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ONCOLOGY

The changing face of cancer diagnosis: From computational image analysis to systems biology

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Key Points

- *Radiomics and radiogenomics will merge radiology, nuclear medicine, pathology and laboratory medicine.*
- *Automation of image data analysis will change the daily routine work.*
- *Image-guided therapy and handling complex radiogenomic data will play a major role.*

Abbreviations

CAD	Computer-aided diagnosis
ELISA	Enzyme-linked immunosorbent assay
MRM	Multiple reaction monitoring
SRM	Selected reaction monitoring

Introduction

The complementarity and the competitiveness of liquid biomarkers, histopathology and imaging features as well as the consequences of digitalization and automation on image analysis and data interpretation will support and change cancer diagnosis and therapy. Furthermore, the increasing ties between diagnostic strategies and therapeutic conduct will shape the face of diagnostic medical professions like radiology, nuclear medicine, clinical chemistry and pathology.

Automated image analysis

Computer-aided diagnosis (CAD) has been broadly implemented in the field of clinical chemistry and in electrocardiography; only the approval of the automatically generated diagnosis is still required by the physician. One may argue that automated analysis of pathological, radiological and nuclear medicine images is much more complex, since the clinical background needs to be considered and the interindividual variability is higher. However, considering the rapid development of machine learning and the ability of computers to compare individual cases with huge databases, it may not take long until many diagnostic propositions can reliably be made by software [1–3]. For example, it has been shown that commercial CAD software solutions are already capable of detecting 89 % of cancers in digital breast tomosynthesis [4] and the majority of pulmonary nodules in chest CT data [5]. In line with this, Kim and co-workers reported an improved assessment of pulmonary nodule sizes if analysed using a semi-automated approach compared to manual measurements [6].

Because there is potential loss of information during image reconstruction, intelligent software can already start feature recognition at the raw data level, thereby potentially improving diagnostic performance. It is also worth mentioning that in non-medical field computer-aided image analysis is even more advanced, e.g. in military satellite software used for surveillance abnormal behaviour of individual people can be detected within a large and heterogeneous area with high precision [7, 8].

Thus, one can envisage that a large percentage of routine image analysis in radiology, pathology and nuclear medicine will be overtaken by computers. Medical doctors may then only need to validate the proposed diagnosis, reducing their daily workload substantially.

Competitiveness and complementarity of liquid biomarkers

If we consider population screening (e.g. for breast, prostate or colon cancer), biomarkers from blood and/or urine are most

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preferable since these are rapidly accessible, cost effective, well accepted by the patient and can cover screening for several tumour entities. Here, great advances have been made in proteomic analysis and multiple new assays are under evaluation using mass spectrometry, selected reaction monitoring (SRM), multiple reaction monitoring (MRM), multiplexed enzyme-linked immunosorbent assay (ELISA) and high-density antibody microarrays [9]. One example illustrating the diagnostic power of such arrays was published by Gerdtsson and co-workers, who were able to show in a multicentre study that a panel of 25 serum biomarkers was capable of discriminating patients with pancreatic cancers from healthy individuals with AU-ROC values of 0.98 [10]. Likewise, Sauter [11] and Shah [12] and co-workers reported on potent serum and/or stool biomarkers for the early detection of breast cancer and colon cancer.

It can be expected that liquid biomarker assays will become the most important tools for the purpose of population screening [9, 13]. While many liquid biomarker assays still suffer from insufficient sensitivity and specificity, it can only be a question of time until powerful markers and marker combinations will be identified considering the current rate of knowledge increase regarding cancer pathophysiology and immunology. In the long run, this may move imaging for tumour screening into the second line of diagnosis, where it will play an important role in tumour staging, biopsy, surgical guidance as well as in making decisions regarding physical and pharmacological therapeutic interventions. Even therapy monitoring and the assessment of cancer progression may partially be covered by liquid biomarkers if these can provide reliable information about the changes in the overall tumour load, which may be sufficient for the majority of therapeutic decisions. In the majority of nonsolid tumours, for example, liquid biopsies and serum biomarker analyses are already providing the most important therapy response data. This means that non-invasive imaging will be performed more selectively, e.g. to monitor tumours growing at critical locations, to control metastases with unpredictable growth rates and to adjudicate in unclear cases. Furthermore, imaging will continue to be used for the assessment of complications of tumour diseases and their therapies, e.g. venous thrombosis or abscess formation [14].

Radio(geno)mics

There are different ways to extract information from reconstructed images; we can here consider how this is done by a radiologist or pathologist. Usually there are several clearly defined characteristics that guide the physicians' decisions and residual uncertainty is reduced by intuition, which is nothing other than the comparison of the current pattern with those stored in our memory. Usually, the defined characteristics are those we pathophysiologically understand, while many features that are responsible for the subconscious pattern recognition are unknown. A computer can easily extract numerous image features from a lesion, thus making the pattern in the physician's memory mathematically describable and quantifiable. If the computer has access to a large database it can compare these features to numerous reference cases and, thus, theoretically become superior to a human. However, the computer also needs to learn weighting the extracted features and to bring them into the clinical context. To some extent, this can be achieved via machine-learning algorithms (e.g. neuronal networks) [1–3]; however, the addition of pre-knowledge (e.g. the information that poorly defined tumour margins, star-like extensions and early contrast enhancement of lung lesions are more indicative of malignancy than a certain mean intensity value) will also strongly contribute to a better performance of the software [1–3]. In this context, it is noteworthy that the success of CAD depends strongly on the quality of the image features and, thus, significant effort should be spent in standardization and validation of image data.

Therapeutic decisions are usually taken by considering information derived from blood biomarkers, noninvasive imaging and histopathology. The different diagnostic measures are collected and interpreted by the responsible doctor or discussed by interdisciplinary tumour boards. However, there is too little structured and collective diagnostic data analysis by the different diagnostic medical disciplines, which makes the development of comprehensive diagnostic concepts difficult. This is going to change with the broad implementation of software solutions enabling clustered data analysis and decision-making based on diverse omics data [15–17] (Fig. 1). In this context, the term radiogenomics is used to describe the integrated hierarchical analysis of image features (radiomics) in combination with other omics data (e.g. genomics, proteomics, lipidomics). A convincing example for the diagnostic potential of radiogenomics was provided by Aerts and colleagues [16]. These authors extracted more than 400 different image features from lung cancers, visible on routine chest CT images, and showed that the consideration of these radiomic features together with genomic data resulted in a significantly improved discrimination of tumour phenotypes with a corresponding different prognosis as compared to using either image or genomics data alone [17].

From radiogenomics to systems biology

In the future, imaging data may play a major role in systems biology. In systems biology mathematical disease models are generated that can be used for prognostication, tumour classification and prediction of patients' responses

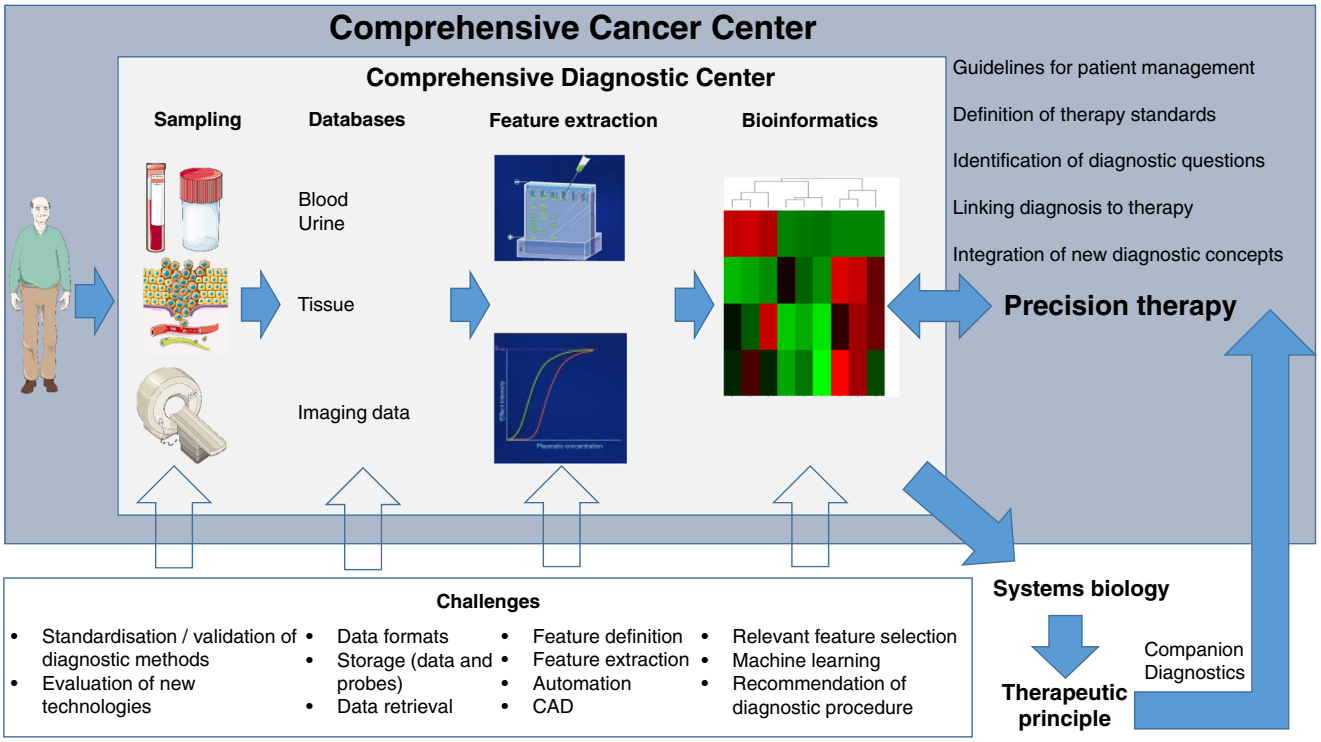

Fig. 1 Sketch illustrating the required infrastructure and challenges for an integrated diagnostic approach. The infrastructure might be institutionalized in a comprehensive diagnostic centre (CDC), which can be part of a comprehensive cancer centre (CCC). The CDC addresses four key areas(i) acquisition of diagnostic data, (ii) data and probe storage, (iii) feature extraction, and (iv) data clustering. These areas fuel research on the challenges specified below the empty arrows. The CDC develops recommendations on diagnostic procedures. In this context, refinements are made, which particularly consider its impact on therapy, the implementability into the clinical workflow and economic aspects. The sketch also illustrates the role of systems biology and its link to radiogenomic analyses for improving precision therapy (Clip art was taken from the Servier's 'Medical Art' database (http://www.servier.com/Powerpoint-image-bank) and modified)

to therapy. These models also support the understanding of tumour pathomechanisms, the refinement of combination therapies and the development of new drugs [18–21]. For example, after mathematical modelling of the growth kinetics of pancreatic cancers, Haeno and co-workers were able to predict the probability of these tumours having metastasized, and showed that using this information concrete recommendations on the therapeutic procedure could be given [22]. Unfortunately, although in the radiomics field scientists have already identified diagnostically potent marker panels and parameter correlations [15–17], not much effort has been spent in systematically evaluating the pathophysiological meaning of the findings, which often is a prerequisite for their integration into systems biology models. The insufficient consideration of radiomic features in the pathophysiological and mechanistic context is one of the main reasons why radiomic studies fail due to the wrong choice of input parameters and the suboptimal selection of complementary imaging methods.

However, despite these strong arguments for the development and use of mathematical disease models, we need to be careful when making therapy decisions based on mathematical models or statistics that are based on data from large cohorts. What might be statistically true for a cohort, does not necessarily apply to the individual, and we need to avoid a situation where this kind of precision medicine starts to drive socio-economic players (i.e. private or public reimbursement bodies) toward decision trees that are adapted to a cohort, while being individually unethical.

Table 1 Developments predicted to change cancer diagnosis and the job profiles of diagnostic disciplines:

- Liquid biomarker panels will replace some indications for imaging in cancer screening and therapy monitoring
- Computer-assisted diagnosis will take over major parts of routine image analysis
- Clustered and combined analysis of radiological, pathological and omics data will dissolve the borders between radiology, nuclear medicine, pathology and laboratory medicine
- Radiologists' job profiles will change by decreasing the time spent for visual routine image-analyses but increasing their involvement in image-guided therapy and the handling of complex radiogenomic data
- Comprehensive diagnostic centres and/or a new kind of specialized physician capable of integrating and handling all diagnostic data of a certain group of cancers may be required

Comprehensive diagnostic centres and the changing job profile of diagnostic medical professions

As a consequence of automated image analysis and the increasing use of liquid biomarkers, less manpower will be required to view the diagnostic data and outsourcing of image analyses will become easier. On the other hand, the handling of diagnostic data will become more complex and integrative. For instance, already now in large centres biopsies are decreasingly needed to confirm the presence of cancer, but instead to acquire information about (genetic) cellular aberrations that are relevant for selecting molecular cancer therapies [23]. In this context, a good example is the HER2-test, which is routinely performed to obtain an indication for trastuzumab antibody therapy [24]. Thus, the overlap in the competence fields of different diagnostic disciplines will increase and their relevance to therapy will get stronger. This calls for a broader education of medical diagnostic specializations and/or new centre structures.

We envisage that comprehensive diagnostic centres will be established next to or even as part of comprehensive cancer centres. These comprehensive diagnostic centres will be responsible for the standardization of diagnostic data acquisition, the installation of large reference databases, refined extraction of (quantitative) image features, the assessment of competitiveness and complementarity of diagnostic information derived from radiology, nuclear medicine, pathology and laboratory medicine, as well as for clustering and interpreting the data (Fig. 1). In this context, new diagnostic medical professions or specializations may develop that are responsible for handling the entire multiparametric diagnostic information for one or several tumour entities across the different disciplines (e.g. a specialist for the diagnostic management of solid cancers). In addition, with the closer ties between diagnosis and therapy, the involvement of radiologists and nuclear medicine doctors in therapeutic decisions and interventions will increase. These will include the image-guided personalization of combination (drug) therapies as well as image-guided interventions such as precise tumour biopsy, tumour ablation or internal radiotherapy.

As a consequence, medical doctors specialized in diagnostic disciplines are being challenged to think about their future and should support the changes needed to reach the next level of cancer diagnosis and precision therapy (Table 1).

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent The paper does describe a study on humans.

Ethical approval Since the paper only discusses literature, no ethical approval was necessary.

Methodology
• Analysis of literature.

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