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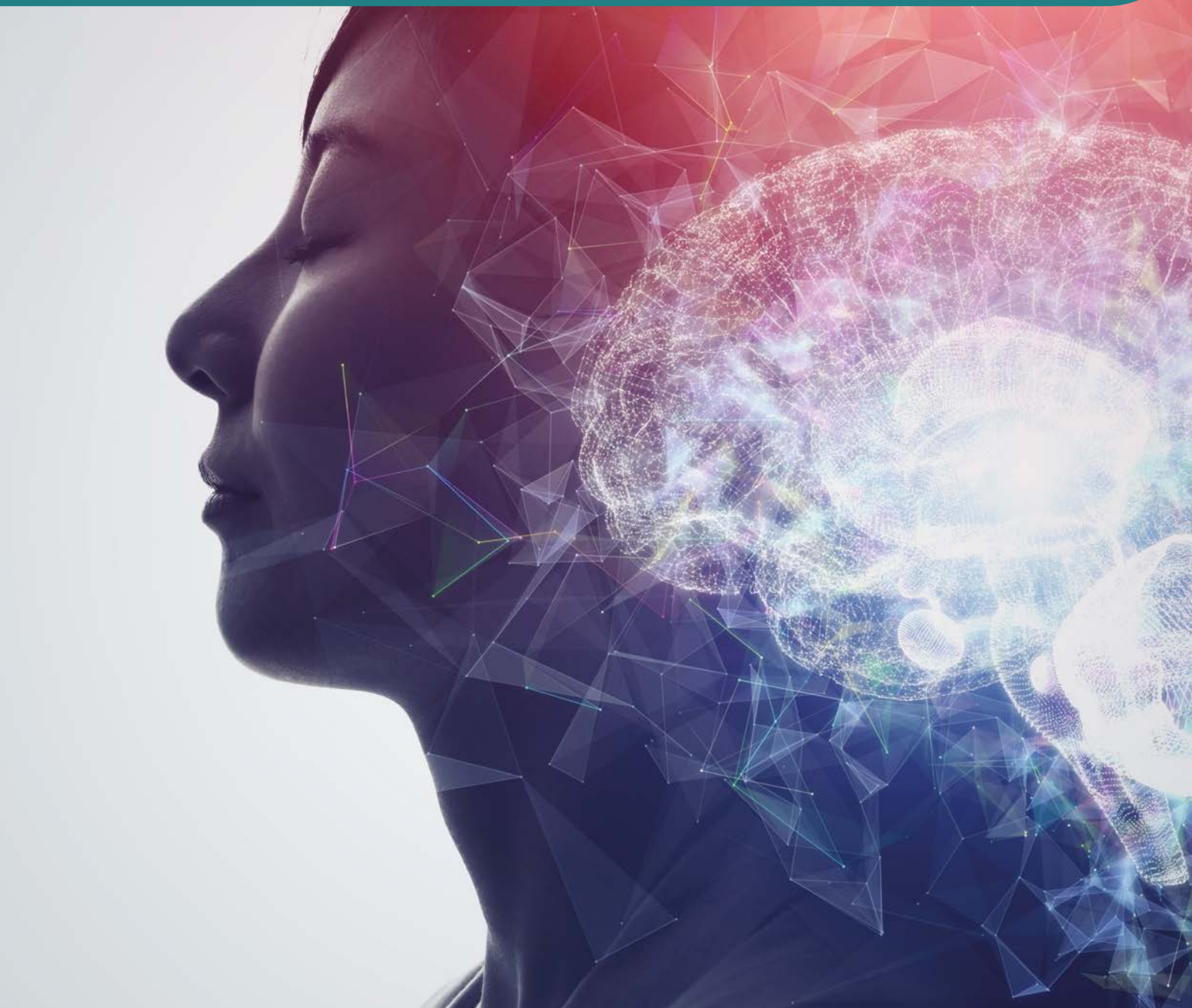
WHITE PAPER

Developing Machine Learning-enabled Digital Medicine

Sleep Management case study



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Foreword: the growing need for advanced digital healthcare

As healthcare faces mounting pressures, there is a growing need for efficient and cost-effective digital services, including digitally enhanced self-care. Integration of Machine Learning (ML) techniques has an important role to play, bringing opportunities to derive new insights using the vast quantities of medical data generated every day.

Recent accelerated developments in the ML domain provide additional opportunities to build automated science-driven predictive solution systems for high-level personalisation and preventive healthcare. However, potential clinical and commercial benefits must be evaluated objectively alongside implementation challenges. ML-enabled health solutions present unique issues due to their complexity, the need for explainability, and the iterative data-driven nature of their development.

Here, we outline a three-step process for developing an ML-enabled digital health solution to support patient/consumer engagement and maximise health outcomes. Such evidence-based solutions constitute 'digital medicine' which measures and intervenes to improve human health.

The process is based on combining multidisciplinary principles and expertise. This enables the build of a multi-channel data foundation and ensures a deep understanding of intended use, including desired clinical benefits and associated risks. We discuss the need to demonstrate the effectiveness, safety, and security of a system to maximise its clinical and commercial potential, as well as the verification and validation needed to obtain FDA clearance or approval if it is a medical device that requires premarket authorisation and CE marking. Finally, we explore commercial matters related to digital healthcare solutions, which is one of the most critical concerns of innovators at present. We consider how commercial uncertainty can be tempered with a good understanding of existing payment mechanisms, and alternative options.

Use of ML and AI in healthcare

Recent advancements in ML include automated training/re-training/deployment of models and increased processing power allowing more widespread use of computationally intensive algorithms. These capabilities provide additional opportunities to build automated science-driven predictive systems for a high-level of personalisation and preventive healthcare.

Progress in ML goes hand in hand with accelerated innovation in generative Artificial Intelligence (AI) tools which unlock the possibility of using AI to digest, search and summarise large volumes of information along with easy-to-use conversational interfaces. This would allow AI-based systems to act as virtual assistants to physicians and other medical and healthcare providers by rapidly searching medical literature, patient medical records, past case histories and other relevant material, returning relevant information for the treatment of patients.

It's important to note the current drawbacks associated with generative AI tools. They are sometimes known to 'hallucinate' because they generate content based on text proximity and affinity between words in texts they have been trained on. Also, these tools may have been trained on dated or invalid content on the internet. Because of this, there is a high risk of generic generative AI tools such as ChatGPT outputting incoherent or false information. In a healthcare context this issue can be tackled with custom retraining of AI models on carefully selected and curated high-quality medical datasets.

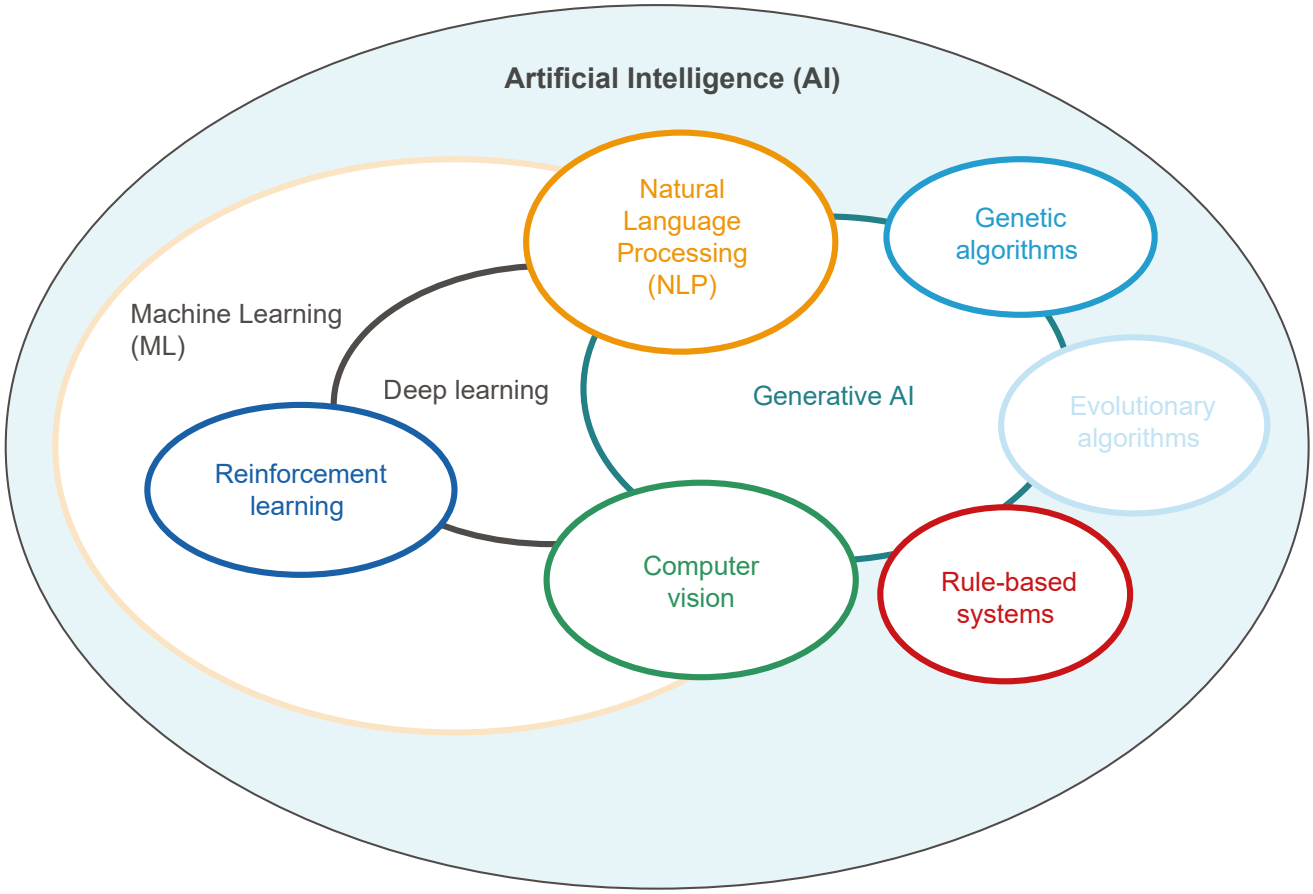


Figure 1: Mapping the AI landscape (not exhaustive presentation based on most well-known branches).

ML-enabled digital medicine: a three-step development process

A pragmatic approach is needed to define the scope of work for development of ML-enabled health solutions. This ensures cost and time efficiency as well as potential scalability of successful models. Figure 2 summarises three key phases: review the clinical associations; design the model; build the model.

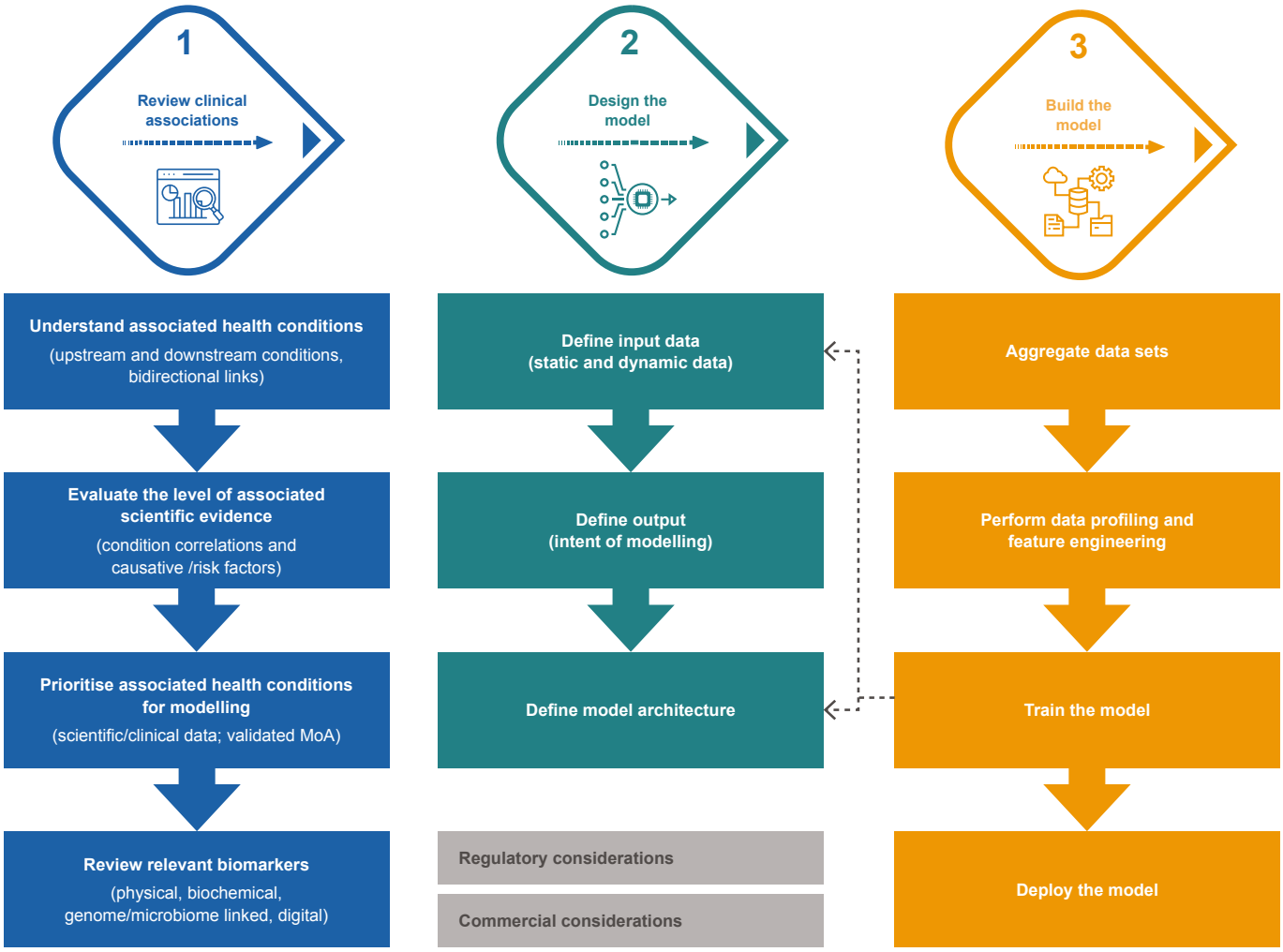


Figure 2: A three-phase approach to the development of ML-enabled digital medicine.

It's the first two phases that most benefit from multidisciplinary input. Applying a good depth and breadth of knowledge during the review of clinical associations and model design ensures a robust foundation for building the model. We'll look at these two phases in greater detail, before illustrating them with a ML-enabled concept we devised to support sleep management.

i. Review clinical associations

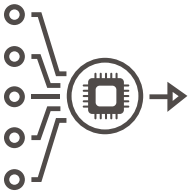
From a clinical perspective, it's important to identify and evaluate any associated health conditions in the target health area. This includes upstream conditions (i.e., causative or risk factors), downstream conditions (i.e., resultant health factors), and bidirectional links between them, in other words, how they affect each other.

These associated health conditions should be further differentiated according to their strength of clinical association. Some may have a slight correlation with the target condition whereas others might have a stronger, clinically validated association.

When modelling, priority should be given to associated health conditions with the strongest clinical evidence. Randomised, double-blinded, placebo-controlled trials conducted on a large sample with measurable biomarkers are preferable to studies reliant on self-reported outcomes. Where possible, longitudinal studies are preferable as they capture the progression of patient health, allowing for more accurate monitoring and analysis of the condition.

The mechanisms of action (MoAs) behind clinical links also need to be reviewed. A clear MoA provides more reason to believe there is a strong clinical association. It is also important to identify and understand other factors likely to affect these health conditions (such as the consumer/patient lifestyle) for consideration in the modelling.

ii. Design the model



A digital solution's performance and subsequent success is dependent on the data it uses.

ML-enabled health solutions need to clearly define 'input data' and 'output' as well as the model architecture. There's a wide range of factors to consider for each of these areas, so we'll explore them individually.

A digital solution's performance and subsequent success is dependent on the data it uses.

Regardless of how data is sourced, digital health innovators need to make its privacy and security a priority to avoid individuals' sensitive health information being compromised.

For a product to be legally marketed in a certain geography, it must comply with all applicable regulatory requirements around data access, management, and usage.

Defining input data

Digital management of health conditions relies on the collection and analysis of various data types, including self-reported, biochemical and digital biomarker, clinical and genomic data. Figure 3 indicates the diversity of potential sources, and how the data might be captured.

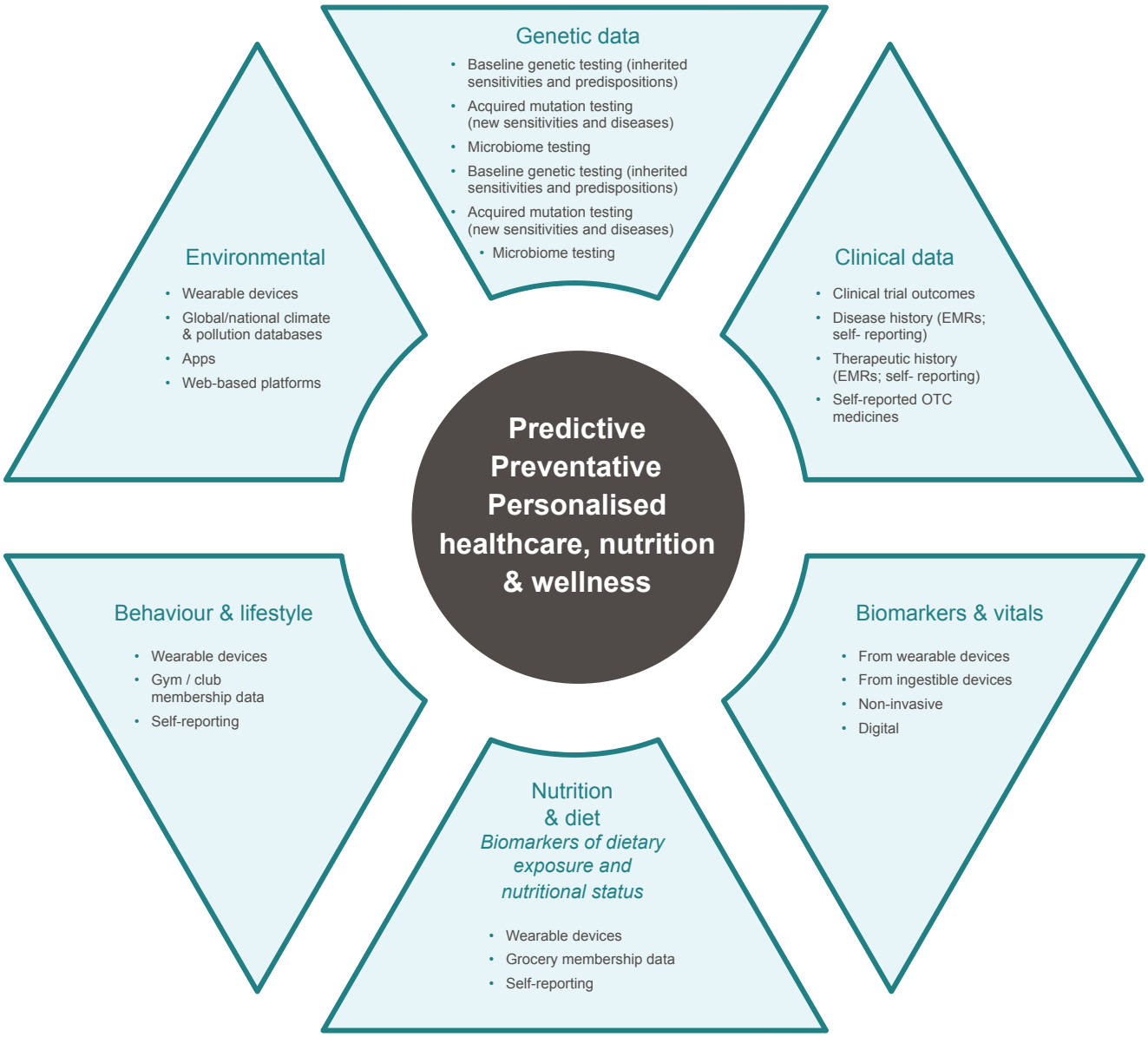


Figure 3: A growing opportunity for using multi-channel data to ensure predictive and preventive healthcare and wellness.

When developing evidence-based and validated algorithm-driven solutions, data collection protocols should ensure that clinical study participants and datasets are sufficiently representative of the intended subject population. This is essential to reduce any bias and identify circumstances where the model may underperform.

Multi-channel data is often difficult and costly to collect. At one end of the spectrum lies clinical data from electronic medical records, which may include medical imaging and laboratory results. This gives the most detailed level of patient information, but privacy regulations and technical barriers can hinder access. At the other end of the spectrum is self-reported data, collected directly from the consumer/patient (e.g., lifestyle habits and activities, medication consumption). This is relatively easy to obtain and potentially reveals valuable insights surrounding behaviour and health status. However, it suffers from subjectivity and is prone to biases and inaccuracies.

Falling between these two extremes is biomarker data. These physiological, bio-chemical, and digital indicators can be obtained from individuals to provide a more accurate and reliable measurement of health status than self-reported data.

To improve the predictive power of digital solutions, researchers increasingly integrate genetic data with clinical and phenotypic data and lifestyle information from multiple sources. However, finding linked genomic and clinical data is a significant challenge. It requires access to existing genomic-clinical data, either from global networks of data partners for a specific research project, or via enterprise license.

Longitudinal data, accuracy, and completeness

The abovementioned datatypes provide information regarding a patient/consumer and their current health status. Yet the digital management of health conditions requires the identification of patterns, or habits in people's lives, which increase vulnerability to health conditions. So, longitudinal data (collected over a period of time) is a more effective input for digital health management tools than non-longitudinal data (collected at a single point in time).

Another consideration is the balance between accuracy and completeness across structured (biomarkers, self-reports, lab results) and unstructured (medical images, medical reports) data.

Accuracy encompasses the level of detail and variability in the data of a patient/consumer, or the sample size of a study. Data completeness refers to the availability of required datatypes for an algorithm to learn and make accurate predictions. This might include information such as patient demographics, medical history, laboratory tests, and imaging results. More complete data enables a higher level of granularity, enabling the digital solution to achieve a higher level of resilience.

In some cases, accurate but incomplete datasets may be sufficient for a minimalist digital solution which performs diagnosis and generates treatment options. However, a more reliable picture of patient health is required to deliver effective, personalised treatment plans. Nevertheless, even where accurate and complete data is available, its management requires the use of advanced analytical tools and expertise for the development of robust solutions.

Defining output

It's important to have absolute clarity on the required output at the model design stage. ML-enabled health solutions are not intended to replace a medical diagnosis in isolation. Rather, outputs are likely to include real-time data illustrations, analytical findings, predictive outcomes (such as predisposition for contracting a disease), or recommendations (which may have clinical or lifestyle implications).

It is possible to define the output even in the absence of input data for the purposes of planning and design. This might involve the following steps:

- Assess the requirements of the digital tool. What is the end goal, and how complex should it be?
- Based on these objectives, decide what type of algorithm would work best, a traditional ML approach or a simple analytics or heuristic algorithm.
- With the requirements and algorithm type determined, define what data will be needed to ensure the solution is robust and accurate.

Defining model architecture

When defining model architecture, multiple factors need to be accounted for. As a rule of thumb, more complex datasets require and enable more robust modelling. Figure 4 plots data analytics, traditional ML, and the ML techniques of deep learning and reinforcement learning in relation to data complexity and solution resiliency. However, there is no one-size-fits-all approach; applications need to be considered on a case-by-case basis.

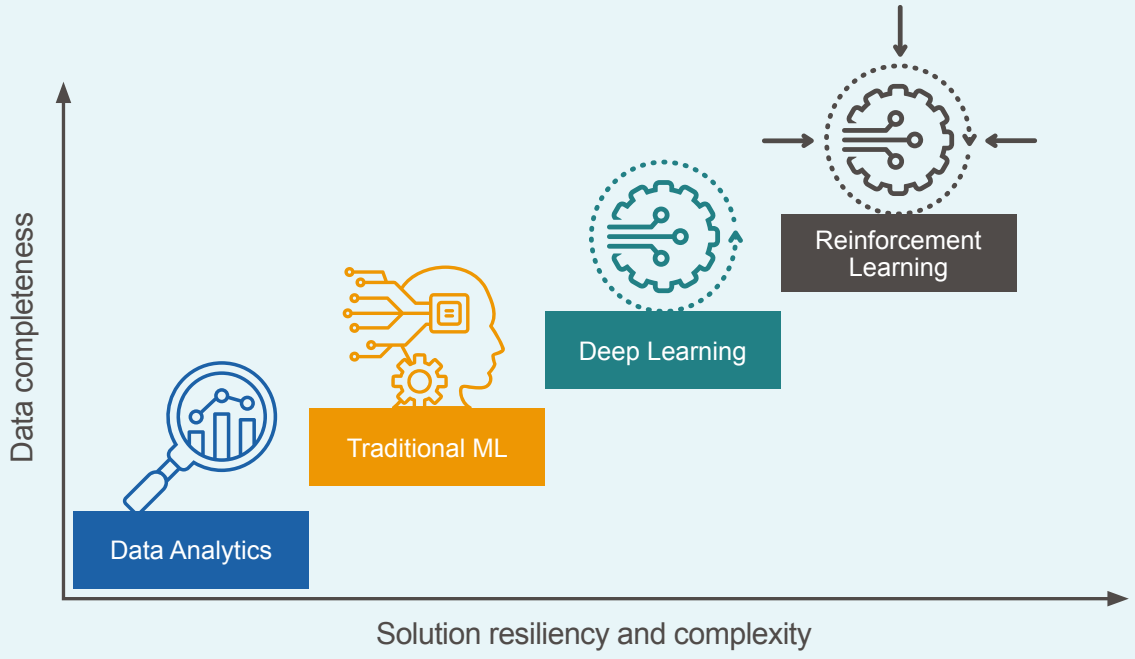


Figure 4: The relationship between data completeness, ML techniques, and solution resiliency.

Low-complexity inputs, such as non-longitudinal data, demographic information, or simple survey responses, impose significant limitations on ML algorithms. With insufficient information for accurate predictions, digital health management tools are restricted to data analytics or heuristic algorithms. These can provide a high-level overview of trends and patterns but cannot capture the nuances of individual cases.

We drill down into the three ML techniques later. But put simply, deciding which approach to use depends on two factors: the output requirements (the intent of modelling / end-goal of the digital tool) and, more importantly, the available input data. Figure 5 summarises key factors and considerations to be aware of during the decision-making process.

		Data Analytics / Heuristic Algorithm	Traditional Machine Learning	Deep Learning	Reinforcement Learning
Input Data	Static Dynamic Longitudinal	Generally rule-based and reliant on human-defined heuristics to make decisions (cannot handle multiple input datatypes). Used for trend analysis in longitudinal data, filtering in medical imaging, and statistical analysis in mobile sensing, self-reported and text data.	More flexible than heuristic algorithms, but still requires feature engineering and does not adapt to changing distributions. These models can handle simple structured non-longitudinal data, such as mobile sensing and self-reported data.	Highly flexible in handling a wide variety of input data, including complex clinical and genome data. However, vast amounts of data are required to train these models efficiently.	Most flexible in terms of handling different input datatypes, learning directly from raw sensory input and adapting to changing distributions. However, data collection is very demanding as specific dataset structures are required.
Output Data	Insight	Less flexible in terms of producing different kinds of insights since models rely on pre-existing rules rather than learning from data. Can be used to derive new insights from data to optimise performance of diagnostic and treatment solutions.	Whilst more flexible than heuristic algorithms, these approaches have limited ability to learn and adapt to new data, hindering the diversity of insights that can be produced. They can be used to assist in diagnosis and help identify people at risk of developing certain conditions.	Highly flexible, being able to learn and adapt to new data, therefore producing a wide range of insights. For instance, increasing the diagnostic accuracy in medical imaging and information extraction to improve decision-making.	These models learn from experience and adapt to new environments. However, they are typically used in scenarios with a well-defined goal, to limit the generation of different kinds of insights. Applications include provision of dynamic recommended actions for treatment solutions, and safe, controlled simulation of clinical environments and test treatment strategies.
	Personalisation	Basic level of personalisation such as personalised dashboards and visualisations.	Less flexible than deep learning and reinforcement learning models, but useful for a wide range of personalisation tasks such as patient segmentation.	High potential for personalisation tasks, especially when used in conjunction with techniques such as attention. These approaches excel in personalised image and voice recognition.	Agents learn from environmental interactions and can adapt according to personalised goals and rewards. Use cases include personalisation of treatment plans based on patient responses, preferences, values, and other factors.
	Predictive Element	These methods are typically used for descriptive analytics, rather than predictive or prescriptive analytics.	The predictive element is typically limited to a small set of predefined outputs that the models are trained to predict.	Greater predictive power and flexibility than traditional ML models, meaning they can solve more complex problems.	Rather than making direct predictions about future outcomes, these models learn a policy that can be used to predict which actions to take in new situations.

Figure 5: Factors to consider when defining the architecture for a connected health management solution.

Case study: sleep management

Sleep disorders are a prime candidate for ML-enabled health solutions. Conditions such as insomnia, breathing disturbances during sleep, movement disorders during sleep and sleep-wake dissociation disorders are extremely common in the general population. What's more, emerging research links lack of sleep to increased risk of other health conditions such as cancer, heart health problems, and more recently, dementia, Alzheimer's, and diabetes. Interest in sleep disorders has further increased following the pandemic due to its impact on post-COVID recovery.

In light of this, we set out to build a science-driven predictive digital solution for consumer healthcare and medical applications based on performance-oriented sleep modelling. We followed the key steps of our three-step development process and leveraged multidisciplinary capabilities from across Sagentia Innovation, including:

- Advisory expertise to review the science of sleep and prioritise the associated health conditions with robust clinical evidence and validated MoAs.
- Bioinformatics expertise to consider genetic and microbiome profiles.
- Data analytics and insights capabilities to review the accuracy and completeness of published sleep datasets, and build the predictive ML model.

Why improved digital solutions for sleep management are needed

Consumer healthcare products and services currently available for sleep management face various limitations and challenges. While many digital products and services exist for sleep monitoring, few address the 'so what?' factor to offer compelling and engaging consumer health intervention. What's more, the most significant health impacts associated with poor sleep emerge later in life, so there's little incentive for the longitudinal user engagement required to improve outcomes.

Step 1: Review clinical associations

We reviewed upstream and downstream health conditions associated with sleep disorders, as illustrated in Figure 6[1-38]. Then we evaluated associated clinical correlations (the level of clinical evidence and demonstrated MoAs) to differentiate between 'correlated' conditions and those with a stronger 'caused by/risk factor' link. Our evaluation included a review of the level, direction, and quality of clinical evidence.

Upstream

Causes of sleep disorders

Individual's health
- Medical conditions
- Medications
- Psychological / cognitive disorders
- Neurological conditions

Lifestyle factors
- Environmental
- Night shift work

Uncontrollable factors
- Genetics
- Aging

→

Sleep disorders

Non-diagnosed issues
- Short / long sleep duration
- Sleep deprivation
- Snoring

Diagnosed disorders
- Insomnia
- Sleep apnoea
- Parasomnias
- Sleep paralysis
- Restless Leg Syndrome (RLS)
- Periodic Limb Movements of Sleep (PLMS) / Periodic Limb Movement Disorder (PLMD)
- Circadian Rhythm
- Disorders
- Narcolepsy
- Hypersomnia
- Non-24-Hour Sleep-Wake Disorder
- Chronic Fatigue Syndrome

→

Sleep-related health conditions

- Cardiovascular conditions: CVD / CHD / myocardial infarction / stroke
- Metabolic disorders
- Cancer
- Immunity conditions
- Fertility issues
- Psychological / cognitive disorders
- Neurological conditions
- Gut dysbiosis
- Death / mortality

Downstream

Figure 6: Upstream and downstream conditions associated with sleep disorders.

Specific attention was paid to longitudinal studies and those involving measurable biomarkers, as opposed to studies that only focused on self-reported outcomes. We also reviewed other reported factors likely to affect these health conditions which should therefore be considered at the modelling stage (e.g., lifestyle).

Based on this analysis, we identified seven health conditions with a strong link to sleep disorders, supported by clinical data and with a clear, validated MoA. As indicated in Figure 7, these include:

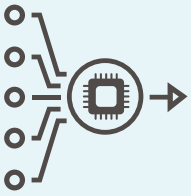
- CVD / CHD / myocardial infarction/stroke
- Hypertension
- Type 2 diabetes
- Obesity
- Mental health (depression)
- Gut dysbiosis
- Increased risk of cancer.

◆ Clear MoA
● Hypothesised MoA

Key to level of scientific evidence:
Strong link
Moderate link
Low link

Sleep issue	Sleep-related health condition													
	Cardiovascular conditions	Metabolic disorders					Immunity disorders		Psychological / cognitive disorders			Neurological disorders		
	CVD / CHD / myocardial infarction / stroke	Hypertension	Dyslipidemia	Type 2 diabetes	Obesity	Cancer	Inflammation	Fertility issues	Psychiatric disorders	Cognitive impairment	Mental health (depression)	Dementia	Alzheimer's	Gut dysbiosis
Short sleep	●	●		◆	●									●
Long sleep	●					●								
Poor sleep quality	●							●			●			●
Sleep deprivation		●												
Circadian rhythm disruption						◆								
OSA								●						
Non-apnoea sleep disorder								●						
Insomnia											●			
Narcolepsy														

Figure 7: Health conditions linked to sleep supported by clinical data and MoA.



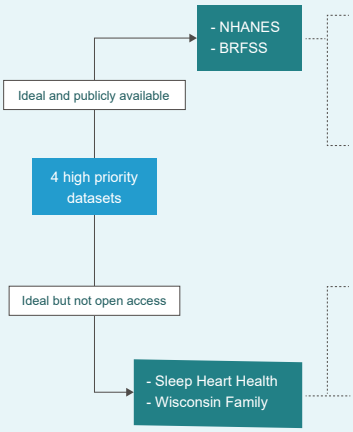
Step 2: Model design

With the review of clinical associations complete, we moved on to model design, beginning with the **definition of input data** for the predictive model. This involved the identification of 43 existing open-source and private datasets related to sleep (including datasets featuring genome and biomarker information). We used the criteria outlined in Figure 8 to assess the relevance and usefulness of each dataset.

Health condition	Availability	Type of Data		Features Contained
Includes data on **sleep linked with a priority health condition**: • Cardiovascular conditions (CVD, CHD, myocardial infarction, stroke) • Metabolic conditions (hypertension, Type 2 diabetes, obesity) • Mental health (depression) • Gut dysbiosis	Publicly available	Biomarker & Genome	Longitudinal dataset	High number of features related to relevant health conditions
Data on: • Priority health condition not linked to sleep data • Non-priority health condition	Private access (requires account and/or accepting agreement)	Biomarker or Genome	Non-longitudinal dataset	Moderate number of features related to relevant health conditions
Sleep-specific disorder	Private access only (requires research proposal)			Low number of features related to relevant health conditions

Figure 8: Criteria to assess the relevancy and usefulness of each dataset for a predictive model.

On this basis, we determined that four of the 43 available datasets were suitable for developing a predictive model related to a prioritised sleep-related health condition. This included two open-access datasets[39-42]. Figure 9 outlines specific characteristics of the datasets, such as sample size, focus, data type, and distinct features.



	Number of Participants	Health conditions linked with sleep	Availability	Type of Data			Distinct Features	Use in other predictive models
			Public access?	Biomarker	Genome	Longitudinal		
NHANES	7739	• Diabetes • Cardiovascular	✔	✔	✘	✘	• Physical Activity • Insulin Level • Total Cholesterol • High Blood Pressure • High Cholesterol Level	✔
BRFSS	523,087	• Diabetes • Cardiovascular • Mental Health	✔	✔	✘	✘	• General health Status • Depression • Heart Attack • Angina or Coronary • Heart health condition • Stroke • Height	✔
Sleep Heart Health Study	5804	• Obstructive • Sleep apnoea • Cardiovascular	?	✔	✘	✔	• Number of Congestive • Heart Failure since baseline • Diastolic and Systolic blood pressure • Apnoea-Hypopnea Index	✔
Wisconsin Family Study	300 families	• Mental Health	✘	✔	✘	✔	• N/A	✘

Figure 9: Priority datasets for developing a predictive model for the sleep-related health condition.*

**Open access data identified are restricted to non-longitudinal datasets, meaning that results provided by the models based on this data would not have a time component associated with them (non-temporal factors only).*

As Figure 10 indicates, this related to monitoring and understanding an individual's probability of suffering from a specified health condition based on sleep quality and/or other factors. The solution would be programmed to recommend healthier sleep or lifestyle habits accordingly.

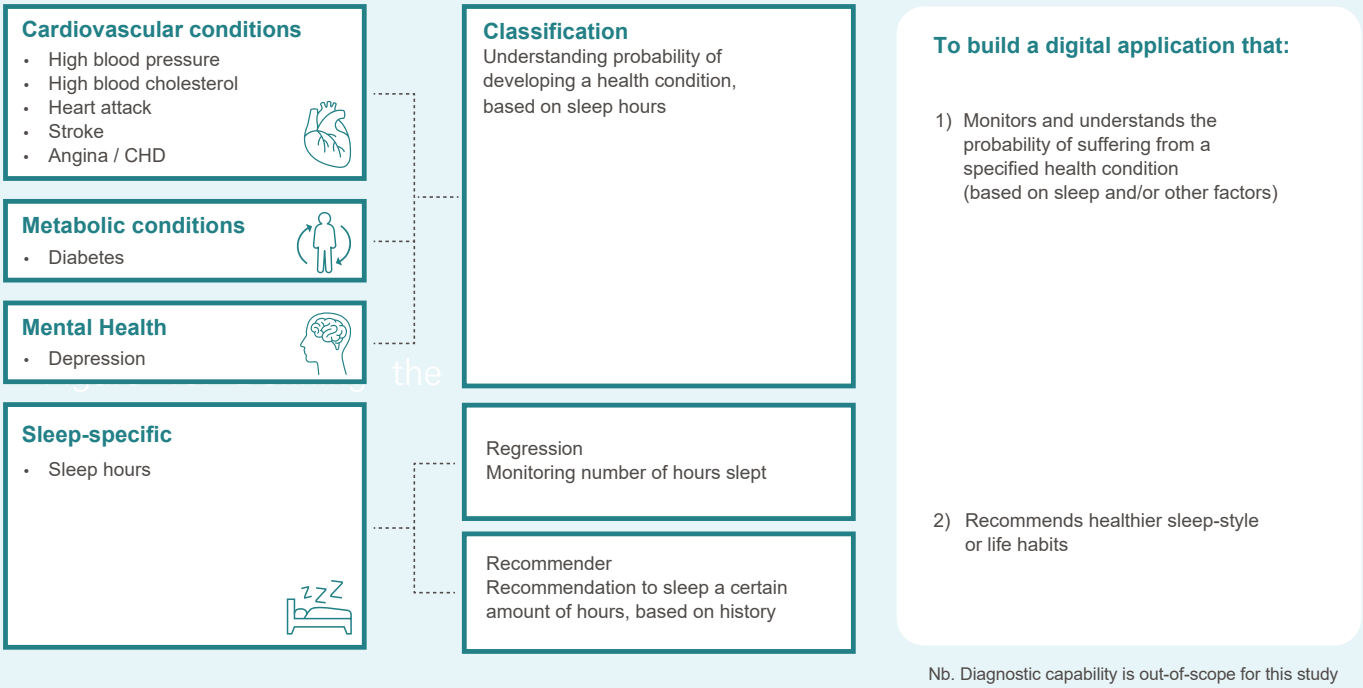
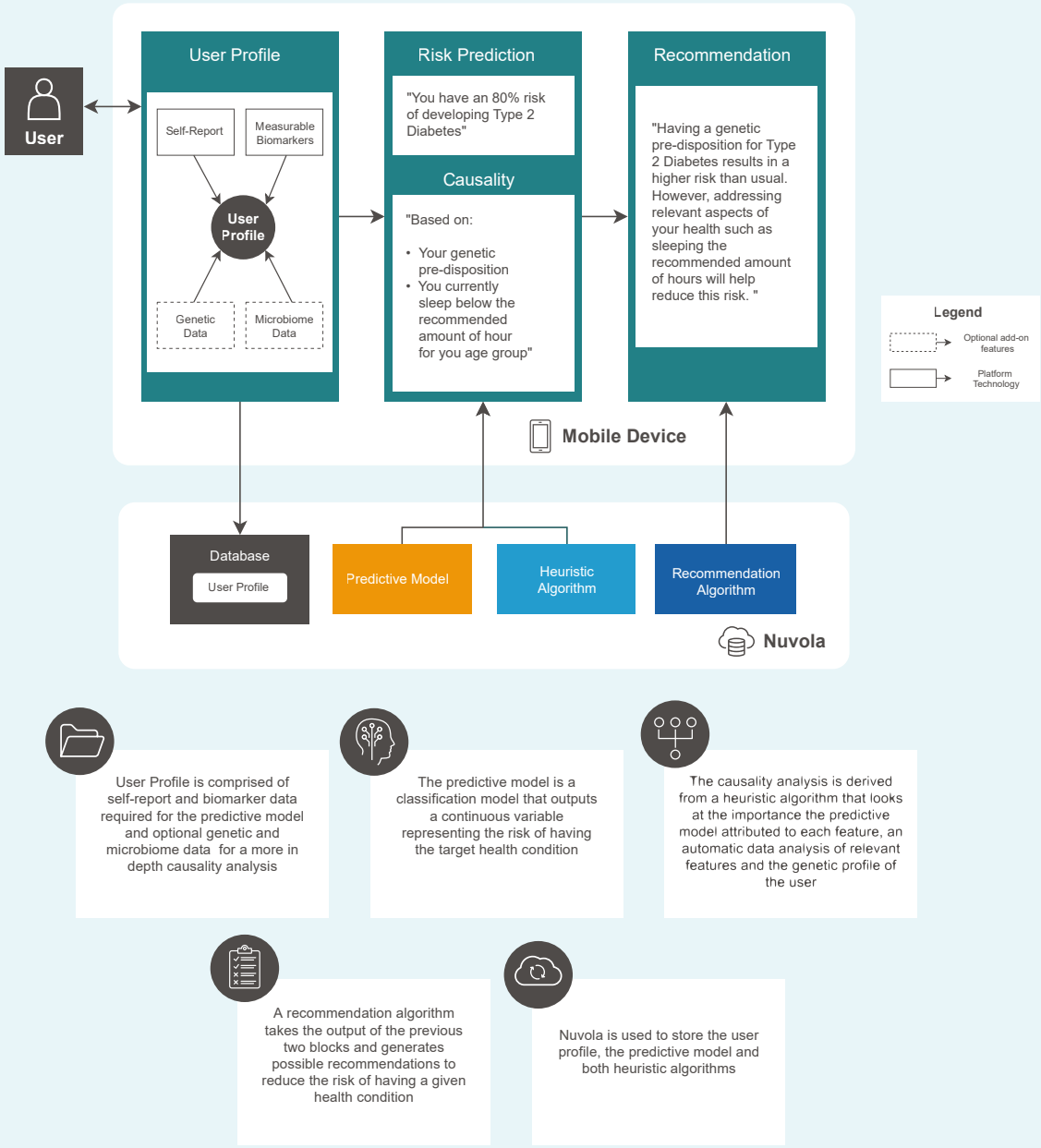


Figure 10: Defining the output data.

This in turn informed how we **defined the solution architecture**. Figure 11 offers a high-level view of how the consumer/patient would engage with the digital application via a mobile device and where the predictive, heuristic and recommendation elements/ blocks would come into play:

- Predictive model block: predicts the risk of the user having the target health condition.
- Heuristic algorithm block: attempts to explain this risk value by evaluating feature importance and the user's genetic profile, as well as the automatic output of exploratory data analysis.
- Recommendation algorithm block: produces contextualised recommendations based on the previous two blocks.



User Profile is comprised of self-report and biomarker data required for the predictive model and optional genetic and microbiome data for a more in depth causality analysis

The predictive model is a classification model that outputs a continuous variable representing the risk of having the target health condition

The causality analysis is derived from a heuristic algorithm that looks at the importance the predictive model attributed to each feature, an automatic data analysis of relevant features and the genetic profile of the user

A recommendation algorithm takes the output of the previous two blocks and generates possible recommendations to reduce the risk of having a given health condition

Nuvola is used to store the user profile, the predictive model and both heuristic algorithms

Figure 12 offers a more detailed illustration of the steps involved in each block of the digital application.

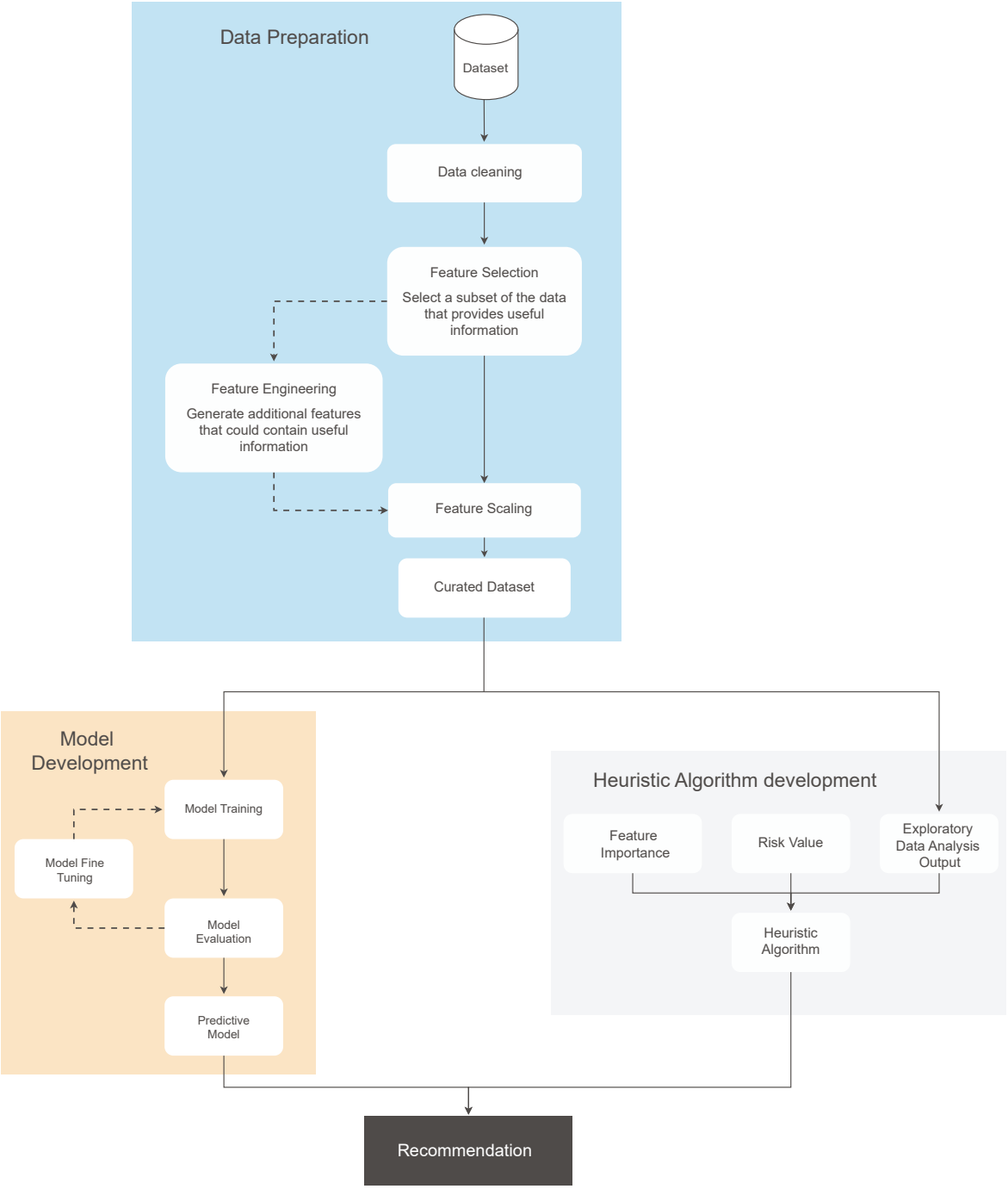
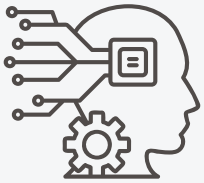


Figure 12: Detailed steps involved in each block of the digital application.

Deep dive into ML techniques



Traditional Machine Learning

With a dataset based on a large sample size and diverse datatypes, traditional ML algorithms can provide detailed output, enabling predictions and classifications based on specific data features. Other compelling reasons to make the transition from data analytics or heuristic algorithms to ML include longevity and scalability. For instance, over time, patterns and trends in data can change. This may result in the obsolescence of existing data analytics outputs or require significant modifications to heuristic algorithms. ML models are more adaptable, as they can be re-trained with new data and scaled to work with larger amounts of data. This allows the models to keep up with evolving data, whilst maintaining state-of-the-art performance.

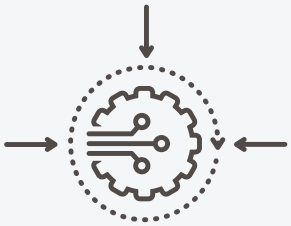
Nevertheless, highly complex datasets with many features and datatypes (e.g., lab results, medical imaging, biomarkers) and a long timespan can limit traditional ML algorithms. They may not be able to capture relevant factors that contribute to a particular health outcome, leading to inaccurate predictions and limited insights.

Deep Learning

With increased data complexity, a shift from traditional ML (e.g., decision trees, support vector machines) to deep learning, utilising neural networks, is required.

Deep learning algorithms can generate highly nuanced outputs. They can detect and account for subtle variations in the data, resulting in better accuracy and detail, which is particularly relevant in healthcare where increased granularity can underpin more informed decisions and better patient care. Advantages of deep learning in healthcare applications include:

- The ability to handle more complex and unstructured data, such as electronic health records, medical imaging, and genetic testing results.
- Automatic extraction of complex features from data without the need for manual feature engineering.
- More accuracy on prediction tasks and better adaptability to new data sources and technologies.
- The handling of temporal data and an ability to learn hierarchical relationships represented in data, handle missing data, and generalise to new types of data.



Reinforcement Learning

Reinforcement learning is a subset of ML that trains 'agents' through interactions with an environment. The agent is the component of the algorithm that learns and makes decisions. **It's important to note that reinforcement learning is an experimental technique; this brings inherent risks which must be handled very carefully in a healthcare context.**

While deep learning algorithms can provide detailed insights and predictions allowing for more accurate diagnosis and treatment recommendations, reinforcement learning takes this a step further. It enables the development of dynamic and interactive models that can continuously learn and adapt to new information. As such, it has the potential to provide personalised treatment plans for individual patients. Outputs might include a detailed map of a patient's health status and personalised treatment recommendations, which can be updated in real-time based on ongoing interactions with the patient and their environment.

The development of such models places significant demands on data complexity and structure. Reinforcement learning algorithms require extremely high-quality data and information on the consequences of each decision made by the agent in the environment. Furthermore, data must be structured to allow the agent to learn from past decisions and adjust accordingly.

The shift from deep learning to reinforcement learning in digital health management requires more dynamic and interactive data collection and processing. Methods must allow for real-time learning and adaptation of the agent's decision-making process. In turn, the developed solution is capable of dynamic decision making in response to changing conditions, which holds much potential for treatment planning and optimisation. Reinforcement learning models can also provide more transparent, interpretable results. In contrast, deep learning is typically used for tasks that involve static pattern recognition and models can be difficult to interpret due to their black-box nature.

Regulatory considerations

ML-enabled health solutions make different levels of claims and present different levels of risk. Requirements for clinical evidence and regulatory oversight vary accordingly.

The US Food and Drug Administration (FDA), Health Canada, and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have jointly identified ten guiding principles to inform the development of Good Machine Learning Practice (GMLP). The aim is to help promote the development of safe, effective, and clinically meaningful ML-enabled solutions[48].

GMLP principles range from the implementation of good software engineering and security practices for model design, to continuous re-training of deployed models, to the appropriate selection of training and test datasets, and data collection protocols. They emphasise the need for multidisciplinary expertise throughout the product lifecycle to ensure in-depth understanding of a model's intended use, desired clinical benefits, and associated risks. GMLP also covers the need to tailor model design to available datasets and intended use, to mitigate overfitting, performance degradation, and security risks.

One of the most important areas relates to data collection protocols, ensuring sample size and training datasets are representative of the intended population. This is where ML models can fail, so it's essential to adopt robust measures that allow results to be reasonably generalised to the population of interest.

ML-enabled devices must also comply with any FDA guidance for the specific device type. As of October 5, 2022, FDA has authorised the marketing of 178 AL/ML-enabled medical devices[49].

Let's consider this in relation to our sleep management case study. For instance, FDA's General Wellness Guidance applies to products that maintain or encourage a general state of health or health activity[50]. If a specific disease or condition is referenced, the product must explicitly state that it promotes, tracks, and/or encourages choices, which as part of a healthy lifestyle, may help to reduce the risk of the chronic disease or condition or may help living well with that chronic disease or condition. FDA provides two examples of disease-related general wellness claims that pertain to sleep:

1. *"Software Product V tracks and records your sleep, work, and exercise routine which, as part of a healthy lifestyle, may help living well with anxiety."*

2. *"Product Z tracks activity sleep patterns and promotes healthy sleep habits, which, as part of a healthy lifestyle, may help reduce the risk for developing type 2 diabetes."*

Sleep assessment devices are regulated as Class II devices which require 510(k) premarket clearance from FDA under product code LEL (Product Classification and 21 CFR 862.5050, which is the device classification regulation for Biofeedback Devices (CFR – Code of Federal Regulations Title 21))[51]. Given that FDA actively regulates sleep assessment devices, it is likely to require premarket authorisation for ML-enabled products which perform that function.

General regulations

Regulatory frameworks for digital health solutions vary based on their intended use and the level of risk. The level of verification, analytic, and clinical validation required for regulatory authorities and CE marking should be determined at the earliest possible stage[43]. Steps should be taken to ensure the quality, effectiveness, safety, and security of the application.

ML-enabled health solutions must be assessed for compliance with regulations like General Data Protection Regulation (GDPR), Medical Device Regulation (MDR) and Software as a Medical Device (SaMD) regulation. Suitable quality management processes have to be implemented and all health data must be protected and secured.

FDA does not regulate low-risk general wellness products (e.g., fitness and nutrition tracker apps that are not implanted and do not require invasive sampling). However, the Agency's narrow definition of such products means that the exception is limited.

Commercial considerations

Despite growing recognition of digital health solutions' clinical effectiveness, they do not easily dovetail with existing revenue models and funding pathways. This remains one of the major barriers to adoption.

Business models can be very different to those for traditional medicated solutions. Revenue streams might encompass new consumer engagement models or anticipate the adoption of new reimbursement policies[44,45].

If a solution is reimbursed by insurers, it signifies that it has undergone an in-depth quality review and complies with rules of market access. Nevertheless, even when doctors are willing to prescribe digital medicine (and patients are willing to use it), getting insurers to pay can be a challenge. **Pear Therapeutics**, which filed for bankruptcy in April 2023, is a prime example[46,52]. This company had three FDA-authorised prescription apps to help treat substance use disorder and insomnia (the first was FDA authorised via de novo review and the next two were cleared through the 510(k) premarket notification process). There were more than 45,000 prescriptions written for Pear's products in 2022. However, only around half were fulfilled and of those that were fulfilled, the company was only able to collect payment for 41%.

So, considering how insurers can be compelled to pay for the technology is a critical part of the development process. In the US a few commercial insurers pay for prescription software solutions (digital therapeutics), as do a handful of state **Medicaid** programs (government-funded health insurance for low-income Americans)[52]. However, **Medicare**, the government-funded health program for seniors, does not.

An alternative is to transfer digital medicine solutions cleared or approved for prescription to non-prescription, over-the-counter status (Rx-to-OTC switch). Sleep management solutions are potentially a very good use case for OTC in some markets, especially when combined into one package/ecosystem with a range of other OTC digital therapeutics. This could be developed as a platform subscription offering, used on-demand by consumers. It might involve a fixed price per month with options to select digital medicine according to current health needs, and it can also be incorporated into corporate health and wellness programs.

Treatment solutions for chronic conditions could particularly benefit from this approach. There are great opportunities for ML-enabled health solutions which involve a social interaction and communication with healthcare providers (HCPs) or clinicians. A three-way engagement (consumer – community health centre/pharmacy – company) provides additional opportunities to deliver the benefits of preventive self-care and inclusivity.

Another important consideration is that management of chronic diseases is overwhelmingly behaviour mediated. Treatment commonly involves long-term use of the therapy, and compliance is key to effectiveness. In many countries, only around half of patients with chronic diseases take their medication as instructed[53,54].

Digital solutions provide potential opportunities to increase therapeutic and non-therapeutic compliance to ensure long-term positive outcomes[55]. This could involve health apps and websites (including those with Cognitive Behavioural Therapy programs), activity-tracking devices, biomarker sensor devices, smart pill dispensing and packaging, and even digital pills.

Creating a viable model will likely require integration between several different players. This will include the model's actual user (patient or consumer), medical or consumer brands, ML-enabled solution providers, security companies, insurers, and HCPs/clinicians. Each player will also need to be incentivised to keep the user healthy. Development costs can be covered by optimising R&D and clinical activities through use of large datasets aggregated using the ML model. This might encompass identification and qualification of new biomarkers and targets, pre-clinical assessment of treatment impact, patient/consumer stratification, optimisation of clinical trial designs, optimisation of efficacy and tolerability of therapies.

Closing remarks

ML-enabled health solutions aggregate and process large datasets, providing unique opportunities to build predictive solution systems for health assessment and intervention. However, there are technical, regulatory, and commercial challenges to implementing these solutions as their complexity and the iterative and data-driven nature of their development present significant risks. Yet, with recent technological innovations, ML modelling is becoming too important to be excluded from predictive and preventive healthcare.

We are experiencing growing interest in this field from consumer health and medical clients alike. They are looking to explore the power of digital modalities to supplement (or sometimes even replace) traditional medicated treatment solutions as well as to provide direct-to-patient/consumer pre- and post-treatment support.

Nevertheless, commercial uncertainty surrounding the adoption of ML-enabled health is a significant concern. Companies need to understand the exact payment mechanisms to cover development and deployment costs and ensure revenue generation. A regulatory review of intended use, user interaction, and risk levels is also required at the early stage of solution development. This enables informed selection of relevant data collection protocols and determines the level of verification and clinical evidence required to ensure the effectiveness, safety, and security of the solution. Region-specific market assessment could provide further understanding of the differentiation and pricing required to gain competitive advantage and better integrate ML-enabled solutions within the existing product portfolio.

This is still a fragmented market with a lot of players exploring the possibilities and trying to make inroads. Building captive business ecosystems and partnering with external players, including companies with specialist expertise in ML/AI-enabled software development and medical device regulation, is an effective strategy. Leveraging multidisciplinary capabilities is the surest way to harness innovation and future growth in this rapidly progressing field.

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Definitions

Digital health -> a broad category that encompasses digital medicine, which in turn includes digital therapeutics.

Digital medicine -> the field of evidence-based digital health solutions, driven by software and algorithms, that measure and/or intervene to improve human health (to support the practice of medicine broadly, including treatment, recovery, disease prevention, and health promotion for individuals and across populations).

ML algorithm -> the procedure, the underlying mathematics behind an ML model.

ML model -> the application of an ML algorithm to a given problem. Once the ML algorithm is trained, we call it an ML model.

Reinforcement learning agent -> the agent is the component of the algorithm that decides what action to take.

About Sagentia Innovation

Sagentia Innovation is a science-led innovation consultancy serving consumer and industrial markets. Based in Cambridge and Epsom, UK, it combines deep science, technology and engineering expertise with robust market insight and sector knowledge. The company supports clients across the innovation lifecycle, from insight and strategy through design and invention to product development. Sagentia Innovation is part of Science Group plc.

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For further information visit us at:
sagentia.com/innovation or
email info@sagentiainnovation.com

Sagentia Ltd
Harston Mill
Harston
Cambridge
CB22 7GG
UK

Sagentia Ltd
First Floor
17 Waterloo Place
London
SW1Y 4AR
UK

Sagentia Inc
1150 18th Street
Suite 475
Washington
D.C. 20036
USA

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