# Personalised medicine from concept to clinical use

**Austin Tanney and Peter Kerr describe how Almac has utilised its expertise in working with formalin fixed paraffin embedded (FFPE) tissue in developing diagnostics for partner companies and in the development of its own pipeline of molecular diagnostics from preclinical biomarker discovery through to full companion diagnostic development and clinical test delivery.**

There is no doubt that personalised medicine is one of the major developments to impact both how patients are treated and how drugs are developed. The blockbuster model of drug development with 'one size fits all' drug treatments is clearly under scrutiny and new models of development and treatment are needed. As such, biomarkers are clearly at the forefront in the industry.

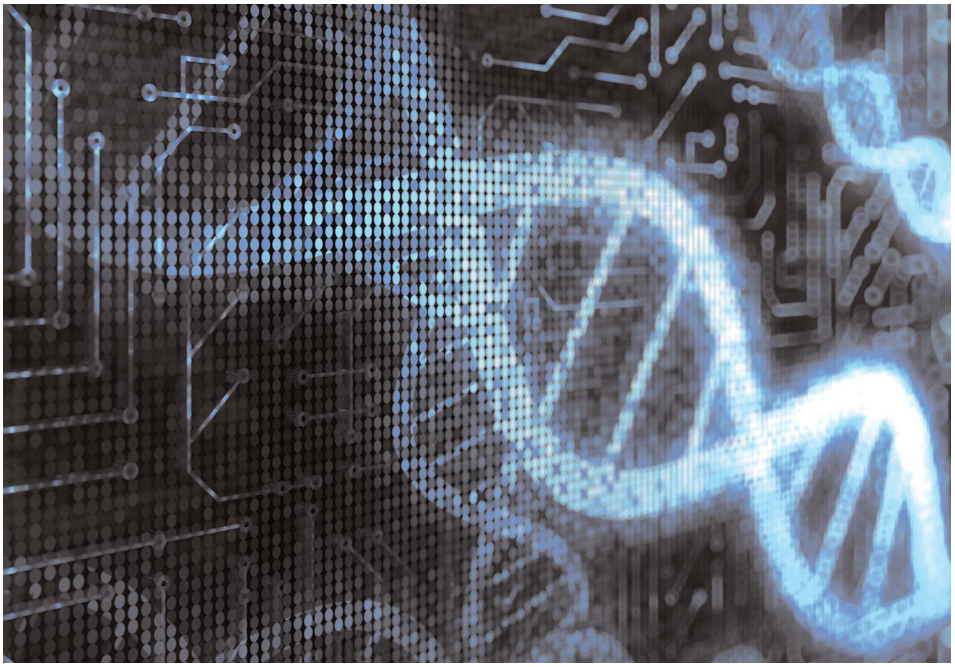
Biomarkers have a wide range of applications from better disease diagnosis to prognosis and prediction of treatment benefit. It is in this prediction of benefit where the majority of focus is at present.

This article focuses on the steps being taken today to bring forward personalised medicine. This involves turning biomarkers from concepts or research-use tools into clinically relevant tests. The ultimate goal of this being improved patient care.

## Biomarker discovery

The first step along this path is the discovery of useful biomarkers. Almac has its own biomarker discovery pipeline which focuses on the development of both prognostic and predictive tests. In the case of predictive tests, the focus is on identifying underlying biological patterns that can identify subgroups of patients who are more or less likely to respond to certain classes of drugs. In addition to this, however, Almac also works with pharmaceutical partners on the development of specific companion diagnostics, biomarkers that are associated with response to specific drugs, with the ultimate aim of developing an on-label diagnostic test that will be used as a prerequisite to drug treatment.

Biomarker discovery itself is a highly complex multi-layered process that is often a pitfall in the development process. The imbalance between the number of high-profile publications on discovered biomarkers and the number of these markers in the clinic is in many ways due to problems in the discovery process and the lack of consideration of the ultimate endpoint, ie the development of a diagnostic test. Almac's biomarker discovery processes are very much focussed on this ultimate end-point from the beginning.



**Molecular profiling and bioinformatics are key elements in the development of personalised medicine.**

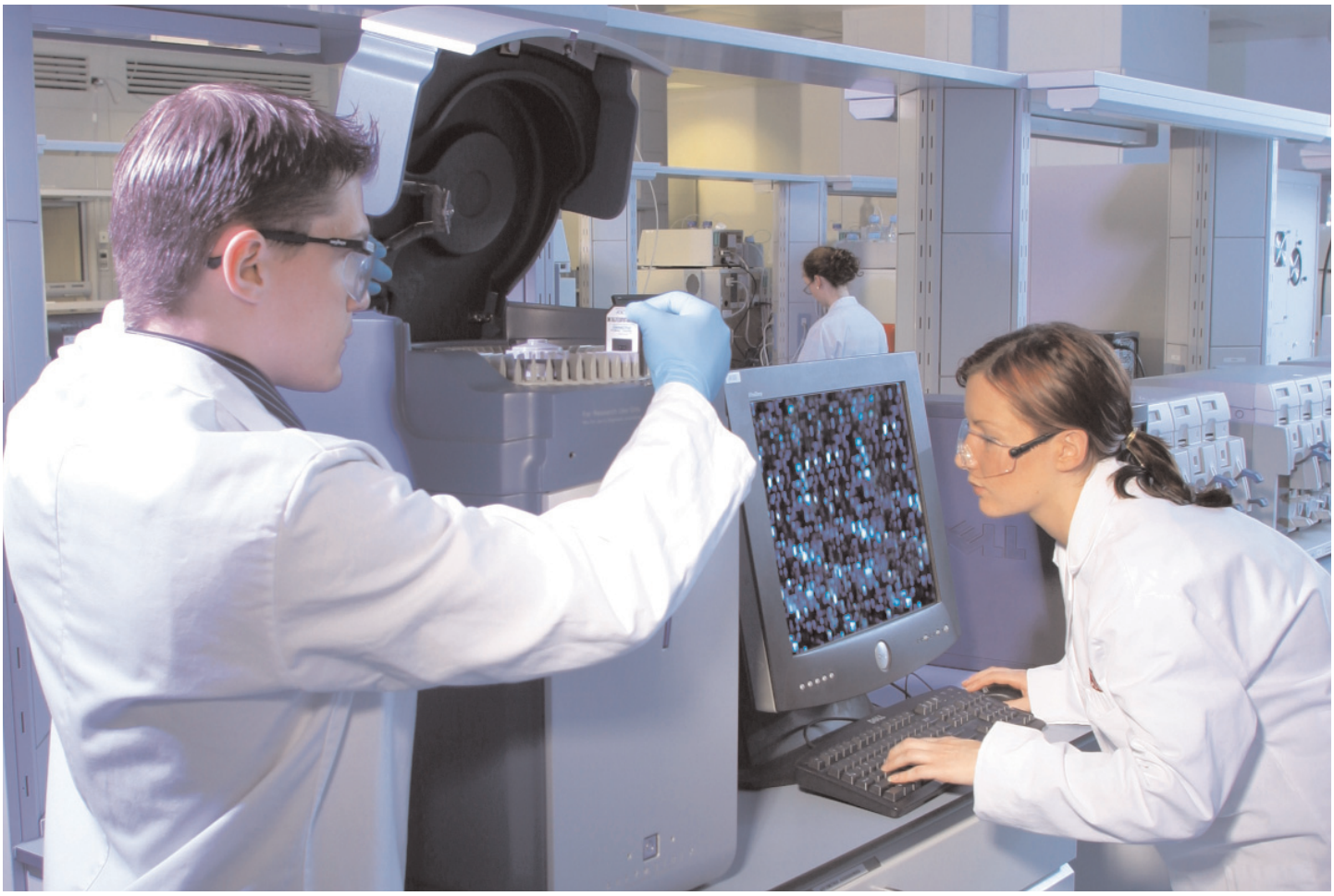
## Successful predictive markers

Successful predictive markers require a number of key considerations. Obviously the first consideration is the successful discovery of the marker and the biology behind it. However, this is only the first step in a long process before this biological marker actually results in a patient treatment decision. Almac works with a number of pharmaceutical clients across the whole pipeline of biomarker development. In some cases the studies worked on start right from the beginning and incorporate the full biomarker discovery process. In other cases, however, clients have candidate markers with varying degrees of validation already carried out. Sometimes these are quite close to clinical readiness with clinical validation carried out. In other cases the candidate biomarker is simply the result of some preclinical exploratory analysis requiring the establishment of analytical properties of the assay, and running clinical validation studies of the assay.

The process of turning a biomarker into a clinical test is a complex technical process. The discovery process may identify a single gene or a number of genes, a gene signature, which is associated with response to a drug. Turning this gene or list of genes into a simple test that can be delivered in a suitable timescale is the process of assay development of a biomarker into a diagnostic.

## Assay development

The first step in the process of turning a biomarker into a clinical test is often an assay migration. For example, if a gene expression based biomarker has been discovered, and even validated, using cell lines or fresh frozen clinical material, the performance of the biomarker as it stands will not necessarily transfer so that it can be used effectively in another matrix such as FFPE tissue. The fixation and degradation effects on the RNA



**Biomarker discovery often utilises high-complexity technologies such as microarray analysis.**

inevitably lead to a change in parameters such as sensitivity or specificity of the biomarker. This may involve potentially substituting genes in a gene signature so that the assay performance can be maintained. Having a biomarker that can be used in FFPE tissue in areas such as oncology can make a massive difference to the clinical utility and uptake of the biomarker.

Another type of migration that may be necessary is a platform migration. Much biomarker discovery takes place using highly complex techniques such as next-generation sequencing or microarray, where numerous targets can be measured simultaneously. Migrating a biomarker that consists of multiple genes or mutations being measured simultaneously as part of multi-variate index assay to a 'simpler' platform such as RT-PCR or immunohistochemistry-based can make that biomarker more amenable as a clinical test. Assays that are run on more complex platforms may be restricted to specialist labs as a service-based offering. Migration to another platform can make the assay feasible as a kit or even point-of-care diagnostic.

One key consideration of platform migration is assay turnaround time. If the biomarker is being used in the context of clinical trial enrichment then delay on the clinician receiving results back to determine eligibility of a patient for a trial can have detrimental effects on trial enrolment. Similarly, in a routine clinical care setting the biomarker result cannot delay patient treatment adversely. Assay delivery platform should be selected with this in mind.

The final example of assay migration is one that Almac has worked with a number of clients to achieve. In this case the assay is migrated from one disease indication to another. The reportable range of the same biomarker in a new disease indication can be very different than the original indication, and similarly assay cut points at clinically relevant thresholds will normally have to be adjusted for the new indication.

Following assay migration, or if there is no need for assay migration, a number of other elements need to be put in place in order to convert a biomarker into a clinical assay. One of these is ensuring that controls and references are established and characterised. Some biomarker assays will require a positive control sample to be processed along with each clinical sample. Similarly, other reference samples are needed to undergo analytical or method validation of the assay, for technical surveillance once the assay is being used to process clinical samples, for proficiency testing and training, and for lot testing of reagents used to process the samples. Because of these requirements, it is important to source controls and references so that there is either an indefinite supply of the material (such as cell lines) or enough to use over a significant period of time and to bridge to the next batch. This control material must also give repeatable, reproducible results over time.

One aspect of assay development often overlooked is that the lab protocols used in biomarker discovery are not necessarily suitable for clinical testing with the biomarker. 'Research Use Only' protocols should be updated to 'Standard Operating Procedures' (SOPs), if necessary conforming to clinical lab guidelines such as CLSI or CAP. The SOPs needed to receive and process clinical samples and output a clinical test result that a clinician can interpret essentially become the assay's 'Instructions for Use'.

The final output of a biomarker assay being used in a research or discovery setting is usually the raw data. For use as a diagnostic, that data needs to be presented as the appropriate clinical result to be interpreted by the treating physician. This can be a relatively straightforward process if a single or small number of independent analytes. However, if

**Almac offers a range of solutions from biomarker discovery to diagnostic development.**

a multi-gene signature employing a mathematical algorithm for data analysis is required then analysis software becomes a component of the assay. Almac has experience of generating such software so that patient sample details can be captured, QC and signature algorithm carried out and clinical patient result can be output.

Once the various components of the assay are in place, the analytical properties of the test can be established. Despite a number of guidelines being in place, the types of analytical studies, as well as what form each analytical study takes, are very much driven by the lab where the test is being developed. Regulatory requirements can have an influence on the level of validation to be performed (eg CLIA offering vs FDA clearance), and the platform will influence the nature of the studies to be carried out, as well as control samples to be used. Individual US states can have specific requirements of validation before allowing testing of patient samples from that state to be carried out. However, in most cases, some measure of precision, such as by reproducibility, will be needed, as well as measures of accuracy, sensitivity and analytical specificity.

## Assay delivery

Once an assay has been developed and the candidate biomarker converted to a diagnostic test, the next stage is the delivery of the test. This can be done in a variety of ways ranging from centralised laboratory testing right through to point-of-care diagnostics. In the case of predictive tests, the first stage is usually the use of the test for the enrichment of a Phase 2 or 3 clinical trial. Almac is currently working on a number of such studies and, as with assay development, this can be a very technical process that is often underestimated.

Prior to the running of the diagnostic, the clinical sites themselves must be prepared for the assay. In order to do this Almac works on the development of operational manuals, carry out clinical site training and audits as well as developing sample collection kits and shipping these to the sites. The company then handles the logistics for sample collection and shipping to its central CLIA laboratory. It is only then that the assay itself is actually run and the results supplied to the clinician within the required turnaround time for the patient to be enrolled in the trial.

## In conclusion

The way that drugs are developed and patient care is administered is changing. Personalised medicine holds the promise of improving patient care and ultimately creating significant benefits for society. The process of developing fully personalised medicine is a journey that has started already and will continue over the coming years. It is clear, though, that the first steps of this journey will depend on discovering scientifically robust biomarkers and turning these into reliable clinical tests.

## Meet Austin Tanney and Peter Kerr of Almac

*Dr Austin Tanney is scientific liaison manager at Almac's Diagnostic business unit. He graduated from the University of Ulster with a PhD in Biomedical Science. His background spans molecular biology and bioinformatics and he has more than 13 years' experience as a researcher and manager in academia and commercial enterprises. He has worked for several start-up biotech companies in scientific and bioinformatics roles and served as a bioinformatics consultant to the Department of Oncology in Queen's University Belfast. Dr Tanney joined Almac in 2003 and was the programme manager responsible for the development of the company's range of disease-focused microarrays, the DSA research tools. He currently works as scientific liaison manager for Almac's Diagnostics business unit, focused on biomarker discovery and development for personalised medicine.*

*Dr Peter Kerr is product development team manager at Almac's Diagnostic business unit developing prognostic biomarkers as part of the internal pipeline and working with pharmaceutical clients on the development of companion diagnostics.*

*He studied at Cambridge University before doing postgraduate work at Edinburgh and Glasgow universities leading to a PhD. He worked on the functions of BRCA1 and BRCA2 in the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research before establishing and managing a microarray facility. He then worked as a programme manager with the NCRI Informatics Initiative before joining Almac in 2006. He was R&D Manager at the company and has now established the product development team at Almac's Diagnostic business unit.*

## Further information

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