Precision Medicine: Australian companies at the forefront of the revolution

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The precision medicine revolution

Precision Medicine (or Personalised Medicine) is healthcare that is specifically tailored to an individual. And Australia is at the forefront of this medical revolution.

Precision medicine's uses include

1. Understanding an individual's risk of developing disease, or complications within a disease;
2. Diagnosis and prognosis; and
3. Selection of the therapy or therapeutic pathway most likely to have the best outcome

Precision Medicine recognises that every individual is different – right down to our DNA. Our unique genes, environment and lifestyles mean that there can be big differences in how we develop disease and how we respond to treatments.

This approach is leading to better outcomes in patient treatment and recovery and in costs to the community.

Cancer the major focus

The major focus of Precision Medicine has been cancer. Cancer is a genetic disease. That doesn't mean all cancers are inherited from our parents, rather that cancer is a disease that begins with our DNA.

DNA is contained within the nucleus of almost every cell in our bodies. As cells age, almost all cells in the human body divide into two to make a new copy of themselves (or replicate) before the old one dies. To do this, the strand of DNA in a cell's nucleus splits into two to form the nucleus of the new cell. The Weizmann Institute of Science in Israel has estimated that around 330 billion cells in our bodies are replaced every day[1]. So it's not surprising that on a tiny fraction of occasions, a gene within the DNA strand is not perfectly copied – instead it mutates. Unfortunately, certain types of mutations can lead to a cell being cancerous.

The breast cancer gene: An example of Precision Medicine

The discovery that mutations of the BRCA1 or BRCA2 gene significantly increase the likelihood of women developing breast or ovarian cancer (and some other cancers) led to recommendations that women with a family history of these cancers should be risk assessed. Genetic testing can then establish whether women who have not yet developed cancer carry a mutation of these genes. The intention is that when an individual is shown to have such a mutation she can discuss her risks with doctors, counsellors and family members and can make an informed decision on the best path for her. Her choices can range from ongoing regular check-ups to pre-emptive double mastectomy. Angelina Jolie's choice to undergo preventative double mastectomy for exactly this reason generated enormous media attention.

This is Precision (or Personalised) Medicine because it is a risk assessment of the likelihood of disease based on an individual's genetic makeup.

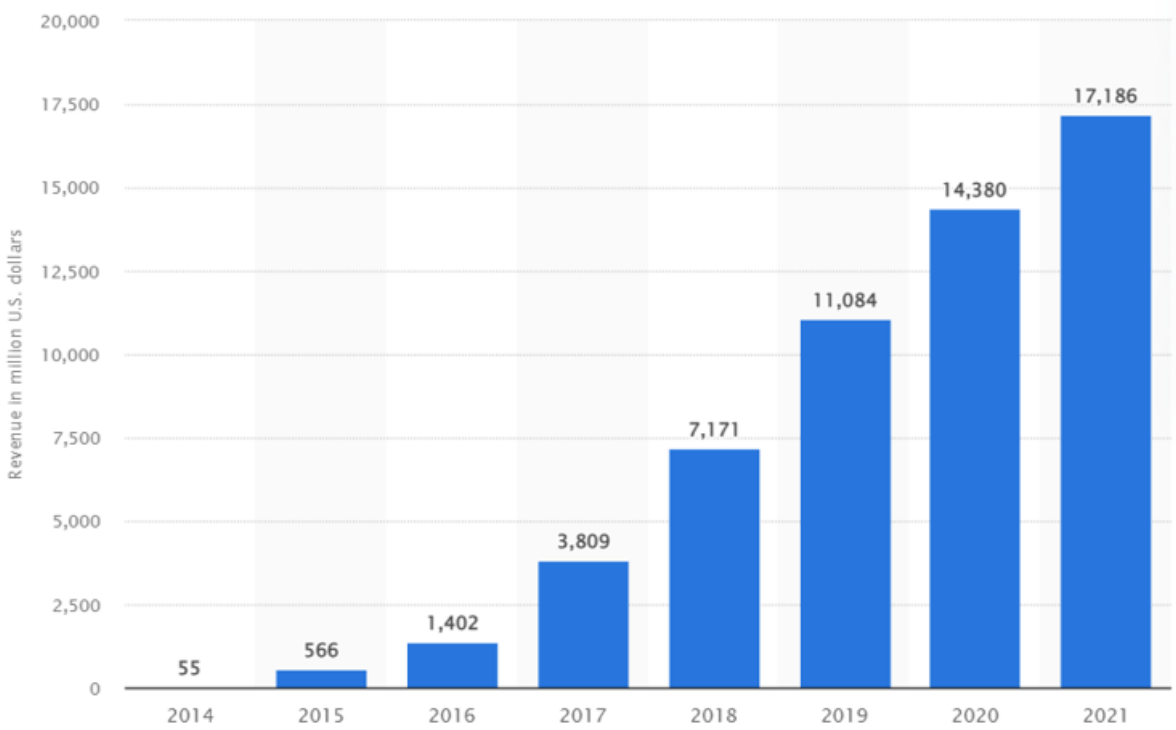
Immunotherapy (or Immuno-oncology) – the Pembrolizumab (Keytruda) example

Another example of Personalised Medicine is Immunotherapy, which seeks to activate the body's own immune system to recognise, attack and eliminate cancerous cells. To date the biggest immunotherapy commercial success has been Merck's Pembrolizumab (tradename "Keytruda") which was launched in 2014 and is currently approved in 13 different types of cancer

[1] "The Distribution of Cellular Turnover in the Human Body," by Ron Sender and Ron Milo, in Nature Medicine, Vol. 27; January 2021
[2] "https://www.statista.com/statistics/1269401/revenues-of-keytruda/

treatment. In 2021 it was the world's fourth highest selling drug (and second-highest selling excluding Coronavirus vaccines) with sales of US$17.2 billion2.

Figure 1: Keytruda revenue from 2014-2021



Source: Statista; 2022

Keytruda's success has been in the treatment of tumours that express a protein called PD-L1. Where patients are PD-L1 negative Keytruda is not considered worthwhile. Before the emergence of this drug, PD-L1 expression was not something of any importance to clinicians. But now there is routine testing of patients for PD-L1 as it is a biomarker that indicates the likelihood of success (or failure) of treatment with Keytruda for each individual patient.

As well as identifying individuals where the treatment is likely to work, being able to measure a biomarker also means that:

1. Time is not wasted with a therapy that is unlikely to work - the patient can be given a more appropriate course of therapy;
2. Because a course of Keytruda costs approx. US$150,000, - healthcare systems can avoid significant expenditure that is unlikely to be of any benefit to the patient.

This is Precision (or Personalised) Medicine because a biomarker can determine whether an individual's tumour is likely to respond to this therapy.

Treating lung cancer with an Australian immunotherapy drug and Keytruda

Immutep (ASX Code:IMM) has run a number of clinical trials of their own immunotherapy drug called Eftilagimod Alpha or "Efti". Efti is used as a combination therapy, meaning it is combined with another therapy to activate the body's immune system to fight tumours. IMM have published interim data from Phase 2 clinical trials in conjunction with Merck in which Efti is given in combination with Keytruda in three different cancer settings.

In first line (metastatic) Non-Small Cell Lung Cancer, "NSCLC" which is one of the largest addressable markets in all of oncology, Phase 2 results suggest that when Efti is added to Keytruda it ***may*** significantly increase the number of patients who respond to treatment compared to using Keytruda alone – possibly even double. If an Efti + Keytruda combination is approved it would also extend patent protection for Merck's most valuable asset by nine years. So, if a Phase 3 trial were successful it would transform treatment for hundreds of thousands of patients around the world each year and be hugely commercially valuable.

Prostate Cancer diagnosis and treatment using Precision Medicine

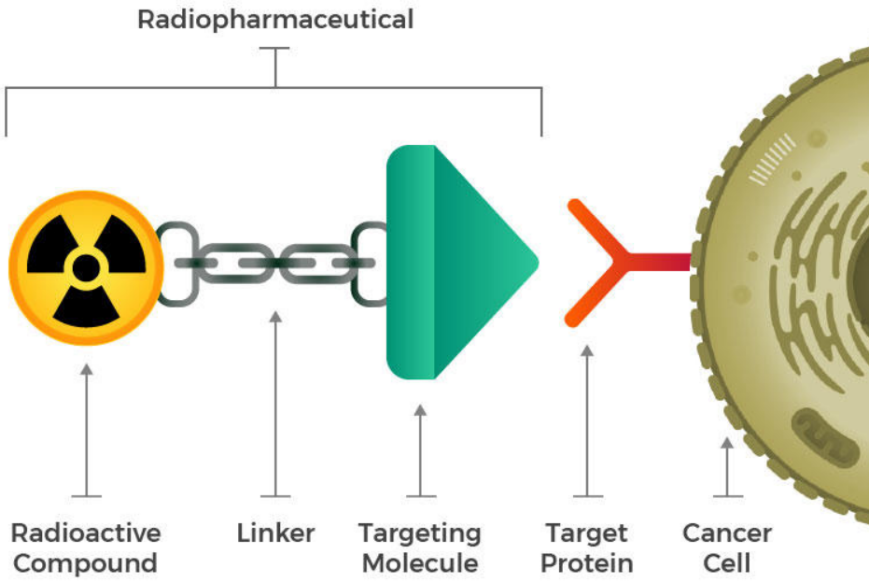
Theranostics and Molecularly Targeted Radiation (MTR) are further examples of Precision medicine. The term "theranostics" is derived from "therapy" and "diagnostic". It describes using a drug called a "radiopharmaceutical" that carries a low dose radiation payload to diagnose cancer and the same drug carrying a higher dose radiation payload to treat cancer.

Certain tumour types often carry particular proteins on their outer surface (or membrane). Perhaps the best-known example is in prostate cancer where around 90% of prostate cancers express Prostate Specific Membrane Antigen or "PSMA".

Hence it is possible to identify a molecule that will target that specific protein and bind to it. A radiopharmaceutical is created by:

1. Identifying the appropriate "Targeting Agent"
2. Manufacturing an appropriate "chelator" which is a cage to hold the radioactive isotope
3. Joining the Targeting Agent to the chelator using a chemical "Linker"

Figure 2: Radiopharmaceuticals in cancer diagnosis and treatment



Source: National Cancer Institute; 2022

If genes within prostate cancer cell DNA express PSMA, they do so regardless of whether that cell is located at the prostate gland or somewhere else in the body – *because they are prostate cancer cells*. Hence, secondary tumours or metastases also attract the same targeting agent and therefore also receive the radioactive payload. The process is simple: the theranostic agent is injected and will then circulate in the patient's blood around the whole body.

The **diagnosis** begins when the targeting agent binds to the PSMA on the surface of tumour cells, including on any secondary tumours. Next, the low dose radiation payload linked to the targeting agent lights up on a PET scan.

Figure 3: PET scan

Source: Telix Pharmaceuticals; 2022

Figure 3 is a PET scan of a prostate cancer patient taken after administering Telix Pharmaceuticals' (ASX Code : TLX) prostate cancer imaging agent "Illuccix". The bright spots show the locations of the radiopharmaceutical which has bound to tumour sites.

Therapy begins when the targeting agent binds to a receptor on the tumour cells surface (just as it did in the diagnostic mode). Next the higher dose radiation payload linked to the targeting agent kills the tumour cells by damaging the cell's DNA.

A tumour's response to therapy can be followed using the same imaging technique as the original diagnosis. If the tumour is not shrinking or is no longer shrinking, clinicians can be immediately aware and determine the most appropriate next course of action.

Time is critical in cancer.

MTR vs traditional radiation oncology

As the term MTR suggests, this new form of radiation oncology delivers radiation directly at the cellular level. It is very specifically targeted unlike traditional External Beam Radiation that is delivered from outside the body and targeted at an anatomical area. It must pass through and irradiate layers of healthy tissue to reach its target and can have a significant impact on the physical health of a patient and often permanent side effects. In contrast, radiopharmaceuticals deliver radiation specifically to the site(s) of the tumour(s), thereby avoiding the unnecessary killing of normal tissue. This is Precision Medicine.

Australian leadership in theranostics

Australia is at the forefront of this new technology. The Peter MacCallum Cancer Centre in Melbourne and St Vincent's Hospital in Sydney are both considered leading research organisations in the field.

Telix Pharmaceuticals' "Illuccix" kit for the diagnosis of certain types of prostate cancer is approved for use in the USA and Australia as well as awaiting approvals in other jurisdictions. Telix also have many clinical and pre-clinical programs including Phase 3 therapeutic trials in prostate cancer and diagnostic and therapeutic trials in kidney cancer, glioblastoma and bone marrow conditioning.

Clarity Pharmaceuticals (ASX Code: CU6) is currently conducting clinical trials of theranostics in prostate cancer, neuroblastoma and neuroendocrine tumours.

A third Australian company, Radiopharm Theranostics (ASX Code: RAD), listed in November 2021.

Antares market & fund updates

Below is a brief review of how the Australian share market performed during the quarter as well as short commentaries on the Antares Funds and model portfolios, outlining their performance and the main contributors to performance.[#]

Australia share market review

The June quarter got off to a bad start and got progressively worse for the Australian equity market. The S&P/ASX 200 TR Index went from 0.9% down in April to 2.6% down in May and 8.8% down in June, to finish the quarter down by 11.9%. This was worse than most global equity markets and a reversal of the resilience shown by the Australian market in the March quarter. The Energy sector again proved a winner (+1.5%) with oil prices remaining elevated as the war in the Ukraine continued. Also finishing ahead was the Utilities sector (+1.7%) which benefits from somewhat predictable revenues that are typically also inflation-linked. In contrast, the Information Technology sector was savaged, down by 27.2% as the more elevated earnings multiples that characterise most tech stocks were marked down. Not surprisingly the Nasdaq Index, home to many tech stocks in the US, was also down by more than 20%. The AREIT sector which is particularly sensitive to rising bond yields also performed poorly, finishing the quarter down by 17.7%.

Dividend Builder

The annual distribution return to 30 June 2022 for Antares Dividend Builder Fund was 5.4%. Dividends were received from Nine Entertainment, Suncorp, Telstra and Westpac. The Fund's net return for the June quarter was -8.0% compared to its benchmark's return of -11.9% [1].

Elite Opportunities Fund

The Antares Elite Opportunities Fund returned -12.8% (net of fees) for the June 2022 quarter, while its benchmark, the S&P/ASX200 Total Return Index returned -11.9% [1]. Overweight holdings in Transurban, QBE Insurance and CSL contributed to performance. Detracting from performance were overweight positions in Northern Star, IGO Limited and Nine Entertainment.

High Growth Shares Fund

The Antares High Growth Shares Fund returned -13.7% (net of fees) for the June 2022 quarter, compared to its benchmark S&P/ASX200 Total Return Index return of -11.9%[1]. Overweight holdings in QBE Insurance, CSL and Transurban contributed to performance. Detracting from performance were overweight positions in Northern Star, IGO Limited and Block Inc.

Ex-20 Equities Fund

The Antares Australian Equities Ex-20 Fund returned -15.0% (net of fees) for the June 2022 quarter, compared to its benchmark S&P/ASX200 Total Return Index ex S&P/ASX 20 Total Return Index return of -13.8%[1]. Overweight holdings in QBE Insurance, Santos and Medibank Private contributed to performance. Detracting from performance were overweight positions in Nine Entertainment, Megaport and Seek.

#All returns are net of fees. Please refer to the following page for a summary of returns which are gross of fees. [1]. Past performance is not a reliable indicator of future performance. Returns are not guaranteed and actual returns may vary from any target returns described in this document. [2]Income yield is calculated as the sum of the income yields over the period to 30 June where the yield is income distributed during the period divided by the unit price (before fees) at the start of the distribution period. Benchmark yield is calculated as the sum of the monthly returns of the S&P/ASX 200 Industrials Total Return Index minus the monthly returns of the S&P/ASX 200 Industrials Index (price index)

*From 1 October 2021, the benchmark for Dividend Builder is the S&P/ASX 200 Total Return Index. This replaces the previous benchmark, the S&P/ASX 200 Industrials Total Return Index.

Antares Investments Returns

Performance to 30 June 2022[1]

Professional Selection		3 mths %	1 yr %	3 yrs % pa	5 yrs % pa	7 yrs % pa	10 yrs % pa	Since Inception % pa
Antares Dividend Builder	**Net Return**	**-8.0**	**2.7**	**4.6**	**4.8**	**5.0**	**9.2**	**7.0**
S&P/ASX 200 Acc Index (#)	Gross Return	-7.9	3.3	5.2	5.4	5.6	9.9	7.6
	Benchmark Return	-11.9	-3.9	4.1	6.1	6.5	10.4	7.3
	Net Excess Return	**3.9**	**6.6**	**0.5**	**-1.3**	**-1.5**	**-1.2**	**-0.3**
	Gross Excess Return	4.0	7.2	1.1	-0.7	-0.9	-0.5	0.3
Antares Elite Opportunities Fund	**Net Return**	**-12.8**	**-6.3**	**3.4**	**5.6**	**6.8**	**9.2**	**9.6**
S&P/ASX 200 Acc Index	Gross Return	-13.0	-6.1	4.1	6.3	7.6	9.9	10.5
	Benchmark Return	-11.9	-6.5	3.3	6.8	6.9	9.3	8.6
	Net Excess Return	**-0.9**	**0.2**	**0.1**	**-1.2**	**-0.1**	**-0.1**	**1.0**
	Gross Excess Return	-1.1	0.4	0.8	-0.5	0.7	0.6	1.9
Antares High Growth Shares Fund	**Net Return**	**-13.7**	**-5.6**	**5.2**	**7.8**	**8.2**	**10.3**	**10.2**
S&P/ASX 200 Acc Index	Gross Return	-13.9	-5.5	6.2	8.9	9.3	11.5	11.7
	Benchmark Return	-11.9	-6.5	3.3	6.8	6.9	9.3	7.7
	Net Excess Return	**-1.8**	**0.9**	**1.9**	**1.0**	**1.3**	**1.0**	**2.5**
	Gross Excess Return	-2.0	1.0	2.9	2.1	2.4	2.2	4.0
Antares Ex-20 Australian Equities Fund	**Net Return**	**-15.0**	**-10.5**	**9.7**	**-**	**-**	**-**	**4.8**
S&P/ASX 200 ex S&P/ASX 20	Gross Return	-14.8	-9.8	11.6	-	-	-	6.9
	Benchmark Return	-13.8	-8.4	6.1	-	-	-	0.5
	Net Excess Return	**-1.2**	**-2.1**	**3.6**	**-**	**-**	**-**	**4.3**
	Gross Excess Return	-1.0	-1.4	5.5	-	-	-	6.4

Note: Performance reporting for the Antares Ex-20 Equities Fund commenced on 2 October 2019. Monthly reports can be accessed on the Antares Equities website. Inception for Dividend Builder (6/9/2005), Elite Opportunities (18/11/2002) and High Growth Shares (7/12/1999).

From 1 October 2021, the benchmark for Dividend Builder is the S&P/ASX 200 Total Return Index. This replaces the previous benchmark, the S&P/ASX 200 Industrials Total Return Index.

Disclaimer:[1] Past performance is not a reliable indicator of future performance. Returns are not guaranteed and actual returns may vary from any target returns described in this document. Investment returns are based on exit prices, and are net of management fees and assume reinvestment of all distributions. Gross returns are provided to show performance against the investment objective.

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