Journal of Cancer Research and Treatment, 2017, Vol. 5, No. 3, 77-85
Available online at http://pubs.sciepub.com/jcrt/5/3/1

DOI:10.12691/jcrt-5-3-1

Molecular Profiling for Clinical Decision Making in Advanced Cancer: A Clinical Appraisal

Jaume Capdevila[1], Federico Rojo[2], Antonio González-Martín[3], Enrique Grande[4], Salvador Martín-Algarra[5], Javier Puente[6], Begoña Soler López[7,*], Ruth Vera[5], Jesús García-Foncillas[8]

[1]Vall d'Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain
[2]Pathology Department, Fundación Jiménez Díaz University Hospital, Madrid, Spain
[3]Anderson Cancer Center, Medical Oncology Department Madrid, Spain
[4]Hospital Universitario Ramón y Cajal, Medical Oncology Department, Madrid, Spain
[5]Medical Oncology Department, Clínica Universitaria de Navarra, Pamplona, Spain
[6]Medical Oncology Department, Hospital Clínico Universitario San Carlos, Thoracic, Urologic & Melanoma Cancer Unit, Madrid, Spain
[7]Medical Department, Las Rozas (Madrid), Spain
[8]Department of Oncology, University Hospital "Fundación Jiménez Díaz", Autonomous University of Madrid, Madrid, Spain
*Corresponding author: bsoler@ecbio.net

Abstract In the past five years, technological advances in the field of precision medicine in oncology have led to the emergence of a number of commercially available services for tumor profiling. There is an increased acceptance of these services that can help in finding treatment options based on molecular alterations as individual case reports have shown outstanding response to targeted therapies. Tumor profiling must seek to augment, rather than replace, existing local testing with the objective of helping more patients to find appropriate treatment options. The opportunity has arrived to integrate these services into the clinical setting, specifically in cases of refractory and rare tumors. The promise of precision medicine is clear but conclusive demonstration of how each of the different services delivers on the promise is not uniformly forthcoming. The selection of which service is most appropriate must be based on demonstrated analytical validation, quality standards, and data on clinical benefit and utility. The aims of this paper are to evaluate three tumor tissue profiling services commercially available and to propose to the physician how molecular profiling information can be used in clinical treatment decisions today.

Keywords: *molecular profiling, cancer, precision medicine, refractory tumors, rare tumors*

Cite This Article: Jaume Capdevila, Federico Rojo, Antonio González-Martín, Enrique Grande, Salvador Martín-Algarra, Javier Puente, Begoña Soler López, Ruth Vera, and Jesús García-Foncillas, "Molecular Profiling for Clinical Decision Making in Advanced Cancer: A Clinical Appraisal." *Journal of Cancer Research and Treatment*, vol. 5, no. 3 (2017): 77-85. doi: 10.12691/jcrt-5-3-1.

1. Introduction

Precision medicine in oncology promises to find the right drug for the right patient at the right time [1]. The high expectations and remarkable results of this field have led to the emergence of a number of commercial services that offer tumor profiling in the routine clinical setting. In the past decade, our increased understanding of many disease-specific molecular alterations in different tumor types has been translated into unprecedented improvements in patients' outcomes [2,3,4]. The precision medicine approach has been widely accepted into contemporary clinical oncology not only because of the medical and economic sense in finding the right drug for each patient and avoiding those that are not likely to work, but also because of the emergence of many new targeted therapies. In the past, pharmaceutical companies did not limit patient populations based on molecular alterations and used a 'one size fits all' approach to drug development. With the advent of targeted therapies, clinical trials run by pharmaceutical companies have now begun to focus on niche subgroups of patients who carry a specific molecular alteration. Most clinics use commercially available companion diagnostic tests to screen for any specific potential alterations and direct patients to the respective treatments. Some institutions have also established molecular screening tools to identify patients suitable for clinical studies. But validation of next generation sequencing for clinical use, for example, requires a huge investment for university and local funding bodies and can only be achieved in few centers. Commercially available tumor profiling services can complement this local tumor testing and in particular help to find the right treatment options for all those patients for whom no clinical trial options could be found.

Also must offer a broader panel of biomarkers and should meet the highest quality standards to ensure a treatment option can be seeked out. It is important that any services use technologies that are appropriate and accurate. Another key element is the predictive evidence that

underlies a treatment association; this should always be based on established and published clinical data. Using treatment associations based on preclinical- or animal models or on scientific assumptions carries a high risk of failure [5]. This kind of association can only be used as the basis for highly experimental treatments for which a good clinical rationale has failed.

All physicians who treat cancer patients in whom standard of care options have failed will find themselves with a therapeutic dilemma where the next treatment decision will not have sufficient scientific evidence to be included in standard of care guidelines. This point will often be reached earlier in patients suffering with rare cancers, where standard treatment options will be limited and many combinations have been tried without generating sufficient evidence to be included in the treatment guidelines [6]. In treating such patients, oncologists must base their decisions on an empirical approach weighing the possible risks against the potential benefits of using off-label therapies if clinical trials are not an option [7,8]. In spite of the lack of evidence supporting off-label drug use, and with the expectation that the response rates decrease with each successive line of cancer treatment, there remains a relevant margin of therapeutic benefit when compared against palliative treatments given after all standard therapies have been exhausted [9,10,11,12]. The selection of appropriate treatments that can improve the survival remains an unmet clinical need and precision medicine is the best way to achieve clinical benefits in these patients.

Precision medicine approaches promise to direct each individual patient to the right drug, but it is critical that the drugs are also accessible, thus allowing redistribution of available chemotherapy resources to those patients who are more likely to benefit. The ability of a precision medicine approach to deliver on this promise must be measured by clinical utility, showing how often the information provided to the physician impacts on a treatment decision.

The field of precision medicine in oncology has developed at a rapid pace since the beginning of this decade. This success has been possible thanks to technological advances, meaning that new diagnostic technologies are more readily accessible to physicians, but also advances in bioinformatics aiding in translating biomarker results to actionable associations. However, the rapid emergence of a number of commercially available services, which deliver tumor profiling services, along with the prevalence of molecular testing at local academic institutes, means that the field is becoming rapidly crowded with different options. There is a risk that inadequate regulation in this field will lead to confusion and frustration of physicians and in disappointment of cancer patients who are being sold on the idea of precision medicine but find that the particular offering they used cannot deliver on the promise. A precision medicine approach makes rational sense in oncology and it is important to carefully evaluate commercial platforms to ensure that the services used provide sufficient evidence of quality, utility and clinical benefit. Only if all requirements are met the promises of precision medicine can be fulfilled and the patients protected from exploitation or research purposes in routine clinical practice. Here we provide a fact-based evaluation of published evidence supporting the three commercial available services focused on tumor tissue profiling.

2. Materials and Methods

An expert panel of multidisciplinary cancer specialists analyzed and compared available tumor profiling platforms in Spain: Caris Molecular Intelligence®, FoundationOne® and OncoDEEP®. An extensive literature review and collection of information from websites of each platform was completed and deeply examined and discussed in a review meeting. As a result one draft consensus document was prepared that was submitted to the review of two external reviewers. No formal systematic literature search was performed.

3. Results

3.1. Comparison of Available Tumor Profiling Services

Many clinics already use a local lab for the assessments of individual biomarkers or small panels. The use of commercial services may bring a number of complementary advantages over local testing, including

- New technologies can be incorporated more quickly once sufficient utility and validation have been demonstrated because of the higher case numbers.
- Global standardization and quality assurance from independent quality organizations, in particular College of American Pathologists (CAP), Clinical Laboratory Improvements Amendment (CLIA), New York State Department of Health (NYS-DOH), consistency of results can be monitored.
- Centralization and high-throughput of analyses allow for quick building of clinical evidence databases with internal comparability.

The analytical comparison of the tumor profiling service is based on three aspects of the offerings:

1.1. Which technologies are used as part of each service and how have they been validated?

1.2. What evidence is used to drive the predictive association between biomarker results and treatments?

1.3. What are the demonstrated quality standards for each service?

3.1.1. Technology and Validation

A number of technologies are currently used in molecular profiling. These include immunohistochemistry (IHC), Sanger sequencing, next generation sequencing (NGS), fluorescent or chromogenic in situ hybridization (FISH and CISH), and polymerase chain reactions. Most local testing today comprise of NGS using commercially available gene panels to look at hotspots in approximately 50-70 genes, and immunohistochemistry or in situ hybridization testing using companion diagnostic kits or validated monoclonal antibodies established in the treatment guidelines. Hotspot panels are useful to identify pre-specified mutations occurring in limited areas of genes of interest. They focus on a narrow subset and tend not to

analyze the entire coding regions or detect all known alterations or classes of alterations. Deeper analyses using full exon coverage could help to complement testing already performed to find further treatment opportunities for patients. Other newer technologies are often available locally but only have application in the research setting and do not have application in the clinical setting due to lack of validation at the present time. The usefulness of most available local NGS panels is for the selection of patients for current clinical trials together with the well defined molecular aberrations with regulatory approved targeted therapies.

Commonly available commercial profiling services include IHC (looking at protein expression), CISH/FISH (looking at amplification, gene copy number variations or gene fusion), NGS (looking for point mutations, insertions/deletions, gene coy number variations) and pyrosequencing (looking for epigenetic changes to the DNA such as promoter methylation). All commercially available services should be analytically validated. A summary of tissue requirements, technologies used and other technical aspects of the three commercially available services has been collated from the respective company websites and included in this review are presented in Table 1. Information was taken from the respective company websites accessed on 05 October 2016 [13,14,15].

Caris Molecular Intelligence® is based on a multiplatform approach that seeks to use all clinically relevant information to find treatment options. Testing currently includes 12-15 IHC tests, 592 genes assessed with full exon coverage by NGS (including copy number variations in 442 genes and an assessment of total mutational load), 10 genes with RNA sequencing to find gene fusions, and other tests such as CISH, pyrosequencing and microsatellite instability performed in certain indications.

FoundationOne® is based on a single platform approach based on NGS alone. The development and validation of the approach has been published [16]. Testing currently includes a panel of 315 genes assessed with full exon coverage plus introns from 28 genes often rearranged or altered in cancer (including an assessment of total mutational load).

Table 1. Methodological Considerations across various commercially available platforms

	Caris Molecular Intelligence®	FoundationOne®	OncoDEEP®
Tissue Requirements			
Fixation	FFPE	FFPE	FFPE
Number of slides needed	1 block or 44 slides	1 block or 8-10 slides	1 block or 25 slides
Surface area required	25mm^2	25mm^2	25mm^2
Minumum Tumor nuclei content	20%	20%	30%
Technologies Used			
Immunohistochemistry	✔	✖	✔
Number of Tests Provided	12-15	-	5-8
Assessment of Phosphorylation of Proteins	-	-	2-5
Next-Generation Sequencing	✔	✔	✔
Number of Genes Tested	592	315	150
Technology Used	Illumina	Illumina	Ion Torrent
Type of Sequencing	Full exon coverage	Full exon coverage plus select introns from 28 genes	Hotspot only
Alterations identified	Point mutations, insertions/deletions, copy number variation (442 genes), tumor mutational load	Point mutations, insertions/deletions, copy number variation, gene rearrangements, tumor mutational load	Point mutations, insertions/deletions, gene translocations (32 genes), copy number variations (53 genes)
Depth of Sequencing (average)	750x	500x	1000x
Sensitivity	>99% sensitivity for base pair substitutions in ≥10% of cells with mutant genes >95% for CNVs from ≥8 gene copies	>99% for base substitutions in >5% of mutant allele fraction >97% for indel for ≥10% of mutant allele fractions >95% for CNVs from ≥8 gene copies in ≥30 tumor nuclei	Up to 0.1% limit of detection with 90% sensitivity and 98% specificity for mutations
Depth of Sequencing (average)	750x	500x	1000x
RNA Sequencing	✔	✖	✖
Platform Used	Archer FusionPlex	-	-
Number of genes	10 validated of 50	-	-
Other Testing	CISH, Pyrosequencing, Microsatellite Instability	NA	Pyrosequencing, Microsatellite instability
Other considerations			
Experience	>100,000 cases	>90,000 cases	>2,000 cases
Laboratory Location	Phoenix, AZ, USA	Cambridge, MA, USA	Gosselies, Belgium
Turnaround Time	10-14calendar days	14 calendar days	10 working days

OncoDEEP® is based on a multiplatform approach that seeks to use all clinically relevant information to find treatment options. Testing currently includes 5-8 IHC tests (including 2-5 tests of protein phosphorylation), 150 genes assessed using a hotspot panel by NGS, gene translocations in 32 genes, and copy number variations in 53 genes and other tests such as pyrosequencing and microsatellite instability performed in certain indications.

3.1.2. Evidence Driving Treatment Associations

Tumor profiling can provide insights into the tumor's fundamental oncogenic mechanisms based on biomarker abnormalities in well-understood cancer signaling pathways. This information helps to provide a more complete picture of an individual patient's tumor and supports clinical judgment in the selection of the best treatment options for an individual patient. Published literature that demonstrates a predictive association between a biomarker and treatment outcome strongly supports the use of biomarker information in a treatment decision. Evidence can be graded according to the United States Preventative Services Taskforce guidelines, which takes both study design and study validity into consideration [20]. Typically, the data for associations based on protein evidence associated with chemotherapies has been graded as Level 1 or Level 2 and have been demonstrated retrospectively. Many of the data linking signaling pathway alterations to targeted therapy response or resistance are based on individual case reports at most, or more likely, based on mechanistic associations. These may be sufficient to use as the basis for experimental treatments but should be used with caution as the likelihood of successful outcome is unknown. A list of the treatment associations available in each commercial platform is provided in Table 2.

Caris Molecular Intelligence®: 96% of associations which appear on the front page of the Caris report are based on Level 1 or Level 2 evidence. Extrapolations based on level 3 clinical evidence or preclinical data are presented as experimental opportunities and provide the basis for the Clinical Trial Connector. The Caris report provides associations for a comprehensive range of chemotherapies, hormone therapies, targeted therapies, immunotherapies and investigational agents.

FoundationOne®: FoundationOne® is a comprehensive and fully informative genomic profile that can reveal all classes of actionable alterations, including those in cancer-driving genes that are rarely or never tested for in solid tumors. The FoundationOne® report often reveals alterations that may lead to additional treatment options for physicians and their patients to consider. The testing is focused on providing associations to targeted therapies and investigational agents. Predictive associations with platinum agents (based on BRCA1/2 mutations) and immunotherapies (through tumor mutational load) are also provided. The level of clinical evidence underlying the proposed associations is not clear and the power of associations is not ranked.

OncoDEEP®: The OncoDEEP® report is focused on targeted therapies with these associations being driven by the results of NGS and protein phosphorylation assays. Predictive associations on selected chemotherapies, hormone therapy, immunotherapies and investigational drugs are also provided. The level of clinical evidence underlying the proposed associations is not clear and the power of associations is not ranked.

Table 2. Treatment Associations tested for all solid tumors.

	Caris Molecular Intelligence®	FoundationOne®	OncoDEEP®
Chemotherapy			
Antimetabolites *(5-FU, pemetrexed, capecitabine)*	✔	✖	✖
Anthracyclines *(doxorubicin, epirubicin, liposomal-doxorubicin)*	✔	✖	✖
Alkylating agents *(temozolomide, dacrabazine)*	✔	✖	✖
Nucleoside analog *(gemcitabine)*	✔	✖	✔
Platinum agents *(cisplatin, carboplatin, oxaliplatin)*	✔	✔	✔
Taxanes *(docetaxel, paclitaxel)*	✔	✖	✔
Topoisomerase inhibitors *(Irinotecan, topotecan)*	✔	✖	✖
Hormone Therapy			
Hormone therapy	✔	✖	✖
Androgen deprivation therapy	✔	✖	✖
Targeted Therapies			
ALK inhibitor *(crizotinib)*	✔	✔	✔
Antiangiogenic agents *(bevacizumab)*	✖	✔	✔
BRAF inhibitors *(vemurafenib, dabrafenib)*	✔	✔	✔
EGFR TKIs *(erlotinib, gefitinib, afatinib)*	✔	✔	✔
HER2-directed therapy *(trastuzumab, T-DM1, pertuzumab, lapatinib)*	✔	✔	✔
mTOR inhibitors *(everolimus, temsirolimus)*	✔	✔	✔
Small molecular kinase inhibitor *(imatinib)*	✔	✔	✔
Immunotherapy			
PD-1 inhibitors (nivolumab, pembrolizumab, atezolizumab)	✔	✔	✔
Clinical Trials			
Investigational Agents	✔	✔	✔

3.1.3. Demonstrated Quality Standards

It is important that both in vitro diagnostics (IVDs) and laboratory developed tests (LDTs) are performed to high analytical standards so that health care providers do not seek unnecessary treatments, delay needed treatments, or expose patients to inappropriate therapies. External quality assessment of both local laboratory testing and the commercially available services by independent bodies is required in order to ensure that all testing can be relied upon. In order for a service to be marketed in the US, external certification by the Clinical Laboratory Improvements Amendments (CLIA) and the College of American Pathologists (CAP) is required. Further, stricter validation is needed from the New York State Department of Health (NYSDOH) to test samples from New York. Together, these three provide quality standards for internal processes as well as for individual tests for biomarkers. Internationally, ISO15189 accreditation can be obtained to achieve quality control in internal processes and is compulsory for all medical laboratories operating in Belgium. A review of adherence to guidelines over the first five years of implementation of ISO15189 in 17 BELAC-accredited laboratories in Belgium found 421 non-conformities, including 19 major findings [21]. None of the commercially available services included in this review has been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary, although it is likely that regulation will follow in 2017. A summary of certifications and accreditations by each laboratory providing services described in this review are provided in Table 3.

Caris Molecular Intelligence®: The Caris laboratory is CLIA, CAP and NYSDOH certified/approved for all testing performed. The Caris Laboratory also holds state licensures from California, Florida, Maryland, Pennsylvania and Rhode Island. In addition, Caris is the only biolaboratory that has received the European ISO15189: 2012 certification in the United States. The service also holds a CE mark. Caris routinely uses commercially available in vitro diagnostic (IVD) kits to perform testing as part of the CMI service. If no kit is available, Caris develops a laboratory-developed test (LDT) to perform the testing.

FoundationOne®: The Foundation medicine laboratory is CLIA, CAP and NYSDOH certified/approved for all testing performed, and also holds a CE mark.

OncoDEEP®: All testing conducted as part of OncoDEEP is performed by the Institute of Pathology and Genetics (IPG) Gosselies. This laboratory holds ISO15189 accreditation, including accreditation for the Ion Torrent genetic sequencing performed as part of OncoDEEP®. All other aspects of the testing platform are not mentioned in the ISO15189 accreditation [22].

3.2. Clinical Utility and Impact on Patient Outcomes

3.2.1. Clinical Utility

Evidence-based guidelines on the use of genetic tests in clinical practice require a systematic assessment of their usefulness, which, following a commonly used framework proposed in1998 by a U.S. Task Force on Genetic Testing is commonly referred to as clinical utility [23]. Clinical utility can broadly refer to any use of test results to inform clinical decision-making. A summary of the impact of the information provided by the various services under review and the number of profiled patients based on the report is presented in Table 4 and detailed below.

Table 3. External Quality Certifications and Accreditations

	Caris Molecular Intelligence®	FoundationOne®	OncoDEEP®
CLIA	✔	✔	✖
CAP	✔	✔	✖
NYSDOH	✔	✔	✖
ISO15189:2012	✔	✖	✔
CE Marked	✔	✔	✔
Quality applies to all testing performed	✔	✔	✖

Table 4. Demonstrated Clinical Utility

	Caris Molecular Intelligence®	FoundationOne®	OncoDEEP®
Decision Impact			
References	*25, 26, 27, 28, 31*	*38*	*Not available*
Number of patients with Planned Line of Treatment recorded	137	132	
Number of Patients with changed treatment plans	120	36	
Decision Impact	**88%**	**27%**	
Percentage of Patients Treated			
References for Clinical Evaluations	*25, 26, 27, 28, 29, 30, 31, 32, 33, 34*	*38, 39, 40, 41, 42, 43*	*Not available*
Patients Profiled	486	1240	
Patients Treated	364	296	
Percentage of Patients treated	**75%**	**24%**	

Caris Molecular Intelligence®: In CMI evaluations where the planned treatment option was recorded prior to receipt of the report (n=137), a comparison to the actual treatment given could be performed. The treatment decision was changed upon receipt of the report in 120 of 137 (88%) cases [25,26,27,28,32]. Three hundred and forty eight of 473 patients (74%) profiled as part of CMI evaluations in routine clinical practice globally were treated in line with the report [25-34]. This figure is lowest in evaluations of gastric cancer (28 of 46 patients; 61%) and pancreatic cancer (30 of 55 patients; 55%). This reflects the aggressive nature of the disease and rapid progression in many cases rendered the patients no longer fit to receive treatment after profiling. The figure is also impacted by the interim nature of results from a prospective study in Austria, which is still enrolling and where many patients still remain untreated, as they had not yet progressed on prior therapy at the time of the snapshot.

FoundationOne®: A study of decision impact using FoundationOne® demonstrated that the treatment decision was switched in 36 of 132 cases (27%) [38]. In studies using FoundationOne® at key academic centres in the United States and Brazil, only 285 of 1,174 profiled patients (24%) received a sequencing guided treatment [38-43].

OncoDEEP®: There is no published record of clinical utility for the OncoDEEP® service.

3.2.2. Clinical Benefit

Another aspect of clinical utility to be considered is the impact of the profiling-guided treatment decisions on the patient outcomes. Measures of benefit include progression-free survival ratio, response or disease stabilization (SD≥6 months/PR/CR), time to next treatment, and overall survival. A summary of the demonstrated clinical benefit is presented in Table 5 and detailed below.

Table 5. Demonstrated Experience and Clinical Benefit.

	Caris Molecular Intelligence®			FoundationOne®			OncoDEEP®
Database Catalogue by Tumor Type							
Manuscripts & Posters	**230**			**100**			
Individual Case Reports							
Published Manuscripts	**12**			**46**			
Physician-Led Studies							
	Tumor Type	Number of Patients Treated	Number of Patients with Clinical Benefit	Tumor Type	Number of Patients Treated	Number of patients with Clinical Benefit	
	Refractory solid tumors [25]	66	18	TNBC [39]	16	5	
	Refractory pancreatic cancers [26]	24	9	Refractory solid tumors [40]	11	3	
	Refractory breast cancers [27]	25	11	Refractory solid tumors [41]	122	23	
	Refractory solid tumors [28]	37	22	Refractory solid tumors [42]	87	30	
	Refractory pancreatic cancers [29]	34	14	Refractory solid tumors [43]	24	8	
	Metastatic adenoid cystic carcinoma [30]	11	8				**No data published**
	Refractory gastric cancers [31]	24	7				
	Refractory solid tumors [32]	69	20				
	Refractory solid tumors [33]	19	7				
	Refractory solid tumors [34]	23	15				
Total Patients Treated & Evaluable	322			260			
Total Patients with Clinical Benefit	131			69			
% patients with Clinical Benefit	**40%**			**27%**			
Observational Registry Results							
Overall survival (OS) (n=1180) [36]	**Median OS 422 days longer in patients treated in line with report**			NA			
Collaborative Network Study							
Time to Next Treatment (TNT) (n=4,729) [37]	**Median TNT 33 days longer in patients treated in line with report**			NA			

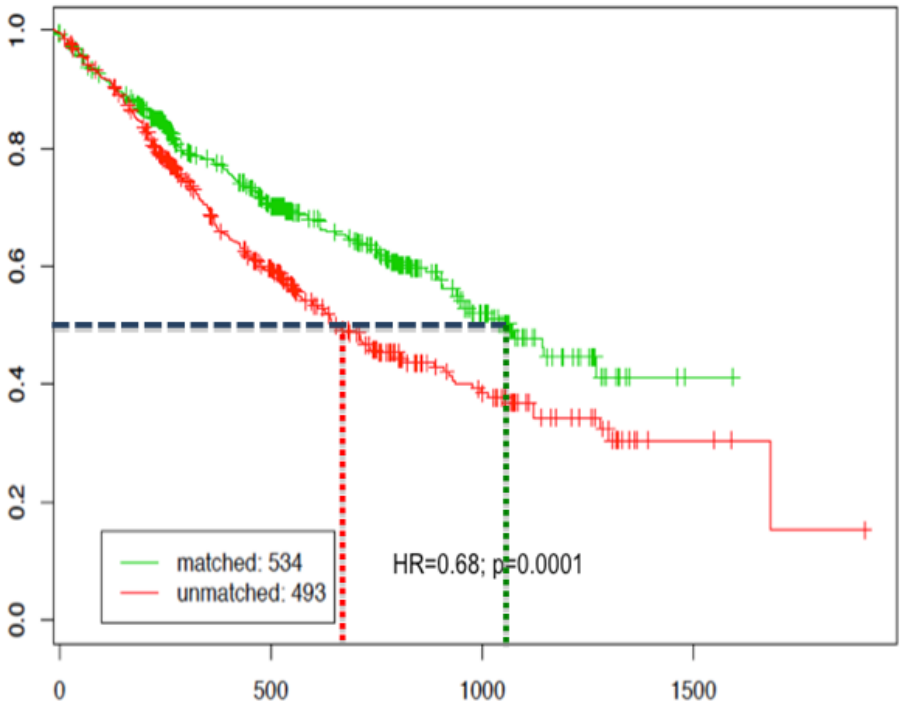

Figure 1. Overall survival results observed in patients who were included in the Caris Registry of patients. Reproduced with permission of Caris [36]

Caris Molecular Intelligence®: Caris has published 12 case reports that show the impact of successful treatment selection in patients across tumor types. In addition, Caris has conducted a number of physician-led prospective and retrospective evaluations of the service [25-34]. A recent independent review of the clinical data for Caris Molecular Intelligence® has been published by key opinion leaders from the UK, Belgium and Italy [24]. Of the 322 evaluable patients in these evaluations, 131 (40%) had clinical benefit as defined by the treating physician. An ongoing prospective observational study is being run which is following over 3,000 profiled patients for overall survival [35]. The study, which started in 2009, presented a first snapshot based on 1180 patients with different types of solid tumors. Patients were divided into two cohorts, based on whether they followed the report or not. The 'Matched' cohort consisted of 534 patients, while the 'Unmatched' cohort had 493 patients. Both groups were balanced in terms of participant's demographics and tumor types involved. As shown in Figure 1, patients in the Matched cohort had a significantly longer overall survival than patients in the unmatched cohort, with a median increase in OS of 422 days (HR=0.68, p=0,001). According to the data from this study, patients in the Matched cohort received less lines of therapy than patients in the Unmatched cohort (median treatment lines after receiving the Caris report of 3.2 versus 4.2 respectively).A paper describing the 9-month median overall survival benefit observed in ovarian cancer patients treated in line with the report was recently published by Herzog and colleagues [36].

In early 2015, Caris established a Centers of Excellence (COE) Network to track and integrate longitudinal clinical outcomes with comprehensive molecular data. Treatment data has been retrospectively collected from the electronic medical records of over 4,700 patients across all solid tumor types who received Caris Molecular Intelligence® profiling as part of their clinical care [37].

Time to next therapy (TNT) was defined as the length of time between the start date of the first treatment received after sample collection and the start date of the second treatment received after sample collection. Given the lack of reliable information about progression in electronic medical records, TNT is used as a surrogate for progression-free survival in this cohort of patients. The robustness of the treatment data captured in the electronic medical records allows for a complete and accurate measurement of TNT.

To assess the influence of Caris Molecular Intelligence® on TNT, two patient cohorts were defined based upon the first treatment administered after the time of specimen collection. The Matched cohort (n=3,011) received only drugs associated with benefit in the CMI report. The Unmatched cohort received at least one drug, which was associated with lack of benefit in the CMI report (n=1,718). TNT is censored after 1 year. Patients in the matched cohorts had a significantly longer time to next therapy (TNT) than patients in the unmatched cohort (median TNT 248 days vs. 215 days, HR=0.85; p=0.00018).

FoundationOne®: Foundation Medicine has actively published case reports showing outstanding clinical benefit in patients with different solid tumor who received guided therapy, 46 individual case reports are currently listed on the company's website. Of the 260 patients treated in a FoundationOne® study, 69 (27%) had clinical benefit [38-43]. The strongest data to date comes from a single center study conducted at MD Anderson in Texas [41]. Of the 339 successfully profiled patients, 317 (93.5%) had at least one potentially actionable alteration. Over a third of patients (36.5%; 122 of 339) received a treatment guided by the profiling results. Of the evaluable 118 patients who received matched therapy, 45 were directly matched while 73 were indirectly matched to the targeted treatment in question. A further 66 patients received an unmatched therapy. Twenty-three (19%) patients in the

matched treatment arm had clinical benefit (SD≥6 months/PR/CR) compared to only 5 of the 64 patients (8%) in the unmatched cohort. The median time to treatment failure was significantly longer (2.8 months versus 1.9 months, p=0.001) and a trend towards longer overall survival was observed (9.3 months versus 7.2 months). Interestingly, the clinical benefit does not appear to translate directly to an OS benefit. In the directly matched subgroup of the matched therapy cohort, 6 of 45 patients (13%) had clinical benefit with a median overall survival of 11.3 months. By comparison, most of the patients with clinical benefit were in the indirect matched subgroup (23%, 17 of 73) but had a shorter median overall survival of 7.3 months.

OncoDEEP®: There is no published evidence of clinical benefit for the OncoDEEP® service.

4. Conclusions

Our review of different molecular profiling services agrees that this new approach has high potential clinical value and, if used wisely can lead to remarkable benefits for patients. One key question to consider is the identification of which patients would need and benefit most of molecular profiling. There are currently several settings in which molecular tests are well justified: First, for patients with diseases for which novel targeted agents are approved. It is important to demonstrate the presence of such targets to give them access to the respective drug. Examples are ALK and EGFR genomic analysis in NSCLC, for which tests are usually performed at local institutions because validated test kits are commercially available.

A second indication is the screening of patients that may be candidate to participate in certain clinical studies of novel agents that need to be tested on patients with tumors holding an specific molecular profile Today, specialized clinics achieve to include a large number of patients into clinical studies; this is only possible when they perform molecular profiling that screens for mutations that can justify inclusion into the respective drug study. Usually broader genomic profiling is performed for this purpose and can be implemented by specialized local laboratory or facilitated by a profiling service like the ones we reviewed.

The third clinical use is for patients for whom the testing of standard biomarkers did not yield an actionable result and participation in a clinical study would not be the first choice. After the standards of care failed, a broad search can be started to find drugs that are potentially active for their disease. These can be drugs that would usually not be considered and the search should be performed across all classes of drugs, ie. includes conventional cytotoxic chemotherapies, hormone therapies, and targeted therapies.

In this task, our review support that Caris CMI offers the most complete multiplatform profile with which favorable clinical outcome data were produced. These clinical outcome data clearly show that with the right approach to clinical use, the broader practice is well justified as the clinical benefit has been demonstrated. This review has the limitation that the information about the use of platforms for molecular profiling is continuously updated, and most of this new information is not formally published and indexed. The analyzed commercial platforms were those available in Spain, but are the most widely spread too. We consider that the general scheme of analysis described can be applied for the evaluation of other platforms.

From the patient perspective pre-test medical information must be clear, transparent and honest, as not all the patients tested will get a clear benefit. Limitations and barriers in the post-test access to the therapy should also be considered, with special mention to a couple of specific and common situations: the rapid deterioration of the patient if the test is ordered in a too-late stage of the disease, and barriers in the access and reimbursement of non-licensed drugs for the specific patient's disease, specially in target therapies.

We believe that it is time for multiplatform profiling to be introduced into general clinical practice. For this it is important to offer them at institutions where experienced oncologists know how to best interpret the data from a molecular profile, where there is access to experts who can help characterize unexpected findings, and where a multidisciplinary exchange is part of the common clinical practice. Currently available services as those reviewed here should complement and augment existing research institute capabilities and could be used for select patients who may benefit. The institutional approval and reimbursement of multiplatform profiling must be considered in certain well defined clinical settings such as for instance rare tumors, carcinoma of unknown primary, triple negative breast cancer or third line colorectal cancer. Only 'proven' services should be reimbursed, they should meet most stringent quality criteria and they should have produced real life data on the benefit they can achieve.

Introduction of molecular profiling into clinical practice must also consider that patients need to be informed adequately by the treating oncologists in order to set the expectations correctly.

Acknowledgements

The authors acknowlegde to Laboratorios Leti (Madrid, Spain) the support for the organization of the experts meeting.

References

[1] Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol, 2013; 31: 1803-5.

[2] Ruckdeschel JC, Finkelstein DM, Ettinger DS et al. A randomized trial of the four most active regimens for metastatic non-small-cell lung cancer. Journal of Clinical Oncology, 1986; 4: 14-22.

[3] Lu S, Yu Y, Chen Z et al. Maintenance Therapy Improves Survival Outcomes in Patients with Advanced Non-small Cell Lung Cancer: A Meta-analysis of 14 Studies. Lung, 2015; 193: 805-14.

[4] Welch H, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? JAMA, 2000; 283: 2975-8.

[5] Le Tourneau C, Delord JP, Gonclaves A et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol, 2015; 16:1324-34.

[6] Miller RC. Problems in rare tumor study: a call for papers. Rare tumors, 2010; 2: e16.

[7] Conti RM, Bernstein AC, Villaflor VM et al. Prevalence of Off-Label Use and Spending in 2010 Among Patent-Protected Chemotherapies in a Population-Based Cohort of Medical Oncologists. Journal of Clinical Oncology, 2013; 31: 1134-9.

[8] Olmos D, A'Hern RP, Marsoni S et al. Patient Selection for Oncology Phase I Trials: A Multi-Institutional Study of Prognostic Factors. Journal of Clinical Oncology, 2012; 30: 996-1004.

[9] Planchat E, Abrial C, Thivat E et al. Late lines of treatment benefit survival in metastatic breast cancer in current practice?. Breast, 2011;20: 574-8.

[10] Reinmuth N, Payer N, Muley T et al. Treatment and outcome of patients with metastatic NSCLC: a retrospective institution analysis of 493 patients. Respiratory Research, 2013; 14: 1-9.

[11] River G, Moore S, Tucker J, Markman M. An Experience with Managing Cancer Patients Reportedly Previously Informed of the Absence of Additional Available Antineoplastic Therapeutic Options. Case Reports in Oncology, 2014; 7: 633-7.

[12] NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol, 2008; 26:4617-25.

[13] Caris Life Sciences profile information at: http://www.carismolecularintelligence.com/solid_tumors_international (accessed 05.02.2017).

[14] Foundation medicine information at: http://foundationone.com/docs/FoundationOne_tech-info-and-overview.pdf (accessed 05.02.2017).

[15] OncoDNA information at: http://www.oncodna.com/distributors/docs/products.pdf (accessed 05.02.2017).

[16] Frampton GM, Fichtenholtz A, Otto GA et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotech, 2013; 31: 1023-31.

[17] Weigelt B, Warne PH and Downward J. PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. Oncogene, 2011; 30 (29): 3222-33.

[18] Hortobagyi GN, Chen D, Piccart M et al. Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from BOLERO-2. J Clin Oncol, 2016; 34: 419-26.

[19] André F, Hurvitz S, Fasolo A et al. Molecular alterations and everolimus efficacy in human epidermal growth factor receptor 2-overexpressing metastatic breast cancers: Combined exploratory biomarker analysis from BOLERO-1 and BOLERO-3. J Clin Oncol, 2016; 34: 2115-24.

[20] Harris, T, Atkins D, Woolf SHet al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med, 2001; 20(3S): 21-35.

[21] Raymaekers M, Cnops L, Vanmassenhove B et al. 2015 Five years of experience with ISO15189 accreditation in Belgian molecular diagnostics laboratories. Presented on behalf of MolecularDiagnostics.be and accessed at http://www.moleculardiagnostics.be/site/data/images/content/files/Van_Lint_EMMD15.pdf (accessed 05.02.2017).

[22] ISO15189 accreditation for Institut de Patholgie et de Genetique Gosselies accessed at http://ng3.economie.fgov.be/NI/belac/medilabs/scope_pdf/381-MED.pdf (accessed 05.02.2017).

[23] Holtzman NA, Watson MS. Promoting safe and effective genetic testing in the United States. Final report of the Task Force on Genetic testing, 1997. https://www.genome.gov/10001733/ (accessed 05.02.2017).

[24] Ussia G, Leonard R, Janssens J. Multi-platform tumour profiling delivers the highest clinical utility and improves patient outcomes in today's routine clinical practice. International Journal of Surgery & Surgical Procedures, 2016, 1: 107.

[25] Von Hoff DD, Stephenson JJ, Rosen P, et al. Pilot study using molecular profiling of patients' tumours to find potential targets and select treatments for their refractory cancers. J Clin Oncol, 2010; 28: 4877-83.

[26] Epelbaum R, Shacham-Shmueli E, Klein B et al. Molecular Profiling-Selected Therapy for Treatment of Advanced Pancreaticobiliary Cancer: A Retrospective Multicenter Study. BioMed Research International, 2015, Article ID 681653, 2015.

[27] Jameson GS, Petricoin EF, Sachdev J et al. A Pilot Study Utilizing Multi-omic Molecular Profiling to find Potential Targets and Select Individualized Treatments for Patients with Previously Treated Metastatic Breast Cancer. Breast Cancer Res Treat, 2014 Oct;147:579-88.

[28] Dean A, Byrne A, Marinova M, and Hayden I. Clinical outcomes of patients with rare and heavily pretreated solid tumors treated according to the results of tumor molecular profiling. BioMed Research International, 2016; Article ID 4627214.

[29] Popovtzer A, Sarfaty M, Limon D et al. Metastatic Salivary Gland Tumours: A Single-center Study Demonstrating the Feasibility and Potential Clinical Benefit of Molecular-profiling-guided Therapy. BioMed Research International, 2015, Article ID 614845, 2015.

[30] Purim O, Shacham-Shmueli E, Beny Aet al.. Molecular profiling-selected treatment in metastatic gastric and esophageal cancer: Real-life clinical experience. BioMed Research International (in press).

[31] El Ahmadie A, Ibrahim T, El Karak F et al. Molecular profiling guided treatment in refractory solid tumours: practical impact and clinical responses: Experience of a single center. European Journal of Cancer, 2015; 51: S43.

[32] Seeber A, Gastl G, Ensinger C, et al. Treatment of patients with refractory metastatic cancer according to a molecular profiling on tumor tissue: an interim-analysis of the ONCO-T-PROFILE Project. Genes Cancer, 2016; 7: 301-8. Chahine G, Nasr F, Saleh K et al. Clinical outcomes of patients with previously untreated advanced or metastatic cancer before or after tumour profiling: results of a monocentric pilot study in Lebanon. Presented at ICACT 2016.

[33] Spetzler D, Xiao N, Burnett K et al. Multi-platform molecular profiling of 1,180 patients increase median overall survival and influences treatment decision in 53% of cases. Presented at ECCO 2015.

[34] Herzog TJ, Spetzler D, Xiao N et al. Impact of molecular profiling on overall survival of patients with advanced ovarian cancer. Oncotarget, 2016;7:19840-9.

[35] Marshall J, Schwartzberg LS, Bepler G et al. Novel panomic validation of time to next treatment (TNT) as an effective surrogate outcome measure in 4,729 patients. J Clin Oncol 34, 2016 (suppl; abstr 11521).

[36] Braiteh F, Sharman J, Richards D et al. Clinical NGS-based cancer genomic profiling impacts physician treatment decisions in advanced solid tumours. J Clin Oncol, 2014; 32:5s(suppl; abstr 11109).

[37] Ganesan P, Moulder S, Lee JJ et al. Triple-negative breast cancer patients treated at MD Anderson Cancer Center in phase I trials: Improved outcomes with combination chemotherapy and targeted agents. Mol Cancer Ther, 2014; 13: 3175-84.

[38] Ferreira AR, Gomes ASDA, Hoff PM et al. Next generation sequencing – A key in search of locks? Ann Oncol, 2014; 25 (suppl 4): iv560.

[39] Wheler JJ, Janku F, Naing A et al. Cancer therapy directed by comprehensive genomic profiling: A single center study. Cancer Res, 2016; 76:3690-701.

[40] Parker BA, Schwaederle MC, Schwab RB et al. Precision oncology: the UC San Diego Moores Cancer Center PREDICT experience. J Clin Oncol 33, 2015 (suppl; abstr 11103).

[41] Sohal D, Rini BI, Khorana AA et al. Prospective clinical study of precision oncology in solid tumours. J Clin Oncol 33, 2015 (suppl; abstr 6585).

[42] David KA and Juhl H. Immunohistochemical Detection of Phosphoproteins and Cancer Pathways. Handbook of Practical Immunohistochemistry, 2015 Chapter 8, pages 85-90.

[43] Swanton C, Soria J-C, Bardelli A et al. Consensus on precision medicine for metastatic cancers: a report from the MAP conference. Annals of Oncology, 2016; 27: 1443-8.