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# Perspectives on Precision Oncology

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## Editorial and study commentary by Dr Angela George



Dr Angela George is the Consulting Editor for the Perspectives on Precision

Oncology series. Born and trained in NZ, she is now Clinical Director of Genomics at The Royal Marsden Hospital (London, UK) specialising in the systemic treatment of gynaecological cancers.

Dr George has authored multiple peer-reviewed publications and book chapters and undertakes a variety of clinical and translational research projects, particularly in cancer genomics and targeted treatments.

In addition to her clinical responsibilities, Dr George is involved in multiple national and international groups, including the National Cancer Research Institute Gynaecological Cancers Group, the Precision Medicine Working Group for the European Society of Medical Oncology and the British Society of Genetic Medicine.

Dr Angela George has been commissioned by Roche Products (New Zealand) Ltd, Auckland, to be the Consulting Editor of the Perspectives on Precision Oncology Educational Series. The editorial and expert comments have been written by Dr George in accordance with the requirements of the Association of the British Pharmaceutical Industry (ABPI) Code of Practice 2019. The views and opinions expressed are entirely those of Dr George. Roche reviews and approves the content for conformity with NZ regulatory and industry compliance requirements. Please consult the full Data Sheets for any medications mentioned in this article at [www.medsafe.govt.nz](http://www.medsafe.govt.nz) before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.



### Abbreviations used in this issue

**ASCO** = American Society of Clinical Oncology  
**CI** = confidence interval  
**ctDNA** = circulating tumour DNA  
**EGFR** = epidermal growth factor receptor  
**GIST** = gastrointestinal stromal tumour  
**HER2** = human epidermal growth factor receptor 2  
**HR** = hazard ratio  
**HRD** = homologous recombination deficiency  
**MSI** = microsatellite instability  
**OS** = overall survival  
**PARP** = poly (ADP-ribose) polymerase  
**PCR** = polymerase chain reaction  
**PFS** = progression-free survival  
**SNP** = single-nucleotide polymorphism

## Shedding Light on Precision Oncology

We have entered an age of oncology where we can now use molecular information from patients and their tumours to match treatments in ways that would have been unthinkable only a decade ago. It is a world in which almost every tumour has the potential to have a molecularly matched drug – if the testing and appropriate drug are accessible.

The studies summarised in this issue provide a brief snapshot of the many ways in which appropriate genomic testing, at the right time for patients, can impact on their existing management and provide information for family members. In forthcoming issues, we will explore in more detail the potential gains we can make for patients through molecular testing and precision medicine.

As we move forward in oncology, we are increasingly incorporating complex genomic information, both somatic and germline, into patient treatment pathways. The benefits of incorporating germline genetic testing for *BRCA1* and *BRCA2* as part of the routine oncology workup have already been demonstrated in ovarian, breast and pancreatic cancers.

In ovarian and pancreatic cancers, identification of a mutation allows the use of specific PARP-inhibitor maintenance treatments, and provides information about prognosis. In breast cancer, knowledge of mutation status can direct the appropriate surgical management or ensure the optimal adjuvant chemotherapy is given. In all cases, genomic information can identify patients with an inherited predisposition to cancer. This also facilitates the identification of others who are at risk of developing cancer, providing them with the option of risk-reducing interventions to mitigate this risk.

By moving genomic testing into oncology management pathways, access to and uptake of testing has improved, while both the cost and time taken to get a result have decreased significantly. In the last two years, we have seen studies reporting the use of PARP-inhibitors in prostate cancer patients with mutations in the HRD genes.

Scheinberg *et al.* report on an Australian study looking at the use of mainstream genomic testing in patients with prostate cancer that found the same high acceptance rate already demonstrated in other tumour types.<sup>1</sup> Rolling out testing across patients with prostate cancer in the same way that this has been undertaken in those with ovarian cancer could not only identify patients who would benefit from a different approach to treatment, but could also reveal a cohort of carriers with the subsequent cascading of testing to family members.

*“Cancer cells are characterised by the genomic mutations that differentiate them from the original cells from which they were derived”*

### PATIENT SELECTION

Selection of patients most likely to benefit from adjuvant chemotherapy and the identification of those who still have residual active cancer cells at the conclusion of chemotherapy has long been an area of intense interest in oncology. There are several studies in breast cancer looking at recurrence risks in those who would normally be considered borderline for chemotherapy. Gene recurrence scores such as MammaPrint and Oncotype DX have shown benefit over standard histopathological features to identify those with a higher risk tumour who require chemotherapy. Sparano *et al.* have demonstrated the benefit of combining both clinico-pathological features and gene-recurrence scores to more clearly define those who benefit from adjuvant treatment.<sup>2</sup> A similar approach was taken in colorectal cancer at Memorial Sloan Kettering, where MSI and clinico-pathological features were incorporated to develop a clinical calculator for predicting future recurrence.<sup>3</sup>

For those with advanced disease who are running out of conventional treatment options, clinical trials from phase I to III are a valuable source of potential therapeutic options. Increasingly, however, these



studies have moved past the random allocation of patients by tumour type, and are instead looking for molecularly matched patients to improve response rates and long-term outcomes. Testing has routinely been performed on either archival tissue or fresh biopsies, but some patients are not able to be biopsied, either because of the site or the nature of their metastases.

Recently, COVID has also been a barrier to patients being able to be biopsied, with increasing interest in the more widespread use of ctDNA as many departments worldwide suspended normal diagnostic pathways, including bronchoscopy and image-guided biopsy. In these cases, ctDNA has provided a path to diagnosis and treatment for some individuals who would otherwise not have been able to access treatment.

### CIRCULATING TUMOUR DNA

Going forward, ctDNA has the potential to revolutionise the oncology management pathway. Potential applications include helping define likely primary tumours in patients with cancer of unknown primary (as demonstrated in the Japanese study by Hayashi *et al.*), testing patients at completion of adjuvant treatment to identify those with residual circulating tumour cells who are at high risk of relapse, and replacing tissue biopsy in patients with relapsed disease to identify a suitable treatment option.<sup>4</sup> In the PlasmaMatch study, Turner *et al.* demonstrated that the latter could be undertaken in patients with breast cancer, where those with metastatic breast cancer were tested and entered into various treatment cohorts based on results.<sup>5</sup> They ran tissue samples alongside ctDNA, finding very high levels of concordance in mutations identified, and a significant number with potential targetable variants. Undertaking ctDNA testing comes at a significantly lower cost than the combination of image-guided biopsy and sequencing of tumours, and provides a real option for the future to replace tissue biopsy and expand precision medicine.

*“Genomic testing must be available to all who would benefit in order for precision medicine to meet its full potential”*

Over the last few months, we have seen Nature Milestones published about both cancer (December 2020) and genomic sequencing (February 2021).<sup>6,7</sup> It is striking to note how many of the milestones in the cancer publication are based on advances in molecular/genomic testing and precision medicine. Cancer cells are characterised by the genomic mutations that differentiate them from the original cells from which they were derived. Now that we are increasingly able to target these mutations, either individually (such as *EGFR* mutations), or *en masse* (as with immunotherapy in those with a high tumour mutation burden), we move closer to finding treatments that make a meaningful difference to patient outcomes.

### INTERNATIONAL GUIDELINES

Such treatments have already seen huge progress made in lung cancer (as summarised in the recent ASCO guidelines; Hanna *et al.*) and melanoma (where we have moved from having no real systemic treatment options to the potential cure of patients with advanced disease).<sup>8</sup> With this, we are also moving to a point of tumour agnostic drug approvals, with molecular subtype being of greater importance than the cell of origin. The recent success of TRK fusion inhibitors (e.g., larotrectenib) in a pooled analysis of small studies in patients with



Kiwis can fly, but most do it under the radar – like London-based Dr Angela George, a world leader in precision oncology and Clinical Director of Genomics at the Royal Marsden Hospital, London. In this new Research Review Educational Series, New Zealand clinicians can learn from her experience.

Central Otago-born, Dr George studied medicine at the Otago Medical School. She completed her advanced oncology training at Christchurch Hospital and worked as a medical oncologist there until 2011. She then moved to the UK to complete her doctorate in cancer genetics at the Royal Marsden and the Institute of Cancer Research. Fast-forward 10 years and her many achievements include the ICR Chairman's Prize for her thesis in ovarian cancer genetics, and specialisation in the systemic treatment of gynaecological cancers with a strong focus on using genomic information.

#### Bringing the strands together

Currently, Dr George is Consultant Medical Oncologist in Gynaecology, Consultant in Oncogenetics and Clinical Director of Genomics at Royal Marsden, where she also undertakes testing for inherited cancer syndromes. *“I love that both strands of my work complement each other – I use genomic information to provide more precise treatment for my oncology patients.”*

As well as providing tailored treatments, Dr George says, *“I think we have only scratched the surface of how we can refine the diagnosis, treatment and follow-up of oncology patients.”*

#### Mainstreaming Cancer Genetics programme

Ask about career highlights and Dr George points to leading the implementation of the Mainstreaming Cancer Genetics programme – incorporating germline testing into routine care for patients with ovarian, breast and pancreatic cancers [go.nature.com/3fchDcs](https://doi.org/10.1038/s41588-021-00800-0) Now adopted across the UK, Dr George has helped implement the programme worldwide, expanding into new tumour types and revolutionising the use of routine genomic information.



appropriate TRK fusions has shown high levels of response with low toxicity across all tumour types (Hong *et al.*).<sup>9</sup>

This raises the issue of how to best identify these patients, or other patients with potentially targetable mutations who may benefit more from targeted treatments than from standard chemotherapy. Studies such as MSK-IMPACT and the University of Michigan study reported here by Cobain *et al.* have demonstrated the feasibility and use of large panel testing on all patients with solid tumours at time of diagnosis.<sup>10</sup> However, RNA panel testing would have to be added to identify patients for whom larotrectinib would be appropriate. This would have additional benefits for a variety of tumour types in which fusions are important both for diagnosis and treatment, such as sarcomas and haematological malignancies. However, this testing is currently not routine practice, meaning that many people could potentially miss out on useful treatment options.

*“We cannot consider use of targeted treatments if there is not a robust system to provide access to testing for patients”*

For many years, genomic testing has been rationed and restricted, but testing must be available to all who would benefit in order for precision medicine to meet its full potential, and fulfil its promise of providing a revolution in diagnosis and treatment. The identification of patients for whom targeted treatments would be appropriate is the first step in being able to assess how many patients require such treatments, and the subsequent provision of therapy. We cannot consider use of targeted treatments if there is not a robust system to provide access to testing for patients. A system where testing is available to only a few patients in some areas of the country will never be equitable.

We hope that you find this editorial and these articles of academic or relevant clinical interest and welcome any feedback you may have.

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**Research Review publications are intended for New Zealand health professionals.**

#### REFERENCES:

References in bold are summarised with additional expert commentary in our Key Publication Summaries section

- Scheinberg T, Goodwin A, Ip E, et al. Evaluation of a mainstream model of genetic testing for men with prostate cancer. JCO Oncol Pract. 2021;17(2):e204-e216**
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- Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: A pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020;21(4):531-540**
- Cobain EF, Wu YM, Vats P, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol. 2021;7(4):525-533**



## KEY PUBLICATION SUMMARIES

- Mainstream genetic testing for men with prostate cancer
- Integrating 21-gene recurrence score and clinical-pathological features in early breast cancer
- Next-generation sequencing for cancer of unknown primary site
- Circulating tumour DNA analysis to direct advanced breast cancer therapy
- Larotrectinib for *TRK* fusion-positive solid tumours
- Clinical benefit of integrative genomic profiling

### Evaluation of a mainstream model of genetic testing for men with prostate cancer

**AUTHORS:** Scheinberg T et al.

**SUMMARY:** This Australian study tested the concept of “mainstreaming” germline genetic testing for metastatic prostate cancer, where counselling and testing are performed by the patient’s oncologist, in order to guide treatment choices and family cancer prevention. Overall, 63 of 66 men offered testing accepted, with 4 pathogenic variants identified (2 *BRCA2*, 1 *NBN*, 1 *MSH6*). Among 59 patients and 9 clinicians who completed questionnaires, satisfaction was high, with all patients pleased to have had testing, 98% pleased to have had testing at their normal oncology appointment, and all pleased to have received results from their usual specialist. Among clinicians, 7 of 8 felt confident, and all were satisfied, with mainstreaming. Mainstreaming required 87% fewer genetic consultations than traditional genetic counselling.

**COMMENT:** This study follows on from similar studies undertaken previously in other BRCA-related cancers for whom knowledge of genetic mutation status may have an impact on treatment decision. To date, incorporating germline genetic testing into the routine management of patients with ovarian, breast and pancreatic cancer has hugely increased access to testing, provided information on prognosis, likely response to treatment, the best chemotherapy options and the suitability of maintenance treatment with PARP inhibitors. Now, as the role of PARP inhibitors in those with mutations in HRD genes in prostate cancers becomes clear, access to germline testing becomes increasingly important in this tumour type. This study showed a high uptake of testing through oncology and very high levels of patient satisfaction with the process. The success of the mainstream approach in this study provides further data on the acceptability of this approach for cancer patients who would benefit from testing as part of their management, whilst identifying other family members at risk of developing cancer.

**Reference:** *JCO Oncol Pract.* 2021;17(2):e204-e216  
[Abstract](#)

### Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer

**AUTHORS:** Sparano JA et al.

**SUMMARY:** This study reports on the development of a tool (RSClin) to integrate the 21-gene recurrence score for distant recurrence with tumour grade, tumour size, and age, through a meta-analysis of individual data from 10,004 women with hormone receptor-positive, HER2-negative, node-negative breast cancer treated with endocrine monotherapy in the B-14 (1982-88) and TAILORx (2006-10) trials or with endocrine therapy plus chemotherapy in TAILORx. The RSClin tool provided greater prognostic information (likelihood ratio  $\chi^2$ ) for distant recurrence than the raw recurrence score or clinical-pathological factors alone (both  $p < 0.001$ ). External validation of the RSClin estimated risk versus observed risk, based on data from 1098 women in the Clalit registry, indicated that the RSClin risk estimate was prognostic for distant recurrence risk (HR 1.73; 95% CI 1.40 to 2.15;  $p < 0.001$ ) and closely approximated the observed 10-year risk. The estimated benefit of chemotherapy was 0-15%, based on the RSClin score in a typical clinical scenario of a 55-year-old woman with a 1.5 cm intermediate-grade tumour with a recurrence score ranging from 11 to 50.

**COMMENT:** The accurate identification of which patients with breast cancer are most likely to relapse and therefore benefit from a more aggressive approach to treatment has been a source of great interest and much research through the years, particularly in those with oestrogen-receptor positive breast cancer. From the initial use of tamoxifen in oestrogen receptor-positive breast cancer, to the classification of tumours to categories such as Luminal A and Luminal B and most recently the use of SNP panels to identify those who would benefit from chemotherapy in addition to endocrine therapy, this has been a rapidly moving field as we identify better ways to select patients. This study reports on combining the histopathological features of the node negative, oestrogen-receptor positive tumours with the 21-gene SNP panel for better prediction of recurrence, further identifying those who will require additional treatment.

**Reference:** *J Clin Oncol.* 39(6):557-564  
[Abstract](#)

### Site-specific and targeted therapy based on molecular profiling by next-generation sequencing for cancer of unknown primary site: A nonrandomized phase 2 clinical trial

**AUTHORS:** Hayashi H et al.

**SUMMARY:** This Japanese, multicentre, phase II clinical trial examined the clinical use of primary tumour site-specific treatment and molecularly targeted therapy based on next-generation sequencing in 97 patients with cancer of unknown primary site. The cancer types most commonly predicted by an algorithm predicting tumour origin based on RNA and DNA sequencing were lung (21%), liver (15%), kidney (15%), and colorectal (12%). Most common gene alterations were *TP53* (46.4%), *KRAS* (19.6%) and *CDKN2A* (18.6%). Among treated patients, 1-year survival probability was 53.1% (95% CI 42.6-62.5), median OS was 13.7 months (95% CI 9.3-19.7) and median PFS was 5.2 months (95% CI 3.3-7.1). In 5 patients with predicted non-small-cell lung cancer (5.2%), targetable *EGFR* mutations were treated with afatinib in 4, of whom 2 achieved a durable PFS of >6 months.

**COMMENT:** Carcinoma of unknown primary is always a diagnostic dilemma, with some patients more challenging to find the primary site than others. For the majority of patients, this can involve a number of invasive procedures in an attempt to identify the primary and select the most appropriate treatment, but many will have insufficient useful information from the biopsy to guide such procedures, or patients may be too unwell. The use of genomic profiling to assess the molecular alterations present in the tumour and identify the likely origin of the tumour is an approach that has been used on both tissue and ctDNA. In this Japanese study, an algorithm predicted the site of the primary tumour and then treatment was initiated based on the genomic profiling. This offers a possible route to treatment for patients who may not otherwise be able to be offered anything, and as the techniques and prediction algorithms improve, is likely to improve outcomes.

**Reference:** *JAMA Oncol.* 2020;6(12):1931-1938  
[Abstract](#)



## Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): A multicentre, multicohort, phase 2a, platform trial

**AUTHORS:** Turner NC et al.

**SUMMARY:** This UK, multicentre, multicohort, open-label, phase IIa platform trial examined the accuracy of circulating tumour DNA (ctDNA) testing in 1051 women with advanced breast cancer and its use in the selection of patients for mutation-directed therapy. Agreement between ctDNA digital PCR and targeted sequencing was 96-99% and overall sensitivity for mutations identified by biopsy tissue sequencing was 93% (95% CI 83-98), with 98% (95% CI 87-100) sensitivity for contemporaneous biopsies. Over a median follow-up of 14.4 months, patients with *HER2* mutations, prescribed neratinib and fulvestrant if oestrogen receptor-positive (cohort B; n = 20), and patients with *AKT1* mutations and oestrogen receptor-positive cancer, prescribed capivasertib plus fulvestrant (cohort C; n = 18) met or exceeded the target number of responses, 25% (95% CI 9-49) in cohort B and 22% (95% CI 6-48) in cohort C. Cohorts A (*ESR1* mutations treated with fulvestrant; n = 74) and D (*AKT1* mutations and oestrogen receptor-negative cancer or *P TEN* mutation treated with capivasertib; n = 19) did not reach their targets; 8% (95% CI 3-17) and 11% (95% CI 1-33), respectively. Raised gamma-glutamyltransferase (16% cohort A), diarrhoea (25% cohort B), fatigue (22% cohort C), and rash (26% cohort D) were the most common grade 3-4 adverse events; 17 serious adverse reactions occurred (11 patients) with one treatment-related death (grade 4 dyspnoea in cohort C).

**COMMENT:** It is increasingly a requirement of selection for novel therapies/studies for patients to undergo biopsy of metastatic disease for molecular matching. For many patients, their metastatic disease may not be in a location that is safe or accessible for biopsy, potentially ruling them out of such an approach. The idea of 'liquid biopsies' with ctDNA is an attractive potential alternative to tissue biopsy but, to date, the practical application of this in selecting patients for treatment has been limited, amid concerns about sensitivity and specificity of the testing compared to tissue. This study was a multi-centre study using ctDNA to molecularly match patients with metastatic breast cancer to specific treatment regimens, depending on the results of the sequencing, and showed that the results correlated well with sequencing undertaken on metastatic disease. The findings provide evidence for using ctDNA in such patients in the future to identify potential treatments.

**Reference:** *Lancet Oncol.* 2020;21(10):1296-1308  
[Abstract](#)

## Larotrectinib in patients with TRK fusion-positive solid tumours: A pooled analysis of three phase 1/2 clinical trials

**AUTHORS:** Hong DS et al.

**SUMMARY:** This pooled analysis of data from a phase I adult, a phase I/II paediatric and a phase II adolescent and adult trial explored use of the selective tropomyosin receptor kinase (TRK) inhibitor larotrectinib in 153 evaluable patients with TRK fusion-positive (fusions between a neurotrophic receptor tyrosine kinase gene and a 5' partner gene) solid tumours. An objective response, according to investigator assessment, was achieved by 121 (79%; 95% CI 72-85) patients, with 24 (16%) achieving a complete response. A safety population of 260 patients, regardless of TRK fusion status, experienced common grade 3-4 larotrectinib-related adverse events including increased alanine aminotransferase (8 patients), anaemia (6 patients) and decreased neutrophil count (5 patients). Larotrectinib-related serious adverse events included alanine aminotransferase (2 patients), increased aspartate aminotransferase (2 patients), and nausea (2 patients). There were no treatment-related deaths.

**COMMENT:** In the last few years, we have seen the rise of tumour agnostic drug approval, based on molecular features. TRK fusions are present in a proportion of all solid tumours, ranging from relatively frequent in a few tumour types (including paediatric tumours, GIST and salivary gland mammary tumours) to present in only a few percent of other tumour types. This study of larotrectinib, together with a similar pooled study in the sister drug entrectinib, show excellent response rates in those with the relevant fusion, irrespective of tumour origin. However, the challenge is in identifying those patients in each tumour type who have TRK fusions, and realistically, widespread testing would have to be initiated as the individual rates of fusions are so low in most tumour types. The institution of a widespread RNA panel testing approach is relatively straightforward once set up, and includes other relevant targetable fusions for other cancers such as ALK in lung cancer and can be highly cost-effective when performed at scale, but requires a co-ordinated approach to succeed.

**Reference:** *Lancet Oncol.* 2020;21(4):531-540  
[Abstract](#)

## Assessment of clinical benefit of integrative genomic profiling in advanced solid tumours

**AUTHORS:** Cobain EF et al.

**SUMMARY:** This cohort study aimed to identify patients who derived the greatest degree of clinical benefit from next-generation sequencing profiling using tumour biopsy and blood samples to provide a genomic profile (whole-exome or targeted-exome capture with analysis of 1700 genes) of paired tumour and normal DNA and tumour transcriptome (RNA). Reports were sent to participating oncologists to determine treatment and subsequent therapy and treatment response was determined from medical records. Next-generation sequencing of tumours was successful in 1015 of 1138 patients (89.2%). Possibly actionable genomic alterations in 817 (80.5%) patients led to sequencing-directed therapy in 132 (16.2%) patients, of whom 49 experienced clinical benefit (37.1%); 26 patients (19.7%) experienced exceptional responses (lasting 12 months or longer). Pathogenic germline variants in 160 (15.8%) patients, included 49 (4.8%) with therapeutic relevance. Among 55 patients with carcinoma of unknown primary origin, next-generation sequencing identified the primary site in 28 and therapy in 13 patients obtained clinical benefit in 7 (53.8%), which included 5 exceptional responses.

**COMMENT:** This study builds on the success of other panel testing programmes such as MSK-IMPACT, where somatic and germline testing is offered to all patients with a solid tumour to enable genomic profiling. In some patients, this identifies a potentially targetable mutation that altered treatment choice; in 15.8% of patients, a previously unknown germline mutation was identified, of which only a third were relevant to the specific cancer, and the remainder were incidental findings that allowed family members to undergo testing to identify their own genetic risk and potentially prevent future cancer diagnoses. In other patients, genomic profiling confirmed or provided the likely origin of the tumour, reducing the need for multiple investigations to confirm the primary site.

**Reference:** *JAMA Oncol.* 2021;Feb 25 [Epub ahead of print]  
[Abstract](#)