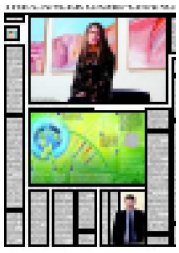

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THE CANCER GAME-CHANGER

A patient's genome can hold the key to a cure

JAMIE WALKER
ASSOCIATE EDITOR

After all she has been through, it was about time something went right for Andreanna Candi, an office worker locked in the fight of her life with cancer. At first, they said she had a uterine fibroid that was best left alone. When it grew to the size of a grapefruit, the surprised surgeon asked why she had taken so long to have it taken out.

Only then did she receive the bad news: the supposedly benign growth was an inflammatory myofibroblastic tumour — a rare, aggressive and hard-to-detect cancer. Worse, malignant spores had been inadvertently seeded through her belly during surgery. Candi endured operation after operation to control the eruption of cancerous tumours, her prognosis worsening at every turn.

She doesn't know where she would be had a research lab, by chance, not gone over her old pathology samples and run them through a genomic screen. Her oncologist's eyes lit up at what the test found — a mutation of the ALK gene at the molecular core of her cancer. "We have a drug that can fix that," she was told last November, the turning point in her long and arduous journey.

"I can't tell you the relief I felt," the Sydney woman says. "I had had two bowel resections ... all kinds of difficult surgery, and I was looking at having to have more and more, because basically that's all they could do for me. It wasn't much to look forward to."

Candi is a beneficiary of a new kind of personalised genomic medicine that is revolutionising cancer care overseas and now in Australia. What started just a few short years ago as a "cottage industry" run ad hoc by medical scientists and cancer doctors for patients who had exhausted their conventional treatment options is entering the mainstream of the health system with startling effect.

This week, Sydney's Garvan Institute of Medical Research launched a program of clinical trials for sufferers of rare cancers, to pair new-generation therapies with individuals on the basis of genetic information. This reflects a fundamental change of approach to a disease that will kill nearly 50,000 Australians this year.

Clinicians have long been accustomed to classifying cancers according to their location in the body — think lung or breast cancer, the most common types in this country. To researchers, what matters more is the genetic short-circuit that makes cells go rogue and multiply madly, causing tumours, and bone marrow or blood to turn malignant. Medicines that zeroed in on a particular genetic mutation would be able to attack a range of cancers wherever they were located.

In Candi's case, drugs targeting the aberrant ALK gene in lung tumours have been let loose on her cancer, so far with promising results. She could actually feel the difference when a 10cm lesion that had been pressing on her ureter shrank by two thirds. "It's crazy," she says, reflecting on how much her life has changed for the better.

The head of the Garvan Institute's cancer division, David Thomas, says the Genomic Cancer Medicine Program will reach people with more than 180 varieties of rare or ultra-rare cancer ranging from his speciality, sarcomas of the bone and connective tissue, to head and neck cancer, cancers of the nervous system, eyes and even of the heart.

Collectively, these account for 30 per cent of all cancers and nearly 50 per cent of cancer deaths in this country. Sufferers complain with some justification that they get a raw deal from the health system, as the big dollars for research and — more crucially — drug subsidisation through the government's Pharmaceutical Benefits Scheme invariably go to the more common cancers.

This is understandable on one level. Richard Vines, chairman of patient advocacy group Rare Cancers Australia, acknowledges that the PBS is "designed to do the greatest good for the greatest number of patients".

Just tell that to Candi. If she were a lung cancer patient, the drugs that are keeping her alive would cost $38 a month through the PBS; yet because they are not listed for the treatment of IMT, she would have had to come up with $7000 a month had she not been secured a dispensation for compassionate access. "It's not until you experience something like this that you realise there are big holes in the system," Candi says.

Thomas says those accepted into the personalised medicine program that the Garvan is running with the National Health and Medical Research Council's Clinical Trials Centre — basically, people with rare cancers who had exhausted standard treatments — will have their tumours genetically profiled and set against a map of their full genome. In about a fifth of cases, this would pinpoint gene mutations that could be targeted with matched drugs.

Patients who didn't have an actionable mutation would be given new and experimental drugs with two objectives in mind. First and foremost, to expose them to as many therapy options as reasonably possible while there is time.

This would then loop back to the wider good, testing potential treatments through a formal clinical trial process. The "adaptive design", with each trial treatment paired to a patient's cancer genetic

profile, should "allow effective treatments to be identified more quickly and efficiently than with a traditional clinical trial", says John Simes, head of the NHMRC's Clinical Trials Centre.

A simultaneous study overseen by Mandy Ballinger of the Garvan Institute will seek to shed light on the genetic basis of cancer risk, especially in the young. "The younger you are when you get cancer, the more likely it is that there is a genetic contributor," says Thomas, whose aim is to make genetic profiling routine for the 6000 Australians under the age of 40 diagnosed with cancer each year.

Cancer, though, is overwhelmingly a disease of older people — a function of its genetic underpinnings. The longer one lives, the greater the chance that the cellular hardwiring will misfire, setting in motion the train wreck that leads to cancer. More than four times as many cancers occur in people over 60 as in younger people, the Cancer Council says. As the population greys, the incidence will increase: Australians who live to 85 have a 50-50 chance of contracting the disease.

Genetic screening did not exist a decade ago on a usable scale. Jump ahead five years and it was still prohibitively expensive — upwards of $50,000 a sequence, as of 2012. But the cost has come down dramatically since then, opening up the possibilities.

At Melbourne's Peter MacCallum Cancer Centre, the tests run by Piers Blombery in the molecular haematology lab cost less than $1000, and are performed at a rate of 200 a month. Most blood cancers diagnosed in Victoria — leukaemia, lymphoma, myeloma and the like — are profiled there. "That's commensurate with the utility," Blombery says. "If something can make a difference, haematologists, oncologists, patients are going to find out about it."

For others wanting access to the technology, the experience has been more hit and miss. The take-up in Australia has been like green shoots — thriving in some places, slow to take seed elsewhere. Until now, there has been an absence of national co-ordination. Many cancer patients sent their samples to the US to be analysed at a cost of thousands of dollars.

As Vines points out, the effort was too frequently wasted. "People pay their $5000 or $6000, get their (genetic cancer) profiles done, but they are not quite sure what to do next," the patient advocate says. "Your oncologist has to be on board with it, you have got to have some way of assessing the treatment, and if it's not PBS-available you've got to be able to fund it yourself. In many cases it's a ... hammer in search of a nail."

Michelle Haber of the Children's Cancer Institute of Australia decided something had to be done. A professor of medicine, she vividly remembers being approached by a clinician brandishing a set of results from overseas. "What do we do with this?" the doctor asked. Haber's answer was the Zero Childhood Cancer initiative, a national trial that aims to cover the full cohort of children who have an incurable cancer or one that has returned after responding to treatment, putting them at extreme risk.

That adds up to about 200 kids and young adolescents a year in Australia. After being genetically profiled and treated at research institutes and hospitals dotted across the country, their progress will be tracked and validated by the German Cancer Research Centre in Heidelberg, to plug the findings into what Haber calls "a global enterprise".

She says the approach is already paying off. Four of the 60-odd children involved in the pilot study had their diagnoses changed after being sequenced. That's right: they were originally being treated for the wrong cancer. In Germany, up to 15 per cent of brain cancer patients in a similar study also had their diagnoses altered. "What that means is the child can be ... on completely the wrong set of drugs," Haber says.

She tells Inquirer: "This is genuinely a new model of care for precision treatment of kids with cancer that will make a difference in terms of improving diagnosis, identifying kids that are at genetic risk of cancer and changing treatments to give optimal treatments for children, and ultimately improving the survival rate and quality of life for these kids."

Enrolments will open when the program is launched next month.

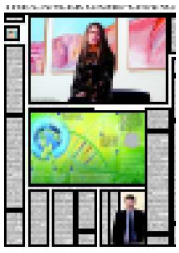
The biggest initiative came on line last week in Brisbane — a partnership between the Queensland government's Metro South Hospital and Health Service, the Queensland University of Technology and service provider Pathology Queensland to type more than 2000 cancer patients a year.

QUT's director of genomics Matt Brown says most patients with a "serious" cancer presenting to Brisbane's second largest public hospital, the Princess Alexandra, will be sequenced. "Metro South has said that if anybody turns up with a reasonable argument, they will fund it," the professor of medicine says.

Have you spotted the missing piece in the jigsaw? It's the federal government. While Canberra is pumping money into the Australian Genomic Health Alliance, an umbrella body to translate genetic research into clinical practice, as well as individual trials and projects, there is no sign of a policy to pull together the programs that are sprouting almost organically across the country.

The British, in particular, are way ahead. England's chief medical officer Sally Davies last month announced a five-year plan to systematically open up genome-based personal medicine for cancer patients through the National Health Service, replacing haphazard testing conducted via regional and local labs operating as a "cottage industry".

Outlining her "genomics



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dream", Davies says she would like to see DNA testing become as routine for cancer patients as MRI or CT scans and biopsies. Within the government, a National Genomics Board would be set up, chaired by a minister, to oversee the development of genomic services and facilitate the rollout of the fast-evolving technology. In the short-term, Davies wants "all appropriate patients" given the opportunity to have their genomes sequenced under expert guidance.

Her Australian counterpart, Brendan Murphy, declined to be interviewed. But there is growing recognition at the government level of the demand for personalised cancer medicine. Launching the Garvan-NHMRC Clinical Trials Centre program in Sydney, state Health Minister Brad Hazzard said: "This is a very significant milestone for cancer research, not just for NSW, but for Australia."

Queensland Health Minister Cameron Dick predicts that "nearly all" patients with significant cancers will have whole genome sequencing done to "inform treatment choices".

The Garvan's Thomas points to a research paper presented in June to the American Society of Clinical Oncology's annual meeting on the experimental precision drug larotrectinib. It shrank tumours in 76 per cent of patients with 17 kinds of incurable cancer who tried it in early-stage clinical trials. A recent meta-analysis — a study of existing studies — cited by Thomas found that response rates were six-fold higher for drugs linked to a genetic target than for conventional chemotherapy.

America's Food and Drug Administration, the world's leading regulator, for the first time in May licensed a drug on the basis of its effectiveness against tumours that shared a molecular "target", wherever they happened to be located. The drug, pembrolizumab, brand name Keytruda, has been obtained by some end-stage cancer patients in Australia.

But in the ordinary course of events larotrectinib would take years to get here; so Thomas has partnered with a supplier to fast-track it on to his personalised medicine program. "Without these trials, the patients might not live long enough to see the day where this drug is registered on the PBS," he says.

QUT's Brown says while there are "pockets" of excellence in genomics research in Australia, overall we are significantly behind Britain, some European countries and increasingly the US in terms of integrating the technology into the health system. "At the moment, there are some very simple genetic tests for cancers that are being funded, but largely the field is unfunded," he says. "Ours is only funded in Queensland because an area health service believed in it."

Thomas says there is "enormous appetite" in the research and medical community for Australia to embark on something similar to the 100,000 Genomes project in Britain, mapping the DNA of NHS patients with rare diseases as well as their families.

CCI's Haber, who is up for a Eureka prize for her work on the Zero Childhood Cancer program, says it in inevitable that "precision medicine has to take its place in the diagnosis and treatment of all cancer patients". She is cautious, however, about setting a British-style time frame. "I think it's a 'yet'," she says of widening the rollout. "My hope is what we are doing at Zero Childhood can become a showcase and a precedent in terms of a platform ... for other cancers. I know those conversations are beginning to happen."

As a medical oncologist who treats brain cancer, NHMRC's Simes knows there is a danger that desperate patients will invest hope in a genetic test, only to be crushingly disappointed. Looking for a cancer mutation linked to a targeted therapy makes sense, but "for that approach to be helpful for a majority of patients is a way off", he warns. "As a clinician, I ... will see patients where we say, 'Look, you've had these tests, but there is nothing in there based on current evidence to say there is something we would be doing different for you', unfortunately."

Thomas says: "I don't think we have got to the point where it's a lay-down misere, that this is the way society should invest its money, but it's sure as hell time for us to invest in finding out."

For further information on the trials mentioned in this article visit:
- *gcmp@garvan.org.au*
- *zerochildhoodcancer.org.au*
- *research.qut.edu.au/translationalgenomicsgroup/*

'This is a very significant milestone for cancer research, not just for NSW, but for Australia'

BRAD HAZZARD
NSW HEALTH MINISTER

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Cancer survivor Andreanna Candi; below, Garvan Institute's David Thomas
MAIN PICTURE: JOHN FEDER

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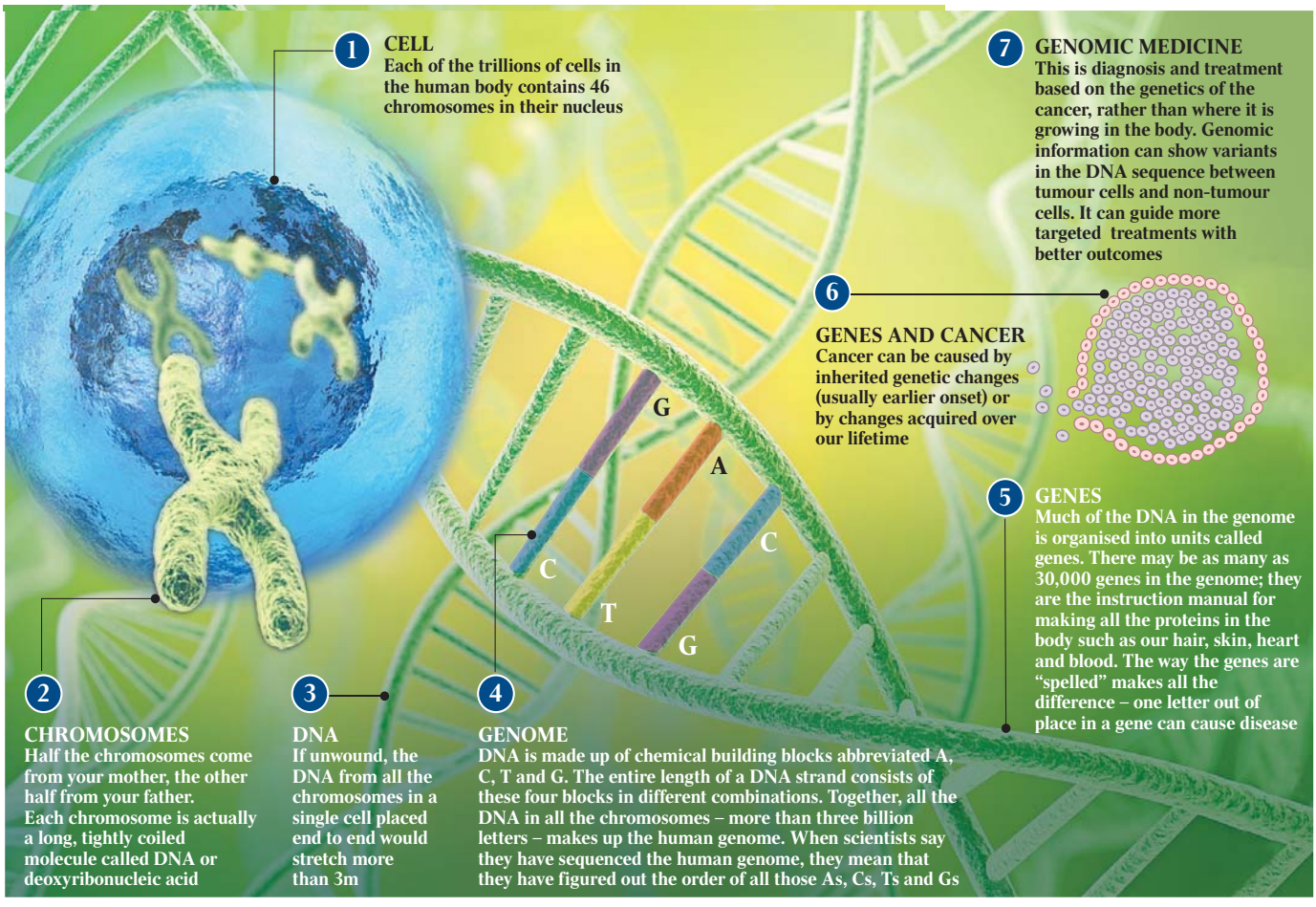
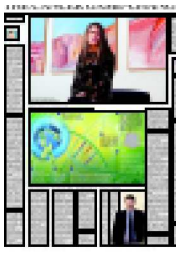
THE HUMAN GENOME AS MEDICINE





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