REVIEW

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Patient-centric trials for therapeutic development in precision oncology

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An enhanced understanding of the molecular pathology of disease gained from genomic studies is facilitating the development of treatments that target discrete molecular subclasses of tumours. Considerable associated challenges include how to advance and implement targeted drug-development strategies. Precision medicine centres on delivering the most appropriate therapy to a patient on the basis of clinical and molecular features of their disease. The development of therapeutic agents that target molecular mechanisms is driving innovation in clinical-trial strategies. Although progress has been made, modifications to existing core paradigms in oncology drug development will be required to realize fully the promise of precision medicine.

Insights into the molecular pathology of disease are creating opportunities for the development of therapies with durable clinical benefit while challenging the existing model of therapeutic development and clinical care[1–3]. Large international consortia — such as the International Cancer Genome Consortium[4,5] — are mapping the genomes of thousands of cancers to identify opportunities for prevention, early detection and treatment[6]. Although genomics is leading the way, high-throughput proteomics and metabolomics are following closely behind[7]. Such methodological advances have ushered in a new era of therapeutics that target specific molecular processes. Although there have been some dramatic successes[8–17], the overall strategy remains in its infancy[18]. The central premise of precision medicine is that matching a drug and its mechanism of action using a marker to select patients — a process often referred to as matching the right drug to the right patient — can offer greater potential for durable clinical benefits.

Initially, these targeted therapeutic agents followed the same clinical development pathway as cytotoxic chemotherapy, that is, based on tumour location and histopathology, driven by the notion that molecular aberrations were tumour specific. Efforts to advance this approach stalled because of the lack of efficacy data in patients with different cancer types that shared a molecular aberration, coupled with early observations that the functional importance of some aberrations varied between tumour types. However, the emergence of programmes that identified molecular targets and matched treatments to molecular subtypes — or segments — led to several reports[19,20,21] that directly linked this approach to improvements in clinical outcome, irrespective of the organ in which the tumour originated. Although many were based on retrospective analyses of tumour samples, and not all reports were equally convincing[22], the utility of broad molecular profiling to guide patients towards specific targeted therapies was established. Researchers moved quickly to implement this new paradigm. To meet emerging requirements, and enticed by the promise of clinical benefit, clinicians recognized that the established pathways of therapeutic development would need to change, However, the practical implications of implementing these changes in the clinic were unclear.

The drivers of precision medicine have been established and discussed elsewhere[18,23,24]. However, fresh challenges for therapeutic development are many and substantial. Fundamentally, a candidate treatment requires a strong platform of evidence to support its clinical testing and must be coupled with robust methods to identify appropriate patients (using molecular assays[25]). Our appreciation of the molecular diversity of cancer and the ever-increasing number of molecular subtypes creates considerable complexity for the development of targeted drugs. When tested in trials of unselected participants, most targeted therapies reveal efficacy only if both the incidence of a responsive subpopulation and the effect size within the group is sufficiently high. Increasing the size of clinical trials to overcome this lack of enrichment yields minimal overall benefits at a cost that makes them unattractive and unaffordable to the community. Designing trials that feasibly evaluate both patient selection and drug efficacy is crucial, and it is essential to define the correct metrics to assess efficacy, particularly when the study needs to be small.

Principles and evolution of clinical trials

Clinical trials are most useful when they assess a potential therapeutic effect that is about the same size or slightly smaller than the effect of the natural variation that exists between individuals. When the variation between individuals enrolled in a trial influences a treatment only randomly, it can be ignored in a biological sense and controlled by replication. These dual strategies for controlling for variation embody the empirical and theoretical aspects of trials. For much of the history of clinical trials, the treatments under investigation were assumed to apply to anyone with the relevant clinically defined condition. Essentially, our understanding of biology suggested that treatments worked through common mechanisms that were set apart from random variation. This assumption was substantially correct for approaches such as cytotoxic chemotherapy that target generic disease mechanisms, and it enabled considerable progress to be made in treating cancer. Towards the end of the twentieth century, concerns arose regarding the potential inhomogeneity of therapeutic effects because of socio-political characteristics such as race or sex. Many clinical trials were designed and analysed to examine such differences. Although motivated by politics and social justice rather than scientific fact, only minimal changes were actually made to the design of such trials — which was probably appropriate given the

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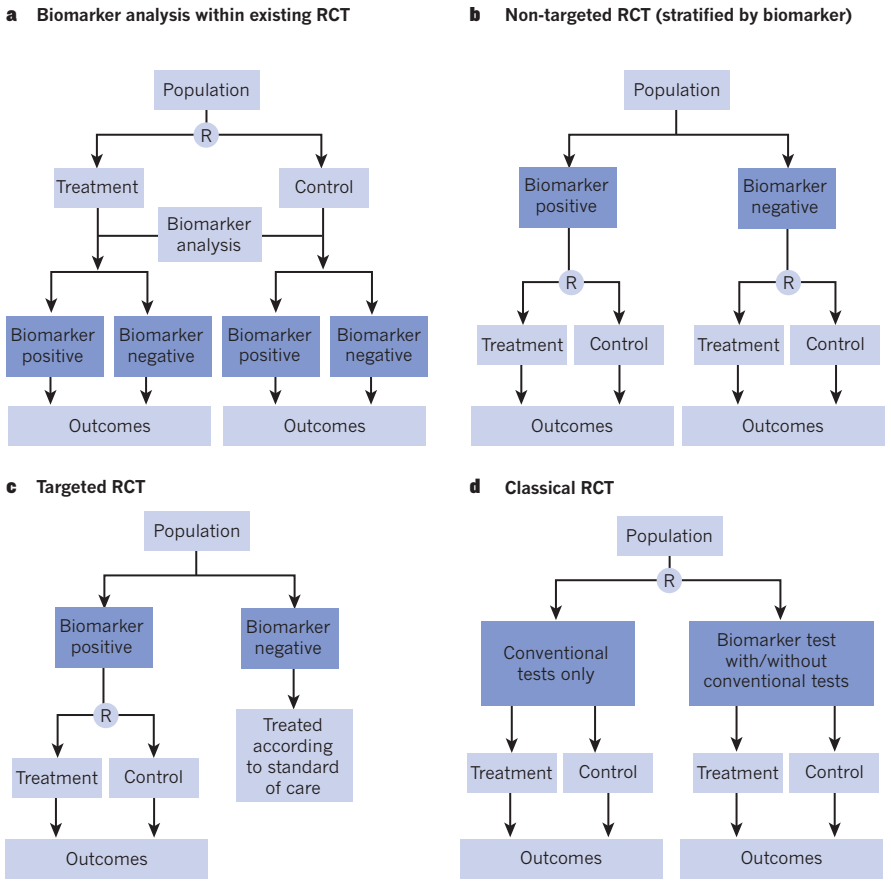

Figure 1 | Randomized controlled trial designs for defining and testing precision-medicine strategies. a, Biomarker discovery is performed in a trial that is used to address a therapeutic question but patient recruitment and treatment allocation are not informed by the marker status. **b**, A non-targeted biomarker study in which the trial is designed and powered to address the biomarker hypothesis to ensure adequate biomarker representation and distribution between arms. **c**, Biomarker-targeted randomized controlled trial (RCT) in which the presence of the selection marker guides patient allocation. **d**, RCT that compares biomarker-directed therapy with conventional therapy, which allows the overall concept of the biomarker approach to be tested as a whole. Adapted with permission from ref. 26. R, randomization.

weak biological basis for differences that can be attributed to these superficial characteristics.

The recognition that clinical trials need to be redesigned to account for non-random variation comes more from knowledge of the disrupted cancer genome rather than of the germ line. The implications of having multiple potential treatments and diseases where once there was just one put enormous pressure on researchers to alter the design of clinical trials. Investigators often approach the challenge of having too many diseases and too few trial subjects as a result of genomic partitioning as a clinical-trial design problem. This creates unhealthy tension between design strategies because although clinical-trial design must be tailored to answer specific questions that arise from targeted therapies, many of these questions are actually standard and can be addressed by well-established methodologies. Consequently, the challenges of conducting clinical testing for most precision-medicine strategies revolve around their feasibility, efficiency and capacity to deal with multiple small-incidence subtypes of cancer and a rapidly evolving knowledge base.

In response, drug-development pathways have evolved to accommodate two important strategies: generating signals that indicate clearly the safety and efficacy of useful treatments, and terminating the development of ineffective treatments as early as possible. The four phases of clinical trials feed into these strategies. The early development phase (phase I) focuses on the safety aspects of a drug, including dosage, in a small group of patients. The middle-development phase (phase II) evaluates the safety and efficacy of a drug in a larger group of patients, and enables a 'go/no-go' decision to be made. The late development phase (phase III) constitutes comparative testing and provides a basis for seeking approval to market the drug. Phase IV trials are sometimes performed after market approval has been granted to examine the safety and efficacy of the drug in other patient populations, as well as any side effects and the implications of long-term use. These studies can also extend the applications or 'indications' of the drug. Through the sequential building of evidence, the use of a new therapeutic agent for a specific indication can be supported or refuted. In this model, a premium is placed on randomized, controlled designs.

Biomarkers — biological characteristics that can be measured in the context of diagnosis and clinical intervention — are often used to drive the selection of participants for trials, a strategy known as enrichment, which is well established for high-prevalence biomarkers. There are a number of methods for assessing the clinical utility of biomarkers (Fig. 1). For example, randomized controlled trial data can be analysed retrospectively (Fig. 1a). Biomarker discovery can also be integrated within the design of the trial to ensure that there is sufficient power to detect signals. Biomarker-positive patients can be equally distributed in each arm (known as biomarker stratification) to ensure statistical power (Fig. 1b), and the biomarker itself can be used to direct the study (Fig. 1c, d)[26–28]. Advances in our understanding of the differences between the molecular pathologies of individual cancers creates challenges for conventional drug-development models, especially as the prevalence of molecular segments decreases[29]. The chances of showing a significant effect in a traditional comparative trial of unselected participants diminish if the prevelance of a

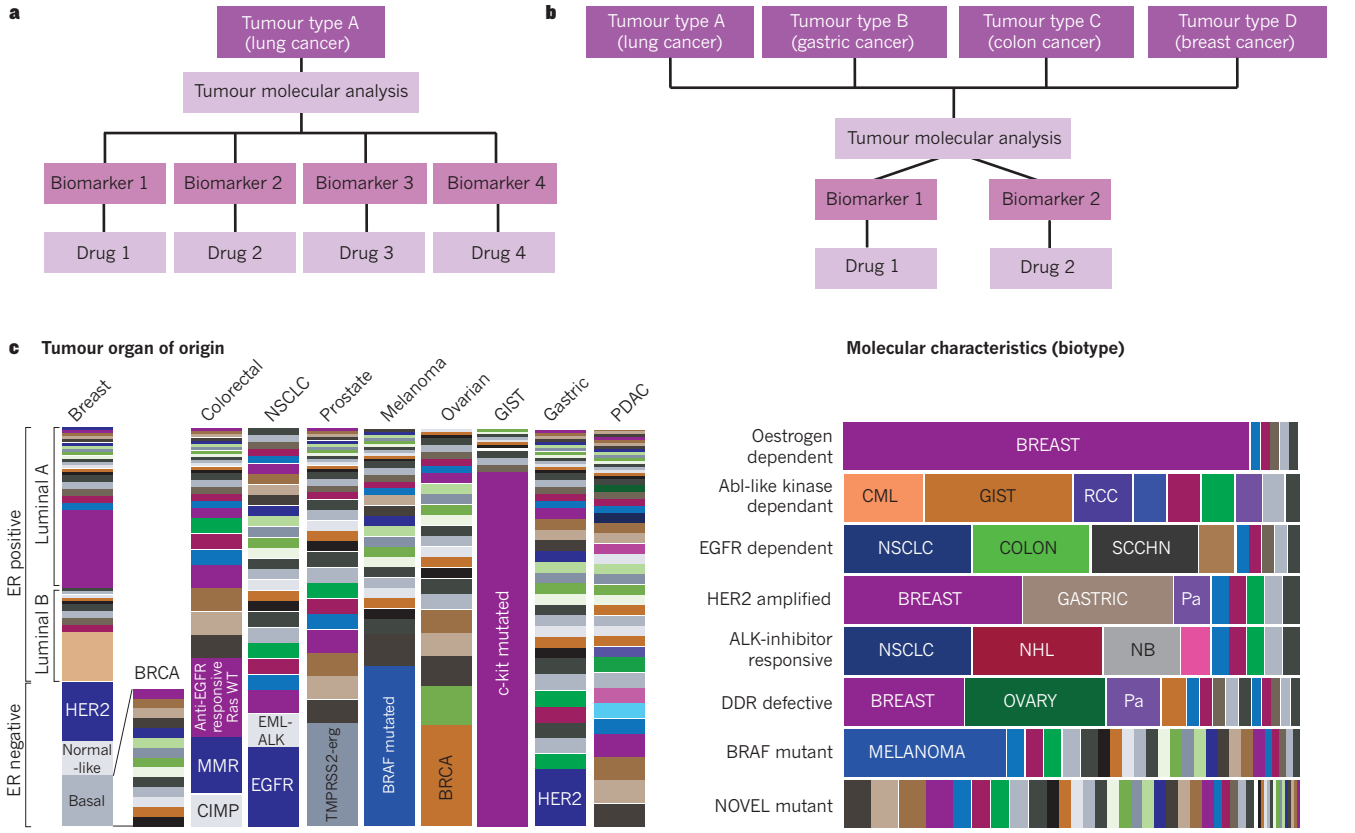

Figure 2 | Design principles that generate efficiencies in clinical trials of targeted therapies. a, In umbrella studies, patients with the same type of cancer are screened for a series of hypothesized predictive biomarkers. They are then allocated to appropriate therapies within the trial architecture. (The biomarker status for each tumour in the study is determined by tumour molecular analysis.) **b**, Basket studies recruit patients on the basis of their molecular characteristics irrespective of the organ in which their tumour originated. **c**, The relative incidence of molecular subtypes can help to guide decisions as to whether an umbrella or basket clinical-trial strategy is most appropriate. Molecular subtypes can be classified by their organ of origin (left) or on the basis of their molecular characteristics or 'biotype' (right). Stratification is helpful when the incidence of a specific molecular class is low across different organs of origin and tends to be tested with a basket approach. Adapted with permission from ref. 75. CML, chronic myeloid leukaemia; DDR, DNA damage response; ER, oestrogen receptor; GIST, gastrointestinal stromal tumour; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; Pa, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma (pancreatic cancer); RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; WT, wild type.

biomarker that identifies tumours most likely to respond to a targeted therapeutic agent is low. For example, if the biomarker is present in only 2% of the population — a typical prevalence for many, if not most, molecular segments[30] — a study of 50–100 patients yields only one or two patients. Unfortunately, no amount of clinical effect in such a small number of patients would be enough to advance the drug's therapeutic development (assuming that there is no clinical effect in the population who test negative for the biomarker).

Evaluating a targeted drug or treatment in the early phases of development will now more frequently require a trial with a selected patient population to minimize the inclusion of individuals who are unlikely to respond for mechanistic reasons. Inevitably, this yields smaller trials and fewer data on which to base decisions about trial-phase transitions. It also creates challenges when developing appropriate comparator populations in early studies. These approaches raise a number of interesting questions. For instance, how many patients must be evaluated to truly understand the safety and efficacy of a drug or treatment? Should later studies remain solely focused on the selected patient population and include just one arm? What are the drug effects in biomarker-negative patients? Owing to errors in diagnosis during routine clinical practice, such patient populations will exist even if they are not selected for investigation during the drug-development process. How can we build the body of evidence needed to support the approved use of a drug or therapeutic agent in a particular indication? As a consequence, challenges are introduced throughout the entire drug-development pathway. These can be basic, such as the practicalities of finding enough patients who have low-incidence markers to investigate, and understanding the utility of the markers used for selection. They can also affect central aspects of the drug-development pathway, such as how to generate the data packages needed for regulatory submissions and market approval.

Patient-centric drug development

The challenges discussed in this Review have resulted in new clinical-trial designs (Fig. 2). An umbrella study (Fig. 2a) typically investigates a single tumour type selected according to the biomarkers relevant to one or more of the candidate drugs, and patients are directed towards different arms of the study — and hence towards different therapeutics — according to the molecular characteristics of their tumour. A basket study (Fig. 2b) also selects tumours according to their molecular characteristics and biomarkers, but is conducted irrespective of tumour type and often focuses on one (or a few) specific markers. The approach that is chosen will be based on various aspects, including the prevalence of a molecular subtype within a cancer type compared with its prevalence across different cancer types (Fig. 2c). Consideration will also be given to whether initiatives led by cooperative groups focussed on specific cancers exist, as well as the practicality of implementing these studies, such as the ability to acquire samples of tumour for analysis.

A solution to some of these challenges in targeted-drug

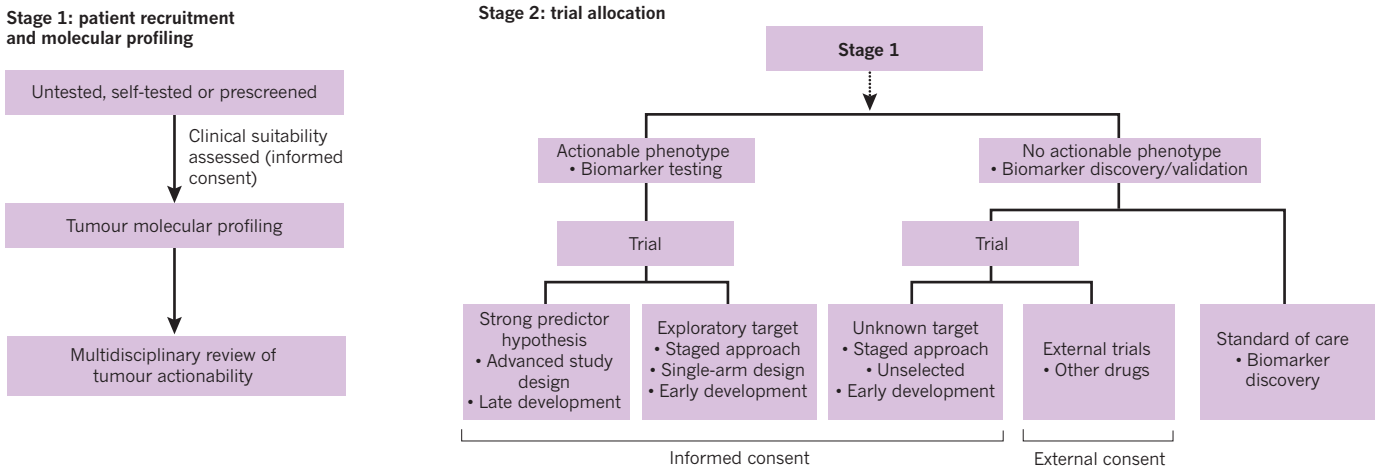

Figure 3 | Master protocols for therapeutic development: a framework for the clinical testing of precision-oncology strategies — or 'finding the trial for the patient'. A guiding principle within the framework is that all patients who are eligible for treatment should receive a choice of therapies. These therapies range from biomarker-directed or unselected new therapeutic strategies (either as part of the trial design or through external trials) to standard-of-care treatment in which patients will still be tracked to inform biomarker discovery opportunities for existing approved therapeutics. The framework can be enacted by a single body or, more pragmatically, through a composite or network of organizations and activities with a co-ordinated management and governance structure. Stage 1 of the framework includes patient recruitment and molecular-testing. Participants are either screened before entering the trial or directed to molecular testing to be done within the trial structure itself or by external providers, if more appropriate. In stage 2, patients and clinicians are presented with a series of attractive clinical-trial options to choose from. This stage also incorporates an additional consent process.

development is the use of a master protocol, some of which have been established for efficiency in certain settings (Fig. 3 and Table 1). Rather than using serial, single diagnostic tests to select participants for different trials, a single, multiplex diagnostic assay is often used to assign participants to different candidate drugs (or arms of a trial) within the same trial, or a network of trials. This is sometimes referred to as a 'tent' protocol, in which multiple trials can be accessed through various mechanisms. Such studies offer more options for patients and can also make patient screening and recruitment more efficient.

Increasingly, adaptive design features are being incorporated. These differ from conventional designs by using accumulated results to modify the course or structure of a trial. The ability to make an early assessment of the clinical benefit or safety of a drug — and to modify the trial in response — is a nimble approach and offers a number of advantages. For instance, the trial can be stopped early or extended depending on the emerging results, or arms or doses can be dropped if no benefit is seen. This approach makes it easier to identify populations of patients who are responding to the drug being investigated, or to identify fruitful combinations of biomarkers and drugs or other therapeutics. It also allows the randomization proportions of the trial population or the rates at which data are accrued to be changed. Finally, it permits the inclusion of multiple stages of drug development within a single trial. Staged approaches such as these can markedly enable the drug-development process (Fig. 4). Examples of clinical trials that use these approaches include the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE)[31] and the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis (I-SPY) series[32–36] of trials for lung and breast cancer.

Targeted therapeutic development is evolving rapidly, and there has been a notable expansion of precision-medicine programmes in recent years (Table 1). Combining a detailed understanding of the molecular pathology of tumours with modern drugs and associated diagnostic technologies for selecting patients has already translated into tangible improvements in survival rates for patients with certain cancer types[10–17], particularly those with non-small cell lung cancer (NSCLC)[13,16]. In addition, significant durable responses to immune modulatory therapies have been discovered in about 15% of patients. These therapeutic agents target specific molecular mechanisms that are currently the focus of intense investigation. Patient selection is also likely to play an important part in the development of these agents, with biomarker hypotheses being actively developed for the identification of trial participants[37]. Data are emerging from early programmes such as SHIVA[38], which broadly evaluated targeted therapies without taking into account the histology of the tumour in end-stage patients for whom standard therapy had failed. Although no difference was identified[39], it is not possible to draw broad conclusions from this finding, exemplifying the challenges ahead.

The oncology landscape is accumulating a growing number of patient and tumour groups[40] that can be identified by (increasingly complex) diagnostic assays, which enables them to be coupled to molecularly targeted drugs. Up-to-date approvals can be found on the websites of the US Food and Drug Administration (FDA)[41–43] and the European Medicines Agency (EMA)[44]. Although most approved therapies have a linear relationship with a single biomarker, emerging data suggest that combinations of biomarkers might better inform therapeutic responsiveness, and will continue to challenge biomarker development. Similarly, multiple biomarkers could indicate sensitivity to a single therapeutic agent, and conversely a single biomarker might define patients that would benefit from several therapeutic options. Such overlaps are inevitable and it is important to define appropriate measures on how to respond to them during the drug-development process. The emerging complexity poses substantial challenges for current regulatory processes. For example, how should researchers assess therapies that do not take the cancer's organ of origin into account, particularly when its prevalence is low in a particular organ? How should therapies be assessed at different stages of the disease, especially in cases where the patient has undergone several prior treatments? A solution might be to apply a broader approach, such as defining the level of reimbursement for a particular disease stage and line of treatment, with decisions on choice of therapy made between clinicians and their patients.

The challenges of early drug development

Clinical testing in the early stage of drug development poorly predicts efficacy in later stages of development[25,45]. Bias in small early trials can raise expectations, only to cause disappointment when they are expanded to include larger, less-selected and unbiased populations. Current tools that provide an improved understanding of the

Table 1 | Precision-medicine studies

Precision-medicine clinical trials

Study	Tumour	Phase/design	Location	Arms	Patients†	Clinical trial ID	References
Bisgrove	All	Phase II, non-randomized	United States	N/A	84	NCT00530192	19
IMPACT	All	Phase I	United States	N/A	1,144	NCT00851032	20
MOSCATO 01	All	Phase I	France	N/A	420	NCT01566019	21
Lung-MAP	Squamous lung	Phase II/III, randomized	United States	5	10,000	NCT02154490	49
BATTLE	NSCLC	Umbrella, route to four phase II randomized	United States	4	300	NCT00409968 (umbrella) NCT00411671 NCT00411632 NCT00410059 NCT00410189	31, 66, 67
BATTLE-2	NSCLC	Phase II randomized	United States	4	450	NCT01248247	N/A
BATTLE-FL	NSCLC	Phase II randomized	United States	4	225	NCT01263782	N/A
I-SPY 2	Breast cancer	Phase II randomized	United States	8	800	NCT01042379	68, 69
NCI-MPACT	All	Phase II stratified, non-randomized	United States	6	700	NCT01827384	70
NCI-MATCH	Solid	Phase II stratified, non-randomized	United States	20	3,000	Umbrella, route to phase II‡	48
V-BASKET	All	Phase II stratified, non-randomized	Global	2	160	NCT01524978	71
CREATE	Selected	Phase II stratified, non-randomized	European Union	6	582	NCT01524926	N/A
WINTHER	All	Stratified, non-randomized	European Union	2	200	NCT01856296	72
SHIVA	All	Phase II stratified, controlled	France	10	1,000	NCT01771458	38
MOST	All	Phase II stratified, randomized	France	5	560	NCT02029001	N/A
SAFIR 02 Lung	NSCLC	Phase II stratified, randomized	France	8	650	NCT02117167	73
SAFIR 02 Breast	Breast cancer	Phase II stratified, randomized	France	18	460	NCT02299999	N/A
Lung MATRIX	NSCLC	Phase II stratified, non-randomized	United Kingdom	21§	2,000‖	EudraCT 2014-000814-73	65
FOCUS 4	Colorectal cancer	Phase II/III randomized	United Kingdom	4	643	EudraCT 2012-005111-12	74
IMPaCT	Pancreatic cancer	Phase II stratified, randomized	Australia	4	90	ACTRN 12612000777897	47

Screening programmes that feed into precision-medicine trials

Study	Tumour	Phase/design	Location	Diagnostics	Patients†	Clinical trial ID	References
I-SPY	Breast cancer	Phase II, diagnostic study	United States	Genomic, imaging	221	NCT00043017	32–35
NCI-MATCH	Solid	Screening, route to phase II	United States	NGS¶	3,000	N/A	48
VIKTORY	Gastric cancer	Screening, route to phase II	Asia	NGS, other#	600	NCT02299648	N/A
LC-SCRUM	NSCLC	Screening, route to phase II/III	Asia	As needed**	Open††	N/A	53
AURORA	Breast cancer	Screening, route to phase I/II/III	European Union	NGS, other‡‡	1,300	NCT02102165	52
SPECTAColor	Colorectal cancer	Screening, route to phase I/II/III	European Union	NGS	2,600	NCT01723969	50
SPECTALung	Lung	Screening, route to phase I/II/III	European Union	NGS	500§§	NCT02214134	51
MOSCATO	All	Screening, route to phase I/II	France	CGH array, sequencing	1,050	NCT01566019	21
SAFIR 01	Breast cancer	Screening, route to phase I/II	France	CGH, sequencing, gene expression array	423	NCT01414933	73
CRUK SMP1	Selected	Screening, feasibility	United Kingdom	Bespoke panel	9,000	N/A	36

BATTLE-FL, Front-Line Biomarker-Integrated Treatment Study in Non Small Cell Lung Cancer; CGH, comparative genomic hybidization; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; IMPaCT, Individualised Molecular Pancreatic Cancer Therapy; IMPACT, Initiative for Molecular Profiling in Advanced Cancer Therapy; MOSCATO, Molecular Screening for Cancer Treatment Optimization; MOST, Adapting Treatment to the Tumor Molecular Alterations for Patients with Advanced Solid Tumors: My Own Specific Treatment; N/A, not applicable; NCI-MPACT, National Cancer Institute-Molecular Profiling-Based Assignment of Cancer Therapy for Patients with Advanced Solid Tumors; NGS, next-generation sequencing; VIKTORY, Targeted Agent Evaluation in Gastric Cancer Basket Korea Study.

†Estimated number of patients to be recruited, or the final number recruited where the study has been completed. ‡The NCI-MATCH programme is a screening programme used to direct patients to single-arm, phase II, signal-seeking studies. §The number of arms will vary because the study progresses as each arm has been designed around a biomarker (for patient selection) and (candidate) drug pair. ‖Once fully operational, the study will screen 2,000 patients per year. ¶FISH and IHC assays will be used as required. #'Other' refers to a selection of bespoke and exploratory diagnostics. **Bespoke diagnostics are deployed as needed to select patients for the individual clinical studies that feed from the screening programme. ††'Open' describes an open and rolling patient-recruitment programme. ‡‡'Other' refers to RNA sequencing. §§500 patients in year 1 then 500–1000 patients, thereafter.

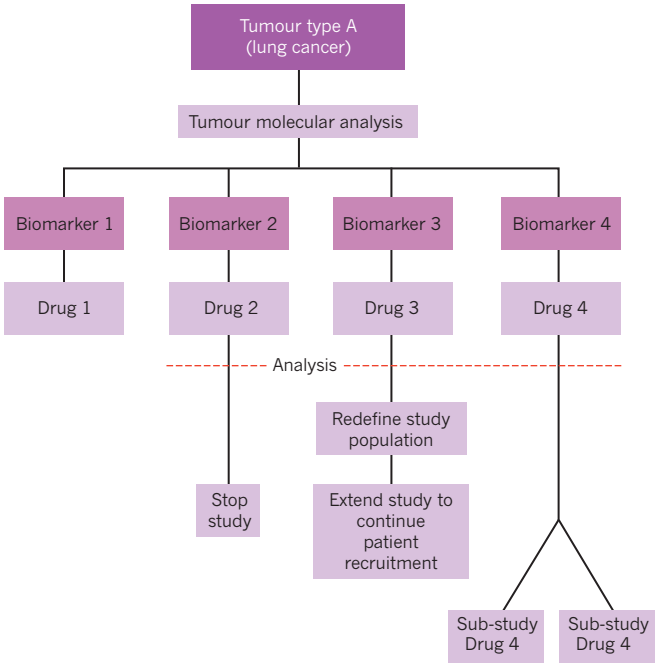

Figure 4 | Adaptive study designs. A within-study analysis or the continual assessment of data can be used to change the course of a clinical trial. First, the biomarker status for each tumour in the study is determined by tumour molecular analysis. After each tumour is allocated to a suitable sub-study, further analysis is conducted. Consequently, the sub-study 2 trial arm can be stopped owing to a lack of evidence to support the clinical benefit of drug 2, and the sub-study 3 trial arm can be extended to include more patients. Meanwhile, the patient population of sub-study 4 can be redefined into two sub-studies, according to the results of responder/non-responder analysis.

molecular pathology of tumours can be used to inform smaller trials as well as to define sources of bias at the molecular level to inform early and ongoing therapeutic development. An emerging approach is the testing of small numbers of patients underpinned by a deep understanding of both the molecular composition of tumours and the mechanism of action of the therapeutic agent. Knowledge acquired through clinical testing can then inform ongoing preclinical strategies, which in turn refine the clinical-testing approach — a process known as forward-and-backward translation (Fig. 5).

Inherent to this approach is a desire to define more effective therapies and to set the bar higher for furthering the progression of a therapeutic agent down the drug-development pathway. A shift is needed away from the current high-investment drug-development approach that is dominated by late-phase trials that predominently fail at great expense, towards an approach in which failures are early and cheap. This will allow a greater number of potential therapies to be assessed while constraining costs. Researchers might even be able to test bolder biological hypotheses, particularly in cancers for which current therapeutic options are poor. With these tools in hand, and developing rapidly, the challenge now becomes to determine how we can implement these strategies in the real world.

Master-protocol clinical trials that use umbrella and basket designs to enable trial stages to be run in parallel are efficient. However, the subdivision of tumour and therapeutic pairs that they create highlights a need for more innovative solutions and approaches, particularly in early drug development[27,46]. For example, there might not be enough patients to test the targeted therapeutic using conventional designs. Figure 6 shows a suggested strategy for the development of therapeutic agents to treat cancer with an overall incidence of 10 patients per 100,000 individuals per year. Supportive evidence for a particular strategy can be classified according to an 'actionability index'. The development of each therapeutic agent will progress within this framework or graduate to pivotal studies when there is sufficient evidence.

Accelerating stratified therapeutic development

The development of precision therapeutics focuses on leveraging the science, however, many important challenges pivot on operational components[47]. These components require the integration of multiple complex processes such as participant screening and recruitment

BOX 1

Delivering multidrug–portfolio studies

A number of diagnostic, protocol and operational requirements must be considered when designing clinical trials that use multidrug portfolios.

- **Participant screening and recruitment** There should be a viable means by which to identify low-incidence patient subpopulations and to direct individuals to an appropriate clinical trial. Patient-centric approaches give individuals access to many options through a single screening process. Such screening programmes are usually region-wide and collaborative. They can be linked to umbrella and basket studies and also to global studies that accept participants from diverse screening routes. Drug portfolios are made available to these trials through collaborations, and safeguards are implemented for proprietary information when multiple partners are involved. The multiplexed diagnostic platforms and systems should be harmonized or cross-validated to allow patients to be recruited irrespective of the technology used by partners. Regulators should be open to changes with respect to how these clinical trials are run. The screening programmes are underpinned by networks, collaborations and reliable partners.
- **Molecular testing** The testing platform and screening or selection algorithm should enable broad yet robust tumour and patient profiling. They should provide viable drug-development routes for larger or global studies, regulatory interactions and markets. Samples must be used efficiently and data generation should be robust. Overall, molecular tests should be cost-effective, transferable and widely deployable. Testing should be performed to agreed standards.
- **Protocols** Trials should start with a flexible protocol that can incorporate both emerging changes in the science and an understanding of patient and tumour biomarkers. Alternatively, they could use a confirmatory development protocol that permits regulatory interactions that accept different types of data. Such protocols can be deployed on their own or in alignment with other protocols. They can be modular, rolling or open ended, and must be reviewed efficiently according to a centralized regulatory and ethics process.
- **Availability and delivery of therapies** Operational machinery must be chosen that allows clinical studies to be conducted in diverse groups of patients and over a broad geographical area. Regulatory and ethics processes and patient screening and recruitment should be aligned and efficient. Therapies can be distributed using hub-and-spoke models and cost-effective and efficient delivery of multiple candidate drugs to multiple sites can be facilitated through a centralized pharmacy. The work should be highly collaborative, spread across many groups and involve reliable partners.

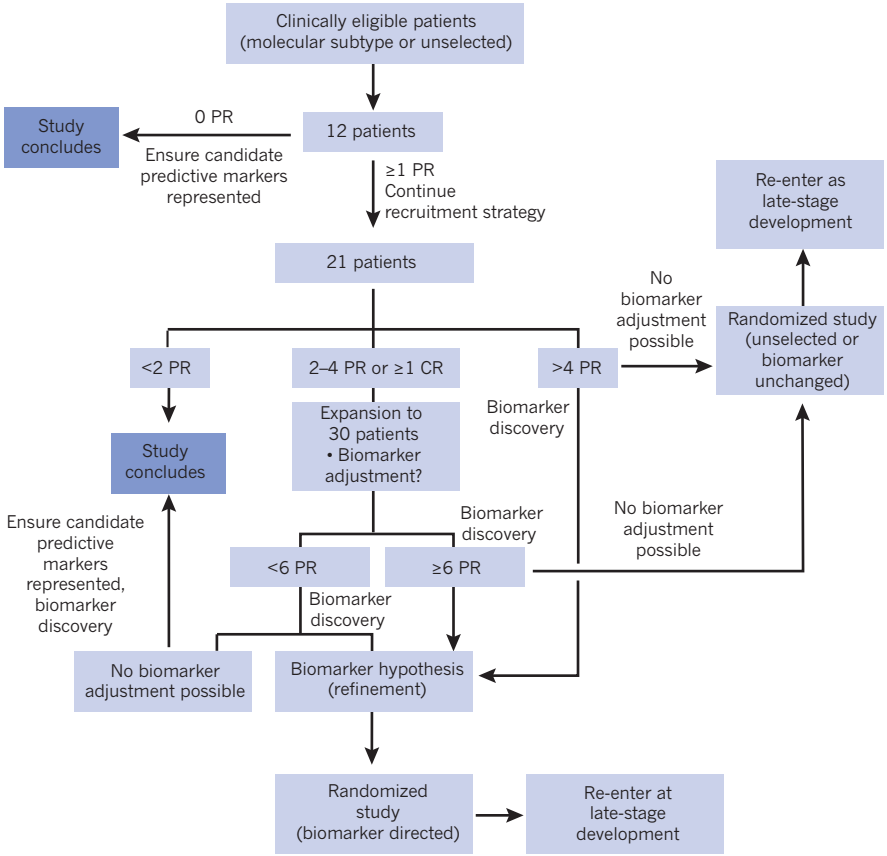

Figure 5 | Early stratified therapeutic development. An important element of early therapeutic development is the use of small trials that are underpinned by a deep understanding of tumour molecular pathology, which guides ongoing trial development. A stepwise development approach is applied, and interim analyses, trial-population expansions and molecular assessments are implemented at specific points. CR, complete response, and PR, partial response, based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria[76].

and the molecular testing of tumours. Rather than pursuing the conventional goal of finding the patient for the trial, the overall goal is to 'find the trial for the patient'. Protocols must also be flexible and therapies must be available and deliverable (Box 1).

Participant screening and recruitment

The realities of the conventional screening approach in clinical drug development are sobering. For example, consider a candidate-drug trial in a subpopulation of patients that were selected by a biomarker with a 2% incidence, which has a typical screening failure rate of 15% and a patient dropout rate of 15%. The trial would need to screen 78 patients to find one patient for recruitment, which effectively means that 77 patients are discarded. The cost of such an approach is equally sobering. Screening using routine single-variable diagnostic approaches, such as immunohistochemistry or a single-gene DNA test, would have a cost of about US$1,125 per assay, which includes performing and processing the assay, as well as logistics and reporting. It would therefore cost $88,235 to screen enough individuals to recruit one participant. To conduct a 20-patient phase I expansion study in this selected patient subpopulation, the trial would need to screen 1,560 patients, at a cost of $1.8 million.

In addition, the patient's experience during the conventional screening approach is often extremely poor and can involve many cycles of disappointment. After first being considered for a trial, the patient might then become ineligible to participate if they do not have the correct biomarker. They must then undergo repeat biopsies during the search for the next biomarker, and ultimately might receive only limited drug options. The physician's experience is similarly poor: his or her options are limited to screening for different biomarkers, and associated trials, so long as tumour material is available. From the operational viewpoint of a clinical trial, this is unsustainable for practical reasons, such as the lack of available tissue and the unwillingness of patients and clinicians to participate.

The need to find sufficient numbers of patients with a specific biomarker has generated many cooperative study groups (Table 1). Consortia provide multiplexed molecular testing assays — in which many biomarkers are measured concurrently — as part of the drug-development process, as well as programmes that offer 'self-tested' patients access to appropriate therapy either as part of clinical trials or through 'off-label' treatment. In the United States, examples include national-level, cross-sector collaborative (including government-based) initiatives such as the National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH)[48] (solid tumours) and Lung Cancer Master Protocol (Lung-MAP, NCT number NCT02154490)[49] (squamous lung cancer) programmes. Other examples include the Screening Patients for Efficient Clinical Trial Access (SPECTA) programmes (SPECTAColor[50] in colorectal cancer (NCT01723969) and SPECTALung[51] in lung cancer (NCT02214134)) and the AURORA initiative in Europe[52] (breast cancer (NCT02102165)), and the Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM-Japan)[53]. Cancer-specific advocacy and charity organizations also lead cooperative study groups, such as the 'Know Your Tumor' programme established by the Pancreatic Cancer Action Network in the United States. Although these models are advancing precision oncology, they are costly because they require intermediaries to navigate the patient through the health-care system. They are also difficult to scale up without fundamental changes in health-service delivery. Meanwhile, patients and clinicians are also driving forwards new approaches. These approaches include clinical trials and other therapeutic options as part of a molecular assay report,

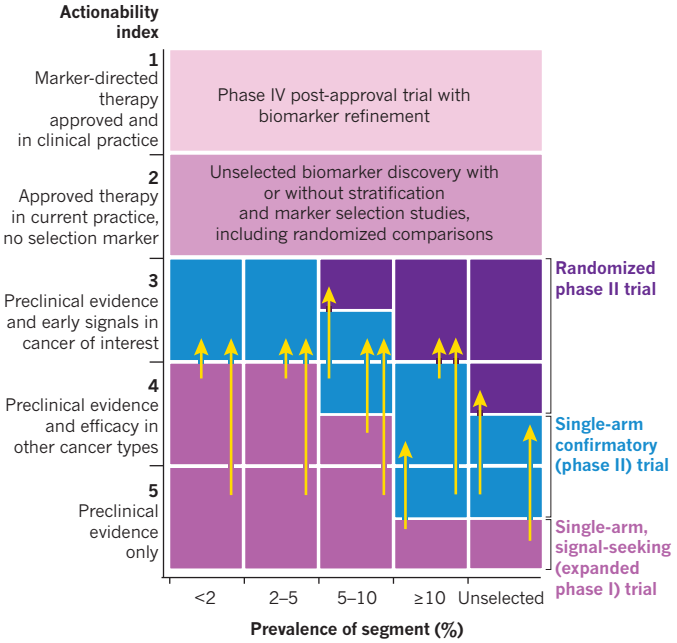

Figure 6 | Clinical-testing strategies. Lower-prevalence segments present a considerable challenge when testing stratified therapeutic strategies. It is also a challenge to determine the level of evidence that is required to embark on later-phase studies. The potential approach shown in this matrix is a function of the existing level of evidence, the prevalence of the segment, which indicates the feasibility of the testing strategy, and current regulatory requirements. Trials can progress as the level of evidence increases, and this progression can be built into the planned stepwise development process.

such as FoundationOne from Foundation Medicine, and connections to further information, consumer-focused advice, communities and patient-led consortia. The broader net that such approaches cast helps to identify smaller and smaller subtypes and opportunities for individual patients. Strategies that provide genomic health advice[54] and navigation, such as Perthera, are also gaining traction. Others have begun to use electronic media to enable patients and clinicians to 'shop around' for the best option. These strategies can markedly improve efficiency and the patient experience. However, despite these efforts, trials using a selection biomarker still constitute only a minority of current studies[55].

Recruiting eligible patients onto a clinical trial represents a major challenge. If the prevalence of eligible patients is low, it is often necessary to open a large number of screening centres — a considerable cost, especially since not all will be able to recruit patients. As screening programmes expand in size, the cost of funding the search for patients shifts from drug developers to health-care systems or research platforms. A possible solution is to open clinical trials at a location that is accessible to the patient only after they have been identified — known as 'just-in-time' accessibility. The cost of rapidly deploying teams to establish a trial location after a patient has been found is likely to be lower than the cost of screening a large number of patients.

Molecular testing

Although multiplex testing of the coding regions of candidate genes offers some options, the complexity of cancer will inevitably require more in-depth analyses[56]. The challenges of delivering molecular assays using advanced technologies are discussed elsewhere[56], however, current tests exploit the relatively direct relationships that exist between a specific mutation and the efficacy of a drug. The appraisal and delivery of more complex assays that might better identify responsive subtypes[57,58] is proving to be difficult despite advances in clinical-grade diagnostics[59]. This is mainly due to the rigidity and inertia of established processes for biospecimen handling. Simple solutions such as liquid biopsies[60,61] are promising, but could lack broad applicability, particularly when complex molecular changes must be analysed. Technology considerations aside, it is more important to understand the relevance of any detected changes or mutations, and the body of evidence that is required to substantiate their use for patient selection. Modern multiplex systems such as next-generation sequencing technologies reveal the molecular changes within a single tumour at an unprecedented level of detail. Many of these changes will not have been widely reported: some are likely to be specific to that tumour (or tumour region) and there will be little previous clinical experience or knowledge for most. In light of this, how should therapeutic selection be informed? Although specific mutations in a particular gene can confer sensitivity to a particular therapeutic agent, what should we do if we discover previously unreported mutations in that same gene? And what should we do if the potential functional consequences have not been investigated yet? Can these mutations reasonably be expected to confer similar therapeutic sensitivity? This challenge is being addressed through trial design and the diagnostic algorithms that are used to assign patients to treatments. We must be careful to avoid reporting a study as negative purely because it has not shown any clinical benefit in a subpopulation that has been defined by mutations of unknown consequence. Not all mutations in a gene will be predictive of clinical benefit. Practical solutions to accommodate such uncertainty often combine adaptations within umbrella- or basket-shaped trial arms that can examine combinations of biomarkers and therapeutics in isolation. Different weightings can then be attributed to mutations of known and unknown clinical or functional consequence — a process called mutation tiering in which groups are designated as either 'tight' markers that have a high level of supportive evidence or 'loose' markers that are more exploratory in nature.

Protocol flexibility

The administrative and logistical challenges of clinical trials are substantial. They impede the ability to respond nimbly to trial findings, particularly if unexpected, or to data emerging from outside the trial. Establishing frameworks and platforms for stratified therapeutics development will facilitate the deployment of 'within-protocol' responses to specific scenarios, which will improve flexibility of trials (Box 1).

Availability and delivery of therapeutics

Conducting molecular analysis without the prospect of a resulting action is of little value. There are comparatively few opportunities in routine health care in which multiplexed testing can be applied to influence clinical decision-making, and access to appropriate therapeutics remains problematic[62]. Negotiating individual clinical trials on an *ad hoc* basis is impractical because of slow legal and administrative processes — a closer relationship must be cultivated between the pharmaceutical industry and other stakeholders to ease this roadblock. The involvement of multiple pharmaceutical partners will ensure that a broader range of candidate drugs and appropriate comparator therapies are available. Wider collaboration between tumour-specific consortia, diagnostic and regulatory groups, as well as major charities and other interested parties, will also be pivotal. A drug-portfolio approach — negotiated as a broad partnership or though a consortium strategy — is a necessity, as is the ability to deliver therapeutic agents through systems such as a centralized pharmacy. The ability to offer patients and clinicians a broad selection of attractive treatment options will enhance participation in clinical trials. At present, only 2–5% of potentially eligible participants[63,64] enrol in such trials. Initiatives such as NCI-MATCH[47], Lung-MAP[49], and the Cancer Research UK Stratified Medicine programmes and the National Lung Matrix Trial (Lung MATRIX)[65] (European Clinical Trials Database (EudraCT) number 2014-000814-73) have set a

precedent for prioritizing participation rates. However, the real value to the patient and health-care system will be when these strategies become commonplace and encompass a greater proportion of drug-development portfolios. This will ensure the broad availability of therapeutics currently in development.

Most advances have been achieved by altering drug-development strategies to fit into established health-care systems. Consequently, progress has been slow. If health-care systems are out of pace with the drug-development process, they could be impeding the development of therapeutic agents. Health-care systems that can implement precision medicine will greatly facilitate therapeutic development. To accelerate progress, health-care systems must be aligned to ensure that they are able to test and deliver precision medicine without the need for costly overlying clinical-trial infrastructure.

Future directions

In recent years, our understanding of the precision-therapeutic development pathway has evolved rapidly. In some areas, targeted-drug development has progressed from concept to reality. The frameworks, platforms and processes involved are now capable of supporting modern oncology drug development. Innovative clinical-trial designs — also a central component of development — are highlighting the need to better appraise tumour biology, drug efficacy and the potential benefits for patients. Emerging drug-development paradigms are driving new ways of working collaboratively to accelerate progress. By generating truly patient-centric clinical trials, we have taken important early steps into the evolving era of precision medicine. In some cases, these steps are already enabling us to 'select' the trial for the patient. However, major hurdles remain, and we must establish broad frameworks and systems that integrate closely with health-care delivery to accelerate progress and realize the true promise of precision medicine. ■

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