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MAP PRESS RELEASE

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Following the tumour DNA trail to crack the secrets of personalised medicine [MAP 2018 Press Release]

MAP Congress 2018, 14-15 September 2018, Paris, France

Paris, France, 10 September 2018 – Individualised therapies that target the specific genetic features of tumours have the potential to transform cancer diagnosis, treatment and care. However, several challenges still need to be overcome before these approaches can be widely used in the clinic. Two DNA testing programmes have been implemented in institutes in Spain and the UK, to match patient tumour profiles with targets of early clinical trials, and to embed whole genome sequencing (WGS) in routine oncology practice, respectively. The results of these programmes, to be presented at MAP 2018 (1), illustrate that new sequencing techniques and process restructuring at the system level can be the drivers of a model that promises new opportunities for the greatest number of patients.

Matching tumour profiles to targeted therapies

In 2010, the Vall d'Hebron Institute of Oncology (VHIO) in Barcelona, Spain, introduced a molecular pre-screening programme (MPP) to match genomic alterations in patients' tumours to targeted drugs and immunotherapies being tested in early clinical trials (ECTs). A recent assessment of the programme's clinical utility (2) shows that the rapid evolution of sequencing techniques over the last eight years has gone hand in hand with the multiplication of alterations being targeted in biomarker matched trials.

There are at least 200 forms of cancer, and many more subtypes. (3) Every one of them is caused by errors in DNA, known as genetic mutations, that make cells in the body grow abnormally fast. In the last decade, cancer genomics research, based on sequencing the full DNA (or genome) of tumours, has been driven forward by several international initiatives that catalogued countless alterations found in the tumour tissue of tens of thousands of patients. These studies revealed that tumours are made up of several different subsets of molecules, each driven by distinct alterations – which suggested that they could be treated according to their individual molecular landscape.

Susana Aguilar, responsible for the MPP review, said: "When we started the programme, there were 13 phase I trials open at our institute, 11 of which were for drugs that targeted the same gene mutation. By 2017, the number of trials had

increased tenfold and targeted a much broader array of alterations – 40% were immunotherapy trials. The MPP grew accordingly, from 207 patients screened in 2010 to 1,168 tumours analysed in 2017."

Initially, patients were screened using so-called IHC (immunohistochemistry), FISH (fluorescence in situ hybridisation) analyses and hotspot mutation panels to search for alterations in a small number of genes and proteins known to play a role in cancer. In the last three years, next-generation sequencing (NGS) was implemented alongside other multigene assays to allow screening for mutations in as many as 61 genes simultaneously.

By 2017, these new molecular profiling techniques were used in most patients in the MPP: 10% of patients were enrolled in early clinical trials as a result, based on 18 different biomarker matches. "This proportion may seem low, but it is partly due to many other factors that determine patients' eligibility for a trial, including their overall clinical condition, distance to get to the hospital and treatment alternatives available," Aguilar explained. "Going forward, the clear trend in favour of immunotherapy trials will guide us in our implementation of new markers and tools to identify them in patients."

Carmen Criscitiello of the European Institute of Oncology in Milan, Italy, commented on the findings: "The evolution of sequencing techniques has allowed us to look for a wider array of mutations. For many of these, there is no registered drug available to target them. That's why a key approach to implementing personalised medicine in the management of advanced-stage cancer is to develop clinical trials that show the effectiveness of drugs in cohorts of patients defined by the same genomic alteration," she said.

"As these trials target more and more distinct alterations in smaller and smaller populations, the main challenge now is patient accrual: with targeted mutations detectable in less than 10% of tumours, we need to screen huge numbers of individuals to find just a handful of people eligible for a trial. Managing the expectations of the many patients for whom analyses don't lead to any meaningful treatment options is an issue that oncologists urgently need to address," Criscitiello added.

Bringing genetic sequencing into the daily clinic

In the UK, the 100,000 Genomes Project is the cornerstone of the country's Personalised Medicine Strategy. As part of this project, an initiative of the National Health Service (NHS) has sought to establish standard operational processes for whole genome sequencing (WGS) of patients' tumours in routine clinical practice. The results of this project (4) indicate that new consent models and coordinated processes for sample collection could make genetic testing for cancer patients viable on a large scale.

Jane Rogan of the Manchester Cancer Research Centre (MCRC) Biobank, which coordinated sample collection and delivered the project for the Greater Manchester area, explained the initial challenges: "One major topic from the start was the length of the consent form: we needed patient consent not just to store their tissue samples in our biobank, but also to sequence the tumour tissue. The former had to be obtained before the surgery to harvest the sample – a time when some patients didn't even have confirmation of their diagnosis yet, and many were in a state of distress," she said.

“To avoid subjecting patients to lengthy discussions about genomic consent unnecessarily, we introduced a two-tiered model whereby the second level of consent was requested only after sample eligibility had been confirmed.”

“Another constraint was that only frozen tumour samples could be admitted for analysis. The most common medium for sample preservation is formalin, but this is not ideal for DNA extraction,” said Rogan. “To ensure that as many patients as possible could be recruited while simultaneously minimising sample failure rates – due to improper preservation or insufficient tumour content, for instance – we had to integrate our biobanking activity with standard clinical pathways.”

This included the rollout of a shared patient tracker to record the status of candidates for the project, a process to guarantee the overnight refrigeration of samples collected outside the working hours of pathology departments, and a “biopsy pathway” to give patients access to the project outside of the surgery setting. “To date, about 900 samples from 18 different tumour types have been submitted for whole genome sequencing in Manchester: since we started collecting them, we have been able to reduce failure rates by over 10%,” Rogan reported.

Reflecting on these achievements, she added: “WGS has the potential to change our entire health system. Bringing it into routine cancer care is expensive – but when we spend money on appropriate diagnosis and finding the right treatment, we save money on ineffective therapies that don’t help patients but do have a long-term healthcare cost.”

Criscitiello commented: “The significant number of samples collected and the 10% reduction of failure rates show that the implemented system was successful. The clear takeaway from this is that although it may be feasible to use WGS as a standard clinical tool, it can work only if there is structured cooperation between all the professional players involved: oncologists, pathologists, research facilities, service providers and hospitals.”

According to Criscitiello, however, the major hurdle to this approach is obtaining the tumour tissue required for genetic testing: “Depending on the tumour type and location, neither surgery nor biopsy are safe or even feasible for many patients,” she said. “Liquid biopsies, which would allow us to collect so-called circulating tumour DNA (ctDNA) from a simple blood draw, are the most promising solution to this problem. As a non-invasive procedure, they would also enable us to do repeat analyses throughout a patient’s treatment, and thus potentially target alterations as they occur in continually evolving tumours – their use as a standard of care is continually expanding.”

However great the difficulties of putting all the pieces of the personalised medicine puzzle together, there is promise of a greater reward. Patients are already benefiting from the first tailored therapies that target their tumours’ genetic mutations: BRCA1 and BRCA2 genes, for example, are important for repairing the damage to DNA that occurs routinely throughout a cell’s life-cycle. Mutations of these genes within a cell can lead to DNA repair errors and ultimately to the cell’s death. In ovarian and breast cancers where such alterations are present, targeted drugs are used successfully to accelerate the death of tumour cells.

One major puzzle for oncologists – the prioritisation of multiple clinically relevant mutations in the same patient to inform therapeutic choices – was recently addressed with the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) published in August 2018. (5) "It provides a classification of known tumour DNA mutations according to the level of clinical evidence supporting the use of specific drugs – registered or in development – to target them, which should simplify our decision-making as oncologists and make treatments even more cost-effective," Criscitiello stated.

To drive the investigation forward, MAP 2018 – Molecular Analysis for Personalised Therapy, a joint initiative of Cancer Research UK, UNICANCER and ESMO, will bring medical oncologists, regulators and industry representatives together with the leading academic experts working in personalised medicine for cancer patients. The event taking place on 14-15 September in Paris, France, will be a platform to present the latest and best evidence available in the field and unlock the secrets of making individualised treatment strategies work for more and more patients.

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Notes to Editors

Please make sure to use the official name of the meeting in your reports: MAP Congress

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References

1 https://www.esmo.org/Conferences/MAP-2018-Molecular-Analysis-for-Personalised-Therapy
2 Abstract 66P 'Adapting a prescreening program to match molecular alterations in over 5,000 patient's tumors with targeted agents and immunotherapies in early clinical trials over the last 8 years' will be presented by Susana Aguilar during the Coffee and Poster walk/viewing Session on 15 September 2018, 14:00 to 15:00 (CEST) in Room Scene AB. *Annals of Oncology*, Volume 29, 2018 Supplement 6. doi: 10.1093/annonc/mdy316
3 https://cancergenome.nih.gov/abouttcga/overview
4 Abstract 23P 'Integrating Personalised Medicine into the Routine Cancer Diagnostic Pathway in Manchester, UK' will be presented by Jane Rogan during the Coffee and Poster walk/viewing Session on 15 September 2018, 14:00 to 15:00 (CEST) in Room Scene AB. Annals of Oncology, Volume 29, 2018 Supplement 6. doi: 10.1093/annonc/mdy316
5 Mateo J, Chakravarty D, Dienstmann R et al. "A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)." *Annals of Oncology 2018*; https://doi.org/10.1093/annonc/mdy263

23P - Integrating Personalised Medicine into the Routine Cancer Diagnostic Pathway in Manchester, UK

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Background: The 100,000 Genomes Project is a central element of NHS England's Personalised Medicine Strategy, which aims to progress the move from a 'one size fits all' approach to patient treatment to more effective personalised therapies. The driver for this lies in the relative inefficacy of generic treatments; leading to at least 40% of patients

receiving treatments that have no clinical benefit. This project is an NHS transformation initiative and aims to embed operational processes for Whole Genome Sequencing (WGS) of patient samples into routine clinical practice.

Methods: The Manchester Cancer Research Centre (MCRC) Biobank has been coordinating central sample collection in Greater Manchester since 2008. Historically, this activity has fallen outside of routine clinical practice, however integration of Biobanking activity and clinical pathways has enabled Manchester to deliver this national project. Steps taken include: Introducing methods in histopathology for routine frozen sample processing and tumour content assessment Roll-out of a shared patient tracker to faciliate recruitment A two-tier consent model enabling biobank consent at the time of surgery, followed by a more detailed genomic consent once sample eligibility has been confirmed Detailed data capture of sample 'failure' reasons to improve sample conversion rate Routine refrigeration of 'out-of-hours' specimens so that frozen tissue can be collected the following day Development of a 'biopsy pathway' to ensure learning can be main-streamed for real life clinical utility post project

Results: To date, Manchester have submitted ~900 samples for Whole Genome Sequencing. Key achievements include: Samples submitted from 18 distinct tumour types Reduction of sample failure rates by >10% Successful introduction of remote consenting model

Conclusions: Delivery of the 100,000 Genomes Project in Manchester is a clear demonstration of holistic working between research infrastructure and clinical service, which will ultimately transform personalised medicine for cancer patients in England.

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66P - **Adapting a prescreening program to match molecular alterations in over 5,000 patient's tumors with targeted agents and immunotherapies in early clinical trials over the last 8 years**

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Background: Since 2010, when the Molecular Prescreening Program (MPP) was established at VHIO, we have adapted the techniques and procedures to improve the identification of genomic alterations in tumors from patients (pts) eligible to Early Clinical Trials (ECTs). Here we report the clinical utility of our program given the evolving molecular testing landscape and trends in drug development.

Methods: In the last 8 years, 5,775 formalin fixed paraffin embedded tumor samples were analyzed: from 2010 to 2014 we used a hotspot mutation panel (Sequenom, 20 oncogenes) plus FISH/IHC of selected markers; from 2015 to 2017 we moved to a custom amplicon-based NGS panel (MiSeq, 61 genes), a copy number (CN) panel (Nanostring, 44 genes) and a fusion + gene expression (exp) panel (Nanostring, 26 genes) with additional FISH/IHC in selected cases, including PDL1 and MSI status.

Results: We found a stepwise increase in the MPP, from 207 pts in 2010 to 1168 pts in 2017. Most common tumors were colorectal, lung, breast, gynecologic, pancreatobiliary, head & neck and gastric. In the last 8 years, the number of ECTs increased tenfold: from 13 in 2010 (11 PI3K inhibitor [inh]) to 137 in 2017 (including 55 immunotherapy [IMT], 11 RAF/MEK/ERK inh, 9 FGFR inh, 8 PI3K inh, 6 EGFR/HER2 inh and 6 antibody-drug conjugates). Inclusion rate in ECTs with targeted agents reduced from 2016 to 2017 (228 to 133), while IMT trial recruitment increased (179 to 245). In 2017, 862 tumors had NGS, 708 tested with IHC, 267 CN panel and 342 fusion + exp assay. As a result of this molecular profiling, 116 pts (10%) were enrolled in ETCs with 18 diffent biomarker matches (5.5% mandatory, 4.5% enrichment) and 220 pts (19%) were recruited in unmatched trials.

Conclusions: The MPP at VHIO is constantly adapting to the needs of our ECTs portfolio. Biomarker matched trials evolved from a "few targets/ large populations" scenario to a complex situation with "many targets/ small populations".

Moreover, the substantial increase of IMT trials had a major impact in trial prioritization, and will guide clinical implementation of new markers currently under development, such as tumor mutational load and inflammatory gene exp signatures.

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Disclosure: All authors have declared no conflicts of interest.

About the European Society for Medical Oncology (ESMO)
ESMO is the leading professional organisation for medical oncology. With 18,000 members representing oncology professionals from over 150 countries worldwide, ESMO is the society of reference for oncology education and information. ESMO is committed to offer the best care to people with cancer, through fostering integrated cancer care, supporting oncologists in their professional development, and advocating for sustainable cancer care worldwide.

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Cancer Research UK (CRUK) is the largest independent funder of cancer research in the world. Every year CRUK invest around £350 million in world-leading research and innovative ideas that they believe will have the greatest impact for the public and cancer patients. CRUK's vision is to bring forward the day when all cancers are cured by supporting excellent research as well as influencing policy, providing information and empowering the public to ensure that the outputs of research are adopted. This work is almost entirely funded through the generosity of the public. CRUK partner with a range of organisations, ensuring that cancer is tackled on a global stage.

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