Aiming for higher ambition: the Roche approach to cracking the code of cancer

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Advances in technology are reshaping healthcare, offering many patients the means to track their own health and giving researchers the tools to gain deeper insights into the causes of cancer and its management. As patients become more knowledgeable, informed and tech savvy, the expectation for innovative and effective treatments increases. However, there is still a need to improve the quality of care in general. Patient outcomes can vary because availability and access to innovative and personalised healthcare is fragmented across countries and healthcare systems; this is due to knowledge gaps as well as a lack of infrastructure and healthcare system funding. We need profound transformation of healthcare systems, on a global scale, to meet these demands and improve patient care.

We see the challenges facing physicians at each stage of care delivery. They are typified by incomplete information at diagnosis, suboptimal access to, or limited awareness of, treatment options, and delayed or incomplete patient monitoring. Although technological advances have resulted in rapid increases in the volume of comprehensive medical information available to clinicians, this has also resulted in more complex decision making. To illustrate the point, the World Health Organization International Clinical Trials Registry Platform reports that more than 12,000 clinical trials were initiated in Europe in 2019, and more than 6,000 clinical practice guidelines were published on PubMed since 2015. A new approach is needed to support integration of the latest evidence into clinical decision-making and ensure that healthcare professionals (HCPs) are able to deliver the best care possible for every patient.

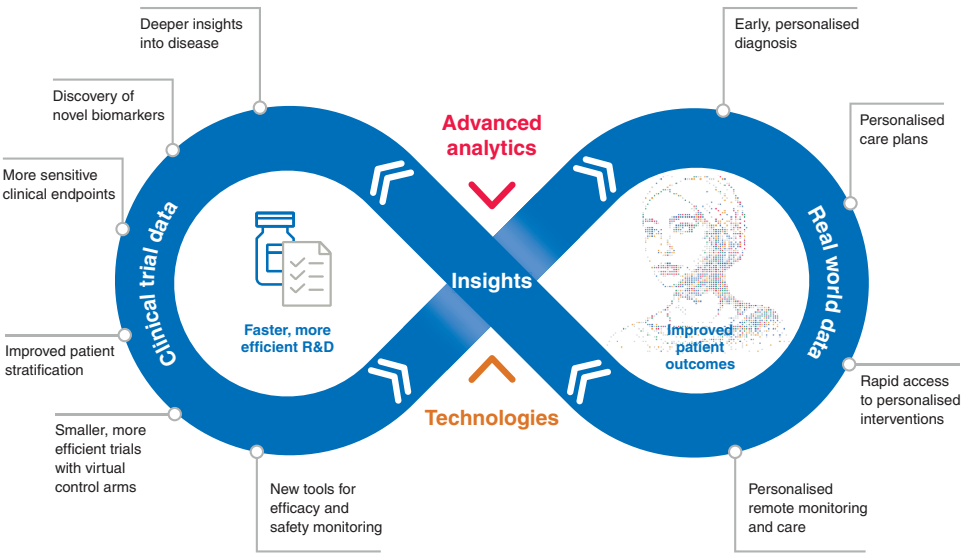

Figure 1. The vision of personalised healthcare: data, technology and analytics provide deeper insights into disease to accelerate research and development and improve patient outcomes.

SHAPING THE FUTURE OF CARE IN ONCOLOGY

At Roche, our vision for the future is personalised healthcare, a patient-centric approach to delivering value-based, outcome-driven healthcare. Personalised healthcare has two key aims: (1) rapid access to treatment and enhanced patient care (2) to increase the speed and efficiency of research and development (R&D). Personalised healthcare is centred on a continuous cycle of insight generation, driven by data, technology and advanced analytics (**Fig. 1**). Large-scale data sets are available from many sources, including imaging, genomics, clinical trials, electronic health records, wearables, apps and lifestyle. Technology and advanced analytics provide the tools needed to derive meaningful, actionable insights from these data. In addition to clinical trials, real-world data can also inform R&D, shape clinical practice and improve patient outcomes.

ADVANCED TECHNOLOGY

The implementation of next-generation sequencing (NGS) has improved our understanding of cancer biology and opened

up new ways of diagnosing and treating cancer; we can use NGS to detect the genomic alterations driving tumour development and provide insights to inform tailored care plans, including targeted treatment and immunotherapy (**Fig. 2**). Through comprehensive genomic profiling (CGP) using NGS, we can analyse hundreds of cancer-related genes and determine the specific genomic profile of an individual tumour. The Roche CGP portfolio spans both research and clinical decision-making, with the AVENIO family of NGS oncology assays available for use in research applications and services from Foundation Medicine, a molecular information company headquartered in Cambridge, Massachusetts, US, for identifying clinically relevant genomic alterations and expanding patients' potential treatment options. The NAVIFY® Mutation Profiler (a clinical NGS reporting solution) and upcoming decentralised solutions combining the AVENIO workflow and Foundation Medicine platform provide data and clinical decision support.

Foundation Medicine has developed the capability for high-throughput NGS analysis of genomic alterations covering more than 300 cancer-related genes. FoundationOne CDx® is the first United States Food and Drug Administration (FDA)-approved tissue-based broad companion diagnostic that is clinically and analytically validated for all solid tumours. The FoundationOne® Liquid biopsy assay was introduced to open up the opportunities for CGP beyond tissue-based testing. It is a minimally invasive blood-based assay, utilising circulating tumour DNA in blood samples to identify genomic alterations that can inform clinical care.

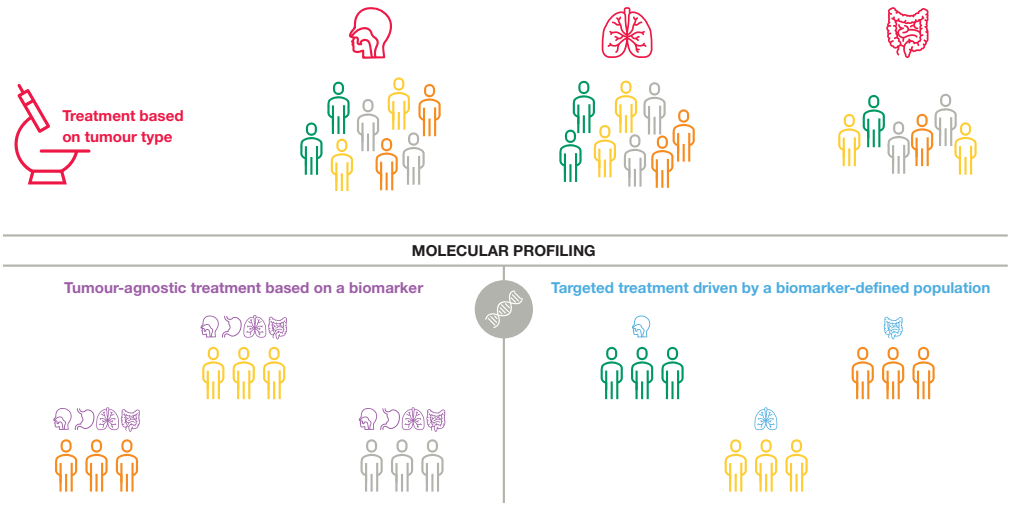

Figure 2. Personalising cancer treatment informed by in-depth characterisation of tumour genomic alterations.

Foundation Medicine is expanding its liquid biopsy services to look beyond individual genes and genomic drivers. The genomic signatures, tumour mutational burden (TMB), microsatellite instability (MSI), and loss of heterozygosity, are becoming more relevant in guiding cancer immunotherapy and targeted treatment options and are part of the Foundation Medicine services. Future potential applications of liquid biopsy will address needs across the full spectrum of the patient journey in oncology: screening, minimal residual disease (MRD) detection, early detection of relapse, systemic treatment initiation and monitoring of response. Through collaborations with Lexent Bio, a precision oncology company that is part of Foundation Medicine, and Natera, a genetic testing company headquartered in San Carlos, California, US, we are seeking to complement current services by co-developing novel patient monitoring and response assessment platforms. Platforms in development utilise whole genome/exome sequencing information and DNA methylation analysis to identify patients who are at higher risk of progression, assess MRD, and detect evidence of relapse, to enable earlier intervention and improve patient outcomes.

CLINICAL TRIAL DESIGNS

Molecular and genomic profiling has consolidated our understanding of cancer as a genetic disease. With the discovery of oncogenic drivers, cancer is being fragmented into molecular subtypes against which we can develop targeted therapies. This change in how we approach cancer treatment has triggered rapid evolution of drug development processes within the field of oncology. We are increasingly detecting these oncogenic drivers across multiple tumour types, resulting in more complex 'tumour-agnostic' or 'histology-independent' trials that maximise screening efforts and resource use, and enable exploration of molecular signatures across multiple cancer histologies (**Fig. 3**). CGP can support the optimisation of such trial designs by aiding patient selection and stratification and longitudinal monitoring of biomarkers. The biomarker-driven approach of basket and umbrella trials is proving particularly beneficial for unlocking new personalised treatments for tumours with low-prevalence genomic alterations and rare cancers with high unmet medical need.

Through a common protocol, basket trials enrol patients with multiple tumour types sharing a specific molecular alteration. The VE-Basket trial (NCT01524978) is a phase II basket trial evaluating early signals of vemurafenib activity in patients with non-melanoma cancers harbouring *BRAF* V600 mutations. The initial design defined six cohorts with prespecified cancers. A seventh cohort permitted enrolment of patients with any other cancer type, with the opportunity for additional analysis cohorts if sufficient numbers of patients were enrolled[1]. This flexibility resulted in two additional cohorts, including one for patients with Erdheim–Chester disease (EDC) or Langerhans' cell histiocytosis. Ultimately, this study resulted in vemurafenib becoming the first FDA-approved treatment for ECD, a rare cancer of the blood associated with very limited life expectancies; vemurafenib also received an orphan designation from the European Medicines Agency (EMA) in this indication. Cancer of unknown primary origin (CUP) has a high unmet medical need; patients are typically treated with

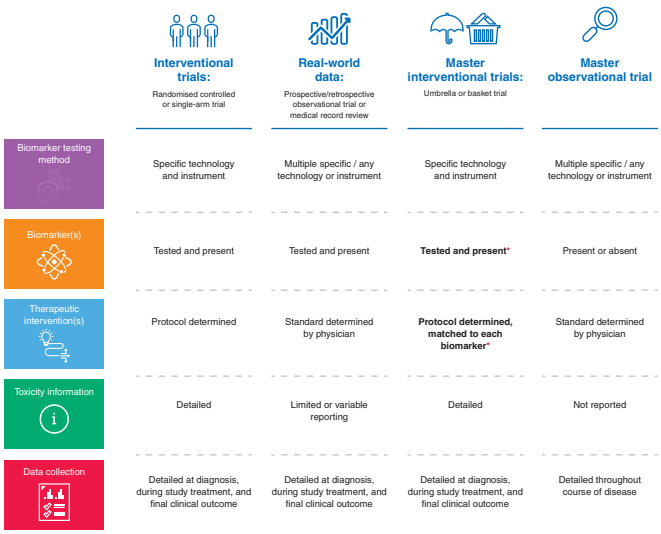

Figure 3. Evolving clinical trial designs to support development of precision oncology. (Adapted from Dickson, D. *et al.*, 2020[5])

chemotherapy and prognosis is very poor, with median survival of less than one year[2]. CUPISCO (NCT03498521) is an umbrella trial in patients with CUP, which is using Foundation Medicine liquid biopsy and tissue assays to determine a comprehensive genomic profile of each patient's tumour[3]. A molecular tumour board, comprising pathologists, CUP specialists and the treating oncologist, matches this profile to the most appropriate treatment, giving patients access to targeted therapies, chemotherapy and immunotherapy. CUPISCO has the potential to be practice changing, by accelerating the development of more effective treatment strategies, increasing our understanding of the disease, improving access to personalised cancer treatment and informing future development of new drugs for CUP. The MORPHEUS trial is evolving the umbrella trial design to inform future personalised cancer treatments based on immune signatures or biomarkers. MORPHEUS is a suite of phase Ib trials designed to generate signal-seeking data versus standard of care for immunotherapy combinations across a broad range of cancers, and to support cross-indication learnings that will ultimately improve patient outcomes. Tissue biopsies and serial blood tests allow longitudinal assessment of biomarkers for response and resistance, and surrogate biomarkers of efficacy.

Our continuing efforts in this field can also been seen in the Blood First Assay Screening Trial (BFAST; NCT03178552) and the MyPathway trial (NCT02091141). In BFAST, the relationship between blood-based biomarkers and the clinical activity of several therapies (atezolizumab, alectinib, entrectinib, vemurafenib and cobimetinib) is being evaluated in patients with advanced non-small cell lung cancer (NSCLC)[4]. BFAST overcomes the traditional challenges of tissue collection by using the FoundationOne Liquid biopsy assay. The modular trial design also allows new treatment cohorts to be added, as new biomarker information becomes available, and for patients lacking actionable biomarkers to be enrolled into a real-world data cohort. In MyPathway, again, several therapies (trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib and atezolizumab) are being evaluated in patients with advanced solid tumours and either mutations or gene expression abnormalities that are predictive of response to one of the therapies being investigated.

Through biomarker-driven trials, the validity of targeting oncogenic drivers across tumour types has been demonstrated. FDA and EMA approvals of larotrectinib (for *NTRK* fusion-positive solid tumours) and entrectinib (for *NTRK* fusion-positive solid tumours and *ROS1* fusion-positive NSCLC) were possible by pooling data and performing an integrated analysis across three phase I/II trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431); and ALKA-372-001 (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267), respectively[6–8]. Both drug approvals were accelerated due to the high unmet need in these patient populations, and relied on consultation with regulatory authorities due to the novel data sets submitted. More recently, pembrolizumab was approved by the FDA for the treatment of patients with advanced solid tumours harbouring either MSI-high (KEYNOTE-177 [NCT02563002]) or TMB-high (KEYNOTE-158 [NCT02628067]) genomic alterations (currently no EMA approval in these indications)[9].

The pace of discovery of new tumour-agnostic treatments is accelerating (**Fig. 4**) and we need to think now about how to identify patients with rare molecular alterations who may benefit and put diagnostic and data infrastructures in place to ensure that future developments in this field are sustainable. Roche recently committed to the development of pralsetinib, an investigational tumour-agnostic drug under evaluation for the treatment of patients with *RET*-altered NSCLC, thyroid cancer and other solid tumours. In entering into this collaboration with Blueprint Medicines, a biopharmaceutical company based in Cambridge, Massachusetts, Roche is affirming its commitment to tumour-agnostic drug development.

UNLOCKING THE POTENTIAL OF REAL-WORLD EVIDENCE

As clinical trial designs have been evolving, so too have the sources of real-world data and our ability to derive meaningful insights (**Fig. 5**). Using real-world data, we can better understand patients and their disease as well as the long-term outcomes and impact of treatment. We can also facilitate more effective, value-based reimbursement and rapid access to treatment, and fulfil post-approval evidence generation commitments.

Real-world data is collected routinely during care delivery and reflects real-life clinical practice. However, due to the lack of standardisation, traditional sources (electronic health records, insurance claims databases, disease and product registries and observational/cohort studies) contain heterogeneous data that are difficult to access, analyse and interpret. We, and many other stakeholders, are working to strengthen data infrastructures and make data more accessible, standardised and inter-operable so that it can be used efficiently. Advances in analytics and technology are also creating new sources of real-world data (wearables, apps and genomics). At Roche, we are creating large-scale multimodal data sets using longitudinal patient-level data from all these sources. Advanced analytics, such as machine learning algorithms, can then be used to derive new insights into disease and treatment. Such algorithms are particularly useful in the field of medical imaging to automate quantification of tumour burden.

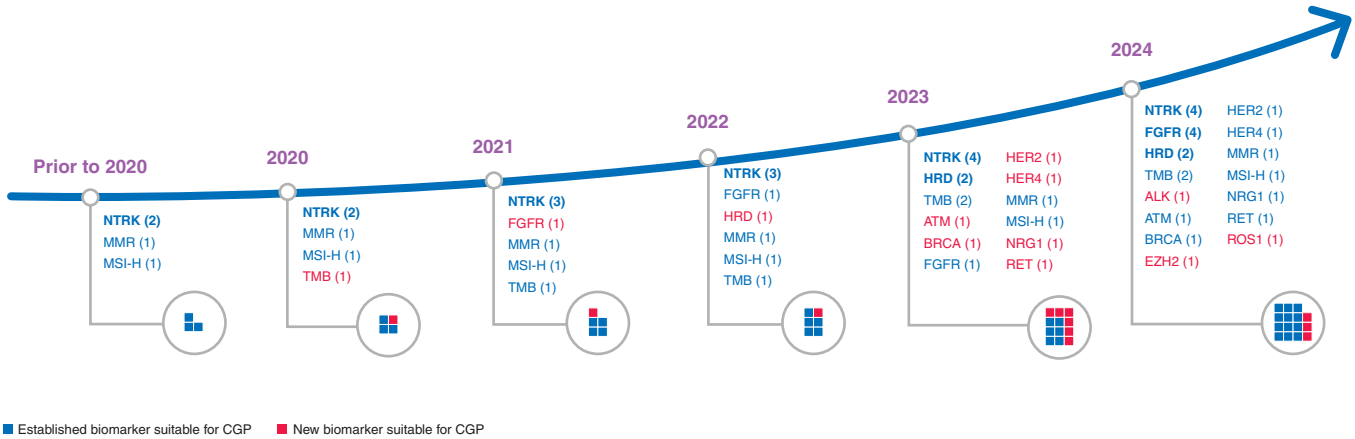

Figure 4. Projected approval of tumour-agnostic treatments targeting actionable genomic drivers from ongoing clinical trial programmes.

Based on phase II and III clinical trials initiated prior to 1 February 2020 and information available as of 1 June 2020. Projection assumes that all ongoing trials lead to approvals. Multiple secondary sources used to cross-validate information, including Trialtrove, Clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials Database, and Chinese Clinical Trial Registry; FDA approval timeline estimated as eight months after phase III primary completion date.

CGP, comprehensive genomic profiling; FDA, US Food and Drug Administration.

CGP has advanced our understanding of genomic alterations and their role in driving cancer, but the relationship between genomic alterations and clinical outcome is only beginning to emerge. A major step in unlocking the potential of real-world data was taken with the creation of the clinico-genomic database, a research platform linking genomic profiling data from Foundation Medicine with real-world clinical data from the electronic health record platform from Flatiron Health, a healthcare technology company based in New York, US. The database currently contains more than 58,000 clinico-genomic profiles and is continuing to grow and evolve as new data are added. Real-world evidence generated from this database will aid identification of genomic profiles that do / do not respond well to treatments, identify and validate new biomarkers, and inform the design of clinical trials through better characterisation and definition of patient populations[10].

We are also pioneering a shareable, global real-world data set. This will include tumour genomic profiles as well as details on patient history, molecular testing, factors influencing treatment decisions and patient outcomes. The large-scale accessible data set will help to accelerate R&D by providing insights on the effectiveness of personalised cancer treatments, inform clinical decision-making and support access and reimbursement discussions to bring new treatments to patients more quickly. Aside from the direct value of the data itself, learnings from the logistics of this initiative will help to guide healthcare systems and policy makers on the specific barriers to cross-border data sharing and the value of core data variables in deriving clinically meaningful information. Of particular interest are the R&D efficiencies that can be gained through combining real-world data and technology. Roche, together with other industry partners, recently took part in an EMA-led 'Workshop on the role of registries in the monitoring of cancer therapies based on genetic and molecular features'. Discussions focussed on the type and quality of real-world data that could be generated to meet regulatory requirements and potential sources of these data, including registries. Open and early dialogue between regulators and all parties involved was considered essential to assess the feasibility of obtaining adequate data from individual registry-based studies.

Roche has recently initiated a prospective clinico-genomic registry (NCT04180176) for patients with advanced NSCLC or extensive-stage small-cell lung cancer planning to start standard-of-care treatment at clinics within the Flatiron Health network. The multi-stakeholder platform will collect clinical data from electronic health records and link real-world tumour tissue genomic profiling, digital imaging and outcomes data to longitudinal blood genomic profiling. Results of the study will show the feasibility of this scalable, prospective approach and provide insights into the relationship between tumour biomarkers and real-world clinical outcomes.

PERSONALISED CANCER TREATMENT

Many regulatory authorities are keen to work with the new trial designs, clinical endpoints and evidence sources utilised in developing treatments for rare molecularly defined populations, including tumour-agnostic drugs. For drugs that receive conditional approvals from regulatory authorities, companies make a post-approval commitment to provide additional data to support evidence submitted at filing, but health technology assessments of such drugs are heterogeneous and lead to differing reimbursement statuses, which challenges broad patient access[11]. To ensure improved patient access, we need to foster greater awareness of the unique nature of targeted and tumour-agnostic therapies among health technology assessment bodies, and partner with them to develop modified appraisal systems for evaluating novel data and endpoints and discuss value frameworks for diagnostic solutions.

Across Europe and North America, countries are starting to put policies in place to integrate real-world data into health technology assessments. In Italy the Technical and Scientific committee (CTS) – which is part of the Italian Medicines Agency (AIFA), a government body – was set up to facilitate rapid access to life-changing drugs. The CTS uses a new algorithm to evaluate non-randomised controlled trial data and clinical endpoints, such as quality of life and tumour response. The 'highly specialised technology' pathway serves a similar purpose for The National Institute for Health and Care Excellence, a UK government body.

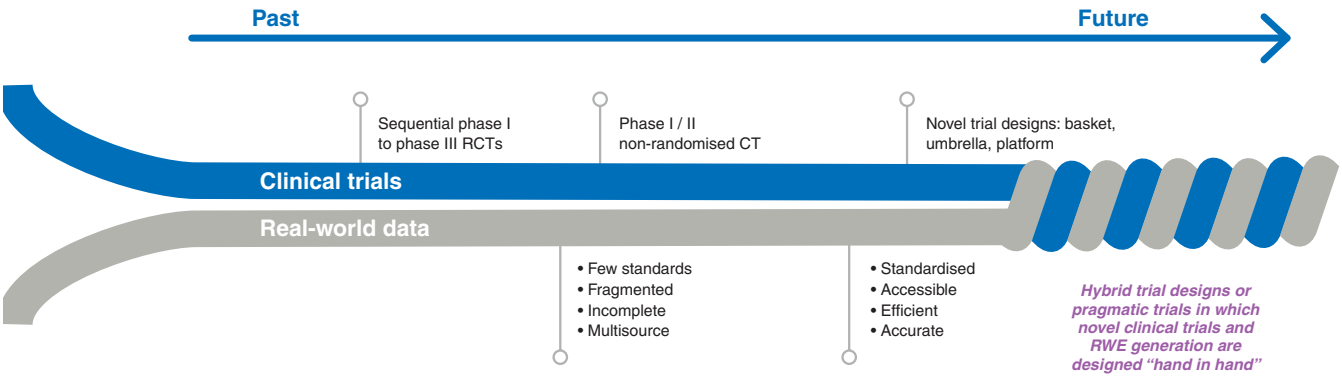

Figure 5. Co-evolution of clinical trials and real-world data. RCT, randomised controlled trial; RWE, real-world evidence.

Reimbursement for two Roche molecules, approved by the FDA and EMA for NSCLC treatment (atezolizumab for second-line treatment in all subpopulations; alectinib for second-line treatment of patients with *ALK*+ disease), was achieved using real-world data from the Flatiron database. Without the insights from real-world data to support survival benefits and generate a retrospective external control arm, respectively, it would have been much more challenging to reach accelerated reimbursement decisions and bring these treatments to patients so quickly. Future hybrid clinical trial designs could incorporate prospective external real-world data controls, to enable smaller and more efficient clinical studies, enable new models of risk-sharing agreements with payers and reduce patient exposure to placebo treatments.

FUTURE DIRECTIONS

High throughput 'omics' technologies show promise in assessing response to investigational drugs and could transform the way we monitor disease, allowing physicians to make faster decisions and adapt treatment or dosage as needed. Real-time symptom reporting is associated with improved survival and quality of life compared with usual care in patients receiving treatment for advanced cancer[12]. Roche and Kaiku Health, a health data company headquartered in Helsinki, have developed an app for patients receiving cancer immunotherapy that allows them to report symptoms directly. Self-reporting of symptoms not only allows healthcare professionals to rapidly triage treatment-related symptoms and optimise treatment plans, but also empowers patients to take a more active role in managing their symptoms. A pilot study conducted at ten hospitals showed promising feedback from physicians, nurses and patients[13].

Automated clinical imaging analytics can improve the efficiency of R&D by unlocking insights from data collected during clinical trials, and we are partnering with technology companies to accelerate development in this field. Clinical decision support solutions are of the utmost importance for physicians faced with increasing volumes of information on which to base care plans. Although multidisciplinary tumour boards are often used to facilitate decision-making and optimise cancer care, they can be inefficient and challenging to organise. The NAVIFY® tumour board aims to make this multidisciplinary approach more efficient by integrating patient data from multiple sources (tissue samples/slides, laboratory tests, imaging, biopsies and genomic tests) to generate a complete patient overview presented on a single patient dashboard. Early indications of the impact of NAVIFY show a 53% reduction in case preparation time for oncologists treating patients with breast cancer[14].

COLLABORATIVE APPROACHES

Our vision of personalised healthcare may be ambitious, but driven by insights from data, technology and advanced analytics, and putting the patient at the centre of care, we have already made huge leaps in deepening our understanding of cancer biology and more efficient ways to develop effective cancer therapies. At Roche, we recognise that if the full potential of personalised healthcare is going to be realised we need to think beyond diagnostics and drugs, and play a leading role in creating integrated solutions with clinical value that healthcare systems can implement. We are investing significant resources into improving global healthcare by focussing on patient-centric solutions, building quality standards for real-world data, and connecting with healthcare systems to ensure infrastructures are in place to facilitate fast access to personalised cancer care. There is no single approach to personalised healthcare; it must accommodate the diversity of healthcare systems across the globe. Roche is forming partnerships, and working with patients, payers, health technology assessment bodies, regulators, governments and healthcare providers, to build the clinical, technological and administrative infrastructures necessary to improve cancer care and patient outcomes on a global scale.

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