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Research Article

Improving Clinical Utility with Molecular Profiling – A Review of Critical Success Factors

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Introduction

Molecular profiling is becoming a new standard to optimize treatment for patients with locally advanced or metastatic solid tumors. Different approaches are currently being adopted for molecular profiling and in a recent review we found substantial differences in the reported clinical outcomes [1]. Here we explain the complex processes required to generate a molecular profile, which will lead to improved treatment outcomes and find reasons for the considerable differences in the clinical outcomes observed between the various approaches to molecular profiling.

Clinical utility, defined as improved patient outcomes in a tested population, has been proposed as the gold standard to assess the value of a new diagnostic method [2]

Other than a drug, which has an immediate effect after its administration to a patient, molecular profiling per se does not have any direct effect and only if the treating physicians change their treatment selection can it have an indirect effect on treatment outcomes. This is a main reason why controlled studies similar to those for new drugs have not been performed for molecular profiling so far. Because of its indirect effect, molecular profiling could not be studied in isolation but only together with the change in treating physician's treatment plans. The complexities of selecting the right treatments for patients who failed treatments according to the guidelines or for whom no clear standard of care exists make it almost impossible to preempt decisions about the treatment plan. Attempts to assess molecular profiling by developing rigid decision algorithms to which physicians had to adhere in a clinical study have so far not been able to demonstrate a clear benefit from molecular profiling. In contrast, patient registries, observational clinical studies, and case series have demonstrated clear differences in the clinical utility outcomes between different approaches to molecular profiling in comparable patient populations [1,3]. The clinical outcomes in patients with locally advanced or metastatic solid tumors with molecular profiling guided treatment decisions are significantly better than in patients who did not get guided treatments[4.5]

While companion diagnostic assays are part of the standard of care at first time diagnosis, comprehensive molecular profiling is usually performed in situations where there are no treatment standards available or a treatment must be selected between multiple different options within the standard of care. In many of the clinical studies of molecular profiling patients already underwent multiple lines of prior therapy.

The long-term adoption of a molecular profiling service will not only be determined by the clinical utility but also by its overall impact on health care costs. A review of health economic data shows that the cost of molecular profiling can only be justified for those services that have a high clinical utility. So far this has only been shown for Caris Molecular Intelligence (CMI)[6,7].

Selection of Biomarkers

Ideally all biomarkers assessed in a molecular profile are predictive of treatment outcomes with a specific drug or drug class. Nevertheless, in practice some biomarkers in a molecular profile may have no or very little relevance for treatment selection at the time of testing and are measured mainly because they might generate relevant information for drug development without adding cost or harm. It is important to resist the temptation of over-interpreting biomarkers, which are not yet clinically proven, as during the course of scientific research results may be produced in experimental settings that will not be reproducible in patients. If biomarkers would be sorted by therapeutic relevance, companion diagnostic markers in the approved indication would rank highest and biomarkers for which only scientific considerations or in vitro data provide a link to a drug that has not yet been fully developed would rank lowest. For clinical decision-making the ranking of biomarkers depends on multiple factors including the indication and the level of supporting evidence. For many patients a treatment alternative, which is supported by strong evidence, may not be available. These patients often receive experimental treatments, which can lead to important single observations that cannot be valued highly enough[8]. If published, the results of these treatments can be taken into consideration for the treatment of future patients with similar biomarkers. Molecular profiling often points to drugs that are not standard of care in a given indication but still should be considered after the respective biomarker has been identified Good examples of off label of drugs leading to a significant clinical benefit are the recent studies of irinotecan in breast cancer and the use of trastuzumab in ERBB2-mutated lung cancer[9,10,11]. In recent publications and guidelines testing of several biomarker panels is recommended, utilizing the advantages of multiple technologies like precision IHC, FISH, and DNA and RNA sequencing[12]. In our review it became clear that only

measurements of DNA, RNA, and proteins together can deliver the best clinical outcomes[1]. In particular the measurement of proteins using precision IHC has been proven to be instrumental in bringing benefit to a large number of patients in clinical practice [4].

Interpretation of the results

For the treating physician the interpretation of the biomarker results is most critical, as the treatment decisions based upon the molecular profile will ultimately determine the clinical outcome in every patient. In patients with locally advanced or metastatic cancer it is no longer possible for a single physician to follow all the relevant biomarker data. Molecular profiling is usually interpreted with the help of experts that support the treating physician. Biomarker experts already contribute at the design stage of a molecular profile by determining which biomarkers are truly predictive and with which technology they should be measured. This ongoing analysis of the available 'big' data results in proprietary algorithms that are constantly reviewed and updated. Careful consideration is also needed to design the semi-automated interpretation of biomarker results and the generation of an electronic report. The report is most critical in supporting treatment decisions and should be easy to read and understand while still containing the relevant depth of information required to prioritize treatments. It should hold information about the technical process with which a biomarker was assessed, clinical and preclinical data supporting the predictive power of a biomarker, and the approval status of the associated drugs. In addition to a report, which separates clinically validated and experimental treatment proposals, Caris Life Sciences routinely offers a consultation with an experienced Medical Oncologist to the treating physicians. This especially supports oncologists who are less experienced with molecular profiling in selecting the drug most likely to be active in an individual patient. Within this consultation every drug in consideration is assessed for its underlying likelihood of benefit in the particular patient and the modification of this likelihood by the presented biomarker results. A ranking of treatment options can be established in the context of the individual medical history and the drugs, which have already been administered. Molecular profiling will contribute to the final treatment decision by shortlisting drugs that are likely active or that are less likely to be of benefit to an individual patient. The avoidance of drugs, which are not active against the tumor but can harm the patient through adverse drug reactions and loss of time, is believed to be a critical factor adding to clinical utility[13]. It is critical to thoroughly understand the predictive power of every biomarker in a given patient. Data generated in clinical studies, case series, or case reports of patients with particular molecular abnormalities are usually more relevant to predict individual treatment outcomes than in vitro or animal data. A link between a molecular abnormality and a drug activity established in an experimental model cannot always be reproduced in patients. The actual understanding of the predictive power of any biomarker usually emerges as new clinical data become available over time. It is necessary to follow the emerging data and assess publications for the technical and medical relevance of new results. A deep understanding of not only the applied technologies but also the interaction with other biomarkers is needed. Every individual patient should be treated in consideration of the latest medical knowledge; this includes study results as well as individual case reports. The pace of emerging knowledge is an important factor driving the continuous emergence of a molecular profile and its interpretation.To keep abreast of this knowledge is challenging and only possible when the work is split between multiple members of a team specialized in this field. It may take many months until treatment guidelines and regulatory authorities adopt new knowledge.

A responsible and highly skilled approach must be taken to the interpretation of the biomarker results, which constitutes a key driver in patient benefit from molecular profiling.

Analytical precision

Recent publications reiterate the growing awareness of the importance of molecular testing in various tumor entities and also highlight the necessity to differentiate between services with levels of quality, integration and experience[1,3].

As the results are critical for the patient's outcome, meeting highest technical quality standards is a mandatory prerequisite for a molecular profiling service. The necessary precision can be proven by approval by the FDA or the New York Department of Health Wadsworth Institute, which is accredited by the FDA as a third party reviewer[14]. For next generation sequencing only platforms validated in clinical settings such as the Illumina NGS platform should be used. Research platforms like the one used by Paradigm or OncoDNA have shown little agreement with solid benchmarks such as Illumina NGS or SNP arrays[15,16]. The initial procurement, storage, and fixation of the tissue specimens by interventionists are of utmost importance. A fresh biopsy should usually be taken with instruments dedicated to harvest tissues for molecular biology[17]. Sufficient amounts of tissue can now be taken from most patients without major safety concerns [17,18,19]. For NGS analysis it can be important to enrich the tumor sample by microdissection. This adds precision and confidence in the results because the tumor cell DNA is less diluted with DNA from normal tissue[20]. Biomarkers measured by immunohistochemistry are being discussed controversially in the literature. Much of the uncertainty around individual biomarkers stems from the fact that technical assay quality is not standardized and many measurements lack analytical precision. The underlying cause lies in the diversity of antibody binding characteristics[21]. Only Caris Life Sciences has developed a quality system that ensures high precision of IHC results for those biomarkers where no FDA approved test exists. This approach led to the validation of the previously much disputed biomarker ERCC1 as predictive biomarker for treatment outcomes with platinum compounds[22,23].

Health economic considerations

After the highest clinical utility has been demonstrated with CMI the next step is the broad introduction in clinical practice also outside the US, where both CMI and FoundationCDX are already reimbursed. Health economic impact of CMI on overall health care cost needed to be demonstrated. Besides the costs for the profiling itself indirect costs from revised drug choices have been analyzed in relation to gains in progression free- and overall survival. While the advertised costs for a CMI and a FoundationONE molecular profile are in the same range ($5000 - $6500) the impact on utilization of drugs is remarkably different. While with a CMI test for most patients a conventional cytotoxic chemotherapy was selected after a FoundationONE test most patients have received novel targeted treatments6 (Figure 1).

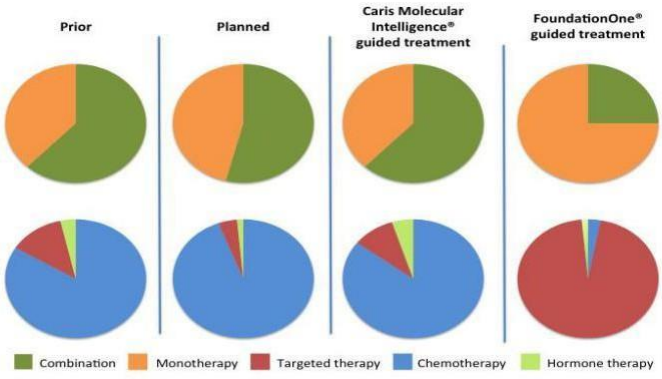

Figure 1: Comparison of molecular profiling-selected treatments with prior and planned therapy

The selection of conventional cytotoxic chemotherapies for most patients profiled with CMI is based upon the availability of precision IHC test results, which also drive selection of hormone therapies. Overall the treatment costs in patients profiled with CMI are not higher than those of the last prior treatment before profiling or those of the treatments planned before the CMI report became available to the physician. In contrast treatments selected based upon a FoundationONE report were significantly more expensive. We had previously reported the utility cost as the cost of profiling per patient with clinical benefit ($19'118 for CMI and $96'667 for FoundationONE)1. Treatment- and profiling costs were incorporated in the overall analysis of cost per PFS gained with CMI and FoundationONE6. As the PFS is expected to decrease with consecutive lines of treatment the cost for the planned treatment (without molecular profiling report) in relation with the PFS reported in a recent case series was used as reference24. The increase in overall costs by the added cost for profiling was outweighed by an increase in observed PFS with CMI. The cost per PFS achieved was almost doubled when FoundationONE profiling was used (Figure 2).

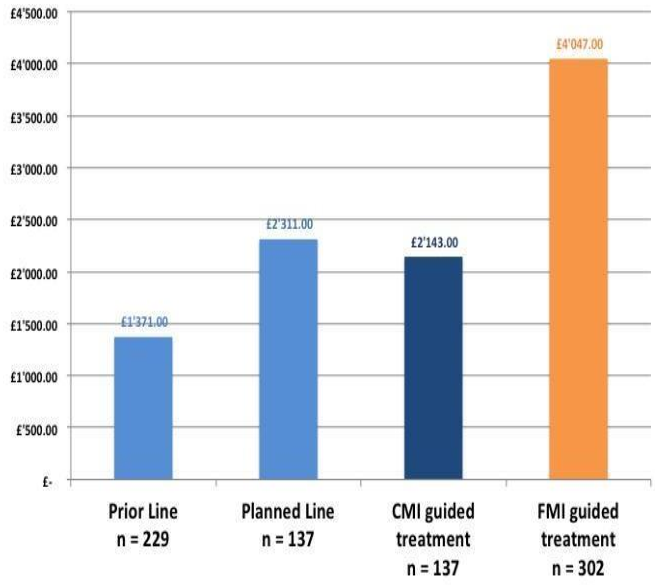

Figure 2: Comparison of overall costs per month of PFS gained

This proves that CMI is cost effective by selecting expensive therapies only for those who really need it, whereas FoundationONE is adding costs without returning a respective PFS-benefit in the population profiled.

In another analysis the overall survival gain from matched treatment compared to the average of the entire population was used to assess the incremental cost effectiveness ratio for CMI profiling. Following an approach similar to the one NICE is taking the added lifetime was calculated per £1000 spend. The NICE threshold for end of life treatments is a cost of £50'000 per life year gained and this threshold was consistently applied to new cancer drugs that have been reviewed recently. Expressed in lifetime gained per £1'000 spend the threshold is 7,3 days. The calculated value for the gain in lifetime with CMI following this approach is 21,2 days. This lies significantly over the threshold and can be compared with the value for the anti-PDL1 antibody nivolumab, a new immune checkpoint inhibitor (Figure 3).

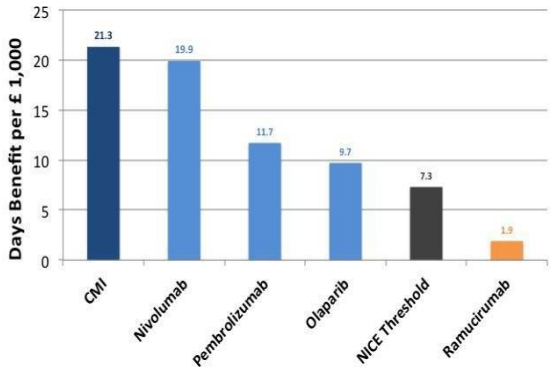

Figure 3: Cost of clinical benefit from drugs recently approved by NICE in comparison with CMI.

Summary and conclusion

Molecular profiling has proven to improve clinical outcomes in patients with locally advanced or metastatic cancer. To be successful, a number of conditions must be met: careful selection of the biomarker profile, use of multiple technology platforms, highest analytical precision, and diligent interpretation of the individual test results. Since our recent review[1] no new data that would meaningfully change the outcomes of our study have been published. The service offered by Caris Life Sciences delivers superior clinical utility when compared to the services provided by Foundation Medicine or ParadigmDx[1,3].Other services often use technical methods better suited for research use and have failed to produce meaningful clinical outcome data. We highlighted some of the complexities associated with molecular profiling and explained that many different factors are critical to achieve high overall clinical utility. A molecular profiling service must constantly evolve with the emerging medical scientific knowledge and address new drugs and biomarkers as they become available. The utility of molecular profiling is expected to further increase with the availability of new powerful drugs such as the immune checkpoint inhibitors and the development of powerful biomarkers guiding their use [25]. Cohort studies and clinical registries are most appropriate to assess the utility of molecular profiling services. We propose to focus on the analysis of such real life studies to further develop the utility of molecular profiling services. CMI has been proven cost effective within widely accepted thresholds in two different model calculations, which assess the gain in lifetime per amount of money spent and the incremental cost effectiveness ratio. The cost effectiveness of FoundationOne could not be proven and the current data suggest that it could increase the overall financial burden on health care. Multiplatform profiling has a significantly higher clinical utility and a more favorable health economic impact. The authors support the broad introduction of high quality multiplatform profiling solutions into routine clinical practice for patients with locally advanced or metastatic solid tumors.

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