Advances and challenges in precision imaging

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Technological innovations in genomics and related fields have facilitated large sequencing efforts, supported new biological discoveries in cancer, and spawned an era of liquid biopsy biomarkers. Despite these advances, precision oncology has practical constraints, partly related to cancer's biological diversity and spatial and temporal complexity. Advanced imaging technologies are being developed to address some of the current limitations in early detection, treatment selection and planning, drug delivery, and therapeutic response, as well as difficulties posed by drug resistance, drug toxicity, disease monitoring, and metastatic evolution. We discuss key areas of advanced imaging for improving cancer outcomes and survival. Finally, we discuss practical challenges to the broader adoption of precision imaging in the clinic and the need for a robust translational infrastructure.

Introduction

Precision or personalised medicine is an increasingly accepted approach to cancer care, in which therapy is planned based on the distinct molecular characteristics of a given tumour. Crucial to precision medicine is the concept that the right combination of drugs should be used at the right stage and time in the progression of the disease. Although historically defined by tailoring treatments to genetic mutations, the clinical translation of precision oncology has proven more complex. Contributing to the complexity are biological factors including the variable nature of the transcriptome, proteome, tumour microenvironment, physiology, lineage plasticity, and dynamic temporal changes due to treatment pressures. Further complicating the choice of therapies is that new mutations evolve over time, and some deleterious mutations can also occur in healthy tissues. Furthermore, the host also has a key role in determining treatment response (ie, different responses to the same dose).

In parallel to the emergence of precision oncology, there have been remarkable advances in imaging diagnostics, radiotheranostics, and image-guided therapy over the past 5–10 years. Imaging has become indispensable in the entire treatment chain of cancer care from screening, detection, and staging, to treatment selection, planning, efficacy monitoring, image-guided treatment delivery, toxicity monitoring, long-term surveillance, and drug development. Yet, imaging is generally not featured in the design and validation of precision oncology. We highlight that to advance personalised medicine, the field should embrace imaging technologies to map the spatial and temporal composition of tumours and surrounding host tissue (figure 1). In other words, to optimise the efficient use of resources and to maximise clinical utility, developments in precision imaging need to be closely aligned with precision medicine guidelines. These developments are even more important given the long lead times of technology development compared with those in the more established, well funded, and reimbursed drug development pipeline. This Review discusses the most recent imaging advances that enable precision oncology and summarises current needs to further the field.

Overview of advanced precision imaging

Broadly, we define precision imaging as advanced imaging approaches that allow increased anatomical coverage, improved spatial and temporal resolution, multiplexing, high-throughput screening, targeted sampling of tissue, and precise delivery of new therapeutics (figure 2). We summarise some of the reasons why these advances are essential to precision oncology (figure 1). Total-body imaging, for example, expands surveillance coverage and allows for better delineation of where the disease is located. Hybrid imaging systems improve the spatial information important for tumour heterogeneity

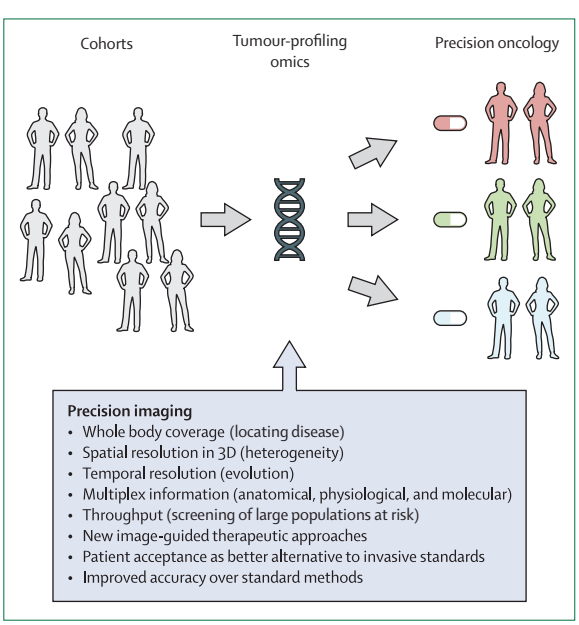

Figure 1: **Precision imaging in precision oncology**
Precision oncology has historically been defined as the use of genetic mutations to identify patient populations who will respond to a given drug–dose combination. Precision oncology has practical limitations, partly related to cancer's biological diversity and spatial and temporal complexity. Precision imaging technologies are being developed to address some of the current shortcomings. These emerging imaging methods strengthen precision oncology by providing clinically relevant information not obtainable by other means.

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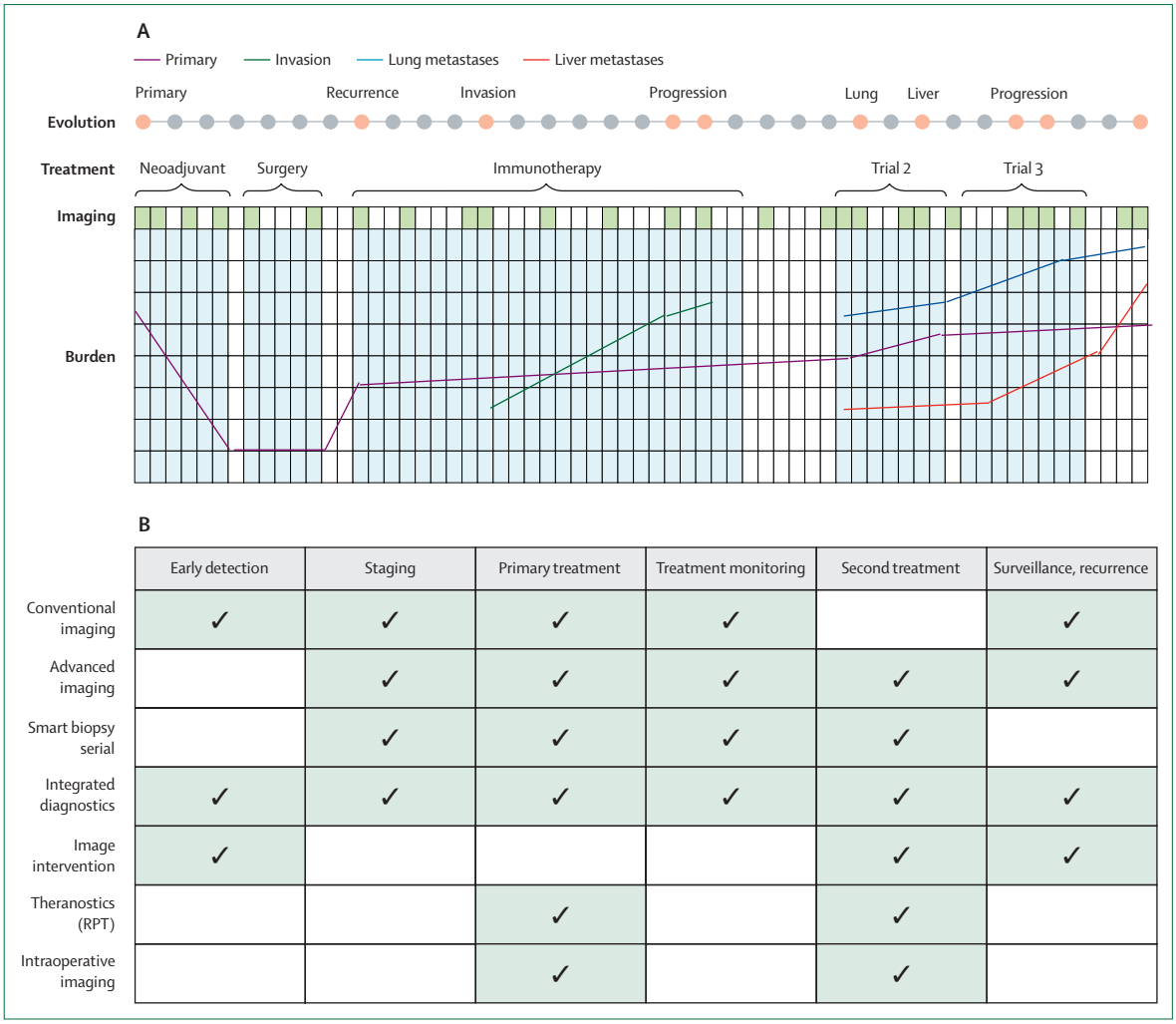

Figure 2: **Examples of precision imaging during the treatment history of cancer**
(A) Case history of a patient with cancer. The lesion size is plotted as a function of time (differs vastly among patients and tumor types) for primary tumour, locoregional invasion, and distant metastases. Orange circles=primary, recurrence, invaison, progression, lung metastases, liver metastases. Grey circles=interval time stamps. Green boxes=imaging is performed. White boxes=intervals where no imaging takes place. Blue boxes=treatment cycles. (B) Role of precision imaging during different cancer stages. The green boxes with checkmarks represent the main applications. Low-dose imaging is mostly for lung cancer (eg, CT) or breast cancer screening (mammography). RPT=radiopharmaceutical therapy.

assessment and permit the acquisition of multiplexed data at the anatomical, physiological, and molecular levels, allowing stratification. Emerging image-guided approaches add to the armamentarium of precision oncology and enable additional treatments, often with better patient acceptance than standard therapies.

Many of the advances in imaging technologies over the past 5 years have vastly improved our current ability to perform anatomical and physiological mapping, staging, and response monitoring (figure 2). Beyond hardware advances, computational advances in artificial intelligence (AI) have provided new ways for algorithms to reduce scan time, increase image quality, reduce the patient radiation dose (eg, in CT scans), automatically quantify radiographical patterns in images, and offer many other advantages. Faster imaging has major benefits, including artifact reduction, higher throughput, better coverage, better patient tolerance, and greater affordability than traditional imaging. Improved spatial resolution has allowed for seamless reconstructions in different planes, the ability to perform CT and MRI angiography, and improved staging. Dose reduction helps with screening and the ability to perform more frequent follow-up imaging and paediatric studies. Targeted molecular imaging has opened new frontiers in therapy selection and treatment monitoring.

Total-body PET

Since 2019, long-axial field-of-view PET scanners have emerged as an exciting new tool for improving image quality and reducing scan time.[1] This development helps to address a key question in precision oncology: where is

the disease located (figure 1)? New-generation scanners (eg, μEXPLORER [United Imaging, Shanghai, China], PennPET [University of Pennsylvania, PA, USA], and Biograph Vision Quadra [Siemens Healthineers, Erlangen, Germany]) can acquire images of the main body organs simultaneously or image the total body with a single bed position (figure 3).[2] The improved sensitivity and spatial resolution of the scanners mean that a PET study can be acquired in a reduced amount of time (eg, 2–4 min; leading to enhanced tolerability), and with a notably improved image quality than is possible with standard digital PET–CT scanners.[6] In addition, substantially reducing the dose of radiopharmaceuticals given for a scan without compromising image quality is possible.[1,2] The ability to perform whole-body dynamic imaging also has immediate relevance for the evaluation of the kinetics and biodistribution of novel radiopharmaceuticals.[6] The cost of the new total-body PET–CT scanners is higher than that of standard PET–CT systems. However, given that these new scanners enable higher patient throughput and decreased radiation doses while providing incremental diagnostic information, they will likely be implemented widely in clinical care and research within the next few years.

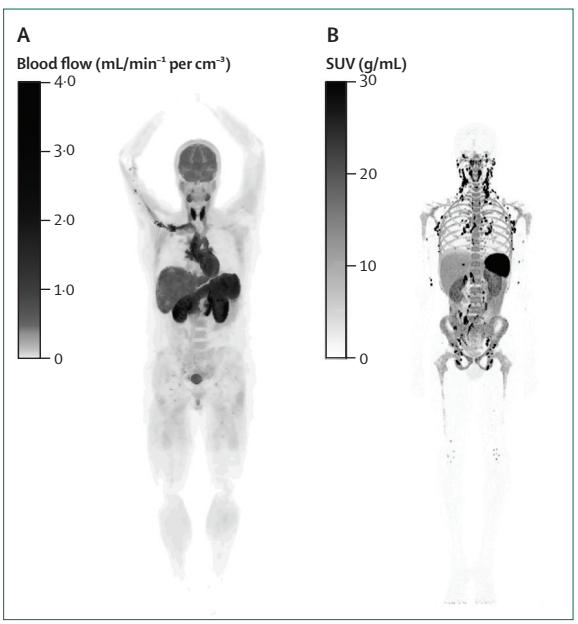

Figure 3: **Total-body PET imaging**
Examples of studies enabled by total-body PET scanners that image the entire body at once with high detection sensitivity. (A) Maximum-intensity projection showing total-body parametric image for blood flow (mL/min^{-1} per cm^{-3}) using [^{11}C]butanol and quantified in absolute units of blood tissue calculated with kinetic modeling[3] (reproduced from Cherry et al).[4] (B) Maximum-intensity projection of the total-body distribution of [^{89}Zr]Zr-crefmirlimab, an antibody fragment that binds to CD8^{+} T cells (reproduced from Omidvari et al).[5] Uptake is observed in the spleen and bone marrow, with exquisite delineation of lymph nodes throughout the body. Image obtained 48 h after injection; the injected dose was 18 MBq to enable repeat imaging. SUV=standardised uptake value.

Hybrid imaging systems

Hybrid molecular imaging refers to the acquisition and integration of information from functional and anatomical imaging, such as with PET–CT, single-photon-emission CT (SPECT-CT), or PET–MRI. Such imaging has two main advantages: display of molecular information on top of anatomical maps (which are often used for image-guided intervention), and improvement of image reconstruction algorithms for PET or SPECT by use of CT or MRI. The clinical adoption of PET–MRI in precision imaging has been relatively slow, although MRI by itself is used extensively in breast, prostate, liver, and brain cancers. The combined information from PET and MRI is particularly useful in predicting outcomes in lymphoma after CAR T-cell therapy,[7] identifying intraprostatic lesions,[8] and predicting overall survival in glioma.[9] In addition to its diagnostic advantages, PET–MRI is preferred over PET–CT in paediatric patients and patients whose diagnostic testing requires information from both PET and MRI (such as patients with advanced-stage cervical cancer or prostate cancer).

Molecular imaging agents

Over the past decade, many new molecular imaging agents have been tested preclinically[10] or through first-in-human microdose-exploratory investigational new drug (IND) applications, and a number of these imaging agents have entered the market.[11] The agents that have entered the market include [^{68}Ga]Ga-DOTATOC (2019), [^{64}Cu]Cu-DOTATATE (2020), [^{18}F]fluoroestradiol (2020), and various prostate-specific membrane antigen (PSMA)-targeting PET probes (ie, [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-gozetotide, and [^{18}F]F-piflufolastat).[12] Additional examples in development include agents for fibroblast activation protein (figure 4)[13] and several labelled antibodies for receptor imaging and cell tracking (eg, immunoPET).[14] The availability of these new probes improves the physiological, pharmacological, and molecular profiling of cancers and enables the assessment of their heterogeneity (figures 2, 4). Novel molecular imaging agents could also be co-developed as companion diagnostics for next-generation therapies.

Companion diagnostic imaging

The integration of imaging agents as companion diagnostics is another frontier in imaging for precision oncology. The goal is to delineate a patient's disease landscape, guiding clinicians with unparalleled clarity towards the most effective therapeutic options. The convergence of imaging technology with standard-of-care treatments and new therapies presents an unmatched opportunity to improve outcomes. For example, [^{89}Zr]Zr-DFO-SC16.56 is being used for the non-invasive in vivo imaging of delta-like ligand 3-expressing malignancies,[15] which has been the focus of emerging therapies such as antibody–drug conjugates, T-cell engager molecules, and CAR T cells for small-cell lung cancer[16] and other neuroendocrine neoplasms.[17] Another example is the use of [^{18}F]fluorodihydrotestosterone, a

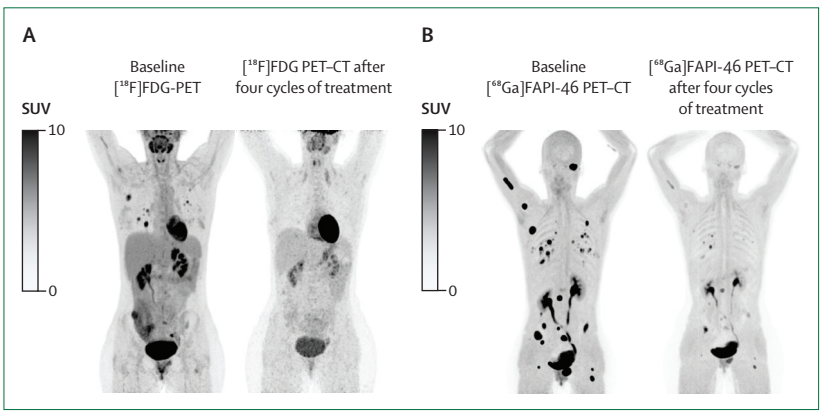

Figure 4: **Whole-body PET imaging with new FAPI tracer**
Female patient aged 38 years with a solitary fibrous tumour of the right abdominal wall presenting with lung, peritoneal, and bone metastases. (A) [^{18}F]FDG-PET maximum projection images before and after four cycles of treatment. (B) As the patient exhausted all treatment options, a [^{68}Ga]Ga-FAPI-46 PET–CT was done, displaying high uptake of fibroblast activation proteins in all [^{18}F]FDG-avid lesions. After four cycles of [^{90}Y]-FAPI-46 radioligand therapy, restaging revealed partial response according to RECIST criteria. SUV=standardised uptake value. FAPI=fibroblast activation protein inhibitor.

PET tracer for detecting androgen receptor expression in prostate and breast cancers, which is used to study new therapeutic agents.[18,19]

Metabolic imaging

The success of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)-PET has firmly established the role of metabolic imaging in oncology. However, [^{18}F]FDG-PET cannot reliably distinguish between glucose uptake in healthy cells (oxidative metabolism) and uptake in cancer cells (glycolytic metabolism with excess lactate production). In 2022, two magnetic resonance spectroscopy-based tests that probe dynamic changes in tissue metabolism emerged: hyperpolarised MRI and deuterium metabolic imaging (DMI).[20] Hyperpolarisation, most commonly of [^{13}C]pyruvate, increases the in vivo magnetic resonance signal and, consequently, hyperpolarisation MRI contrast. This increase magnetic resonance signal allows for rapid acquisition of spatial metabolic maps within seconds of infusion. Although all downstream metabolites of hyperpolarised [^{13}C]pyruvate can be assessed, the conversion of hyperpolarised [^{13}C]pyruvate to hyperpolarised [^{13}C]lactate is the most relevant hyperpolarised MRI parameter to assess cancer metabolism. Several other hyperpolarised probes are being investigated in preclinical research, including [^{13}C]urea, [^{13}C]fumarate, and [^{13}C]dehydroascorbate. The shortcoming of hyperpolarised MRI is the loss of hyperpolarisation and associated signal decay that occurs within minutes after intravenous injection. DMI enables metabolic imaging for more than 1 h after oral administration of [^{2}H]substrate, and assessment of the conversion of [^{2}H]glucose to [^{2}H]lactate. However, DMI is limited by the spatial resolution and sensitivity that can be achieved for a target organ. Both hyperpolarised MRI and DMI hold clinical potential for in vivo interrogation of tumour biology and early assessment of treatment response. Because MRI scanners are far more abundant than PET scanners, hyperpolarised MRI and DMI—although currently still experimental—could potentially improve patient management and speed up treatment decisions.

Smart biopsies

Precision oncology has increased the need for accurate tissue sampling (figures 1, 2). Advanced imaging has especially contributed to identifying specific sites for targeted biopsies. Tissue sampling is necessary to better understand the heterogeneity of cancer, measure temporal changes in expression profiles and somatic mutations, analyse immune cell infiltration as a response to treatment, perform spatial biology for biomarker discovery, and supply tissue aliquots to drug trial sponsors as part of their reporting requirements. Although core biopsies (16–18 gauge needles) have many advantages for tissue acquisition, they also have some downsides, such as procedural complication risks in some specific types of biopsies, long turnaround times, and a substantial fraction of non-diagnostic specimens, partly because of conventional analyses that require large sample sizes. Because of these reasons, new, smarter types of biopsies are being explored to improve information content, reduce complication rates, and improve throughput.[21,22]

Fine-needle aspirates are performed with 21–25 gauge needles and typically yield cells rather than core tissue. Fine-needle aspirate sampling has been firmly established for conventional cytopathology and flow cytometry analysis in the context of lymphoma. Highly multiplexed analyses of scant specimens have been developed by use of DNA origami[23] and bio-orthogonal chemistries[24] for staining, which do not require the use of harsh chemicals that would destroy cells during cycling. Point-of-care analytical systems are being explored for multiplex sample processing, especially for resource-constrained locations and countries.[25] Fine-needle biopsies use small-gauge (20–22 gauge) specialty needles that are designed to obtain microcores with preserved tissue architecture.[26] The microcores are commonly procured by endoscopic ultrasound, but fine-needle biopsies are also being adapted to percutaneous procedures.

Percutaneous fibreoptic sampling is yet another method that allows precision biopsy. An example of a new development in the interventional community is biopsy guided by a fibreoptic with forceps (eg, SpyGlass [Boston Scientific, MA, USA]).[27] This emerging field is particularly suited for tumours in otherwise inaccessible locations, such as peripheral intraductal cholangiocarcinoma. A second and complementary development is the adaptation of miniaturised cholangioscope to multiplexed fluorescence imaging by use of probes, an approach similar to fluorescence-guided surgery. These

probes can be designed to highlight cancer features, which can be either diagnostic by themselves or have a biopsy sample taken for further analysis.

Integrated diagnostics and the complementary roles of liquid biopsies and imaging

Integrated diagnostics is an emerging field that involves the use of complementary imaging, laboratory biomarkers, pathology, and patient demographic data augmented with information technology. Integrated diagnostics can offer greater diagnostic accuracy than single tests by identifying complementary biomarkers, shorten the time from diagnosis to delivery of molecularly informed therapy, and improve the longitudinal monitoring of outcomes through alternating use of redundant biomarkers.[28] Incorporating diagnostic imaging into AI-based integrated diagnostic algorithms is essential for developing the strongest possible predictive and prognostic biomarkers to direct precision oncology.

Liquid biopsy[29] refers to the sampling of body fluids, such as peripheral blood, for analysis of analytes that include cell-free DNA, circulating tumour DNA (ctDNA), circulating tumour cells, and extracellular vesicles and proteins. Similar to imaging, the field of ctDNA analysis is changing rapidly. Introductions of fragmentation analyses,[30] mutational signatures,[31] and analysis of repeat elements,[32] have made ctDNA analysis more accurate over the past decade, including for early-stage disease. Liquid biopsy is generally believed to complement advanced imaging and allows upstaging or downstaging of intermediary imaging findings. However, future studies are required to compare methodological approaches directly for specific cancers and clinical indications. Thus, AI-informed integrated diagnostics will likely have a growing role in the future.

There are several uses for liquid biopsies in oncology. For early tumour detection, several large-scale clinical trials, such as those using the multicancer detection Galleri test (ISRCTN91431511; based on cancer-specific DNA methylation patterns), reported high specificity (99–100%) but only moderate sensitivity (51·5%).[33,34] Sensitivity depends heavily on the tumour stage because not all patients with localised early tumours will have sufficient quantities of ctDNA.[35] In one study, ctDNA of *KRAS* mutation alone could only diagnose 25% of patients with stage 1 pancreatic cancer.[36] Similar results were also observed in a large cohort of gynaecological, lung, or gastrointestinal tract cancers, with 24·2% sensitivity for detecting stage 1 cancer.[37] For some cancers such as lung cancers, imaging tests can be superior to liquid biopsies. For example, a study on lung cancer screening showed the sensitivity of CT to be more than 80%, with a negative predictive value of 97·7–100%, but a positive predictive value of only 3·3–43·5%[38]

In patients with metastatic disease at initial presentation, liquid protein biomarkers might be helpful in identifying the primary tumour, which can then be confirmed with anatomical or molecular imaging followed by image-guided biopsies. Liquid biopsy and imaging biomarkers might complement in outcome prediction and prognostication, given that both types of biomarkers by themselves have shown potential in different malignancies and treatment scenarios. So far, data on the integrated use of both methods are scarce; however, a 2023 study in follicular lymphoma reported 88% sensitivity and 100% specificity for 2-year progression-free survival for the combination of [^{18}F]FDG-PET and ctDNA.[39] Some emerging studies indicate that liquid biopsies might be more sensitive than imaging in patients who are mutation-positive, which will likely lead to the generation of new guidelines. Minimal residual disease (MRD) is closely associated with disease recurrence, and ctDNA has been explored as a new biomarker for MRD. Emerging data suggest that postoperative ctDNA can be a strong prognostic marker of regression-free survival.[40] How imaging and liquid biopsy will improve MRD analysis remains to be studied.

Image-guided therapeutics

Radiopharmaceutical therapy (or radiotheranostics) refers to the combined imaging and delivery of precision radiotherapeutics, where what you treat is what you see (figures 4, 5). The growth of radiopharmaceutical therapy in oncology has been exponential in the past 5 years,[41,42] partly due to clinical success, marked by improved outcomes, low off-target toxicities, and better quality-of-life data compared with alternative therapies, such as chemotherapy external radiation. Although different forms of radiopharmaceutical therapy have been explored experimentally and clinically,[41–44] clinical practice has seen various mainstream applications approved by the US Food and Drug Administration (FDA). These have included systemic administration of small molecules (eg, [^{223}Ra]Ra-dichloride[45] or [^{131}I]I-sodium iodide),[46] radioligands (eg, [^{177}Lu]Lu-PSMA-617[47] or [^{177}Lu]Lu-DOTATATE),[48] antibodies (eg, [^{131}I]I-tositumomab),[49] and selective transarterial tumour embolisation with yttrium-90 (^{90}Y) and holmium-166 (^{166}Ho) microspheres.

As the availability of isotopes for diagnostic and therapeutic purposes increases and delivery platforms become more sophisticated, truly personalised treatment models can be realised.[42] Furthermore, many radiopharmaceutical therapy approaches are being deployed in earlier stages of disease, and ongoing trials are underway where therapy is started soon after diagnosis. One example is the NETTER-2 trial,[50] establishing [^{177}Lu]Lu-DOTATATE as first-line treatment in newly diagnosed patients with advanced grade 2 and grade 3, well differentiated gastroenteropancreatic neuroendocrine tumours. Another example is in the treatment of prostate cancer, for which treatments are transitioning from usual late-stage metastatic or advanced disease therapy to earlier-line

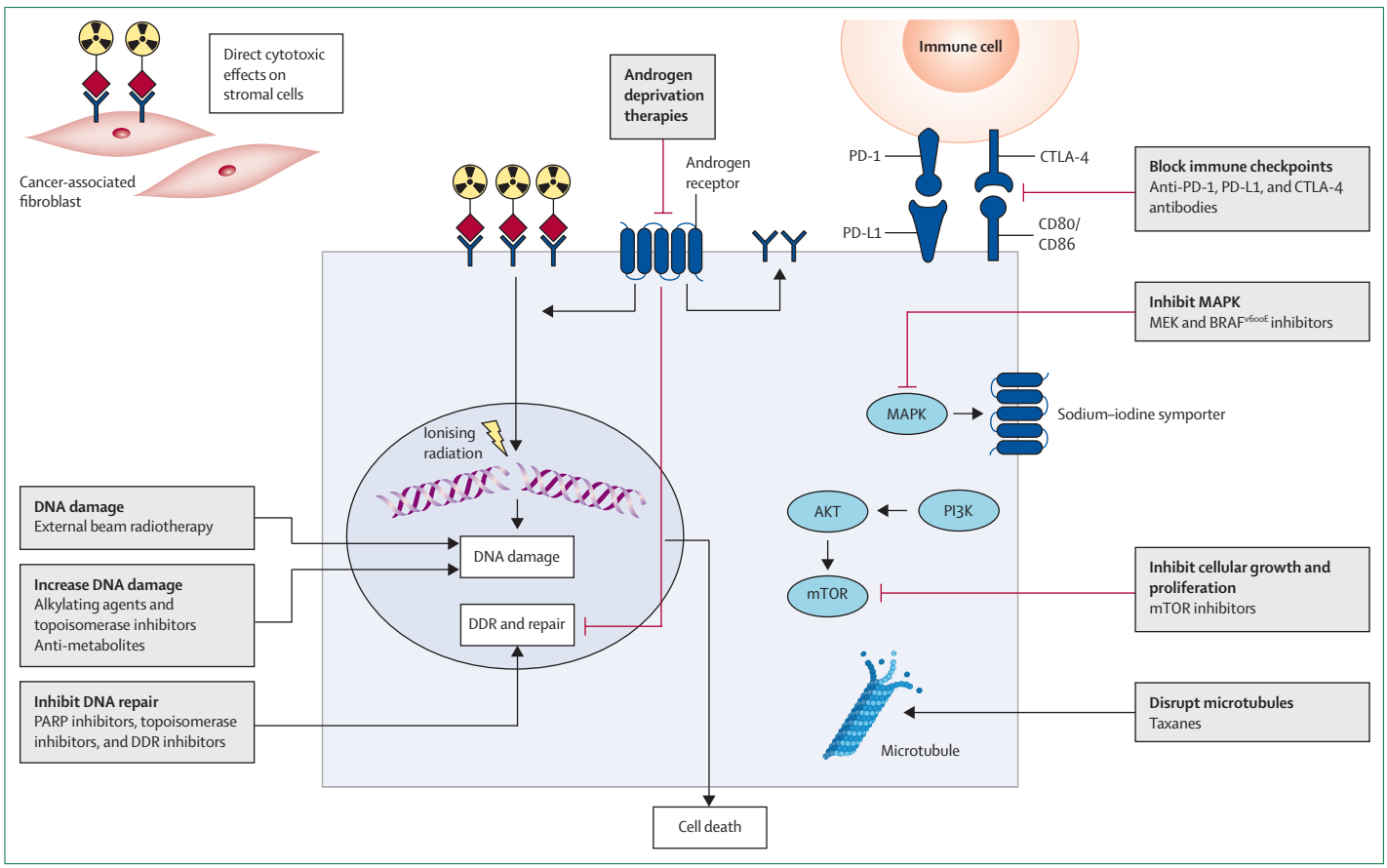

Figure 5: **Therapeutic approaches involving radiotheranostics**
Therapeutic effects on cancer cells caused by DNA damage induced by either α-emitting, β-emitting, or auger-emitting radionuclides can be enhanced via a combination of drugs that either cause direct damage to DNA (such as chemotherapies), inhibit DNA damage repair directly (such as PARP inhibitors), or through modulation of the associated signalling pathways (eg, with novel androgen deprivation therapies). Radiotheranostics can also target the tumour microenvironment (eg, fibroblast activation protein) and kill stromal cells, which can indirectly lead to tumour regression. Bystander effects, owing to the use of β-emitters, on the DNA of cancer cells that do not express radiotheranostic target proteins can still lead to tumour cell death. Targeted radionuclide therapies might also induce antigen presentation following cancer cell death and, when combined with immune checkpoint inhibitors, lead to enhanced anti-tumour activity. V300E=Val600Glu. DDR=DNA damage response. PARP=poly-ADP ribose polymerase.

treatment settings, such as metastatic hormone-sensitive disease (eg, the PSMAddition tria) and even before prostatectomy (eg, the LuTectomy trial).[51] There is also excitement about the concept of using radiopharmaceutical therapy in combination with established systemic therapies, including targeted therapies and immunotherapy (eg, NCT04343885, NCT05146973, NCT03874884, NCT05109728, and NCT03658447), as well as for accessing previously unexplored targets that were not suitable for traditional systemic therapies (figure 4).

The expansion of the field is not without challenges,[52] including isotope production and supply,[53,54] workforce expertise, and regulations;[42,55–57] however, efforts to address these issues have been initiated by governments, industry and major professional organisations, and in a *Lancet Oncology* Commission[58] that explores the global availability of theranostics and makes recommendations for improving patient access.

Transarterial radioembolisation (also known as selective internal radiation therapy) with ^{90}Y microspheres is a liver-directed therapy for primary and metastatic disease, of which indications have developed following FDA approval and efficacy trials.[59] In transarterial radioembolisation, hepatic artery branches are accessed with microcatheters, injecting ^{90}Y glass or polymer microspheres. These microspheres lodge in tumour-feeding arteries, and ^{90}Y induces locoregional cellular damage. The current indications for transarterial radioembolisation include primary treatment of hepatocellular carcinoma in non-surgical candidates, bridging to transplant in hepatocellular carcinoma, primary treatment of isolated oligometastatic liver lesions (radiation segmentectomy), radiation lobectomy to induce hypertrophy before resection, and palliation or delay of progression for advanced tumour burdens.[60] To improve dosimetry, planning angiography with the administration of technetium-99m (^{99}mTc) macroaggregated albumin is being performed to exclude patients with lung shunting or aberrant abdominal supplies. Cone-beam CT with intra-arterial contrast material injection is often performed

to exclude non-target perfusion and measure the perfused treatment volume. Bremsstrahlung SPECT-CT or ^{90}Y PET can also be performed after transarterial radioembolisation for dosimetry purposes and patient-centric future planning. In 2020, the clinical use of ^{166}Ho microspheres was shown providing additional therapeutic options complementary to peptide receptor radionuclide therapy (eg, in patients with neuroendocrine tumour liver metastases in the HEPAR Plus trial).[61]

Image-guided percutaneous ablation methods have transformed the treatment approaches for many primary and metastatic tumours, especially in non-surgical patients. The tumour ablation methods include microwave, radiofrequency, cryoablation, electroporation, histotripsy, and chemical ablation, among others.[62] Although the different methods each have their own advantages and disadvantages, they generally rely on image-guided precision placement of applicators into cancerous lesions in the liver, kidneys, lung, bone, prostate, thyroid, and soft tissue. After receiving precision treatments during a short procedure, patients can be discharged from hospital the same day. There are usually short recovery periods, less bleeding, and more preservation of organ parenchyma, thus expanding future treatment options.

Image-guided precision drug delivery allows patient-specific administration of next-generation therapeutics (eg, viral therapeutics, cell therapeutics, and immune modulators) through catheters and needle-based approaches. This approach allows for high local drug concentrations while minimising systemic therapies. Precision drug delivery might be of particular value to early drug developers in efforts to drive new applications.

Intraoperative imaging

Intraoperative imaging with ultrasound, fluoroscopy, or MRI has long been used for conventional surgery. In the past 5 years, however, there has been a shift to precision surgery, with resections being individualised to patients. This shift potentially allows for improved resection accuracy, sparing essential structures, and faster convalescence. These trends and public demand have contributed to the growth of minimally invasive surgery, especially robotic surgery and image-guided surgery technologies. Most applications have been in prostate, breast, colorectal, and lung cancer and glioma resections. For example, the main challenge in radical prostatectomy is complete cancer excision with the preservation of continence and erectile function. Positive margins still occur in up to 35% of tumours. In breast-conserving surgery, the primary goal is to prevent local recurrence with acceptable cosmetic outcomes. Rates of residual cancer following initially negative lumpectomy margins have been shown to exceed 40% in some studies.[63]

Near-infrared fluorescence imaging uses a combination of injectable fluorescent imaging agents with specialised detection systems to visualise cancers and their margins more accurately (figure 6). The emergence of the field dates back nearly 25 years,[64] and many different agents and imaging systems have been developed during this period.[65–67] Despite these efforts, commercialising systems and then testing their efficacy prospectively in large-scale studies has been challenging. An FDA-approved system is Lumicell's (Newton, MA, USA) activatable fluorescent imaging agent (pegulicianine)[68] combined with a handheld device.[69] In one prospective trial with 406 patients with breast cancer (NCT03686215), the margin status was assessed with or without pegulicianine fluorescence-guided surgery (PFGS). In 27 (8%) of 357 patients undergoing surgery, PFGS for surgical margins removed tumours left behind after standard lumpectomy. PFGS prevented second surgeries in nine (15%) of 62 patients with positive margins.[70] Alternative methods are being explored to enable intraoperative imaging. Early proof-of-principle studies primarily validate the emerging technologies in resection specimens, but the overall future goal is imaging of the resection cavity. The latest modality to be evaluated for assessment of margins is PET–CT.[71] Additional methods include Cherenkov, Raman, and photoacoustic imaging.[72]

AI in precision imaging

Discussions on AI have become central to precision medicine.[73] For the past several years, AI has been proposed to increase sensitivity in disease detection, enhance measurement reproducibility, reliably extract quantitative disease markers, recognise new patterns encoded within complex data, and serve as an inference engine after empirical training using real-world, large-scale data. Since its earliest days, AI has been integral to the imaging sciences.[74,75]

Most AI-driven imaging workflows focus on the later stages of care management, including tumour detection, segmentation[76] and staging, serial monitoring of tumour metrics, defining prognosis, radiation treatment planning,[77] and determination of tumour heterogeneity.[78] Vendors (ie, health-care providers and medical technology companies) have rapidly adopted AI at the start of imaging care to improve image quality, accelerate imaging times, calculate dosimetric profiles for theranostics, and predict whether or not a patient's tumour has a sufficient amount of target to undergo targeted therapy.

Despite the tremendous promise noted, the use of AI in precision imaging is not without bottlenecks and controversies, such as the inadequate amounts of data to train convolutional neural networks. To decrease the need for human resources and tedious annotation of images in preparation for training, we would need to focus on AI methods that are unsupervised; however, that is not always possible, since available datasets are either too small or cannot provide reliable images due to non-standardised acquisition parameters.[79] This problem

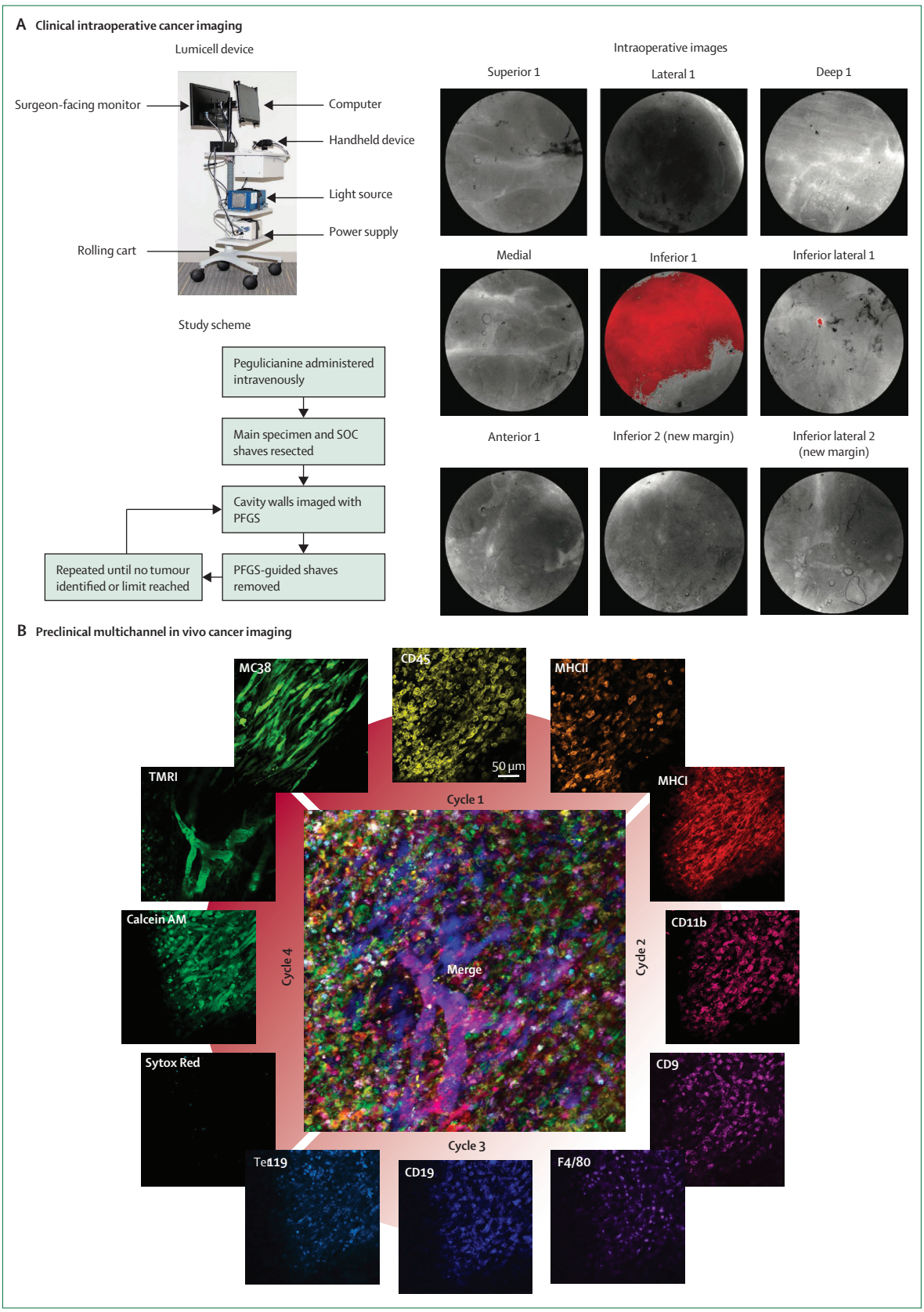

Figure 6: **Fibreoptic and intraoperative imaging**
Fluorescence-based cellular and molecular imaging is a promising modality, primarily used for endoscopic and intraoperative imaging. (A) Results from fluorescent-guided surgical detection of residual tumour in the resection cavity by use of the Lumicell system approved by the US Food and Drug Administration. (B) Use of bio-orthogonal chemistry has enabled in vivo cyclic imaging for up to 12 different targets. SOC=standard of care. PFGS=pegulicianine fluorescence-guided surgery

has led to the development of methods for creating synthetic images.[80] For example, through generative adversarial networks,[81] transfer learning, and collaborative or federated learning.[82] Trustworthiness has become a mounting challenge to the use of AI, even with large-scale datasets. Algorithms can be biased towards one racial group or gender, produce unpredictably erroneous results, and make predictions that have no basis in physical reality. Most of the data presented in the literature to date are from retrospective studies. Prospective studies comparing AI performance with more traditional decision-making processes are needed to define AI's true potential.

Additional challenges and future developments

Although the advances in imaging technologies achieved during the past decade have been nothing short of astounding and have exceptional promise, several opportunities present themselves to facilitate more rapid progress in precision imaging for oncology. The co-development of companion imaging diagnostics will ensure the success of next-generation patient-specific therapies. Unfortunately, developing and validating imaging probes is often an afterthought and still underfunded. Unlike therapeutic development, development of imaging agents is mostly investigator-driven, relying on lengthy funding cycles and often delaying clinical introduction. With the exceptions of [^{68}Ga]Ga-PSMA-11 (Illuccix [Telix Pharmaceuticals, Melbourne, Australia], [^{68}Ga]gozetotide; 8 years for FDA approval in 2020), [^{18}F]F-PSMA (Pylarify [Lantheus, MA, USA], [^{18}F]piflufolastat; 11 years for FDA approval in 2022), and [^{177}Lu]Lu-PSMA (Pluvicto [Novartis, Basel, Switzerland], [^{177}Lu]Lu vipivotide tetraxetan; 7 years for FDA approval in 2022),[47] the estimated average length of imaging approval is still approximately 13 years, which is too long to be practical for precision oncology needs. The development and validation of companion imaging diagnostics should occur in the preclinical stage. Many first-in-human imaging studies could be done rapidly as phase 1 trials to show safety and proof-of-concept. Currently, phase 3 trials are expensive and burdensome if industry is not involved, and regulatory approvals are often held to the same standard as for therapeutic drugs. Therefore, regulatory bodies should develop imaging agent-specific or modality-specific pathways so that approval can be fast-tracked, and phase 3 trials will not require the large-scale cohorts associated with therapeutic drug trial design.

For precision oncology and imaging to be synergistic, ongoing dialogue and collaboration between different specialties is needed. Except at specialised cancer centres, oncology and imaging or diagnostic departments often continue to operate differently for historical and financial reasons. Although a primary oncologist typically follows up with a single patient longitudinally, different imaging physicians will perform and interpret scans during a patient's journey (figure 2). Naturally, this process can lead to discrepancies and interobserver variability, complicating longitudinal assessments. AI and multidisciplinary conferences will hopefully present venues for minimising discrepancies in longitudinal image analysis.

Although imaging centres have been at the forefront of AI developments, tighter integration with digital pathology, molecular diagnostics, and AI in clinical oncology seems logical and well justified. Together, we need to find ways to manage the growing IT costs and invest in the future of integrated diagnostics. Capital costs of imaging systems, infrastructure, and new therapies are considerable and should be harmonised across academic medical centres. Confounding the issue is that reimbursements are decreasing for imaging, just as they are for almost all specialties. Despite the aforementioned challenges, there continues to be enormous enthusiasm for future developments and tighter integration of advanced imaging in clinical trials and care.

Search strategy and selection criteria

References for this Review published between Jan 1, 2000, and April 30, 2024, were identified through searches of PubMed using the search terms "imaging", "AI", "theranostics", and "biopsy". Articles were also identified through searches of the authors' own files. Only papers published in English or German were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Review.

Conclusion

Recent advances in medicine and biotechnology have enabled more personalised cancer therapy approaches. However, all too frequently, minimal biomarker analyses are performed on tumours, often before treatment. Because of the dynamic nature of tumour evolution, addressing therapy resistance is an ongoing challenge requiring sophisticated tools to measure evolution. In this Review, we have summarised the extraordinary breadth of progress in developing diagnostic and therapeutic imaging approaches and how these can aid in precision oncology. Advanced imaging and image-guided treatments will continue to have essential roles in precision oncology and will improve cancer outcomes and survival.

Contributors

All authors contributed to the writing and revision of the manuscript.

Declaration of interests

HH serves on the board of directors for Ion Beam Applications; the external advisory board of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University; the international advisory board of the University of Vienna; the scientific committee and board of trustees of the DKFZ (German Cancer Research Center); the board of directors of iCAD; the advisory board of *The Lancet Oncology*; and receives stock

options from iCAD. KH receives grants from Novartis and Sofie Biosciences; has consulted for Advanced Accelerator Applications, Amgen, AstraZeneca, Bain Capital, Bayer, Boston Scientific, Convergent, Curium, Debiopharm, EcoR1, Fusion, GE Healthcare, Immedica, Isotopen Technologien München, Janssen Pharmaceuticals, Merck, Molecular Partners, NVision, POINT Biopharma, Pfizer, Radiopharm Theranostics, Rhine Pharma, Siemens Healthineers, Sofie Biosciences, Telix, Theragnostics, and Y-mAbs Therapeutics; has stock options in Sofie Biosciences, Pharma15, Vision, Convergent, Aktis Oncology, AdvanCell; is an advisory board member of Fusion and GE Healthcare; receives honoraria from PeerView; and has received travel support from Janssen Pharmaceuticals. JSL reports research support from Clarity Pharmaceuticals and Avid Radiopharmaceuticals; has acted as an advisor for Alpha-9 Theranostics, Boxer, Clarity Pharmaceuticals, Earli, Curie Therapeutics, Evergreen Theragnostics, West Street Life Sciences, Inhibrx, Luminance Biosciences, NexTech Venture, Sanofi US Services, Solve Therapeutics, Suba Therapeutics, TPG Capital, Telix Pharmaceuticals, pHLIP, and Precirix; is a co-inventor on technologies licensed to Diaprost, Elucida Oncology, Theragnostics, CheMatech, Daiichi Sankyo, and Samus Therapeutics; is the co-founder of pHLIP; holds equity in Summit Biomedical Imaging, Telix Pharmaceuticals, Clarity Pharmaceuticals, and Evergreen Theragnostics; and is supported by National Institutes of Health grant R35 CA232130. MGP has consulted for CraniUS, UCLA Cancer Center, Ventyx, Einseca, and ModeX; receives royalties from Lantheus Holdings, Novartis, Intuitive Surgical and Cyclotek; has 70 patents issued or filed related to imaging or informatics; and has stock options in D&D Pharmatech, PlenaryAI, Earli, and Immunosity. AMS reports trial funding from EMD Serono, ITM, Telix Pharmaceuticals, AVID Radiopharmaceuticals, Fusion Pharmaceuticals, and Cyclotek; research funding from Medimmune, AVID Radiopharmaceuticals, Adalta, Antengene, Humanigen, Telix Pharmaceuticals, and Theramyc; and payment for participation in advisory boards of Imagion and Immunos. RW has consulted for ModeRNA, Boston Scientific, Lumicell, Seer Biosciences, Earli, and Accure Health. All other authors declare no competing interests.

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