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Review

The application of artificial intelligence in hepatology: A systematic review

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ABSTRACT

The integration of human and artificial intelligence (AI) in medicine has only recently begun but it has already become obvious that intelligent systems can dramatically improve the management of liver diseases. Big data made it possible to envisage transformative developments of the use of AI for diagnosing, predicting prognosis and treating liver diseases, but there is still a lot of work to do.

If we want to achieve the 21st century digital revolution, there is an urgent need for specific national and international rules, and to adhere to bioethical parameters when collecting data. Avoiding misleading results is essential for the effective use of AI. A crucial question is whether it is possible to sustain, technically and morally, the process of integration between man and machine.

We present a systematic review on the applications of AI to hepatology, highlighting the current challenges and crucial issues related to the use of such technologies.

1. Introduction

The recent developments in the field of artificial intelligence (AI) were made possible thanks to the increasing availability of huge amounts of data, resulting from the ability to digitally transform information and from the recent increases in computational power. AI mimics human intelligence processes and increases the chance of successfully solving problems. Indeed, intelligent systems can use neural networks not only to examine and perceive the external world (e.g., natural language, vision, sensors etc.), but also to dissect and learn about complex biological systems [1].

AI includes many sub-fields ranging from advanced statistical modelling to machine learning (ML) and deep learning (DL) algorithms. Healthcare is a field that is thought to be highly suitable for the applications of different AI approaches. In the field of health, in fact, AI may have multiple applications. AI algorithms and platforms can identify clinical patterns that might provide a decisional support to healthcare professionals, can interpret the

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imaging data thus assisting radiologists, but also generate automating systems for the analysis of big datasets to improve precision medicine [2].

However, the large-scale application of AI tools and innovative statistical methods is subject to challenges related to the collection, standardization and interpretation of heterogeneous datasets, for data sharing and the safeguarding of sensitive data. Moreover, further concerns regarding the quality of health-related data need to be addressed to be able to apply AI in clinical practice. In fact, the application of AI may be problematic, because algorithms that are flawed or used incorrectly could cause major harm to patients [3,4].

It is essential to define and validate the best algorithms to diagnose and treat liver diseases in real life similarly to many other conditions, to support patients to manage their own liver pathologies, to avoid medical mistakes, and improve economic sustainability by reducing healthcare costs related to liver diseases.

In this review, we present an overview of the last 10 years of the AI-based approaches application in liver diseases and discuss the most urgent issues, challenges and future directions.

2. Methods

A literature search was performed in the electronic database of PubMed using the following search terms: “artificial intelligence”, “learning”, and “liver diseases”. A restriction for English language has been applied. Case reports, case series, pre-clinical studies, and reviews were excluded. Only human studies published in the past decade (from January 2011 to January 2021) were included.

The search and initial screening of the articles were conducted by two expert authors.

The initial search in the electronic database generated 334 articles. Next, two independent researchers did the screening of the articles. One-hundred eighty-four articles were excluded after reviewing their titles and abstracts because they did not fulfil the criteria of search. A total of 150 studies were selected. However, the object of this systematic review will be the 66 articles describing the application of AI approaches developed to improve hepatocellular carcinoma (HCC) and liver metastasis diagnostics (Supplementary Table 1) [5-70], and the 41 articles that use AI to improve non-alcoholic fatty liver disease (NAFLD) and fibrosis diagnostics (Table 1 and Supplementary Table 2) [71-111]. Since the wide diversity of objectives, methods, and metrics precluded a quantitative approach, we performed a clustering of manuscripts based on the type of data that have been used to construct the algorithms. We identify three major clusters of articles that use AI in liver diseases: digital epidemiology data, omics data, and medical imaging and radiomics data. Some of the selected articles were discussed in dedicated specific sections together with other interesting articles in the same field.

Among the 46 residual omitted articles most of them were related to hepatology topics, including liver transplantation, drug-induced liver injury, and hepatitis B and C, that have been recently discussed or that merit to be addressed separately [112,113].

3. AI and liver diseases

AI has numerous potential applications in liver diseases. In this section, we provide examples of how AI, applied to digital epidemiology, analysis of omic datasets, imaging and radiomics, not only contributes to improving diagnosis and treatment of liver diseases, but also plays a central role in future hepatology research.

3.1. Digital epidemiology data

Epidemiology is the scientific study of the distribution and the determinants of health-related states and events in specific populations [114]. Salathé defines “digital epidemiology” as the branch of epidemiology that leverages data generated for purposes different from epidemiology itself [115], such as data coming from Google Maps or social networks. On the same note, in the early 2000s, Gunther Eysenbach coined the term “infodemiology” [116]. Infodemiology is a new area of scientific research which aims to analyse health data that users deposited into the internet [116]. The current pandemic of coronavirus disease 2019 (COVID-19) has fostered the infodemiological approach, which had previously shown to offer quicker answers than normal syndromic surveillance methods in the context of other infectious diseases (e.g. influenza, SARS, HIV) [117–119].

Digital epidemiology is often linked to the use of AI and ML. Indeed, one peculiarity of digital epidemiology is the additional use of unstructured data, i.e. data who lacks annotations, labels or predefined forms of organization [120,121]; this data format requires specific analytical methods, such as data mining and natural language processing ones [1].

Similarly to what is happening to infectious diseases, hepatology can greatly benefit from the development of digital epidemiology. Among others, some viable applications can be: a) to improve prediction of the future epidemiological trends of liver diseases; b) to refine the development of cost-effective solutions to diagnose and treat liver diseases; c) to elaborate new predictive models for risk stratification of liver conditions and to improve liver organ allocation for transplantation.

As regards models to predict the burden of liver diseases in the future, there is an increasing body of evidence showing that the prevalence of NAFLD will increase worldwide for at least another decade, and will be followed by an increase in advanced liver disease [122,123], making it a relevant public health issue. A recent systematic review of ML applications to diagnose NAFLD can be found in the publication by Decharantanachart et al [124]. A good accuracy was reported across the studies where AI-assisted techniques and clinical parameters have been employed in the NAFLD [71-77], even though there is a need of further validation before moving them forward into the clinic.

Additional examples of digital epidemiology applications in the field of prediction can be found in several hepatological domains. Recently Kanwal et al [91] have proposed a simple ML model that using clinical variables produces a new score to forecast cirrhosis mortality.

Risk stratification in rare liver diseases is likely more challenging [125]; diseases like primary sclerosing cholangitis (PSC) are particularly difficult to model, due to the hectic and irregular disease course, the absence of reliable biomarkers and the different possible outcomes that can be assessed [126]. Nonetheless, Mayo Clinic researchers have recently generated two prognostic tools based on a ML algorithm (gradient boosting machine) to predict the incidence of hepatic decompensation within 5 years in 425 patients affected by PSC. The first algorithm leveraged clinical data [127] while the second one utilized plasma bile acid profiling [128]. Despite some limitations (e.g., tertiary centre bias, lack of some covariates), they represent the actual application of ML to burning open questions in the field and offers new perspectives to investigate the long-standing issue of risk stratification in PSC.

Models based on ML have been introduced in the setting of solid organ transplantation too, where prognosis depends on a complex, multidimensional and nonlinear relationship between variables pertaining to the donor, the recipient and the surgical procedure. In the setting of liver transplantation, ML models have been developed to predict pre-transplant survival in patients with

Table 1
Application of AI techniques in the NAFLD field.

Type of data	Ref.	N of subjects	Type of study	Aim	AI approach applied	Performance
Digital Epidemiology	71	2970 (2920 training + 50 validation)	Monocentric prospective	To perform diagnosis of liver steatosis	Different ML algorithms	Fatty Liver Index + Glucose + Age+ Sex, sensitivity=0.979, specificity=1. Abdominal Volume Index + Glucose + GGT + Age + Sex, sensitivity= 0.985, specificity 1. Body Roundness Index + Glucose + GGT + Age + Sex, sensitivity=0.967, specificity=0.99
Digital Epidemiology	72	N/A	Large-scale public dataset	To predict NAFLD development	Quantitative Structure Activity Relationship model constructed using ML tool TANAGRA	Sensitivity=0.66, specificity=0.74
Digital Epidemiology	73	2239	Monocentric retrospective	To investigate the prevalence of NAFLD features and its comorbidities	Supervised ML algorithms including least absolute shrinkage and selection operator (LASSO) and RF classifier	Final model: sensitivity=0.70, specificity=0.79
Digital Epidemiology	74	577 (377 NAFLD + 200 no NAFLD)	Monocentric retrospective	To perform stratification of NAFLD	Different ML algorithms	RF (10 fold cross validation): sensitivity=0.871, specificity=0.858
Digital Epidemiology	75	N/A	Large-scale public dataset	To perform stratification of NAFLD	Different ML algorithms	XGBoost: AUC=88%
Digital Epidemiology	76	10,508 (2,522 + NAFLD)	Monocentric cross-sectional	To predict NAFLD development	Different ML techniques implemented Weka open-source software	SVM: sensitivity=0.725, specificity=0.946
Digital Epidemiology	77	922	Monocentric prospective	To perform diagnosis of steatosis	Laboratory parameter-based ML model	For NAFLD ridge score sensitivity=0.92, specificity=0.90
OMICs	78	1514	Multicenter prospective	To perform stratification of NAFLD	Different models combining omics data with clinical data	Sensitivity and specificity were assessed at different cut-offs but they higher than for other scores
OMICs	79	80 (31 NAFLD + 49 no NAFLD)	Monocentric case-control	To perform stratification of NAFLD	Different ML methods that combine measurements of lipids, glycans and biochemical parameters	Model with lipidomics discriminates fibrosis with sensitivity=0.95 and specificity=0.99
Radiomics	80	204	Monocentric prospective	To quantify the liver steatosis	One-dimensional CNN algorithms for NAFLD diagnosis and fat fraction estimation	For the test cohort, sensitivity=0.97, specificity=0.94
Radiomics	81	60	Monocentric prospective	To quantify the liver steatosis	ML-based model that combines several ultrasound parameters	Model by using the combination of all parameters, sensitivity=0.875; specificity=0.928
Radiomics	82	9552	Monocentric retrospective	To quantify the liver steatosis	Automated DL algorithm for liver segmentation and liver fat quantification	For categorizing a patient as healthy (no steatosis), sensitivity 0.826, specificity 0.963
Radiomics	83	256	Monocentric retrospective	To perform diagnosis and quantification of liver steatosis	Automatic liver attenuation ROI-based measurement (ALARM) pipeline	ALARM center-ROI: sensitivity=0.737-0.79, specificity=0.991-1. ALARM periphery-ROI: sensitivity=0.737-0.842, specificity=0.996-1
Radiomics	84	55	Monocentric prospective	To perform diagnosis of liver steatosis	Inception-ResNet-v2 DCNN	AUC=0.977
Radiomics	85	63 subjects (27 normal + 36 abnormal)	Monocentric retrospective	To perform stratification of NAFLD	DL architecture of convolution + pooling + rectified linear unit + dropout + inception model	Accuracy=99%, AUC=1.0
Radiomics	86	652	Multicentric retrospective	To perform diagnosis of liver steatosis	Algorithm developed by NLP	NLP algorithm detected steatosis with an accuracy exceeding at least 96%
Radiomics	87	12	Monocentric prospective	To perform liver steatosis grading	ELM-based approach	Accuracy=96.75%, AUC=0.97
Radiomics	88	100 (42 normal + 58 abnormal)	Monocentric prospective	To perform liver steatosis grading	Computer aided diagnostic techniques	DT classifier AUC=0.933, Fuzzy classifier AUC=0.883.
Medical Imaging	89	36	Monocentric retrospective	To quantify the liver steatosis	DELINEATE model based on Deep Neural Network	For comparison between steatosis 0 vs. 1-3 with DELINEATE Steatosis Pixel% and DELINEATE Steatosis Count%: sensitivity=0.968, specificity=1. For comparison between steatosis 0-1 vs. 2-3 with Aperio Steatosis Pixel%: sensitivity=0.913, specificity=1
Medical Imaging	90	63 subjects (20 normal + 27 abnormal)	Monocentric retrospective	To classify liver steatosis	Supervised ML classifiers	Overall accuracy=89%

cirrhosis, to assess the best donor-to-recipient match during allocation processes, and to foresee post-operative complications and outcomes [129-134]. An interesting narrative review on the role of ML in the field of liver transplantation, high-lighting strengths and pitfalls, and future perspective has been recently published [113].

Despite the encouraging evidence, before application into the clinic, digital epidemiology need rigorous methodology and large validation cohorts with a full representation of each sex, different ethnicities and different socio-economic conditions [1,135].

3.2. Omics data

Most of the common liver diseases are complex, and determined by a combination of multiple factors, thus, liver pathophysiology includes a multitude of highly dynamic physical and functional interactions between the genome, transcriptome, proteome, metabolome, and epigenome. These words describe complete biological "omics" that provide a huge amount of data in a very short period of time and with an unbiased approach. Despite the first studies were focused on the single-omic approach, nowadays it widely recognized that the combination of more than one omic signature (multi-omics) may lead to stronger scientific conclusions and can be effective for developing diagnostic tools or identifying novel therapeutic targets [136,137].

Hoverer, multi-omics datasets are big and multi-dimensional, thus strategies to manage their storage and wide accessibility, as well as their networking and interpretation in terms of clinical relevance, are important issues in precision medicine [138,139]. Fortunately, the rapid evolution of ML and DL in the last years has facilitated the accurate analysis and the clinical translation in several liver diseases of large datasets produced by omics. Moreover, genomic, epigenomic, proteomic and metabolomic data analyses integrated in computational platforms have the potential to provide precise and reliable biomarkers for personalized diagnosis and treatment of liver diseases [137].

Among liver diseases, NAFLD is the most heterogeneous for both histologic patterns and metabolic features, thus multi-omics approach could be particularly fruitful to identify different phenotypes.

Therefore, intelligent systems that consider a large number of variables from multiple sources may provide an important contribution for the identification of specific omic signatures for patient's stratification in NAFLD [78,79,137].

Genomics and genome-wide association studies are the most active fields of research in NAFLD, revealing a large number of genetic loci linked to an increased susceptibility to disease and its progression [137]. The inclusion of genetic risk factors into risk models, which were obtained by polygenic risk scoring or ML approaches, has improved the accuracy of individual prediction to NAFLD [140]. However, genetic information alone could be limiting for precision medicine and, in fact, several studies recently highlighted that the knowledge of the effects of genetic variants on proteins and lipids is also required to gain novel insights in NAFLD pathophysiology [141].

Recently European researchers of the multicentric prospective cohort study IMI DIRECT developed a total of 18 different models by ML combining omics and clinical data, which allowed to identify biological features associated with intra-hepatic fat accumulation [78]. Interestingly, the study revealed that proteomic markers yielded the highest predictive accuracy when combined with the available clinical data and/or lifestyle data.

A growing literature about NAFLD and other liver diseases has also highlighted the role of gut-associated omics, such as metagenomics and microbiome-related metabolomics, as additional promising tools for discovery of biomarkers and drugs [142]. Accordingly, it could be foreseen as possible to estimate individual glycaemic response to specific foods based on the corresponding specific microbiome by the use of algorithm-driven analysis of multimodal data collection [143–146], but also to identify a specific stool-microbiome derived signature associated with robust diagnostic accuracy for the detection of NAFLD-related [147].

HCC diagnosis and treatment may also benefit from the use of multi-omic datasets. Indeed, the past few years have witnessed the generation of large amounts of molecular omic data that have been elaborated with AI-technologies to classify the liver lesions, and to predict response to transarterial chemoembolization (TACE) or survival of patients with HCC [5-15]. New lines of evidence have pointed out the need of the integration of the available omic signatures of HCC with imaging and electronic medical data, to better define patient sub-groups of disease and translate all information into therapy achievements [148].

Finally, multi-omic approaches may also contribute to the discovery of minimally invasive biomarkers of acute cellular rejection in liver transplant recipients, and some of these datasets could be integrated into diagnostic algorithms to assist clinical decision making with a high degree of accuracy, reducing the need for invasive liver biopsy [149].

3.3. Medical imaging and radiomics data

Hepatologists usually detect, characterize, and monitor liver diseases by assessing medical images, using their skills and experience. However, not too rarely diagnostic conclusions are subjective and inaccurate making more reproducible and accurate assessment an unmet need. To this end, AI may be useful for supporting clinicians. Algorithms can classify images by learning from a large dataset and can even take into account reconstructed dynamic images obtained by computed tomography (CT) or magnetic resonance image (MRI) [150]. The analysis of liver images by DL algorithms proved not only to be more accurate to achieve reproducible imaging diagnosis by automatically recognizing imaging information, but also to be useful for deciding the most appropriate therapy to be adopted. However, it is always mandatory to standardize the methods of acquisition and storage of the acquired bioimages [151].

The generation of large amounts of data using innovative imaging instruments has motivated several liver pathology research groups to explore the use of ML-based algorithms for assessing the stage of HCC, NAFLD and fibrosis [89,90,152].

The results obtained with second-harmonic generation microscopy, which are highly sensitive to the structure of collagen fibrils and fibers and can highlight changes that occur in diseases such as cancer, fibrosis and, connective tissue disorders, are particularly noteworthy [153]. Convolutional neural networks, a DL algorithm pre-trained using multiple sources of images, have provided effective results in determining the degree of severity of liver fibrosis [154]. The use of DL and neural networks reduce computational costs and achieves an area under the curve (AUC) of 1, representing an excellent performance (100%) for risk stratification of NAFLD patients [85].

Quantification of the phenotypic features of a lesion from medical imaging is a recent achievement of AI. Indeed, with the term "radiomics" we currently define the automated high-throughput extraction of image features and "imaging biomarkers" [155,156]. Radiomic data are extracted and processed with bioinformatics tools and can be combined with other patient data (bio-humoral, clinical, genetic, histologic…) to develop models for the improvement of diagnostic, prognostic, and predictive accuracies. The "omics" concept applies to quantitative tomographic imaging on multiple levels (one multi-layer or three-dimensional images from one patient may easily contain millions of voxels). Complex images with high-dimensional data are generated, corresponding to

measurable biological characteristics. Radiomics fulfils the goal of precision, predictive, preventive, personalized medicine in which stable, reproducible and validated molecular biomarkers are used to identify "*the right cure for the right person at the right time*" [157,158].

In the field of radiomics different ML and DL algorithms has been recently developed for assessing NAFLD and liver fibrosis stages, showing radiomics able to provide additional contributions to identify the severity and the progression of liver disease [80-88,93-111].

The imaging surveillance of patients at risk of developing HCC enables us to make diagnoses at earlier stages, when curative treatments are still practicable. Therefore, DL- and ML-based radiomics is rapidly becoming an extremely promising technique for accurate diagnosis and grading of HCC, and for supporting clinicians in choosing personalized treatments [16-67]. In 2018 the Food and Drug Administration approved a plan for AI medical algorithms, including the "Arterys" algorithm for the diagnosis of liver cancer obtained by MR and CT analysis ([51,155], https://www.prnewswire.com/news-releases/arterys-receives-first-fda-clearance-for-broad-oncology-imaging-suite-with-deep-learning-300599275.html).

ML and DL may also be particularly useful for preventing and predicting toxicity as they can be used for segmentation of tumours and surrounding at-risk organs to ensure guiding delivery treatment. Due to such improvements in target delivery, stereotactic body radiotherapy is increasingly administered for treatment of liver cancers. Baseline liver metabolic function has been used to predict toxicity risk. In particular, it has been found that irradiation of the proximal portal vein incurs in twofold toxicity risk compared to the left portal vein [159,160].

So far, most radiomic studies in hepatology were performed to identify prognostic or predictive models of malignant lesions [161]. In the last two years, four retrospective multicentric studies demonstrate that MRI and ultrasound radiomics models based on automated- and/or dynamic- DL algorithms were able to better detect and distinguish benign from malign focal liver lesions, improving the ability to make diagnosis of HCC [20,22,29,42]. Algorithms predict recurrences, the occurrence of post-hepatectomy liver failure, the presence of tumour microvascular invasion and future clinical deterioration, too [18,31,33,34,162-165]. Akai et al. used texture analysis to predict disease-free survival and overall survival [166]. Noteworthy, in a multicentric prospective study, as well as in several monocentric studies, DL model presents a good performance in predicting the response of patients with intermediate-stage HCC undergoing TACE [30,26,46]. Furthermore, radiomic analysis was used to produce a predictive score for tumour response and overall survival in patients with unresectable HCC to be treated with trans-arterial radioembolization using Yttrium-90 [167,168].

In summary, AI based studies of functional, molecular, and structural bio-imaging are providing an extraordinary new opportunity for the *in vivo* study of liver pathophysiology.

4. Challenges and future directions

4.1. Big Data use and implications

Big data is an evolving concept describing a massive volume of structured and unstructured datastes (omics, clinical features, images) that can be processed by AI techniques in order to understand and solve complex problems [169,170].

Large amounts of data are distinguished by volume, veracity, variety and velocity [171,172]. Furthermore, big data analysis must be unbiased and reliable in order to support clinical decisions, but accurate extrapolation can only be achieved through the use of rigorous theoretical underpinnings and reliable health-related data. AI algorithms must be fed with large quantities of reliable data to be able to "learn" complex and non-linear relationships between variables and outcomes of interest [173]. Although the production of a huge number of health-related structured (e.g. clinical trials registries, electronic medical records, medical images, biomarker data, -omics data, administrative databases), and unstructured data (e.g. social networks, media, internet etc.) [171] is expected in the future, at present it is difficult to obtain good sources of information to feed algorithms.

The available structured healthcare data are largely obtained from randomized controlled trial (RCT). The current most reliable registries (http://www.eltr.org/; https://rare-liver.eu/registry) for liver diseases [174,175] contain data that vary significantly in quality [176] and are derived from diverse sources, including clinical observations, medical imaging, medical devices and molecular science.

The most exciting new AI applications in health care are in the areas of ML and DL. However, until their effectiveness in improving clinical practice will not be validated, the produced data cannot be considered of real value, even when achieving AUC of 0.99 [1]. In fact, the features of structured big data cannot be aggregated and shared, and errors do not disappear in big data, on the contrary they become worse [177,178]. The manipulation of data by AI technologies might become really harmful for health-care systems, generating unexpected and unintentional outcomes with capacity to negatively and/or unfairly influence medical decisions.

While we wait for the creation of new reliable databases, we must deal with a large number of smaller separate databases that do not have the features of "big data". This means implies that demanding and time-consuming data cleaning and pre-processing procedures are always to be set in place to create databases that aims at limiting errors as much as possible, before we could start to use intelligent systems to evaluate the reliability of health studies. If we do not pay careful attention to data training, which begins with finding new ways to train computers using small datasets, even the most powerful algorithm will fail to meet expectations and will produce unpredictable and unreliable outputs [178–181]. One interesting strategy for working with small databases could be devising AI applications capable of "unsupervised learning" that is learning without labelled data. However, we are far from achieving this goal.

Driving innovation in the medical field also requires fast, secure, and interconnected infrastructures for interoperable data systems. The infrastructures must adhere to international standards and use internationally shared medical terminologies to convey accurate medical information.

Finally, there is an even more important and urgent need for transparency, and the deconvolution of "black box" algorithms. The concept of "black box" refers to opaqueness of algorithms currently in use, which makes it difficult to understand how outputs have been determined [182]. Therefore, an extensive simulation and validation of the obtained results, systematic error corrections and revision are essential for an AI algorithm to play a relevant role in clinical practice [183].

In **Fig. 1**, we propose a flowchart that shows how big data should be well-processed through the use of ML and DL algorithms.

4.2. Privacy and data security

The European Commission considers both storage and protection of sensitive data the most important and urgent problems related to the different healthcare systems. In a near future, technologies and data protection will become predominant. In the field

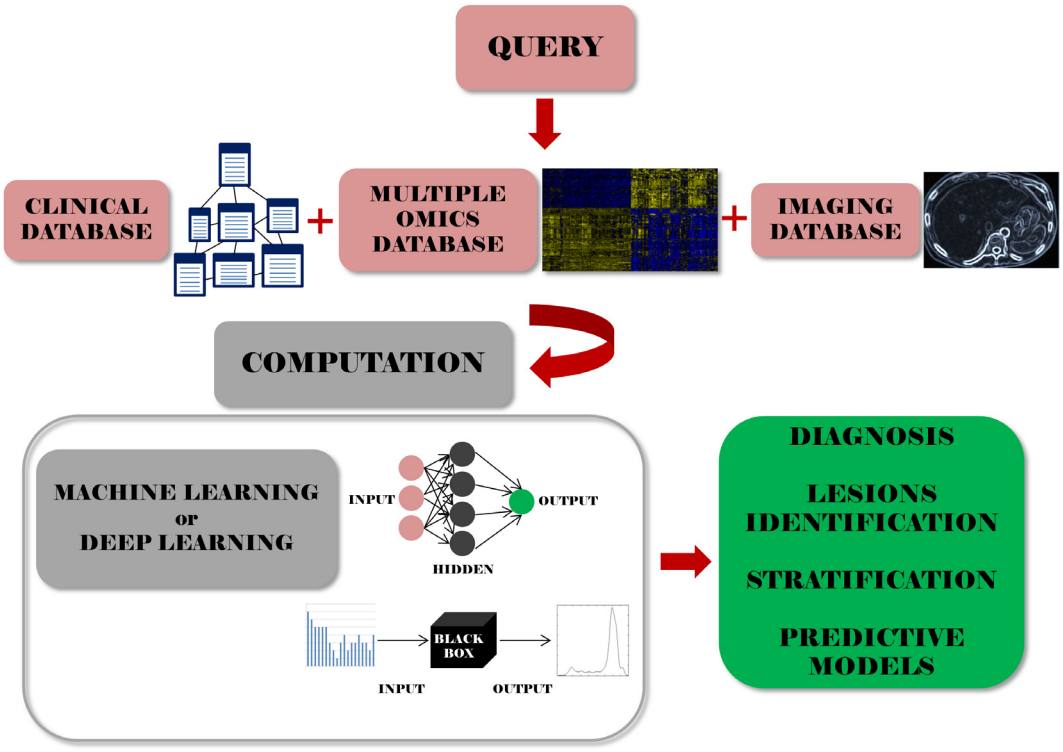

Fig. 1. Flowchart from big data to AI validation through Machine and Deep Learning.

of medicine, the main issue to the future of AI is to ensure privacy and security of patient's data [184,185].

Developing algorithms often incurs the risks of revealing sensitive personal data, including patient's medical history, up to considering that recent advances in facial recognition technology is making always easier to identify patients [186].

The latest pandemic infection by SARS-CoV-2 is helping us better understand the key role of AI: how it can speed up new solutions for identifying track, forecasting outbreak, as well as for diagnosing and treating this global pandemic. Clinicians, academics, and governments around the world, together with technology startups are involved in activating each ready-to-use technology as soon as possible to counteract the dissemination of the virus.

However, up to date, the balance between privacy and health is particularly difficult to manage without previous and shared rules. The creation of new secure shared platforms regulated by governmental legislation, which has already been achieved in Estonia (https://e-estonia.com/solutions/security-and-safety/), is necessary in all European countries to avoid serious security issues that will otherwise hamper advances in AI in the field of medicine. Currently, most research institutions use fragmented and protected infrastructures that cannot be shared and aggregated. To address this problem, over the last decade UE grants have supported the development of platforms for protected and well-structured shared "data spaces" where sensitive data, such as anonymized data and data coming from RCT, can be collected and used to advance knowledge in the field of health care [187]. The General Data Protection Regulation (GDPR) states: "*In order to ensure fair and transparent processing in respect of the data subject […] the controller should use appropriate mathematical or statistical to […] secure personal data in a manner that takes account of the potential risks involved for the interests and rights of the data subject and that prevents, interalia, discriminatory effects on natural persons.*"

However, the European Union's GDPR and the recent ethical guidelines for trustworthy AI (https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai) are the first steps of a long path.

4.3. Other ethical questions and considerations

These innovative and promising AI techniques raise some important questions and considerations. Could AI autonomously modify the guidelines provided by experts? What is the best way to safeguard the patient-doctor relationship? What about self-diagnosing and self-medication? Is it acceptable to use non-transparent algorithms for patient care? What should be done to improve and clarify the outcomes obtained by AI methods? What should Europe do to remain competitive?

In terms of scientific publications in AI and health, Europe is extremely well positioned, but competition is increasing [188]. In recent decades, Europe has suffered a "brain drain", as a significant number of talented individuals left the Continent to work outside. A similar 'brain drain' from academia to industry is increasingly taking place. A growing number of scientists are if fact leaving academia for more profitable roles in global technology companies. Likewise, in recent years, the number of AI publications authored by individuals with company affiliation has grown exponentially [189].

At last, it is also very important to remind, that the training of algorithms must be performed in a meticulous way to prevent AI from worsening pre-existing disparities. For example, an algorithm was created to identify skin cancers without considering different skin colours. It is relatively easy to create algorithms that fail to include minorities in the datasets [190]. In the health sector, standards must be established, and non-profit and industrial research policy strategies must be developed to monitor and control all aspects of the value chain from infrastructure to data, skills, and services.

4.4. Future directions

Even though AI technology applications in health are promising, there are still many obstacles and pitfalls. Machine and deep learning are not magic wands that can transform any data into gold. Considering the large amount of information (e.g. personal

history of the patient, family diseases, genomic sequences, tailored treatments) that a physician should evaluate before making a decision, it is easy to understand how intelligent systems could be extremely useful for supporting healthcare personnel [191]. To date, the direct utilization of DL and ML methods in liver diseases has been scarce, but AI promises to increase the integration of multi-omic datasets with clinically available data enabling us to understand the molecular complexity of disease in hepatology. Computational models may provide non-invasive comprehensive multiscale characterization of liver, taking into account microenvironment and the features of patients, thereby giving important supports to clinicians for diagnostic, prognostic, and predictive decisions. Furthermore, integrated biomarkers may improve non-invasive patient selection, stratification, prognoses and for choosing specific targeted therapies. Liver diseases need composite multiscale synergistic approaches and tools for the analysis of clinical features, genetic patterns, and radiographic, histopathologic and biophysical data to speed up innovative and virtuous management of patients. However, we must be careful and parsimonious when using machines to support clinical decisions, because excess use and confidence in machines could reduce, in a worrying way, the professional skills of physicians and may have serious consequences in cases where intelligent systems malfunction [191]. Even though intelligent systems leverage families of algorithms helping to unravel different classes of problems, physicians must still acquire skills, experience, and knowledge to enable them to choose how and when AI techniques can be used to solve diagnostic or treatment problems.

If regulated and controlled, AI has certainly the potential to help us provide better assistance to patients affected by liver diseases and to reduce the considerable economic resources necessary to address diseases such as chronic hepatitis, liver tumours and liver transplant.

In the near future, we firmly believe that we will experience a deep transformation in hepatology practice by AI, that will overcome embedded prejudices and eventually be fully integrated into the daily clinical practice.

Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.06.011.

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