

## Review

# Computational Models for Clinical Applications in Personalized Medicine—Guidelines and Recommendations for Data Integration and Model Validation



Catherine Bjerre Collin <sup>1</sup>, Tom Gebhardt <sup>2</sup>, Martin Golebiewski <sup>3</sup>, Tugce Karaderi <sup>4</sup>, Maximilian Hillemanns <sup>2</sup>, Faiz Muhammad Khan <sup>2</sup>, Ali Salehzadeh-Yazdi <sup>5</sup>, Marc Kirschner <sup>6</sup>, Sylvia Krobitsch <sup>6</sup>, EU-STANDS4PM consortium <sup>+</sup> and Lars Kuepfer <sup>7,\*</sup>

- <sup>1</sup> Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 N Copenhagen, Denmark; catherine.bjerre.collin@cpr.ku.dk
- <sup>2</sup> Department of Systems Biology and Bioinformatics, University of Rostock, 18057 Rostock, Germany; tom.gebhardt@uni-rostock.de (T.G.); maximilian.hillemanns@uni-rostock.de (M.H.); faiz.khan3@uni-rostock.de (F.M.K.)
- <sup>3</sup> Heidelberg Institute for Theoretical Studies gGmbH, 69118 Heidelberg, Germany; martin.golebiewski@h-its.org
- <sup>4</sup> Center for Health Data Science, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 N Copenhagen, Denmark; tugce.karaderi@sund.ku.dk
- <sup>5</sup> Max-Planck-Institute for Multidisciplinary Sciences, 37077 Göttingen, Germany; ali.salehzadeh-yazdi@mpinat.mpg.de
- <sup>6</sup> Forschungszentrum Jülich GmbH, Project Management Jülich, 52425 Jülich, Germany; m.kirschner@fz-juelich.de (M.K.); s.krobitsch@fz-juelich.de (S.K.)
- <sup>7</sup> Institute for Systems Medicine with Focus on Organ Interaction, University Hospital RWTH Aachen, 52074 Aachen, Germany
- \* Correspondence: lkuepfer@ukaachen.de; Tel.: +49-241-808-5900
- + Coordinator contact of EU-STANDS4PM; Membership of EU-STANDS4PM consortium is provided in the acknowledgements.

**Abstract:** The future development of personalized medicine depends on a vast exchange of data from different sources, as well as harmonized integrative analysis of large-scale clinical health and sample data. Computational-modelling approaches play a key role in the analysis of the underlying molecular processes and pathways that characterize human biology, but they also lead to a more profound understanding of the mechanisms and factors that drive diseases; hence, they allow personalized treatment strategies that are guided by central clinical questions. However, despite the growing popularity of computational-modelling approaches in different stakeholder communities, there are still many hurdles to overcome for their clinical routine implementation in the future. Especially the integration of heterogeneous data from multiple sources and types are challenging tasks that require clear guidelines that also have to comply with high ethical and legal standards. Here, we discuss the most relevant computational models for personalized medicine in detail that can be considered as best-practice guidelines for application in clinical care. We define specific challenges and provide applicable guidelines and recommendations for study design, data acquisition, and operation as well as for model validation and clinical translation and other research areas.

**Keywords:** personalized medicine; computational models; data integration; model validation; guidelines and recommendations; clinical translation; ethical and legal requirements

Citation: Collin, C.B.; Gebhardt, T.; Golebiewski, M.; Karaderi, T.; Hillemanns, M.; Khan, F.M.; Salehzadeh-Yazdi, A.; Kirschner, M.; Krobitsch, S.; EU-STANDS4PM consortium; et al. Computational Models for Clinical Applications in Personalized Medicine – Guidelines and Recommendations for Data Integration and Model Validation. J. Pers. Med. 2022, 12, 166. https://doi.org/10.3390/jpm12020166

Academic Editor: William J. Duddy

Received: 19 November 2021 Accepted: 20 January 2022 Published: 26 January 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

# 1. Introduction

The amount of personalized data in today's medicine is continuously increasing and holds great promises for both diagnosis and therapy at the single patient level. In the face of these complex and heterogenous data volumes, computational models support a functional understanding of the mechanisms and factors that drive certain diseases. Likewise, they allow the design of personalized treatment strategies in response to central clinical questions [1]. Computational models thus have the potential to translate in vitro, preclinical and clinical results (and their related uncertainty) into descriptive or predictive expressions. Over the last decades, the added value of such models, also called digital evidence, in medicine and pharmacology has increasingly been recognized by the scientific community [2,3], as well as regulatory bodies, including the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) [4–7]—irrespective of their ultimate use or application. Computational models are now integrated in different fields in medicine and drug development expanding from disease modelling and biomarker research to the assessment of drug efficacy and safety. In silico processing and interpretation of clinical measurements can be either data-driven or theory-based (Figure 1). Though, both concepts are rather complementary, and they share the common general requirements for data standardization and data documentation. Mechanistic models aim for a structural representation of the governing physiological processes in the model equations to support a functional understanding of the underlying mechanisms. Vice versa, data-driven approaches, such as machine learning (ML) and deep learning (DL), which use algorithms and models that try to mimic (human) intelligence and that are commonly referred to as artificial intelligence (AI) [8,9], aim for knowledge discovery in big data through multidimensional regression analysis. In consequence, mechanistic models require a structural understanding of a process, yet the demand for data can be limited. Concepts in machine learning, in turn, are fundamentally based on large data sets, yet these models do not necessarily need any prior functional understanding (Figure 1). Applied in personalized medicine, these modelling approaches allow stratification of patients into specific groups with similar characteristics - a prerequisite for advanced diagnosis, targeted therapies, and prevention strategies. In the following section, the most relevant modelling approaches for clinical applications in personalized medicine will be briefly introduced.



**Figure 1.** Computational concepts for patient stratification in personalized medicine. The modelling process starts with collection of data from various sources (data input). The two basic modelling tools are depicted as mechanistic models (theory-based) and machine learning (data-driven). Model analysis leads to either a structural reconstruction of physiological mechanisms that drive disease or to pattern identification from large data sets. The information obtained by these approaches can be used to generate knowledge for stratification of patients into specific subgroups facilitating discovery, diagnosis, and therapy in personalized medicine.

## 2. Modelling Approaches for Clinical Applications in Personalized Medicine

## 2.1. Mechanistic Models

The aim of a mechanistic model is to functionally understand, examine, and predict the emergent properties of individual components of a biological system and the manner in which they are coupled. It also predicts the complex non-linear dynamics of system variables and simulates the underlying dysregulations in processes that drive a healthy state into a specific disease. To deal with this complexity, various systems biology and systems medicine approaches have been developed. By incorporating biochemical, physiological, and environment interactions, these approaches produced successful results to understand the non-intuitive behavior of biological systems and especially of the human body [10-12]. Models are developed from available knowledge describing physical/biochemical relationships among species, and kinetic parameters are retrieved from data under investigation to mimic the biological reality. After calibration, simulations are performed that generate new hypotheses to design new experiments. If experiments validate model-based hypotheses, it will generate new knowledge, which may be used for constructing another model, thus iteratively improving the functional understanding. In this way, the systems-biology/systems-medicine approach iterates in data-driven models and model-driven experimentations. Models are an abstract representation of reality, and thereby their validity and usefulness depends on the context and assumptions being made. Modeling approaches have different levels of abstraction, predictive power, advantages, and limitations. Previously established concepts range from static molecular interaction maps and constraint based modelling to qualitative logic-based models to more detailed quantitative kinetic models. The choice of a model formalism depends on the availability of data, the type of research question and the size and structure of the system. The most relevant mechanistic models are described in the following section.

## 2.1.1. Molecular Interaction Maps

Molecular interaction maps (MIMs) are static models that depict the physical and causal interactions among biological species in the form of networks [13]. They serve as a knowledge-base containing information about different pathways and regulatory modules involved in a disease, such as Parkinson's [14] or signaling in cancer [15]. MIMs can be computationally analyzed using graph-theory concepts to identify network static properties such as (i) identification of the most influential nodes, (ii) community detection by a clustering approach, and (iii) link prediction for the discovery of hidden links. Furthermore, upon overlying expression data, such maps serve as visualization tools for the activity level of regulators and their targets of established disease markers, which will provide the simplest mechanistic visualization of data.

## 2.1.2. Constraint-Based Models

Constraint-based models, such as GEnome-scale Metabolic models (GEM), provide a mathematical framework to gaining an understanding of metabolic capacities of a cell, enabling system-wide analysis of genetic perturbations, exploring metabolic diseases, and finding the essential enzymatic reactions as well as drug targets [16]. GEMs have received substantial attention, and many investigations have been done about their applications in different aspects of medical sciences. This modeling approach has been applied to various fields, ranging from cancer [17] to obesity [18] and Alzheimer disease [19].

#### 2.1.3. Boolean Models

Boolean modelling (BM) is the simplest form of logic-based models where nodes (e.g., a gene, protein, a transcription factor, or microRNA, etc.) are described by one of two possible states: 1 (ON, activation) or 0 (OFF, inactivation) [20]. The regulatory relationship from upstream nodes (regulators) to downstream nodes (targets) are expressed by the logical operators AND, OR, and NOT. Such models do not require detailed kinetic data for parameter estimation, which makes them fit to apply to large biological systems and easier/quicker to calibrate/train with data. In the context of systems medicine, this approach is often applied for cancer research [21,22].

## 2.1.4. Quantitative Models

Quantitative modeling, such as the ordinary differential equations (ODEs)-based approach, quantitatively analyses the behavior of a biochemical reaction over time. It comprises a set of differential equations containing variables (which are quantities of interest, e.g., the concentration of biological species) and parameters that describe how the system responds to different stimuli or perturbations (an extensive resource of ODE models represents the BioModels database [23]). Parameter values are fixed and can be personalized by either each experimental setup or a patient to make a model match the given data. This approach describes biological-systems dynamics in detail; however, it usually applies for a single pathway or only a few reactions due to the requirement of detailed kinetic data for parameter estimations. In personalized medicine in the context of patient stratification, ODE models are applied for individual biomarker discovery [24], drug response, and tailored treatments [25].

## 2.1.5. Pharmacokinetic Models

Pharmacokinetic models are a particular application of ODE models that describe the concentration of a drug in plasma or different tissues. Drug pharmacokinetics are frequently used as a surrogate for drug-induced responses since they may be used to estimate on-target and off-targeted drug exposure and in turn a to-be-expected effect strength. They can either be described by compartmental pharmacokinetic (PK) modelling [26] or by physiologically based PK (PBPK) modeling [27–29]. Compartmental PK models, also referred to as population PK (popPK) models, are top-down models that derive an empirical model structure from plasma PK. Model building usually starts with a simple one-compartment model, which is extended by linear absorption as well as clearance rates. Changes in model structure such as peripheral compartments may become necessary during model development. There are domain-specific standard formats available to structure and share them, such as PharmML (Pharmacometrics Markup Language [30]) as an exchange format for the encoding of models, associated tasks, and their annotation in pharmacometrics. In contrast to compartmental PK approaches, PBPK modelling aims to reproduce the physiology of an organism at a large level of detail [29,31,32]. Different organs are explicitly represented in a PBPK model, and they are assigned specific physiological properties such as volumes, surface, composition, and blood-flow rates. PBPK modelling allows to integrate very diverse patient-specific information ranging from the molecular scale to physiological properties at the whole-body level. This is because of the large granularity of PBPK models, which may represent physiological information from different levels of biological organization. A frequent application for the individualization of PBPK models is their specification to represent specific cohorts of patients such as elderly [33] or diseased patients from a base reference model [34]. This benchmark usually represents an average individual with mean values of physiological parameters.

#### 2.1.6. Software Resources and Tools

In the following, we provide a list of widely used resources and tools for the construction, visualization, and simulation of MIMs, including qualitative and quantitative models and pharmacokinetic models (summarized in Table 1). The choice of a single resource or tool is difficult; however, some resources, e.g., OmniPath [35] and Regulatory INteraction Graph (RING) [36], retrieve interactions from multiple repositories, which can, for example, ease MIM construction. Similarly, each tool is designed to address specific challenges in modeling, e.g., CellNetAnalyzer (CNA) [37] can be used to easily simulate a model for large combinations of inputs and perturbations (tens of thousand), but encoding models with graphical view is time consuming. CellCollective [38] is a webbased simulation tool for community-driven model development and requires no complex mathematical equations to encode. Gene Interaction Network simulation suite (GINsim) [39] is a powerful tool for attractor analysis but for a large model and a large number of inputs and perturbations, it may not be ideal.

**Table 1.** Resources and tools used to construct MIMs, quantitative and qualitative models, and pharmacokinetic models.

<b>Research Field</b>	Resources	Tools	
	SIGnaling Network Open Resource (SIGNOR)	CellDesigner [46], Cytoscape & plugins [47], Molecu-	
	[40], Reactome [41], SignaLink [42], InnateDB	lar Interaction NEtwoRks VisuAlization (MINERVA)	
Molecular interaction	[43], Atlas of Cancer Signalling Network	[48], NaviCell [49], Newt [50]	
maps	(ACSN) [15], OmniPath [35], RING [36], Wik-		
	iPathways [44], Kyoto Encyclopedia of Genes		
	and Genomes (KEGG) [45]		
Boolean models	CellNetAnalyzer (CNA) [37], CellCollective	CNA [37], Genetic Network Analyzer (GNA) [48],	
	[38], GINsim [39], PyBoolNet repository [46],	CellCollective [38], GINsim [39], SQUAD-Boolsim	
	BioModels [47]	[49], BoolNet [18], Markovian Boolean Stochastic	
		Simulator (MaBoSS) [50], CellNOpt [51]	
Constrained-based mod- els	BioModels [47], BiGG (Biochemical, Genetic	COnstraint-based Reconstruction and Analysis	
	and Genomic knowledge base) [52], Human	(COBRA) toolbox [55], Sybil package [56], CO-	
	metabolic atlas [53], Virtual Metabolic Human	BRApy [57], ModelSEED [58]	
	[54]		
Quantitative models	BioModels [59], Java Web Simulation (JWS) [60],	COmplex PAthway Simulator (COPASI) [62],	
	Physiome Model Repository [61]	CellDesigner [63], JWS [60]	
Dharma colcinotia readala	PharmML (Pharmacometrics Markup Language	Monolix, SimCyp <sup>™</sup> , GastroPlus <sup>®</sup> , PK-Sim <sup>®</sup>	
	[30], Open Systems Pharmacology		
	Resources: comprises repositories of manua	ally curated causal interactions and published models	

Resources: comprises repositories of manually curated causal interactions and published models that can be used for the construction of new models. Tools: includes software programs with user interface to construct, visualize, or dynamically simulate the models.

Several tools and resources can be combined to workflows for model development, simulation, and publication. For example, a model could be constructed in CellDesigner [63], simulated in JWS Online [60] and published in BioModels [47]. Community-driven harmonization efforts led to several standards and formats that support the interoperability of the tools and resources. Over time, different, partially overlapping communities have been established, which take responsibility for the maintenance and development of the standards and formats. The Computational Modeling in Biology Network (COMBINE) community [64] develops standards to store and exchange computational models. Prominent examples are the Systems Biology Markup Language (SBML) [65], CellML [66] and The Systems Biology Graphical Notation (SBGN) [67]. Their standards are supported by many tools for MIMs and quantitative models. The Disease Maps Project [68] is a large-scale community with the goal to enhance the understanding of diseases. Their efforts focus on MIMs, including map and tool development. The consortium for Boolean models is CoLoMoTo (http://colomoto.org), which develops standards for model representation and exchange, especially SBML Qual [69].

## 2.2. Machine Learning and Deep Learning

Data-driven approaches treat the causal mechanism as unknown and aim to model a function that operates on large-scale data input to predict the outcome, regardless of the unknown physiological processes. Since the mechanisms operating in the systems being modelled, i.e., which factors together drive outcomes, are considered too complex to be determined, ML and DL are often referred to as black-box models. Consequently, the rationale for the outputs generated is inscrutable not only by physicians but also by the engineers who develop them. There are ambitious attempts to make data-driven models explainable or understandable [8] by providing information on underlying model mechanisms and the factors driving predictions. In the context of personalized medicine, this requires examination of the concepts of explainee, explanandum, and explanans, amongst others. For example, the explainee, the person to whom an explanation is addressed, e.g.,

a patient, clinician, or researcher, will determine what constitutes an appropriate explanation of model predictions [70]. The object of the explanation (the explanandum) is not the patient/the disease course but the model/the model's prediction, and the explanans that explains the prediction may in itself be complex mathematics. Clear causality is not provided, although explanations may make intuitive sense to explainees.

For example, models that provide post-hoc feature-importance visualisation often show age or pre-existing disease to be features that drive predictions toward a negative outcome. While this does not give information about causality, the explainee "provides" the causal link in his/her own interpretation of the explanation. Clear causal understanding is not provided, although data-driven models can be hypothesis-generating and can therefore provide clues to understanding. Understanding is epistemologically complex, but an explainee (for example, a biologist or a clinician) can be said to understand when they are in a position to move forward. For example, a post-hoc model providing visualization of the factors driving a clinical prediction for a patient can give a clinical sufficient understanding to move forward with recommending a clinical course of action to her patient [71]. A biologist can be said to understand when a biological area has been identified which seems to recur in model-prediction feature drivers; or a bioinformatician can be said to understand when reapplying the model's code and examining output.

The quality of such black-box models is assessed through the accuracy of their predictions, which are tested in a variety of ways. As a subset of AI, ML works cyclically and learns through experience and is largely used for prediction models and pattern recognition (Figure 1). A special case of ML that is used for integration of complex data such as omics and clinical data is DL. In DL, Deep Neural Networks can extract and process information from given data. DL mimics the human brain via connecting multiple artificial neurons in deep and densely connected layers [72–74]. ML/DL approaches provide an opportunity to move away from interpretive attempts to apply group-level associations and instead predict responses in individual patients, i.e., enabling more personalized medicine. Group-level associations, unlike individual-level predictions, are interpreted in a largely unstructured way for the treatment of an individual and may not provide the optimal treatment approach for that individual. Thus, classical group-based clinical studies and ML/DL approaches represent two distinct paradigms: the first provides information based on associations at the level of a patient group, while the second, the ML/DL approach, builds a prediction at the level of an individual patient [75,76].

ML attempts ever more accurate clustering or classification to a high level of accuracy and a high level of confidence. Different types of ML are employed as appropriate according to input data and the aim of analysis, i.e., according to the clinical question. ML approaches learn the theory automatically from the data through a process of inference, model fitting, or learning from examples [77]. ML can be supervised, unsupervised, or semi-supervised. Unsupervised learning has the potential to take all features into account, to comprise dimensionality reduction, permit feature elicitation, and big-data visualization, all of which allow for better understanding of big medical data and the factors driving disease initiation and progression. Unsupervised learning offers the ability to discover new knowledge, which can be used to refine outcome prediction for the individual patient. In supervised learning, the model is supplied with labeled input features that are considered when predicting a predetermined outcome from new data, either through regression (for continuous results such as number of days or months before disease debut) or classification (for discrete results such as survival/death or for image classification). Supervised ML clinical-decision support tools allow ML the possibility to tailor prediction to the individual patient. Semi-supervised learning employs both labelled and unlabeled data for training. In all of these ML approaches, model validation is essential, and the accuracy of ML results is verified using independent test sets [74].

Even though best practices of ML have been developed, they are either not applied at all or applied only partially for selected aspects of the models, meaning an inconsistent or incomplete documentation and reporting as well as sharing of ML models and their evaluation [78]. This issue often results in vague and inconsistent decision making by the ML algorithms when re-used, making it difficult or even impossible to reproduce the results, with many uncertainties [79]. Particularly in clinical research and application, it is absolutely mandatory to develop and report ML/DL-derived models following established standards for gaining trust in the resulting decision making. In this context, especially reporting guidelines for the corresponding models and their validation are most relevant providing a list of attributes and elements to describe them properly. Recent examples are the SPIRIT-AI [80] and CONSORT-AI [81] checklists for the reporting of clinical trials that involve ML methods. The AIMe registry for AI in biomedical research (https://aime-registry.org) recently has been introduced as a community-driven platform for reporting biomedical AI systems [82]. The AIMe registry has a web interface that guides authors of new ML algorithms through the newly developed AIMe standard, a generic minimal information standard that allows the reporting of any biomedical AI system and is divided into five sections: Metadata, purpose, data, method, and reproducibility.

# 3. Models in Clinical Research for Discovery, Diagnosis, and Therapy

It is to be expected that patients will greatly benefit in the future from developments that equip personalized medicine with predictive capabilities to investigate in silico clinically relevant questions. Currently, there are a number of computational-modelling approaches in pre-clinical and clinical research that are able to address these questions in greater detail and, therefore, play a leading role for the future development of personalized medicine. The following section contains an illustrative overview of successful computational analyses in the discovery, diagnosis, and therapy of clinical research.

### 3.1. Discovery

Model applications in discovery are usually mechanism-based, such as MIMs, GEMs, BMs, and ODEs, since they are frequently hypothesis driven. This is because the availability of data at this level is commonly not sufficient for purely data-driven analyses. Mechanistic models in discovery play a significant role in a wide range of clinically relevant questions ranging from representation of disease mechanisms to identification of drug targets or simulations of disease-specific phenotypes (summarized in Table 2):

Research Field	Content				
	Molecular interaction maps				
Inflammation	Knowledge-base, disease mechanisms, data interpretation [83]				
Neurodegenerative disease	Knowledge-base, disease mechanisms, data interpretation [14]				
Cancer	Knowledge-base, disease mechanisms, data interpretation [15]				
Rheumatoid Arthritis	Knowledge-base, critical nodes (drug targets) [84]				
Asthma	Disease mechanisms [85]				
Atherosclerosis	Disease mechanisms, data interpretation, critical nodes (drug targets) [86]				
	Boolean models				
Cancer	Disease mechanism, patient stratification [17]				
Type 2 diabetes	Disease mechanism, patient stratification [87]				
Obesity	Disease mechanism, patient stratification [18]				
Non-alcoholic fatty liver disease	Disease mechanism, patient stratification [88]				
	Genome-scale metabolic models				
Cancer	Disease markers, drug targets, patient stratification [22]				
Auto-Immune diseases	Target identification, biomarkers, patient stratification [89]				
Cancer	Personalized combination therapy [21]				
Cancer	Disease signature, drug targets, patient stratification [90]				
Cancer	Disease markers, drug targets, patient stratification [22]				
Auto-Immune diseases	Target identification, biomarkers, patient stratification [89]				
Cancer	Personalized combination therapy [21]				

Table 2. Examples for mechanistic modelling in discovery.

A recently published map on inflammation resolution provides functionality to visualize Omics data and allows making hypotheses on the role of connected molecules in a disease phenotype [83]. Another well-known example for MIMs is the disease map of Parkinson's [14]. These maps serve as a knowledge platform and represent the mechanisms of the disease in a standardized visualization. Thereby, they structure the growing knowledge of the field in a comprehensible manner. Another interesting example of MIM is the atlas of the cancer signaling network [15], which depicts in detail the molecular mechanisms involved in cancer. High-throughput data can be visualized on the map to perform functional analysis and identify dysregulated pathways. Wu et al. constructed a comprehensive molecular interaction map for rheumatoid arthritis containing detailed molecular mechanisms of the processes in patients affected by rheumatoid arthritis [84]. The map was analyzed for topological properties to suggest diagnostic and therapeutic markers for rheumatoid arthritis.

Disease-specific GEMs were used for the identification of biomarkers and drug targets in metabolism-related disorders including: cancer [17], type 2 diabetes [87], obesity [18], non-alcoholic fatty liver disease (NAFLD) [88], and Alzheimer's disease (AD) [19]. In 2017, Uhlen et al. generated GEMs of 17 types of cancer by integrating transcriptome data into a network of human metabolism using the task-driven integrative network inference for tissues (tINIT) method [91]. In addition to predicting driver genes for tumor growth, they demonstrated a widespread metabolic heterogeneity in different patients, highlighting the necessity of personalized medicine for cancer treatments [17]. Varemo et al. generated manually curated GEMs to identify signatures of a diabetic muscle. They suggested a gene signature, which successfully classified the disease progression of individual samples [87]. Mardinoglu et al. (2013) reconstructed an adipocyte-specific GEM and showed that the metabolic activity of androsterone and ganglioside GM2 increased in obese subjects, and their mitochondrial metabolic activities decreased compared to lean subjects [18]. They also identified chondroitin and heparan sulphates as suitable biomarkers for the staging of NAFLD by analyzing the reconstructed iHepatocytes2322 [88]. In 2014, Stempler et al. reconstructed an AD-specific GEM and predicted several metabolic biomarkers of the AD progression, including succinate and prostaglandin D2 [19].

Patient-specific data have been integrated in Boolean models amongst others to simulate patient disease phenotypes and to identify disease signatures and drug targets and subpopulations of responders and non-responders to drug treatment [22,89]. Recently, another interesting study used Boolean models to integrate patent data to derive a personalized model, which can reproduce and analyze the gain-of-function or loss-of-function of mutated genes in specific diseases [21]. The model predicted dissimilarity in the PI3K-AKT pathway that resulted in heterogeneity in pancreatic cancer patients. Models also successfully simulated the known dynamics of invasive cancer in the breast and the bladder and predicted disease signatures and possible therapeutic targets that can revert invasive to non-invasive phenotypes [90]. Further, model-predicted signatures were used to stratify patients in long and short survivals.

ODE models have been used to simulate clinical trials and to propose individualized diagnostic and therapeutic targets, such as highly heterogeneous prognostic markers for neuroblastoma and patient stratification into low and high survival based on model simulations [92]. They were also used to predict the patient response to apoptosis-inducing therapeutics and revealed significantly different inter-individual responses [93].

## 3.2. Diagnosis

In diagnosis, the amount of personalized data is frequently sufficient to allow application of ML/DL concepts. In addition, the provided data types are often too heterogeneous, such that a structural presentation of the governing processes is impossible due to an incomplete functional understanding. ML/DL models can make discoveries by analyzing large sets of input data to identify patterns and associations relevant to the outcome of interest. These computational models can function as clinical-decision support systems to assist clinicians in diagnosis and therapy [94,95]. In the following, successful examples for the analysis of patient data with concepts from ML/DL are discussed (summarized in Table 2):

ML has been shown to be an effective analysis tool in a wide variety of medical and biological disciplines. The use of ML models may lead to a better understanding of diseases and the mode of action of drugs as well as to precision medicine. Mason et al. showed that optimized therapeutic antibodies can be found by predicting antigen receptor specificity with ML. It aids in integrating information from several individual receptors into a single pan-receptor model [96]. In metabolomics, Goodwin et al. used Self-Organizing Maps (SOM) to structure microbial metabolic responses, and hence, were able to identify a response metabolome [97].

Thorsen-Meyer et al. showed that a time-sensitive ML model can help predict 90-day mortality in patients administered to the intensive-care unit. In addition, they were able to highlight features contributing to a certain prediction at any time-point, allowing a physician to alter treatment. A further prominent example of ML/DL in clinical application is image analysis [98,99]. ML image analysis is most commonly used for radiological assessment and related decision making in the clinic, and models used can be categorized as either classification tasks or regression models. In the most commonly used classification tasks, models make decisions about categorical end-points such as a disease score or whether a clinician should take a closer look at an X-ray scan. In regression models, the aim is to predict a continuous variable, for example, the survival time of a patient, which often is not categorized into distinct portions. In 2018, Abramoff et al. debuted the first FDA-autonomous AI diagnostic system in medicine [100]. This development marked a milestone as ML models only assisted physicians in their diagnostic decisions previously. Abramoff et al. developed a convolutional neural network (CNN) that was able to correctly classify diabetic retinopathy with a sensitivity of 87.2% and a specificity of 90.7%. In recent months, ML has been widely used to diagnose and detect COVID-19-induced lung pneumonia (i.e., novel COVID pneumonia (NCP)), in computed tomography (CT) images. Zhang et al. developed a multi-scale approach that can not only distinguish NCP from other forms of lung lesions but also predict the progression of a patient into critical illness [101]. They were also able to correlate the features detected in segmented lung scans to clinical parameters like serum C-reactive protein (CRP) and albumin levels.

Another important example for the use of ML models in clinical application is polygenic risk scores (PRS) for common diseases based on findings from genome-wide association studies (GWAS). PRS are estimated to predict the risk of an individual for having a disease based on the individual's genetic make-up. GWAS that scan the genomes of thousands of individuals offer a very powerful method to identify the multiple genetic risk factors for having the disease that are used in PRS estimation. The potential of PRS is that it can aid in disease prevention and early diagnosis as well as precision medicine, leading to better health outcomes for individuals. There are currently different approaches developed for the estimation of PRS that may lead to some improvement over the other [102–112]. Examples of PRS studies include those on educational attainment [113], schizophrenia [114,115], diabetes [116–118], blood pressure [119], depression [120], coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer [102,116]. Table 3 provides an overview of the discussed modelling approaches and their application in clinical diagnosis.

<b>Research Field</b>	Content		
	Deep Learning and Convolutional Neural Network Models		
Ophthalmology	The first FDA-authorized autonomous AI system for the detection of diabetic retinopathy [100]		
Radiology	DL based model that is able to detect COVID-19-induced pneumonia on chest X-ray images [101]		
Ophthalmology	Two models for quality assurance and diagnosis of diabetic retinopathy on retinal images [121]		
De the allower	Assistance to pathologists for improving classification of lung adenocarcinoma patterns by automati-		
Pathology	cally pre-screening and highlighting cancerous regions prior to review [122]		
Imaging flow cytometry	Automated image de-blurring of out-of-focus cells in imaging flow cytometry [123]		
Ophthalmology	A DL model for the diagnosis of glaucoma based upon images and domain knowledge features [124]		
Oncology	Automated detection of oral cancer on hyperspectral images [125]		
	Deep Learning and Deconvolutional Neural Network Models		
Drotoomico	Neural network that is able to predict signal peptides (SP) from amino-acid sequences and distin-		
Froteonnics	guish between three groups of prokaryotic SPs [126]		
Antihadu anginagring	Prediction of antigen specificity via DL, which leads to optimized antibody variants for therapeutic		
Antibody engineering	purposes [96]		
Intensive care	ML analysis of time-series data in intensive care units led to an improvement in the prediction of 90-		
intensive care	day mortality [71]		
Deep Learnii	ng, Machine Learning, Random Forest, and Deconvolutional Neural Network Models		
Peychiatry	A model that detects autism spectrum disorder risk for newborns with up to 95.62% from electronic		
1 Sychiatry	medical records [127]		
Neurology	A study with the aim to differentiate between cognitive normal people and patients with Alz-		
	heimer's disease using various ML/DL techniques on blood metabolite levels [128]		
	Machine Learning and Polygenic Risk Score Models		
Coronary artery disease	Patients with high genome-wide PRS for coronary artery disease may receive greater clinical benefit		
coronary artery disease	from alirocumab treatment in the ODYSSEY OUTCOMES trial [102]		
Coronary artery disease,	Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to		
atrial fibrillation, type 2 dia-	monogenic mutations. Use of PRS to identify individuals at high risk for a given disease to enable		
betes, inflammatory bowel	enhanced screening or preventive therapies [116]		
disease, and breast cancer	entancea sereenmig of preferance atemptes [110]		
Machine Learning, Self-Orga	anizing Maps, Random Forest, K-Nearest Neighbors, Support Vector Machines, Self-Operating Maps		
Metabolomics	SOM analysis of response metabolites detected by mass-spectroscopy leads to the identification of		
	similar responses (ML/Self, Organizing Maps (SOM)) [97]		
Imaging flow cytometry	An open-source toolbox for the analysis of imaging flow cytometry images (ML/RF) [129]		
Radiology	Classification of COVID-19 and non-COVID-19 patients based on features extracted from chest X-ray		
En de min ele ma	Images (NIL/KINN) [130] Dradiation of diskates based on second blood values on d other nations in diaco (MIL/CVIM DE) [121]		
Endocrinology	Prediction of diabetes based on several blood values and other patient indices (ML/SVM,KF) [131]		
Metabolomics	source analysis of response metabolites detected by mass-spectroscopy leads to the identification of		
	CNN: Convolutional Normal Normale De Dandom Earost DNN: Deconvolutional Normal Nor		
	work SOM: Solf Operating Mans, SVM: Support Vector Machines, KNN: K Magreet neighbors, DPC		
	work, John Jen-Operating waps, 3 vivi. Support vector watchines, KIVIN. K-mearest heighbors, FKS:		

Table 3. Examples for the application of machine learning and deep learning algorithms in diagnosis.

Polygenic Risk Score.

Further technical details about different ML/DL methodological approaches commonly used (such as convolutional neural network (CNN), random forest (RF), support vector machines (SVM), and K-nearest neighbors (KNN)) and current best-practice recommendations, especially for biological applications, were reviewed and discussed elsewhere in detail [74]. The Polygenic Risk Score Task Force of the International Common Disease Alliance also published a recent comprehensive perspective on PRS with regards to the current application of PRS and challenges faced for improved use in clinical practice [132].

## 3.3. Therapy

Applications in therapy are rather mechanism-based since a functional understanding in the resulting computational simulations is mandatory for exhaustive risk assessment, e.g., in clinical-trial simulations. Moreover, extrapolation between different patient cohorts, treatment schedules, or even species is a frequent requirement in pharmaceutical development. Illustrative examples for applications of mechanistic modeling in therapy are discussed in the following section and summarized in Table 4.

Table 4	. Example	es for	mechanistic	modelling	in therapy.
---------	-----------	--------	-------------	-----------	-------------

<b>Research Field</b>	Content			
Mechanistic Models				
Pediatrics	Pediatric extrapolation [28]			
Geriatrics	Geriatric extrapolation [33]			
MIPD	Prediction of personalized drug exposure [133]			
	Prediction of the incidence rates of myopathy in different genotypes			
rnarmaco-genomics	[134]			
Disease models	Prediction of drug PK in cirrhotic patients [135]			
MIDD. Model informed presision desing DK. Dharmaselinetic				

MIPD: Model-informed precision dosing, PK: Pharmacokinetic.

PBPK models can be used to support pediatric investigation plans [28], where PK profiles in children, toddlers, or neonates are simulated based on a reference PBPK model for average grown-ups. The wealth of such pediatric extrapolations lies in the fact that children are not just small adults but differ amongst others in terms of their body composition (fraction of water, fat, and protein, respectively) and a resulting change in drug distribution within various tissues. Similarly, maturation of absorption, distribution, metabolism, and excretion (ADME) of proteins has a significant effect on drug PK in different age groups. Another prominent example for specifications of PBPK models are patient cohorts with hepatic or renal impairment [136,137]. PBPK models for such patient subgroups can be used to simulate and analyze the effect of reduced drug clearance and to assess the resulting increase in drug exposure, which may lead to adverse events. For cirrhotic patients, such concepts have been used to represent pathogenesis according to the Child-Pugh score A to C in terms of, for example, ADME gene expression, plasma protein concentration, or glomerular filtration rate (GFR) rates. Pediatric extrapolations or patients with impaired drug clearance are not fully-personalized models, but they represent an important conceptual application for knowledge-based individualization of mechanistic computational models.

Another concept in pharmacology that is even closer to personalized medicine is model-informed precision dosing (MIPD). MIPD is currently only applied to a few drugs that are subject to therapeutic drug monitoring and for which appropriate PK models are available. Of note, such models basically require the creation of virtual twins, which are individualized based upon information well beyond population demographics [133]. In a recent study, the benefit of using individual patient information to improve PK predictions was systematically assessed [138]. A PBPK model of caffeine was stepwise personalized by using individual data on (i) patient biometry, (ii) patient physiology, and (iii) *CYP1A2* phenotype of 48 healthy volunteers participating in a single-dose clinical study. Model performance was benchmarked against a caffeine base model simulated with parameters of an average individual. The key outcome of the analysis was that consideration of subject-specific data in personalized PBPK models may increase the accuracy of the PBPK predictions but that the degree of improvement is largely dependent on the match between the patient data and the specific pharmacology of the drug.

### 4. Challenges and Recommendations

As outlined above, considerable results have already been achieved with computational models in personalized medicine. However, there are still significant challenges until a full adoption of model-based workflows in clinical research and practice will be reached. Interestingly, despite obvious technical differences between the computational concepts in mechanistic modelling and ML/DL, challenges regarding data availability/harmonization, model development/validation as well as standardization, model reuse and reporting are common to both fields.

## 4.1. Challenges

## 4.1.1. Data Availability and Data Harmonization

The first step in generating a model is collating the data that need to be integrated into the model. This task heavily relies on the data being formatted and annotated correctly. Reporting and annotation checklists, or "minimum information guidelines" are available for many different kinds of datatypes and can be found and accessed via the FAIRsharing portal (www.fairsharing.org). For availability and data harmonization, both mechanistic modelling and ML/DL fundamentally rely on clinical measurements for both model development as well as independent model validation. A significant challenge for data availability is confused reporting, which makes it difficult to harvest the full benefit of results, navigate the biomedical literature, and generate clinically actionable findings (Varga et al. 2020, under review). As a putative consequence, incomplete sets of data may arise such that specific features have to be left out of the analysis or missing data have to be imputed. Another challenge, particularly in multicentric studies, is the heterogeneity of input data from different laboratories, which, as such, significantly hampers the comparability of results as well as subsequent analyses. Metastandards, such as the novel ISO 20691 "Biotechnology-Requirements for data formatting and description in the life sciences" (https://www.iso.org/standard/68848.html), help in guiding through the consistent formatting and annotation of data used for modelling.

## 4.1.2. Model Development and Model Validation

A common challenge for model development and model validation is that all computational models are highly context specific; therefore, they cannot be generalized for different scenarios due to limited extrapolability. Common to all in silico models is a need for validation [139] and predictive accuracy. However, model-validation methods are considered to be individual and type-specific. It is important that any algorithm performs well on novel data that have not been used in training the algorithm; i.e., the model should be able to generalize to new data from the same domain [140]. Uncertainty in model parameters as well as inter-individual variability are hard to assess as such significantly impeded model identification. Likewise, there are errors in basic model structure from prior assumptions, group associations, or pre-determined correlations in clinical relationships, which may bias outcomes. For many types of models and corresponding formats, the model setup and simulation environments can be documented in a standardized format, the Simulation Experiment Description Markup Language (SED-ML) that was designed to record such descriptive information necessary to re-run a model, such that it can be exported from one simulation tool and imported into another.

#### 4.1.3. Model Standardization, Model Re-use, and Reporting of Results

Model standardization, model re-use, and reporting of results are also largely hampered by the context specificity of most models. Moreover, many software tools still do not provide open-access rights, long-term maintenance, versioning, or standard software qualification. Likewise, very frequently, best practices are often not applied routinely, even if they are available and supported by several tools, such as the COMBINE archive for simulations [141]. In consequence, there is a lack of practice for standardization model development and the use of community defined formatting standards including Extensible Markup Language (XML)-based machine-readable formats for the model itself. Notable exceptions are SBML as a standardized interchange format for computer models of biological processes; CellML, a standard format to store and exchange reusable, modular computer-based mathematical models; or NeuroML (Neural Open Markup Language), which allows standardization of model descriptions in computational neuroscience and others [142].

## 4.1.4. Legal and Ethical Issues

Legal and ethical issues include data protection and the anonymity of patient data. Additionally, questions of liability may arise in the case of malfunction, which may be hard to address, and are particularly a constant matter of debate [143]. Legal aspects are largely covered by the general data protection regulation (GDPR). Challenges for computational modelling arise, for example, in data minimization, especially in data-driven models where it is not known which data will be necessary. Likewise, proprietary aspects of data and models may be of relevance. Finally, it may be important to exclude that important decisions are made by automated processing including the right to transparency.

In essence, computational models must go through a process of peer review and validation, and if they are to be adopted by clinicians, they must be assessed through research and state procedures including randomized clinical trials (RCTs) and medical devices regulation (MDR). Source input data should fulfill standard requirements in terms of data quality and representativeness, i.e., for example, inclusion of people of different genders or ethnicities. The generation of large amounts of knowledge about patients beyond the issue patients seek treatment for may be problematic, in particular since this explicitly implies the "right not to know." Additionally, the success rates for translatability into clinical practice should be openly communicated to the patients.

#### 4.2. Recommendations

The four key challenges discussed above can be used to formulate a set of recommendations that apply to different stages of a research project, starting from early ideation to implementation in clinical practice. The recommendations will be discussed in the following (illustrated in Figure 2). Inevitably, these recommendations may remain a little generic for specific studies, given already the complementary character of mechanistic models on the one hand and data-driven approaches on the other. However, the reader is encouraged to compare the recommendations given here in the face of the various examples discussed above (Tables 2–4). Additionally, some of the software packages discussed provide best-practice guidelines for study design as well as online resources (Table 2), which can be used for their own applications.



**Figure 2.** Basic recommendations for the use of computational models from early ideation to implementation in clinical practice. For each of the four key challenges (outer circle), a specific set of basic recommendations is given in the corresponding color. Stand.: Standardized.

## 4.2.1. Study Design

At the start of a research project, the study design itself should be defined and agreed on. Additionally, it should be decided whether the to-be-expected amount of data on the one hand and the structural knowledge of the underlying relationships on the other indicates the use of either ML/DL or mechanistic modelling. Ideally, an analysis plan should be formulated to address specific requirements and, above all, to meet the clinical needs of a study. Such preparatory discussions about the study design also support early involvement of all stakeholders and, in particular, their expertise in an interdisciplinary project team. This early-project stage also involves the definition of clear rules about general data protection regulation (GDPR) compliance and data ownership. Additionally, it should be agreed whether the automated processing of data by systems including models is allowed or ruled out such that the physician makes the final decision.

## 4.2.2. Data Acquisition and Operation

To increase the diversity of data as well as the sample size, multicentric studies are clearly preferable. Additionally, data harmonization needs to be discussed and addressed at the beginning of a study. Informed consent of patients should be taken care of as well. It should be communicated that data donation for the good of future patients and that consent to treatment implies consent to one's data being processed. Acquisition of patient data also should include structured and standardized reporting of all relevant clinical characteristics measured as well as patient anthropometry, physiology, disease state, and other phenotypic information and further influencing factors. This disease and phenotype information should be shared, respecting data privacy where applicable, and following a standardized structuring format, such as Phenopackets (http://phenopackets.org), linking phenotype descriptions with disease, patient, and genetic information, enabling clinicians, biologists, and disease and drug researchers to build more complete models of disease. If possible, electronic health records of patients should be used, for seamless data interoperability ideally formatted in accepted standard formats, such as Fast Healthcare Interoperability Resources<sup>®</sup> (FHIR<sup>®</sup>; http://hl7.org/fhir/) of the health-care standards organization Health Level Seven International (HL7). Data should be as comprehensive and unbiased as feasible, rather than using selected data based on potentially flawed existing knowledge. Additionally, data should be available in both processed and unprocessed forms. Data used in creating models and in applying them must be representative, comparable, fairly sourced, and logically analyzed. Representativeness and completeness of data point towards state collection of standardized, harmonized data across the population, provided as a non-commercial resource to research projects, which is the current system in many countries and is provided for by exceptions to the requirement for consent in specific national and EU legislation. Data input into models and model validation should be quality-checked thoroughly and on a running basis, with a high level of transparency, to achieve the best possible level of correct results for patients individually and collectively, as is the case with other tools used by clinicians.

#### 4.2.3. Model Development and Model Validation

For model development and validation, one should start with the simplest model structure, and if results are not sufficient, increase complexity in small steps. A key question during model building always is whether the model generalizes well enough and how it responds to unknown data. This follows the usual concept of training and validation. In general, simulation outcomes should be compared to standard measures for benchmarking of the computational predictions. To support the re-use of results, software tools applied should support documentation as well as versioning. Reporting of simulation results should follow best-practice guidelines. With regard to safety and transparency, data used in healthcare models should include information about the source of data and inspection of data quality, to be ensured by rigorous scientific testing and licensing through well-funded licensing agencies.

Validation of models to be used clinically must include extensive and frequent testing by scientific peers and licensing agencies, as well as continuous quality reporting by centres using these systems. Commercial and scientific application of models involves different routes to validation and are difficult to discuss together, but the testing and validation process should in either case be rigorous, planned, ongoing, and well-financed. Licensing fees can, for example, cover the cost on continual testing of commercial applications. Companies should be required to disclose both data and models to regulatory agencies and/or peer reviewers and journals for the purposes of proper quality control. Third-party validation and replication of results requires access to the data used for the development and training of the models. While access to health-care data used is theoretically possible by application to relevant authorities, preprocessing and harmonizing the data to replicate results is time-consuming and unrewarded. Therefore consistent, high-quality model validation requires that systems be created allowing the return of enhanced (pre-processed, harmonized) medical data to the state.

There are guidelines and methods for validating models, which are accurate and confident in predictions, both in terms of accuracy and confidence in predictions. Performance evaluation of in silico models should be transparent and consistent to existing guidelines, explaining the reasons for not doing so when alternative methods are chosen. Mechanistic models can serve multiple purposes, which makes it difficult to have a strict set of guidelines for validations. Further, for clinical practice, models are still striving to become a reliable partner to understand mechanisms underlying diseases, identify biomarkers (diagnosis and prognosis), and support clinical-treatment decisions. Towards these purposes, the model will pass through a large set of testing and validation procedures to ensure that model predictions hint to physiologically plausible states for realistic levels of parametric uncertainty. After parameter estimation, one has to compare the overall behavior or stimulus-response pattern and match this with evidence from the literature to ensure that the model represents the biological reality. This "matching" is a judgement and a discussion that continues an iterative process of model refinement. Ultimately, the usefulness of a model is not only measured by the accuracy of representation but how well it supports the generation, testing. and refinement of hypotheses and make predictions based on which patients are stratified between responder and non-responder to a specific therapy [144]. Model validation is crucial, and the accuracy of ML/DL results must be verified using independent test datasets. Supervised ML/DL clinical-decision support tools use ML algorithms to make individual patient-level predictions.

#### 4.2.4. Translations and Applications

The final step is translation and application such that the results can actually be brought back to the clinic. Here, the model results may be used for the generation of testable hypotheses or to simulate clinical studies. Likewise, clinical scores and markers may be an outcome. In this regard, it is of utmost importance that the confidence in the computation predictions is frankly disclosed. Likewise, underlying model assumptions and uncertainties should be openly discussed in particular with regard to potential consequences for the patient. This also involves algorithmic fairness. Biases should be addressed through analysis of input data both at the licensing and at the application of the systems to new populations, as indeed, should be the case in all tools used in medicine. We have seen many cases of medical discoveries and tools being used on populations for whom they were not designed, to the detriment of these patients' treatment and outcomes. Continuous analysis of the applicability of a model to a target population should be a part of data integration and model validation-however, the perfect should not be the enemy of the good, and where data on a given population is missing, the tool should still be used if it can be shown to generate better outcomes for patients than not using it. The GDPR has gone a long way to ensuring that people and corporations dealing with personal data protect them, and these efforts should be continued and redoubled to ensure technical security accompanies legal measures. Technical measures also include data federation and the creation of synthetic data, which can be shared with fewer restrictions. However, real data that have been identified, encrypted, harmonized, standardized, validated, and properly curated are more likely to lead to both better science and patient treatment, and they also offer significantly better transparency and quality control. This should therefore be the gold standard required for models used in treatment, while synthetic data can be used as sandboxes for hypothesis generation.

# 5. Conclusions

There is a rapidly growing amount of personalized data in today's medicine. The availability of these measurements holds immense promises for both diagnosis and treatment of diseases at the single-patient level. The complexity of the data, however, poses significant challenges in its general usability, amongst others due the underlying heterogeneity of samples as well as inter-patient variability. Computational models provide a structural framework to analyze these data through their contextualization in mathematical descriptions, be it mechanistic modelling or ML/DL. As discussed here, there are numerous successful examples for the application of computational models in discovery, diagnosis, and therapy (Tables 2–4). However, several challenges remain to fully realize the possibilities of personalized data in clinical practice, in particular regarding data provision, model building, and model filing as well as legal issues and ethics. To support successful study outcomes, key guidelines can be formulated that refer to different stages of project work:

- Careful planning of study design is of utmost importance at the project start;
- Common standards for data sampling, data acquisition, and data operation should be fulfilled;
- Data harmonization is crucial to ensure data compatibility and comparability;
- Data should be divided in data sets for training and validation;
- Model documentation should be written according to best practice guidelines;
- It is important to openly communicate model assumptions and biases in the computational results;
- New patient data should be continuously used for benchmarking of the computational results.

We strongly believe that compliance to these guidelines will significantly support the realization of computational precision medicine in the future.

**Author Contributions:** Writing—original draft preparation, C.B.C., T.G., T.K., M.H., F.M.K., A.S.-Y., M.K., S.K., M.G., L.K.; writing—review and editing, C.B.C., T.G., T.K., M.H., F.M.K., A.S.-Y., M.K., S.K., M.G., L.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors of this article are part of the EU-STANDS4PM consortium (www.eustands4pm.eu) that is funded by the European Union Horizon 2020 framework programme of the European Commission under Grant Agreement # 825843. Faiz Muhammad Khan received additional funding from The German Federal Ministry of Education and Research (BMBF) and the SAS-Kit project (FKZ 01ZX1903B). Tugce Karaderi is supported by the Novo Nordisk Foundation Data Science Investigator grant (NNF20OC0062294).

Acknowledgments: The EU-STANDS4PM consortium: Rolf Apweiler, Stephan Beck, Catherine Bjerre Collin, Niklas Blomberg, Søren Brunak, Tom Gebhardt, Eugenijus Gefenas, Martin Golebiewski, Kalle Günther, Mette Hartlev, Maximilian Hillemanns, Vincent Jaddoe, Tugce Karaderi, Marc Kirschner, Ingrid Kockum, Sylvia Krobitsch, Lars Küpfer, Vilma Lukaseviciene, Arshiya Merchant, Heike Moser, Faiz Muhammad Khan, Miranda Mourby, Wolfgang Müller, Flora Musuamba Tshinanu, Katharina Eva Ó Cathaoir, Uwe Oelmüller, Tito Poli, Philip Rosenstiel, Ali Salehzadeh-Yazdi and Olaf Wolkenhauer.

Conflicts of Interest: The authors declare no conflict of interest.

# References

- 1. Wolkenhauer, O.; Auffray, C.; Brass, O.; Clairambault, J.; Deutsch, A.; Drasdo, D.; Gervasio, F.; Preziosi, L.; Maini, P.; Marciniak-Czochra, A.; et al. Enabling multiscale modeling in systems medicine. *Genome Med.* **2014**, *6*, 21.
- 2. Apweiler, R.; Beissbarth, T.; Berthold, M.R.; Bluthgen, N.; Burmeister, Y.; Dammann, O.; Deutsch, A.; Feuerhake, F.; Franke, A.; Hasenauer, J.; et al. Whither systems medicine? *Exp. Mol. Med.* **2018**, *50*, e453.
- 3. Pison, C.; The CASyM consortium. The CASyM roadmap-Implementation of Systems Medicine across Europe. 2014. Available online: www.casym.eu (accessed on 18 November 2021).
- 4. Morrison, T.M.; Pathmanathan, P.; Adwan, M.; Margerrison, E. Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories. *Front. Med.* **2018**, *5*, 1–11.
- Musuamba, F.T.; Skottheim Rusten, I.; Lesage, R.; Russo, G.; Bursi, R.; Emili, L.; Wangorsch, G.; Manolis, E.; Karlsson, K.E.; Kulesza, A.; et al. Scientific and Regulatory Evaluation of Mechanistic In Silico Drug and Disease Models in Drug Development: Building Model Credibility. *CPT Pharmacomet. Syst. Pharmacol.* 2021, 10, 804–825.
- 6. EMA. Guideline on the Reporting of Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulation; European Medicines Agency: Amsterdam, The Netherlands, 2018.
- Morrison, T.M. Reporting of Computational Modeling Studies in Medical Device Submissions Guidance for Industry and Food and Drug Administration Staff; O.o.S.a.E. Laboratories, Ed.; U.S. Department of Health and Human Services Food and Drug Administration: Silver Spring, MD, USA, 2016.
- Barredo Arrieta, A.; Díaz-Rodríguez, N.; Del Ser, J.; Bennetot, A.; Tabik, S.; Barbado, A.; Garcia, S.; Gil-Lopez, S.; Molina, D.; Benjamins, R.; et al. Explainable Artificial Intelligence (XAI): Concepts, taxonomies, opportunities and challenges toward responsible AI. *Inf. Fusion* 2020, *58*, 82–115.
- 9. Dimiduk, D.M.; Holm, E.A.; Niezgoda, S.R. Perspectives on the Impact of Machine Learning, Deep Learning, and Artificial Intelligence on Materials, Processes, and Structures Engineering. *Integr. Mater. Manuf. Innov.* **2018**, *7*, 157–172.
- 10. Wolkenhauer, O. Why model? Front. Physiol. 2014, 5, 21.
- 11. Wolkenhauer, O.; Auffray, C.; Jaster, R.; Steinhoff, G.; Dammann, O. The road from systems biology to systems medicine. *Pediatr. Res.* 2013, 73, 502–507.
- 12. Wolkenhauer, O.; Green, S. The search for organizing principles as a cure against reductionism in systems medicine. *FEBS J.* **2013**, *280*, 5938–5948.
- 13. Kitano, H.; Funahashi, A.; Matsuoka, Y.; Oda, K. Using process diagrams for the graphical representation of biological networks. *Nat. Biotechnol.* **2005**, *23*, 961–966.
- 14. Fujita, K.A.; Ostaszewski, M.; Matsuoka, Y.; Ghosh, S.; Glaab, E.; Trefois, C.; Crespo, I.; Perumal, T.M.; Jurkowski, W.; Antony, P.M.; et al. Integrating pathways of Parkinson's disease in a molecular interaction map. *Mol. Neurobiol.* **2014**, *49*, 88–102.
- 15. Kuperstein, I.; Bonnet, E.; Nguyen, H.A.; Cohen, D.; Viara, E.; Grieco, L.; Fourquet, S.; Calzone, L.; Russo, C.; Kondratova, M.; et al. Atlas of Cancer Signalling Network: A Systems Biology Resource for Integrative Analysis of Cancer Data with Google Maps. *Oncogenesis* **2015**, *4*, e160.
- 16. Thiele, I.; Palsson, B.O. A protocol for generating a high-quality genome-scale metabolic reconstruction. *Nat. Protoc.* **2010**. *5*, 93–121.
- 17. Uhlen, M.; Zhang, C.; Lee, S.; Sjostedt, E.; Fagerberg, L.; Bidkhori, G.; Benfeitas, R.; Arif, M.; Liu, Z.; Edfors, F.; et al. A pathology atlas of the human cancer transcriptome. *Science* **2017**, *357*, eaan2507.
- 18. Mardinoglu, A.; Agren, R.; Kampf, C.; Asplund, A.; Nookaew, I.; Jacobson, P.; Walley, A.J.; Froguel, P.; Carlsson, L.M.; Uhlen, M.; et al. Integration of clinical data with a genome-scale metabolic model of the human adipocyte. *Mol. Syst. Biol.* **2013**, *9*, 649.
- 19. Stempler, S; Yizhak, K.; Ruppin, E. Integrating transcriptomics with metabolic modeling predicts biomarkers and drug targets for Alzheimer's disease. *PLoS ONE* **2014**, *9*, e105383.
- 20. Wang, S.R.; Saadatpour, A.; Albert, R. Boolean modeling in systems biology: An overview of methodology and applications. *Phys. Biol.* **2012**, *9*, 055001.
- Eduati, F.; Jaaks, P.; Wappler, J.; Cramer, T.; Merten, C.A.; Garnett, M.J.; Saez-Rodriguez, J. Patient-specific logic models of signaling pathways from screenings on cancer biopsies to prioritize personalized combination therapies. *Mol. Syst. Biol.* 2020, 16, e8664.
- Udyavar, A.R.; Wooten, D.J.; Hoeksema, M.; Bansal, M.; Califano, A.; Estrada, L.; Schnell, S.; Irish, J.M.; Massion, P.P.; Quaranta,V. Correction: Novel Hybrid. Phenotype Revealed in Small Cell Lung Cancer by a Transcription Factor Network Model. That Can. Explain Tumor Heterogeneity. *Cancer Res.* 2019, 79, 1014.
- 23. Malik-Sheriff, R.S.; Glont, M.; Nguyen, T.V.N.; Tiwari, K.; Roberts, M.G.; Xavier, A.; Vu, M.T.; Men, J.; Maire, M.; Kananathan, S.; et al. BioModels-15 years of sharing computational models in life science. *Nucleic Acids Res.* **2020**, *48*, D407–D415.
- 24. Kolch, W.; Fey, D. Personalized Computational Models as Biomarkers. J. Pers. Med. 2017, 7, 9.
- Hastings, J.F.; O'Donnell, Y.E.I.; Fey, D.; Croucher, D.R.; et al. Applications of personalised signalling network models in precision oncology. *Pharmacol. Ther.* 2020, 212, 107555.
- Pérez-Urizar, J.; Granados-Soto, V.; Flores-Murrieta, F.J.; Castañeda-Hernández, G. Pharmacokinetic-Pharmacodynamic Modeling: Why? Arch. Med. Res. 2000, 31, 539–545.
- 27. Edginton, N.A.; Willmann, S. Physiology-based simulations of a pathological condition: Prediction of pharmacokinetics in patients with liver cirrhosis. *Clin. Pharmacokinet.* **2008**. 47, 743–752.

- 28. Maharaj, R.A.; Edginton, A.N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacomet. Syst. Pharm.* **2014**, *3*, e150.
- Jones, H.M.; Chen, Y.; Gibson, C.; Heimbach, T.; Parrott, N.; Peters, S.A.; Snoeys, J.; Upreti, V.V.; Zheng, M.; Hall, S.D. Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective. *Clin. Pharmacol. Ther.* 2015, 97, 247–262.
- Swat, M.J.; Moodie, S.; Wimalaratne, S.M.; Kristensen, N.R.; Lavielle, M.; Mari, A.; Magni, P.; Smith, M.K.; Bizzotto, R.; Pasotti, L.; et al. Pharmacometrics Markup Language (PharmML): Opening New Perspectives for Model. Exchange in Drug Development. *CPT Pharmacomet. Syst. Pharm.* 2015, *4*, 316–319.
- Kuepfer, L.; Niederalt, C.; Wendl, T.; Schlender, J.F.; Willmann, S.; Lippert, J.; Block, M.; Eissing, T.; Teutonico, D. Applied Concepts in PBPK Modeling: How to Build. a PBPK/PD Model. CPT Pharmacomet. Syst. Pharm. 2016, 5, 516–531.
- Matsuzaki, T.; Scotcher, D.; Darwich, A.S.; Galetin, A.; Rostami-Hodjegan, A. Towards Further Verification of Physiologically-Based Kidney Models: Predictability of the Effects of Urine-Flow and Urine-pH on Renal Clearance. *J. Pharmacol. Exp. Ther.* 2019, 368, 157–168.
- Schlender, J.F.; Meyer, M.; Thelen, K.; Krauss, M.; Willmann, S.; Eissing, T.; Jaehde, U. Development of a Whole-Body Physiologically Based Pharmacokinetic Approach to Assess. the Pharmacokinetics of Drugs in Elderly Individuals. *Clin. Pharm.* 2016, 55, 1573–1589.
- Maharaj, R.A.; Edginton, A.N.; Fotaki, N. Assessment of Age-Related Changes in Pediatric Gastrointestinal Solubility. *Pharm. Res.* 2016, 33, 52–71.
- Turei, D.; Korcsmaros, T.; Saez-Rodriguez, J. OmniPath: Guidelines and gateway for literature-curated signaling pathway resources. *Nat. Methods* 2016, 13, 966–967.
- Politano, G.; di Carlo, S.; Benso, A. 'One DB to rule them all'-the RING: A Regulatory Interaction Graph. combining TFs, genes/proteins, SNPs, diseases and drugs. *Database* 2019, 2019, baz108.
- Klamt, S.; Saez-Rodriguez, J.; Gilles, E.D. Structural and functional analysis of cellular networks with CellNetAnalyzer. BMC Syst. Biol. 2007, 1, 2.
- Helikar, T.; Kowal, B.; McClenathan, S.; Bruckner, M.; Rowley, T.; Madrahimov, A.; Wicks, B.; Shrestha, M.; Limbu, K.; Rogers, J.A. The Cell Collective: Toward an Open and Collaborative Approach to Systems Biology. *BMC Syst. Biol.* 2012, 6, 96.
- 39. Naldi, A.; Berenguier, D.; Faure, A.; Lopez, F.; Thieffry, D.; Chaouiya, C. Logical modelling of regulatory networks with GINsim 2.3. *Biosystems* **2009**, *97*, 134–139.
- Licata, L.; Lo Surdo, P.; Iannuccelli, M.; Palma, A.; Micarelli, E.; Perfetto, L.; Peluso, D.; Calderone, A.; Castagnoli, L.; Cesareni, G. SIGNOR 2.0, the SIGnaling Network Open Resource 2.0: 2019 update. *Nucleic Acids Res.* 2020, 48, D504–D510.
- 41. Jassal, B.; Matthews, L.; Viteri, G.; Gong, C.; Lorente, P.; Fabregat, A.; Sidiropoulos, K.; Cook, J.; Gillespie, M.; Haw, R.; et al. The reactome pathway knowledgebase. *Nucleic Acids Res.* **2020**, *48*, D498–D503.
- 42. Csabai, L.; Fazekas, D.; Kadlecsik, T.; Szalay-Beko, M.; Bohar, B.; Madgwick, M.; Modos, D.; Olbei, M.; Gul, L.; Sudhakar, P.; et al. SignaLink3: A multi-layered resource to uncover tissue-specific signaling networks. *Nucleic Acids Res.* **2022**, *50*, D701–D709.
- Breuer, K.; Foroushani, A.K.; Laird, M.R.; Chen, C.; Sribnaia, A.; Lo, R.; Winsor, G.L.; Hancock, R.E.; Brinkman, F.S.; Lynn, D.J. InnateDB: Systems biology of innate immunity and beyond-Recent updates and continuing curation. *Nucleic Acids Res.* 2013, 41, D1228-1233.
- Slenter, D.N.; Kutmon, M.; Hanspers, K.; Riutta, A.; Windsor, J.; Nunes, N.; Melius, J.; Cirillo, E.; Coort, S.L.; Digles, D.; et al. WikiPathways: A multifaceted pathway database bridging metabolomics to other omics research. *Nucleic Acids Res.* 2018, 46, D661–D667.
- 45. Ogata, H.; Goto, S.; Sato, K.; Fujibuchi, W.; Bono, H.; Kanehisa, M. KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Res.* **1999**, *27*, 29–34.
- Mussel, C.; Hopfensitz, M.; Kestler, H.A. BoolNet-An R package for generation, reconstruction and analysis of Boolean networks. *Bioinformatics* 2010, 26, 1378–1380.
- Glont, M.; Nguyen, T.V.N.; Graesslin, M.; Halke, R.; Ali, R.; Schramm, J.; Wimalaratne, S.M.; Kothamachu, V.B.; Rodriguez, N.; Swat, M.J.; et al. BioModels: Expanding horizons to include more modelling approaches and formats. *Nucleic Acids Res.* 2018, 46, D1248–D1253.
- 48. De Jong, H.; Geiselmann, J.; Hernandez, C.; Page, M. Genetic Network Analyzer: Qualitative simulation of genetic regulatory networks. *Bioinformatics* **2003**, *19*, 336–344.
- 49. Di Cara, A.; Garg, A.; De Micheli, G.; Xenarios, I.; Mendoza, L. Dynamic simulation of regulatory networks using SQUAD. *BMC Bioinform.* 2007, *8*, 462.
- 50. Stoll, G.; Caron, B.; Viara, E.; Dugourd, A.; Zinovyev, A.; Naldi, A.; Kroemer, G.; Barillot, E.; Calzone, L. MaBoSS 2.0: An environment for stochastic Boolean modeling. *Bioinformatics* 2017, *33*, 2226–2228.
- Terfve, C.; Cokelaer, T.; Henriques, D.; MacNamara, A.; Goncalves, E.; Morris, M.K.; Van Iersel, M.; Lauffenburger, D.A.; Saez-Rodriguez, J. CellNOptR: A flexible toolkit to train protein signaling networks to data using multiple logic formalisms. *BMC Syst. Biol.* 2012, *6*, 133.
- 52. King, Z.A.; Lu, J.; Drager, A.; Miller, P.; Federowicz, S.; Lerman, J.A.; Ebrahim, A.; Palsson, B.O.; Lewis, N.E. BiGG Models: A platform for integrating, standardizing and sharing genome-scale models. *Nucleic Acids Res.* **2016**, *44*, D515–D522.
- 53. Pornputtapong, N.; Nookaew, I.; Nielsen, J. Human metabolic atlas: An online resource for human metabolism. *Database* **2015**, 2015, bav068.

- Noronha, A.; Modamio, J.; Jarosz, Y.; Guerard, E.; Sompairac, N.; Preciat, G.; Danielsdottir, A.D.; Krecke, M.; Merten, D.; Haraldsdottir, H.S.; et al. The Virtual Metabolic Human Database: Integrating Human and Gut Microbiome Metabolism with Nutrition and Disease. *Nucleic Acids Res.* 2019, 47, D614–D624.
- Schellenberger, J.; Que, R.; Fleming, R.M.; Thiele, I.; Orth, J.D.; Feist, A.M.; Zielinski, D.C.; Bordbar, A.; Lewis, N.E.; Rahmanian, S.; et al. Quantitative prediction of cellular metabolism with constraint-based models: The COBRA Toolbox v2.0. *Nat. Protoc.* 2011, *6*, 1290–1307.
- 56. Gelius-Dietrich, G.; Desouki, A.A.; Fritzemeier, C.J.; Lercher, M.J. Sybil-Efficient constraint-based modelling in R. *BMC Syst. Biol.* **2013**, *7*, 125.
- 57. Ebrahim, A.; Lerman, J.A.; Palsson, B.O.; Hyduke, D.R. COBRApy: Constraints-Based Reconstruction and Analysis for Python. BMC Syst. Biol. 2013, 7, 74.
- Seaver, S.M.D.; Liu, F.; Zhang, Q.; Jeffryes, J.; Faria, J.P.; Edirisinghe, J.N.; Mundy, M.; Chia, N.; Noor, E.; Beber, M.E.; et al. The ModelSEED Biochemistry Database for the Integration of Metabolic Annotations and the Reconstruction, Comparison and Analysis of Metabolic Models for Plants, Fungi and Microbes. *Nucleic Acids Res.* 2021, 49, D575–D588.
- Chelliah, V.; Laibe, C.; le Novere, N. BioModels Database: A Repository of Mathematical Models of Biological Processes. *Methods Mol. Biol.* 2013, 1021, 189–199.
- 60. Peters, M.; Eicher, J.J.; Van Niekerk, D.D.; Waltemath, D.; Snoep, J.L. The JWS online simulation database. *Bioinformatics* **2017**, 33, 1589–1590.
- 61. Yu, T.; Lloyd, C.M.; Nickerson, D.P.; Cooling, M.T.; Miller, A.K.; Garny, A.; Terkildsen, J.R.; Lawson, J.; Britten, R.D.; Hunter, P.J.; et al. The Physiome Model Repository 2. *Bioinformatics* **2011**, *27*, 743–744.
- 62. Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. COPASI-A Complex Pathway Simulator. *Bioinformatics* **2006**, *22*, 3067–3074.
- Matsuoka, Y.; Funahashi, A.; Ghosh, S.; Kitano, H. Modeling and simulation using CellDesigner. *Methods Mol. Biol.* 2014, 1164, 121–45.
- 64. Hucka, M.; Nickerson, D.P.; Bader, G.D.; Bergmann, F.T.; Cooper, J.; Demir, E.; Garny, A.; Golebiewski, M.; Myers, C.J.; Schreiber, F.; et al. Promoting Coordinated Development of Community-Based Information Standards for Modeling in Biology: The COMBINE Initiative. *Front. Bioeng. Biotechnol.* **2015**, *3*, 19.
- Hucka, M.; Bergmann, F.T.; Chaouiya, C.; Drager, A.; Hoops, S.; Keating, S.M.; Konig, M.; Novere, N.L.; Myers, C.J.; Olivier, B.G.; et al. The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2. *Mol. Syst. Biol.* 2020, 16, e9110.
- 66. Clerx, M.; Cooling, M.T.; Cooper, J.; Garny, A.; Moyle, K.; Nickerson, D.P.; Nielsen, P.M.F.; Sorby ,H. CellML 2.0. J. Integr. Bioinform. 2020, 17, 2–3.
- 67. Le Novere, N.; Hucka, M.; Mi, H.; Moodie, S.; Schreiber, F.; Sorokin, A.; Demir, E.; Wegner, K.; Aladjem, M.I.; Wimalaratne, S.M.; et al. The Systems Biology Graphical Notation. *Nat. Biotechnol.* **2009**, *27*, 735–741.
- Mazein, A.; Ostaszewski, M.; Kuperstein, I.; Watterson, S.; Le Novere, N.; Lefaudeux, D.; De Meulder, B.; Pellet, J.; Balaur, I.; Saqi, M.; et al. Systems medicine disease maps: Community-driven comprehensive representation of disease mechanisms. NPJ Syst. Biol. Appl. 2018, 4, 21.
- 69. Chaouiya, C.; Berenguier, D.; Keating, S.M.; Naldi, A.; Van Iersel, M.P.; Rodriguez, N.; Drager, A.; Buchel, F.; Cokelaer, T.; Kowal, B.; et al. SBML qualitative models: A model representation format and infrastructure to foster interactions between qualitative modelling formalisms and tools. *BMC Syst. Biol.* **2013**, *7*, 135.
- Mourby, M.; Cathaoir, K.Ó.; Collin, C.B. Transparency of machine-learning in healthcare: The GDPR & European health law. Comput. Law Secur. Rev. 2021, 43, 105611.
- 71. Thorsen-Meyer, H.-C.; Nielsen, A.B.; Nielsen, A.P.; Kaas-Hansen, B.S.; Toft, P.; Schierbeck, J.; Strøm, T.; Chmura, P.J.; Heimann, M.; Dybdahl, L.; et al. Dynamic and explainable machine learning prediction of mortality in patients in the intensive care unit: A retrospective study of high-frequency data in electronic patient records. *Lancet Digit. Health* 2020, 2, e179–e191.
- 72. LeCun, Y.; Bengio, Y.; Hinton, G. Deep learning. Nature 2015, 521, 436-444.
- 73. Kim, J.; Kim, J.; Jang, G.J.; Lee, M. Fast learning method for convolutional neural networks using extreme learning machine and its application to lane detection. *Neural Netw.* **2017**. *87*, 109–121.
- 74. Greener, J.G.; Kandathil, S.M.; Moffat, L.; Jones, D.T. A guide to machine learning for biologists. *Nat. Rev. Mol. Cell Biol.* **2021**, 23, 40–55.
- 75. Weissler, E.H.; Naumann, T.; Andersson, T.; Ranganath, R.; Elemento, O.; Luo, Y.; Freitag, D.F.; Benoit, J.; Hughes, M.C.; Khan, F.; et al. The role of machine learning in clinical research: Transforming the future of evidence generation. *Trials* **2021**, *22*, 537.
- 76. Beaulieu-Jones, B.K.; Yuan, W.; Brat, G.A.; Beam, A.L.; Weber, G.; Ruffin, M.; Kohane, I.S. Machine learning for patient risk stratification: Standing on, or looking over, the shoulders of clinicians? NPJ *Digit. Med.* **2021**, *4*, 62.
- 77. Baldi, P.; Brunak, S. Bioinformatics: The Machine Learning Approach; MIT Press: Cambridge, MA, USA, 2001.
- Liu, X.; Faes, L.; Kale, A.U.; Wagner, S.K.; Fu, D.J.; Bruynseels, A.; Mahendiran, T.; Moraes, G.; Shamdas, M.; Kern, C.; et al. A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: A systematic review and meta-analysis. *Lancet Digit. Health* 2019, 1, e271–e297.
- 79. Stupple, A.; Singerman, D.; Celi, L.A. The reproducibility crisis in the age of digital medicine. NPJ Digit. Med. 2019, 2, 2.

- Liu, X.; Cruz Rivera, S.; Moher, D.; Calvert, M.J.; Denniston, A.K.; The SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: The CONSORT-AI extension. *Nat. Med.* 2020, *26*, 1364–1374.
- Cruz Rivera, S.; Liu, X., Chan, A.-W.; Denniston, A.K., Calvert, M.J.; SPIRIT-AI and CONSORT-AI Working Group; SPIRIT-AI and CONSORT-AI Consensus Group. Guidelines for clinical trial protocols for interventions involving artificial intelligence: The SPIRIT-AI extension. *Nat. Med.* 2020, 26, 1351–1363.
- 82. Matschinske, J.; Alcaraz, N.; Benis, A.; Golebiewski, M.; Grimm, D.G.; Heumos, L.; Kacprowski, T.; Lazareva, O.; List, M.; Louadi, Z.; et al. The AIMe registry for artificial intelligence in biomedical research. *Nat. Methods* **2021**, *18*, 1128–1131.
- 83. Serhan, C.N.; Gupta, S.K.; Perretti, M.; Godson, C.; Brennan, E.; Li, Y.; Soehnlein, O.; Shimizu, T.; Werz, O.; Chiurchiu, V.; et al. The Atlas of Inflammation Resolution (AIR). *Mol. Asp. Med.* **2020**, *74*, 100894.
- 84. Wu, G.; Zhu, L.; Dent, J.E.; Nardini, C. A comprehensive molecular interaction map for rheumatoid arthritis. *PLoS ONE* **2010**, *5*, e10137.
- Mazein, A.; Knowles, R.G.; Adcock, I.; Chung, K.F.; Wheelock, C.E.; Maitland-Van Der Zee, A.H.; Sterk, P.J.; Auffray, C.; AsthmaMap Project, T. AsthmaMap: An. expert-driven computational representation of disease mechanisms. *Clin. Exp. Allergy* 2018, 48, 916–918.
- Parton, A.; McGilligan, V.; Chemaly, M.; O'Kane, M.; Watterson, S. New models of atherosclerosis and multi-drug therapeutic interventions. *Bioinformatics* 2019, 35, 2449–2457.
- Varemo, L.; Scheele, C.; Broholm, C.; Mardinoglu, A.; Kampf, C.; Asplund, A.; Nookaew, I.; Uhlen, M.; Pedersen, B.K.; Nielsen, J. Proteome-and transcriptome-driven reconstruction of the human myocyte metabolic network and its use for identification of markers for diabetes. *Cell Rep.* 2015, *11*, 921–933.
- 88. Mardinoglu, A.; Agren, R.; Kampf, C.; Asplund, A.; Uhlen, M.; Nielsen, J. Genome-scale metabolic modelling of hepatocytes reveals serine deficiency in patients with non-alcoholic fatty liver disease. *Nat. Commun.* **2014**, *5*, 3083.
- 89. Ruiz-Cerda, M.L.; Irurzun-Arana, I.; Gonzalez-Garcia, I.; Hu, C.; Zhou, H.; Vermeulen, A.; Troconiz, I.F.; Gomez-Mantilla, J.D. Towards patient stratification and treatment in the autoimmune disease lupus erythematosus using a systems pharmacology approach. *Eur. J. Pharm. Sci.* **2016**, *94*, 46–58.
- Khan, F.M.; Marquardt, S.; Gupta, S.K.; Knoll, S.; Schmitz, U.; Spitschak, A.; Engelmann, D.; Vera, J.; Wolkenhauer, O.; Putzer, B.M. Unraveling a tumor type-specific regulatory core underlying E2F1-mediated epithelial-mesenchymal transition to predict receptor protein signatures. *Nat. Commun.* 2017, *8*, 198.
- 91. Agren, R.; Mardinoglu, A.; Asplund, A.; Kampf, C.; Uhlen, M.; Nielsen, J. Identification of anticancer drugs for hepatocellular carcinoma through personalized genome-scale metabolic modeling. *Mol. Syst. Biol.* **2014**, *10*, 721.
- Fey, D.; Halasz, M.; Dreidax, D.; Kennedy, S.P.; Hastings, J.F.; Rauch, N.; Munoz, A.G.; Pilkington, R.; Fischer, M.; Westermann, F.; et al. Signaling pathway models as biomarkers: Patient-specific simulations of JNK activity predict the survival of neuroblastoma patients. *Sci. Signal.* 2015, *8*, ra130.
- Hector, S.; Rehm, M.; Schmid, J.; Kehoe, J.; McCawley, N.; Dicker, P.; Murray, F.; McNamara, D.; Kay, E.W.; Concannon, C.G.; et al. Clinical application of a systems model of apoptosis execution for the prediction of colorectal cancer therapy responses and personalisation of therapy. *Gut* 2012, *61*, 725–733.
- 94. Velickovski, F.; Ceccaroni, L.; Roca, J.; Burgos, F.; Galdiz, J.B.; Marina, N.; Lluch-Ariet, M. Clinical Decision Support. Systems (CDSS) for preventive management of COPD patients. *J. Transl. Med.* **2014**, *12*, S9.
- 95. Sutton, R.T.; Pincock, D.; Baumgart, D.C.; Sadowski, D.C.; Fedorak, R.N.; Kroeker, K.I. An. overview of clinical decision support systems: Benefits, risks, and strategies for success. *NPJ Digit. Med.* **2020**, *3*, 17.
- 96. Mason, D.M.; Friedensohn, S.; Weber, C.R.; Jordi, C.; Wagner, B.; Meng, S.M.; Ehling, R.A.; Bonati, L.; Dahinden, J.; Gainza, P.; et al. Optimization of therapeutic antibodies by predicting antigen specificity from antibody sequence via deep learning. *Nat. Biomed. Eng.* 2021, *5*, 600–612.
- 97. Goodwin, C.R.; Covington, B.C.; Derewacz, D.K.; McNees, C.R.; Wikswo, J.P.; McLean, J.A.; Bachmann, B.O. Structuring Microbial Metabolic Responses to Multiplexed Stimuli via Self-Organizing Metabolomics Maps. *Chem. Biol.* **2015**, *22*, 661–670.
- Babu, R.V.; Bar, Y.; Blair, J.; Bradley, A.P.; Carneiro, G.; Chen, H.; Dam, E.B.; Diamant, I.; Dou, Q.; Feldman, M.D.; et al. *Contributors*, in *Deep Learning for Medical Image Analysis*; Zhou, S.K., Greenspan, H., Shen, D., Eds.; Academic Press: Cambridge, MA, USA, 2017.
- 99. Chan, H.P.; Samala, R.K.; Hadjiiski, L.M.; Zhou, C. Deep Learning in Medical Image Analysis. *Adv. Exp. Med. Biol.* 2020, 1213, 3–21.
- 100. Abràmoff, M.D.; Lavin, P.T.; Birch, M.; Shah, N.; Folk, J.C. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit. Med.* **2018**, *1*, 39.
- 101. Zhang, K.; Liu, X.; Shen, J.; Li, Z.; Sang, Y.; Wu, X.; Zha, Y.; Liang, W.; Wang, C.; Wang, K.; et al. Clinically Applicable AI System for Accurate Diagnosis, Quantitative Measurements, and Prognosis of COVID-19 Pneumonia Using Computed Tomography. *Cell* 2020, 181, 1423–1433.e11.
- 102. Damask, A.; Steg, P.G.; Schwartz, G.G.; Szarek, M.; Hagstrom, E.; Badimon, L.; Chapman, M.J.; Boileau, C.; Tsimikas, S.; Ginsberg, H.N.; et al. Patients with High. Genome-Wide Polygenic Risk Scores for Coronary Artery Disease May Receive Greater Clinical Benefit from Alirocumab Treatment in the ODYSSEY OUTCOMES Trial. *Circulation* 2020, 141, 624–636.
- 103. Duncan, L.; Shen, H.; Gelaye, B.; Meijsen, J.; Ressler, K.; Feldman, M.; Peterson, R.; Domingue, B. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat. Commun.* **2019**, *10*, 3328.

- 104. Marquez-Luna, C.; Loh, P.R.; South Asian Type 2 Diabetes (SAT2D) Consortium; SIGMA Type 2 Diabetes Consortium; Price, A.L. Multiethnic polygenic risk scores improve risk prediction in diverse populations. *Genet. Epidemiol.* 2017, 41, 811–823.
- Grinde, K.E.; Qi, Q.; Thornton, T.A.; Liu, S.; Shadyab, A.H.; Chan, K.H.K.; Reiner, A.P.; Sofer, T. Generalizing polygenic risk scores from Europeans to Hispanics/Latinos. *Genet. Epidemiol.* 2019, 43, 50–62.
- 106. Pare, G.; Mao, S.; Deng, W.Q. A machine-learning heuristic to improve gene score prediction of polygenic traits. *Sci. Rep.* **2017**, 7, 12665.
- 107. Vilhjalmsson, B.J.; Yang, J.; Finucane, H.K.; Gusev, A; Lindstrom, S.; Ripke, S.; Genovese, G.; Loh, P.R.; Bhatia, G.; Do, R.; et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am. J. Hum. Genet. 2015, 97, 576–592.
- Okser, S.; Pahikkala, T.; Airola, A.; Salakoski, T.; Ripatti, S.; Aittokallio, T. Regularized machine learning in the genetic prediction of complex traits. *PLoS Genet.* 2014, 10, e1004754.
- Wray, N.R.; Yang, J.; Hayes, B.J.; Price, A.L.; Goddard, M.E.; Visscher, P.M. Pitfalls of predicting complex traits from SNPs. *Nat. Rev. Genet.* 2013, 14, 507–515.
- 110. Dudbridge, F. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 2013, 9, e1003348.
- International Schizophrenia Consortium; Purcell, S.M.; Wray, N.R.; Stone, J.L.; Visscher, P.M.; O'Donovan, M.C.; Sullivan, P.F.; Sklar, P. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009, 460, 748.
- 112. Wray, R.N.; Goddard, M.E.; Visscher, P.M. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res.* 2007, 17, 1520–1528.
- 113. Lee, J.J.; Wedow, R.; Okbay, A.; Kong, E.; Maghzian, O.; Zacher, M.; Nguyen-Viet, T.A; Bowers, P.; Sidorenko, J.; Karlsson Linner, R.; et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* 2018, *50*, 1112–1121.
- 114. Bigdeli, T.B.; Genovese, G.; Georgakopoulos, P.; Meyers, J.L.; Peterson, R.E.; Iyegbe, C.O.; Medeiros, H.; Valderrama, J.; Achtyes, E.D.; Kotov, R.; et al. Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry. *Mol. Psychiatry* 2020, 25, 2455–2467.
- 115. Rammos, A.; Gonzalez, L.A.N.; The Schizophrenia Working Group of the Psychiatric Genomics Consortium 2; Weinberger, D.R.; Mitchell, K.J.; Nicodemus, K.K. The role of polygenic risk score gene-set analysis in the context of the omnigenic model of schizophrenia. *Neuropsychopharmacology* 2019, 44, 1562–1569.
- 116. Khera, A.V.; Chaffin, M.; Aragam, K.G.; Haas, M.E.; Roselli, C.; Choi, S.H.; Natarajan, P.; Lander, E.S.; Lubitz, S.A.; Ellinor, P.T.; et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 2018, 50, 1219–1224.
- 117. Qi, Q.; Stilp, A.M.; Sofer, T.; Moon, J.Y.; Hidalgo, B.; Szpiro, A.A.; Wang, T.; Ng, M.C.Y.; Guo, X.; MEta-analysis of type 2 DIabetes in African Americans (MEDIA) Consortium; et al. Genetics of Type 2 Diabetes in U.S. Hispanic/Latino Individuals: Results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes* 2017, 66, 1419–1425.
- 118. Lall, K.; Magi, R.; Morris, A.; Metspalu, A.; Fischer, K. Personalized risk prediction for type 2 diabetes: The potential of genetic risk scores. *Genet. Med.* 2017, *19*, 322–329.
- Hoffmann, T.J.; Ehret, G.B.; Nandakumar, P.; Ranatunga, D.; Schaefer, C.; Kwok, P.Y.; Iribarren, C.; Chakravarti, A.; Risch, N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat. Genet.* 2017, 49, 54–64.
- Wray, N.R.; Ripke, S.; Mattheisen, M.; Trzaskowski, M.; Byrne, E.M.; Abdellaoui, A.; Adams, M.J.; Agerbo, E.; Air, T.M.; Andlauer, T.M.F.; et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* 2018, 50, 668–681.
- 121. Xie, L.; Yang, S.; Squirrell, D.; Vaghefi, E. Towards implementation of AI in New Zealand national diabetic screening program: Cloud-based, robust, and bespoke. *PLoS ONE* **2020**, *15*, e0225015.
- 122. Wei, J.W.; Tafe, L.J.; Linnik, Y.A.; Vaickus, L.J.; Tomita, N.; Hassanpour, S. Pathologist-level classification of histologic patterns on resected lung adenocarcinoma slides with deep neural networks. *Sci. Rep.* 2019, *9*, 3358.
- 123. Zhang, F.; Lei, C.; Huang, C.J.; Kobayashi, H.; Sun, C.W.; Goda, K. Intelligent Image De-Blurring for Imaging Flow Cytometry. *Cytom. A* **2019**, *95*, 549–554.
- 124. Chai, Y.; Liu, H.; Xu, J. Glaucoma diagnosis based on both hidden features and domain knowledge through deep learning models. *Knowl. Based Syst.* 2018, 161, 147–156.
- 125. Jeyaraj, R.P.; Nadar, E.R.S. Computer-assisted medical image classification for early diagnosis of oral cancer employing deep learning algorithm. J. Cancer Res. Clin. Oncol. 2019, 145, 829–837.
- 126. Almagro Armenteros, J.J.; Tsirigos, K.D.; Sonderby, C.K.; Petersen, T.N.; Winther, O.; Brunak, S.; Von Heijne, G.; Nielsen, H. SignalP 5.0 improves signal peptide predictions using deep neural networks. *Nat. Biotechnol.* **2019**, *37*, 420–423.
- 127. Rahman, R.; Kodesh, A.; Levine, S.Z.; Sandin, S.; Reichenberg, A.; Schlessinger, A. Identification of newborns at risk for autism using electronic medical records and machine learning. *Eur. Psychiatry* **2020**, *63*, e22.
- 128. Stamate, D.; Kim, M.; Proitsi, P.; Westwood, S.; Baird, A.; Nevado-Holgado, A.; Hye, A.; Bos, I.; Vos, S.J.B.; Vandenberghe, R.; et al. A metabolite-based machine learning approach to diagnose Alzheimer-type dementia in blood: Results from the European Medical Information Framework for Alzheimer disease biomarker discovery cohort. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 2019, *5*, 933–938.
- 129. Hennig, H.; Rees, P.; Blasi, T.; Kamentsky, L.; Hung, J.; Dao, D.; Carpenter, A.E.; Filby, A. An open-source solution for advanced imaging flow cytometry data analysis using machine learning. *Methods* **2017**, *112*, 201–210.

- Elaziz, M.A.; Hosny, K.M.; Salah, A.; Darwish, M.M.; Lu, S.; Sahlol, A.T. New machine learning method for image-based diagnosis of COVID-19. *PLoS ONE* 2020, 15, e0235187.
- Mir, A.; Dhage, S.N. Diabetes Disease Prediction Using Machine Learning on Big Data of Healthcare. In Proceedings of the 2018 Fourth International Conference on Computing Communication Control and Automation (ICCUBEA), Pune, India, 16–18 August 2018.
- 132. Polygenic Risk Score Task Force of the International Common Disease Alliance; Adeyemo, A.; Balaconis, M.K.; Darnes, D.R.; Rippati, S.; Widen, E.; Zhou, A. Responsible use of polygenic risk scores in the clinic: Potential benefits, risks and gaps. *Nat. Med.* 2021, 27, 1876–1884.
- 133. Polasek, T.M.; Tucker, G.T.; Sorich, M.J.; Wiese, M.D.; Mohan, T.; Rostami-Hodjegan, A.; Korprasertthaworn, P.; Perera, V.; Rowland, A. Prediction of olanzapine exposure in individual patients using physiologically based pharmacokinetic modelling and simulation. *Br. J. Clin. Pharmacol.* **2018**, *84*, 462–476.
- Lippert, J.; Brosch, M.; Von Kampen, O.; Meyer, M.; Siegmund, H.U.; Schafmayer, C.; Becker, T.; Laffert, B.; Gorlitz, L.; Schreiber, S.; et al. A mechanistic, model-based approach to safety assessment in clinical development. *CPT Pharmacomet. Syst. Pharm.* 2012, 1, e13.
- 135. Rasool, M.F.; Ali, S.; Khalid, S.; Khalid, R.; Majeed, A.; Imran, I.; Saeed, H.; Usman, M.; Ali, M.; Alali, A.S.; et al. Development and evaluation of physiologically based pharmacokinetic drug-disease models for predicting captopril pharmacokinetics in chronic diseases. *Sci. Rep.* **2021**, *11*, 8589.
- Heimbach, T.; Chen, Y.; Chen, J.; Dixit, V.; Parrott, N.; Peters, S.A.; Poggesi, I.; Sharma, P.; Snoeys, J.; Shebley, M.; et al. Physiologically-Based Pharmacokinetic Modeling in Renal and Hepatic Impairment Populations: A Pharmaceutical Industry Perspective. *Clin. Pharmacol. Ther.* 2021, *110*, 297–310.
- 137. Shah, K.; Fischetti, B.; Cha, A.; Taft, D.R. Using PBPK Modeling to Predict Drug Exposure and Support. Dosage Adjustments in Patients with Renal Impairment: An Example with Lamivudine. *Curr. Drug Discov. Technol.* **2020**, *17*, 387–396.
- 138. Fendt, R.; Hofmann, U.; Schneider, A.R.P.; Schaeffeler, E.; Burghaus, R.; Yilmaz, A.; Blank, L.M; Kerb, R.; Lippert, J.; Schlender, J.F.; et al. Data-driven personalization of a physiologically based pharmacokinetic model for caffeine: A systematic assessment. *CPT Pharmacomet. Syst. Pharm.* 2021, 10, 782–793.
- 139. Debray, T.P.; Riley, R.D.; Rovers, M.M.; Reitsma, J.B.; Moons, K.G.; Cochrane IPD Meta-analysis Methods group. Individual participant data (IPD) meta-analyses of diagnostic and prognostic modeling studies: Guidance on their use. *PLoS Med.* **2015**, *12*, e1001886.
- 140. Baldi, P.; Brunak, S.; Chauvin, Y.; Andersen, C.; Nielsen, H. Assessing the accuracy of prediction algorithms for classification: An overview. *Bioinformatics* **2000**, *16*, 412–424.
- 141. Scharm, M.; Waltemath, D. A fully featured COMBINE archive of a simulation study on syncytial mitotic cycles in Drosophila embryos. *F1000Research* **2016**, *5*, 2421.
- 142. Golebiewski, M. Data Formats for Systems Biology and Quantitative Modeling. In *Encyclopedia of Bioinformatics and Computational Biology*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 884–893.
- 143. Cohen, J.F.; Korevaar, D.A.; Altman, D.G.; Bruns, D.E.; Gatsonis, C.A.; Hooft, L.; Irwig, L.; Levine, D.; Reitsma, J.B.; De Vet, H.C.; et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: Explanation and elaboration. *BMJ Open* 2016, 6, e012799.
- 144. Enderling, H.; Wolkenhauer, O. Are all models wrong? Comput. Syst. Oncol. 2020, 1, e1008.