Regulatory and Ethical Issues in the New Era of Radiomics and Radiogenomics

EDITOR'S PICK

The field of radiology is rapidly integrating radiomic and radiogenomic approaches into standard practice. The Editor's Pick by Pesapane explores the vitality of regulation and ethics when establishing and maintaining these pathways.

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Abstract

Radiomics is a science that investigates a large number of features from medical images using data-characterisation algorithms, with the aim to analyse disease characteristics that are indistinguishable to the naked eye. Radiogenomics attempts to establish and examine the relationship between tumour genomic characteristics and their radiologic appearance. Although there is certainly a lot to learn from these relationships, one could ask the question: what is the practical significance of radiogenomic discoveries? This increasing interest in such applications inevitably raises numerous legal and ethical questions. In an environment such as the technology field, which changes quickly and unpredictably, regulations need to be timely in order to be relevant. In this paper, issues that must be solved to make the future applications of this innovative technology safe and useful are analysed.

INTRODUCTION

In the current landscape of medicine, radiomics is an emerging translational field of research geared towards extracting mineable, high-dimensional data from radiological images with the aim to reach robust and reliable models that can be transferred into clinical practice for the purposes of prognosis, noninvasive disease tracking, and evaluation of disease response to treatment.[1,2] Through a similar process, radiogenomics investigates the relationship between the imaging characteristics of a disease, namely the imaging-phenotype or radio-phenotype, and its gene expression patterns, gene mutations, and other genome-related features.[3,4]

What is the practical significance of elucidating this relationship? Using innovative technology, radiogenomics aims to develop imaging

biomarkers that can predict risks and patient outcomes, allowing for better stratification of the patients and more precise management.[5]

TECHNOLOGIES BEHIND OMICS SCIENCES

Certain supporting technologies of radiogenomics can measure and quantify imaging features, whilst at the same time analyse the characteristics of a large family of genes, proteins, or even metabolites.[6] These technologies need large datasets,[7] nowadays defined as big data. The Cancer Imaging Archive[8] is an example of a service that hosts a large archive of anonymised medical images of cancer with related data (e.g., patient outcomes, treatment details, genomics, pathology, expert analyses) accessible for public download. This huge amount of information is data whose scale, diversity, and complexity would present difficulties in searching and analysis using the traditional data-processing methods.[9]

The method to analyse these data currently incorporates artificial neural networks, which are flexible mathematical models that use multiple algorithms to identify complex nonlinear relationships within big data. Machine learning (ML), a subfield of artificial intelligence (AI) science that allows computers to learn without being explicitly programmed, has been applied in radiogenomics.[10,11] Among the techniques that fall under the ML umbrella, deep learning (DL) has emerged as one of the most promising.[12] While ML commonly reaches an error rate that cannot be further lowered even with the addition of other data to the process, DL allows a continuous improvement towards a continuously better performance, namely a continually lower error rate.[13]

ETHICAL AND LEGAL CONSIDERATIONS IN RADIOMICS AND RADIOGENOMICS

The great enthusiasm towards and dynamism surrounding the development of software based on ML and DL is shown by the highly correlative trend of related publications in the literature in the last 10 years. Equally, there are no doubts that the use of radiogenomics represents a relevant topic for research teams, with initial promising results.[14,15]

Radiomics, using morphological features from radiological images, has been able to distinguish cancer from normal tissue and even define the histological grade for certain tumours.[16-18] Recent studies have been able to discriminate prostate cancer from benign prostate tissue (and even add information about aggressiveness through Gleason Score), as well as determine whether a meningioma was high or low grade.[19-21] Further examples of aggressiveness determination include a work regarding the use of radiomic assessment of pancreatic intraductal papillary mucinous neoplasm to stratify patients for surgical resection,[22] as well as a study that assessed the metastatic potential of lung cancer through 35 radiomic features.[23]

Radiogenomics investigates the relationship between disease imaging characteristics, namely the imaging-phenotype or radio-phenotype, and its gene expression patterns, gene mutations, and other genome-related features. Radiogenomics has already been utilised for identifying hepatocellular carcinoma subtypes more sensitive to immunotherapy,[3] and for work in breast cancer investigating a delicate situation such as that of neoadjuvant chemotherapy for locally advanced disease.[24]

However, radiomics and radiogenomics still need time before cementing a significant practical role in cancer research due to limitations of the available big data that, currently, lacks complete characterisation of the patients and poor integration of individual datasets.[9]

Moreover, in addition to the technical limits that are still to be addressed, some ethical challenges are straightforward and need to be guarded against. The intent behind the design of such studies needs to be considered to avoid unethical use, such as to perform clinical actions that would generate increased profits for suppliers (i.e., recommending drugs, tests, or medical devices) but not necessarily reflect better care.[25] Therefore, there is urgency for serious regulations and policy initiatives regarding the use of ML and DL systems for radiogenomics, especially when the correct detection of a disease's genomic background and the best management of a patient can be controversial.[9]

As with AI, one of the most important issues to consider is classification.[9] If the software and algorithms used in radiogenomics are to be considered medical devices, a full set of specific legislations have already been developed and would apply.[9,26] If, on the contrary, these software and algorithms will not be classified as medical devices, it is vital to produce specific policies and legislation to regulate this growing field. There are two main approaches that could be taken in producing the necessary legislation: the precautionary principle approach imposes limits on certain applications of AI, ML, and DL systems due to their potential risks, while the permission-less innovation approach allows experimentation to proceed freely, and regulates issues that arise as they present themselves.[27] Clearly, the former would be beneficial for the diffused fear discussed below, whereas the second would allow enhanced research and both faster and impactful development.[28]

Furthermore, companies are improving their understanding of the potential of ML and DL, and are continuously collecting new types of data to process.[29] Therefore, serious regulations and policy initiatives concerning radiogenomics are a very hot topic, and the pursuit of one approach rather than the other will make a material difference. As far as we know, no governments have legislated about radiogenomics, despite the fact its applications are ready to change several national healthcare systems around the world.[9] Nevertheless, there have been some legal developments in the right direction. In 2016, the USA signed into law the 21st Century Cures Act, which is designed to help accelerate the development of medical products and encourage innovations and advances.[30] In addition, the Health Insurance Portability and Accountability Act (HIPAA) regulates data collection and processing in healthcare,[26] while the U.S. Food and Drug Administration (FDA) sets requirements in relation to cybersecurity[9,27] and is in charge of approving genome-based testing and radiomic studies.[30] In Europe, the European Union (EU) is now in the process of updating its data protection and cybersecurity legislation, with the General Data Protection Regulation (GDPR) and the Directive (EU) 2016/1148 on cybersecurity.[31]

The adoption of Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on *in vitro* diagnostic devices (IVDR) changed the European legal framework for medical devices, introducing new responsibilities for European Medicines Agency (EMA) and for national competent authorities.[32-34] This reform originated from the awareness that the existing directives created in the 1990s[32,34,35] were not fit to deal with new, evolving technologies such as AI systems, and from the identification of some flaws in this regulatory system, for example the lack of control on notified bodies. Some of the main characteristics of this reform will be the extended scope to include a wider range of products, extended liability in relation to defective products, strengthening of requirements for clinical data and traceability of the devices, more rigorous monitoring of notified bodies, and improved transparency through making information relating to medical devices available to the public.[9,36]

However, considering the thousands of algorithms that will likely be developed, governmental regulatory agencies are ill-equipped to perform regulations in this field internally.[37-41] Moreover, the sheer number of algorithms that will likely be submitted for regulatory approval could place considerable burdens on the regulatory reviews process. Therefore, public–private partnerships between regulatory agencies and trusted organisations such as medical specialty societies could play an important role in validation of AI algorithms, collecting the real-world evidence that support the ongoing efficacy and safety of AI algorithms in clinical practice.[37-42]

Although the gap of clear regulation could seem a problem for the future, this might change in a few years. One relevant example is the insurance system, which might discriminate patients with medical conditions that are determined to be predominantly genetic and not lifestyle related. Recently, an insurance provider in the USA announced that it will no longer offer policies that do not include digital fitness tracking that collect health data through wearable devices such as a smartwatch. Policy holders can earn discounts and rewards such as gift cards for hitting exercise targets and activity-tracking devices can record how much exercise somebody is doing and can be used to log dietary choices.[43] Although the efficacy, in terms of benefits, of interventions that use apps to

improve diet, physical activity, and sedentary behaviour have been demonstrated,[44] some privacy advocates may warn that insurers could use tracking data to punish customers who fail to meet targets,[45] however it is the belief of the author that this is not the biggest issue to face. Foreseeing the future applications of radiogenomics, which laws do governments have to implement in order to prevent insurance companies from requesting the genetic profile of their customers before stipulating a contract? In this dystopian scenario, insurance companies may provide patients with insurance assuming they are allowed access to all of the patient's data, including radiogenomic data. Based on this, companies may decide to set patients' premiums based on their own genome.

On the other hand, is it true that genome sequencing reveals a patient's fate? Many people fear that healthcare might attempt to 'play creator' with the use of genome sequencing or gene modification. Despite radiogenomics being capable of revealing possible health conditions and risks for some diseases, we must remember that our health is not entirely determined by our genome.[46] For this reason, the aim of radiogenomics is not to identify a predisposition to a disease, but to detect the genetic alterations of a disease once it has already manifested itself in order to choose the most precise treatment and improve the patient's outcome, otherwise known as precision medicine.

Nevertheless, nowadays there is diffuse fear about this approach. As in earlier historical eras, the origins of fear stem from the lack of knowledge and experience with the particular technology. It is the author's belief that this gap of knowledge can be filled by the one who is responsible for this kind of investigation, namely the radiologist.[7,37,47] In the past, shortly following Wilhelm Conrad Röntgen's discovery of the X-Ray, people were scared that this technology might read their thoughts and see through their body and soul.[13] Since then, radiologists have been on the wave front of the digital era in medicine. In being the first medical professionals to pioneer the adoption of computer science in their daily work, they are now arguably the most digitised arm of healthcare professionals.[48,49] Even though the introduction of new technologies has mostly been perceived as new approaches for producing images, innovation has also deeply changed ways to treat, present, and interpret images.[49,50] Moreover, the role of radiologists will be enhanced by radiogenomics if they choose to embrace this technology for acquiring more information regarding an imaging finding, including those not only pertaining to diagnosis but even features which are useful for treatment and prognosis.[5,16,51-53] This technology may also be used for saving time they currently give to routine and monotonous tasks, with a strong volition to dedicate the saved time to communicate with patients and to interplay with colleagues in multidisciplinary teams.[50]

Similarly, forward-looking legal notions and principles will be necessary for the near future, as the first scenarios with narrow AI and clinical applications of radiomics and radiogenomics may arrive as early as within a year at the medical malpractice law firms. Healthcare regulators, agencies, and lawyers need to face these new challenges.

DATA PROTECTION AND CYBERSECURITY ISSUES

Data protection and cybersecurity implications of the radiomic data represent another challenge that needs to be addressed. An ongoing debate about balance between privacy and the need to obtain a large amount of data is developing, especially when it comes to sensitive data such as medical information.[9,13,47] As discussed above, the lack of appropriately organised big datasets for training radiogenomic algorithms is a key obstacle preventing the introduction of these systems in healthcare.[7,11,54,55] One of the problems is that sensitive data should be collected from unknown sources[56] because of the lack of unique and clear regulations.[57,58] In the era of electronic medical records, radiogenomics complicates an already complex cybersecurity landscape;[59] the concept of confidentiality requires that a physician withholds information from the medical record in order to truly keep it confidential.[25]

A possible solution for cybersecurity could come from blockchain technology (BCT), namely an open-source software that allows the creation of large, decentralised, and secure public databases containing ordered records arranged in a block structure.[60] Different blocks are stored digitally, in nodes, using the computers of the blockchain

network members themselves, who are both users and maintainers of the entire system. The information on all transactions, present and past, are stored in the nodes.[61] Although the best-known use of BCT is in the field of economics (i.e., cryptocurrencies), its usefulness is extending to other fields, including healthcare. Particularly, BCT appeals to radiogenomics due to its emphasis on sharing, distribution, and encryption.[61] Newer BCT efforts such as smart contracts, second-layer systems, and permissioned blockchains further the potential healthcare use, and there has been limited hype surrounding the potential of the technology in medicine.[62] As the blocks are impossible to change, it is impossible to delete or to modify anything without leaving a trace, and this is critical in the case of sensitive data such as medical information.

Unfortunately, there is another side of the coin: at this moment, to obtain greater security, the privacy is lost. The patients should accept to share their sensitive data, without a central authority to decide what is right or wrong. The author's opinion is that the time is not yet ripe for such an eventuality. This is also because BCT currently guarantees integrity of patient information but not the privacy security, meaning further development needs to be considered before healthcare application.

CONCLUSIONS

These innovative technologies that rely on sensitive data to improve patient care and treatment are needed. However, several challenges such as the regulation of data protection and cybersecurity, the new policy initiatives, and the discussion about the fiduciary relationship between patients and medical systems will have to be addressed as soon as possible. A good employment of radiogenomics may be helpful, powerful, and valuable. Vice versa, an unethical use of this technology may be dangerous: regulatory authorities, scientists, physicians, and patients must work together to prevent this.[55] The most important means of dissolving fears around radiogenomics is education; this is the time to discuss and debate how technologies such as radiogenomics will change our lives and what are the things we do not want to happen.

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