Bringing personalised cancer treatments to the people

Elizabeth DeVita-Raeburn

Personal genetic signatures may help assess a person's risk of getting cancer, predict risk of recurrence, or identify the best treatment for them. At a Meet the Experts session, nine ASCO luminaries explained to press and public why it is crucial to invest in this area of research.

Cancer detection, treatment and prevention was, until recently, something of a one-size-fits-all proposition. Treatments were chosen based on where the cancer originated and where it had spread. And the inherited and acquired changes unique to each individual's cancer were, for the most part, subtleties beyond reach. The Human Genome Project, completed in 2003, promised to make it easier to reveal the molecular nuances of each individual's cancer, and to tailor treatments to their particular tumour. The question was, how, and how fast, could that promise be brought to patients?

Last December, nine leading cancer experts gathered in New York City to give a status report at an ASCO event entitled *Personalized Cancer Medicine: Translating Breakthroughs in Biology into Better Treatment for Patients*. They offered short answers to the big questions: personalised medicine has enormous potential to transform day-to-day practice, identifying who really needs adjuvant care, for instance, and what drugs work best for a specific tumour and a particular individual. And it's happening now – but not fast enough.

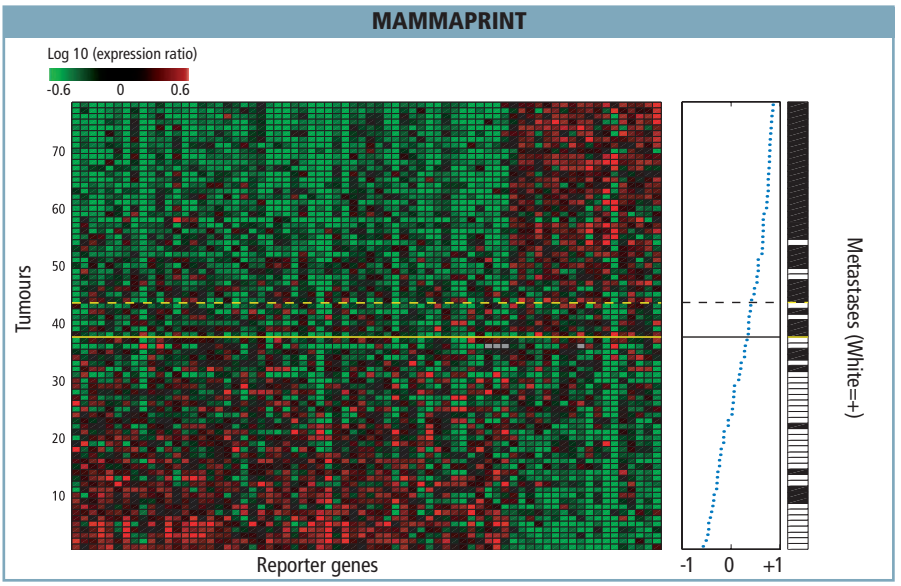
"On a scale of one to ten, where ten is perfect application and zero is pie in the sky thinking out loud, I think we're in a two to three stage," said Mark Robson, assistant attending physician of the clinical genetics and breast cancer medicine services at Memorial Sloan Kettering Cancer Center in New York City, and one of the day's speakers. "We're definitely making progress, but it's not going to happen overnight."

Adjuvant care – who needs it?

In the past it's been difficult to identify which cancers, in a pool of patients, might recur, and what treatments might work best to keep patients free from disease. That resulted in some not getting enough treatment, and others getting too much. A case in point: oestrogen-positive, node-negative breast cancer. "We know that 80% – 85% of these patients are adequately treated with local therapy and endocrine therapy," said Joseph Sparano, professor of medicine and women's health at the Albert Einstein College of Medicine in New York City. And the other 15%–20% of women could cut their risk of recurrence by about 25% if they were to add chemotherapy to that regimen. But almost everyone gets chemotherapy. "Our current practice guidelines recommend chemotherapy based on risk, not on predictive factors," said Sparano, "which results in chemotherapy being recommended for most patients."

That's now changing. Most oncologists in the US now use the Oncotype dx assay, a commercially available test in which a sliver of tumour is placed on a microchip so that 21 genes that portend recurrence can be 'read', thus identifying who really needs chemotherapy and who can be spared the ordeal.

Recently, the 'MammaPrint', a new assay that looks at a panel of 70 genes to predict recurrence, became available. It remains to be seen whether studying 70 rather than 21 will lead to better prediction. Two large clinical trials currently underway, one in the US and one in



Good genes, bad genes. The MammaPrint shows how the on-off pattern of 70 'reporter genes' correlates (from -1 to +1) with the average good prognosis profile *(vertical dotted line)*, and can be used to identify which breast cancer patients will benefit from adjuvant chemotherapy. Oncotype dx does the same sort of thing using 21 reporter genes. Ongoing trials are expected to reveal which has the greatest predictive power – and indeed how far either are superior to information that could be obtained using lower-tech, cheaper technologies

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Europe, should answer that question. The US trial, the Tailorx (Trial Assigning IndividuaLized Options for Treatment Rx), will evaluate the Oncotype dx assay. Women will be studied for ten years, with an additional follow up of up to 20 years. The European trial, MINDACT (Microarray in Node Negative Disease May Avoid Chemotherapy), will measure the effectiveness of the MammaPrint. Results are expected in 2018 (three years accrual and 7.5 years follow up).

"People are working on these types of tests in just about every type of cancer there is," said Allen Lichter, ASCO executive vice-president and chief executive officer. In support of this, in 2005, the National Cancer Institute and the National Human Genome Research Institute formed The Cancer Genome Atlas (TCGA), the goal of which is to explore the entire spectrum of genetic changes involved in all forms of cancer. That's helped lead to the next assay most likely to become available, designed to predict which patients with early-stage non-small-cell lung cancer are likely to relapse. In one trial, the model was 72%–79% accurate in predicting recurrence.

Other assays in other cancers aren't far behind. "Eventually, well down the road, but in our lifetime, one can picture a day in which each cancer is tested and each therapy is individualised for the particular characteristics of that cancer, rather than its anatomical location," said Lichter.

Tailored treatments

In some ways, therapies are already being tailored to patients. Doctors already stain cells to identify certain proteins on the surface that identify subsets of cancer that will respond better to a particular treatment. Her2 neu and trastuzumab (Herceptin) is a prime example. But now researchers are poised to go beyond that. "The new technology will give us the ability to say not only, 'Yes, this patient needs chemotherapy,' but, 'This cancer will respond better to this drug or that drug, or this patient has a mutation that causes this cancer to be resistant to the drug we typically use for this cancer, so we can go to another drug,'" said Lichter. "Those things are in the relatively near term."

In 2006, four prospective trials reported that erlotinib (Tarceva) and gefitinib (Iressa) are most effective in lung cancer patients whose tumours have mutations in the epidermal growth factor receptor (EGFR) gene. Another study in patients with gastrointestinal stromal tumour (GIST), resistant to the standard treatment imatinib (Glivec), found that response to sunitinib (Sutent) was associated with mutations in the KIT and PDGFRA genes.

Two phase III studies in patients with anaplastic oligodendroglioma that evaluated chemotherapy and radiotherapy versus radiotherapy alone found that a subset of patients with a particular genetic profile experienced better overall survival, regardless of which treatment they got (see also Impact Factor, p 48).

Fine-tuning doses

Another aim of personalised medicine is deciphering which patients might require more or less dosing, depending on their ability to metabolise drugs. "There are some people who have certain variations in drug metabolising pathways that may make them at increased risk of toxicity with some drug. Or some drug may be less efficacious on them because they can't process it well," said Robson. There are, he said, examples of this already. The gene UGTIA, for example, has been linked with high toxicity in certain drugs used to treat colon cancer. Researchers are also looking at a variation on the gene CYP2D6, which might predict difficulty in metabolising tamoxifen.

"There's actually already a reasonable amount of discussion in the psychiatric literature on CYP2D6, because it's involved in the metabolism of some SSRIs [selective serotonin reuptake inhibitors, used to treat depression]," said Robson. "There's a suggestion that there's an increase in toxicity if you have the polymorphism. So the discussion is, before you start the agents, do you see if someone carries that polymorphism? Right now," he said, "it's a one-gene-at-a-time approach. But I suspect in the future a broader profile of each individual will be taken to see what drugs would work best for each individual."

Detection and prevention

Other work is building on what's already known about the breast cancer genes BRCA1 and BRCA2. There are subtler varieties of inherited risk that have eluded detection thus far. "We have a lot of patients who tend to be at a bit of an increased family risk, but when we test them they're negative for BRCA1 and BRCA2," said Julie Gralow, associate professor of medicine and oncology at the University of Washington School of Medicine. "But it could be a combination of a couple of different genes as opposed to a big whopping gene like BRCA1 and BRCA2 that is increasing their risk."

In the future, if these genes are identified, people who carry them can be picked up before they develop cancer, and treated with agents that modify gene expression. "If the profile says gene one is overactive and gene two is underactive, a patient can potentially take something to deactivate the activity of one and increase that of two, and be brought into balance," said Robson.

Identifying these cases, said Gralow, is not that far off. "I tell patients who come to me because they have a family history but don't have BRCA1 or BRCA2, that we need to touch base every couple of years – that's how close it is. In five years," she said, "we'll be better able to do much bigger panels on patients. It still won't be 100%. It will just say they have higher risk." But if those higher-risk women are separated from the general pool, they could be screened differently, with MRI in addition to mammogram, for example. "If we offered every woman MRI, the country would go bankrupt," said Gralow. "But if we used it on just these higher-risk women, we could save money and lives."

The tissue tussle

Of course, there are roadblocks. Among them, an ongoing tussle over tumour tissue samples – a necessity if one is to do the studies to identify these genes. "There's often been a question of ownership of the specimens," said Gralow. "There are situations where, even if a patient enrols in a trial and says, 'Yes, you can use my tissue,' the institute or pathology lab says 'we need it in case some issue comes up in the future, and we're not going to send it.'"

In other cases, a patient might have given permission for his or her tissue to be used for testing, or in one clinical trial, but to be used for a different research would require getting permission a second time.

"In our highly mobile society, finding patients [to ask to use their tissue samples once again] is very difficult at times," said Lichter. Institutional review boards, which have been charged with protecting patients' privacy, have made it difficult to get around these obstacles. "The time is right for us to take a look at the system and see how much of these regulations are essential and need to be maintained, and how many of them can be modified so valuable work can proceed without harm to people," said Lichter. "We've had members tell us they won't participate in protocols that require tissue approval because it's just too complicated."

Some of the best samples come from clinical trials. "The specimens come from many of the very best tissue banks," said Lichter. "You know the patients' history, the tissue is well characterised, everyone got the same treatment and the follow up was standardised." But only 3% of the US adult cancer patient population participates in clinical trials, making this a small pool to pick from. And the current lag in funding for cancer research may mean a further 10% cut in trials. "When you're talking about a 10% cut, when you already have an absurdly low number of patients that end up on research studies, it's a body blow," he said.

Another potential problem are the paradigm changes that such radical changes bring. Right now, for instance, most of the tissue taken from patients is fixed in formalin. But some of the new assays, like the MammaPrint, rely on frozen tissue, which better preserves DNA, but is much more expensive to collect. "You need to immediately freeze fresh tissue in the operating room," said Gralow. "If you let it sit, the DNA starts degrading. At our institution, for research purposes, we try to collect frozen tissues on the majority of patients. But it costs a lot of money," she said. "We have one person we pay just for breast tissue. It's not practical."

Overall, the mood at the conference was positive, with an undertone of urgency about support for the research. "There's never enough funding. You will never talk to a scientist who says we have more than enough to do all that we want to do," said Lichter. "But the current flat funding is just a dreadful thing to have happen right now. The number of terrific opportunities we're passing on has gotten quite large. We're passing up more than is prudent if progress is to be made as rapidly as we think it can."