"Finding the trial for the patient": the new paradigm of therapeutic development for precision oncology.

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Abstract

Our increasing understanding of the molecular pathology of disease, particularly through genomic studies, has created significant opportunities for the development of therapeutics that specifically target discrete molecular subclasses, but equally, has generated substantial challenges in how to develop and implement these strategies. Variously termed personalised, stratified, individualised or precision medicine, the approach is centered on delivering the optimal therapy for an individual based on specific clinical and molecular features of their disease. The development of new therapeutics that target molecular mechanisms has driven considerable change and innovation in clinical trial strategies. We have made progress through improved efficiency and changes in clinical trial design, yet continued innovation through the modification of existing core paradigms in oncology drug development and clinical care are required to fully realise the promise of precision medicine.

Introduction

Insights into the molecular pathology of disease are creating opportunities for more durable clinical benefit, but are also challenging the existing paradigm of therapeutic development and clinical care [1-3]. Large international consortia such as the International Cancer Genome Consortium [4,5] are mapping thousands of cancer genomes 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 advances have ushered in a new era of therapeutics that target specific molecular processes. Although we have had some dramatic successes [8-17], the overall strategy remains in its infancy [18]. The central premise of precision medicine is that by matching a drug and its mechanism of action to select patients we can offer greater potential for durable clinical benefit - often referred to as "matching the right drug to the right patient".

Initially, targeted agents followed much the same clinical development pathway as cytotoxic chemotherapy based on tumour location and histopathology; driven by the then notion that molecular aberrations were tumour specific. A lack of efficacy data in patients with different cancer types harbouring a shared molecular aberration, coupled with early observations that the functional significance of (some) aberrations varied between tumour types, stalled efforts to advance these approaches. However, the subsequent emergence of programmes that identified molecular targets and matched treatment to molecular subtype led to several reports (M.D. Anderson Cancer Centre

[19]; MOSCATO study [20]) which directly linked this approach to improvements in clinical outcome, irrespective of the organ of origin. Although the data were based on retrospective analysis of tumour samples, and not all reports equally as convincing [21], the utility of broad molecular profiling to guide patients to specific targeted therapies had been established. Researchers moved quickly to implement this new paradigm. In turn, established pathways of therapeutic development would need to change to meet these emerging requirements, and although the practical implications of clinical implementation were less clear, the promise of clinical benefit was enticing...

The drivers for precision medicine are established and robustly discussed elsewhere [18,22,23], however, the new challenges for therapeutic development are many and substantial: Fundamentally, a candidate therapeutic strategy requires a strong platform of evidence to support clinical testing coupled with robust methods to define the right patients (using molecular assays [24]). Our appreciation of molecular diversity of cancer and the ever-increasing number of molecular subgroups (segments) creates significant complexity for targeted drug development. When tested in trials of unselected participants, most targeted therapies reveal efficacy only when both the incidence of a responsive sub-population and the effect size in this 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. Trials that feasibly evaluate both patient selection and drug efficacy are key, and it is essential to define the correct metrics, particularly with the smaller studies that are required.

Principles and evolution of clinical trials

Clinical trials are most useful when it is important to assess a potential therapeutic effect that is about the same size or smaller than natural person-to-person variability. When subject variation influences a treatment only randomly, it can be ignored in a biological sense and controlled by replication. These dual strategies for controlling variation embody the empiric and theoretical aspects of trials. For much of the history of clinical trials, the treatments under investigation have been assumed, correctly or not, to apply to anyone with the relevant clinically defined condition; i.e. our understanding of biology suggested treatments worked through common mechanisms apart from random variation. This assumption was substantially correct for therapeutics that targeted more generic mechanisms such as cytotoxic chemotherapy, and enabled significant progress against cancer to be made. Towards the end of the 20th century, concerns arose regarding potential inhomogeneity of therapeutic effects based on socio-political characteristics such as race or sex, with many clinical trials designed and analysed to examine such differences. Although the motives were based on politics and social justice rather than science, the trial designs employed were little changed, which was likely appropriate given the weak biological basis for differences attributed to these superficial characteristics.

The recognition of non-random variation that demands altered clinical trial design has come more from knowledge of the disrupted cancer genome rather than the germ line. The implications of having multiple potential treatments and diseases where a single one once stood creates enormous pressure to alter study design – and many investigators approach the challenges of too many diseases and too few subjects created by genomic partitioning of cancer as a clinical trial design problem. This can create unhealthy tension because although new designs must follow new questions, many of the questions of targeted therapies are actually standard, and well-established methodologies remain appropriate. Consequently, the challenges of clinical testing of most precision medicine strategies revolve around feasibility, efficiency and adaptability to deal with multiple small incidence subtypes and a rapidly evolving knowledge base.

Staging of drug development evolved to accommodate the 2 strategies required: generating strong safety and efficacy signals for effective treatments, and terminate development of ineffective ones as early as possible. In broad terms: 1) Early development (phase I) focuses on dosing and safety; 2) middle development (phase II) examines a larger group of patients to further evaluate safety and efficacy for a critical go-no-go decision; 3) Late development (phase III) constitutes definitive comparative testing and provides a basis to seek market approval. Phase IV studies are sometimes performed following market approval to examine additional patient populations, side effects, long term use, and to potentially extend indications. Iterative building of evidence either supports or refutes the use of the new therapeutic for a specific indication. In this paradigm a premium is placed on randomised, controlled designs.

The strategy of biomarker driven patient selection (enrichment) is well established for high prevalence biomarkers and is either based on retrospective analysis of randomised controlled trials; biomarker discovery integrated within the design to ensure sufficient power to detect signals; and equal distribution of marker positive patients in each arm (confusingly termed biomarker stratification); and biomarker directed studies (Figure 1) [25-27]. However, advances in our understanding of differences in the molecular pathology of individual cancers raises inevitable challenges around typical development paradigms as the prevalence of molecular segments decreases [28]. For example; if the incidence of a marker that identifies tumours most likely to respond to a targeted therapeutic is only ~2% (a typical prevalence for many if not most molecular subgroups), then the chances of a successful outcome in a traditional comparative trial are diminishing small [29]. Two percent of patients yields only 1-2 patients in a 50-100 patient study. No level of clinical effect in such few patients would be sufficient to advance therapeutic development, assuming there is no clinical effect in the marker negative population.

Evaluating a new targeted drug or treatment in the early phases of development requires a trial that minimises the inclusion of patients unlikely to respond for mechanistic reasons, i.e. a selected patient population. This inevitability yields smaller trial sizes, smaller data packages for making decisions on trial phase transitions, and challenges in developing appropriate comparator

populations in earlier studies. The questions such approaches raise are how many patients are required to be evaluated to truly understand the safety and efficacy of the drug or treatment; should later clinical phase studies remain focused solely on the selected patient population and use single arm studies; what are the drug effects in marker negative patients (which will happen in routine clinical practice due to diagnostic inaccuracies even if such patient populations are not investigated during development); how we build the body of evidence needed to support the approved use of a drug or therapeutic in a particular indication. As a consequence, the entire development pathway becomes challenged – from the basic practicalities of how to find sufficient patients selected by low incidence markers to investigate and how to understand the utility of the markers used for selection, through to central aspects of the development pathway such as how to generate the data packages needed for regulatory submissions and market approval.

The emerging model of patient-centric drug development

The challenges above have produced umbrella and basket trials. Umbrella studies are within tumour types, selected by different markers for single/multiple candidate drugs, and basket studies are across tumour types, often selected by a single marker or for a single candidate drug (figure 2). An umbrella study typically investigates a single tumour type, for example lung cancer, and has patients directed to different arms of the study and hence different therapeutics based on their tumour's molecular characteristics. A basket study also uses selection based on tumour molecular characteristics and selection markers but irrespective of tumour type and is often focused on one, (or a few) specific markers. The choice of approach is based on various aspects from the relative prevalence of the molecular subgroup within versus across different cancer types (figure 2), initiatives of tumour-specific cooperative groups, or the simple practicalities of implementing these studies such as the ability to acquire tumour material for analysis.

One solution to some of the challenges in development discussed above is the use of Master Protocols, some of which have been established for efficiency in certain settings (figure 3)(table 1). Rather than using serial, single diagnostics to select participants for different trials, a single multiplex diagnostic assay is often used to assign participants to different candidate drugs (or trial arms) within the same trial, or a networked trial architecture. Some refer to this as a "tent" protocol, where multiple trials through various mechanisms are available. Such studies offer greater options for patients with potential for significant efficiencies for screening and trial recruitment.

Increasingly, adaptive trial design features are incorporated. These differ from many traditional designs by using accumulating results to modify the trial course or structure. The ability to make an early assessment of clinical benefit (or safety) and to modify the trial subsequently allows for a nimble approach. Advantages are: 1) the decision to stop early or extend accrual based on emerging results, 2) dropping arms or doses if no benefit is seen, 3) finding responder populations, or combinations of markers and drugs/therapeutics, 4) changing randomisation proportions, 5)

changing accrual rates, and 6) allowing multiple stages of development to be included in a single trial. Such staged approaches can significantly enable the drug development process (figure 4). Examples of trials using these approaches include the BATTLE [30] and I-SPY series [31-35] of trials for lung and breast cancer.

Oncology drug development is now evolving rapidly, with notable expansions of precision medicine programmes in recent years (table 1). The understanding of the molecular pathology of tumours in unprecedented detail coupled with modern drugs and associated diagnostic technologies to select patients has enabled tangible improvements in survival rates in some cancer types [10-17]; particularly exemplified in patients with Non Small Cell Lung Cancer (NSCLC) [13,16]. More recently, significant durable responses to immune modulatory therapies are emerging in ~15% of patients. These agents mostly target specific molecular mechanisms, which are currently the focus of intense investigation. It is likely that patient selection will also play a significant role in the development of these agents, with biomarker hypotheses actively being developed [36]. Data are beginning to emerge from early programmes such as SHIVA [37], which broadly evaluated targeted therapies using a histology agnostic approach in end stage patients who failed standard therapy. Although no difference was identified [38], it is not possible to draw broad conclusions, exemplifying the challenges ahead.

The oncology landscape continues to evolve towards an increasing number of patient/tumour groups[39] identified by (increasingly complex) diagnostic assays to enable coupling to molecular targeted drugs. (For additional information and up-to-date approvals, see U.S. Food and Drug Administration (FDA) [40-42] and the European Medicines Agency (EMA) [43]). Whilst most approved therapies have a linear relationship with a single marker, emerging data suggest that combinations of markers or different readouts may better inform therapeutic responsiveness, and will continue to challenge biomarker development strategies. Similarly, multiple markers may confer sensitivity to a single therapeutic, and a single marker may offer several therapeutic options. Such overlaps are inevitable and defining appropriate measures on how to respond during the drug development process are important. The emerging complexity is posing substantial challenges to current regulatory processes. How are therapies independent of organ of origin assessed, particularly when the prevalence is low in an organ type? How do we deal with therapies at different stages of the disease with several prior treatments? Perhaps we could look to broader approaches, such as reimbursement defined for a particular disease stage and line of treatment, with decisions on choice of therapy made between clinicians and their patients.

Overcoming the challenges of early drug development

Clinical testing in early development poorly predicts efficacy in late development [24,44]. If this were not the case, late development would be unnecessary. Bias in small early trials can raise

expectations, only to disappoint when expanded to larger, less selected and "unbiased" populations. We now have the tools to better understand the molecular pathology of tumours to inform smaller trials, and importantly define sources of bias at a molecular level to inform early and on-going therapeutic development. An emerging approach is testing small numbers of patients underpinned by a deep understanding of the molecular composition of tumours and the mechanism of action of the therapeutic, with knowledge acquired through clinical testing informing ongoing pre-clinical strategies, which in turn further refine the clinical testing approach (backward and forward translation)(figure 5).

Inherent to the latter approach is the desire to define more effective therapies and set the bar higher for progression of the therapeutic down the development path. With the multitude of emerging potential therapies and molecular subgroups, we need to move from a high investment drug development approach with a dominance of late phase failures, to one that "fails early" and "fails cheaply" so that more potential therapies can be assessed and costs be constrained; and perhaps bolder biological hypotheses could be reasonably tested. With these tools in hand, and developing rapidly, the challenge becomes how, or if we can implement these in the real world.

Whilst parallelised master protocol clinical trials using umbrella and basket designs create efficiencies, the subdivision of tumour/therapeutic pairs continues to push for more innovative solutions and approaches, particularly in early drug development [27,45]. There may simply not be enough patients to test the therapeutic based on traditional approaches. Figure 6 shows a suggested strategy for the therapeutic development of a cancer type with an overall population incidence of 10 per 100,000 per annum. Supportive evidence for a particular strategy is classified based on an "Actionability Index". Approaches for each therapeutic may progress within this framework, or to pivotal studies when there is sufficient evidence to do so.

Accelerating stratified therapeutic development – overcoming operational challenges

Precision therapeutic development focuses around leveraging the science, but many key challenges pivot around operational components[46]. These require integration of multiple complex processes such as 1) participant screening and recruitment; 2) molecular testing; 3) protocol flexibility; and 4) availability and delivery of therapies (Table 2) .

Participant screening and recruitment: The realities of conventional screening approaches for clinical drug development are sobering. For a study testing a new candidate drug in a patient sub-population selected by a molecular marker with a 2% incidence, with indicative rates of screening failure (for technical reasons; 15%) and patient drop-out (for clinical reasons; 15%), the trial would need to screen 78 patients to find 1 patient for recruitment, and 77 patients would effectively be discarded. The costs are equally sobering: if screening uses (even just) an existing routine single variable diagnostic approach such as immunohistochemistry (IHC) or a single gene DNA test, each

with an approximate cost of $1,125 US/assay (including assay, processing, logistics and reporting), it would cost $88,235 to screen sufficient numbers to recruit 1 patient to the study. Putting this in context; if we wanted to conduct a 20 patient phase I expansion study in this selected patient sub-population, it would require screening some 1,560 patients, with an associated screening cost of $1.8 million US.

The patient experience is also extremely poor with cycles of disappointment; being first considered for a trial, only then to be ineligible if the marker is not present; the necessity of repeat biopsies for the next marker, and ultimately limited drug options (only those for which a "serial" screen has been possible). The physician experience is similarly poor with limited options other than to keep screening for different markers, and trials, as long as tumour material is available. From a clinical trial operational viewpoint, this is unsustainable.

The need to find sufficient numbers of patients with a specific marker has generated many co-operative study groups (table 1b). Consortia provide multiplexed molecular testing (measuring many markers in one assay) for recruitment 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 "off label" treatment. Such examples include national-level, cross-sector collaborative (including government-based) initiatives such as the NCI-MATCH [47] (for solid tumours) and Lung-MAP [48] (in squamous lung cancer, NCT02154490) programmes in the USA; the SPECTA programmes (SPECTAcolor [49] in colorectal cancer, NCT01723969; SPECTALung [50] in lung cancer; NCT02214134) and the AURORA initiative in Europe [51] (breast cancer, NCT02102165); the LC_SCRUM (and SCRUM-Japan) programmes [52] in Japan; or those lead by cancer specific advocacy and charity organisations eg: The "Know Your Tumour" programme established by the Pancreatic Cancer Action Network in the United States [53]. These models are advancing precision oncology, yet are costly, requiring intermediaries to navigate the patient through the health system. They will be difficult to scale without fundamental changes in health service delivery. Some emerging approaches are driven by the patient and their clinician. These include clinical trials and other therapeutic options as part of a molecular assay report e.g. Foundation ONE® from Foundation Medicine [54]; and connections to further information, consumer-focused advice, community and patient consortia [55]. These approaches cast a broader net to identify smaller and smaller subgroups and identify opportunities for individual patients. More recently, strategies that provide genomic health advice [56] and navigation are gaining traction e.g. Perthera [57]. Others are looking towards electronic media to enable patients and their clinicians to "shop around" for the best option for them. These strategies can significantly improve efficiency and the patient experience. Despite these efforts, trials using a selection marker constitute still only a minority of studies currently underway [58].

A major challenge, once an eligible patient is found is recruiting them onto trial. With the low prevalence of eligible patients, large numbers of sites may need to be opened, at significant cost,

and many may not recruit a single patient. As screening programmes develop, the cost of finding patients shifts from drug developers to health care systems or research platforms. A possible solution is to open trials at a site that is feasible for the patient once they have been identified. This represents a type of "just-in-time" accessibility. The cost of having rapidly deployable teams to establish sites once a patient is found is likely to be less than screening large numbers of patients.

Molecular Testing: While multiplex testing of the coding regions of candidate genes offers some options, the complexity of cancer will require more in depth analyses [59]. The challenges of delivering molecular assays using advanced technologies are well discussed elsewhere [59], however current tests exploit relatively direct relationships between a specific mutation and drug efficacy. Appraising and delivering more complex assays that may better identify responsive subgroups [60,61] is proving difficult despite advances in clinical grade diagnostics [62] mainly due to the rigidity and inertia of entrenched processes for biospecimen handling. Simpler solutions such as liquid biopsies [63,64] are promising, but may lack broad applicability, particularly when complex molecular changes need to be analysed. Technology considerations aside, it is more important to understand the relevance of detected changes/mutations and the body of evidence required to substantiate their use for patient selection. Modern multiplex systems such as next generation sequencing (NGS) technologies reveal unprecedented levels of detail of the molecular changes within a single tumour, many of which may not have been widely reported; some of which are likely to be individual to that tumour (or tumour region), and for most there may be little prior clinical experience or knowledge. How then, do we understand which should inform therapeutic selection? Whilst specific mutations in a particular gene may confer sensitivity to a particular therapeutic, what decision do we make if we find different mutations not previously reported in that gene: can we reasonably expect these to similarly confer therapeutic sensitivity? This is a challenge for trial design and the diagnostic algorithm used to assign patients to treatment. We need to guard against reporting a study as negative based on a lack of clinical benefit seen in a subpopulation defined by mutations of unknown consequence. Although some mutations in a gene may be predictive of clinical benefit, others may not, so we need to accommodate these unknowns. Practical solutions may combine adaptations as above with basket or umbrella trial arms that can examine combinations of markers and therapeutics in isolation, along with diagnostic mutation tiering where mutations of known clinical or functional consequence are weighted differently to those of unknown consequence.

Protocol Flexibility: The administrative aspects and logistical challenges of clinical trials are substantial and impede the ability to nimbly respond to trial findings, particularly if unexpected, or data emerge from elsewhere. Establishing frameworks and platforms for stratified therapeutic development will allow standardisation of within protocol responses to specific scenarios to improve flexibility (table 2)

Availability and Delivery of Therapeutics: Molecular analysis without the prospect of a resulting action is of little benefit. There are still comparatively few opportunities in routine care where multiplexed testing can influence clinical decision-making and access to appropriate therapeutics is still problematic [65]. Negotiating individual clinical trials "ad-hoc" is impractical due to slow legal and administrative processes, and a closer relationship between the pharmaceutical industry and other stakeholders is essential. The collective involvement of multiple pharmaceutical partners to allow availability of a broader range of candidate drugs and appropriate comparator therapies; and wider collaboration between tumour-specific consortia, diagnostic and regulatory groups; major charities and other interested parties will be pivotal. A drug portfolio approach is a necessity, which is negotiated as a broad partnership or through a consortium strategy, and the ability to feasibly deliver the therapeutic through systems such as a centralised pharmacy are essential. The ability to offer patients and their clinicians a broad selection of attractive opportunities, where each patient has a real option, will enhance participation in clinical trials, increasing enrolment from the current dismal low proportion of some 2 to 5% of potentially eligible participants [66,67]. Initiatives such as NCI-MATCH [47], Lung-MAP [48], and the Cancer Research UK Stratified Medicines Initiative and MATRIX National Lung Cancer Trial [68] (EudraCT: 2014-000814-73) have set the precedent but the real value to the patient and healthcare systems will be when this becomes commonplace and encompasses more portfolios of drug development companies to ensure broad availability of developmental (and on market) therapeutics.

We have made advances, but mostly through altering development strategies to fit with established healthcare systems, and progress has been slow. Perhaps it is time to ask if health care systems are out of pace with the science and the development process and as a consequence impeding therapeutic development? Health care systems that can implement precision medicine would greatly facilitate therapeutic development, and accelerating progress will require the adjustment of these systems so that they are aligned and capable to test and deliver precision medicine without the need for costly overlaying clinical trial infrastructure.

Summary

In recent years our understanding of precision therapeutic development has evolved rapidly, and in some areas has progressed from concept to reality. The development of frameworks, platforms and processes involved are significantly enabling modern oncology drug development. A central component of this is innovative clinical trial designs that have facilitated the need to better appraise tumour biology, drug efficacy and patient benefit. New developmental paradigms are emerging, and driving new ways of working collaboratively to accelerate progress. In an evolving era of precision medicine, we have made significant early steps forward in generating truly patient-centric clinical trials and can claim that we are now often able to "select the trial for the patient". However, significant hurdles remain and we need to establish broad frameworks and systems that integrate

closely with health care delivery to accelerate progress and realise the true promise of precision medicine.

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A: Precision Medicine clinical trials

Study	Tumour/s	Phase/Design	Location	Arms[1]	Patients[2]	Clinical Trial ID[3]	Refs
Lung-MAP	Squamous lung	Ph.2/3 randomised	USA	5	10,000	NCT02154490	48
BATTLE	NSCLC	Umbrella – route to 4x Ph.2 randomised		4	300	NCT00409968 (umbrella); NCT00411671 NCT00411632 NCT00410059 NCT00410189	30,69,70
BATTLE-2	NSCLC	Ph.2 randomised		4	450	NCT01248247	-
BATTLE-FL	NSCLC	Ph.2 randomised		4	225	NCT01263782	-
I-SPY 2	Breast cancer	Ph.2 randomised		8	800	NCT01042379	71,72
NCI-MPACT	All	Ph.2 stratified, non-randomised		6	700	NCT01827384	73
NCI-MATCH	Solids	Ph.2 stratified, non-randomised		20	3,000	Umbrella, route to Ph.2[4]	47
V-BASKET	All	Ph.2 stratified, non-randomised	Global	2	160	NCT01524978	74
CREATE	Selected	Ph.2 stratified, non-randomised	EU	6	582	NCT01524926	-
WINTHER	All	Stratified, non-randomised		2	200	NCT01856296	75
SHIVA	All	Ph.2 stratified, controlled	France	10	1,000	NCT01771458	37
MOST	All	Ph.2 stratified, randomised		5	560	NCT02029001	-
SAFIR 02 Lung	NSCLC	Ph.2 stratified, randomised		8	650	NCT02117167	76
SAFIR 02 Breast	Breast cancer	Ph.2 stratified, randomised		18	460	NCT02299999	-
Lung-MATRIX	NSCLC	Ph.2 stratified, non-randomised	UK	21[5]	2,000[6]	EudraCT: 2014-000814-73	68
FOCUS 4	Colorectal cancer	Ph.2/3 randomised		4	643	EudraCT: 2012-005111-12	77
IMPaCT	Pancreatic Cancer	Ph.2 stratified, randomised	Australia	4	90	ACTRN12612000777897	46

B. Screening Programmes – feeders to precision medicine trials

Study	Tumour/s	Phase/Design	Location	Diagnostics	Patients[2]	Clinical Trial ID	Refs
I-SPY	Breast cancer	Ph.2, diagnostic study	US	Genomic, imaging	221	NCT00043017	31-34
NCI-MATCH	Solids	Screening, route to Ph.2		NGS, (IHC/FISH)[7]	3,000	-	47
VIKTORY	Gastric cancer	Screening, route to Ph.2	Asia	NGS, other[8]	600	NCT02299648	-
LC-SCRUM	NSCLC	Screening, route to Ph.2/3		As needed[9]	Open[10]	-	52
AURORA	Breast cancer	Screening, route to Ph.1/2/3	EU	NGS, other[11]	1,300	NCT02102165	51
SPECTAColor	Colorectal cancer	Screening, route to Ph.1/2/3		NGS	2,600	NCT01723969	49
SPECTALung	Lung	Screening, route to Ph.1/2/3		NGS, other		NCT02214134	50
MOSCATO	All	Screening, route to Ph.1/2	France	CGH array, sequencing	1,050	NCT01566019	20
SAFIR 01	Breast cancer	Screening, route to Ph.1/2		CGH, sequencing, gene expression array	423	NCT01414933	76
CRUK SMP1	Selected	Screening, feasibility	UK	Bespoke panel	9,000	-	35

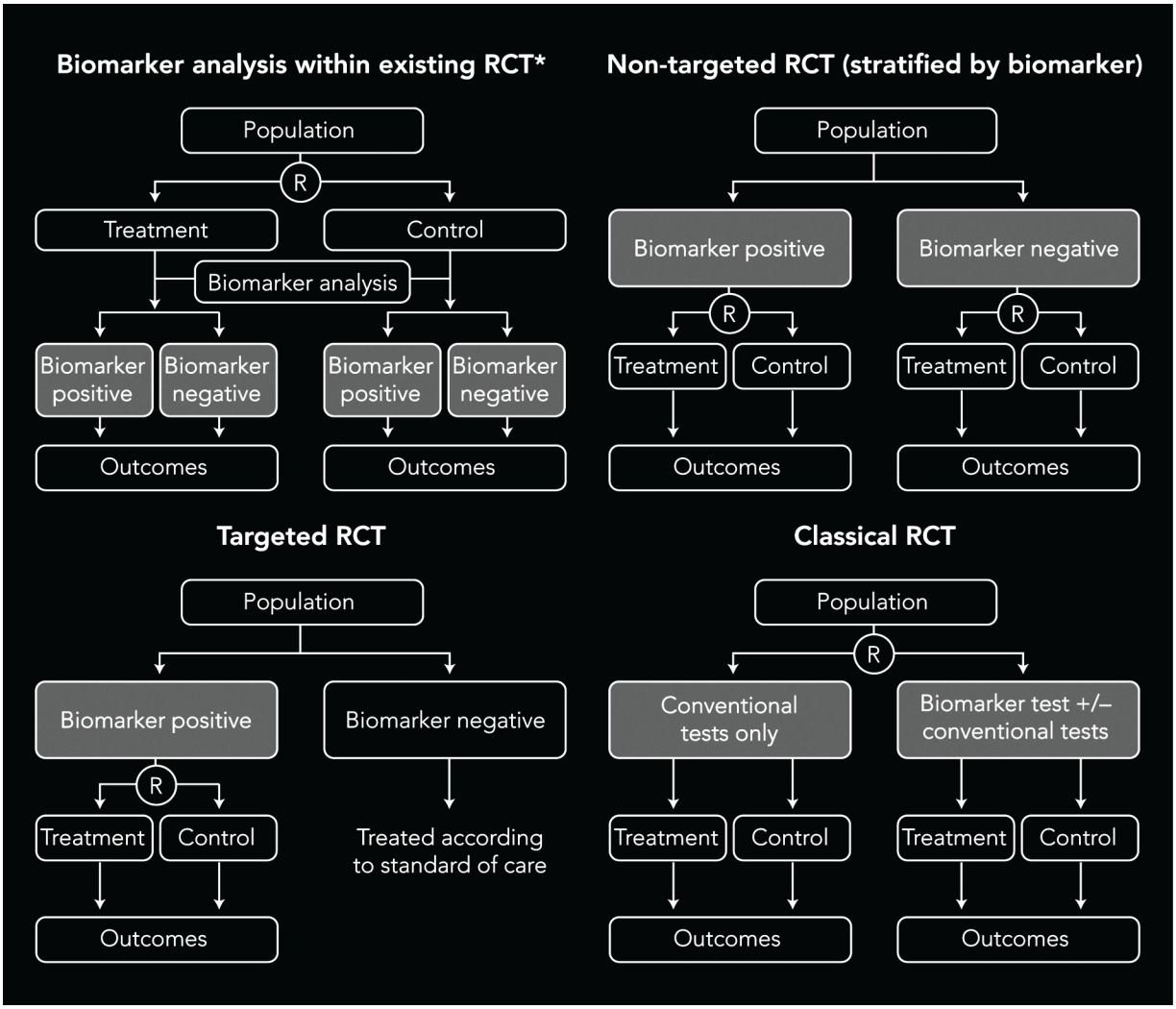
Table 1: Precision medicine studies

Selected examples of a) Precision Medicine clinical trials, and b) Screening Programmes acting as feeders to precision medicine clinical trials (including diagnostic and feasibility studies). Clinical Trial ID - detailed information is available for each study via the ClinicalTrials.gov (NCT) or European Clinical Trials Register (EudraCT) identifier/number. Ph., phase (clinical trial phase 1, 2 or 3); NSCLC, non-small centre lung cancer; NGS, next generation sequencing; IHC, immunohistochemistry; FISH, fluorescent in-situ hybridisation; CGH, comparative genomic hybidisation. [1]Arms – number of experimental arms included in the reported study design, specific details available via the ClinicalTrials.gov identifier; [2]Estimated number of patients to be recruited, or final number recruited where the study has completed; [4]The NCI-MATCH programme is a screening programme used to direct patients to single-arm, phase 2, signal seeking studies; [5]The number of arms will vary as the study progresses, each arm designed around a marker (for patient selection) and (candidate) drug pair; [6]screening 2,000 patients per annum once the study is fully operational; [7]FISH and IHC assays will be used as required; [8]other – a selection of bespoke and exploratory diagnostics; [9]bespoke diagnostics as needed to select patients for the individual clinical studies that feed from the screening programme; [10]an open and rolling programme; [11]other – RNA sequencing (RNA-Seq).

1. Participant screening and recruitment in to trials	
Requires a viable means to identify low incidence subpopulations and direct individuals to an appropriate clinical trial, through a patient-centric approach whereby each individual can have access to many options via the one screening process	• Region-wide and collaborative screening programs • Links to umbrella and basket studies • Links to global studies – with global studies able to accept participants from diverse screening routes • Drug portfolios available – via collaboration – and safeguards for proprietary information when using many partners portfolios • Harmonised and/or cross-validated multiplexed diagnostic platforms and systems – to allow recruitment irrespective of technology • Regulators open to change in how clinical trials need to be run • Networks, collaborations and good partners
2. Molecular testing	
Requires a system (platform, screening/selection algorithm) that enables broad but robust tumour/patient profiling and provides viable development routes for larger/Global studies, regulatory interactions and support for markets	• Platform • Screening/selection algorithm • Broad patient profiling • Sample efficient • Robust data generation • Cost-effective • Transferable, widely deployable • Works to agreed standards • Viable development route • Support regulatory interactions • Support for markets
3. Protocol flexibility	
Requires an early development protocol that is flexible allowing change to emerging science and understanding of patients/tumour markers, and/or a confirmatory development protocol permitting regulatory interactions using different types of datasets	• Single or aligned protocol • Aligned and efficient review – using a centralised Regulatory/Ethics process • Flexible • Modular • Rolling – open ended • Adaptable to emerging science • Allows different datasets to accumulate • Allows regulatory interactions
4. Availability and delivery of therapies	
Requires an operational machinery that allows studies to be conducted over diverse groups and geographical areas with aligned and efficient regulatory and ethics processes, patient screening/recruitment and ability to distribute multiple candidate drugs to multiple sites in a cost-effective and efficient manner	• Hub-and-spoke models • Must accommodate diverse groups and geographical areas • Centralised Pharmacy – to enable cost-effective delivery of multiple drugs to multiple sites • Highly collaborative working – across many different groups • Good partners

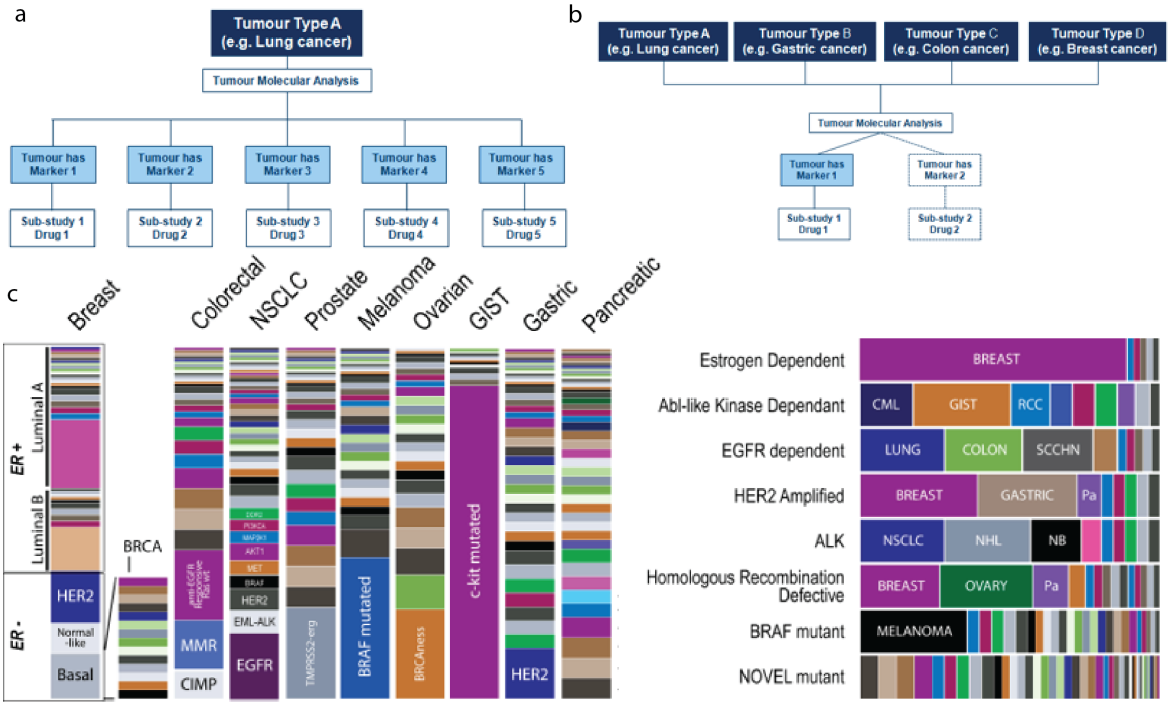
Table 2: Successful delivery of multidrug portfolio studies requires innovation across clinical trial design and implementation; key aspects to consider for diagnostics, clinical protocol and operational delivery.

Figure 1: RCT and Biomarker Driven Designs



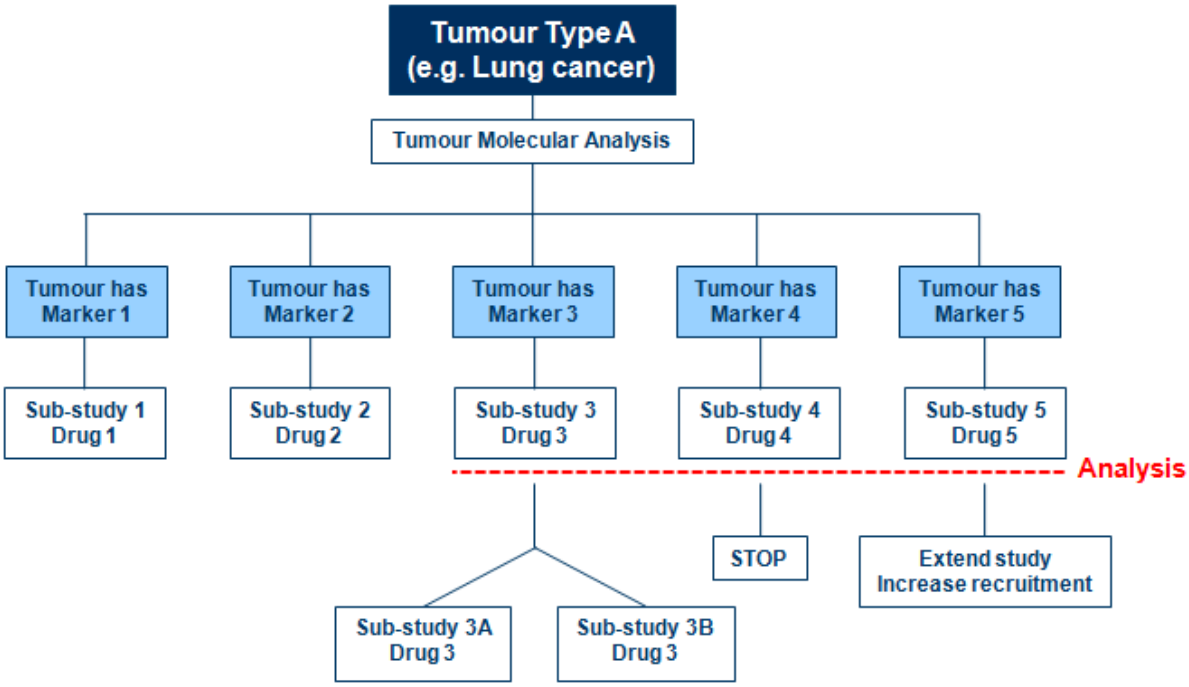
Randomised clinical trial (RCT) designs to define and test precision medicine strategies: a) Biomarker discovery and development within a trial addressing a therapeutic question and patient recruitment or treatment allocation not informed by biomarker status, b) Non-targeted biomarker study where the trial is designed and powered to addres the biomarker hypothesis to ensure adequate biomarker representation and distribution between arms, c) Biomarker targeted RCT where the presence of the selection marker guides recruitment, and d) where the overall concept of the approach can be tested as a whole when biomarker directed therapy is compared to conventional therapy (adapted from Chee et al.).

Figure 2



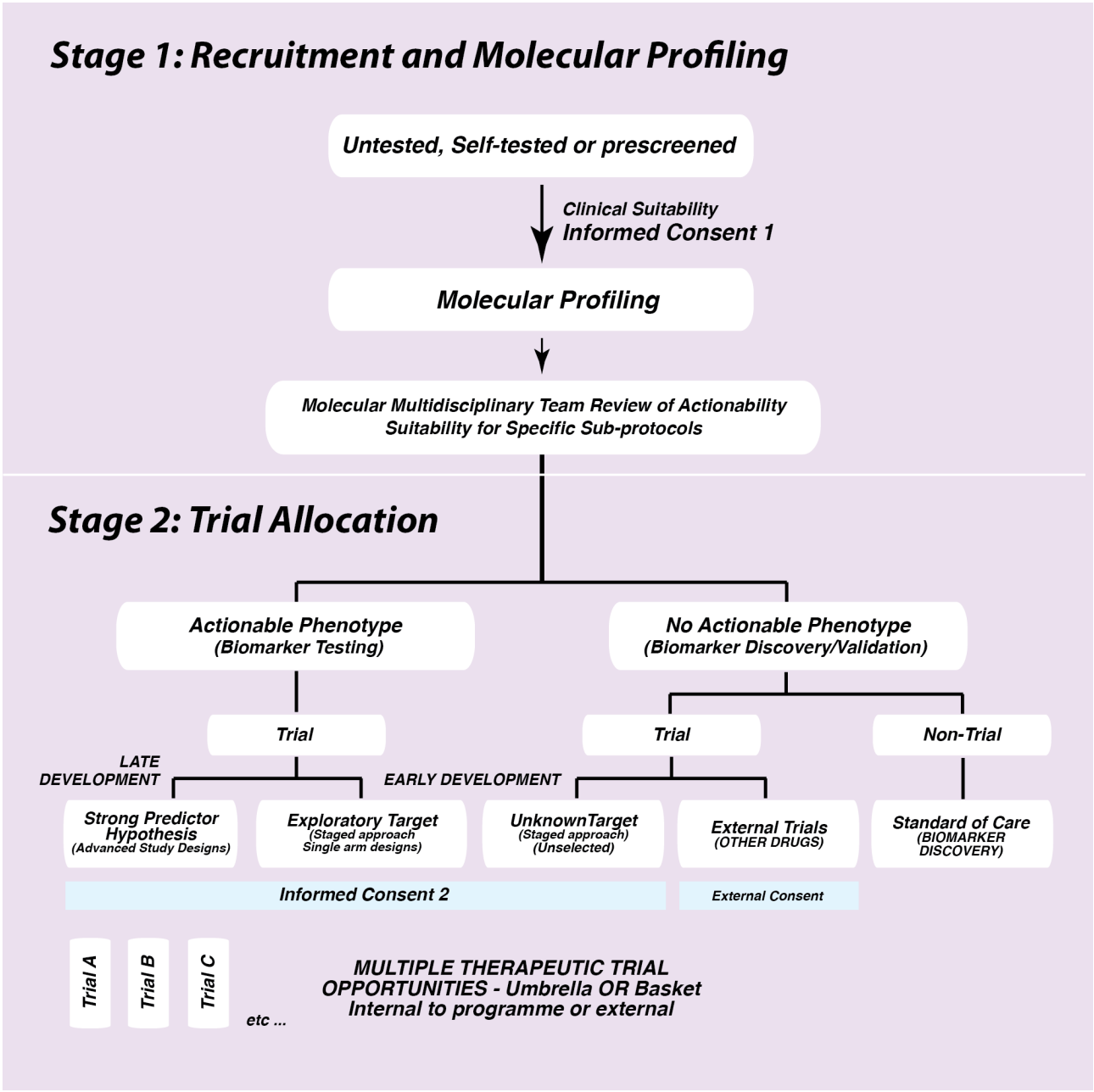
Clinical trial principles that generate efficiencies in clinical trials that tested targeted therapies: a: Umbrella study design – where patients with the same cancer type are assayed for a series of hypothesised predictive markers and allocated to appropriate therapies within the trial architecture. **b: Basket study design** – where participants are recruited based on molecular characteristics irrespective of the organ of origin. **c: Prevalence maps of molecular subtypes within and across cancer types:** The relative incidence of molecular subtypes can help guide decisions as to which clinical trial strategy may be most appropriate when deciding between an "umbrella" or a "basket approach. Left: Molecular subtypes when classified by organ of origin and stratified by molecular subtype. Right: A "biotype" classification based on molecular subtyping and stratified by organ of origin may be more appropriate operationally when the incidence of a specific molecular class is low across different organs of origin and tested with a "basket" approach. (Adapted from ref 76 [78]).

Figure 3



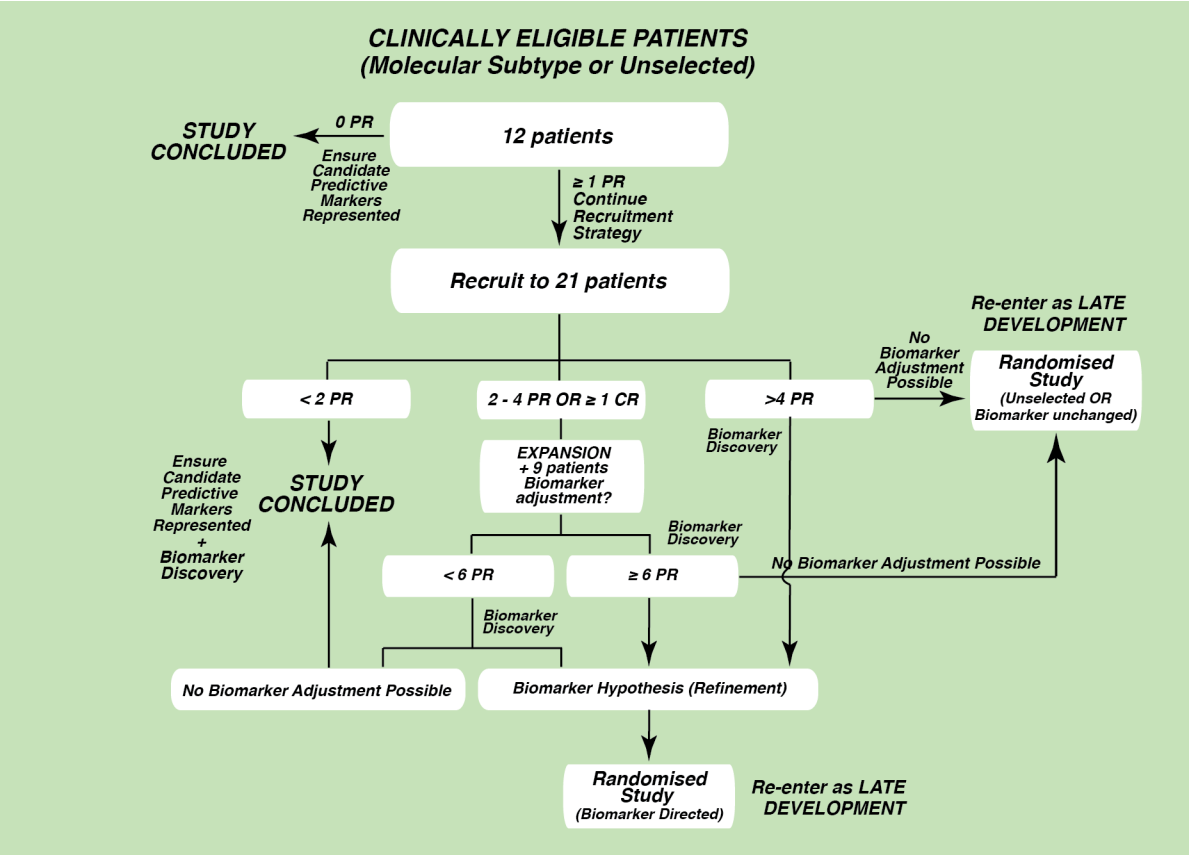
Adaptive study designs - a within study analysis or continual assessment of data is used to change the study course; for example, to stop trial arms on lack of clinical benefit, to extend trial arms to increase numbers for further analysis, or to redefine subpopulations based on responder/non-responder analysis.

Figure 4



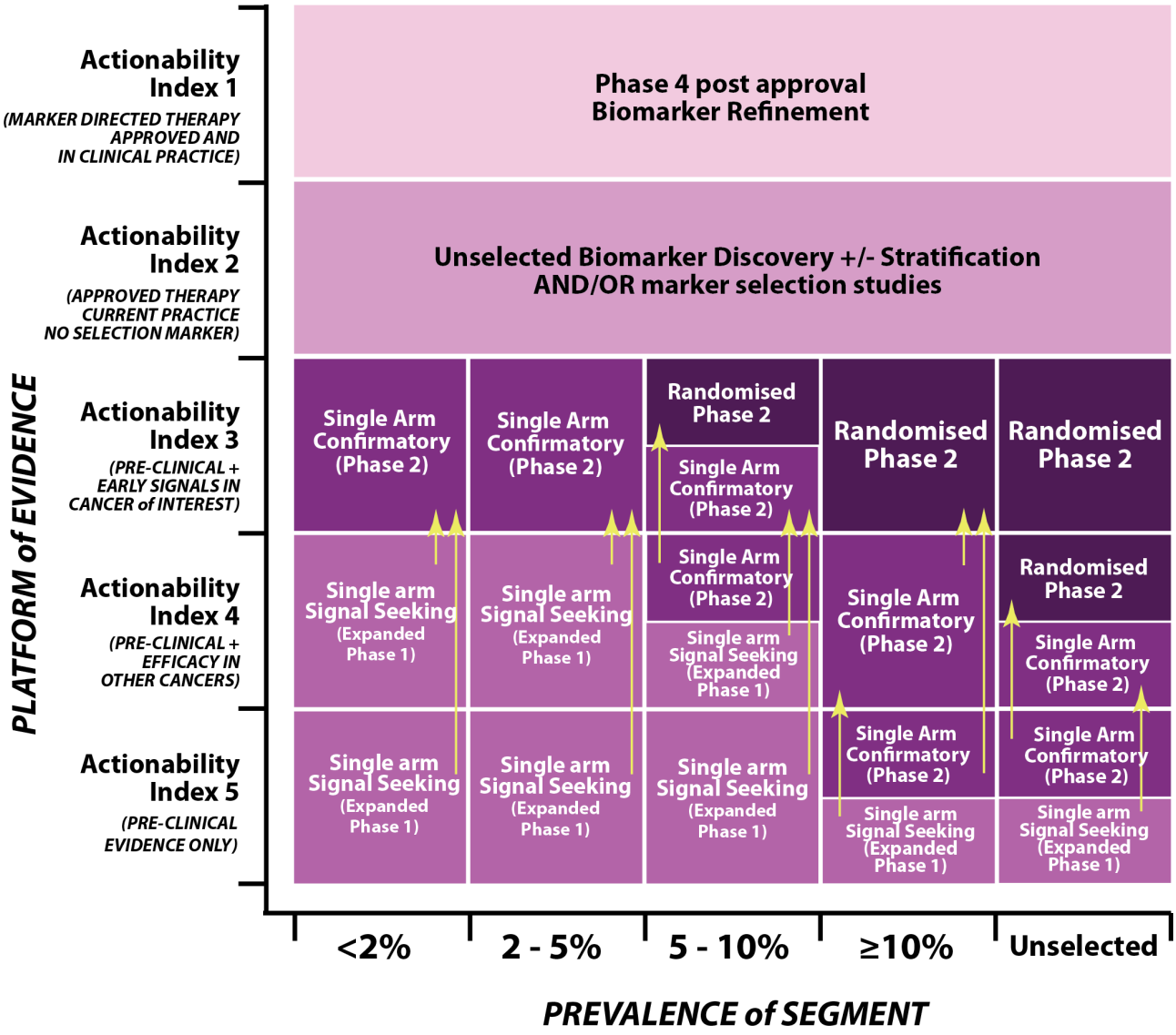
Master protocols for therapeutic development: Example of an overarching schema for clinical testing of precision oncology strategies. The overriding principle is that all patients that are suitable for treatment are offered a choice of therapies, from biomarker directed or unselected novel therapeutic strategies either as part of the structure or for external trials; through to standard of care, where they are still tracked to inform biomarker discovery opportunities for existing approved therapeutics. The strategy could be enacted either under the auspices of a single body or more pragmatically a composite or network of organisations and activities through an agreed co-ordinated management and governance structure. The framework is enacted in 2 stages. Stage 1 includes patient recruitment and molecular testing. Participants can enter either pretested or directed to molecular testing wither within, or by external providers. A series of attractive options are available for patients and clinicians to choose from with a second stage consent process for trials.

Figure 5



Early stratified therapeutic development. A key element is the strategy for early therapeutic development are small trials underpinned by a deep understanding of patient and tumour molecular pathology in order to guide on-going development. A step-wise development approach is used with interim analyses, expansion and molecular assessment at specific points. PR: Partial Response based on RECIST 1.0 criteria [79].

Figure 6



Clinical Testing Strategies. A significant challenge in testing stratified therapeutic strategies is approaching lower prevalence segments and the level of evidence acceptable to embark on later phase studies. This matrix shows a potential overall approach, which is a function of the existing level of evidence, the feasibility of the testing strategy (prevalence of segment) and regulatory requirements. Trials may also progress as the level of evidence increases, and this progression may be built into planned step-wise development process.