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Cancer clinical trials

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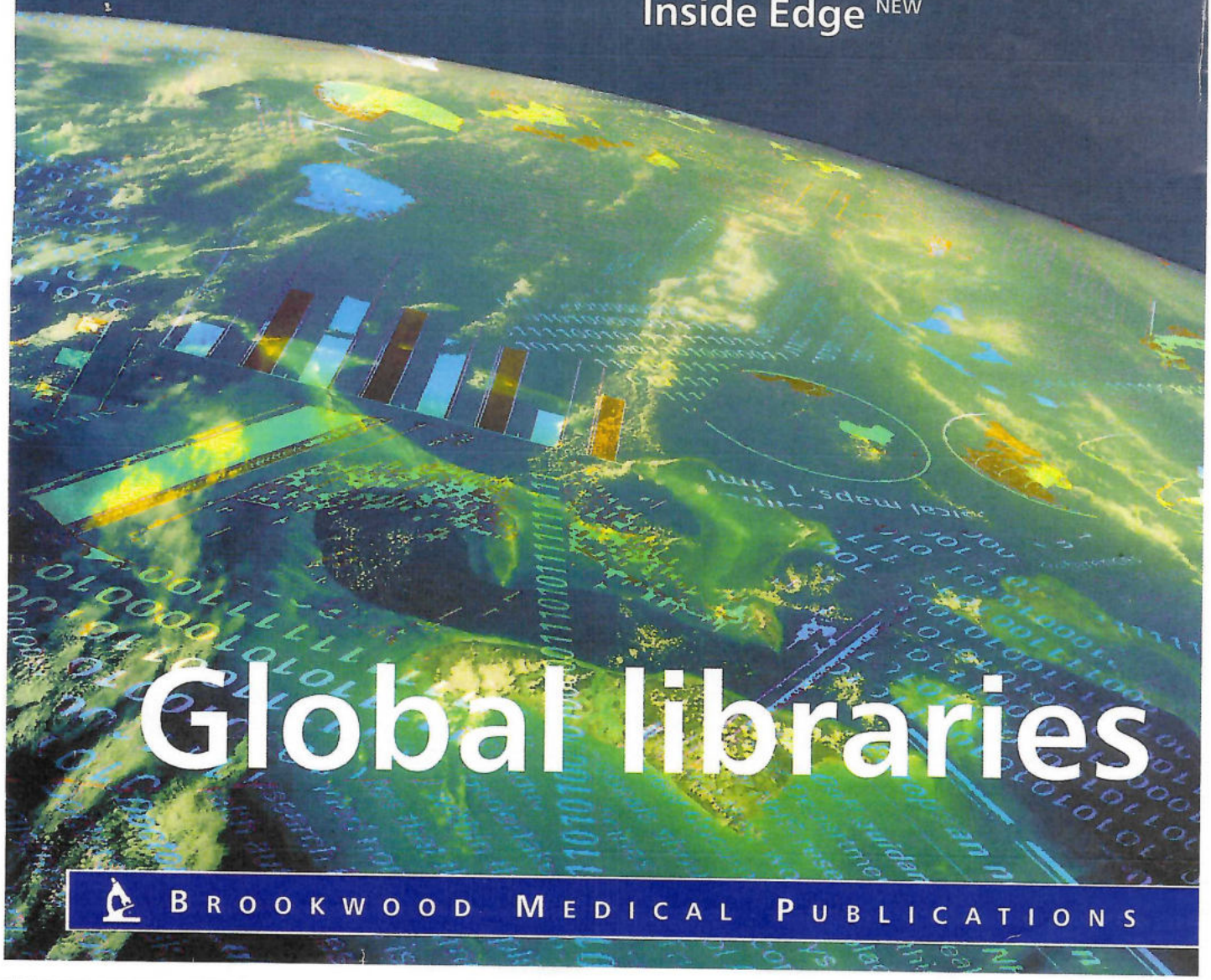

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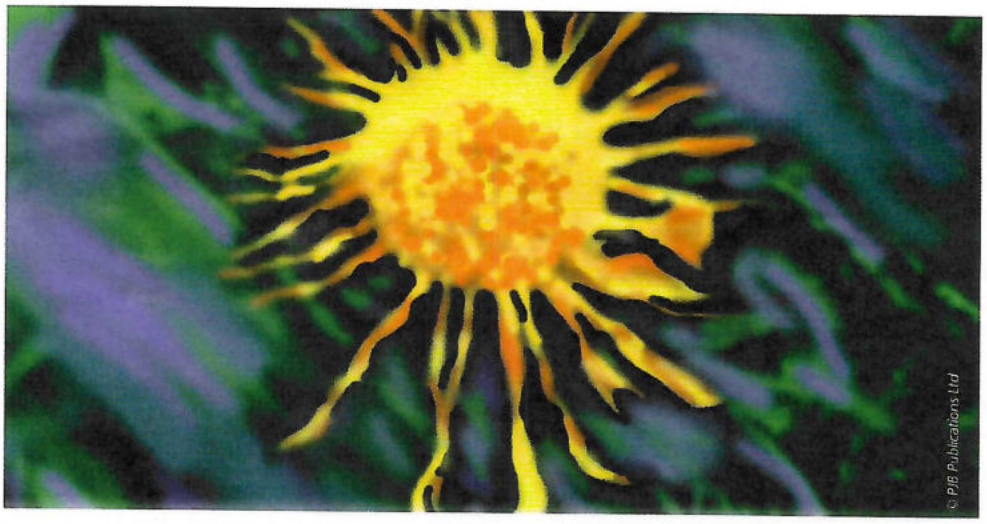
The challenges of cancer clinical trial patient enrolment



Oncology clinical trials are poised to benefit from novel approaches to patient recruitment. Efforts that address psychosocial, financial and biological barriers to clinical trial participation are designed to facilitate efficient clinical development. This in turn leads to rapid approval of drugs evaluated under fast track review by the FDA in the United States and other regulatory agencies around the world.

Noah Berkowitz, MD, PhD and **Anu Saad**, PhD present the obstacles and solutions of oncology research and development, in particular patient recruitment and enrolment.

The accelerated pace of genomic discovery and the industrialisation of drug development, while recognised as an invaluable strategic weapon for the pharmaceutical industry, is behaving like a double-edged sword. The industry is seeing many new drug candidates fill its pipeline, yet it is finding that these candidates cannot be moved through the clinical development stage at a pace adequate to prevent a backlog of projects. The therapeutic area of cancer is certainly a high-profile area of study and, possibly, the most affected by this development conundrum. The global pharmaceutical industry generates 14% of its revenue from drugs designed to cure or palliate cancer. The ageing of the 'baby boomer' population in the United States has created a strong political and social framework for the promotion of increased research and development of cancer therapeutics. Responding to these forces, the pharmaceutical industry has pushed so many drugs to the advanced stage of clinical development, that more than 800 cancer drugs will be tested during the next five years. With more than 180 pharmaceutical products awaiting marketing approval by the FDA in the United States, cancer is reported to be the therapeutic category with the most pending applications. An important phenomenon observed in recent years is that some cancer drugs languish in review for several years, pending the collection of more comprehensive safety and efficacy data. The one greatest barrier to data collection is anaemic clinical trial, namely subject enrolment.

Obstacles to patient enrolment

It is reported that fewer than 3% of adult cancer patients elect to participate in oncology drug trials,

while as many as 20% may be eligible. These statistics become even more disappointing in the appropriate context. Cancer is a therapeutic area that boasts few *curative*, ethical pharmaceuticals. Most drugs in this area are simply palliative. Specifically, with the exception of haematological malignancies and rare germ cell tumours, one cannot identify a single type of solid tumour that can be cured by current therapies. Consequently, the most common killer of Americans after heart disease has concocted a tragic irony. On one hand, it is under attack by the largest cohort of drug candidates in memory, advancing through the drug development pipeline. On the other hand, the disease finds protection in the inability of pharmaceutical companies to test these candidates rapidly and effectively. One of the public health requirements, therefore, for the advancement of cancer research is to break down the obstacles to patient recruitment.

Low patient enrolment on cancer clinical trials may be attributable to multiple factors. For practicality, these factors tend to fall into a variety of descriptive categories: behavioural/social, epidemiological and biological.

At the crux of the behavioural/social issues that impede patient recruitment are the attitudes of patients and their physicians. As is true in all areas of healthcare, patients have grown to expect certainty from their physicians. They want to know their diagnosis and prognosis and to consider a physician's recommendations. Randomised clinical trials that offer patients two treatment arms in a comparative mode frustrate both patients seeking certainty and physicians trained to respond to patient needs. Physicians are often uncomfortable recommending a study in which the best therapy is unknown as it portrays them as 'unknowing'. Other issues that influence physician recommendations and patient choices are economic in nature. For most physicians in the United States, practising in non-capitated markets, treatment on clinical trials means lost revenue to the medical oncologist. This conflict of interest created by the reimbursement structure, which allows oncologists to purchase drugs wholesale and resell them retail to insurance plans covering the care of patients being prescribed those drugs by their own physicians, is recognised by Health Care Financing Administration (HCFA) and the American Society of Clinical Oncology, which are slowly renegotiating the reimbursement structure in the field of medical oncology. Patients face similar conflicts, in that participation in clinical trials may lead to out-of-pocket expenses not covered by insurance. The Clinton administration attacked this unfortunate disincentive for clinical trial participation by broadening the coverage of clinical trials by HCFA, yet, this policy change still impacts a minority of patients with cancer.

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The epidemiological obstacles to patient recruitment are a consequence of the research community's failure to recognise a shift in patient care. Until about 10 years ago, the focal point for quality cancer care was in academic medical centres. These centres served as tertiary care referral centres and provided a convenient, central location for drug testing. Yet, over the past ten years, cancer care has rapidly decentralised. The increased feasibility of safely treating patients in an office or community practice setting, and the ability to avoid hospital admission while delivering standard care (safer and easier to deliver drug regimens), are the root cause of this transformation. Yet, despite these dramatic changes, the drug development community has been slow to adapt its focus on community patient recruitment. Early, misdirected efforts at expanded clinical trial enrolment were focused on recruiting patients out of community practice settings to cancer centres. The evolving, more realistic trend is to bring clinical trials to patients – in other words, to rely on well-trained community practice physicians for investigational drug testing. The field of medical oncology has demonstrated tremendous flexibility and enthusiasm for this change. When medical oncologists complete research-intense subspecialty training and enter private practice, they retain an interest in clinical research and an awareness of good clinical practice. Any efforts to bring clinical research opportunities to such physicians with appropriate administrative and business support are bound to succeed.

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An emerging efficiency in the area of oncology clinical development is one in which investigational trials are offered to networks of physicians who share standards of care, maintain good clinical practice and submit to administrative support for regulatory submissions, contracting and sponsor interactions. Companies managing these clinical trial services, resembling site management organisations, are breaking down barriers to patient recruitment and accelerating the process of clinical development. At least two companies in the United States, US Oncology and IMPATH Inc, have recognised these trends in clinical trial operations. US Oncology, by virtue of its ownership of 14% of all US-based oncology private practices, has effectively managed the administrative burdens of clinical research for its physicians. IMPATH has created research participation agreements with clinical practices in which the practices outsource the administrative, regulatory and data management of oncology clinical research.

Solutions

Patient recruitment efforts may benefit greatly from a focus on patient and physician geographic location and psychosocial and economic motivation, but the most important emerging challenge to successful patient recruitment is biologic in nature. As biopharmaceutical companies focus increasingly on targeted therapeutics and entertain the possibility of holistic therapy, in which personalised therapy (based on marker analysis) is offered to cancer patients, the screening of patients based on biomarkers will determine the success of clinical trial recruitment. To understand the evolving role of biomarkers in patient selection, one must consider the transformation in the biological characterisation of cancer.

One of the most critical scientific realisations that has moulded the field of cancer research over the past two decades is that cancer is a genetic disease. All forms of cancer involve a deregulation of cell growth and/or differentiation attributable to some genetic defect that may be inherited or induced by a toxin or pathogen. As genetic defects can be measured directly, the field has seen a surge in gene or protein markers that can predict predisposition to disease or responsiveness to treatment. Benefiting from advances in molecular biology and the evolving fields of genomics and proteomics, the field has been ushering in a new universe of 'prognostic' markers (markers that predict outcome). Not so long ago the most important prognostic feature of cancer outcome was cancer stage. In the standardised staging technique agreed to by the American Joint Commission on Cancer (AJCC), cancer stage is measured by calculating tumour size, nodal involvement and degree of local or distant spread. Patients with metastatic colon cancer (Stage IV) have a shorter life expectancy than patients with localised colon cancer (Stage I). Pathological features, such as grade, in particular, have helped further define prognosis. In the case of prostate cancer, patients with a low Gleason's score (tumour with well-differentiated features) have a better prognosis than patients with a high Gleason's score (undifferentiated features). Until recently, few markers have been identified that provide more predictive information than these pathological characteristics.

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Given that, for decades, gross pathological characteristics were the dominant prognostic tool for the field of oncology, all treatments have been tested and stratified on the basis of those same features. As it is imperative for pivotal Phase III studies to compare efficacy rates in patient populations that share, at the outset, similar outcome expectations, all oncology clinical trials have grown accustomed to the obligate demonstration that both treatment arms in randomised, double-blind trials contain comparable patients on the basis of age, gender, stage and tumour grade. The ability to prognosticate on the basis of genetic markers turns this tradition on its head. Suddenly, it seems possible to ensure that a drug designed to induce cytotoxicity through the disruption of pyrimidine metabolism is delivered to patient populations that not only demonstrate comparable age, gender, stage and pathological grade, but also share the same expression pattern of genes involved in the metabolism of pyrimidines.

The possibility arises that one can identify subsets of patients on the basis of molecular genetic analysis of their tumours, in whom response to treatment with one or a number of therapies is more likely. It may be possible to take a drug discovered and developed through rational drug design and test its efficacy through *biomarker-based* study-subject selection. This holistic approach to drug development, in which drug therapies become personalised, is a revolutionary idea being carefully considered by pharmaceutical companies. The debate surrounding pharmacogenomics (loosely used in this discussion as the genetic basis for drug efficacy and toxicity) centres less on whether these discoveries will ever happen, and more on how quickly they will be incorporated into the drug development pathway. Logic dictates that diagnostic and prognostic markers, tested and reported in research-oriented or clinical pathology laboratories, will become critical tools for patient screening and enrolment on clinical trials. Successful strategies for patient recruitment and enrolment on clinical trials will embrace the increasingly important role of reference laboratories in performing the marker analysis essential for screening on clinical trials.

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Surrogate markers

To appreciate the opportunity for reference laboratories to impact this screening process, one must first consider the positive impact of surrogate marker selection on clinical trial design. There are numerous ways in which molecular diagnostic markers may increase the safety and likely success of drug development. It may be possible to reject patients from participation in clinical trials when their set of metabolism genes render them susceptible to severe drug toxicity. Why give a patient a drug that becomes toxic in the absence of a gene that promotes its hepatic metabolism and excretion, when it can be shown that the patient lacks that hepatic enzyme? More