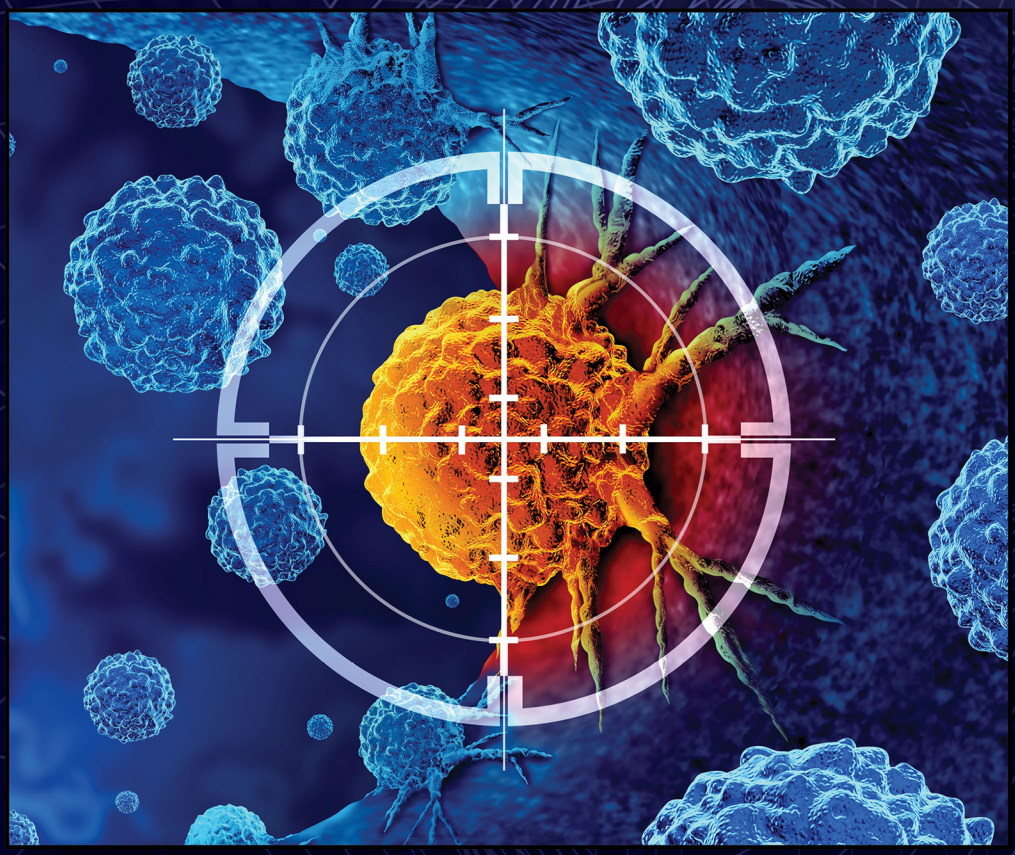
PRECISION DIGITAL ONCOLOGY

Disruptive Science in the Fight Against Cancer



EDITED BY

WASSWA SHAFIK, JAY KUMAR PANDEY,
AND HAIPENG LIU

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Precision Digital Oncology

This book offers an in-depth exploration of how innovative technologies are reshaping the landscape of cancer diagnosis, treatment, and care by examining the intersection of precision medicine, digital health, and disruptive scientific advances in oncology and focusing on the integration of molecular profiling, artificial intelligence, and digital health infrastructures to revolutionize cancer care. Through 21 detailed chapters, the book covers a range of cutting-edge topics, including the application of AI and deep learning in oncologic imaging, the rise of liquid biopsy techniques for non-invasive cancer detection, and the powerful synergy of radiogenomics in personalizing patient treatment. It delves into how multi-omics integration and systems biology are being leveraged to understand tumor biology better, predict disease progression, and identify novel therapeutic targets. The book also addresses the evolving role of AI in predictive modeling and decision support systems, providing clinicians with advanced tools for risk stratification and prognostic analysis. It explores the ethical and regulatory challenges of integrating digital technologies into clinical practice and offers a global perspective on the barriers to equitable access in cancer care. Designed for oncologists, researchers, data scientists, biomedical engineers, and healthcare professionals, *Precision Digital Oncology* bridges the gap between cutting-edge research and real-world application, providing a comprehensive, forward-looking roadmap for the future of cancer treatment. Whether you're exploring the impact of AI in cancer care or seeking insights into the future of digital health technologies, this book offers critical knowledge for anyone interested in the next generation of cancer research and therapeutic strategies.

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Preface

More than 10 million people die of cancer each year, more than 20 million are diagnosed, and the overall clinical outcomes remain unsatisfactory. Furthermore, cancer treatment costs are escalating, increasing the economic burden of healthcare systems that already face numerous challenges. To a large extent, contemporary medicine is reactive: Patients are diagnosed and treated only at late disease stages, mostly in Africa. *Precision Digital Oncology* introduces a novel shift in cancer research, drug development, diagnosis, and care by combining state-of-the-art artificial intelligence and machine learning technologies with multimodal big data sources to deliver information at unprecedented speed. The proposed science incorporates a wide range of capabilities, from the continuous monitoring of patients through smart bracelets to the prediction and synthesis of patient outcomes, including optimal treatment approaches and estimated survival likelihoods. These capabilities involve the integration of smart and low-cost data acquisition devices with potent cloud- or edge-based computational facilities capable of circumventing institutional constraints and deploying robust artificial intelligence and machine learning models over complete datasets generated by all participating data contributors. In particular, the strengths and limitations reside in the nature of the datasets used. The vast majority of predictive models trained within the domain of digital pathology have relied on data from a single institution or multiple institutions that generate and annotate these data in a congruent manner.

Precision Digital Oncology endeavors to establish next-generation science and technology that enable a paradigm shift in the approach to cancer. The focus of *Precision Digital Oncology* is the early and accurate detection of various cancers and a corresponding response. The intention is not to prevent the onset of cancer, but to create an integrated oncology care pathway within which invasive and non-invasive cancers can be detected and addressed in a timely manner. With most patients ultimately dying from cancer, and considering all forms of cancer together, it is an issue of risk assessment rather than prevention. In the first decades of the 21st century, oligometastatic cancer progression was proposed and subsequently confirmed by clinical studies. Oligometastatic progression indicates that, in a subset of patients, only a few secondary tumors develop, the growth of which may remain limited over a prolonged period, or permanent spontaneous remission may occur. Furthermore, it is now known that certain cancers acquire blood vessel formation before the onset of invasion, earlier than previously thought. Multi-plexed expressions of specific biomarkers has been shown to allow the identification of pulmonary, thyroid, or renal cancers years before the clinical onset of the corresponding primary tumor. It is reasonable to hypothesize that a much larger subset of patients may benefit from a precision oncology approach based on real-time monitoring and adaptive therapy, and that it may be applicable in parallel with early cancer detection.

A comprehensive listing of the major data sources and data acquisition protocols should be presented, together with the primary preprocessing, normalization, and integration strategies employed across the studies. Major aspects of data quality, standardization, and interoperability should also be considered. A systematic delineation of the computational models, analytic pipelines, validation schemes, and reproducibility measures employed should accompany a comparative synopsis of the methods used. Finally, a thorough inventory of the AI and ML techniques – together with auxiliary algorithms for image processing, model types, training regimes, and performance measures; and the role of analytical processes in decision support – should be compiled. The associated internal and external validation frameworks, translational pathways, and criteria for clinical adoption must also be identified. The oral cavity is a complex ecosystem teeming with microorganisms, including bacteria, fungi, and viruses. The interplay among these key players, virus/bacteria, bacteria/bacteria, and virus/fungi, causes variations of the oral microbiome and predisposes special health outcomes, such as the development of HIV infection, diabetes, schizophrenia, and oral squamous cell carcinoma (OSCC). In this context, combining oral and salivary metagenomic data with host demographic and clinical information can contribute to the diagnosis of early-stage OSCC. The first step involves obtaining information about patients with and without early-stage OSCC and performing next-generation sequencing (NGS) analysis for taxonomic profiling of oral cavity and salivary samples. Subsequently, for each early OSCC case under analysis, the NGS data obtained from these samples are combined with clinical information into a single data frame, which is used to feed ensemble classifiers, support vector machines (SVMs, including modified versions), and a deep learning classifier. The analysis is then expanded using a leaders-successions-Martensen model and successions-evaluations-diagnosis-recurrence-successions-attitude analysis associated with voting, to prove the connection of a non-dwelling microbiome with the high early-phase risk factors of OSCC, and the closeness of the microbiome/dysbiosis variations-transition-successions-delivery with the microbiome/dysbiosis-production-wealth. Finally, features up- and downstream of successions-connected taxa are tested using "Gneiss" for scaling out non-dwelling members from the core microbiome of early OSCC.

An array of data types is either required or may contribute significantly to generating evidence for clinical decision-making. Apart from the classifiers and predictors directly derived from diagnostic and prognostic digital pathology and radiomics pipelines, clinical characteristics

of the patient population are vital components in precision digital oncology, providing essential modulators or confounders. Vital signs, blood or urine test results, KPS, organ dysfunction status, prescribed medications such as steroids, and current or prior history of smoking may significantly influence the course of treatment or a patient overall prognosis. In the absence of early-stage genomic and/or multi-omics data, treatments targeting known actionable mutations may also be adversely affected in patients with pathogenic mutations in DNA damage repair genes, even when detected at later stages of disease progression. Given the impact of such clinical and treatment-related variables on patients' clinical outcomes, healthcare system data enabled by modern edge computing and the Internet of Things is proving to be vital in developing image- and/or multi-omics–based classifiers or predictors of early detection of treatment-related systemic complications or disease progression. These factors are crucial for directly supporting the therapeutic decision-making process or monitoring the clinical course of patients during treatment. In contemporary clinical practice, real-time warehousing of such data – collected from wearables or other IoT-based devices constituting tele-healthcare – is already enabling adaptive therapy, where alterations in treatment strategy are proposed, in close to real time, based on deviations of clinical observations that could either be vital signs or lab test abnormalities from the expected interpolated duration/progression trajectory defined by digital twin models. Integrating such patient-specific adaptive therapy feedback loops with the standard-of-care treatment strategy should further enrich model predictions across multiple cancers and treatment modalities.

Precision Digital Oncology encompasses application domains that extend beyond traditional laboratory-based diagnostics and therapeutic decision-making toward real-time therapy delivery, remote patient monitoring, and treatment adaptation based on evolving patient responses. Such innovative capabilities offer new prospects for precision oncology but also demand novel implementation models, extended data ecosystems, and clear integration into existing or emerging clinical workflows. A formal clinical definition thus articulates the mature vision: Adaptive therapeutic concepts that exploit real-time patient monitoring to more finely tune cancer treatment based on a better and timelier understanding of patient responses. While real-time monitoring and feedback loops for adaptive therapy constitute the ultimate expansion opportunity, detection capabilities can be enhanced by digital pathology support and detailed genomic/multi-omics profiling. For many patients, tissue sampling is still a major complication; for virtually all patients, genomic information is still limited. Supporting conditions thus require advanced digital diagnostic pipelines incorporating established pathology capabilities, expanding routinely obtained hematopoietic tissue snapshots to a heterogeneous multi-omics view of the tumor system, and facilitating the integration of the information into the decision-making process.

Data from histopathologic tissue specimens, the best-established gold standard diagnostic tool in oncology, currently used with a degree of success for about a century, are the sources for several different artificial intelligence-driven solutions in *Precision Digital Oncology*. Digital pathology supports the radiogenic, feature engineering-based extraction of up to thousands of high-dimensional features, working at a statistical level. Conversely, radiomics refers to the analysis of accessible medical/clinical images of small and large tumors or lesion areas and aims to reveal information on important textural features of the tumor micro-environment. Radiomics features are directly computed through the application of filters to the original images, ultimately at a more interpretable level compared to deeplearning features, and in cases where thousands of samples are available, using classical machine learning. The rich amount of data generated during the genomic multi-omics profiling of the patient – with direct clinical actionability, interpretative, or predictive relevance – is finally augmented using the clinical setting, which is closing the loop.

Histological slides are still the best-established gold-standard tissue specimen in oncology, for both diagnostics and prognosis/evolution predicted with clinical data of outcomes. Histologic whole slide images represent huge data sources (>30,000 × 30,000 pixels; >100×10^{16} pixels per million) for the development and application of artificial intelligence technology toward generalizability and usability in decision support systems for clinical and preclinical real-world institutions worldwide, and provide support for true multimodality investigations of oncological problems on the whole-organ scale. Digital pathology–based features can be merged with other types of artificial intelligence systems for accurate prediction of lesions, disease behavior, patients' survival, correlating with expansiveness and other biological features, improving the pipeline chain between departments and disciplines, and contributing to the training of less-experienced professionals.

Comprehensive genomic and multi-omics profiling comprises a potent clinical decision support tool for precision oncology and has become a routine component of patient care in leading hospitals. Algorithms enable primary sequence generation from fresh and archival specimens, followed by DNA, RNA, and protein extraction and quantitative analyses. These critical primary and ancillary data sources inform risk scoring, therapy sensitivity/resistance prediction, molecular subtype classification, targeting, and efficacy of available therapies (inhibitors, vaccines, antibody drug conjugates), and off-label agents (informed by selective vulnerability assessments). Moreover, deep learning models exploit these data flows to guide multimodal response prediction under multi-agent/multi-modality adaptive therapy paradigms. Emerging and present-day genomic and multi-omics profiling capabilities deliver predictive/enrichment scores for therapy-response modulation at multiple levels (genome, transcriptome, proteome, microbiome) and ultimately inform decisions on adaptivity, connection to feedback mechanisms, and degree of non-multiplicity.

Translational expertise and resource investment continue to expand the clinical applicability of genomic and multi-omics profiling, thereby enhancing the success of precision digital oncology endeavors. Model development pipeline accessibility; scalability; multi-institutional, communally resourced operation; and infrastructure-connected data supply flow (e.g., facility–onsite–edge–cloud–data ecosystem alignments) are leveraged to broaden the range of risk-scoring information and therapy-guiding signature profiles enabled by precision oncology service providers.

Complementing the directions above, the concept of real-time monitoring, whereby a patient's tumor is evaluated continuously or at certain time intervals, plays a pivotal role in treatment adjustment. The process of patient evaluation involves periodic imaging, histopathological assessment, and possibly other analyses, with certain results guiding adaptive therapy during clinical response assessment. However, the time frame of activity in this conventional approach is often too broad for the particular tumor evolution patterns. Some patients could benefit from an earlier therapy adjustment, within the framework of the principle of treating a tumor as a dynamic system rather than an immutable entity. If responses to a specific therapy change within a short time, the action taken may be different. If, say, several chemotherapy cycles have been completed and the patient reacts well after each evaluation, a delay in re-evaluation may be acceptable. But if the direction changes between two evaluations, i.e., the tumor is no longer responding to the therapy, an adjustment is overdue. The real-time monitoring perspective involves discussions about continuous evaluation of histopathology and imaging-based monitoring. Mythological issues affect the early phases of histopathological assessment in terms of image transfer and evaluation, the time-reaction of pathology, and the burden of real-time monitoring in exceedingly complex cases or in phases with no great tumor variation. Still, the very discussion implies a review of classical activity times and the possible establishment of faster response systems that would enable the team to modify patients' therapies as swiftly as possible. The temptation to perceive tissue as static while the tissue microenvironment is recognized as a dynamic area during evolution would lead to a real-time analysis platform, assuming that tumor biochemical alterations can be detected through periodic non-invasive procedures.

Wearable devices enhance oncology care pathways by continuously collecting diverse health data outside traditional clinical settings. Integrating these impactful longitudinal datasets with traditional data supports real-time and budget-minimal disease monitoring. Edge computing architectures enable real-time data processing, generating timely and privacy-preserving alerts for serious conditions. Incorporating advanced and distributed electronic systems into usable edge devices decreases physical strain, simplifies use, increases ubiquity, and encourages monitoring across ample and diverse populations. Any innovation must fit smoothly within existing hospital infrastructures and regulations and support and accelerate international and local clinical workflows. Cloud-based collaboration platforms and data sharing frameworks foster data exchanges among institutions, universities, hospitals, and companies. Established models promote transparent, joint, repeatable, and traceable work across stakeholders. Enabling collaborative analysis with enhanced communication between specialists and minors consolidates institutions' roles and strengthens training. Integrating privacy-preserving analytics bias in raw data improves learning performance. Supporting federated learning enables distributed learning while addressing privacy, data sharing, and quality barriers.

Wearable tracking devices equipped with sensors that monitor physiological parameters, lifestyle behaviors, indoor and outdoor activities, geolocation, digital environment, and emotional states are emerging as critical elements of the future digital ecosystem. Devices already available on the market or undergoing clinical validation support clinical investigation and therapy, facilitating lifestyle interventions, qPCR testing, and preclinical diagnostics. Mass use and interaction with disease pose a considerable technological challenge. Debilitating cancer syndromes create an imbalance between blood flow to and from the site of fuel burns in the muscles and other tissues, leading to central fatigue. The associated decrease in heart and respiratory function may be detectable in measurements obtained from even low-cost wearable devices. Data on blood oxygenation obtained with inexpensive devices may help location-aware monitoring of patients under radiotherapy to indicate location-specific dearth of oxygen in the areas of the body being irradiated. An edge structure where an increasing number of disruptive artificial intelligence algorithms work in real-time in edge computing units close to the patients, feeding a central cloud-based artificial intelligence system, is emerging as a digital-oriented computing architecture in which the edge units constitute a colosseum supporting a significant functional analytics processing hub. The wearable devices act as tools for the recognition of signs of diseases. They have to be appropriately used and integrated with machine learning algorithms in edge computing architectures to modulate the artificial intelligence models operating in the central cloud and provide real-time monitoring in precision digital oncology. Edge computing configurations using sensor networks of wearable devices are emerging as systems able to maintain multiple analytic platforms running actionable multimodal monitoring-based tools that support lifestyle interventions for patients that are not receiving standard therapeutic approaches.

Cloud computing platforms and architectures have revolutionized academic research by facilitating data sharing and encouraging collaborative teams comprising scientists from multiple institutions. Collaboration accelerates the development of novel healthcare technologies, offers access to greater computing power for processing large datasets, streamlines data access for users without local resources, and promotes the honing of algorithms across heterogeneous datasets. Moreover, data sharing initiatives

that target specific healthcare applications can yield very large datasets that benefit a wide range of research groups that address common-use problems but do not possess the scale of data required for robust model creation and validation. Many cloud sharing platforms enable users to upload raw and processed data. Some platforms also allow users to download digital medical images from centralized, open-access repositories and manage the tasks of segmenting the images and evaluating predictive models with radiomic signatures. Despite these advances, successful data governance remains crucial to addressing the privacy of sensitive data, enabling future biomedical research, and creating AI models with widespread applicability. Hence, the planning of governance frameworks requires process-oriented thinking.

Federated learning (FL) enables cross-institutional analytics without centralizing sensitive data, thereby maintaining patient privacy and compliance with institutional regulations. Patient data never leaves the institution; rather, local models are trained on local data, and only their updates are shared with a centralized server. FL addresses privacy, confidentiality, security, and data governance needs while supporting the development of robust machine learning (ML) models by facilitating access to datasets with large populations. FL enables a wide range of uses, such as healthcare disease developments, risk group identifications, complications developments, and comorbidity predictions. The Markov Chain Monte Carlo algorithm is used to train client risk-free models during unbalanced datasets. Analysis of a skin disease dataset shows that it reduces the testing time. Privacy-preserving federated learning (PPFL) provides an efficient privacy-preserving collaborative training of neural networks in cross-device federated learning scenarios, considering one-party data integrity attack in orthogonal banks. The PPFL adopts the security module secure multi-party computation, facilitates secure relaying of data messages, provides dynamic access control for secret shares, and realizes linear computation. Aiming at bypassing the effectiveness loss resulting from cheap but susceptible secret share solutions, its distortion-resilient secret share mechanism avoids construction based on directly susceptible shares, guarantees resharing consistency among secret-sharing flows in devices, and detects modification attempts in the relaying Fog Gateway (FG). Six analytical dimensions inform implementation planning: (1) integration within clinical workflows; (2) contribution to multidisciplinary decision support; (3) health system economics; (4) regulatory and ethical considerations; (5) governance; and (6) equity.

The widespread adoption of precision digital oncology faces challenges whose mitigation is important for reducing risks, ensuring safety, and maximizing potential benefits. Common obstacles to reliable data analytics via conventional machine learning and deep learning algorithms include data quality, interoperability, and standardization. Addressing these barriers can fortify precise decision support mechanisms, enhance generalization capabilities across different geographies and populations, and enable the transfer of externally validated models into clinical practice. Security, incident response, and patient de-identification measures are also pertinent. Efforts to overcome these challenges should transparently examine potential bias and discrimination in treatment and prevention paradigms based on adaptive learning, real-time symptom monitoring, or integrated quality-of-life assessment. Cost-disproportionately affected communities may warrant increased attention and resources within the precision oncology network. Overarching precision health issues – namely, data quality, interoperability, and safety – command concerted action for risk reduction, patient protection, and outcome equity; addressing them serves not only digital precision oncology but also precision health across other domains. Such advances also mitigate bias, generalizability, robustness, and sensitivity concerns stemming from varied training and validation datasets.

Translational pipelines are outlined, key milestones identified, and stakeholder roles defined for the successful implementation of precision digital oncology. Considerations for education, training, and workforce development are integrated to address capacity-building requirements. Successful implementation of precision digital oncology hinges on the availability of rich datasets underpinned by robust validation-linking-and-replication approaches, coupled with effective integration into clinical workflow. These elements, in turn, shape clear, reproducible, statistically robust decision support packages that account for deployment within multidisciplinary teams for validation in real-world applications. The translation of research findings from bench to bedside, therefore, involves a complex pathway of iterative steps across data generation, analysis, validation, integration into clinical workflow, and impact evaluation. The operationalization of precision digital oncology is fundamentally a fusion-based problem that involves the coming together of several factors that can be categorized into three broad areas: Data value linkage within training, validation, decision support, and workflow-integration frameworks; educational upskilling pathway convergence; and longer-term governance and maintenance considerations for sustaining functionality across the ecosystem. Ideally, the first of these categories serves as a focal point, helping delineate the education and upskilling needs of users, developers, and system administrators. Educational and upskilling needs are defined in more detail below; however, a general set of educational guidance underpinned by a process for supporting the execution of formal textbooks or curricula for unlocking the required capacity of precision digital oncology has also been developed.

Next-generation data ecosystems are envisioned as participatory collaborative networks involving a diverse range of stakeholders, spanning patients, citizen scientists, clinical researchers, and commercial entities. Such contributions are expected to result in a wide variety of data types, including semistructured clinical reports, collaborative-supporting citizen-generated web surveys, multi-omic

profiles prepared by biobanks, therapeutic-response information from clinical-stage disease, and protocol-driven curated databases, among others. Innovative governance models are essential for maintaining high standards on issues such as data accuracy, completeness, and privacy while facilitating wide accessibility. The rapid evolution of quantum computing holds the potential to break existing limits in storage and processing capabilities, enabling the read-out of simulations and predictions to complement directed labs and cohorts. Within this context, data characterizing the environment of disease onset might transition from secondary sources, such as supplier databases, to direct lab analysis. The possible association between the functioning of biological systems, microwave–infrared signals, and human health also brings attention to the capacity of the quantum-computing paradigm for predictive analytics based on these signals. Although these perspectives remain in early-stage development, quantum computing offers the possibility of fast predictions for which indicators of premature deterioration might be easily available.

Despite the impressive improvements in cancer diagnosis, monitoring, and therapies in the past several decades, cancer care remains quality- and outcome-sensitive to human decisions that are still largely based on individual experience rather than analytic data. Cancer evaluation, treatment, and outcome strongly depend on the presence of the right specialist at the right moment. When such a condition is not fulfilled, patients risk receiving suboptimal therapy and subsequently having worse prognoses. Emerging scientific directions, scientific disciplines, and technological advancements enable rethinking of how humans can return to focusing on creative and intuitive decision-making without neglecting the analytic aspect of decisions in complex systems where interdependent variables confluence into the common outcome. Precision decision support systems within multidisciplinary cancer evaluation, therapy, and follow-up teams will not replace any individuals but will integrate updated knowledge from all past clinical interventions. They will allow them to fulfill more quickly, exhaustively, and objectively all the steps needed to reach the right diagnosis, therapy plan, and follow-up program supported by the available clinical data (from patients and their digital twins). Just like the musculoskeletal system of humans allows any individual to run or jump faster than any horse but emerges from the equilibrium of the collective heart action of the involved muscles, thanks to the interaction with the brain as controlling central unit, the precision digital oncology paradigm returns the optimal decision-making capability to the heart and brain of the multi-specialistic human cancer decision support system by adding the digital twin of the patient that transmits in real time to the team any change in their state of health. The heart re-establishes a dynamic feedback supported coordination of its internal and external environment, offering to the decision support group the ability to change the predictive therapy activity over time while adapting the current therapy and remedying any possible early adverse effects.

ABOUT THIS EDITION

This book defines the evolving domain of precision digital oncology and highlights its inherently multidisciplinary nature, merging insights from computational biology, molecular medicine, AI, clinical oncology, and health informatics. It explores the paradigm shift toward data-driven and personalized cancer care, emphasizing predictive analytics, deep learning, and molecular genomics as cornerstones of modern oncology. The book elucidates how digital sensing technologies, biosensors, nanomedicine, and quantum tools are revolutionizing cancer detection, diagnosis, and treatment by enabling real-time, patient-specific therapeutic decisions and enhancing the precision of oncologic interventions.

It presents a comprehensive view of AI-powered approaches in oncologic imaging, histopathology, and predictive modeling, demonstrating how machine learning and federated AI frameworks transform diagnostics, prognosis, and drug discovery. The book also examines cutting-edge therapeutics, from immunotherapies to cell-based treatments, and addresses the ethical, legal, and privacy challenges emerging from digital health ecosystems. Furthermore, it investigates the growing role of blockchain for data security, the integration of real-world evidence into clinical trials, and strategies to ensure global equity and access in digital cancer care.

This book will be an indispensable resource for oncologists, data scientists, biomedical researchers, health scientists, and healthcare policymakers seeking to understand and shape the future of precision oncology. It also serves educators, clinicians, and innovators by providing a strategic roadmap for implementing AI-driven tools and ethical governance frameworks that support sustainable, inclusive, and transformative progress in the fight against cancer.

THE BOOK STRUCTURE

The book is structured into four interconnected parts, each addressing a distinct yet complementary dimension of precision and digital oncology. It moves from theoretical and technological foundations to real-world clinical applications, ethical considerations, and strategic pathways for the future. The sequence ensures a holistic understanding, from concept to clinic, and from data to decisions, reflecting how digital transformation is reshaping cancer diagnosis, treatment, and management.

The first part establishes the intellectual and scientific foundation for precision and digital oncology. It explores the transition from conventional cancer care to a data-driven, individualized approach that integrates artificial intelligence, molecular profiling, and advanced therapeutics. Chapter 1 introduces the evolution from traditional oncology to precision and digital oncology. It highlights the convergence of genomics, data science, and personalized medicine as a transformative force in cancer care. Chapter 2 examines how predictive analytics and AI algorithms are

being leveraged to improve diagnostic accuracy, treatment planning, and patient outcomes. Chapter 3 discusses the application of machine learning and deep neural networks in imaging and pathology for tumor detection, segmentation, and classification. Chapter 4 reviews emerging therapeutic innovations such as CAR-T cell therapy, immunotherapy, and gene editing, emphasizing how digital tools support their optimization and monitoring. Chapter 5 explores genomic profiling, biomarker discovery, and how molecular data guide precision treatment strategies and personalized patient care.

The second part delves into the integration of digital sensing, AI, and predictive technologies in modern oncology. It emphasizes tools that enable continuous monitoring, early detection, and tailored interventions. Chapter 6 presents how digital sensors, wearables, and remote monitoring systems transform patient tracking, symptom management, and post-treatment care. Chapter 7 highlights cutting-edge tools, nanotechnology, biosensors, and quantum computing that enhance diagnostic precision and therapeutic delivery. Chapter 8 provides a comprehensive overview of predictive modeling approaches, clinical validation issues, and integration into medical practice. Chapter 9 offers a focused case study connecting predictive AI methodologies to broader oncology contexts, emphasizing model design, validation, and implications for women's health. Chapter 10 explains how digital platforms, real-world data, and adaptive trial designs are revolutionizing clinical research efficiency and regulatory decision-making.

The third part emphasizes practical and translational dimensions, bridging digital innovations with ethical, regulatory, and global challenges in oncology. Chapter 11 addresses the ethical and legal implications of AI deployment in healthcare, focusing on patient consent, data protection, and regulatory compliance. Chapter 12 investigates disparities in access to digital health technologies and proposes strategies for equitable integration across high- and low-resource settings. Chapter 13 reiterates the clinical applications of these advanced technologies, linking them to real-world implementation and translational research outcomes. Chapter 14 outlines strategic pathways for harmonizing innovation, policy, and healthcare infrastructure to accelerate digital oncology adoption. Chapter 15 synthesizes the state of AI in oncology, discussing implementation barriers, evolving trends, and opportunities for interdisciplinary collaboration.

The final part consolidates the ethical, technological, and strategic aspects shaping the future of digital oncology, emphasizing trustworthy AI, federated systems, and next-generation therapies. Chapter 16 explores how bioinformatics platforms and clinical decision support systems enable precision diagnosis, risk stratification, and treatment and personalization. Chapter 17 discusses federated learning as a privacy-preserving approach that enhances collaboration across institutions without sharing sensitive patient data. Chapter 18 demonstrates the practical deployment of ensemble deep learning models in breast cancer detection, highlighting accuracy and clinical implications. Chapter 19 examines blockchain's role in strengthening data integrity, transparency, and traceability in decentralized AI systems. Chapter 20 focuses on the next generation of nanomedicines that enable targeted delivery, reduced toxicity, and enhanced therapeutic efficacy. Chapter 21 concludes with a comprehensive reflection of the legal frameworks, accountability mechanisms, and governance models needed for responsible AI-driven oncology.

Editors

Wasswa Shafik is an IEEE member and Team Lead at the Dig Connectivity Research Laboratory (DCRLab) in Kampala, Uganda. He holds a PhD in Digital Science (Computer Science) from the School of Digital Science, Universiti Brunei Darussalam. Dr. Shafik also earned a master's degree in Information Technology Engineering from Yazd University, Iran, and a bachelor's degree in Information Technology from Ndejje University, Uganda. He has received specialized training from the National Institutes of Health (NIH), the US Department of Health and Human Services, and the Bloomberg School of Public Health, focusing on data quality, monitoring and evaluation fundamentals, and protecting human research participants. Before his PhD, he worked as a Community Data Officer at Pace-Uganda, a Research Associate at TechnoServe and Mercy Corps, a Research Assistant at PSI-Uganda, a Research Lead at the Socio-economic Data Centre (SEDC–Uganda), and a former Agricultural Managing Director at Asmaah Charity Organisation. His research focuses on developing computationally efficient models for challenges in health, agriculture, and ecology. He specializes in artificial intelligence, computer vision, neural networks, and the Internet of Things, with applications in smart agriculture, digital health, and ecological informatics.

Jay Kumar Pandey is currently working as an Assistant Professor in the Department of Electrical & Electronics Engineering at Shri Ramswaroop Memorial University, Barabanki (U.P.) India. Dr. Pandey has a PhD and has done his MTech. with specialization in Power Control (Instrumentation) and also received his MBA in Finance and Marketing. His subjects of interest are related to artificial intelligence, biomedical and healthcare, image processing, machine learning, and renewable energy. He has 15 years of teaching and research experience. He has published more than 30 research papers in national and international journals/conferences and contributed book chapters to titles published by CRC Press/Taylor & Francis, NOVA, Springer, and IGI. Dr. Pandey is an editor of books published by Apple Academy Press, IGI, Elsevier, Wiley-IEEE, NOVA, Bentham Science, IAP, Emerald Publication, CRC Press/Taylor & Francis, and Cambridge University Press. Dr. Pandey is also the Editor of the *Journal of Technology Innovations* and *Energy United States.* He has reviewed conference, journal, and book chapters, such as the *Journal of Supercomputing Journal of Security and Communication Networks, Journal of Biomimetics, Biomaterials and Biomedical Engineering* (JBBBE), and *Advanced Engineering Forum* (AEF).

Haipeng Liu received his bachelor and master's in Engineering from Zhejiang University, China, in 2012 and 2015, respectively, and his Doctor of Philosophy in Medical Sciences from the Chinese University of Hong Kong, in 2018. From 2019 to 2020, he was a research fellow with the Medical Technology Research Center, Anglia Ruskin University. Since 2020, he has been a research fellow at Coventry University, UK. He is the author of more than 60 journal articles and 10 conference papers. He has delivered 12 invited talks for international conferences, universities, and research institutes. He is a recipient of two British Heart Foundation Travel Awards, a Director of Studies (DoS) of two PhD students, and an editorial member of six academic journals. He is a reviewer of more than 60 articles from 24 journals, four international conferences, and one book proposal. His research interests include biomechanics, physiological measurement, and computational simulation of cardiovascular diseases.

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Contributors

Sumathi A.
Department of Computer Science and Engineering
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Lalith Reddy A.
Department of NWC
SRM Institute of Science and Technology
Chennai, Taminl Nadu, India

Ssentumbwe Male Abdul
Department of Computer Science
and Engineering
Faculty of Computing and Informatics
Makerere University Business School
Kampala, Uganda

Shahanawaj Ahamad
College of Computer Science and Engineering
University of Hail
Hail City, Saudi Arabia

Sumanth Banakar
University of the Cumberlands
Williamsburg, Kentucky

Hari Babu Bathini
School of Management
Siddhartha Academy of Higher Education
(Deemed to Be University)
Vijayawada, Andhra Pradesh, India

Asma Channa
Khalifa University
Abu Dhabi, United Arab Emirates

Sri Shakthi Sarath Chintapalli
School of Computing
SRM Institute of Science and Technology
Kattankulathur, Tamil Nadu, India

Oliver Dias
University of Barcelona
Gran Via de les Corts Catalanes
Barcelona, Spain

Jacinta Dsilva
See Research Centre
See Institute, Sustainable City
Dubai, United Arab Emirates

Kamlesh Kumar Gautam
Department of Computer Science
Mewar Institute of Management
Ghaziabad, Uttar Pradesh, India

Heartlin Maria H.
Department of Electronics and Communication
Engineering
SRM Institute of Science and Technology
Chennai, Tamil Nadu, India

Shobha Rani Rajeev Hiremath
Department of Pharmacy Practice
Aditya Bangalore Institute of Pharmacy Education
& Research (ABIPER)
Bangalore, Karnataka, India

Kassim Kalinaki
Department of Computer Science
Islamic University in Uganda
Mbale, Uganda

Adan Khan
School of Engineering
University of Kent
and
Education and Research Unit
Diversity in Medical Academia (DIMA)
Canterbury, United Kingdom

Jyotsana Khera
School of Computer Science and Applications
IIMT University
Meerut, Uttar Pradesh, India

Jinu Mathew
Institute of Sustainability for Chemicals, Energy and
Environment (ISCE2)
Agency for Science, Technology and Research (A*STAR)
Jurong Island, Singapore
and
Centre for Intelligent Healthcare
Coventry University Coventry
United Kingdom

Madeha Memon
Mehran University of Engineering and Technology
Karachi, Sindh, Pakistan

Yasra Memon
Liaquat University of Medical & Health Sciences
Karachi, Sindh, Pakistan

Mohamed Osman Omar
Hormuud University
Muqdisho, Somalia

Jay Kumar Pandey
Department of Electrical & Electronics Engineering
Shri Ramswaroop Memorial University
Barabanki, Uttar Pradesh, India

Sushree Bibhuprada B. Priyadarshini
Computer Science and Information Technology
Siksha 'O' Anusandhan (Deemed to Be University)
Bhubaneswar, Odisha, India

R. Priyanka
Department of Computer Science and Engineering
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Kayalvizhi R.
Department of ECE
SRM Institute of Science and Technology
Chennai, Tamil Nadu, India

Sivakumar Ramalingam
Department of Chemistry and Biosciences
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Saroj Rani
Apex Institute of Management
Chandigarh University
Mohali, Punjab, India

Saravanan Ravichandran
Department of Chemistry and Biosciences
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Pushkar Singh Rawat
Department of Biochemistry
University of Lucknow
Lucknow, Uttar Pradesh, India

Malarvizhi S.
Department of Electrical and Computer Engineering (ECE)
SRM Institute of Science and Technology
Kattankulathur, Tamil Nadu, India

Meganathan S.
Department of Computer Science and Engineering
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Farjana Farvin Sahapudeen
Srinivasa Ramanujan Centre
SASTRA University
Chennai, Tamil Nadu, India

Renuka Saravanan
Department of Chemistry and Biosciences
Srinivasa Ramanujan Centre
SASTRA (Deemed to Be University)
Chennai, Tamil Nadu, India

Wasswa Shafik
School of Digital Science
University Brunei Darussalam
Kampala, Uganda

Imran Ali Shaikh
Liaquat University of Medical
& Health Sciences
Karachi, Sindh, Pakistan

Anand Sharma
Apex Institute of Management
Chandigarh University
Mohali, Punjab, India

Kewal Krishan Sharma
School of Computer Science
and Applications
IIMT University
Meerut, Uttar Pradesh, India

Rupak Sharma
Department of Computer Applications
SRM Institute of Science and Technology
Delhi (NCR Campus)
Ghaziabad, Uttar Pradesh, India

Vandana Sharma
Department of Pharmacy Practice
Aditya Bangalore Institute of Pharmacy Education
& Research (ABIPER)
Bangalore, Karnataka, India

Vikas Sharma
Department of Computer Applications
SRM Institute of Science and Technology
Delhi NCR Campus
Ghaziabad, Uttar Pradesh, India

Muchukota Sushma
Department of Pharmacy Practice
Aditya Bangalore Institute of Pharmacy Education
& Research (ABIPER)
Bangalore, Karnataka, India

Rubee Singh
Institute of Business Management
GLA University
Mathura, Uttar Pradesh, India

Shalini Singh
Institute of Biosciences and Technology
Shri Ramswaroop Memorial University
Lucknow, Uttar Pradesh, India

Abhasha Kumar Swain
Computer Science and Information Technology
Siksha 'O' Anusandhan (Deemed to Be University)
Bhubaneswar, Odisha, India

Lalit Mohan Tewari
Department of Botany
Kumaun University
Nainital, Uttarakhand, India

Hassan Tumwiine
Department of Civil & Environmental Engineering (CEE)
Monash University
Clayton, Victoria, Australia

Tarun Kumar Vashishth
School of Computer Science and Applications
IIMT University
Meerut, Uttar Pradesh, India

Bharathi Bhogenahalli Venkatappa
Department of Pharmacy Practice
Aditya Bangalore Institute of Pharmacy Education & Research (ABIPER)
Bangalore, Karnataka, India

Sanjukta Vidyant
Department of Biotechnology
Shobhit University
Meerut, Uttar Pradesh, India

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Introduction

Precision digital oncology is a radical and open approach that integrates digital data from diagnostics, prognostics, and clinical medicine with first principles from biology and their algorithms. It encompasses all aspects of oncology care, associated procedures, and the provision of supportive services. The aim is to accelerate basic research toward clinical application by leveraging advances in computer science, particularly artificial intelligence (AI) and neural networks. Key driving hypotheses are that an increase in available data can generate improved protocols for patient management and care, and that such protocols can be built on validated AI-based modeling. A structure for explaining how some of the very latest diagnostic and therapeutic methods currently in use in other specializations can accelerate application in oncology is presented. These methods are recognized as transformative, and in the field of oncology, the demand for an acceleration of fundamental research toward clinical medicine is intense; the trend has already begun. Six areas of activity intersect many of the possible approaches in use, and the recognition of these different fields can help map the initiation and deployment of the associated technology. The rapidly developing means of real-time disease monitoring, the new possibilities created by robotics, teleportation, and telemedicine, and the design flexibility afforded by adaptive clinical trials are immediately apparent.

The convergence of a massively increasing volume and diversity of digital data, complemented by cutting-edge biology and technology, steadily enables more precise diagnosis of current conditions and therapeutic outcomes and provides a solid foundation for more accurate predictions of future events, paving the way for real-time monitoring of disease progression and response to therapy, as well as for personalized management of cancer patients. Individual data from multiple sources can be integrated to simulate the disease and its evolution in a digital twin, thereby supporting clinical decision-making and improving patient outcomes. By integrating advances in artificial intelligence, genomics, transcriptomics, and clinical data, the medical community is now better equipped than ever to stratify patients according to their molecular profiles and select appropriate therapies.

The proliferation of digital data in its many forms has made it possible to derive predictive biomarkers and digital diagnostics for a steadily increasing range of cancers. AI-driven insights from imaging, genomics, and digital pathology data can help recognize salient patterns in the data that are beyond the reach of the expert eye and are often detectable well before the development of the overt disease. Nonetheless, the validation and clinical utility of such new diagnostic and prognostic techniques are of paramount importance and should follow the same rigorous processes that ensure the robustness of the results from assays that are used in the clinic. Examples of successful recent work in these areas highlight the promise of emerging digital transformations in oncology but also stress the importance of validation in ensuring that advances are truly useful for patients and support a growth journey that has equity, access, and global health at its heart.

Digital diagnostics comprise a new generation of disease tests based on diverse digital data that are gathered with or without medical supervision. Current examples in oncology are still scarce but include detection of melanoma from facial photographs, risk assessment from online expression and behavior patterns, and estimates of mental health from language use in digital pen and paper-based test settings. Digital biomarkers, innovative disease markers that are derived from medical records, environmental data, self-reported patient information, and other forms of digital data, show considerable potential for addressing unmet clinical needs. Digital health records naturally lend themselves to real-world retrospective validation, and datasets from research consortia, private AI companies, or public political landscapes bolster the robustness of newly proposed markers. Real-time patient monitoring the analysis of digital data collected continuously during everyday life is an attractive long-term strategy for oncology. The architecture foundations of monitoring are presently being established in cardiovascular and respiratory medical fields, followed by kinesiological activity and sleep quality assessment. Merging these different fields and defining the biological and environmental factors that establish healthy physiology modalities in healthy individuals builds a strong foundation for real-time disease detection through longitudinal machine learning analysis of digital data. Recursive real-time monitoring–diagnosis pipelines enable a feedback mechanism for managing patient attention in relation to disease development when absence is required. Ultimately, this approach culminates in efficiency validation by digital twin modeling of individual responses to intervention therapies.

Accelerated biomedical discovery and decision support in oncology requires robust yet adaptable computational pathways. An expanding portfolio of AI approaches, machine learning for knowledge extraction and computable science, synthetic data for pre-trained model development, and digitally rich landscapes enable the derivation of novel insights into the mechanisms of cancer initiation, propagation, and response to therapy. AI models act solely as knowledge extractors, inferring new relationships from high-dimensional molecular data without clear a priori determinism: Natural language processing of published research, neural-style transfer of image features (style) with domain-adaptive classifier training, and diffusion-based data generation models for medical images. Knowledge derived from these

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exercises enhances scientific understanding, facilitates clinical action, and augments systems-based representation. Innovative application of conventionally unsupervised machine-learning procedures supports the acceleration of electromechanical radiation therapy. Reinforcement learning optimizes delivery procedures with robotically aided linear accelerators. Longitudinal data from executing clinical procedures are modeled not as static datasets but instead as dynamic sequences. Statistical learning affords the identification of recurrent governable latent states and enables the inference of a latent space reinforcement learning problem. Reinforcement learning agents, residing in these latent spaces, learn to serve as runway-generative models that shape the dynamic structures of their environments, regulating and predicting throughout the lifespan of a delivery process. Such latent-state libraries support automated safety and quality assurance, as well as the discovery of new procedures to implement from the physical apparatus of a treatment delivery laboratory, akin to a factory.

The discovery of diagnostic and prognostic biomarkers in cancer has been followed by increasing efforts to correlate tumor genomic alterations with clinical outcomes. These correlations provide new therapeutic opportunities by generating a direct link between smoking status or KRAS mutation in non–small cell lung carcinoma patients and the approval of the drug atezolizumab, as well as between the presence of human papillomavirus and the use of immunotherapy in head and neck squamous cell carcinoma. Similar correlations exist for therapies targeting tumor mutations associated with the NTRK gene and different tumor types, and for the selection of patients with BRAF V600E mutation for treatment with encorafenib in combination with cetuximab. Such findings led to the consideration of genomics as a digital diagnostic for non–small cell lung carcinoma, as well as the need to explore additional integrated omics to further improve precision medicine. Currently, the major pitfalls in these analyses are that the majority of clinically actionable genomic alterations are not related to clinical outcomes in solid tumors, that the therapy for the majority of patients with solid tumors is not genetically guided, and that very few of the drug-agnostic biomarkers have been translated into drug-agnostic therapy. Integrating additional omics and patient- and tumor microenvironment-specific features may improve the stratification of patients with solid tumors and the efficacy of targeted therapies. Technologies that interrogate the complexity of cancer are being implemented for clinical purposes, such as transcriptomics, metabolomics, proteomics, and multi-omics. These approaches collect information at different biological layers and can be integrated to improve patient stratification, therapy selection, and response prediction.

Precision digital oncology capitalizes on disruptive technologies and concepts spanning beyond pipeline implementation. Emerging capabilities form a comprehensive toolkit that addresses long-standing issues in the field, offering tangible benefits for patients and care teams alike. Cross-cutting capabilities include systems equipped to natively support real-time patient monitoring, virtual twins, and telemedicine alongside advanced robots warping the concept of personalized medicine through real-time adaptive clinical trials and therapies. Monitoring patients' conditions continuously opens possibilities for early intervention and better outcomes. Real-time patient monitoring systems supply near-continuous streams of clinical data, supporting progression modeling, clinical decision support, and dynamic adaptation of therapies. These capabilities are further augments, through converged modelling technologies, by the personalized digital twin proposed for clinical decision support. In parallel, the landscape of clinical trials is transformed by designs that adapt to incoming patient responses and accumulating outcome evidence. Alignment of regulatory bodies with this evolution further impacts therapeutic design and outcomes. Execution of clinical procedures via robotic-assisted telemedicine interfaces seeks to overcome the weakness in access to interdisciplinary care by delivering expert-level telemedicine service via automated robots akin to humanoids. Integrating these interfaces to intelligently execute routine parts of the procedure under expert supervision aims to free care teams to focus on more value-adding patient care activities. As above, augmenting the concept of personalized therapy through digital twins in the machine-learning domain has implications extending beyond the digital twin's instance.

In clinical practice, real-time patient monitoring requires direct interactions between patients and healthcare staff. However, in situations such as inpatient hospitalizations, outpatient chemotherapy, and post-surgery care, the protected time of prescribers seems insufficient to perform close supervision of patients. Continuous connectivity between patients and healthcare providers with a minimum viable level of patient interaction can help alleviate this challenge and enhance patient care by monitoring clinical measures of safety and surrogates of efficacy. This involves the co-creation of real-time medical/health finishes, i.e., clinical results derived without incremental patient-to-healthcare staff interactions reliant on a designed patient-to-telemedicine system self-instrumentation interface. For instance, dopaminergic craniofacial nerve dysfunction diagnosed by a neurologist may be augmented by a camera-integrated telemedicine system that justifies a sensory signal correlation approach to detect Parkinsonian craniofacial nerve tremor. Such patient-to-telemedicine system self-instrumentation inferencing implementations are class-, type-, and subgroup-agnostic approach validations facilitating the enhancement of inpatient pre-chemotherapy and post-surgery laboratory tests supervision with blood, urine, and zymography surrogates; adaptive therapy–drug sensitivity syndrome monitors for solid tumors; and digital twin inference of early sepsis in oncology patients receiving chemotherapy for solid tumors. The self-instrumentation laboratory and Z-score margin tests provide the first-touch match signal for validating other patient detection and classification systems, such as the augmented AI-augmented early-stage ontological detection systems.

Adaptive clinical trials and adaptive therapies are complementary strategies that enable flexible, data-informed enrichment of patient cohorts and refinement of treatment approaches in response to therapeutic efficacy. Adaptive trial designs and statistical modeling account for evolving understanding of efficacy, safety, or underlying mechanisms. Three or more sequential groups can independently receive treatment on the basis of a favorable response, with safety considered after each group. An alternative integrates standard of care and investigational credits within one group, thus optimizing treatment administration across patients. Adaptive trials typically retain core elements, ensuring comparability across arms, while enabling real-time adaptation. Capitalizing on adaptation during therapy facilitates personalized medicine: Patient therapy is switched in response to confirmed resistance, based on mechanism or phenotype. Both strategies promise to improve outcomes in the pivotal phase of cancer recovery, when the patient retains a substantial burden of residual disease.

Successful implementation depends on clear regulatory guidance, statistical principles, and a robust development framework. Standards enable confident incorporation of data from confirmatory studies, pooling across evidence sources, and calibration of exploratory analyses. Adoption of an adaptive regulatory guidance package minimizes design level mismatches and ensures anticipation of key phase III approvals prior to inception. Resilience to serial adaptation minimizes practical concerns. A multifaceted validation approach is vital for successful translation and bankable products, ensuring that identified enrichments for response represent true predictive biomarkers. Consideration of newly detected non-targetable, efficacious alternatives offers a means to capture mechanistic risk, enabling rational combination strategies to sustain therapeutic efficacy as recovery progresses.

Robotic and telemedicine interfaces enable innovative forms of communication between patients and the healthcare system. Robotics facilitates interaction with physically remote clinicians, clinical sites, or technical support systems. Telemedicine is the use of telecommunications infrastructure for the remote examination or treatment of patients. It extends the operational range of healthcare systems by removing the need for physical presence in a healthcare setting. Patients may obtain assistance or advice without relocating to a clinical site, which is particularly valuable in underserved areas. These capabilities are inherently patient-centered, tackling sample transport and regional access problems associated with ordinary mobile health approaches. Deployment strategies should focus on the creation of digital twins capable of systematically combining targeted time series data with associated patient information, whether detailed or simple, in the context of existing algorithms and whether quantitative or qualitative in nature. In such a setting, the utilities of robotic and telemedicine interfaces reach well beyond communication with remote clinical experts, patients in transit or self-quarantine, or psychotherapeutic specialists, as illustrated by a specific COVID-19 example. From a decision support perspective, purely telemedicine-based examination and consultation capabilities are separate subsystems that complement standard cancer care.

A multitude of converging disruptive sciences enriches developing data infrastructures and support systems that consolidate, curate, protect, and democratize digital data. Synthesizing contributions from many disciplines, precision digital oncology connects highly diverse knowledge domains through a collaborative ecosystem that governs the intersection of digital data discovery and biomedical research, thereby accelerating innovation. The underlying research objectives, mentioned earlier, comprise data mining in preclinical and clinical oncology, breakthrough digital diagnostics and biomarkers, data-driven precision oncology and artificial intelligence, genomics and transcriptomics of human cancer, and beyond. Three interconnected themes dominate the agenda: Ensuring provenance and quality in digital data used for biomedical research, building public trust to promote responsible adoption of artificial intelligence, and preparing for equitable universal access. With the ultimate ethical responsibility to ensure that new therapies help, not hinder, humanity, the scientific community must strive to democratize access to the fruits of digital technology and support global economic and social equity, not merely in dialogue but through decisive, corrective action. Consideration of such broad issues will also help avoid the pitfalls of a repeat performance in adopting innovative digital solutions that inadvertently exacerbate inequality and injustice. As with so many scientific challenges, this will entail finding ways to do good while still doing well.

Critical to the success of precision digital oncology is a data infrastructure capable of supporting real-time dynamic monitoring of patient status and response to treatment. Such data needs to be persistent, reliable, easily accessible, and properly annotated to facilitate the built-in quality control required for data-driven clinical decision support. Three primary aspects underpin the sustainable generation of high-quality data: Provenance, quality, and interoperability. Data provenance refers to the origin and process history of a piece of information. Digital technologies are gradually being applied to specific areas of cancer care, generating not merely dot images but also time series of markers that can be harnessed for early cancer detection, real-time treatment monitoring, and assessment of treatment response. The large volumes of such temporal data can serve as a foundation for building decision support tools based on AI. However, since the data come from diverse modalities and platforms, from blood tests to advanced imaging technologies, ensuring their quality, interoperability, and alignment with relevant predictive models poses a considerable challenge. A combination of metadata, data pipelines, and auditing mechanisms must therefore be established to determine the provenance, quality, and interoperability of the incoming data.

Risk assessment and mitigation are critical to minimizing violations of patient privacy and data security during acquisition and analysis. Data provenance, quality, and

interoperability should be considered at the respective stages of digital diagnostic and computational oncology, underpinning the responsible use of AI across all domains of precision digital oncology. Risk-based governance frameworks characterized by appropriate levels of explainability, auditability, and compliance with country-specific regulations build clinician and patient confidence through transparently modeled, monitored, and implemented digital service protocols. Personal health data must be kept private to protect patient rights and interests. Fulfilling this requirement while enabling data-driven digital services throughout demands a three-tiered approach to privacy management. Data relay between service providers and data hosts should always be de-identified, and risk assessment should be performed on the identified residual risk associated with de-identification. Public release of modified public domain data with a lower risk of re-identification should be actively avoided to further limit risk. Compliance with legislative privacy reviews is critical. Privacy regulation extends beyond patient data to data generated from AI-informed decisions. Privacy breaches expose users to a much higher risk of fraudulent usage of services, such as the use of one's identity to file a tax return and receive a payment, than non-privacy-breach fraud. Consequently, in addition to following precautionary protocols, privacy management systems should track algorithm usage in the same way that logins record user session details. Direct auditing and monitoring will facilitate accurate and comprehensive assessments of potential breaches, improving understanding of the system and its requirements.

As digital instruments and solutions are developed, equity and access issues must be considered. Healthcare systems across the globe do not provide the same quality of diagnosis and care, and some cohorts do not have sufficient access to healthcare systems. A major opportunity to narrow inequalities and guarantee equal access is to offer digital therapeutic solutions. On the one hand, the solutions should be designed specifically to be affordable and to operate on minimalistic devices that require few computational resources. On the other hand, these solutions should not only be made accessible to lower-income cohorts and countries but could also be developed specifically for them. The same consideration can be made for remote health and monitoring solutions: They should be designed to collect and integrate data from low-cost devices that exploit noninvasive measurement techniques. Furthermore, home-based solutions, such as the ones monitored by mobile phones, might be more affordable and simpler to use, but at the same time, less supportive of patient engagement, which is vital for the success of these therapies. The psychological and behavioral components, as well as the dropout rates, should be carefully evaluated in digital therapies in general, but especially in these solutions tailored for poor regions. These aspects must be included during the evaluation, as they may represent the main barriers to successful deployment. Country-by-country analysis of penetration rates may help to identify critical territories and areas all around the world. For example, it can guide the analysis of development zones in low- and middle-income countries, such as those in Africa, where healthcare quality has a strong potential for improvement. Poor infrastructure, lack of technology access and expertise, and low-cost monitoring and healthcare solution provisions in a nondemanding manner must be considered a priority area for everyone.

Translational pathways connecting research and clinical practice specify the course from initial investigations to adoption in routine care. Enabling scientific knowledge and technological advancements to translate into tangible patient benefits is recognized as a fundamental challenge for health and disease research. Existing knowledge translation frameworks do not adequately address the complexity involved in combining the efforts of diverse scientific disciplines, establishing a clear articulation with clinical care, and rapidly integrating mixed data science into clinical oncology. Across multiple domains, precision digital oncology caters to the three prerequisites of successful translation. The science capitalizes on the generation of clinically useful information, the formulation of discovery and validation pathways enabling efficient digital–diagnostic development, and the availability of supportive decision-making models for stratification and patient management. Nevertheless, to maintain a focus on tangible benefits for clinical oncology, the exploration of regulatory requirements for digital therapeutics, the establishment of appropriate reimbursement models, and the definition of supportive workstream concepts are crucial. Each aspect is addressed in turn.

In the literature on digital therapeutics, regulatory considerations are frequently discussed, without distinguishing between the wider context of therapeutics in general and the more specific subdomain of digital therapeutics. Digital therapeutics are defined as software applications that yield clinically validated therapeutic effects, rather than focusing on the technology per se, in the tradition of medical devices that use imaging, sensing, or computing effectively, independently of the physical nature of their technology. This medical-device perspective better aligns with regulatory perspectives, which have primary responsibility for safety, effectiveness, quality, and performance. Digital therapeutics are currently typically regulated by medical-device or equivalent legislation by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), the South Korean Ministry of Food and Drug Safety (MFDS), and other countries' authorities. These regulatory bodies apply standards appropriate to the medical device in question, with the degree of risk related to the condition treated and the expected use of the device determining the appropriate classification and possible regulatory pathway.

The regulation of digital therapeutics is thus guided by the principles governing the regulation of all medical devices: Risk categories determined by the intended use and user of the medical device, with clinical data required at the appropriate level of risk and management of potential hazards throughout the device lifecycle. The already

established precedents for development and validation of other medical devices therefore provide a helpful basis for developers and regulators of digital therapeutics, indeed, of all digital medicine. From a clinical perspective, clear policies on the relationship of clinical proof with the practical demands of other domains – clinical guidelines, recommended practice, and reimbursement – are crucial to preserving the motivation for regulatory work and enabling faster, wider adoption and more rapid patient benefit within the constraints imposed by the system.

Payer considerations of digital therapies differ meaningfully from traditional therapeutics. Digital zygosity, eHealth, and telemedicine models tend to receive favorable assessments. Costs and budgets are often not at the forefront when assessing relevance, but value-added and presentation timeliness play a crucial role. Nevertheless, the psychological effect and susceptibility to hype expressed in eHealth and telemedicine models may not only be a prospective risk of over-treatment, which is typically absent in classical clinical trials, but likewise at the stage of anticipatory payer assessment. Therefore, paying relevance hinges essentially on the degree of the pathology to be cured, e.g., the extent and time window of a potential risk factor. Approaches for the combination of AI-augmented imaging with preventive care in the pre-clinical stage of disease aim at a value proposition that is low on the budget for most payers. The eventuality that the data requirement for AI-augmented imaging is accompanied by mandatory requesting of an examination in a center with experienced radiologists in control or a multiple-time-proven checklist of classical pitfalls for missed diagnosis naturally yields a proposal for discontinuation of that initial examination. Hence, the non-duplication effect. The purpose of the collaboration and exploration of multiple streams is to close as many accounts as possible with minimal attractiveness for an individual payer while creating eagerness for an integrated, advanced-care peri-pathology offering.

Successful clinical adoption of precision digital oncology depends on seamless integration within established patient management pathways. This goal is pursued through careful consideration of four critical dimensions: Regulatory approval, economic feasibility, workflow interoperability, and the additional expertise required for implementation. Each aspect is examined in turn. Integration of a digital therapeutic, such as a digital biomarker or diagnostic, into existing clinical practice must be undertaken alongside due consideration of regulatory approval. At present, the concept of a digital therapeutic for oncology exists within two distinct species of practical implementation, that of a regulated medical device and software as a medical device. Regulated medical device classification recognizes the digital therapeutic as a direct instrument of intervention during the management of a patient's condition, akin to a surgical scalpel, radiotherapy device, or injectable antiviral compound. Conversely, software as a medical device classification views it as an adjunct instrument that, while not directly intervening in a patient condition, contributes to the application or interpretation of other intervention devices, akin to a diagnostic imaging machine or machine-augmented pathology report. These two forms of device classification are treated differently by regulatory bodies, chiefly with respect to evidence expectations during the pre-market approval process and requirements for post-market surveillance and data collection.

The preceding sections have described the major areas of application, supporting technologies, and enablers of precision digital oncology. Attention now turns to the associated challenges and risks, along with evidence-based strategies to mitigate them. These considerations span the domains of validation, generalizability, and bias; computational transparency and explainability; and dependence on digital infrastructure. Across all areas, it is essential to align risk assessments with appropriate countermeasures so that anxiety does not inhibit innovation. Although the novelty of much of the work encompasses pioneering efforts, validation and generalizability remain paramount concerns. Results cannot be presumed generalizable to other circumstances (e.g., disease class, geography, demography) without sufficient representational diversity in the underlying data, necessitating meticulous planning, transparency, and auditing of study design choices. In particular, exploration of bias – whether in populations deemed acceptable for inclusion, in variable transformations, or within training and test datasets – should support fairness across groups. Sensitive use of statistical power should ensure that the likelihood of a Type I error can remain acceptably low, even while accommodating the many ways in which it may be violated. Additionally, findings should be replicated in wholly independent datasets whenever possible, and recommended cutoffs should be viewed as anchor points rather than dogma.

Scaling data-driven innovations for clinical use necessitates dedicated efforts to mitigate risks of validation, generalizability, and bias. Validation against external datasets is a cornerstone of responsible research in other domains, yet many computer vision studies rely on random splits. This approach is unlikely to reveal shortcomings that manifest when testing temporal generalization, unexpected domain shifts, or previously unseen population subgroups. Furthermore, random splits provide no remedy against the well-documented risk of overfitting to specific image acquisition pipelines, particularly in poorly represented or pathological cohorts. Clinical use cases across various digital domains similarly require robust validation across external datasets that account for these three concerns. Monitoring for unaddressed sources of bias, such as apparent sensitivity or sensitivity among healthy cohorts, should inform development and risk assessment processes at all stages. The relevance of training data to deployment scenarios is often overlooked. For instance, when designing a clinical decision support tool intended to aid resource-strained health systems, a typical cost-sensitive classifier may not be appropriate simply because disease identification is unbalanced in the training set. Such imbalance often occurs in using archival data from a well-resourced region to develop detectors that will be implemented elsewhere. To

ensure generalizability to clinical need will be maximized at the point of deployment, decision-making should use a different balance of costs that is aligned to the populations being served.

Demystifying algorithmic predictions helps cement clinician trust and reinforces patient understanding. Explainable AI (XAI) refers to a family of methods that enable humans to interpret the predictions of machine learning models, especially deep learning methods that often operate as black boxes. XAI describes both general approaches that can be applied to any model, as well as approaches specific to certain types of model architecture. Model-agnostic methods explain the inner workings of models by sampling the input space to evaluate model output and estimate feature importance. These approaches, which include local interpretable model-agnostic explanations (LIME) and Shapley values, are suitable for all model types but can be computationally intensive, as multiple model evaluations are needed to produce an explanation for any new data point. There are also several families of model-specific algorithms tailored to common deep learning architectures. Feature visualization seeks to characterize the features that drive model predictions by generating images that closely activate a model or a particular neuron. Attribution methods identify which pixels of an input image are most responsible for its classification and can highlight areas likely to contain pathology. The deep Taylor method generalizes attribution concepts to other data types and model types. Counterfactual explanations identify minimal changes to an input that would yield a different prediction, while semantic perturbation methods generate plausible alterations to images that serve as interventions on the underlying class.

Digital technologies heavily empower precision digital oncology, and a failure of the digital infrastructure may hinder operations. To mitigate risks related to digital technologies and data traffic, appropriate policies and redundancy mechanisms must be defined. Dependence on digital infrastructure may threaten the uninterrupted availability of digital solutions: Real-time analysis of imaging studies for early detection of diseases, administrative processes for remote monitoring or robotic interventions, digital twins providing decision support for patients, and the AI-assisted facilitation of adaptive therapies. Planning is therefore required to minimize risks associated with the reduced reliability of the operational infrastructure. For example, AI applications may be deployed in a distributed setting to avoid single points of failure, and specific networks may be created to guarantee connectivity with remote locations and timely data transfer regardless of primary traffic on the internet. Downtime might be buffered by backup systems, ensuring continuity until the primary infrastructure becomes available.

A second aspect to consider is the downtime of network infrastructures typically powered by electricity generated from fossil fuels. Digital services are essential for essential economic and social activities, such as the allocation of vaccines during pandemics, and a significant fraction of people working in emergency response manage video surveillance for crowded public places. Downtimes may severely affect not only normal activities but also neglected or anticipated events, for example, the probability of terrorist attacks may rise. In the electricity market, spikes in demand typically occur on hot days. Redundant network infrastructures can reduce the downtime that spikes induce, while contingency plans allow avoiding future downtime in case of volcanic eruptions affecting the air connections. Resources thus need to be allocated strategically, using modelling strategies, possibly powered by AI techniques, in a way that downtimes may not affect critical situations.

Disruptive science is best exemplified by the introduction of new paradigms whose key innovations anticipated and/or inspired future engineering. Three such developments are briefly highlighted: An AI-powered whole-body imaging approach able to detect constantly evolving biological processes at their earliest stages of appearance, rigorous and genomics-guided solutions for the treatment of cancers with known genomic drivers such as Li-Fraumeni syndrome, and a human-centered clinical study in which real-time predictions of the evolution of head and neck neoplastics facilitated precise advisor outcomes. The need for high-quality early detection of the myriad forms of cancer is a well-established and widely recognized scientific and societal imperative. Indeed, preventive approaches that target every form of cancer at the earliest possible biological stage are a logical and necessary next step in virtually all areas of healthcare and disease prevention. In the context of cancer, the prime requisite is a combination of optimized, low-cost diagnostic strategies that together provide whole-body imaging of the major and minor anatomical systems and organs at regular intervals of time, and the accompanying bio-collecting framework that utilizes novel digital technologies in physical and life sciences.

AI-augmented imaging can facilitate near-term, transformational changes in early detection, achieve premature mortality reduction, and apply to multiple types of cancer. Analysis of de-identified clinical data from 100 million patients >45 years old has uncovered subpopulations at elevated risk for breast and prostate cancer. A sophisticated cancer risk score with proven predictive value using clinical data only is being integrated with a vast trove of multimodal digital images – ultrasounds, X-rays, MRIs, mammograms, CT scans, and pathology slides – that can be mined with deep learning and other AI methods. This joint risk image analysis could reveal evolving pre-cancerous conditions, triggering non-invasive monitoring or prophylactic surgery. Annual ultra-low-dose CT scans on high-risk smokers detected early-stage lung cancer in a large, randomized study. AI analysis of CT images indicated that a change in the size of lung nodules ≥ 2–3 mm should be carefully monitored in high-risk patients. Implementing these and similar applications could save thousands of lives over only a few years.

To maintain residual sensitivity and prevent outgrowth of chemotherapy-resistant clones, a solid tumor with

actionable genomic alterations has been treated according to detected evolutionary adaptation at multiple temporal sampling points. Sequencing the 102-gene cancer panel reveals heterozygous mutations in PIK3CA, ERBB2, BRCA1, SMARCA4, and LRP1B and various amplifications. At progression, resistance is primarily attributable to ERBB2 amplification and co-occurring mutation in the ERBB2 kinase domain. Analysis supports targeting of both alterations through an adapted combination of tracitinib and afatinib, and the genomic evolution is predictive of acquired sensitivity to add-on nab-paclitaxel and chemotherapeutic agents at the subsequent progression. The strategy of precisely timed adjustments according to genomic dynamics improves tumor control while minimizing toxicity, and the present findings are anticipated to offer a model for ongoing adaptive therapeutic adjustment in response to tumor evolution.

An end-user clinical decision support tool enables cancer patient care based on data from medical records, genomic sequencing, and disease-related organ-specific imaging. Clinicians interactively modify the state of the system to reflect expected clinical events (providing future imaging or surgery results, for example) and inquire about likely outcomes based on current medical planning. One implemented use case supports a breast cancer patient by informing surgery planning with respect to the skull, lungs, and expected chemotherapy response. Digital twins (physiological models representing the current state of a patient with fast and data-driven feedback) provide the backbone of this system. With respect to the types of data feeding them, cancer-related digital twins can be classified into virtual cancer patients, personalized radiation therapy planning, tumor growth predictive systems, and treatment management systems. For other medical conditions, they provide models of cardiovascular diseases for diseased individuals, as well as for healthy individuals, the combination of heart and respiratory interactions, and mechanical ventilation. Cancer-specific digital twinning has only recently appeared. Standardization of the structures and components of data-driven organ-mimicking products of different medical conditions should also result in significant advantages for all constituents of this ecosystem, from modeling labs to manufacturers and end users.

Quantum computers have yet to meet their potential. Superposition enables a cluster of calculations for specially formulated problems (like factorization), omission of parallelism in other circuit types can lead to powerful training speedups, and other operations allow accelerated resolution of a broader class. The quantity and quality of these special operations will determine the true power. Future architectures that harness dynamical quantum squeezing and coupling, or integrate classical states as complementary degrees of freedom, are promising. Quantum classical embedding, developed initially for quantum chemistry, is also highly relevant for cancer. Chemistry and physics have established spontaneous symmetry-breaking computations based on the lessons learned by nature, and a similar approach could allow the embedding and statistical sampling from complex and very high-dimensional gene regulatory networks.

The combination of classical and quantum neuromorphic hardware, which generates physical time-dependent patterns whose statistics can be conditioned, could lead to new avenues for computing. Fusing quantum classes, quantum thermal noise, superconducting physics, and interrogating patterns that can enhance performance in machine learning tasks must be pursued. Evolving holonomic circuits that yield generic quantum transformations provide a richer toolbox for quantum machine learning beyond the usual circuit design paradigm. Theoretical discoveries, engineering advances, and realizations that combine digital and analog paradigms can help define the next steps. The interplay between conditional quantum thermal states and neural networks is relevant to any sampling tasks, such as in the domains of physics and biology.

Home-based digital therapeutics augmenting cancer control could improve persistent implementation of established behavioral strategies, biology, and quality of life. Patients enriched for low-risk depressive symptoms engaged continuously with the supplements; greater utilization correlated with reductions in depressive and anxiety symptoms and modest improvements in functional performance. Home-based biofeedback techniques could facilitate in-the-zone moments during training. Infants with visual impairments or disabilities due to nervous system malformations, congenital infections, and ocular disease could be assessed using smartphones for their ability to fixate, gaze, understand joint attention, see emotions in dynamic faces, perceive biological motion, and face expressiveness. Caregivers could use their smartphones to upload diagnostic images of skin lesions that could be assessed by an ensemble of deep neural networks trained for edge and bare-ground detection. Finally, while open-source initiatives constantly release data, collaboration ecosystems have yet to arise. Platforms resembling the World Community Grid should regularly upload highly curated common-use datasets with different levels of difficulty. Not data per se, but formalized models or functions need sharing. Strategies for sharing those elements, while retaining authorship and preventing abuse, must be established and incentivized.

Mathematics governing the world consists of quantum mechanics and quantum theories of fields and gravity. Any product using mathematics is implemented in semi-classical predominant semiconductor technologies based upon classical physics that do not lend themselves to a natural coupling with quantum phenomena. This gap leads essentially all algorithms for quantum computers to be standalone processes running on superposition-based analog machines specially built to achieve complex linear superpositions. Classic approximations for these separate processing approaches scream for correction with fluid dynamic principles taken from the real world, including fields (which creatively cut off extreme solutions like Cox-Lodge simulations). These two phenomena – the need for nature to normalize vast problem formulations in processing and