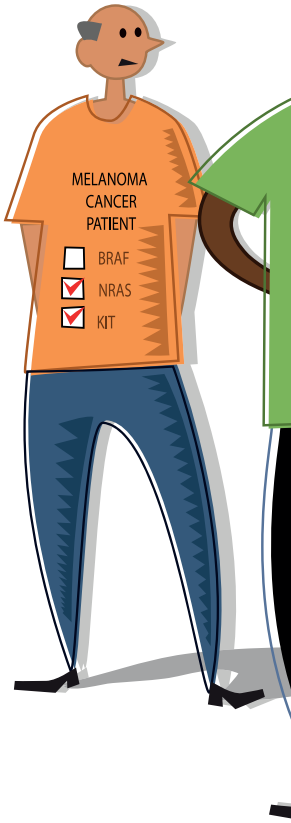
Who's who in the world of personalised cancer treatments?



Anna Wagstaff

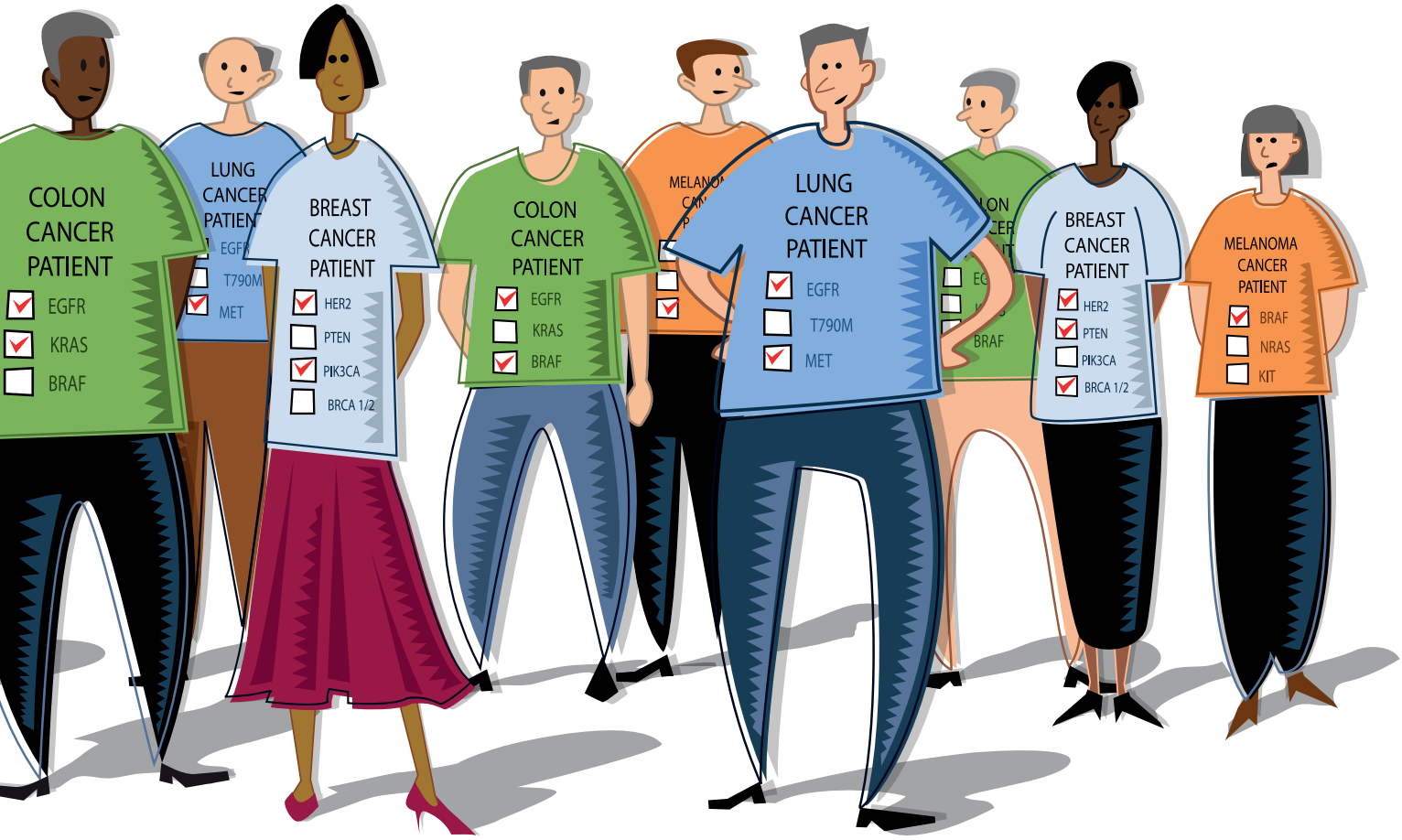
The number of gene mutations implicated in cancer is growing at a steady pace – one cancer centre is now screening for 124 of them. The number of drugs being developed to target specific mutations is also rising steadily. But finding which targeted therapies work best for which sets of mutations is proving an elusive goal.

It's been many years since biologists first offered the tantalising prospect of a future in which every cancer patient could be prescribed a tailor-made treatment aimed at the unique molecular 'signature' of their particular disease. In the intervening years, an ever-growing list of overexpressions, amplifications, translocations and deletions has become part of the academic oncologist's vocabulary with its own bewildering dictionary of acronyms – KRAS, BRAF, VEGFR, EGFR, HER2, ALK, c-KIT, exon 9, mTOR, MEK, PDGFR, BRCA – to name but a few. In routine clinical practice, however, only a tiny minority of patients are actually tested for these 'biomarkers' and treated accordingly.

So what's the hold up? This question has increasingly been exercising Patrick Johnston, head of the Centre for Cancer Research and Cell Biology at Queens' University, Belfast. A specialist in '-omics' diagnostics (genomic, proteomic, metabolomic…), he says we now have targets a-plenty to aim at and a wealth of new drugs – some in the clinic, many more in the pipeline – to aim at them. But despite hugely powerful technologies that can do whole-genome sequencing or identify the expression of thousands of genes in a matter of 24 hours, we still do not know which signatures (or sets of biomarkers) predict response or resistance to which drugs. This work is simply not being done, says Johnston, or at least not well enough.

"In my own disease, colorectal cancer, there are something like 60–70 new drugs currently in various phases of development. There are small molecules, antibodies, peptide-related things and even some novel antisense type molecules. All these are in the mix now. The challenge to the drug companies today is no longer of finding novel targets," says Johnston, "it is finding where those drugs are likely to produce most benefit."

But this is not proving easy. Herceptin (trastuzumab) was approved on the basis of an immunohistochemical assay that was meant to identify patients who stood to benefit, but turned out to be less than satisfactory. "The histochemical assays did not correlate well with the genomic assays for gene expression that we were doing," says Johnston. "We went forward and marketed the test even though it had never been properly quality assured within the literature or beyond." Though it has now largely been replaced by the FISH (fluorescent



in situ hybridisation test), this too has never been validated in a randomised controlled trial and is widely believed to miss some patients who would benefit from Herceptin.

Then there is Erbitux (cetuximab), another important targeted drug, which was designed to block the expression of epidermal growth factor receptors (EGFRs), and was originally approved for use in all metastatic colorectal cancers and in head and neck cancers that showed positive for EGFR overexpression. Only after the drug was brought to market did it come to light that a substantial proportion of the target group of patients (estimated at more than 25% of colorectal cancer patients) receive no benefit from the drug, due to a mutation in KRAS – a gene that plays a role earlier in the signal pathway.

This indicates a methodological failure, says Johnston, in the development of both Erbitux and Vectibix (panitumumab) – a similar EGFR inhibitor, also approved in colorectal cancer. "It is only serendipity that has suggested that actually KRAS is a discriminator." The importance of KRAS could have been identified much earlier, he argues, if a systematic approach had been taken early in the trials of both drugs to measure the various components of the signalling pathway – MEK, KRAS, BRAF, EGFR – in parallel with studying the main target. "This is where the intellectual and the

"The intellectual, preclinical and clinical strategies need to be thought of together, rather than in isolation"

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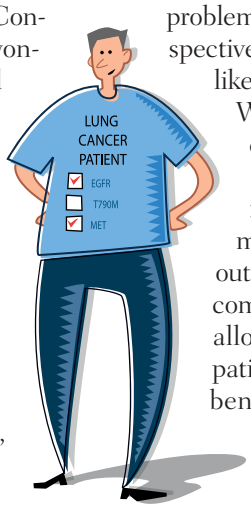
preclinical and clinical strategies need to be thought of together, rather than in isolation. Sometimes, even so, a drug candidate will come forward without really having due reference to what has been discovered preclinically."

"We are trying our best," is the response from the industry. Confounding the sceptics who wondered why big pharma would dedicate resources to identify biomarkers that would narrow down the market for their therapies, drugs companies really do seem to have spent the last few years restructuring themselves around the new paradigm of developing the right drug for the right patient. Most now have teams bringing together biologists, preclinical, translational and clinical specialists, with good technical platforms and biostatistical backup, who try to identify what distinguishes responders from non-responders and develop and validate tests that can be used in the clinic to identify which patients will benefit from the drug.



A COMPETITIVE EDGE

They are motivated in part by increasing demands from the regulators that, in order to get approval of new therapies, sponsors will need to demonstrate which patients respond, and come up with a test to reliably identify them. As important, however, is the recognition that, with so many agents chasing so many targets, market share is now all about who can identify most quickly and accurately the marker that predicts which patients will really benefit.

As Wolfgang Wein, head of Global Oncology at Merck Serono (Merck KGaA) points out, "You have a competitive advantage if you are ahead of the game. If you are a follower, and a biomarker pops up while your study is already underway, then you have the problem that you have to do a retrospective analysis, which is not much liked by the regulators." As far as Wein is concerned, the discovery that patients with a mutant KRAS gene do not respond to Erbitux – a drug marketed by Merck Serono outside the US – is entirely to the company's benefit. "The KRAS allows us to identify those patients who are most likely to benefit from treatment with Erbitux. This can be shown whether you are looking at time to progression, overall survival, response rate or however you want to measure it," he says. "It strengthened the profile of the drug compared to the competition."

Yet, as he points out, drug companies are limited by the current state of knowledge of the disease. "Biomarker development somehow emerges from academia. It is an expression of where academia stands at a certain point in time. You may start your trial using one biomarker, but it might turn out during the trial to be not a very precise one, or better biomarkers come up in the meantime. I see the problem as one of validation: to know when it is really confirmed as a good biomarker. There are examples where a biomarker has been proposed, there are several publications, and then it turned out that they could not be confirmed in a randomised study."

What critics often don't appreciate, he adds, is that when it comes to exploring how your drug works in real cancer patients, you can rarely conduct the studies most likely to answer your questions. Most targeted therapies are developed and approved in combination with other, usually cytotoxic, therapies, because the regulators would not accept that a patient could be denied the current standard of care. Yet the combination of therapies may muddy the signals of who is responding to the targeted therapy and who is not.

It is also in the very nature of cancer, he adds, that you often need to hit several targets at once. Four drugs, hitting four targets, could give you a very clear signal of response in patients with tumours relying on that particular signalling network, while any one of those drugs tested alone might produce no such signal. Again the regulators, for understandable reasons, have resisted giving approval to more than one experimental drug at a time – though Wein says they are increasingly open for discussion on such 'novel–novel' approaches.

"We are therefore limited in what we can really do by what can be funded and what is acceptable in terms of efficacy and toxicity," says Wein. "Even with the best intentions, you can just try to gain ground within these limits." Just how difficult this can be was most recently demonstrated by attempts to find a marker of response to Erbitux among patients with non-small-cell lung cancer – which, as Wein points out, is really an umbrella term for a collection of cancers with different histologies. "We did an enormous amount of work, but we didn't find a solution," says Wein. Last

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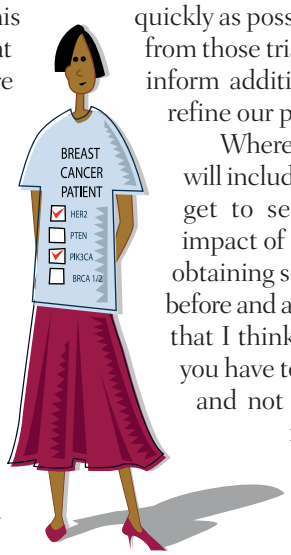
year EMEA turned down an application for Erbitux to be extended for use in non-small-cell lung cancer on the grounds that the added benefit did not outweigh the additional toxicity in an undifferentiated patient population.

That's science for you

David Reese, Executive Director of Medical Sciences at Amgen, which developed the EGFR inhibitor Vectibix, doesn't necessarily agree with Johnston's assertion that the development of the drug was flawed and that KRAS was later identified as a biomarker of response by 'serendipity'. Reese speaks from a certain experience, having both worked with Dennis Slamon's team at the UCLA (University of California, Los Angeles) when Herceptin was being developed, and later helped on the team that unravelled the KRAS story.

KRAS, he says, was among the first human oncogenes to be identified. Although we have known for 30 years that activating mutations in this gene could drive tumour cells, at the time of the early trials there was very little literature delineating the role that KRAS plays in the signalling network that fed into the target Vectibix aimed to block, says Reese. In addition, preclinical models were a little misleading, "because there are cell lines with the KRAS mutation that appear to respond to Vectibix, or other anti-EGFR therapies *in vitro*, whereas in the clinic we have not really seen that."



Later on, when a number of studies "primarily single-arm, single-institution retrospective studies" began to flesh out the components of EGFR signalling pathways and flag up mutant KRAS genes as possible predictors of resistance to drugs such as Vectibix, Amgen went back to the tumour samples it had collected during the phase III trial to do its own retrospective analysis. "We were able to obtain KRAS status on 92% of patients in that study. The analysis showed a very strong correlation between the presence of KRAS mutations and resistance."

It may not be the ideal way to identify your biomarker of response, says Reese, but that's science for you. We are all working with an incomplete understanding of the disease, and the challenge and the art is to identify the right questions to ask.

"It is an iterative process," he adds. "Observations are made in the lab. It is incumbent upon us to try to sort those out in our early-phase clinical trials as quickly as possible. Often observations from those trials will then feed back to inform additional work in the lab to refine our preclinical models."

Where feasible, says Reese, this will include looking beyond the target to see the wider biological impact of the drug, for example by obtaining serial tumour biopsies for before and after exposure. "One thing that I think is now apparent is that you have to view these as pathways and not even pathways but signalling networks. Understanding the effect on the network is critical in terms of understanding what sort of effect your drug may be having."

Where he does agree with Johnston is that the technologies for gathering the necessary biological readouts from samples are no longer a limiting factor. But the issue then becomes what you do with those readouts. "It can also mislead you if inappropriately used, because of the massive amount of data that pour out. It is more critical than ever to ask very careful questions with an extremely well-defined hypothesis."

Getting the question right is, however, only the half of it. To find the answers they must convince clinicians and patients to take part in what can often be a logistically complex, time consuming and sometimes unpleasant process – for instance where repeat biopsies or PET scanning may be required.

It may be significant that, when asked to name some 'model trials' currently underway, Johnston found the question hard to answer – and the two at the top of his list – one being run by ECOG and the other by the EORTC – were both having difficulty accruing patients. "The fact that I can't point to very well-defined trials that are set up in this way shows the problem," he says.

Some questions can't be answered

As Anne-Marie Martin, Director for Clinical Biomarkers and Clinical Development, Oncology R&D, at GlaxoSmithKline, explains, "Something that can be done with a very controlled set of experiments in a lab or with animals does not necessarily translate into the clinical setting. So it is important not

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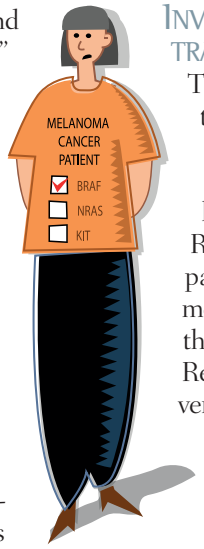
only to ask the right questions, but also to balance what we are able to do in our preclinical research with what is clinically feasible."

Identifying patient groups where there is a strong unmet medical need remains important for clinical development, says Martin, but it is also important to choose a disease indication where you believe a high proportion of patients are likely to respond. "For instance, in our early development portfolio, we are developing a BRAF inhibitor. We know there are mutations in the BRAF gene and those mutations are commonly found particularly in malignant melanoma."

However, BRAF mutations are also known to be present in some colorectal cancers and papillary thyroid cancers, and Martin says their team could explore the effect of their inhibitor in these cancers as well, but it makes sense to start with malignant melanoma, where approximately 50% of patients' tumours have this mutation.

Critical to the whole process, she says, is enabling the preclinical scientists, the clinicians and the translational scientists to work effectively together. "My team straddles the bridge between basic research and the clinical groups. Working closely with the project teams, my team understands the issues from a basic science point of view which leads to the questions that we may want to ask in the clinic."

She accepts, however, that this sort of research requires cooperation at the clinical level with a wider team in addition to the treating oncologist. "In order for us to be entirely successful in translational research, we will need to rely on pathologists, interventional radiologists and maybe even surgeons to access the right samples to perform translational research. We have found that it's better to do that little bit of extra legwork upfront, and by reaching out to these individuals, explaining the purpose of the research and how important it is, usually we are successful in obtaining the right samples and hopefully on our way to answering the key questions."



Investing in translational research

The importance of high-quality tissue sampling is one of the things Astra Zeneca is now focusing on in a major collaboration with Cancer Research UK to accelerate the pace of biomarker development. The initiative is centred at the Paterson Institute of Cancer Research at Manchester University, and coordinated through the NCRI (National Cancer Research Institutes). From Astra Zeneca's point of view, it represents a strategic attempt to address the single biggest challenge to realising the dream of getting the right drug to the right cancer patient: boosting translational research efforts to understand the basic mechanisms of the disease.

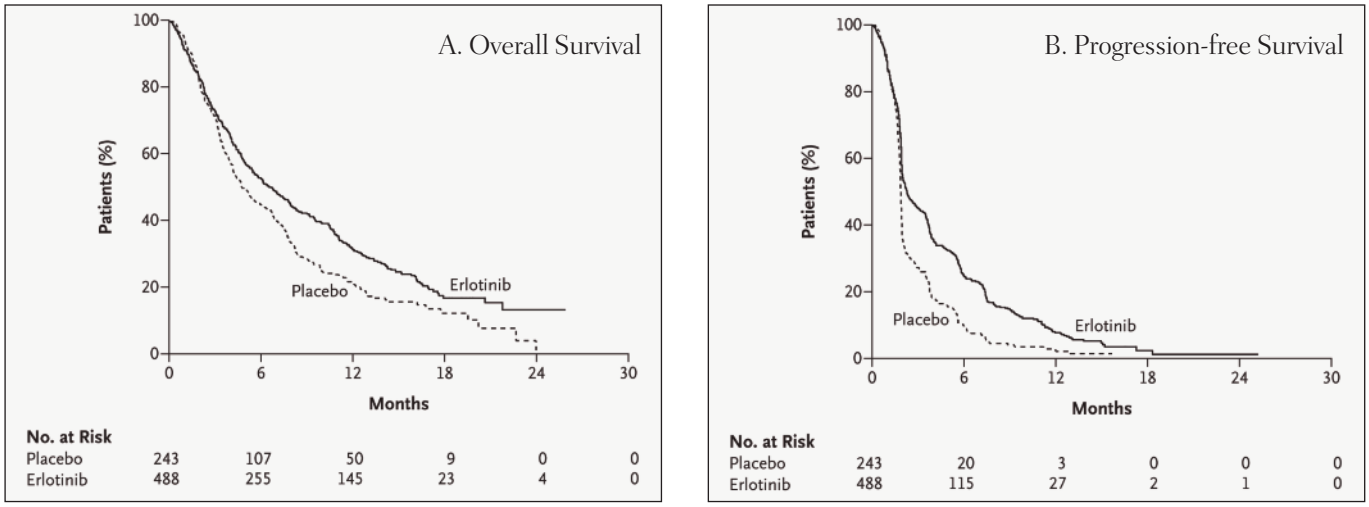
This is how Astra Zeneca's Head of Early Clinical Oncology Development, Andrew Hughes, describes the problem. "Take the target Akt. You can look in many different types of cancer and see that Akt is upregulated, but as to which cancers are addicted to that upregulation of Akt versus those that are not, i.e. which cancers are most likely to respond, it's an open question, despite the fact that we have now very potent and selective inhibitors of Akt."

The result, he adds, is that we have an increasing number of targeted drugs coming through development without understanding how best to use them.

"We are looking very much to science external to Astra Zeneca to help us understand the basic biology of human cancer," says Hughes. "Once we understand which part of the molecular lesion in a cell the cancer is addicted to, then of course pharma is well suited to applying its high-throughput screening, its molecular chemistry, its pharmacokinetics, its optimisation and drug manufacture to go capitalising upon that innovation. But pharma I don't think has the same spectrum of resources as academia has to unlock the basic understanding of cancer question."

The trouble is, says Hughes, that academia faces the same challenges obtaining human cancer tissue as industry. "There has been an awful lot of investment in yeast, non-mammalian systems, cell lines because they are easy to acquire. But to ask researchers to research on human disease material requires them to step out of their labs and into clinics and hospitals to partner with a research-minded physician, and appropriately consent patients to use their tissue to try and understand human diseases." The funding is more expensive and the multidisciplinary infrastructure becomes more of a challenge. "In the

IT'S ALL ABOUT THE TAIL



The tail ends of these curves show that a small minority of patients with non-small-cell lung cancer derive very significant benefit from the EGFR inhibitor Tarceva (erlotinib). Progress towards personalised cancer treatments is all about learning how to determine in advance which patients are likely to benefit and which will not

Source: FA Shepherd et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. *NEJM* 353:123–132, reprinted with permission

region of translational research there has been less than we would have liked to have seen."

Finding ways to reorientate cancer research away from the headline-hitting basic science towards more expensive, logistically demanding translational studies is a challenge that has preoccupied many in the cancer research community over recent years. In collaborating with CRUK's biomarker programme, Astra Zeneca is now looking to give the company the answers it needs to inform some of its own clinical trials while at the same time boosting the general capacity of the academic sector to undertake this sort of research. Amongst other things, the funding goes towards running a joint, co-funded PhD course in translational research, and raising the quantity and quality of tissue available for research by placing technicians with the appropriate skills in cancer hospitals.

LOOKING FOR THE BIG RESPONSES

Efforts to improve the research community's access to quality-controlled biological specimens is something every pharmaceutical company would applaud. But Bill Sellers, Global Head of Oncology for Novartis, wants to go one step further. He would like those quality-controlled specimens to have been pre-screened for biomarkers known to be of interest.

Sellers is looking for the big responses he believes are waiting to be found, and argues that, if and when you find them, all the issues about identifying who is responding, finding biomarkers and developing a test for that biomarker become highly manageable. He cites, as an example, the extension of Glivec [imatinib] to treat KIT-mutant GIST patients.

"The mutation in KIT was actually discovered by a group in Japan. A second group then showed that cell lines with those mutations were highly responsive. Patients with GIST were identified by detection of cKIT by immunohistochemistry for anti-CD117(cKTIT) and then treated with Glivec. At that time it had not been shown that this specific test for CD117 identified all KIT-mutant patients nor all patients who responded to Glivec. However, the immunohistochemistry test itself showed good technical performance, and the FDA (US regulators) did not demand validation of that test as a precondition of extending the indication of Glivec to KIT-mutant GIST patients. It asked, instead, for a post-marketing commitment from Novartis to 'assure the availability of a validated test for detection of CD117 tumour expression by immunohistochemistry.'"

Far from being a special case, says Sellers, that is the future we can look forward to. He mentions an ALK inhibitor for lung cancer patients with a rearranged

ALK gene, and various BRAF inhibitors for melanoma patients with BRAF mutations as examples of therapies in the pipeline that are showing promising results in their target patient population.

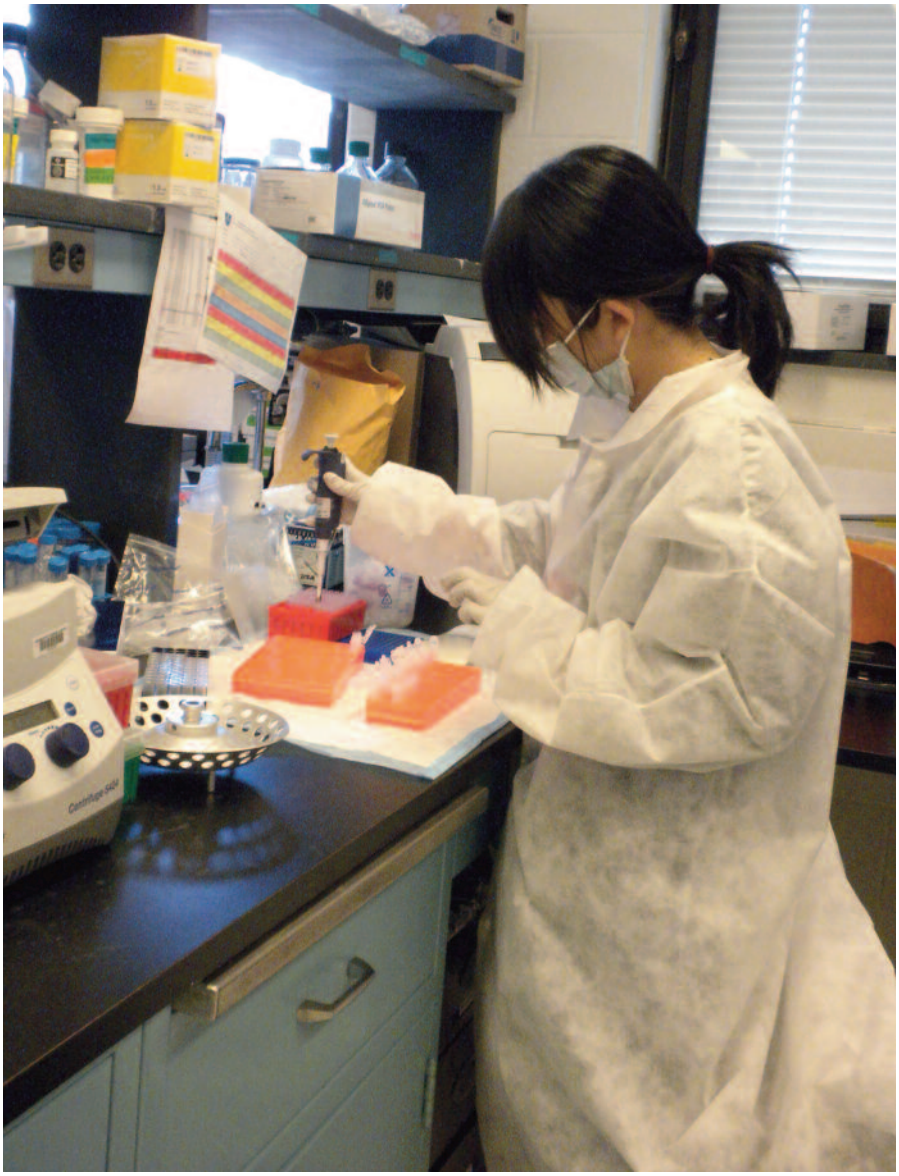
"In the case of melanoma we are doing a trial of our drug Tasigna [nilotinib] in KIT-mutant melanoma only, because given the emerging phase II data, where essentially five out of the first seven patients treated with Tasigna have responded, there would be no way to do the trial in KIT-null patients at this point."

What is holding back progress towards personalised therapies, says Sellers, is the time and effort it takes to recruit the particular patients you need to the trials you want to carry out.

"Imagine you are doing a trial in a population of lung or breast cancer, or melanoma, where only 10% of patients have the mutation that you want. You start the trial and no one out there has been screened for that mutation. Then every patient who enters the trial, you have to consent for the trial, do the test and then tell them you are not eligible nine out of ten times."

Tracking down the patient's tumour sample can itself be a tricky business. "Sometimes that tumour was isolated at a different hospital, and not at the hospital where they are now being treated. You have to find the tumour. You have to make DNA from the tumour; have it sequenced, so it takes time. And then they might not have the right mutation for your trial."

Not surprising, then, that clinicians and patients are not always enthusiastic. How much better, suggests Sellers, if this genetic profiling for alterations considered to be important for cancer genetics was



KATIE MARQUEDANT/MGH CANCER CENTER

Towards truly tailored treatments. In this translational research laboratory at the Massachusetts General Hospital Cancer Center, specimens from lung and colorectal cancer patients are routinely tested for 124 biomarkers. Prospectively profiling patients in this way should greatly facilitate translational research to discover which combinations of biomarkers are significant for which treatments in which cancers

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done on a routine and regular basis, rather than only when they are about to become eligible for a clinical trial.

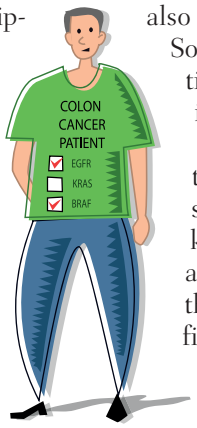
One way this could be done is through a lead-in epidemiology trial to profile patients, so that ahead of time researchers already know how many patients there are at which centres who are bearing this mutation. Better still, says Sellers, is the practice that has recently been adopted at Massachusetts General Hospital and other cancer centres, where many cancer patients are now being offered the option of profiling for sets of mutations and being consented. "When some company has an interesting drug for one of those mutations, they will know if they are eligible."

A SIGN OF THINGS TO COME

The initiative at Massachusetts General Hospital (MGH) could signal an interesting restructuring of cancer research efforts, tying the patient care side into the translational research side on a scale that has never previously been done. More than that, it would seem to represent the first rays of the long-awaited dawn of the new era in which cancer therapies are routinely personalised in everyday clinical practice.

The hospital is not generating a genetic fingerprint for every cancer patient – at least not yet. But as part of its routine clinical practice, it is now testing some patients for the steadily increasing number of markers that have been identified in the literature as playing a role in driving certain cancers, and it is using this information to direct the patients towards the therapies that are most likely to benefit them. Darrell Borger, Co-Director of the MGH Translational Research Laboratory, points out that there's nothing to stop your average cancer hospital from doing likewise – indeed a number of hospitals across the US are now taking part in a lung cancer project using the assays developed at MGH.

"We've developed assays and software methods that are easily portable that we can transfer across different institutions. It makes that equipment readily available – plug and play – to do this kind of clinical genotyping." The beauty of it, says Borger, is that it is becoming a routine test for some clinicians. "There is nothing additional that the patients need to provide. They fill out a consent form so they understand that their tumour will be tested and they agree to that testing. Then after the diagnosis is made, our pathology department sends the very same sample that they evaluated themselves to our laboratories, and we take a little bit more of that sample to extract the genetic information that we test for. So we use all the material that is currently provided at all institutions to the pathology departments. We don't need anything extra."



All the information relating to the assays developed at the MGH Cancer Center will soon be available in the literature, he adds, and other institutions are welcome to use or improve on them. He hopes that companies could develop some assays as kits that would be commercially available at a price affordable even for small institutions.

Currently all lung and colorectal cancer patients at MGH can have their tumours tested for 124 important cancer gene mutations, chosen according to which are most common over all cancers as a whole. "In lung cancers we know what the important genes are to look for, and of course we look for those," says Borger, "but by having this broad fingerprint, we are finding that there is a small number of patients who also have uncommon mutations." Some of these 'uncommon' mutations could well be very common in other types of cancer, he explains. "And this is the question we will be addressing fairly soon: Can you take what you know in a particular cancer with a particular mutation and apply that in another cancer where you find that same mutation?"

Many other institutions are now also "very very close" to bringing personalised cancer therapies to their patients, according to Borger, in both the US and across Europe. Interestingly, soon to take up his post as Chief of the Division of Hematology/Oncology and Associate Director of the MGH Cancer Center is José Baselga, immediate past president of ESMO (European Society for Medical Oncology). Borger expects the presence of Europe's chief champion of translational research will strengthen collaboration across the Atlantic. "What we are interested in is providing a model that many people can benefit from, incorporate and even improve on. A big collaborative effort, and we all have our contribution to make."