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Stratified medicine for cancer therapy

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As knowledge of the biological processes underlying malignant transformation becomes increasingly sophisticated, apparently similar diseases can be redefined according to the critical disrupted biological pathways and networks. The key genetic changes in most cancers can be mapped to one of a relatively few pathways, making it possible to classify tumours by their abnormal pathways and to identify potentially treatable – 'druggable' – targets within these. The aim of the stratified approach to cancer therapy is to improve the effectiveness, tolerability and affordability of novel therapeutic agents.

The model for drug development in cancer is shifting towards 'stratified medicine': the identification of key molecular changes in tumours that can define a sub-population with a high probability of response. There is a rapidly growing list of potential targets, as the expansion of genomic and other high-throughput studies yields ever more detail. The challenge now is to provide diagnostic infrastructure and trial designs that can keep up.

There are two main drivers for the changes in cancer drug development: on the positive side, the torrent of information from molecular and cell biology, in particular the output from genomic studies yielding unprecedented detail on the abnormalities present in cancer cells. The other impetus comes from the relative failure of previous approaches, in which broadly applied therapies for common cancers have yielded treatments of modest utility at great cost. Many companies have migrated, often with reluctance, from the pursuit of drugs for all cases of a particular tumour type, towards the identification of molecular changes in tumours that will define a sub-population with a high probability of response. This selection of therapy based upon the presence of specific target lesions is referred to as stratified medicine [1], although the concept of selection is by no means new, nor unique to oncology. What is relatively recent is the exploitation of specific events in pathogenesis as points for therapeutic intervention. The use of hormone receptor blockade in breast and prostate cancer was based upon interference with normal growth signals, whereas the use of monoclonal antibodies to target cell surface molecules in lymphoma was based upon tissue selectivity. An early signal that exploiting the molecular determinants of malignant transformation might be effective came from the use of all-trans retinoic acid (ATRA) to treat acute promyelocytic leukaemia, where the t(15;17)(q24;q21) translocation results in a hybrid protein including the retinoic acid receptor-alpha, causing abnormal DNA binding [2]. However, it was only with the development of imatinib that a key pathogenic target, the ABL kinase, constitutively activated by the *BCR-ABL* gene fusion in chronic myeloid leukaemia, yielded an effective therapy by blockade of the active site [3]. Imatinib has since been applied to a different clinical indication, following the discovery that gastrointestinal stromal tumours have a high prevalence of c*KIT* gene mutations [4]. It is the shift from tissue-selective to pathogenesis-selective therapy that has driven this field.

It is notable that the key changes in most cancers can be mapped to one of a relatively few pathways, making it possible to classify tumours by the abnormal pathways and to identify 'druggable' targets within these. Initial success came from using monoclonal antibodies to target the cell surface receptors of the epidermal growth factor receptor (EGFR) family, which are at the top of several important cellular signalling pathways, and have been found to be either overexpressed or mutated in a variety of epithelial tumours [5–8]. Subsequently, the downstream signalling apparatus has been a fertile area for the application of small molecule inhibitors, with benefits over conventional chemotherapy agents including oral bioavailability and superior tolerability. To date, the most successful targets have been kinases, although the proteasome, the mammalian target of rapamycin (mTOR), the

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Bcl-2 family of apoptosis modulators and histone deacetylase have also proven fruitful and yielded clinically active drugs.

In this article we discuss recent developments in the field of cancer research, with specific reference to cancer genomics, techniques and molecular pathology. We describe how these discoveries have led to the evolution of the stratified medicine approach, with implications for drug development and clinical trial design in addition to potential obstacles to implementation.

The genomic landscape of cancer

The development of new molecular technologies has driven the rapid pace of discovery in cancer biology. The modern concept of carcinogenesis encompasses genetic and epigenetic changes in addition to the importance of interaction between the tumour, the surrounding microenvironment including the stroma, and the wider immune system.

The clinical description of hereditary cancer predisposition syndromes paved the way for the identification of tumour-initiating and promoting oncogenes and inactivated tumour suppressor genes. Li Fraumeni syndrome is an example in which the clinical features were described in the 1960s; however the causative *TP53* gene mutation leading to abnormal function of the p53 protein product was not identified until the 1990s [9]. The Knudson 'two-hit' hypothesis describes the process of carcinogenesis in a patient with an inherited predisposition syndrome (i.e. germline mutation in one allele of a tumour suppressor gene, followed by a somatic mutation leading to dysfunction of the second allele [10]). Patients with germline tumour predisposition syndromes develop cancer at a younger age than that at which sporadic cancers occur owing to a mutational 'head-start' [11].

Array-based techniques such as array comparative genomic hybridisation (aCGH) enable large-scale evaluation of copy number variation, in terms of gain and loss, across the cancer genome [12]. More recently, copy number assessment has been undertaken using massively parallel paired-end sequencing [13]. Integrated genomics combine aCGH with other methods, such as gene expression profiling to provide additional information about cancer-implicated genes and pathways and generate specific 'gene signatures' as markers for prediction of disease outcome [14].

The sequencing of a rapidly increasing number of whole cancer exomes (all coding regions of the genome) has led to valuable insights into the over-arching themes of key mutations. The commonly observed driver mutations in the cancers sequenced so far appear to cluster within a dozen major intracellular pathways concerned with cell signalling and adhesion, proliferation, metabolism and DNA repair [15–17]. An illustrative example of this is given in Fig. 1. Somatic mutations can be divided into those with gain-of-function dominant activity (i.e. oncogenes) and

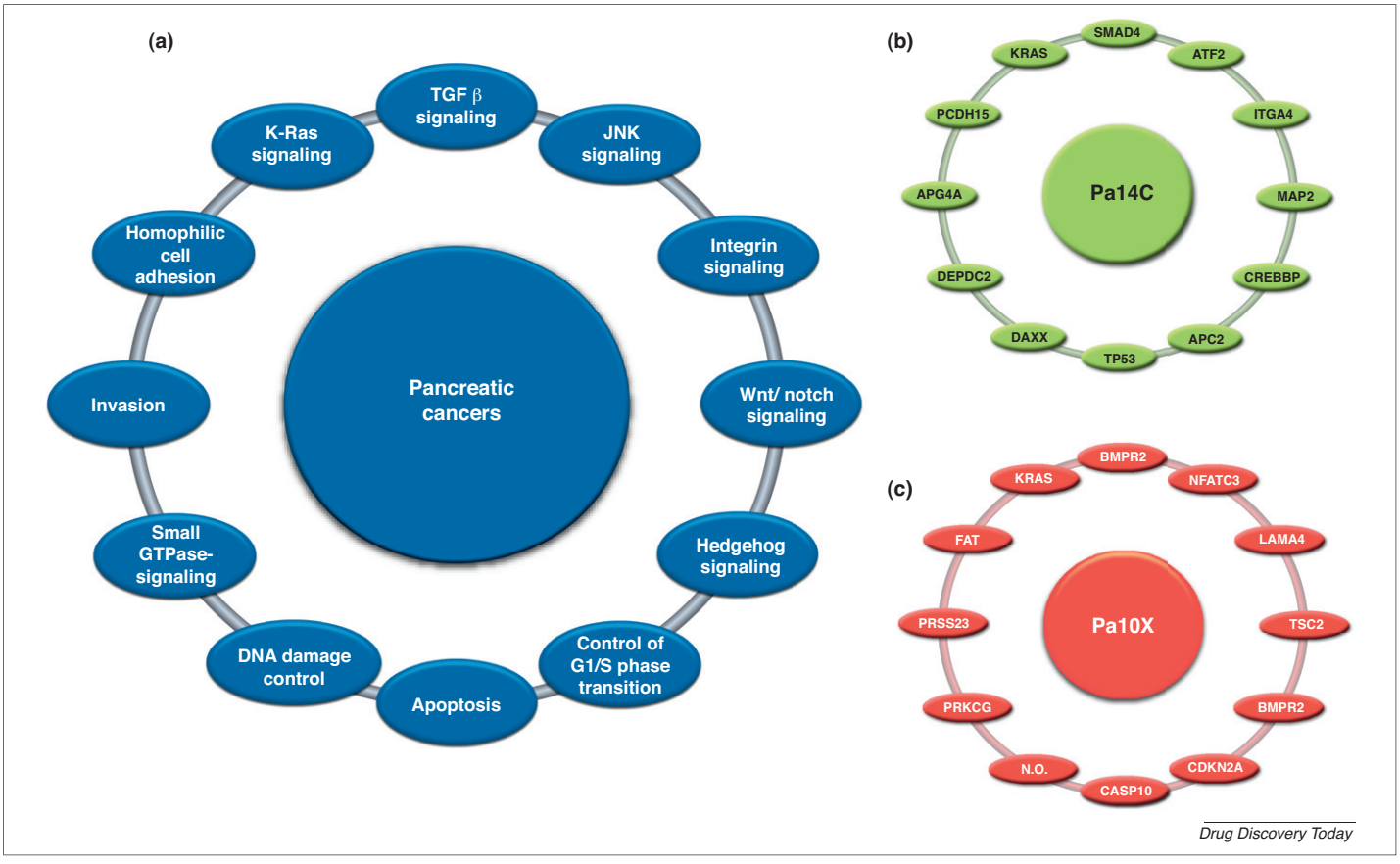

FIGURE 1

A summary of the major disrupted cellular pathways in a series of pancreatic cancers, according to data on genetic abnormalities detected by sequencing, microarrays and transcriptomics **(a)**, with the specific gene alterations discovered in two of the cases mapped in detail (**b**, case Pa14C and **c**, case Pa10X). N.O. = [genetic abnormality] not observed.

Abbreviations: JNK: Jun N-terminal kinases; TGF-β: transforming growth factor-beta.

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those with recessive effects where loss of both alleles of the gene causes loss of tumour-suppressing activity (i.e. tumour suppressor genes). A total of 90% of known somatic mutations discovered to date in over 350 genes are oncogenic and only a minority of 10% affect tumour suppressor genes [18].

MicroRNAs (miRNAs) represent a sub-population of non-coding cellular RNA with regulatory functions including control of gene expression. The first evidence implicating miRNAs in cancer causation was from work on chronic lymphocytic leukaemia, published in 2002 [19]. Since then it has become apparent that regions of the genome coding for miRNAs are frequently hotspots for cancer-associated mutations [20].

Epigenetic changes to DNA and associated histone proteins through acetylation and methylation represent a significant emerging area of interest over the past decade, and have been implicated in the causation and progression of cancer [21]. Epigenetic modification of chromatin occurs through methylation-mediated suppression of gene promoter regions leading to inactivation or 'silencing' of tumour suppressor genes and effects on the function of genes encoding regulatory miRNAs.

Methods for molecular characterisation of tumours

Some of the novel methods and technologies that have contributed to knowledge of tumour biology are summarised in Table 1. The discoveries arising from these approaches are likely to inform the process of disease classification and the selection of therapy in future. The International Cancer Genome Consortium and other large cancer genome sequencing programmes will increasingly catalogue the somatic mutations, gene expression patterns and epigenetic modifications in thousands of human cancer genomes from many different types of cancer [22].

The different levels of study applied to the genome and its output have enabled a greater appreciation of the complexity in the system. For example, the existence of multiple overlapping alternative reading frames within the genome [23] and alternative splicing and post-transcriptional modification of proteins through

TABLE 1

A summary of selected techniques used to examine cancer biology

Level of approach	Methods	Description	Example of application [Refs]
Genomic (DNA)	Gene mutation analysis by various methods including targeted sequencing	Identification of therapy sensitising and resistance mutations in tumour specimens	*EGFR* and *KRAS* gene status in lung and colorectal adenocarcinoma respectively [5,24]
	Exome and whole genome sequencing	Characterisation of entire protein coding region or entire genome using Sanger sequencing, next generation or third generation (single molecule) sequencing	Detection of novel gene and pathway abnormalities to understand pathogenesis and identify potential therapeutic targets e.g. identification of *IDH1* gene mutations in a series of glioblastomas [25]
Epigenetic (DNA modification and regulation)	Methylation profiling	Methylation-specific arrays, bisulphite pyrosequencing	Genome-wide DNA methylation profiling to provide evidence of progression from pre-cancerous through pre-invasive to invasive lesions [26]
	miRNA profiling	Profiling of subgroup of non-coding RNA molecules with regulatory functions including control of gene expression	e.g. discovery of frequent deletion of specific miRNA coding genes in chronic lymphocytic leukaemia [19]
Transcriptomic (mRNA)	Gene expression profiling	Profiling of gene expression levels using microarrays to quantify mRNA levels	Molecular classification of breast cancers [27] Molecular subtyping of diffuse large B cell lymphoma [28]
	Transcriptome sequencing	Characterisation of all RNA molecules within a sample: 'RNA-seq'	Information about gene expression levels and alternative splice variants, e.g. discovery of *FOXL2* gene mutation in granulosa cell tumour of the ovary [29]
Proteomic (Protein)	Electrophoresis and mass spectrometry	Analysis of the protein profile of a cell, organ tissue or entire organism in order to determine protein expression by the genome	e.g. mapping the core protein signalling network of the Bcr-Abl oncogenic fusion protein [30]
Metabolomic (Metabolic products)	Gas/liquid chromatography; mass spectrometry NMR spectroscopy	Quantification of the endogenous metabolite content of cells/tissues/body fluids	Research into markers of renal cell carcinoma in urine [31]
Kinome profiling (Protein phosphorylation)	Various including fluorescence-activated cell sorting (FACS), short interfering (si)RNA screens, peptide array- and mass spectroscopy	Study of protein phosphorylating enzymes	Identification of potential new therapeutic targets in breast cancer [32]

glycosylation or phosphorylation, lead to a human protein complement that is far more diverse than predicted from earlier interpretations of the genome, where one gene was presumed to code for one protein.

Drugs targeting molecular changes in cancer

The most tractable targets for small molecule inhibition have proven to be the kinase enzymes, in which the active sites are often mutated in epithelial tumours and serve as an excellent target for therapy. A large number of inhibitors of greater or lesser specificity have been developed and in some cases licensed for routine use. Many of them have significant oral bioavailability. Other potential targets such as the Bcl-2 family members that modulate apoptosis have also been targeted with some success, whereas potent targets such as cMYC or K-RAS have proven more difficult to modulate.

Protein kinases catalyse the phosphorylation of cellular proteins, an essential regulatory function responsible for controlling cell signalling in addition to other key cellular activities. Although more than 500 different human protein kinases have been identified to date [33], the two main classes are receptor kinases (acting at the cell surface in association with trans-membrane receptors) and non-receptor kinases (acting in the cell cytoplasm, nucleus or internal aspect of the cell membrane at downstream sites). Examples of kinase inhibitors in clinical use are given in Table 2. Protein phosphorylation occurs mainly at serine, threonine and tyrosine residues and kinases can be broadly subdivided according to these differing sites of action. Tyrosine kinase receptors and their function can be disrupted in several ways during carcinogenesis [34]:

(i) A balanced chromosomal translocation leading to a fusion protein that produces constitutive tyrosine kinase activation (e.g. BCR-ABL fusion in chronic myeloid leukaemia). This type of abnormality is particularly common in haematological malignancies.

(ii) Mutations leading to alteration of kinase autoregulation (e.g. point mutations in the EGFR kinase domain leading to increased receptor sensitivity to ligand binding in pulmonary adenocarcinoma).

(iii) Changes in levels of expression [e.g. amplification of the gene encoding the human epidermal receptor 2 (HER2) in carcinoma of the breast leading to HER2 over-expression and conferring sensitivity to anti-HER2 trastuzumab therapy].

(iv) Decreased inhibitory factors leading to increased tyrosine kinase activity (e.g. silencing of the cytokine signalling-1 gene in acute myeloid leukaemia by hypermethylation [35]).

Therapeutic tyrosine kinase inhibition can be achieved directly by small molecules, or by inhibition of dimerisation through antibody binding, ligand neutralisation and receptor internalisation [34]. Inhibitors of heat shock proteins (e.g. Hsp90) can adversely affect receptor stability and impair protein binding, and this approach has received interest as a method of overcoming resistance to tyrosine kinase inhibitors [36].

The EGFR tyrosine kinase inhibitors gefitinib and erlotinib have led the way for the adoption of stratified medicine in malignancies of epithelial origin. Gefitinib was licensed for use in advanced *EGFR*-mutated non-small cell lung carcinoma after its superiority over dual-agent standard first-line chemotherapy was demonstrated in the IPASS (IRESSA Pan-Asia Study) Phase III trial [37]. Erlotinib has also demonstrated a benefit in overall and progression-free survival in randomised clinical trials in non-small cell lung cancer [38] but in the UK has only received approval from the National Institute for Health and Clinical Excellence (NICE) for use as second-line therapy in place of docetaxel [39].

The United States Food and Drug Administration (US FDA) has recently approved the use of both vemurafenib for *BRAF* mutant metastatic malignant melanoma [40,41] and crizotinib for *ALK*-translocated in non-small cell lung cancer. In the case of crizotinib, this approval was granted unusually early and before data was available from Phase III trials [42].

The mTOR is a serine/threonine kinase, which represents a key cellular protein involved in cell growth and survival. An mTOR inhibitor, temsirolimus, is licensed by the FDA for use in renal cell carcinoma. A second generation of mTOR inhibitors currently in development are targeted at the C1 and C2 catalytic subunits of mTOR [43].

TABLE 2

Examples of kinase inhibitors in clinical use

Cellular targets	Drugs	Clinical utility [Refs]
ABL **c-KIT** **PDGFR**	Imatinib Dasatinib Nilotinib	Chronic myeloid leukaemia [44] Gastrointestinal stromal tumour [45]
BRAF	Vemurafenib Sorafenib	Metastatic malignant melanoma [40,41]
EGFR	Erlotinib Gefitinib	Pulmonary adenocarcinoma [37–39]
ALK	Crizotinib	Pulmonary adenocarcinoma [42]
PDGFR **CD117/c-KIT** **VEGFR**	Sunitinib	Imatinib-resistant GIST [45,46] Renal cell carcinoma [47]
mTOR	Everolimus	Renal cell carcinoma [48]

Synthetic lethality as an approach to cancer therapy

The recognition that the *BRCA* inherited cancer susceptibility genes modulate homologous-recombination DNA repair led to the suggestion that in patients with one germline mutated copy, tumours with loss of the wild-type allele would be substantially more sensitive to inhibition of alternative pathways of DNA repair [49,50]. The repair of DNA single-strand breaks through the repair of base excisions is mediated by poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1, and inhibition of this by drugs such as olaparib yielded promising early results, not only in those with germline mutations [51] but also some tumours with acquired allelic loss [52]. However, recent trials of PARP inhibitors have failed to demonstrate a convincing treatment response in patients with germline *BRCA* gene mutations and epithelial ovarian cancer, hinting at further complexities, such as somatic mutations causing restoration of BRCA activity and therefore PARP inhibitor resistance [53]. AstraZeneca (http://www.astrazeneca.co.uk/) have since announced that olaparib will not enter Phase III trial development, despite a randomised Phase II study in recurrent ovarian cancer showing an increase in time to progression, but which did not translate into improved overall survival.

The approach of targeting synthetic sickness and/or lethality, is now being explored using the broader approaches of functional screening with RNAi or chemical compound libraries. These are beginning to yield a range of other therapeutic possibilities, where functional dependence of cancer cells upon specific patterns of expression or mutation permits the targeting of the compensatory or buffering mechanisms [54]. Recent examples of this include the identification of interaction between DNA mismatch repair proteins and proofreading DNA polymerases [55], and between EGFR and Notch signalling pathways [56].

Pharmacogenomics and cancer

Several genetic polymorphisms have been identified during recent years that are associated with varying responses to chemotherapy drugs, although to date these have not been widely exploited in routine oncology practice. Polymorphisms occur in the *CYP2D6* gene encoding cytochrome P450 2D6 isoform, the enzyme that catalyses the conversion of tamoxifen to its active metabolite, resulting in differential drug responses among treated patients [57]. Germline variants might also be influential in the prediction of toxicity, as in the case of polymorphisms in the *UGT1A1* gene. The *UGT1A1*28* variant has been found to cause impaired hepatic elimination of the topoisomerase I inhibitor irinotecan, used in metastatic colorectal cancer, thus predisposing to toxicity [58].

In the case of some recently licensed drugs, efforts have been made following approval to further refine prediction of likely response. For example, response to pazopanib, an angiogenesis inhibitor licensed in the USA for use in advanced renal cell carcinoma, has recently been linked to germline single nucleotide polymorphisms (SNPs) in genes linked to its metabolism and mode of action [59].

Implementation of stratified cancer medicine

The current conception of stratified cancer medicine relies on the characterisation of disease by specific molecular markers. These can be broadly classified as diagnostic, prognostic or predictive in nature. Diagnostic markers are used to support and refine a histopathological diagnosis, for example the detection of characteristic gene rearrangements in soft tissue tumours and sarcomas. Prognostic markers enable prediction of treatment outcomes including the probability of recurrence, distant dissemination or overall survival. An example of this would be assessment of the proliferation rate in a malignant melanoma, which can be correlated to overall survival [60]. These markers can be used to inform treatment decisions in groups of patients of differing prognosis, where the risk to potential benefit ratio of adjuvant treatments such as chemotherapy will vary. Predictive markers could be used to give an indication of the likelihood of therapeutic response or toxicity in a patient exposed to a particular therapy. An example of this is oestrogen receptor (ER) expression in breast cancer as a predictor of response to tamoxifen therapy.

There remain important potential obstacles to the stratified medicine approach, particularly inter- and intra-tumoural heterogeneity. Between different tumours, there are a multitude of possible gene mutations within the same pathway and although certain mutation 'hotspots' do occur, to a certain extent the mutations are 'private' to each tumour [61]. It is also apparent that genomic instability is a characteristic of high-grade malignancies [18] and thus the overall number of mutations is greater, with multiple subclones present in the tumour acting as potential reservoirs of mutations conferring primary drug resistance [62]. This complex biological phenomenon also confounds prediction of the overall clinical behaviour, as illustrated in a recent case report describing the presence of two distinct *KRAS* gene mutations present not only in morphologically different areas of a primary colorectal cancer but in two associated local lymph node metastases [63].

These subtleties highlight the problem of designing assays for mutation detection that maximise sensitivity while somehow identifying only significant genetic changes that are likely to influence the overall biological behaviour of a tumour rather than minor sub-clones. This demonstrates the importance of linking detected mutations to patient outcome data using robust outcome markers in clinical trials.

Pathway redundancy and the presence of naturally occurring 'escape variants' in a tumour can limit the effectiveness and duration of response of some of these agents. Tyrosine kinase inhibitors produce dramatic results in some patients, suggesting that the targeted mutation represents part of a single critical pathway, a situation described as 'oncogene addiction'. However more commonly, pathway redundancy is observed, where the therapeutic response is not sustained reflecting a switch within the tumour to alternative signalling and proliferation pathways and networks [64].

Mutational context appears to be important in predicting drug response, necessitating assessment of abnormalities in more than one gene or pathway to fully understand response the effect of a particular agent. For example, in a study of the use of EGFR tyrosine kinase inhibitors in glioblastoma, response was correlated to immunohistochemical co-expression of phosphatase and tensin homologue deleted in chromosome 10 (PTEN) and EGFR mutant deletion variant III (EGFRvIII) but not to *EGFR* gene amplification as assessed by fluorescent *in situ* hybridisation (FISH) [65]. EGFRvIII is a constitutively active deletion variant of EGFR that has been demonstrated to cause persistent activation of the phosphatidylinositol 3′ kinase (PI3K) signalling pathway, demonstrating oncogene addiction and conferring sensitivity to tyrosine kinase inhibitors. The PTEN tumour suppressor protein, which is commonly absent in glioblastomas, inhibits the PI3K pathway. There is evidence that loss of PTEN confers resistance to tyrosine kinase inhibitors since the action of the latter relies on the interaction with downstream PI3K signalling. These interdependent receptor–pathway interactions explain why response to EGFR inhibition is dependent on EGFRvIII and PTEN.

Practical considerations also have a significant impact on the success of the stratified medicine approach. Obtaining tumour tissue for the purposes of clinical trials, drug development or diagnostic testing with suitable preservation for nucleic acid-based detection methods represents a significant challenge for diagnostic histopathology laboratories. Conventional tissue fixation methods employ formalin, and this causes extensive fragmentation and cross-linking of DNA. This damage renders the DNA suboptimal for modern techniques, particularly whole-genome sequencing, and can cause technical artefacts, such as over-representation of certain sequences within the genome [66]. An alternative to testing formalin-fixed material is the provision of snap-frozen fresh tissue, but it is impractical to assume that this can

form a part of routine practice. Techniques such as interphase FISH can be performed to good effect on formalin-fixed paraffin embedded tissue sections, and RNA of sufficient quality for diagnostic reverse-transcriptase polymerase chain reaction (RT-PCR) can also be extracted [67]. Molecular mutation detection techniques can also be applied to malignant cells present in cytology specimens using sections from cell blocks prepared from spun samples embedded in paraffin wax [68]. This is of particular relevance to patients with lung cancer where the procedures to obtain samples are challenging, and opens up the possibility of using samples obtained by fine needle aspiration of pleural effusions, lymph nodes or through the endobronchial route with ultrasound guidance.

Apart from the biological and logistic considerations, progress in the implementation of stratified cancer medicine is also held back a lack of infrastructure for molecular diagnostics in many healthcare systems [69]. In general provision remains heterogeneous, with a mixture of public healthcare, academic and commercial laboratories, and often a there is no connection between reimbursement of the drugs and the diagnostic tests required for their appropriate use. This difficulty is worsened by the low frequency of some of the molecular targets being sought, requiring the screening of large numbers of tumours to reach a small number of patients.

Implications for clinical trial design

The overall aim of the 'stratified' approach to cancer therapy is to improve the effectiveness, tolerability and affordability of novel therapeutic agents by using one or more molecular markers to identify before treatment groups of patients for whom benefit appears more likely, thus reducing unnecessary toxicity to those who lack the marker for predicted response. The recognition of such predictive markers represents a new driving force in clinical trial design, with multi-stage, multi-arm adaptive approaches aiming to streamline and accelerate the evaluation and approval of novel therapeutic agents. The adaptive trial design enables for modification of different arms of the trial according to the progress of different molecularly-defined cohorts of patients throughout the study period. The principle is that creating sub-groups stratified according to the presence of relevant biological predictors close to the point of trial entry maximises the chances of demonstrating a response, and reduces the size of the cohort of patients necessary to demonstrate an effect. This has also led to a trend towards submission of companion molecular diagnostic products for approval with the drug, as in the case of several recent FDA decisions [FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268241.htm; FDA approves Xalkori with companion diagnostic for a type of late-stage lung cancer: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269856.htm]. It is clear that the complexities of cancer genomics are still being elucidated, and it is important to establish and maintain stringent quality control procedures for testing for the future when mutation testing in cancer becomes part of routine care.

Increased collaboration between drug companies is likely to be required, as the effect of combination drug therapy on cellular targets is explored through clinical trials. The use of several drugs at a time could improve the duration of response to targeted therapy and also demonstrate efficacy in a greater number of drugs. Novel surrogate endpoints are likely to be required to assess treatment response but should be interpreted where possible with reference to more traditional endpoints in addition to patient reported outcome measures. Biomarker identification and understanding of treatment effects can be facilitated by repeat biopsies during therapy, and this is another factor that could become increasingly common in protocols for future trials, for example the I-SPY2 breast cancer trial which is currently underway in the USA [69I-SPY 2 trial: Neoadjuvant and personlized adaptive novel agents to treat breast cancer: http://ispy2.org/]. There might also be a role for retrospective analysis of clinical trials for drugs that have failed during development, to identify sub-groups in whom benefit might have been masked when analysed as part of the larger cohort [70].

Stratified medicine initiatives

Worldwide, several large-scale initiatives are in progress to investigate the stratified medicine approach to cancer care and to create a structure for testing tumour DNA and funding the relevant therapies. In France, The National Programme in Cancer Genomics was initiated in 2006 and is overseen by The Institut National de Cancer (INCa). This provides centralised funding to cover the cost of targeted tumour gene mutation testing in a range of laboratories. Large institutions in the USA such as MD Anderson Cancer Center and Massachusetts General Hospital Cancer Center have set up similar tumour molecular profiling programmes. In the UK, the Cancer Research UK Stratified Medicines Programme has just been launched in conjunction with Astra Zeneca and Pfizer (http://www.pfizer.co.uk/default.aspx), the UK Technology Strategy Board and Department of Health. A pilot study involves obtaining prospective consent from 9000 cancer patients to collect routine clinical diagnostic, treatment and outcome data and perform DNA mutation testing on tumour samples for several genes associated with therapies that are either licensed or in development.

Concluding remarks

This is a rapidly evolving field both in terms of biological understanding and technological progress (Table 3). Next generation sequencing techniques will undoubtedly have a key role in the near future, enabling detailed interrogation and characterisation of the whole genome. Affordable whole-genome sequencing is coming rapidly closer. The challenges presented by this deluge of genomic information will include sorting key 'driver' mutations from bystander 'passenger' mutations to target new treatments at the molecular root causes and driving forces behind cancer pathogenesis. Complex bioinformatics will have a prominent role in the post-genomic era of cancer management, and data handling capacity in addition to the number and availability of expert bioinformaticians will need to substantially increase to support progress.

One vision for the future of cancer medicine is to undertake molecular profiling of a tumour biopsy before selecting several therapeutic agents with predicted benefit according to the key driver mutations identified in the tumour. The available data from clinical trials to date suggests that while responses to appropriately targeted agents can be dramatic, tumours are quick to undergo

TABLE 3

Supplementary information relevant to stratified medicine

Type of information	Details	Link
The Cancer Genome Project, including the COSMIC database	Cancer genome database curated by the Wellcome Trust, Sanger Institute, Cambridge	http://www.sanger.ac.uk/genetics/CGP/
International Cancer Genome Consortium (ICGC)	International collaboration to document genomic, transcriptomic and epigenomic changes in 50 common human cancer subtypes	http://www.icgc.org/
I-SPY 2 Breast Cancer Trial	Current adaptive, randomised Phase II clinical trial involving multiple treatment regimes, serial tumour biopsies and molecular profiling	http://ispy2.org/
UK NEQAS	Organisation providing external quality assurance in UK laboratory medicine	http://www.ukneqas.org.uk/
The Biomarkers Consortium	A biomedical research partnership managed by the Foundation for the National Institutes of Health and collating information on emerging biomarkers	http://www.biomarkersconsortium.org/
Cancer Research UK Stratified Medicine Programme	Current two-year pilot study of routine provision of tumour mutation testing for cancer patients receiving treatment in the NHS	http://science.cancerresearchuk.org/research/how-we-deliver-our-research/others/by-programme/stratified-medicine-programme/

genomic evolution by further mutation or pathway redundancy and therefore responses can be short-lived.

Despite these considerations it does not seem unrealistic to anticipate the integration of a panel of molecular tests into the clinical practice of cancer diagnosis and management in the near future. This will require a solid evidence base to increase the awareness and acceptability of these techniques to oncologists, pathologists, patients and policymakers, among others.

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