POST-MEETING HIGHLIGHTS REPORT

1st November 2019,
DoubleTree by Hilton,
Bristol

POWERFUL INSIGHTS FOR PERSONALISED TREATMENT

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Foreword

One of the most important developments in oncology in recent decades has been the emergence of the personalised medicine approach, which allows us to tailor treatment decisions to the individual patient. A method to achieve this is by using comprehensive genomic testing, with tests like FoundationOne® CDx and FoundationOne® Liquid demonstrating actionability and utility across multiple tumour types. Now is the time to embrace these technologies, maximise progress and ensure the best possible outcomes for our patients, but first we need to understand the who, what, how and when of genomic testing.

To help take the first steps along this pathway, I was pleased to chair *Powerful insights for personalised treatment in oncology*, a Roche-sponsored meeting with applications across the multidisciplinary team. Judging by feedback from the meeting, it is clear, with overall scores of 8.9/10 for relevance and quality of content, that this meeting served its purpose. The future is exciting, but more importantly, the future is now. We must acknowledge the importance of moving forward with this technology together today.

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Consultant Clinical Oncologist

Faculty

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POWERFUL INSIGHTS FOR PERSONALISED TREATMENT IN ONCOLOGY

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Executive summary

The healthcare landscape in oncology has been evolving for the past few decades, with an increasing focus on determining prognosis, predicting outcomes and tailoring treatment to the individual patient. Around 40 healthcare professionals from across several multidisciplinary teams (MDT) gathered in Bristol for this inaugural meeting to learn how to maximise this developing opportunity, with a focus on utilising genomic testing.

Although genomic testing has not been adopted as a routine tool in all NHS hospitals, the faculty emphasised that this was no longer just an opportunity for the future but a resource available now that can make a real difference to the lives of patients with cancer.

"This is not the future, this is the present... and we'd better be ready for it" – Professor Amit Bahl

Participants were encouraged to harness genomic testing to inform treatment options throughout the patient journey.

FoundationOne® is a comprehensive genomic profiling (CGP) service that has demonstrated actionability and utility across a number of tumour types.[1–4] Using a combination of patient case studies and discussions, the faculty shared their experience of ordering CGP and using the results to inform their practice.

Participant feedback

The day was met with enthusiasm from the participants, who openly shared their own expertise and challenges as they explored what the genomic era of personalised medicine may hold. **The meeting was awarded universally strong feedback by delegates (with relevance and quality of content rated 8.9/10).** Participants stated that key takeaways from the meeting included a better understanding of genomics, **seeing genomic profiling being the way to achieve personalised medicine and realising the importance of managing patient expectations.**

Success of personalised medicine to date and perspectives for the future

Professor Amit Bahl

What is personalised medicine and why do we need it?

The model of personalised medicine accounts for the fact that no two patients are identical and so, in order to optimise outcomes, treatment needs to be individualised to the patient and their preferences.[5–7] Compared with a non-personalised strategy, personalised medicine has been shown to improve efficacy outcomes across a diverse range of tumour types,[8] and the benefits may extend throughout society; for example, by cutting down waiting times, allowing early disease detection and improving population health.[6]

At the individual patient level, tailoring treatment has the potential to reduce medication-related side effects, potentially minimising the impact of therapy on quality of life.[9] Professor Bahl suggested that the ability to predict whether a patient is likely to respond to a particular therapy could prevent them from enduring side effects without the potential for clinical benefit.

How do we currently utilise a tailored approach?

Considering current clinical practice in oncology, Professor Bahl commented that we have already come some way to achieving a personalised approach (Table 1). Where chemotherapy was once the "backstop treatment", targeted medicines are now available, which are selected based on both histology and biomarkers identified using genomic testing.[5,10,11] Now, we are moving into the era of tumour-agnostic medicines, which treat disease based on genetic or molecular features only, rather than categorising by primary tumour. This development will impact the design of clinical trials and the way that drugs are licensed and funded;[12,13] therefore, it will be imperative that the MDT understand how the genomic make-up of a tumour will determine eligibility of patients for trials and funding.

Table 1: Potential of personalised medicine in oncology[14–17]

Target	Application
HER2/neu receptor	Anti-HER2 drugs for HER2-positive breast cancer
BRCA1	Inherited risk of breast cancer, predict response to treatment
CYP2D6	Guide prescription and dose adjustment of tamoxifen
TDM	Optimise dosing to improve outcomes and reduce occurrence of adverse events

TDM: therapeutic drug monitoring

Where are we now?

"Medicine is changing quite significantly. Where we are today... 20 years ago I didn't think we would be here"

Personalised medicine has already become a cornerstone of management in multiple disciplines in the UK, but, while the potential exists, we are not yet making the most of this opportunity in oncology. Professor Bahl urged participants to reflect on how this concept could be used more within their clinical practice, as this is not something to be considered for the future, but a method that we can use today.

The genomic testing armamentarium

Dr Mark Davies

Cancer is a disease of the genome, and different mutations that affect how the cell operates and drive cancer have become hallmarks of the disease.[18] Genomic signatures, such as tumour mutational burden (TMB) and microsatellite instability (MSI), are characteristic patterns of mutation that have clinical implications, such as a predisposition to malignancy or affecting response to immunotherapy.[19,20] Useful clinical information can be derived from these hallmarks and signatures; Dr Davies stressed the importance of understanding the genomic profile of a tumour in order to maximise the opportunity to act upon this information. Genomic tests not only help to identify genomic alterations but can also inform treatment decision-making by curating them and providing context, such as highlighting which alterations may be actionable.

Actionability: successfully matching a genetic alteration within a tumour with an effective targeted therapy that can subsequently improve survival for that patient.[21]

Foundation Medicine

FoundationOne® is one of a number of genomic services available.[1,2] FoundationOne® CDx is the only CGP test to receive Food and Drug Administration (FDA) approval, is approved as a companion diagnostic for 17 FDA-approved drugs and has been used in over 200,000 clinical cases.[22,23] The FoundationOne® CDx tissue-based service detects alterations across 324 cancer-relevant genes and tests 95 markers of MSI, compared with only five sets routinely tested in current clinical practice (Figure 1).[24–26]

Figure 1: Genomic alterations detected by FoundationOne® CDx[24,25]

✔	✔	✔	✔	✔
Base substitutions	Insertions and deletions	Copy number alterations	Rearrange-ments	CIT biomarkers
BRAF V600E	*EGFR* exon 19 deletion	*HER2* amplification	*ALK* fusion	TMB and MSI

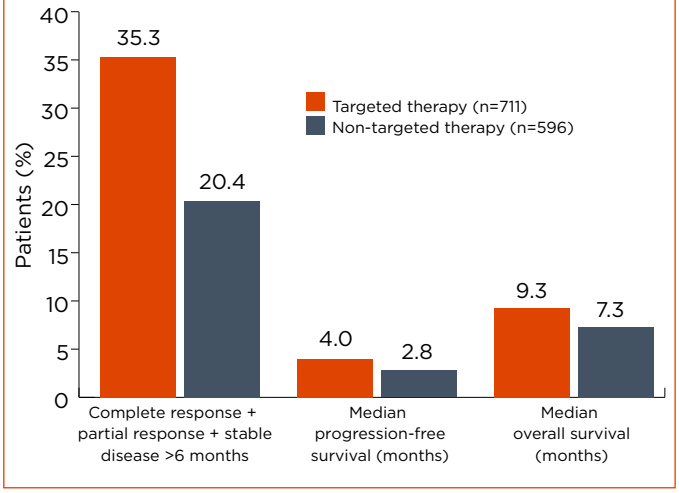
CIT: cancer immunotherapy

Real-world data have demonstrated the utility of FoundationOne® across multiple tumour types, with at least one actionable genomic alteration identified in up to 90% of patients.[3,27–29]

Those who receive therapy targeting genomic alterations may have improved outcomes compared with those who receive therapy that is not targeted (Figure 2)[30] – based on data from the US, up to one-third of patients receive targeted therapy based on their FoundationOne® profiling.[28,29]

Figure 2: Clinical outcomes in patients receiving therapy targeted to the tumour genomic profile[30]

Cancer is an evolving, genetically unstable disease.



Tumours change throughout the stages of cancer and subclones with different genetic information may exist,[31] which means a tissue biopsy may not be able to sample all the different populations and the chosen therapy may not target all mutations. The FoundationOne® Liquid test can sample DNA secreted by all tumours and clones into the bloodstream,[32] providing a composite of all the genomes, thus extending the benefits of CGP to more clinical situations, with demonstrated high concordance with the tissue test.[2,33,34]

Dr Davies noted that there is a fantastic opportunity in oncology treatment in the UK and predicted the use of genomic testing will change the way we practice through greater trial enrolment and use of tumour-agnostic drugs. He emphasised the need to understand the difference and potential of tissue and liquid testing, to ensure we maximise the opportunity for each patient whilst taking the fewest risks.

"The future is here now, and we have this fantastic opportunity with a real major impact on the patient"

The first point of clinical uncertainty

Genomic testing can be used to aid treatment decision-making, particularly when there is uncertainty about the next step in the patient journey. Three faculty members discussed where uncertainty first occurs in their tumour type of focus and where to consider utilising genomic testing in the treatment pathway.

Lung cancer – Dr Jason Lester

Dr Jason Lester explained how the treatment paradigm has changed beyond all recognition in lung cancer over the past 10 years. Platinum chemotherapy has been the standard therapy for many years;[35,36] however, targetable genomic alterations that predict sensitivity to particular therapies are now being routinely identified in clinics.[37–39] He predicted the treatment paradigm is due to change again with the development of new targeted therapies and increasing use of CGP tests such as FoundationOne®.

There are a multitude of actionable genomic alterations in lung cancer;[40] however, there is increasing complexity and uncertainty as to which mutation to act on and which treatment to choose. Genomic testing provides a useful tool to aid this decision-making, particularly in identifying resistance mutations where it is critical to prevent use of ineffective and potentially damaging therapies.[41]

"It's important we do everything we can to pick up these driver mutations"

It remains important to understand the limitations of current testing methodologies; for example, up to 35% of *ALK* mutations may be missed by fluorescence *in situ* hybridisation testing meaning that a proportion of patients who would respond to an *ALK* inhibitor will not be identified.[42] FoundationOne® provides the opportunity to identify actionable mutations in lung cancer.[1] Across 101 patients with advanced lung cancer undergoing hybrid capture-based next-generation sequencing (NGS), 83% had an actionable genomic alteration, 15% of which were negative by previous *EGFR* or *ALK* testing. Of 34 evaluable patients who received genome-directed targeted therapy, the objective response rate was 65%, with five patients achieving a complete response.[43]

Dr Lester also shared his clinical experience with FoundationOne® CDx by discussing the case of a patient who presented with lung cancer with bone metastases. FoundationOne® CDx was utilised to inform the treatment decision; in this case, no actionable mutations were identified above those initially targeted with therapies. This result provided reassurance that the team were not missing anything and allowed a focused discussion on the options of chemotherapy and/or immunotherapy for this patient.

Dr Lester suggested there will be questions and challenges regarding the identification of non-targetable mutations or off-licence treatment recommendations; however, he stated that he would prefer to have as much data as possible in order to have an informed discussion with the patient.

"Having the testing done all in one place, such as NGS testing, whether blood or tissue, has to be a good option"

Breast cancer – Dr Mark Verrill

There are many therapies available for breast cancer meaning decisions can be challenging,[44] creating the need for a method of determining which therapy is most suitable for that individual patient. Four factors should be considered:

- Tumour biology
- Tumour site
- Previous treatment
- Patient factors (e.g. performance status [PS], patient choice)

Dr Verrill noted caution should be used when assessing tumour biology as this evolves over time and tumours can become resistant to therapies and drug combinations.[31] To combat this, we need to understand these resistance mechanisms and the importance of considering a new biopsy. When acting on these assessments, he suggested that as we identify narrower tumour subtypes it will not be practical to test for each individual mutation separately – by using NGS testing we can identify clinically relevant pathways that may be missed by single tests.[45] FoundationOne® has demonstrated actionability in breast cancer – across 83 profiling reports using FoundationOne®, 41% of patients were recommended a change in treatment based on CGP.[46]

Dr Verrill provided his positive outlook for the current era of personalised medicine – there is now potential to change patients' treatment by understanding the molecular components of the breast cancer and the targets that may exist. He predicted that within the next 10–15 years genomic testing will be completed for every patient, at the beginning of their cancer journey, alongside creating truly personalised therapies.

Carcinoma of unknown primary – Dr Robert Jones

Carcinoma of unknown primary (CUP) is, perhaps, the epitome of clinical uncertainty in oncology. Encompassing a group of tumours that cannot be classified within any other category, CUPs are notoriously difficult to treat.[47] Although improvements in technology and the ability to assign a primary site mean that the incidence of CUP has decreased over the last 30 years, around 8,900 new cases were diagnosed in England in 2014.[48]

Challenges remain for those involved in the management of CUP:

- Delay in diagnosis[42]
- Patient population – older, poor PS, comorbidities[42]
- One-year survival is about 16%[49]
- Lack of ownership among the MDT/specialities
- Heterogeneous disease[42]
- No access to novel therapies or immunotherapy via site-specific trials

There are three potential strategies to overcome these challenges.

Strategy 1: find the molecular primary
Molecular profiling by RNA expression has been used to define the tumour of origin. However, no significant improvements in median progression-free survival have been demonstrated when patients receive traditional therapy versus treatment tailored to tumour site according to RNA expression analysis.[50]

Strategy 2: find the therapeutic molecular target

FoundationOne® profiling has been used successfully in CUP – across 4,650 patients with CUP, 36% had an actionable genomic alteration that could be targeted with one of eight common targeted therapies/immune checkpoint inhibitor strategies.[51]

However, outcomes with targeted therapy can be unpredictable even within the same tumour type, so Dr Jones emphasised the need to consider the context of the disease when making treatment decisions.[52–54]

Strategy 3: access a clinical trial
Upcoming trials will investigate how targeted therapies can benefit patients with CUP based on molecular profiling.

Dr Jones explained that, in his view, the outstanding challenge in CUP is gaining funding for treatment. Funding is not available unless an access scheme is available; therefore, how we licence and fund treatments needs to evolve in line with our developing knowledge and technologies.

An overview of accessibility, including recommendations for working effectively with funding authorities

Professor Amit Bahl

Certain CGP tests have been made available to some hospital trusts within the UK; however, there is no routinely commissioned test available on the NHS. In the private sector, many insurers have a policy on funding genomic testing; however, each decision is made on an individual patient basis and policies are evolving. Professor Bahl shared his recommendations for working effectively with insurance companies to gain access to testing.

Recommendations for working effectively with insurance companies

- Explain the relevance and necessity of the test, detailing how this will guide the treatment pathway (e.g. disease parameters, lack of response to standard therapy or lack of licensed therapies)
- Ensure discussion in the specialist MDT, include the notes and approval date on your application
- Provide feedback on how the results impacted on the pathway (avoiding ineffective therapies, accessing a clinical trial), to strengthen the platform for subsequent applications

If a treatment is recommended based on CGP that is not routinely available on the NHS, Professor Bahl suggested reviewing the application within a tumour-specific MDT or genetic review board, as some insurance companies will only consider the request once this has been completed.

Workshop 1
Genomic testing: which patient, which test?

Dr Mark Davies

We now have access to large gene panels that report information on hundreds of genes; however, there is still debate around the optimal time to biopsy.

Biopsies are associated with caveats such as risk to the patient, added cost and issues of accessibility, while tissue from an earlier biopsy may have been exhausted.[31,55,56] As such, Dr Davies suggested taking the following approach:

- To aid a particular treatment decision, you may wish to use a new biopsy
- To identify any actionable mutations within the tumour, the original biopsy may be suitable

Foundation Medicine has a portfolio of genomic tests available, but a key question to ask when applying for a test is whether a tissue-based or liquid (blood) sample is most appropriate (Table 2).[1,2]

Table 2: FoundationOne® genomic testing portfolio[1,2]

	FoundationOne® CDx	FoundationOne® Liquid
Target tumour types	All solid tumours	All solid tumours
Specimen	Formalin-fixed paraffin-embedded tissue	Peripheral whole blood
Number of genes	324	70
Immunotherapy biomarkers	MSI and TMB	MSI
Companion diagnostic	FDA-approved for 17 targeted therapies	

Liquid biopsy may be suitable when:[31,55,57,58]

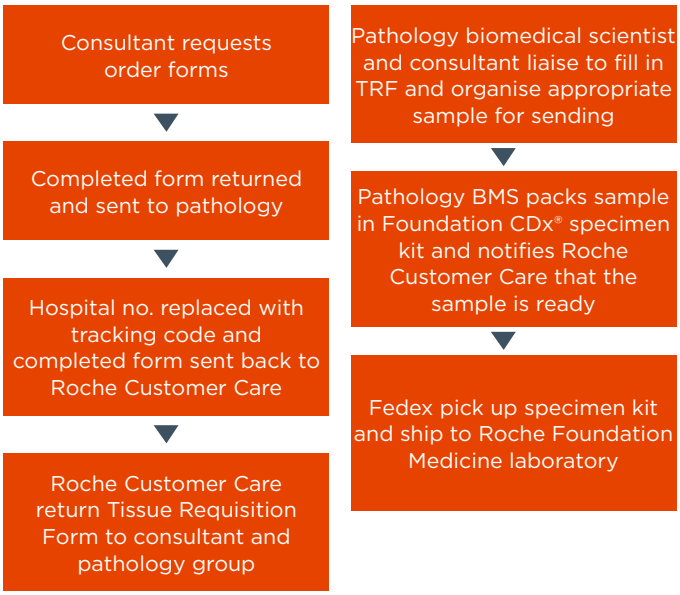
- Tissue biopsy is difficult or poses a high risk
- The patient has insufficient, inadequate or exhausted tissue
- Disease progression or resistance is suspected
- Complementary information to the prior tissue results are required

Although we are currently limited by the sensitivity of tests, Dr Davies felt that we may begin to use liquid biopsies to detect residual disease, monitor response to treatment and monitor clonal evolution or resistance.[59] When discussing genomic testing with the patient, it is pertinent to manage their expectations and counsel them appropriately. In some cases, no actionable mutations will be identified. This result can provide reassurance that the patient is not missing out on possible therapy options or clinical trials and may even be perceived by the patient as a positive, helping them to know that everything possible has been attempted.

Workshop 2
The testing pathway – the Bristol experience
Denise Gibson

Denise Gibson shared her experience of implementing the FoundationOne® testing pathway in Bristol, highlighting how this could be implemented at other institutions while also discussing how this pathway is likely to evolve (Figure 3).

Figure 3: The FoundationOne® CDx pathway implemented in Bristol



In the current state, Denise highlighted that most key stakeholders (consultants, nursing team, coordinator) are engaged, allowing discussion of cases at relevant MDT meetings. This is seen as a one-stop clinic managed by a specialty registrar (SpR) – patients are identified, referred to the SpR for consenting and then tests can be prepared the same day. However, Denise suggested the patient experience might be improved by offering the genomic test and consenting on the day of clinic review, rather than waiting for referral to the SpR.

The Foundation Medicine service will be managed via an online portal – this will reduce duplication of paperwork and it may even be suitable for the identification of eligible patients before they attend the clinic.

Offering advice to others hoping to implement a similar pathway, Denise highlighted that for the process to run as efficiently as possible, a review of infrastructure and capacity will be required, as well as involvement of other key staff groups such as the pharmacy team.

Workshop 3
Clinical experience and understanding uncertainty
Dr Mark Verrill

Dr Verrill shared his clinical experience with NGS testing in breast cancer by sharing two patient cases and encouraging participants to consider what treatment decisions they would have taken.

Case 1: breast or lung?

- History of breast cancer; complete mastectomy in 2006
- 2016: feeling unwell with abnormal liver function – working diagnosis of lung cancer with liver metastases
- Progressed on two lines of therapy, referred to Phase I unit
- Genomic testing identified *HER2* amplification and a *HER2* variant, suggesting possible breast cancer – now a candidate for anti-*HER2* therapy
- At review in September 2019, the patient showed an excellent response to treatment

"If we could save one life then we should be doing the [genomic] test and this was a life that could be saved"

Case 2: predicting resistance

- Oestrogen receptor+, HER2- breast cancer; mastectomy and previous chemotherapy with tamoxifen, development of rib metastases
- Patient initiated and continued hormone therapy before detection of liver metastases
- Initiated paclitaxel and simultaneously referred for liquid NGS testing
- *ESR1* mutation identified, suggesting potential resistance to conventional therapy options and highlighted a therapy option that previously would not have been considered for breast cancer

"Highlights the potential contribution of NGS and demonstrated a fundamental shift in what we were able to do"

Dr Verrill highlighted that NGS testing prevented the patient from undergoing treatment that was unlikely to be effective and suggested a potential off-licence therapy that would not have been previously deliberated. He encouraged participants to consider NGS testing in all patients to ensure important potential options are not missed but reiterated the importance of managing patient expectations prior to accessing the test.

Panel discussion – Genomic testing: which way now?

Chaired by Professor Amit Bahl
Dr Mark Davies, Dr Jason Lester
Dr Robert Jones, Dr Mark Verrill

The panel delved into how they currently use personalised medicine within their clinics and provided their perspectives for how their roles and ways of working may evolve in the near future, covering the following key areas:

- Molecular profiling is already becoming more important than standard histopathology testing, which could trigger a fundamental re-think about the testing pathway and tumour classification by professional bodies

- With increasing experience and confidence with genomic testing, only a select number of patients may require a more specialist review with a local specific genetic review board
  - To maximise the current opportunity and build the foundation of knowledge across the MDT, the feasibility of a local or regional genetic review board needs to be assessed to ensure involvement of members with a firm understanding of the technology to provide context and interpretation

- Clinicians often plan ahead, looking at possible future lines of treatment and trying to predict the pathway. Genomic testing can aid this planning by providing clinically relevant information and new possibilities such as off-label treatment or clinical trial enrolment

- In tumours such as lung cancer most driver mutations are mutually exclusive; however, dual mutations have been identified in clinical trials, which further complicates treatment decisions. Genomic testing such as FoundationOne® provides a matrix for data collection and could help provide a solution to this dilemma
  - Many of the driver mutations are so rare only one or two may be identified in a lifetime – a method of sharing real-time clinical experience on an international scale would be useful in such cases

- Molecular profiling is currently available to all consultants in Swansea and Cardiff, with no restrictive patient criteria. Clinicians receive training to enable interpretation of the genomic report and in some centres the trials units can aid in interpretation
  - Genomic testing has provided an avenue for patients that did not believe they would be eligible for a clinical trial by identifying rare mutations that allow admission into a relevant trial

- Liquid testing using blood is an attractive option and should not be overlooked. Blood should be used when tissue may not be representative of the tumour and to save solid samples for other testing

- If a tissue sample needs to be taken the most accessible site that will cause the least morbidity to the patient should be biopsied. It is also important to biopsy where there is uncertainty, such as where there are competing populations of cells (e.g. isolated metastases in liver with primary breast cancer)
  - In high-risk cases or where the biopsy will be difficult, perhaps due to vertebral sites, initiate the treatment that is likely to be most appropriate, then, if the patient doesn't respond as predicted, do the biopsy

Providing his summary message for participants, Dr Jason Lester encouraged teams to work together to maximise the opportunity ahead:

"This will scare some people, but... don't be frightened of it, the more information we have the better, there will be uncertainty and unknowns, but they will be shared."

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