White Paper

Future of care: Patient-centricity with real-world predictive analytics

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Inhalt

Executive Summary

For centuries, patients have sought medical help for their ailments. Just as in the past, however, there are still many illnesses – both well-known, widespread diseases and rare conditions – that initially cause few or inconclusive symptoms, and many patients leave the doctor’s office with an incorrect diagnosis. In addition, diseases may progress slowly or quickly depending on the individual. Sometimes it is best to “watch and wait”, while in other cases patients should receive intensive treatment from an early stage. In the context of ever-increasing scientific knowledge, such complex medical decisions present physicians with great challenges. We are inundated with digital information. As digitization of healthcare systems progresses, new and previously unimagined opportunities to improve patient care come to light.

For example, machine learning and artificial intelligence technologies are making it possible to elicit important information from routinely collected health data: Who is most likely suffering from a certain disease but remains undiagnosed? Which patient is at a high risk of progression – and which patients are most likely to benefit from a new treatment?

In this white paper, we present practical case studies for artificial intelligence applications in medical care. We describe important methodological approaches for the development of what are known as predictive algorithms and show ways in which these algorithms are already being employed successfully in healthcare practice today. We also discuss the future outlook for the widespread use of predictive algorithms in medical practice as well as potential obstacles that may impede it.

Introduction

The Institute of Medicine (IOM) has defined quality of care as the "degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."

The correct and timely diagnosis of diseases is one of the fundamental challenges faced by global healthcare systems. In the U.S., an estimated 5% of outpatients are misdiagnosed every year. The actual number is likely higher. Diagnostic errors of this kind are particularly common in critically ill patients, and it is not uncommon for patients to suffer harm as a result.

Thanks to the increasing generation of evidence in health services research, physicians are now able to observe very different disease progressions in patients, but the factors influencing these progressions often remain unclear.

New therapeutic approaches target molecular signaling pathways, which in turn are subject to complex regulatory mechanisms. This complexity means that each patient responds differently to new precision medicine approaches. While identifying the patient populations most likely to benefit from selected therapies can be difficult in practice, the sweet spot for predictive analytical methods supported by artificial intelligence is found precisely in large and complex data sets.

Figure 1: Healthcare system challenges and areas of application for AI-powered analytical methods

DISEASE DETECTION

- 5 % estimated outpatients in US receive the wrong diagnosis every year
- Pulmonary embolism (PE) known as "great masquerader" is challenging to diagnose, has very mild symptoms, and it is an incidental finding in approximately 3 % of chest CTs
- Error rates in the tissue diagnosis of cancer are as high as 15 %
- Later diagnosis of Parkinsons disease results in shorter life expectancy. "The risk for early death increased by about 40 % for every 10-year increase in age at diagnosis"

DISEASE PROGRESSION

- For Parkinsons disease "There was a remarkable variability in time to death, ranging from 2 to 37 years after (motor symptoms began)"
- "In cardiology, most diseases are slow, heterogeneous, multimorbid, chronic processes where pathogenesis may begin decades before any ultimate disease manifestation"
- In CLL, 91 % of venetoclax (BCL2 inhibitor) treated CLL patients eventually acquire BCL2 mutations in resistance
- In Duchenne muscular dystrophy, 87.6-100 % patients have cardiomyopathy as a disease progression by age 25

TREATMENT SUPPORT

- CNN offers an accuracy of over 90% in the diagnosis of and treatment suggestions for congenital ocular disease
- Interaction trees and subgroup analyses were used to get appropriate tPA dosage based on patient characteristics and thereby evaluate the performance of stroke treatment
- Cardiology is increasingly using AI to improve treatment support, e.g., a recent study has demonstrated the usefulness of Support Vector Machines, by predicting in-stent restenosis with 90 % accuracy from plasma metabolite levels

Source: a detailed literature list can be requested from the authors

Leveraging patients' digital footprints

Today, physicians routinely collect a wide range of data from their patients. Artificial intelligence algorithms recognize patterns in these data, which help to identify diseases more quickly and treat them more effectively.

Medicine has gone digital. Patients routinely leave electronic footprints in many places, for example in connection with insurance claims or as part of electronic medical records. Many diseases develop over a long period of time and often start with non-specific symptoms. For example, the time to diagnosis for rare diseases averages 4.8 years. During this time, large quantities of data accumulate as part of the patient history. Algorithms can be used to find patterns in these data sets that can point to a rare disease, for example. This approach can significantly shorten the long time until correct diagnosis. Ultimately, using past data for future diagnoses can help ensure that a greater number of patients receive the correct treatment, optimizing overall healthcare spending, reducing medication errors, and improving patients' quality of life.

In some cases, patterns in the data are quite obvious. For example, the risk of undiagnosed type 2 diabetes can be calculated with reasonable accuracy based on factors such as age, height, body mass index (BMI), ethnicity, hypertension, family history, physical activity, etc. The American Diabetes Association has even developed a risk calculator based on a small number of parameters[1].

However, many diseases lack these kinds of clear, known associations. In some cases, clues can be found in the scientific literature, but these are not routinely recorded in real world care. In other cases, especially in the case of rare or complex diseases, little is known about the patterns that might be useful for diagnosis.

That is exactly where artificial intelligence (AI) and machine learning (ML) come into play as advanced, empirical analytical methods. They recognize complex data patterns to provide answers to specific questions: Who is most likely to suffer from a particular disease? Who might benefit from early treatment or from a new, innovative drug?

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Predictive analytics – the methodological approach

Predictive analytics make it possible to improve care.

For years, different study designs have shaped the landscape of medical and pharmaceutical research. There are purely primary data collection approaches such as randomized clinical trials, or prospective registry studies, and secondary approaches such as database studies. In addition, new study designs gain importance, for example pragmatic randomization or synthetic control arms. Finally there is tremendous potential in predictive analytics, an area involving machine learning and artificial intelligence.

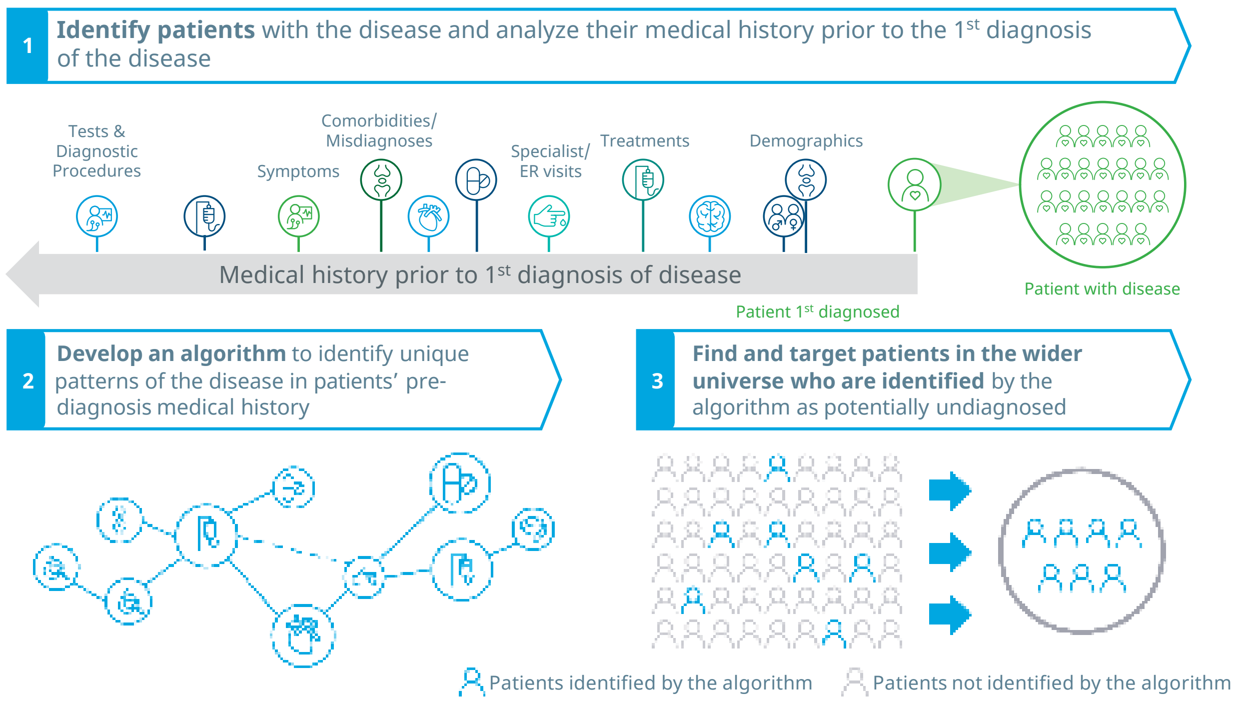
The basic idea of predictive analytics in medical care is to identify patterns and make predictions based on data routinely collected in patient care. The more extensive these data, the more accurately these algorithms can make predictions.

The first step is to generate real-world data. Longitudinal prescription records and electronic health records, for example, contain valuable information. New technology for the extraction of anonymized data from systems in physicians' offices and hospitals can be used to leverage interesting data points in patient histories, for example by extracting parameters from pulmonary function tests via a specially built interface to the pulmonary function device in the physician's office. Other valuable data sources include laboratory systems and biobanks – the larger the quantity and the greater the depth of the data, the better. In addition, other new data sources are available, e.g., from telemedicine care or from "wearables" and digital patient diaries. Of course, any applicable data protection regulations must be observed at all times, especially when working with sensitive health data.

A population of interest includes patients who have been diagnosed by physicians with certain conditions. Their medical history can be reviewed retrospectively to identify characteristic patterns. These patterns may pertain to basic characteristics like age and gender, previous symptoms, diagnoses, or prescriptions, and are identified on the basis of pattern recognition in longitudinal, anonymized patient data using artificial intelligence or machine learning algorithms.

IQVIA applies patterns of this kind to large data sets in order to make certain predictions. Pattern recognition algorithms are highly likely to predict who has an undiagnosed disease, who is eligible for a specific treatment, or who is at a high risk of rapid disease progression. In general, the data stem from anonymized patient profiles that are compliant with all data protection regulations. The algorithms are applied to large data sets. For example, IQVIA's prescription database (LRx) covers approximately 75 percent of the German population. In the sections that follow, we will present selected examples from the areas of pulmonology, hereditary diseases, liver diseases, and hematology-oncology.

Figure 2: Using the digital footprints of diagnosed patients to develop AI/ML for risk assessment in potentially undiagnosed patients



Source: IQVIA, 2019: White Paper, "Finding undiagnosed patients: Applying Artificial Intelligence and Machine Learning to drive earlier diagnosis." Online at: https://www.iqvia.com/library/white-papers/applying-artificial-intelligence-and-machine-learning-to-drive-earlier-diagnosis

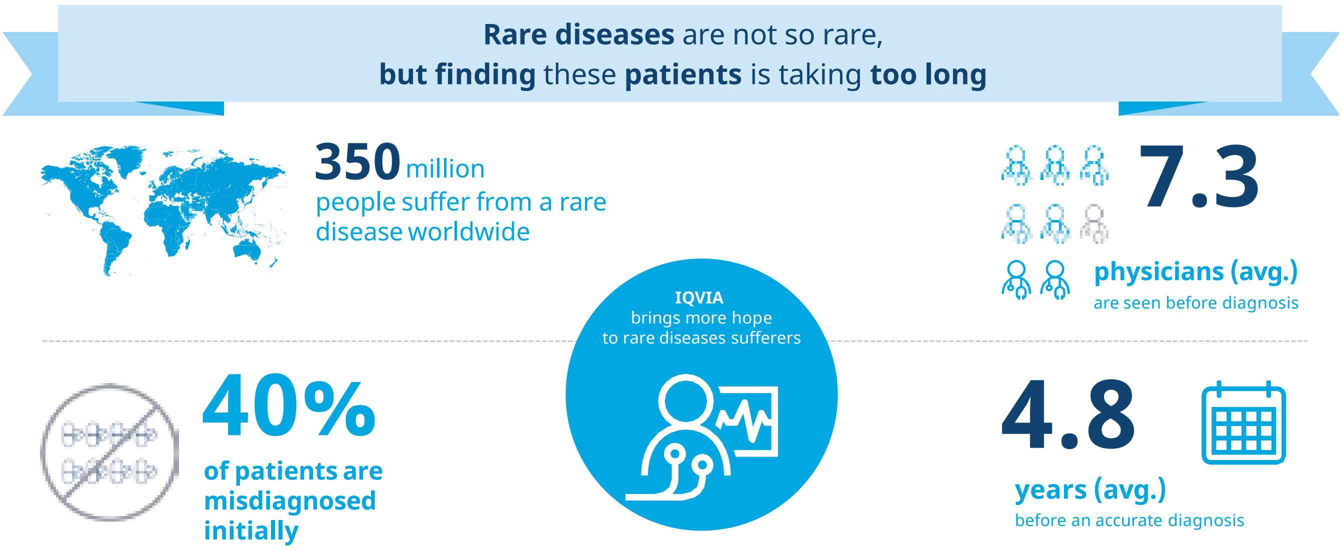
Physicians can benefit from the use of predictive analytics to aid in disease diagnosis

Some diseases hardly cause any symptoms at the beginning – and a great deal of time may pass until a diagnosis can be made. Artificial intelligence and machine learning algorithms support physicians in this process.

Many patients around the world struggle through healthcare systems in search of a correct diagnosis. Instead, they experience misdiagnoses and are treated with the wrong medications. Patients often lose hope of ever receiving the correct diagnosis/treatment. The fact that there are effective therapies in many cases but these are not applied because physicians do not make the right diagnosis is particularly frustrating.

The reasons are manifold. Some conditions cause no – or only non-specific – symptoms. Perhaps physicians focus on more common conditions while the patient actually has a rare condition. Laboratory tests may be lacking, with only exclusion diagnoses leading to a solution. This takes time that physicians often do not have. The figures below illustrate the fundamental problem in a nutshell (Fig. 2 and Fig. 3).

Figure 3: Example: "Rare diseases" – not so rare, but finding these patients takes too long



Source: IQVIA White Paper (2019): Finding Undiagnosed Patients: Applying Artificial Intelligence and Machine Learning to drive earlier diagnosis, p. 8
Online at: https://www.iqvia.com/library/white-papers/applying-artificial-intelligence-and-machine-learning-to-drive-earlier-diagnosis

Two real-world examples:

Idiopathic pulmonary fibrosis (IPF)[2] typically occurs in elderly patients. It usually leads to non-specific symptoms such as shortness of breath, pain, and fatigue. Patients may think that their symptoms are simply a part of getting older and may not seek medical help. There are no clear, rapid tests to detect IPF; physicians' only option is a diagnosis by exclusion. The average survival time of patients with IPF is just 2.5 years, but evidence suggests that patients who are diagnosed and treated early live significantly longer. This underscores the need to look for ways to detect IPF earlier.

Poor awareness and early age of onset are important factors in the misdiagnosis or late diagnosis of the hereditary disease **Alport syndrome**[3]. Initial symptoms typically appear in early childhood, with most cases exhibiting unexplained hearing loss, hypertension, and nephrological complaints. Progressive loss of kidney function may not be recognized until the later stages of the disease, threatening patient survival. Although there is currently no curative therapy for the condition, early diagnosis can help preserve kidney function for a longer period of time.

The solution: Algorithms help physicians to use electronic patient records to identify individuals who have not yet been diagnosed with a specific disease and also support them in selecting the best possible therapies. They also help to ensure that research findings are integrated more quickly into clinical practice.

CASE STUDY: UNDERDIAGNOSIS OF NON-ALCOHOLIC STEATOHEPATITIS (NASH)

IQVIA has demonstrated the potential of predictive, AI-supported analytics using the example of non-alcoholic steatohepatitis (NASH) – the most common progressive liver disease in Europe with a prevalence of approximately 3 percent. There are currently no therapies for this condition. The disease causes hardly any symptoms, especially in its early stages, leading to a high number of undiagnosed cases. A research-based pharmaceutical manufacturer working on a treatment option and preparing for launch needed information on the actual epidemiology of the disease – and not just on the number of initial diagnoses.

The project was based on anonymized electronic patient data from approximately 2,500 medical practices in Germany including information on patient characteristics, symptoms, comorbidities, diagnoses, and other risk factors.

IQVIA used machine learning technologies to identify patterns in the data set. The prevalence in Germany calculated using this approach is estimated at 4.5 percent, i.e., higher than expected. This finding is, of course, important in quantifying the unmet need, and may influence discussions regarding market access and reimbursement.

The strength of predictive analytics lies in its ability to detect cases that would have gone undetected in the physician's office. The method supports physicians in making diagnoses and decisions.

Predictive analytics help physicians predict disease progression and make better therapeutic decisions

Patients with chronic obstructive pulmonary disease are more likely to suffer exacerbations leading to hospitalization as the disease progresses.

By applying machine learning methods to electronic medical records and data from Swedish national disease registries, it was possible to predict the imminent exacerbation of COPD based on a model. The findings on the driving factors for exacerbation will be used in the development of clinical screening tools to reduce future hospitalization of patients through early risk detection and preventive therapeutic intervention.

CASE STUDY: TREATMENT OF RHEUMATOID ARTHRITIS

Disease progression was also the focus of another IQVIA project. In Germany, approximately 0.8% (0.3-1%) of the adult population suffer from rheumatoid arthritis, with another 20 to 40 people per 100,000 inhabitants developing the disease every year[5]. Physicians treat patients with various pharmaceuticals in accordance with treatment guidelines. The well-known folic acid antagonist methotrexate plays a central role as a basic therapeutic agent[6]. The challenge for rheumatologists is to select suitable second- and third-line therapies if the first-line therapy fails to control the disease. Methotrexate is often up-titrated before these second- and third-line therapies are selected.

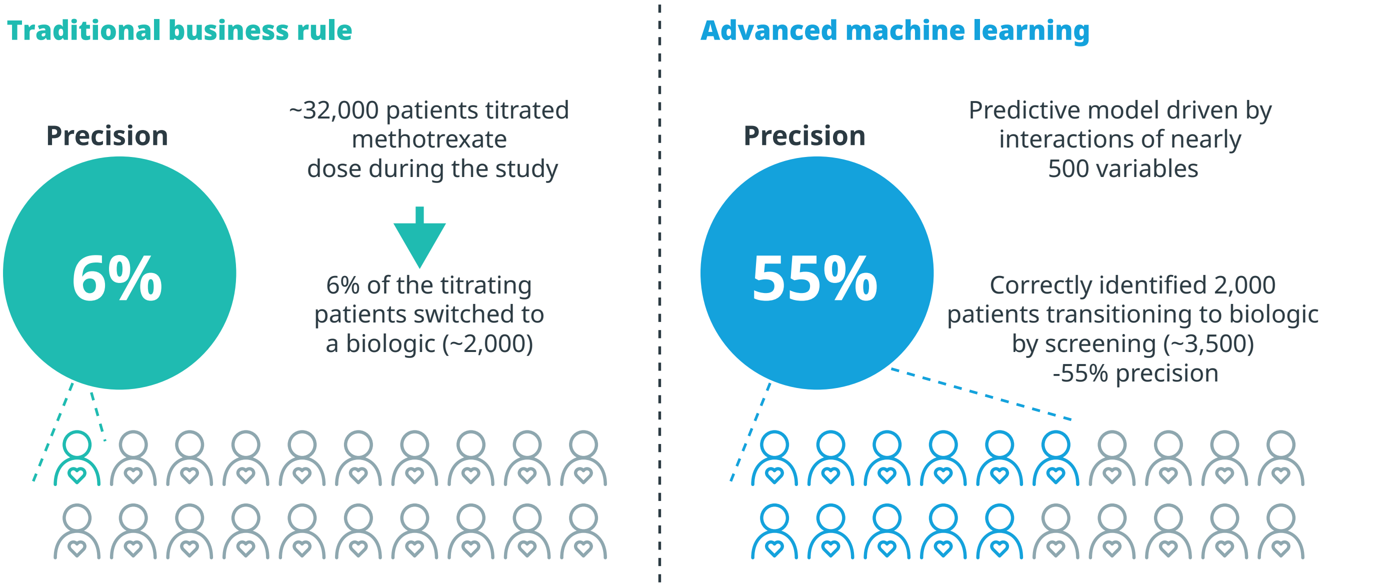
This titration rule was tested for accuracy using data from IQVIA medical records linked to longitudinal prescription data[7].

A cohort of 393,000 methotrexate-only patients and 15,000 new biologics patients with rheumatoid arthritis was formed. During the 6-month study period, only 6% of all patients whose methotrexate dose was increased received a biologic agent – compared with about 13,000 patients without dose adjustment. This titration rule did not lend itself to predictions.

IQVIA therefore used artificial intelligence both to identify patients who would be switched to other therapies and to determine disease progression factors.

Using the same patient populations, an AI model was developed and its accuracy in predicting the initiation of biologics therapy evaluated. As part of an iterative process, the model was trained using hundreds of clinical variables to identify those patients most likely to be switched from methotrexate to a biologic drug. The AI model was almost ten times as accurate in its predictions as the titration rule. It was trained to predict upcoming therapy changes within a specific time window. In this case, a switch to a biologic agent was predicted 30 days before the actual event.

Figure 4: Rheumatoid arthritis case study. Comparing rule-based prediction to advanced machine learning



IQVIA White Paper (2020): Using Artificial Intelligence to Predict Disease Progression. Targeting therapy transition with precise HCP and patient engagement; S. 9 https://www.iqvia.com/library/white-papers/using-artificial-intelligence-to-predict-disease-progression

Predictive analytics support physicians in treatment selection

The development and introduction of new therapy options in everyday care is progressing very rapidly, with market launches increasing steadily for several years, especially in the field of precision medicine. While this speed is good for patients, it poses significant challenges for physicians. Despite consistent physician trainings in highly advanced healthcare systems (e.g., in Germany), the multitude of therapy options can be overwhelming. Predictive analytics can support physicians in selecting the right treatments, as shown below using the example of multiple myeloma.

The new tool outperformed Cox regression, the best-known model for survival analysis, by 22% and identified the key predictors of progression or overall survival for different therapies. This allows physicians to estimate survival based on factors such as age, line of therapy, ECOG (Eastern Cooperative Oncology Group) performance status score, time since diagnosis, and previous therapies. All results are provided in an intuitive, easy-to-understand format. Based on these, physicians can select possible treatment regimens, taking into account the predicted survival time.

CASE STUDY: MULTIPLE MYELOMA

Over the past two decades, immense strides have been made in multiple myeloma therapy, starting with

autologous stem cell transplants and followed by immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and histone deacetylase inhibitors. As a result, the age-standardized mortality rate for the condition has decreased significantly.

Nevertheless, many patients experience relapses, and treating relapsed/refractory multiple myeloma is particularly challenging, as the patients affected do not respond to conventional treatments, have shorter remission periods, and their disease progresses rapidly.

Treatment outcomes in relapsed/refractory multiple myeloma are influenced by several factors.

Age at diagnosis, age-related frailty, cytogenetic abnormalities, clonal evolution, and comorbidities play a major role. Physicians are still faced with the challenge of selecting the right treatment on an individual basis. Especially for new therapies, data are often only available from experimental studies, which usually do not include representative patient populations. This makes it difficult to draw conclusions about general day-to-day care.

This is precisely where a new technology from the field of machine learning comes into play. The goal was to supply physicians with a decision-making aid that would provide them with easily interpretable recommendations. The programmed software offers predictions for disease progression and overall survival when different therapy options are used. It is based on data from more than 6,000 patients from eight different EU countries.

Predictive analytics in practice (1): “Clinical Decision Support“ systems

In the previous sections, we have shown that AI-based algorithms can reliably identify patients of interest in large anonymized data sets. This is done through pattern recognition in longitudinal, anonymized patient histories. These approaches provide in-depth insights pertaining to epidemiological questions, e.g., by predicting the number of undiagnosed patients in large populations. But how can individual physicians and patients benefit from AI-supported predictive analytics?

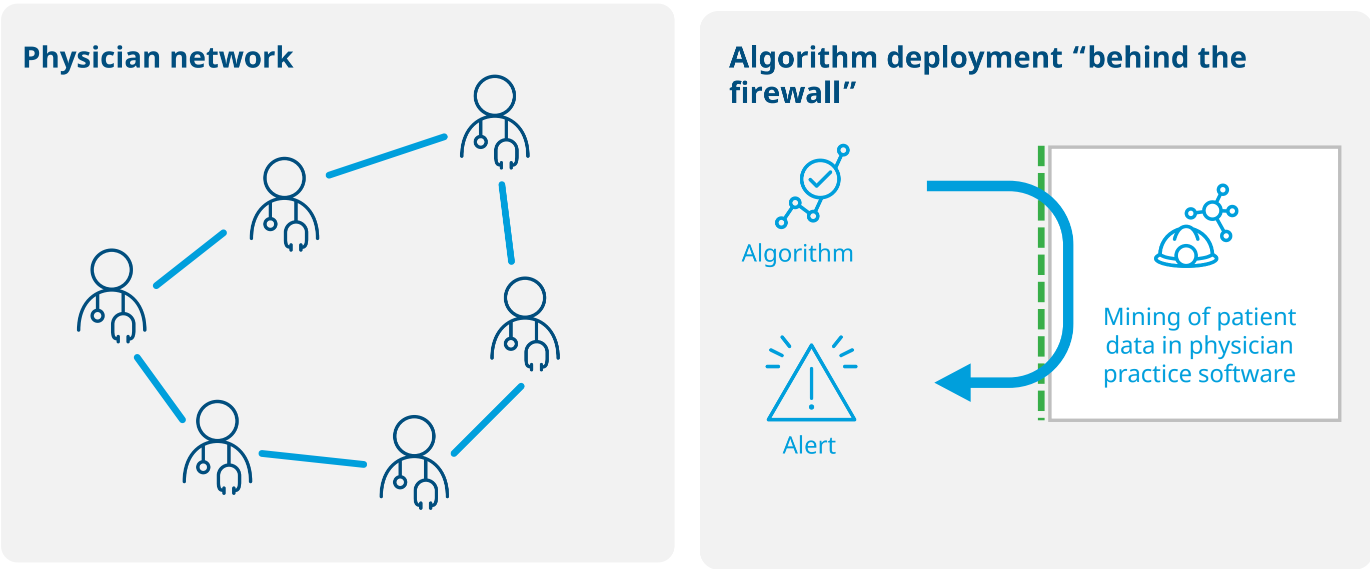
Individual health data is subject to strict privacy regulations that must be respected.

Only the physician has access to patient data – and all personal data are generally subject to medical confidentiality obligations.

IQVIA has therefore developed a new concept and implemented it successfully in medical practices: “algorithm deployment behind the firewall“ (Fig. 5). Algorithms are developed on the basis of anonymized patient data and then deployed into the physician‘s software. Depending on the question being examined, the algorithm identifies patients with an undetected underlying disease, a high risk of progression or the potential to benefit from new, innovative therapies. However, patient data never “leave” the medical facility. Nevertheless, it is possible to identify (de-anonymize) the patients in question within the physician’s office and to trigger an alert.

The physician thus receives support in their daily practice and benefits from the analysis of millions of patient histories as well as (successful and unsuccessful) therapy decisions made by other physicians with regard to similar patients. These clinical decision support systems are currently being developed in many therapeutic areas and are being used with increasing success.

Figure 5: “Algorithm deployment behind the firewall“ (concept)



Source: IQVIA

Predictive analytics in practice (2): Patient-centered physician targeting during the launch of new therapies

Predictive analytics can also aid physicians in another, more indirect way by effectively identifying suitable patient groups for a newly-launched treatment. The pharmaceutical industry traditionally takes a volumetric approach to identifying relevant prescribers. Pharmaceutical companies (with the support of, e.g., IQVIA) analyze the historical prescribing behavior of physicians in relevant therapy classes. However, in new, patient-centered targeting approaches, the question is not “Which physician frequently prescribes drug XYZ?“ but “Which physician has many patients who will benefit from a newly-launched therapy?“. Here, too, the focus is on the relevant patients – not the relevant prescriptions.

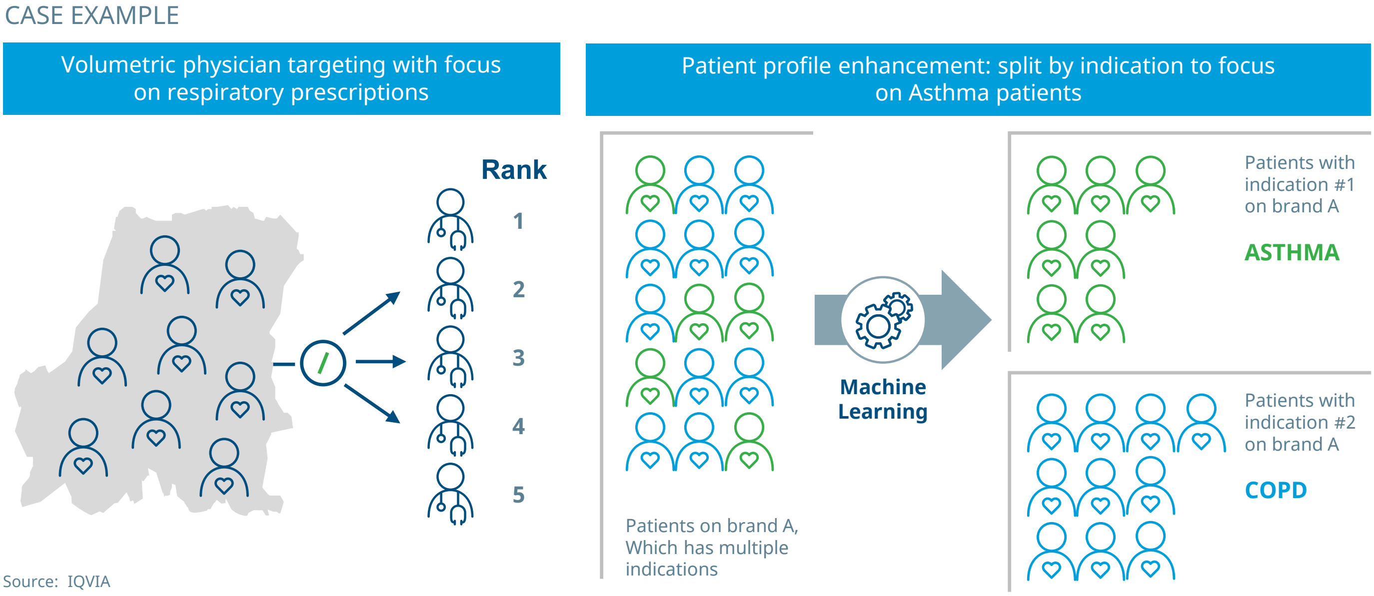
Technologies of this kind have proven useful, for example, in determining which physicians are treating many patients with a specific lung disease. For one client from the pharmaceutical industry, it was important to separate patients with asthma from patients with chronic obstructive pulmonary disease (COPD) because its product is only suitable for a limited patient population with asthma. Since prescription data alone do not provide this information, the traditional approach involving the volumetric targeting of physicians was not sufficient in this case.

Also in this example, predictive algorithms were developed from anonymized electronic medical records on the basis of longitudinal patient histories. These algorithms were then applied to national German prescription databases, allowing relevant patients of interest to be identified in full compliance with data protection guidelines.

This expanded, patient-centered approach makes it possible to identify which prescribers are primarily treating patients with asthma – rather than COPD – in order to make the newly-introduced therapy available to them in the future.

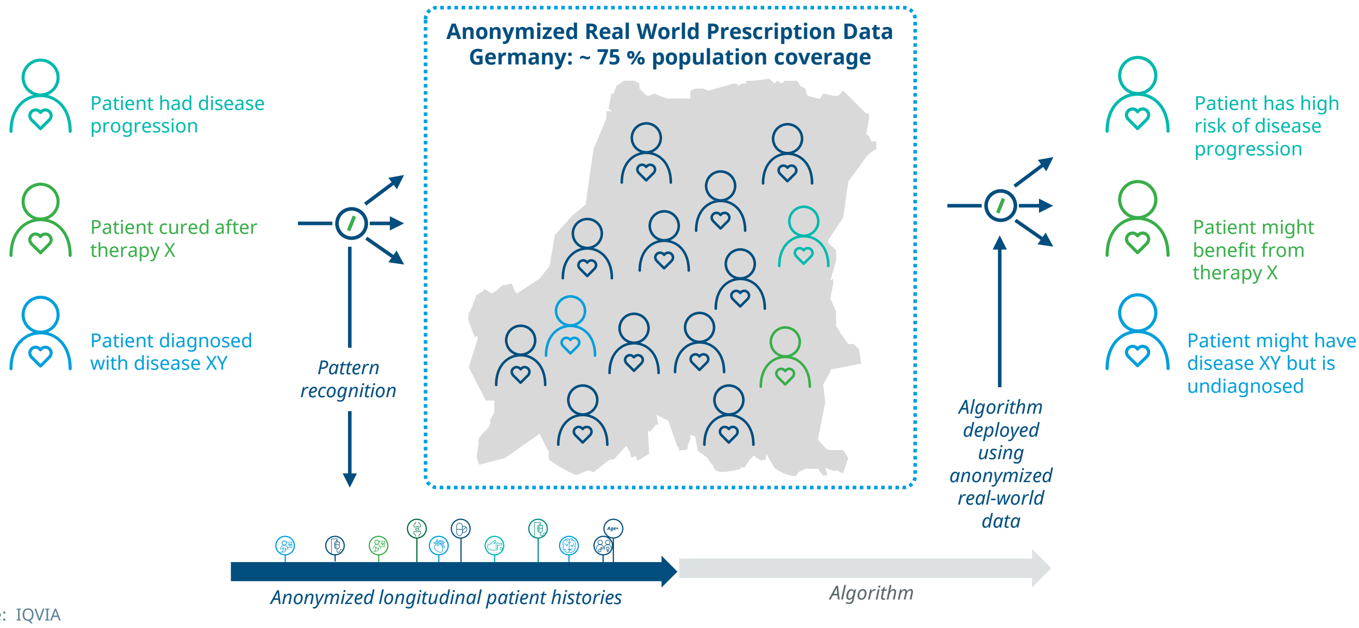
It was also possible to specifically identify patients with uncontrolled asthma and direct them to appropriate therapy.

Figure 6: Case study: Lung diseases, distinguishing between asthma and COPD



Source: IQVIA

Figure 7: The underlying concept is AI/ML-powered pattern recognition using anonymized real-world patient data



Source: IQVIA

Summary and Conclusion: Using algorithms for the benefit of patients – opportunities loom while challenges remain

In this white paper, the use of artificial intelligence in healthcare is discussed, with a focus on „connected intelligence". This refers to the intelligent connection of data assets, which can lead to new evidence. The increasing digitization of healthcare systems provides new opportunities to improve patient care, and AI technologies, such as machine learning, are being used to extract important information from health data. Case studies are presented to show how predictive algorithms are being used in medical care.

New „algorithm deployment behind the firewall" concepts are being tested for physicians to benefit from AI-supported predictive analytics while respecting patient data privacy regulations. Algorithms are developed from anonymized patient data and then deployed into the physician's software, providing support for their daily practice by identifying patients with undetected diseases or high risk of progression. Clinical decision support systems are being developed and used with increasing success in many therapeutic areas.

Also, predictive analytics can help pharmaceutical companies to effectively target suitable patient groups for newly launched treatments. The traditional approach of targeting physicians based on their historical prescribing behavior is replaced by a patient-centered approach, where the focus is on identifying relevant patients, not relevant prescriptions. As a result, it is possible to direct patients with uncontrolled asthma to appropriate therapy and make the newly introduced treatment available to them, in full compliance with data protection guidelines.

In all presented case studies, the concept of „connected intelligence" highlights the potential for the integration and analysis of data to drive innovation and improvement in healthcare.

In conclusion, the use of AI/ML algorithms in disease detection and other use cases has immense potential, but requires cross-sector collaboration during development and deployment. These algorithms can be used in medical settings to detect various conditions, either at the point of care or through alerting practice managers. Overcoming challenges such as scalability, interoperability standards and ensuring the absence of bias in data and algorithm design is crucial for the widespread adoption and affordability of these new solutions. Bias in data can result in incorrect predictions or misdiagnosis and it is important to address this issue during the development and implementation of these algorithms to ensure they benefit patients effectively.

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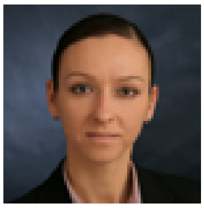

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ABOUT IQVIA

IQVIA is a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry. IQVIA creates intelligent connections across all aspects of healthcare through its analytics, transformative technology, big data resources and extensive industry expertise. IQVIA Connected Intelligence™ delivers powerful insights with speed and agility, enabling customers to accelerate the clinical development and commercialization of innovative medical treatments that improve healthcare outcomes for patients.

With approximately 82,000 employees, IQVIA conducts operations in more than 100 countries.

IQVIA is a global leader in protecting individual patient privacy. The company uses a wide variety of technologies and safeguards in the generation, analysis, and processing of information.

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