emaciated. His only possessions were a burlap tunic and walking staff. When he ate, which he did irregularly due to frequent fasting, his meals typically consisted of wild fruits and turnips. Rarely did he consume meat or cooked foods, and when thirsty, allowed himself only minimal amounts of water.

In this new life, St. Francis became a contemplative hermit, itinerant preacher, and restorer of derelict churches. He ministered to the poor and infirm with simple acts of charity. He had a special affinity for lepers, whom he embraced and "washed all the filth from them, and even cleaned out the pus of their sores."[1]

St. Francis' health was generally poor, though stable, until he was 31-years-old, when he experienced a bout of depression that lasted six weeks. When finally recovered, a barefoot journey from Italy to Spain in inclement weather precipitated additional attacks of chills and fever and episodes of gastritis, manifested as right upper quadrant abdominal pain, dyspepsia, and nausea. For a brief period, he also was delirious in that he was unable to speak or to understand what was said to him. He made a gradual, complete recovery from the dysphasia, but was so exhausted by the illness that for the next four years he was forced to restrict his activities.

When St. Francis was 37-years-old, he accompanied a military expedition to Egypt. Sanitation was poor, and tropical diseases were so prevalent that an estimated one-fifth of the expeditionary force perished from disease. St. Francis survived, but upon returning to Italy a year later, a new disorder was added to his attacks of fever and gastritis. His eye lids had become irritated and thickened; his eyes burned and teared constantly; and both bright day light and night time fire light caused intense eye pain. Sometimes he was unable to see at all, and even when his vision improved, images were frequently blurred.

Thereafter, St. Francis' condition spiraled progressively downward. He was confined to bed, blind with pus oozing constantly from his eyes. His color was waxen, his upper limbs rail-thin, and his legs and abdomen swollen. Severe abdominal pain and dyspepsia made eating difficult. Moreover, his skin was covered with sores and ulcers, which he tried in vain to hide from visitors.

Doctors were summoned and applied red-hot irons to both sides of St. Francis' face from his cheeks to his eyebrows. They also cut open the veins of his temples in a futile effort to cure his eye disorder. They then inserted red-hot irons into his ears.

Throughout the length of his illnesses and desperate treatments, St. Francis offered no complaint. His suffering finally ended at age 44 years on October 3, 1226.

Differential diagnosis

Numerous disorders have been proposed as the etiology of St. Francis' final illness, including peptic ulcer disease,[3] quartan malaria,[3-6] tuberculosis,[3,7,8] gastric cancer,[9] brucellosis,[10] ocular trachoma[3] and leprosy.[2] Analysis of St. Francis' case summary using individual, artificial, and collective intelligence, respectively, produced the following diagnoses.

Individual intelligence

Sr. Schatzlein and Sulmasy diagnosed leprosy, specifically borderline or tuberculoid leprosy, as the disorder most likely responsible for St. Francis' fatal illness. They based their diagnosis on St. Francis' medical history and the signs and symptoms of his final illness as delineated in the case summary.

They were also influenced by certain paleopathological findings (i.e., preferential decay of finger, toe and facial bones) seen in photographs of his bony remains,[2] which was information not given to either the Isabel Differential Diagnosis Generator or the Human Diagnosis Project consultants.

Artificial intelligence

The Isabel Differential Diagnosis Generator,[11] is one of several advanced internet computer programs that use algorithmic search techniques and machine learning to generate differential diagnoses of medical disorders. One-and-a-half seconds after receiving the clinical information contained in the case summary, the Isabel Generator reported borderline leprosy as St. Francis' most likely diagnosis, sarcoidosis as less likely and arsenic poisoning as least likely.

Collective intelligence

A third opinion as to St. Francis' diagnosis was rendered by more than 600 users from 45 countries participating in the Human Diagnosis Project,[12] an online, e-consult system that queries generalist and specialist consultants regarding the diagnoses of difficult cases.

Both the Isabel Generator and the Human Diagnosis Project consultants were given all of the information contained in the case summary except for the identity of the patient described, and in the case of the Isabel Generator, the year of the patient's death.

To determine the collective differential diagnosis, the Human Diagnosis Project uses a weighted average of responses based on the frequency with which a diagnosis is included in users' differentials, as well as the relative location of the diagnosis within each user's differential.

Leprosy appeared in the differentials of 40 percent of users and was the top diagnosis within the group. Syphilis and tuberculosis were the second and third most frequently listed diagnoses, with 26 percent and 21 percent of users, including them in their differentials.

It took four days to collect and analyze users' responses.

Extensive and complex

Medical knowledge is now so extensive and complex that no one clinician, or team of clinicians, can keep up with more than a small fraction of relevant clinical information. The capacity of clinicians to properly diagnose difficult cases, as that of St. Francis, is compromised further by the limited amount of time they can devote to any one patient.

Correct diagnoses are often missed because of human cognitive errors such as anchoring bias (fixation on an initial impression), framing bias (over-reliance on the way in which a question is posed), availability bias (tendency to jump to a conclusion based on a recent incident), search satisfaction (not considering other possibilities once a probable answer is found), and premature closure (acceptance of an answer before it is verified).[13]

For more than four decades, advanced computer systems, like the Isabel Differential Diagnosis Generator, have been looked to as a means of obviating these problems by empowering clinicians with the most current, unbiased patient care information available.[13,14] Such artificial intelligence (AI) involves an iterative computational technique called machine learning, that ranges in complexity from regression analysis to various complicated algorithms known as advanced convolutional neural networks. This allows the computer software to learn or remain current with the medical literature. It also enables systems to identify relationships between various clinically relevant variables overlooked by clinicians when diagnosing and/or treating patients.

In a recent study, one such system suggested the correct diagnosis 96 percent of the time when presented the

Countries of origin of more than 600 human diagnosis project solvers' submitting diagnoses*	
Argentina (1)	Japan (2)
Austria (2)	Mexico (2)
Bangladesh (1)	New Zealand (5)
Belgium (1)	North Macedonia (1)
Brazil (36)	Pakistan (1)
Canada (27)	Philippines (1)
Chile (1)	Poland (1)
Colombia (3)	Portugal (2)
Costa Rica (1)	Romania (1)
Denmark (2)	Saudi Arabia (1)
Dominican Republic (2	Slovenia (1)
Ecuador (1)	South Africa (5)
Germany (7)	Spain (5)
Greece (1)	Sri Lanka (1)
Hungary (3)	Switzerland (4)
India (3)	Turkey (1)
Indonesia (1)	United Kingdom of Great Britain (13)
Ireland (1)	United States of America (471)
Israel (5)	Viet Nam (1)
	Other (31)
*Number of solvers from each country is shown in parentheses	

key findings of difficult cases.[15] Moreover, these systems synthesize patients' clinical information with lightning speed in rendering diagnoses (1.5 seconds in the case of St. Francis). And yet, they are far from perfect.[16]

AI systems

Artificial intelligence systems are not immune to human bias in that the data analyzed must be selected and entered by humans. Machine learning systems like the Isabel Generator identify correlations, not causal relationships, and cannot articulate what they're thinking or develop personal relationships with patients.

AI systems are also expensive, both in terms of their cost in dollars and their carbon footprints. One study estimated that it cost $1 million to $3.2 million to reproduce just one such model using publicly available cloud computing resources, while generating approximately five times the amount of CO_2 an average car emits over its lifetime on the road.[17] However, the actual running of the program, once developed, costs only a fraction of a penny of computer power.

How accurate AI systems are with respect to diagnosis and treatment recommendations (the above report not withstanding) is not yet known. In addition, how such services will be funded, and how associated medicolegal liability, privacy and security issues will be managed have yet to be determined.[16]

Crowd-sourcing medicine

Crowd-sourced decision support, a form of collective intelligence, has recently been tapped by the Human Diagnosis Project as an alternative means of assisting clinicians with differential diagnosis and treatment decisions. This online consultation service boasts a cadre of nearly 7,000 clinicians in 70 countries, brought together in variable numbers to render independent opinions as to the diagnoses of cases submitted to them as electronic consults.

According to Dr. Shantanu Nundy (AΩA, Johns Hopkins University School of Medicine, 2008), former director of the Human Diagnosis Project, "[When] combining multiple physicians together [in this manner, one achieves a diagnostic accuracy] of 86 percent...compared to 63 percent...for an individual doctor."[18]

These results, like those obtained with AI systems in analyzing contemporary cases have limited relevance for their accuracy in diagnosing historical cases, like St. Francis'.

Paradoxically, groups of consultants, like those participating in the Human Diagnosis Project, produce the best results when each member of the group thinks and acts independently.[19] Although such is the case with the Human Diagnosis Project consultants, at a diagnostic accuracy of 86 percent, the project is also far from perfect even in analyzing contemporary cases. In St. Francis' analysis, the participants' second most popular diagnosis, syphilis, is a case in point. Although participants were given the year of the death of the unnamed patient in the case summary (1226), 26 percent failed to recognize that syphilis could not have been his diagnosis as it did not exist in Europe until transported there from the New World by Columbus' crew in 1493 C.E., nearly 300 years after St. Francis' death.[20]

St. Francis' terminal illness

Sr. Schatzlein and Sulmasy, the Isabel Generator, and the Human Diagnosis Project users all concluded that leprosy was the most likely etiology of St. Francis' terminal illness. Were they correct? There are numerous features we know about the illness that fit tuberculoid leprosy better than tuberculosis, gastric cancer, brucellosis, or any other diagnosis proposed to date. These include, St. Francis' chronic eye disease with excessive tearing and eventual blindness, his lack of response to the application of red-hot irons to his face and ears (suggesting trigeminal neuropathy); his dropsy (suggesting nephrosis); the chronic, ulcerated wounds of the hands, feet, and flank (suggesting the 'Lucio phenomenon'); and his prolonged, intimate exposure to lepers—all of which are classic features of leprosy.

Although known to the ancient Hebrews, Greeks and Romans, leprosy was relatively rare in Europe until the sixth century C.E., when it began appearing sporadically among the region's poor. In the 13th and 14th centuries C.E., cases of the infection increased sharply throughout Western Europe, most likely as the result of an influx of the infection among Crusaders returning from the Middle East. The disease then gradually subsided for unclear reasons until losing its significance as a public health threat in the 16th century C.E.[21]

At the time St. Francis was embracing lepers as one of his many "simple acts of charity," lepers were viewed with horror by the general public. Lepers were unsightly due to the disfiguring destruction of their skin, face and limbs, and their disease was believed to be the result of sin, spiritual uncleanliness and the presence of the Devil within.[21] The actual cause of leprosy would not be known until 1873, when Norway's G. H. Armauer Hansen, isolated the etiologic agent, *Mycobacterium Leprae*, from a patient with the disease.[22]

Given the limited clinical information available for analysis in this exercise, the problem of biased sampling of the information, and the absence of laboratory tests and imaging results, leprosy, the diagnosis endorsed here, remains speculative. Only if St. Francis' remains were once again exhumed, subjected to forensic molecular analysis, and shown to contain *Mycobacterium leprae* antigens, would we know for certain that leprosy was at least in part responsible for his terminal illness. Even then, we would not know if he also suffered from other disorders—post-traumatic stress disorder, seemingly the cause of his bout of depression, malaria as the cause of his recurrent attacks of chills and fever, or *Helicobacter pylori* as the cause of his chronically impaired digestion.

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