

EFLM Paper

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The value proposition of integrative diagnostics for (early) detection of cancer. On behalf of the EFLM interdisciplinary Task and Finish Group “CNAPS/CTC for early detection of cancer”

<https://doi.org/10.1515/cclm-2022-0129>

Received February 14, 2022; accepted February 15, 2022;
published online February 24, 2022

Abstract: Disruptive imaging and laboratory technologies can improve clinical decision processes and outcomes in oncology. However, certain obstacles must be overcome before these technologies can be fully implemented as part of the standard for care. An integrative diagnostic approach represents a unique opportunity to unleash the full diagnostic potential and paves the way towards personalized cancer diagnostics. To meet this demand, an interdisciplinary Task Force of the EFLM was initiated as a consequence of an EFLM/ESR during the CELME 2019 meeting in order to evaluate the clinical value of CNAPS/CTC (circulating nucleic acids in plasma and serum/circulating tumor cells) in early detection of cancer. Here, an overview of current disruptive techniques, their clinical implications

and potential value of an integrative diagnostic approach is provided. Furthermore, requirements such as the establishment of diagnostic tumor boards, development of adequate software solutions and a change of mindset towards a new generation of diagnosticians providing actionable health information are presented. This development has the potential to elevate the position and clinical recognition of diagnosticians.

Keywords: cancer; circulating tumor cells (CTC); colorectal cancer; ctDNA; integrative diagnostics; liquid biopsy.

Introduction

Various disruptive technologies have emerged in diagnostic medicine within the last 10 years and are currently on the threshold of implementation into routine care. This has substantially changed both diagnostic procedures and treatment strategies and subsequently improved patient outcomes within a wide variety of diseases [1].

This is of particular importance for oncology, where disruptive technologies like liquid biopsy (LB) or positron emission tomography and magnetic resonance imaging (PET/MRI) combined with radiomic feature extraction that investigate the molecular tumor biology provide better insights into disease pathology and facilitate new therapeutic options. In detail, LB enables a minimal-invasive assessment of the cumulative tumor mutational profile in real time with the benefits of (i) prognostic assessment [2], (ii) detection of minimal residual disease (MRD) [3–5], (iii) detection of early recurrence with lead-time-reduction compared to standard of care [6–8], (iv) guidance for targeted therapies (companion diagnostics) [5, 9, 10], (v) therapeutic monitoring [11–14], (vi) actionable health guidance for adjuvant therapy in early stage of cancer [3–5], and (vii) detection of reversal mutation in genes like

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BRCA1/2 giving resistance to PARP-1 inhibitors [15]. Similarly, PET/MRI provides (i) a higher sensitivity compared to standard of care imaging [16], (ii) information on tumor biology, aggressiveness and metabolic activity [17], (iii) optimized therapy guidance for surgical and interventional treatment [16], and (iv) lesion-based assessment of therapy response [18]. However, the clinical value of these technologies is currently limited by availability, lack of implementation into clinical workflows and guidelines, cost-concerns (reimbursement), as well as lack of decision support for clinical interpretation of highly complex diagnostic results in an integrative personalized context [19]. An integrative diagnostic evaluation of the information about the genetic tumor evolution obtained by LB and the topological and metabolic information obtained by PET/MRI is a prerequisite for a topologically-stratified and targeted therapeutic approach. Thus, further augmentation by artificial intelligence (AI) [20] and clinical decision support systems (CDS) promises to realize the maximum diagnostic potential of each modality and facilitate an integrative multidisciplinary evaluation as a prerequisite for personalized cancer diagnostics.

In 2019, during a strategic conference of the European Federation of Laboratory Medicine (EFLM) on disruptive technologies in Mannheim, a cooperation agreement between European Society of Radiology (ESR) and EFLM was signed. As a result, an interdisciplinary task force of EFLM has been established in order to evaluate the potential of an integrative diagnostic approach for an (earlier) detection of cancer (<https://www.eflm.eu/site/page/a/1569>). This paper summarizes the task force's recommendations for the

implementation of emerging disruptive diagnostic modalities in oncology, investigates their clinical impact at all stages of the oncology treatment process, elucidates the proposed clinical value of integrative diagnostics and, finally, highlights the need for a closer collaboration between imaging and laboratory medicine in the future with potential realization strategies.

Disruptive diagnostic techniques for cancer detection

Most notable disruptive diagnostic technologies in oncology with major implication for clinical decision making can be classified as into one of the following categories (Figure 1).

Liquid biopsy

The main applications of LB in oncology include the analysis of circulating tumor DNA (ctDNA) that is facilitated by the identification of tumor associated genetic or epigenetic variations in the body fluids of tumor patients, and the detection and further characterization of circulating tumor cells (CTC), exosomes and microvesicles.

Disruptive technologies like BEAMing [21], digital PCR, and Next-Generation Sequencing (NGS) using unique molecular identifiers (UMIs) have improved the analytical sensitivity of molecular genetic tests [22]. This sensitivity of detecting a variant allele frequency (VAF) down to 0.01%

	Laboratory Medicine Liquid Biopsy*	Imaging PET/MRI*	Data-driven Medicine AI / CDS*
Benefits	• Prognosis • MRD • Monitoring • Companion Dx • Early recurrence	• Higher sensitivity • Metabolic activity • Therapy guidance • Lesion-based response	• Big Data • Objective assessment • Improved TAT
Limitations	• Lack of topology • Lack of lesion-specificity	• Lack of appropriate timepoint • Lack of biological resistance	• Lack of clinical experience • Limited to structured data

Figure 1: Benefits and limitations of disruptive diagnostic technologies in laboratory medicine, imaging and data-driven medicine.

*As compared to standard of care techniques.

opened the possibility to analyze ctDNA and evaluate the clinical potential for cancer detection, treatment stratification and (therapeutic) monitoring. The clinical value and benefit for patients has been demonstrated for a wide variety of cancer types including colorectal cancer [3, 23, 24], malignant melanoma [6], non-small cell lung cancer (NSCLC) [25], and breast cancer [26].

Enumeration of CTCs, has been shown in numerous studies to be of prognostic significance in many types of solid cancers, and has gained FDA clearance as a test in metastatic breast, prostate and colorectal cancer [27]. Moreover, CTC molecular characterization at the gene expression, DNA mutation and DNA methylation level has revealed a high degree of heterogeneity in these cells even within the same patient [28]. The detection of specific molecular markers in CTCs in different types of cancer can give important information for the therapeutic management of patients and for the selection of targeted therapies and even reveal very early lack of response to specific treatments like the presence of AR-V7 in CTCs of metastatic castration resistant prostate cancer [29]. Numerous technologies have been developed for CTC isolation and detection, and all highly sensitive and specific technologies used for ctDNA analysis like digital PCR and NGS can be applied for the analysis of genetic material derived from CTCs [30]. However, since introduction of CTC analysis into the clinical setting in 2004, further clinical utility and widespread implementation have been limited [31].

Despite the significant clinical value of the described techniques, one of most relevant limitations is the lack of a topological assignment of the identified genetic variations, along with lack of harmonization in terms of i) timing of sample processing, ii) type of gene panels suitable for each cancer entity, and iii) setting of molecular-barcoded NGS and alternative molecular pipelines. Hence, it is possible to predict an earlier recurrence of disease without having the possibility to identify the metastatic site. In particular, when a resistant subclone is detected by LB, a lesion-specific assignment would be essential to stratify surgical or interventional treatments; this is not feasible with the current standard of care.

Molecular imaging

In medical imaging, revolutionary developments of multiparametric MRI, including diffusion-weighted imaging (DWI) [32], and imaging of vascularity [33] have resulted in a paradigm shift from purely morphologic towards functional and metabolic imaging. This was supported by the successful implementation of nuclear medicine detector

techniques within a strong magnetic field, resulting in the clinical establishment of PET/MRI [34]. This additional biological information layer enables a more precise and differentiated analysis and classification of lesions in imaging. Thus, besides classical diameter-related tumor response assessment [35], an evaluation of the biological response of tumor lesions becomes viable [36].

However, the availability of these highly sensitive imaging techniques is limited by cost (feasibility and specificity), and therefore the optimal time point for follow-up cannot be determined easily. Furthermore, the highly accurate topological characterization of response provides limited information on the biological resistance mechanisms and thus cannot be translated into improved choice of targeted therapeutics.

Artificial intelligence and data-driven diagnostics

Both mentioned disruptive technologies in imaging and laboratory medicine are accompanied with a high volume of complex data that needs to be assessed appropriately in order to provide actionable health information for clinicians. AI has arisen as a ground-breaking methodology in handling vast amounts of data. Currently AI is being used for augmentation of specific imaging and laboratory tests separately. AI-based imaging applications include the detection of lesions like lung nodules [37], extraction and analysis of quantitative imaging markers (Radiomics) [38] and their application as diagnostic and prognostic predictors [39]. Compared to imaging, AI in laboratory medicine is not yet firmly established. Nevertheless it has been demonstrated that AI can be used for cytological evaluation of blood smears to detect hemato-oncological disorders [40] that could be used to rapidly and precisely evaluate cytocaryograms or next-generation sequencing data [41]. In particular, AI represents a potentially promising approach for evaluation of genetic tumor data and guidance to select appropriate targeted therapeutics. However, at present diagnostic data is not assessed by an integrative interdisciplinary approach representing an enormous, yet unachieved potential to further enhance diagnostics and CDS in oncology.

Emerging integrative approaches in oncology

Even if the potential value of integrative diagnostics is not fully elucidated, first high impact studies have demonstrated

the applicability of this approach and highlighted the possibility of providing actionable health information for tumor patients. In detail, initial data has proved the benefit of this approach for various levels of the treatment process ranging from correlation of findings and improved cancer monitoring to the suitability of integrative screening approaches in sub cohorts with increased pretest probability.

Integrative cancer monitoring

Currently, follow-up of cancer patients is performed in accordance with existing guidelines at predefined serial timepoints and usually includes clinical evaluation together with well-developed imaging methods like computed tomography (CT) scans, according to structured imaging response assessment as well as the analysis of protein tumor markers. Disruptive technologies like PET/MRI or the serial ctDNA-based monitoring are sometimes offered for clinical care.

A publication by Grossmann et al. in 2017 [42] proved the additional prognostic value of combining imaging, tumor stage, histopathological markers, and gene expression for overall survival of lung cancer patients. This was further extended by Gill et al. [43] who included ctDNA levels into a radiomics approach in a small cohort of 15 stage IV melanoma patients and first highlighted that both may serve as complementary tools for treatment monitoring. A recently published paper by Lafata et al. supports these findings by demonstrating an association between radiogenomic patterns, cfDNA level, and *TP53* mutations in ctDNA after initiation of chemoradiotherapy in locally advanced lung cancer [44]. However, the first study that provided a profound understanding of the need for a more comprehensive integrative approach was published in 2018 by Siravegna et al. [45]. This study revealed organ and metastasis-specific evolutionary patterns in colorectal cancer by simultaneously analyzing ctDNA profiles and performing lesion-specific imaging assessments and genetic tests. This demonstrated that biological resistance mechanisms can be detected by ctDNA analysis, but a detailed imaging approach is required in order to discriminate between responsive and non-responsive lesions. These findings have led to further studies analyzing the value of combining laboratory and imaging findings for cancer monitoring. Accordingly, Magbanua et al. combined serial ctDNA analysis with functional tumor volume assessment by MRI in early breast cancer after neoadjuvant therapy and demonstrated a significant additive value when combining both techniques to assess the risk of metastatic recurrence and death [46]. Furthermore, Gombos

et al. used a disruptive imaging approach with PET/CT in combination with ctDNA to predict treatment response to everolimus in metastatic breast cancer patients that showed a significant increase in the negative predictive value (NPV) for progression-free survival (PFS) (63.6% NPV imaging, 64.3% NPV ctDNA, 77.8% NPV combined) [47]. Yousefi et al. extended this approach by adding radiomics features and clinical data and showed an improved PFS prediction of targeted therapy outcomes in non-small cell lung cancers (NSCLC) patients, c-statistic 0.77 when adding radiomics features, compared to c-statistic 0.73 without [48].

These studies demonstrate the additive value of integrative diagnostics for the estimation of prognosis and response. While the benefit of ctDNA for earlier detection of disease recurrence has already been proven in various studies for several types of cancer [2], a systematic integrative approach has not been performed so far. This might be particularly important in earlier detection of recurrence as ctDNA positivity might guide the optimal timepoint to perform highly sensitive imaging approaches addressing a limitation of existing imaging techniques.

Integrative diagnostics for screening

In 2018, the CancerSEEK approach published in Science by Cohen et al. raised significant scientific attention [49]. They combined LB with classical protein tumor markers as a pan-cancer screening test including eight common cancer entities for early detection and localization of cancer. For a total of 1,817 patients they reported a specificity of >99% with an overall sensitivity of 62% (depending on the cancer type, up to 98%) resulting in a positive predictive value (PPV) of 98.9%. However, a major limitation was the overestimation of tumor prevalence in the study cohort of 48%. When applying the same approach to a general population with a cancer prevalence of 0.3%, the PPV is reduced to 18.6%. This demonstrates that this test cannot be applied for general cancer screening. Nevertheless, the study has proved that by combining different types of cancers, the PPV can be increased from 0.8 to 7% for an individual type of cancer, and to 18.6% when applied as a pan-cancer test. This highlights the value of increasing the pre-test probability to facilitate cancer screening and this idea has been subsequently realized in other studies:

One of these studies is the PapSEEK approach for early detection of endometrial and ovarian cancer, which employed LB of Papanicolaou test samples with a sensitivity of 81% for endometrial cancer and 92% for ovarian cancer with a specificity of over 99% [50].

In a comparable approach, Alunni-Fabbroni et al. increased the pre-test probability for screening of hepatocellular carcinoma (HCC) limiting a cfDNA approach in combination with MRI, to a patient collective with known liver cirrhosis [51]. By analyzing a cohort of 40 patients they identified HCC-predictive genetic alterations and revealed an additive value of this combined approach.

Finally, the limitations of the CancerSEEK approach were addressed by the DETECT-A consortium, which limited the screening to women at age of 65–75 years and thereby increasing the pre-test probability [52]. Furthermore, they performed a confirmatory CancerSEEK test with exclusion of clonal hematopoiesis (CHIP) in case of positivity of the first test, thereby increasing the PPV through increasing specificity. Finally, they added PET/CT as an independent diagnostic technique. Hereby, they further increased the specificity from 95.3 to 99.6% and the PPV from 5.9% of an unconfirmed blood test, over 19.4% for a confirmed blood test after CHIP reduction to 28.3% for the combined approach with PET/CT.

These proof-of-principle studies have opened a new diagnostic field with a high potential to improve cancer screening and foster earlier diagnosis of cancer.

Future perspectives

These scientific findings need to be translated to clinical practice within the next years. In the next chapter, we will highlight promising approaches for a successful clinical implementation of integrative diagnostics and the clinical value of providing actionable health information for personalized cancer diagnostics and treatment. Given that this implementation process poses significant challenges for organizational structures, interdisciplinary collaboration, training of diagnostic medicine professionals and acceptance by clinicians, laboratory and imaging stakeholders should actively embrace the topic of integrative diagnostics and foster implementation of required structures for a successful and sustainable collaboration in the future.

Personalized oncologic diagnostics

To meet the demand for individualization in oncology, molecular tumor boards have been established in cancer centers worldwide to facilitate therapeutic decision making based on a patients' individual tumor profile. These molecular tumor boards combine the clinical expertise of an interdisciplinary medical team in which diagnostic

experts are often under-represented [53]. Thus, despite personalized treatment, the diagnostic process still lacks individualization according to the patients' needs. Figure 2 illustrates the difference between the current state of the art-cancer monitoring and an integrative individualized diagnostic approach. In detail, instead of relying on fixed time intervals and pre-defined diagnostic procedures, individualization of the diagnostic modalities requires an adaptation and refinement of diagnostic procedures depending on an integrative evaluation of all diagnostic findings and stratification for the next diagnostic steps and time points. To enhance this decision process, adequate software tools and dashboards to visualize the complex data over time are needed, particularly excluding from reporting those variants without any biological effect or without any impact on patients' management. For example, criteria for variant filtering are not completely consolidated so far.

Integrative diagnostic dashboards

The integrative and shared decision process outlined above requires a corresponding software infrastructure which collects and combines all diagnostic data, enables a combined analysis and allows for data-driven multimodal AI analytics to individualize the diagnostic process as a clinical decision-support system [54]. Figure 3 highlights the variety and multiple layers of diagnostic data needed to achieve appropriate interdisciplinary diagnostic strategies which cannot be realized in a modality-specific limited solution. To reach this goal, integrative diagnostic dashboards that include relevant clinical imaging and laboratory findings are needed. Cut-off of VAF reporting should also be defined in order to optimize interpretation of genomic data. This demand has already partly been recognized by healthcare IT-providers. Consequently, platform-based interdisciplinary software tools are increasingly replacing highly specific, but functionally limited closed solutions.

The Diagnostic Tumor Board

Highly complex data obtained by the application of disruptive technologies can be processed by AI-driven algorithms and visualized in integrative diagnostic dashboards. However, in order to provide actionable health information, an interpretation of obtained data in the diagnostic context by an interdisciplinary diagnostic team should be implemented through a Diagnostic Tumor Board. This concept is illustrated in Figure 4. The establishment of a Diagnostic Tumor Board will have significant

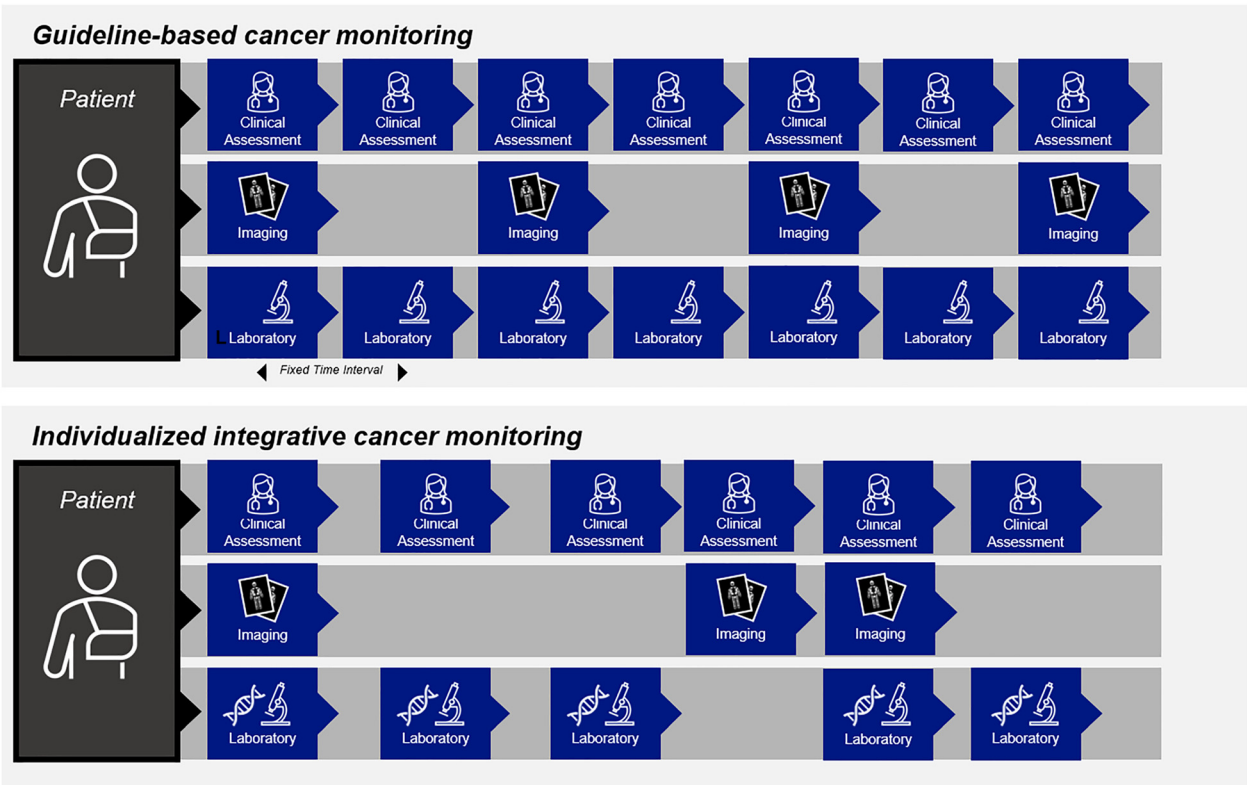


Figure 2: Comparison of guideline-based cancer monitoring with an individualized integrative approach.

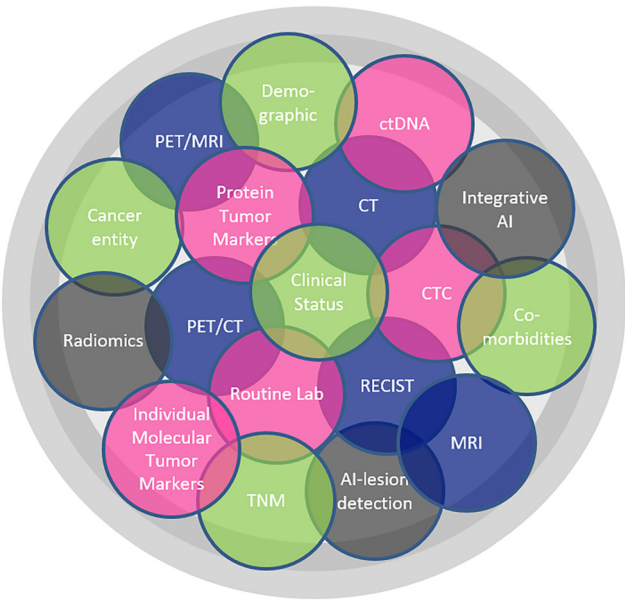


Figure 3: Multidimensional clinical, laboratory and imaging data points required for an integrative diagnostic dashboard.

benefits on multiple levels: (i) individualized frequency and appropriate choice of diagnostic procedures for each individual patient, (ii) interpretation of complex data by diagnostic professionals within an interdisciplinary

team, (iii) correct assessment of inconclusive and discordant findings, (iv) integrative report as diagnostic recommendation and clinical decision support for the molecular tumor board, (v) increased efficiency by streamlined decision processes and avoidance of inappropriate or redundant diagnostics, (vi) increased visibility of diagnostic disciplines.

The diagnostician

This increased collaboration between diagnostic disciplines and their implementation into the treatment process will foster a strong partnership on multiple levels including training, organizational structures and combined research [55]. As a result, a comprehensive understanding of each diagnostic fields including their inherent limitations and resulting complementary strengths will be the prerequisite for truly integrative diagnostics in the future. The strategic cooperation agreement between ESR and EFLM marks a first cornerstone on this way. We foresee expansion of collaboration between diagnostic disciplines in Medicine as instrumental for improved resource utilization, stronger validity of findings and interpretation and – eventually – better outcome and benefit for the patient. This is further

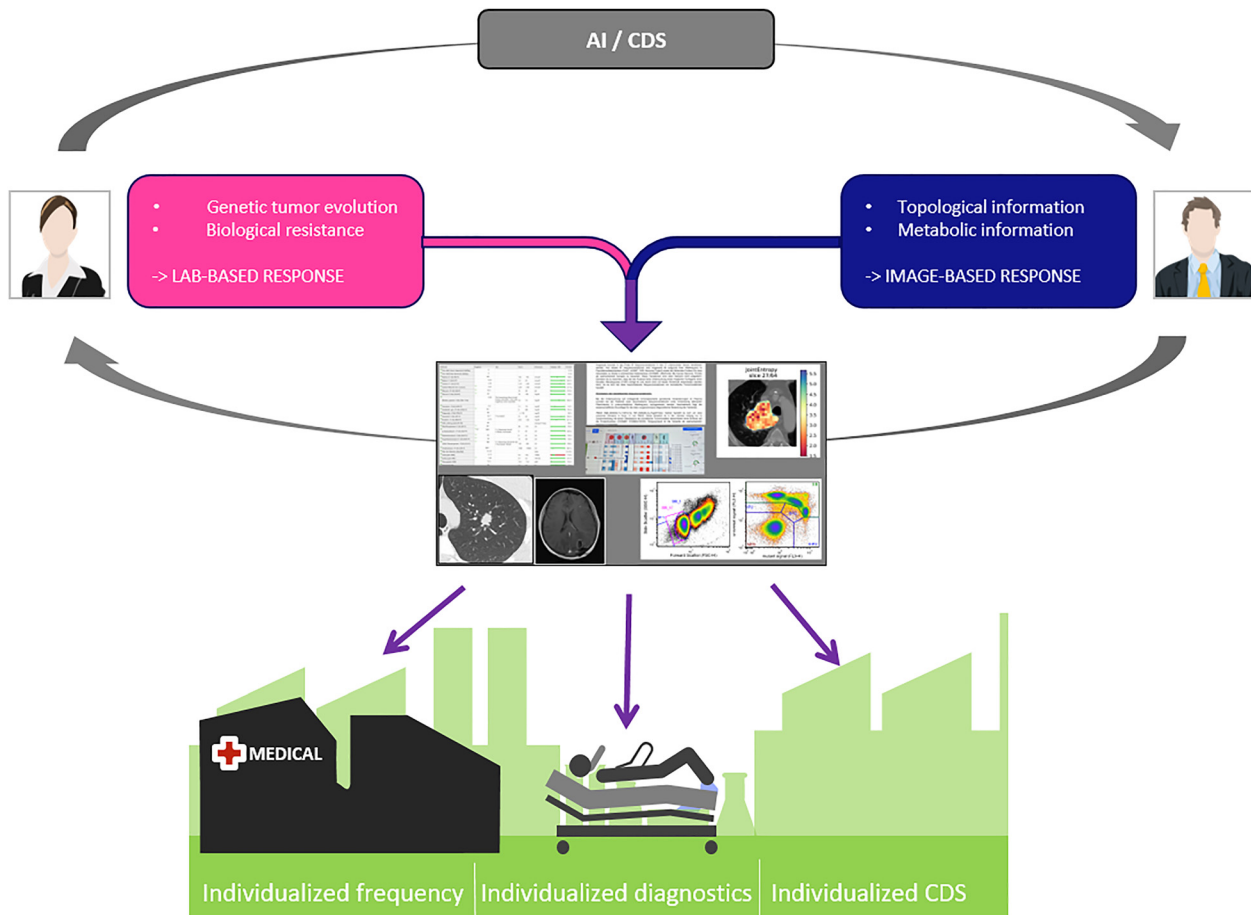


Figure 4: The Diagnostic Tumor Board.

Within the Diagnostic Tumor Board information obtained by laboratory and imaging techniques is processed by AI-driven algorithms, visualized by an integrative dashboard and finally evaluated by diagnosticians in order to provide actionable health information for clinicians in terms of an individualized frequency of customized diagnostic procedures.

enhanced by interdisciplinary working groups and will require a close cooperation to establish joint educational programs for diagnosticians in the long term.

Conclusions

In various clinical studies, the diagnostic value of integrative diagnostic approaches has been proven for earlier detection of cancer along with multiple additional benefits for both clinicians and diagnostic disciplines. This integrative diagnostic approach emphasizes the value of diagnostic physicians in oncology and should therefore be pursued by these disciplines with the support of adequate software solutions. These developments may further lead towards the convergence of diagnostic processes and the emergence of a new generation of diagnosticians, who actively embrace integrative data and AI-driven analytics

in order to provide actionable health information for clinicians.

Research funding: None declared.

Author contributions: Manuscript writing and preparation of Figures: M.F.F., E.S.L., V.H. Manuscript editing: M.F.F., E.C., Z.K., S.J.P., E.S.L., V.H. Conceptualization: M.F.F., E.C., Z.K., S.J.P., E.S.L., V.H. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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