Reasons to be testing: the dawn of complex molecular profiling in routine oncology practice.

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Parallel advances in sequencing technology and synthetic chemistry have delivered a near-complete lexicon of genomic cancer drivers alongside the ability to therapeutically target a growing compendium of diverse oncogenic molecules. This has raised the expectation that a precision medicine approach to treatment can improve patient outcomes; however, clinical progress has been slow. Barriers to the full realisation of the power of cancer genomics include the availability and reimbursement of genomic testing and access to suitably comprehensive profiling. This, in turn, has impeded the development of novel therapeutic strategies by limiting the ability to select appropriate participants for clinical trials. To address these issues, several healthcare systems, including the UK's National Health Service, are investing in the provision of comprehensive genomic profiling for all cancer patients. This is being catalysed by progress in the capacity, expertise and infrastructure required to enable the clinical adoption of state-of-the-art knowledge and technology, which in turn facilitates the delivery of benefits to the patient and healthcare system.

This article highlights key factors underpinning the rationale for mainstreaming complex molecular profiling into routine oncology practice.

1. Iterative testing is expensive and wasteful of tissue.

In malignancies such as lung cancer where several genomic markers already exist, a single well-designed assay, available upfront for all patients, is both faster and cheaper than sequential testing (Steuten 2019, Pennell 2019). Importantly, biopsies are getting smaller whilst tissue demands are increasing (McCall 2019). This can lead to tissue exhaustion such that molecular testing is not possible, resulting in patients being denied access to biomarker defined clinical trials and, on occasion, standard of care therapy. Lack of tissue is, in turn, driving the increasing use of circulating tumour DNA for the detection of targetable genomic events; however, clinical concerns remain around this technology, including suboptimal sensitivity, problematic artefact and uncertain clinical utility (Sabari 2018, Merker 2018, Stetson 2019). Upfront comprehensive genomic profiling of tissue biopsies, including biomarkers for both approved and emerging therapies, offers a tissue efficient means to ensure patients can access standard of care and experimental treatment.

2. Rare indications are increasingly common; iterative single marker testing is not feasible.

Genomically tailored therapy is subdividing cancer into an expanding number of increasingly rare conditions, presenting major economic and logistical challenges to current models of single marker testing. As an example, anti-PD-1 immunotherapy is FDA approved for all microsatellite unstable (MSI) tumours; however, limiting MSI testing to patients with advanced colorectal or endometrial cancer (as is common in current clinical practice) only identifies around a third of eligible patients. Importantly, close to 50% of eligible patients harbour tumours with a sub-5% prevalence of MSI+ disease. Even more challenging are NTRK fusions with a pan-cancer prevalence of around 0.3%, where targeted therapy, approved in the US & EU, frequently produces striking responses for eligible patients. Testing all patients for rare markers using a specific or bespoke single gene or small panel test is not feasible; the solution is to test all patients upfront with a single assay providing comprehensive coverage of clinically relevant genomic markers.

3. Catalyst indications are changing the testing landscape.

A catalyst indication is often required to initiate widespread molecular testing in a given cancer type. As an example, approvals for IDH and FGFR inhibitors are on the horizon in cholangiocarcinoma (Mahipal 2018), thus paving the way for routine molecular profiling for this tumour. As molecular testing, initially for a small number of events, spreads across more cancer types, the opportunity to introduce comprehensive profiling expands. The emerging utility of tumour mutational burden may represent a broad catalyst for comprehensive molecular profiling in many tumour types (Samstein 2019). Comprehensive genomic profiling future-proofs for emerging clinical trial indications, including indication extension, and paves the way for innovative approaches to therapeutic development such as expanded access programmes that can be implemented within healthcare systems to share cost and risk.

4. Current state-of-the-art knowledge is not being consistently applied in clinical practice.
According to current UK guidelines, patients with KRAS/NRAS wild-type advanced colorectal cancer are eligible for anti-EGFR therapy. Resistance to anti-EGFR drugs is also well-documented in the presence of a BRAF mutation; however, inconsistent access to testing and lack of clear guidance results in some BRAF-mutant patients receiving anti-EGFR therapy and some not. Additional markers of resistance include ERBB2 mutation/amplification, MET amplification and PI3-kinase activation (Zhao 2017). Similarly, genomic profiling identifies a subgroup of EGFR-mutant lung cancer patients with primary resistance to anti-EGFR therapy (Morgillo 2016). Incorporation of additional relevant markers into routine clinical practice can protect patients from receiving ineffective therapy, allow expedient identification of alternative therapeutic options and deliver significant cost savings to the healthcare system. In clinical situations such as these, it may be that existing data are insufficient to provide physicians with the confidence to alter therapeutic pathways. Additional supportive data are ideally generated in real-world settings, driven by comprehensive genomic profiling of all patients within a self-learning healthcare system (expanded in more detail below).

5. Development of novel tailored therapeutics is hampered by insufficient trial enrolment and suboptimal genomics.
UK enrolment in oncology clinical trials has increased significantly in the last few years and now stands at around 16% (Ajithkumar 2017). However, this remains well below ideal and achievable levels when compared to trial enrolment and consequent progress in the treatment of haematological malignancies. Whilst clinical trial recruitment remains inadequate to power precision medicine, a growing body of opinion states that clinical trials should be considered as part of the patient care pathway (Fiore 2016, Weber 2017). Considering that around 164,000 people per year in the UK run out of therapeutic options and die of cancer, the potential health and economic benefits of remodelling current systems are substantial. Identification of relevant clinical trial biomarkers at diagnosis, through the use of a comprehensive genomic assay, would allow patient-tailored horizon scanning for emerging therapies and planning of treatment pathways beyond approved agents. It would also avoid the current practice of iterative molecular eligibility screening on a trial-by-trial basis, with its attendant risk of tissue exhaustion, adverse psychological impact and ultimately failing to find the right trial for the patient.

Disappointing outcomes from clinical trials of targeted anti-cancer therapy (Le Tourneau 2015, Trédan 2019) have led some to question the value of this approach (Tannock 2019). Unfortunately, flaws in the designs of these studies compromise their ability to adequately interrogate the concept of precision oncology. Limitations include suboptimal biomarker-therapy matching, inclusion of poor therapeutic options and suboptimal identification of driver mutations (the majority of somatic mutations play no direct role in the biology of cancer; Martincorena 2018). Importantly, trials have frequently employed limited genomic analyses optimised for the detection of small variants only, thus failing to capture and interrogate the entirety of the clinically relevant genomic landscape, the majority of which resides in copy number and structural alterations. Additional concerns include recruitment of end-stage patients and potential delays introduced whilst profiling is performed. A more general issue relates to the prevalence of trials testing single agents. Current knowledge of cancer biology informs us that single agent molecularly targeted therapy will always fail due to pre-existing resistance (González 2018), thus mandating studies of combination approaches. Unfortunately, the myth that targeted combinations are unfeasible due to toxicity still reverberates. In reality, the majority of combinations tested have targeted similar/overlapping pathways (Park 2013), whereas therapeutic progress will require the combined targeting of distinct cellular processes (González 2018). Specific approaches to minimise toxicity, including the finessing of dosing and scheduling, are currently being explored.

Much of the current targeted anti-cancer armamentarium has yet to be tested in a well-designed clinical trial where clinical outcomes are understood in the context of the full range of somatic genomic alterations. As further targets are identified and brought into the clinic, access to comprehensive genomic profiling becomes increasingly important to inform on the entirety of the patient treatment pathway, and thus increase the proportion of patients able to access experimental therapy.

Summary

Self-learning healthcare systems are becoming a reality. As boundaries between research and healthcare delivery become increasingly blurred, there is an emerging opportunity to accelerate learning through the cyclical integration and analysis of patient phenotype, treatment and clinical outcome. Opportunities already exist to save money through the more efficient use of targeted and immune-based therapies (Morgillo 2016, Zhao 2017, Keenan 2019), with a self-learning healthcare system representing an ideal environment for real-world hypothesis testing. Accumulated evidence suggests that interrogation of the genomic events driving cancer can be used to improve patient outcomes. Relatively few studies, however, have integrated complex genomic profiles with deep annotation of patient phenotype, treatment and outcome; where this has been performed, the full potential of genomics to impact the patient pathway has been revealed (Gerstung 2017).

A single, well-designed genomic assay can deliver >95% of all clinically relevant information for common adult tumour types, including the molecular examples outlined above. Importantly, these data can be delivered in real-world settings, from small amounts of formalin-exposed DNA, in clinically compatible turn-around times at a cost that is affordable to public healthcare systems. Integration of cancer genomic profiling into a self-learning healthcare system represents an opportunity for a step change in how cancer is diagnosed and treated, with beneficial impact on health economics and patient outcomes.

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