Preventive, predictive, and personalized medicine for effective and affordable cancer care

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Abstract

Preventive, predictive, and personalized medicine (PPPM) has created a wealth of new opportunities but added also new complexities and challenges. The European Cancer Prevention Organization already embraced unanimously molecular biology for primary and secondary prevention. The rapidly exploding genomic language and complexity of methods face oncologists with exponentially growing knowledge they need to assess and apply. Tissue specimen quality becomes one major concern. Some new innovative medicines cost beyond any reasonable threshold of financial support from patients, health care providers, and governments and risk sustainability for the health care system. In this review, we evaluate the path for genomic guidance to become the standard for diagnostics in cancer care and formulate potential solutions to simplify its implementation. Basically, introduction of molecular biology to guide therapeutic decisions can be facilitated through supporting the oncologist, the pathologist, the molecular laboratory, and the interventionist. Oncologists need to know the exact indication, utility, and limitations of each genomic service. Minimal requirements on the label must be addressed by the service provider. The interventionist is there to bring the most optimal tissue sample to pathology where the tissue is expanded to a variety of appropriate liquid-based samples. The large body of results then should be translated into meaningful clinical guidance for the individual patient. Surveillance, with the appropriate application of health economic indicators, can make this system long lasting. For governments and health care providers, optimal cancer care must result in a cost-effective, resource-sustainable, and patient-focused outcome.

Keywords Predictive preventive personalized medicine · Molecular biology · Patient selection · Cancer care · Biopsy
Genomic profiling · Health economics

Introduction

The exploding tsunami of new medicines in oncology, almost all resulting from progress in molecular biology, opens new avenues to more powerful treatments with less side effects. Innovative drugs prove regularly that quality of life can significantly be extended, at least in some subgroups. In general, about 30% of the treated patients have an objective benefit from this extension in life and decrease in suffering, resulting in clinical meaningfulness [1].

Global activity in life science research about molecular biology is growing almost exponentially since the early 1990s (Fig. 1), not only the number of publications and research groups, but also power, range, and complexity of available services, platforms, and tests. In the 1990s, a mutational analysis took several days; now, billions of genes can be examined with one machine in one day [2]. Almost every university performs gene analysis, numerous start-ups appeared, and a growing number of internationally operating commercial companies offer services that excel in complexity, parameter control, certificates, and overall quality. So, in parallel to cancer drugs, a new world of diagnostic tools has emerged during the last 20 years that can be of tremendous help to cancer patients [3], if implemented in the right way [4].

Biomolecular tests can provide substantial additions to traditional guidelines. The latter proved useful because they emerge mainly from sound scientific evidence from clinical trials and are accepted by the majority of practicing oncologists nowadays. About 85% of cancer patients take advantage

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Fig. 1 Number of publications in Pubmed during the last 30 years. They represent growth of number of research units, complexity of tests (big data), and interest from the pharmaceutical industry for molecular biology. The incremental increase in the most recent years can largely be attributed to personalized oncology. Prevention-related articles remain a small fraction of not even 2.5% of the total number

of this international guidance when cancer is detected. Rules on primary treatment can be stratified rather easily because at detection, cancers from the same organ look alike. Primary cancer patients are therefore traditionally allocated to site-specific treatment groups based on extension (e.g., TNM) and histological features. These were the known variable oncologists had to rely on, at least up to the 1990s. And they are still in place and working. Also, in recurrent diseases or in case of exclusion of local treatments, the algorithms provided remain partially useful. But for advanced cancer, it is common knowledge that only 35% will respond to treatment, even with the newest and most powerful medicines [5]. So, there are limits for this kind of evidence.

There are number of reasons why traditional guidelines are offering limited benefits:

- Established guidelines that offer treatments with an average response rate of 35% are difficult to accept by patients and their family. A notorious example is docetaxel in non-small cell lung cancer. Even recent duplet checkpoint inhibitors, which for sure represent another milestone in the fight against cancer, have average response percentages of less than 20% [6].
- Guidelines are usually softened during their development to make them acceptable to more oncologists. Reduction of therapy options in the hope to increase “wide-acceptance” comes from a magical mix of dogmatic comfort in addition to proven scientific evidence.
- Guidelines make preferentially use of recent literature. This bias favors newer treatments instead of older ones, even if the head-to-head comparison is not well studied,

e.g., usage of temozolomide and procarbazine in glioblastoma. In a substantial percentage, patients guided to a modern targeted option might have more benefit from the older conventional chemotherapy alternative.

- Guidelines are based mainly on clinical trials where the patient is compared to but not necessarily belonging to. Guidelines therefore can only give recommendation based on an average of patients; they cannot specify on the individual one. Inclusion and exclusion criteria (e.g., age) might restrict the outcome of a clinical trial to a kind of “proof of concept.” Sometimes, these results are difficult to apply as basis for real-life practice. In some studies, inclusion is based on a validated central laboratory test of which a non-validated alternative is present in the local hospital.
- Up to 5 years ago, updating guidelines was a yearly to a 5-yearly event depending on the issuing organization, representing emerging knowledge. With the exponentially growing numbers of publications and the complexity of diagnostic and therapeutic options available, this frequency is no longer tenable. Already now, NCCN (National Comprehensive Cancer Network) updates several times per year many of their site-specific recommendations [7]. It is expected that this version-wise updating must be adapted to a continuous process to accommodate all existing and newly appearing evidence.
- Some international organizations recommend their own guidelines with different corporate views.
- Guidelines fit better for primary cancers. But as the disease develops, growth will depend on dedifferentiation, host resistance, and interference with prior and existing medications. Increase in differences between patients will lead to the request for a more personalized approach, increasing importance of biological processes compared to clinical parameters, and growing unpredictability of a dedifferentiating tumor in a declining host.
- Guidelines have been developed most of the time as site-specific recommendations, bearing a non-conditional linkage to the organ where the tumor started to develop. This may lead to differences in treatment where there is no biological ground for it. Many examples have been seen in the past, e.g., chorionic cancer in ovary and testis and hormonal treatments in breast and prostate cancer. But also, more recent site-specific differences in treatments are seen: neuroendocrine tumors in pancreas are treated differently from those in the lungs.
- Amazingly, scientific communications at international clinical meetings rarely refer to guidelines. Even large institutions that propose guidelines do not always apply them internally. Guidelines sound as a quality system that does not cover the needs of the patients in all situations, especially not for patients with rare and advanced cancer, e.g., treatments of large, extensive, recurrent, or rare soft tissue

cancers are not well covered in guidelines. Identifiable subgroups or extremely rare cancers are sometimes even not described at all (e.g., pseudomyxoma).

About 15% of metastatic cancer patients will require additional and meaningful information at the time of diagnosis to be able to take an informed decision. Uncertainty often leads to panic whereby the patient and entourage grasp towards new and often the most expensive options because these, frequently experimental, are most visible in media.

Personalized oncology

In its most idealized version, the oncologist should take the cancer patient to the pharmacy and say “based on what we found in your cancer tests, this is the best treatment for you.” This treatment then would be based only on the susceptibility of the cancer cells and on the availability of drugs that influence defined metabolic steps. That does not mean that only targeted drugs are to be considered. The importance of non-selective medicines or medical devices and their role as the backbone for effective cancer treatment should not be underestimated.

Most oncologists would agree that assessing the tumor and finding the molecular profile of metastasized, recurrent, or infrequent cancers are now “standard of care” [8]. Nevertheless, implementation is not as expected due to challenges in skills, capabilities, and infrastructural deficiencies.

In addition to the growing number of labs and researchers (Fig. 1), the tests are becoming much more powerful with use of high throughput in vitro laboratory equipment. Of course, complexity in terms of scale and scope of technologies makes communication with the hospital even more difficult than it was before. The almost unimaginable power from developments in next generation sequencing (NSG), whole genome sequencing (WGS), whole exome sequencing (WES), and chromosome microarray

technologies with comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) is not easily understood and is positioned along with copy number analysis, RNA (transcriptomic research) and protein (proteomic) research, and progress in immunohistochemistry. Additionally, many welcome “liquid biopsy” or taking a blood sample to find molecular markers in serum or other body fluids to monitor treatment or detect early recurrence. For the time being, approaches on serum biomarkers have not been validated for clinical treatment decisions. Another factor adding complexity is that R&D (research and development)-driven initiatives often fail in acceptable translation into clinical routine. For example, data from animal models are not readily applicable to human clinical questions. All this wealth of information could be considered for clinical use, provided that clinical utility and added value for the patient have been proven with sound evidence (Fig. 2).

Due to these developments, number of different available tests, various levels of tests in the genomic expression, complex and high data output together with difficult-to-gauge quality of good laboratory practice, quality of the starting materials, and also the combination of different tests and platforms in an offered service while considering the developments in medical devices and pharmaceutical products create challenges for all specialists who are involved in genomic guidance. For the oncologist, this means new and additional tasks: finding the right service, platform, and test together with the interpretation of the results and translating this back to clinical real-life patient-focused oncology.

As a supplement, molecular biology has shed new light on carcinogenesis, origin of cancer, primary prevention measures, monitoring, and secondary prevention. Altogether, genomic progress, implementing not only genomic research but all kinds of omics in different stages of oncology, has created a new momentum in medicine that can be best described as “predictive, preventive, and personalized medicine (PPPM).” It is this term that will be used throughout this review [9].

Fig. 2 Multiplatform tests in predictive, preventive, and personalized medicine are much more than simple genomics

Choice of the test

Evidently, one molecular profiling service is not like the other. Clinical utility of one service is not easily applicable to competing tests and largely depends on the interlinked chain of all steps done with high quality: from sample procurement via molecular profile assessment to clinical translation. This complexity is expected to even increase in view of continuous innovation worldwide, e.g., evidence of predictive value of biomarkers. Given the ever-rising quantity of available tests with different scopes and clinical questions to solve, the choice of the right test is pivotal and should not be biased with anything else than the well-being of the cancer patient [10]. Some call this approach also patient-centered or value-based, integrating the patient perspective.

The clinical question must be carefully defined. Is the service an extension of genetic counseling, prognosis evaluation for adjuvant treatment, selection of drugs, companion test, treatment monitoring, or anything else? *The label of the test* should contain this clear indication or intended use statement, comparable to leaflets of drugs and medical devices.

Validation should touch clinical utility, impact, and benefit as the main goal. Information about pricing is most helpful together with some technical specifications that

allow health economical evaluation. More comprehensive tests integrating various technologies will return more meaningful information but are often more expensive. In general, reduction in platforms or tests to answer specific medical questions (e.g., because of costs) dilutes also clinical applicability. This delicate balance between cost-effectiveness of an in vitro test can be evaluated in exact the same way as for new treatments. Currently, the most applicable analysis is ICER, the incremental cost-efficacy ratio. This methodology could be an integral part in the assessment and implementation of omic tests [11].

The wealth of available tests needs a kind of classification. There are numerous ways to organize and a practical approach can be the starting point to form the patient's interest. An example how some common commercial tests could be seen in the patient's clinical journey is given in Fig. 3. Quite many tests are site-specific and reimbursed accordingly; some are companion tests that are linked to response to certain targeting drugs. Some services allow for treatment decisions (predictive and prognostic tests) in a multiplatform environment. The complexity of technologies including clinical usefulness and quality often is a factor explaining the large variation in costs ranging from 100 up to even 25,000 Euro nowadays.

Fig. 3 Place of commercial tests, useful in predictive, preventive, and personalized medicine, according to the clinical situation of the patient. It is one of the many ways to select the right test according to intended

use. But also, utility, impact, and benefit should be clear on the label in a way that is very similar to other health products such as medicines and medical devices

Sample preparation

Given the costs of high output services and the importance for the patient, the pre-analytical quality of the sample needs special attention (<http://www.spidia.eu/>). Microscopy remains an essential step in the diagnostic work-up and is almost entirely performed on microtomed slides for histology, histochemistry, and immunohistochemistry. Microdissection as one essential process step selects specific cells to obtain better data from non-contaminated materials. Almost all molecular biology tests use liquids either coming from body fluids or liquid phase solid tissues and need special preparation in line with the tests that follow (https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf). The pathologist receives the tissues and is likely the key person, responsible for transforming solid tissue specimen into liquid phase homogenates.

Some genomic platforms study robust and stable molecules. DNA for example can be studied even 2000 years after mummification. Other molecules such as RNA and proteins deteriorate in a matter of a few minutes. Both interventionist and pathologist must know the purpose, characteristics, and implications of the test so that appropriate measures can be undertaken to ensure the best starting materials. The sample can be deteriorated, contaminated, diluted, or changed in any way without being readily detected by the laboratory staff. Integrity of RNA can be quantified, but for proteins, this is much more difficult. According to the NCCN guidelines, prior to any genomic test, quality of the sample should be guaranteed. It is the responsibility of interventionist and pathologist to have sufficient quantity and high-quality tissue available for further testing [12].

Recent research has focused on taking biopsies from almost all parts of the human body in the most comfortable way with an appropriate sample size to accommodate all tissue research. Cell viability in modern transdermal biopsy samples is extremely high because of rapid diffusion of the specific fixators [13]. Heterogeneity of cancers is providing arguments for repeated biopsies, and microbiopsies with tru-cut needles of 20 to 14 G can obtain samples up to 20 mg. The first sample is usually the best since this contains the purest tumor tissue. By the second take, intratumoral bleeding will cause the first type of contamination. But to get enough tissue, at least several samples need to be taken and more non-tumor tissue will enter the sample and comfort decreases with repeated sampling. To comply with international standards and pre-analytical quality requirements of larger labs, enough tissue means at least 50 mm² on a slide that are at least six tru-cut samples (Fig. 4). For the pathologist, this does not pose a problem since he can focus on the target zone in the sample and from this part, he can deduct appropriate and meaningful information. The problem starts for molecular biology. Homogenates, made of many tru-cut biopsies, will contain a significant amount of contamination. It is estimated that up to

Fig. 4 Contribution of biopsy method to sample quality for predictive, preventive, and personalized medicine. Multiple small samples from a cancer are not identical to one large sample when high degree of purity and freshness is pivotal

80% of homogenates may contain contamination that reduces the percentage of target tissue to less than 20%. In such a test, it is a challenge to see the difference, so probability is high to measure lower amounts of target molecules resulting in an overlap between patient groups. This gray zone, so hated by the patients and oncologists, becomes wider again with loss of discrimination or specificity [14]. Collectively, meaningful clinical useful data can only be achieved when all the segments in the chain are offered with the highest quality.

For the scientist, overlap is not such a problem. He can increase the power of an experiment by adding multiple patients to the study until significant differences can be detected, even in the presence of a substantial gray zone. But this is true horror for the patient who is keen in knowing to what treatment group he belongs, or if he needs or not (adjuvant) treatment, or if the planned treatment has the highest chance of success and should be the treatment of choice. Discriminative tests or tests with high specificity can only be generated with samples of highest quality to start with.

Molecular biology therefore starts with the right sample with sufficient quality, purity, and freshness. A minimal quantity of 100 mg that contains at least 50% of the target with excellent preservation is a requirement that has been generally accepted [15]. Macrobiopsies are recently available that can guarantee purity and quantity [16–18]. Dedicated fixators such as RNALater type of solutions can preserve the sample

from deterioration of target molecules. As cited above, deterioration is one of the mechanisms that increase gray zones and needs to be avoided.

Essential requirements for molecular biology tests

Omic tests are fundamentally different from histopathological examinations. Molecular biology uses a test molecule (probe) to react with a target molecule in the homogenate. In its most simple form, one test molecule binds one target. The most modern tests might be more sophisticated in a way that more probes will be used in one test vial, but basically, one probe binds one target and is detected in that way. Quantitatively, the more target, the higher the test outcome, resulting usually in a linear fashion and expressed as concentration. Consequently, if the sample is not pure, the concentration measured will be lower. If the sample is not fresh, labile molecules will deteriorate and the concentration decreases also. Even more dangerous is that the molecular biologist has no clue about the quality of the sample. This is in total contrast to the pathologist who immediately sees the quality of the sample. He will also immediately see the site-specificity, i.e., from which organ the sample derives. Unlike the pathologist, the molecular biologist must trust from the beginning of the pre-analytical work-up that the sample is the right one and is offered in the best conditions. The phrase “rubbish in–rubbish out” is well describing this phenomenon and the pathologist must be in control of this important step. This is also why diagnostics, based on blood samples only, need to be validated with tissue-derived information, including pathology of the sample to obtain clinically meaningful information.

Is it also a prerequisite that lab testing the specimen works according to highest standards of internal processes and used materials. Not only the quality of specimen is important, but also the quality of the antibodies used for testing is crucial. As only a small range of biomarkers for molecular profiling can be assessed using commercially available kits, like HER2, all other tests need to be developed and validated as laboratory established tests (Fig. 5).

Whatever the nature of service, platform, or tests might be, all of them must demonstrate adherence to some basic essential requirements like, e.g., quality certifications from New York State Department of Health. This information should be summarized and attached also to a readable label, as described above. It is imperative that oncologists and patients know when and why a test is useful with proven added value for the patient and traceable clinical usability for an affordable cost. All this information should be clearly explained on the label: name of the test, indication, cost, and validation.

As budget within health care is limited, innovative diagnostics and treatments should be welcomed as they provide

Fig. 5 Shift from microscopical analysis only to integrated histological and molecular biology for predictive, preventive, and personalized medicine poses challenges for the pathologist

new opportunities for cancer patients. Health economy evaluation is therefore a delicate but indispensable tool to guarantee continuity and optimal care within a financially sustainable health care frame. Strategic considerations endorse transfer of part of therapy costs towards better selection of patients and treatment, optimizing resource allocation. Hereto, the work and tools of the interventionist, pathologist, molecular biologist, and oncologist but also the health economist must be reimbursed to save important financial resources in the therapeutic phase. Only this optimization in financial allocations can guarantee a continuation of state-of-the-art oncological care and guide prevention strategies. Oncology should not accept gray zones in reporting results as cancer patients are interested in decisive decision-making based on discriminative results. Discriminative test results are methodologically evaluated by sensitivity or, far more importantly, by specificity or by true prediction rate, being the striking variable [14].

Yearlong experiences show that patients and families much easier accept results from molecular biology on own tumor tissue instead of being allocated to treatment groups based on international accepted guidelines. This is particularly true in situations when standard of care has failed, and the patient is advised that no standard treatment is available anymore and would be considered to be transferred to palliative care. Patients understand very well that for each person and per consequence, each tumor is different and that this difference between patients and between cancers becomes larger over the time. Centers that more commonly use genomic profiling as an established tool and adopted its policy experience a change in treatment decision in up to 88% of the cases [19]. Interestingly, this change from prior profiling planned treatment to molecular-guided treatment is in 88% in favor of conventional chemotherapies, 8% for targeted therapies, 1% hormonal therapies, and 3% for investigational products. Therapies guided by comprehensive molecular profiling do not lead to high costs automatically but optimize the usage of all treatment options available

matching the patient's needs. This results in a high probability for non-expensive, well-established conventional chemotherapies, still offering huge potential benefits for patients. Only uncertainty, lack of comprehensive understanding of molecular profiling, and the underlying algorithms of probability of success combined with wrong financial incentives often lead to the rather unreflected application of the newest, most expensive, targeted therapies.

Of course, there exist also clinical measurable impacts. Two criteria are cited. The first one is the percentage of patients that experience a “significant prolongation of life with adequate quality.” Significance is often defined as an increase of minimal 30% versus the prior treatment line [20]. The other parameter is the disease-free survival (DFS). How long does it take before a patient with complete remission shows sign of recurrent disease? Both intermediate markers can be taken as proxies for overall survival. Recent literature shows in different reports that genomic profiling is useful and can improve those measurable outcomes significantly. Some indicate a doubling in survival and an almost tenfold increase of number of patients that experience increased meaningful survival [21]. For the prolongation of DFS, one often thinks at new and powerful targeted drugs only, which is in fact not true. In contrast to that assumption in 2016, oncologists discovered for the first time that the right diagnostic test can increase DFS without bias interference. Hereby, new diagnostic service providers can now be compared to most powerful drugs regarding NICE (National Institute for Health and Clinical Excellence) [20, 22] threshold levels, demonstrating also a clear positive health economic impact. Therefore, reimbursement of molecular biology tests, including all preparatory steps, must be considered as important as access to new drugs. It is the totality in patient care and the interlinked chain from prevention, early detection to treatment that saves lives. In addition, it proved to be meaningful to patients and their families.

Implementation

PPPM will fulfill its promises of significant improvement of patient care if the quality of services is optimal over the whole range of the diagnostic workup, from indication evaluation over sample procurement up to interpretation of the results. Each part of the chain carries responsibilities and threats towards the impact on treatment decision and patient's welfare. For the implementation of PPPM in oncology, there is need to optimize the sample procurement and processing, right choice of the test, communication of the results, and health economic surveillance (Fig. 6).

Sample procurement and processing

More than ever, the pathologist is the center of tissue processing and key for success of the next molecular test. Pathology

Fig. 6 Steps to molecular biology for cancer patients: the interventionist for sample procurement, the pathologist for transformation of the biopsy sample into homogenates, the biomolecular service, and the clinician who decides about the right indication and the translation of the results into meaningful clinical practice changes

must decide how the sample is immediately handled in the intervention room. The sample is received in a solid or liquid (body fluids) phase and must be processed into both solid and liquid phase representative materials. It is an activity that needs multidisciplinary, because it should consider the exact nature of the clinical question, the state of the sample, knowledge of the necessary tests, and international criteria of good laboratory practice. International organizations have put forward minimal requirements for quality work, including the pre-analytical quality assessment [23].

Pathology will tie the sample with the other parts of the diagnostic work-up such as medical imaging and physical examination and judge quality of the sample. Combining all these elements of the diagnostic work-up highlights also the importance of the right interpretation of the results in a meaningful diagnostic aid to the cancer patient, especially when thousands or millions of data must be interpreted.

Choice of omic test

The available services, offered by different laboratories, differ largely in:

- *Pre-analytical quality control.* Some laboratories apply stringent criteria; others are less critical. As much as the service is meaningful, pre-analytical quality decides for a large part of the meaningfulness and applicability of the results.

- *Indication.* Some laboratories define exact medical conditions in which the test can be useful with description of clinical utility and added value.
- *Type and combination of tests offered.* Strict genomic testing on DNA can be meaningful in certain clinical conditions such as in companion tests. In other circumstances, multiplatform tests including immunohistochemistry, in situ hybridization, and RNA-gene fusion analysis beside DNA-NGS mutation analysis in combination with histopathology provide the essentials for clinical utility.
- *Costs.* Some tests proved to be cost-efficient according to ICER calculation. Some do not offer value in terms of health economy. In an era, where quality control is almost as important as the technology itself, costs must cover a range of activities that altogether provide the basis for meaningful results and add value for patients.
- *Applicability in the clinical care path of the patient.* Some tests predict the risk, and some the indication of adjuvant treatment in site-specific cancers. Other tests will guide in precision medicine for refractory and rare cancers, and others guide in treatment monitoring. Depending on the patient's needs, the oncologist must be sure about the scope for various tests.
- *Validity of evidence.* It is of highest importance that data used for biomarker/drug associations are validated. Some tests use extrapolation from animal data, which bears a huge risk for misinterpreting when used in humans. Also, the level of evidence used must be shown transparently.
- *Trial enrolment.* Due to the increasing number of innovative treatments especially in the field of targeted therapies, linked information between molecular profiling, treatment options, and matching trials can help patients and physicians have access to those experimental drugs.
- *Clinical usability.* Is the test helpful for decision-making? Does the treatment choice differ based on the results of the test from the originally planned treatment choice?
- *Clinical added value.* Impact for the individual patient regarding increase in DFS, overall survival, or increase in number of patients that experience a meaningful extension of quality life
- *Clinical relevance of biomarkers.* Besides the quality of the test results, the interpretation of the clinical relevance is equally important, as some biomarkers prove to be more relevant (e.g., prostate-specific antigen) than others (e.g., CA 15.3 in breast cancer).
- *Turnaround time.* Patients like to see the results in time, when they need the results for further treatments. Long turnarounds due to technical issues or low throughput numbers reduce the chances of utility or added value.

An example of difference in service between four commercial companies illustrates these key criteria and can give a clear guidance for the appropriate test [20, 24]. Laboratories

that provide commercial services in molecular biology must comply to many requirements, far beyond all standards currently in place for research and development, as these laboratories produce test results which are crucial for the patient's treatment decision.

Communication of results

The enormous burden of data, some coming from high output data analysis, after molecular profiling must be translated in clinical useful strategies creating meaningful impact for patients. Common questions to consider are as follows: Is the result a mutation or polymorphism that is related to the malignancy? What does the result mean: risk prediction, therapy selection, prognostic parameter or is it monitoring the disease activity? The rapid evolution of number and type of publications (traditional, open access, prints) and the expanding series of scientific journals let the right filtration of relevant scientific articles becoming a specialized discipline. The bridge between life sciences and the specialized clinical cancer care centers seems to grow as both disciplines develop. When the findings of molecular tests are not interpreted in the right way with contemporary knowledge, the patient might be harmed. Communication between the service providing laboratories and oncology departments needs to be continuously updated and detailed. Given the rapid expansion of knowledge, a constant training and formation is required. Talking to oncological patients and their family and friends also requests communication skills and psychological insights. Time must be spent on the collection of all clinical and molecular biology data available as a solid basis for consultation.

An example of how results can be useful and communicated is shown in Table 1. In this example, the authors choose two real cases of triple negative breast cancer (TNBC). The results of multiplatform testing were summarized in meaningful data, resulted in treatment suggestions that were very different in two similar patients, illustrating the clinical impact and usefulness of the service.

More specifically, the first TN breast cancer patient (A) has androgen receptor expression; this is associated with benefit from enzalutamide and other hormone therapies [25]. Patient B has an activating Her Exon8/S310F mutation. In triple negative breast cancer, this poses an issue sometimes as there is benefit from Her2-targeted therapies, but many health systems object the prescription of those for TNBC. Clinical studies of novel Her2-directed drugs usually require “failure of at least one prior Her2 directed therapy” [26]. These examples clearly illustrate about the massive heterogeneity of patients with cancers even within the same conventional tumor classification (in these cases being TNBC), resulting in different treatment options associated with a potential benefit.

Table 1 Two real cases of triple negative breast cancer cases

Patient A	Patient B
Potential benefit	Potential benefit
– Olaparib	– Capecitabine, fluorouracil
– Bicalutamide–enzalutamide	– Carboplatin, cisplatin
– Carboplatin, cisplatin	– <i>Ado-trastuzumab-emtansine</i>
	– <i>Lapatinib, nexatinib</i>
	– <i>Pertuzumab</i>
	– <i>Trastuzumab</i>
Potential absence of benefit	Potential absence of benefit
– <i>Ado-trastuzumab-emtansine</i>	– Anastrozole, exemestane, letrozole
– Lapatinib, nexatinib	– Fulvestrant
– Pertuzumab	– Tamoxifen, toremifene
– Trastuzumab	– Megestrol acetate
– Anastrozole, exemestane, letrozole	– Goserelin, leuprolide
– Fulvestrant	– Bicalutamide, enzalutamide
– Tamoxifen, toremifene	
– Megestrol acetate	
– Goserelin, leuprolide	

Health economic surveillance

In view of the massive entry of new services, platforms, tests, and products, it is imperative that the quality and health budget are under permanent control and linked to each other. Regulator mechanisms with up-front objective criteria are and must be installed to guarantee management of acceptable and rejected intentions from hospitals and commercial companies. Monitoring of ICER and costs per QALY per service provider can be used accordingly [27, 28].

Conclusions and expert recommendations

Comprehensive molecular profiling services can be a solution for better cancer care with improved outcomes at stable costs, adding value to patients and society. The large array of innovative tests and new treatment options may currently not be available to the individual cancer patient as established standards because of following reasons:

- *The patient* with an advanced and/or rare cancer disease has limited time to follow a nearly unlimited route in which he can try all available and potential useful services and products. He needs a clear strategy. Treatments are exhausting and socially debilitating and leave almost no room for “try-outs.” At each moment, one question pops up: what is the best move now? In addition, the patient is

normally not expected to be able to pay for highly expensive services and products.

- *Tissue* is needed for each assessment; sequential testing requires more tissue than parallel testing; in many cases, tumor quantity is not sufficient.
- *The health care provider* is challenged by the sheer number of newly approved treatments and diagnostic tools, trying to give financial support for all patients in need while keeping the health care system affordable and sustainable. This rising complexity and development of increasingly more subgroups within a given disease-entity makes it ever more difficult to optimize resource allocation. Even in the time of molecular profiling, a continuous investment in education, R&D, and clinical utilization is needed. Many health care providers still look at the direct costs only and do not consider comprehensive health economic calculations, adding transparency and giving support to decisions in health policy.

The overwhelming knowledge, generated in molecular biology, and the expectation that much more is coming offer nevertheless unprecedented opportunities for cancer patients. Even in 2016 already, studies can demonstrate that the choice of the right tests might double survival expectations. It is anticipated that this prolongation of quality life will increase further as quality of diagnostic services and targeted treatments increases.

The selection of patients and treatments, through improved prognostic and predictive diagnostics, is an absolute and urgent necessity to control the health budget of oncology. The way to get there is to focus on three steps that will bring molecular biology into routine clinical practice: formation of oncologists, critical evaluation of offered services, and pre-analytical sample procurement.

Communication between clinicians and laboratories should be open-minded at both sides and intense to cope with future developments. Many new paradigms will appear that were not evident before. For example, hormone-dependent cancers from prostate and breast might have more in common than differences. Much information is coming from big data analysis that learns us about origin of cancer, prevention, prediction of response, and this more for the individual than for large patient groups. It is expected that much more information will become available that needs continuous implementation into epidemiological research and clinical practice. But at the same time, omics research should remain understandable to other disciplines to maximize applicability.

Focus on continuous follow-up of literature and industrial activities is mandatory to keep oncologists in line with the best that can be offered. At the same time, the biomolecular oncologist should also be a physician with training in communication, cancer biology, and available options in surgery, radiotherapy, traditional chemotherapy, and hormonal therapy. All combined, the function of the biomolecular oncologist is a

discipline or skill that needs to be developed to comply with actual and coming strong evolutions of oncology care.

Biomolecular tests and offered services are extremely diverse and almost none are identical. Hence, essential requirements such as costs, discriminative results, influence on treatment decisions, and added value for the patient differ largely. It is crucial to extract the right questions or requests from the clinical situation and identify the necessary test to answer that question. Several categories of services can be distinguished according to stage of patient in the clinical path whether or not accompanying drugs.

Tissue processing has been largely focused on preparing and coloring histological slides for microscopical analysis until recently. Biomolecular research in contrast is mainly achieved in homogenates: the liquid phase of tissues, or in body fluids. Liquid phase tissue samples are prone to many detrimental threats. A smooth and trustful preparation of liquid phase tissue samples should be done with attention to the highest quality and with communication hence and forth between the pathology and molecular biology lab. This step can only be successful in a dedicated pathology lab with the proper tools and knowledge.

Altogether, implementation of PPPM is feasible and, at the same time, necessary to offer optimal oncological care for the cancer patient now and in the future.

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Compliance with ethical standards

Not applicable

Conflict of interest The authors declare that they have no conflict of interest.

Statement of informed consent Patients have not been involved in the study.

Statement of human and animal rights No experiments have been performed including patients and/or animals.

References

- Davis C, Naci H, Gurpinar E, Poplasvka E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. *BMJ*. 2017;359:j4530.
- Stephens Z, Lee S, Faghri F, Campbell R, Zhai C, Efron M, et al. Big data: astronomical or genetical? *PLoS Biol*. 2015;13(7): e1002195. <https://doi.org/10.1371/journal.pbio.1002195>.
- Aftimos PG, Barthelemy P, Awada A. Molecular biology in medical oncology: diagnosis, prognosis, and precision medicine. *Discov Med*. 2014;17:81–91.
- Hyman DM, Taylor BS, Baselga J. Implementing genome-driven oncology. *Cell*. 2017;168:584–99.
- Jackson DB. Clinical and Economic impact of the nonresponder phenomenon—implications for systems-based discovery. *Drug Discov Today*. 2009;14:380–5. <https://doi.org/10.1016/j.drudis.2009.01.006>.
- Alexandrescu DT, Ichim TE, Riordan NH, Marincola FM, Di Nardo A, Kabigting FD, et al. Immunotherapy for melanoma: current status and perspectives. *J Immunother*. 2010;33:570–90. <https://www.nccn.org>
- Surrey LF, Luo M, Chang F, Li M. The genomic era of clinical oncology: integrated genomic analysis for precision cancer care. *Cytogenet Genome Res*. 2016;150:162–75.
- Golubnitschaja O, Baban B, Boniolo G, Wang W, Bubnov R, Kapalla M, et al. Medicine in the early twenty-first century: paradigm and anticipation—EPMA position paper 2016. *EPMA J*. 2016;7:23.
- Janssens J, Gallagher WM, Dean A, Ussla G, Stamp G. Tumor profiling-directed precision cancer therapy—comparison of commercial and academic clinical utility. *Int J Surg Surgical Proced*. 2017;2:123.
- Gabriel S, Normand SL. Getting the methods right—the foundation of patient-centered outcomes research. *N Engl J Med*. 2012;367:787–90.
- Basik M, Aguilar-Mahecha A, Rousseau C, Diaz Z, Tejpar S, Spatz A, et al. Biopsies: next-generation biospecimens for tailoring therapy. *Nat Rev Clin Oncol*. 2013;10:437–50.
- Agorku D, Janssens J. Isolation and analysis of tumor cells from human solid tumor tissue extracted by needle biopsy. Application Note Miltenyi Biotec. 2017;
- San Miguel L, Hulstaert F. The importance of test accuracy in economic evaluations of companion diagnostics. *J Com Eff Res*. 2015;4:569–77.
- Simon R, Roychowdhury S. Implementing personalized cancer genomics in clinical trials. *Nature Rev Drug Discov*. 2013;12:358–69.
- Cornelis A, Verjans M, Van den Bosch T, Wouters K, Van Robaey J, Janssens J, et al. Efficacy and safety of direct and frontal macrobiopsies in breast cancer. *Eur J Cancer Prev*. 2009;18:280–4.
- Lalji UC, Wildberger JE, Zur Hausen A, Bendek M, Dingemans AC, Hochstenbag M, et al. CT-guided percutaneous transthoracic needle biopsies using 10G large-core needles: initial experience. *Cardiovasc Intervent Radiol*. 2014;38:1603–10. <https://doi.org/10.1007/s00270-015-1098-z>.
- Ocak S, Duplaquet F, Jamart J, Pirard L, Weynand B, Delos M, et al. Diagnostic accuracy and safety of CT-guided percutaneous transthoracic needle biopsies: 14-gauge versus 22-gauge needles. *J Vasc Interv Radiol*. 2016;27:674–81.
- Dean A, Byrne A, Marinova M, Hayden I. Clinical outcomes of patients with rare and heavily pretreated solid tumors treated according to the results of tumor molecular profiling. *Biomed Res Int*. 2016;2016:4627214–9. <https://doi.org/10.1155/2016/4627214>.
- Temple R. Clinical measurement in drug evaluation. Ningano W, Thicker GT, eds. John Wiley and Sons Ltd: 1995; Von Hoff, D.D. c 1999; Dhani et al. *Clin Cancer Res* 2009; 15: 118–123.
- Radovich M, Kiel PJ, Nance SM, Niland EE, Parsley ME, Ferguson ME, et al. Clinical benefit of a precision medicine based approach for guiding treatment of refractory cancers. *Oncotarget*. 2017;7: 56491–500.
- Eifert C, Pantazi A, Sun R, Xu J, Cingolani P, Heyer J, et al. Clinical application of a cancer genomic profiling assay to guide precision medicine decisions. *Per Med*. 2017;14:309–25.
- Cree IA, Deans Z, Ligtenberg MJL, Normanno N, Edsjö A, Rouleau E, Solé F, Thunnissen E, Timens W, Schuurings E, Dequeker E, Murray S, Dietel M, Groenen P, Van Krieken JH, European Society of Pathology Task Force on Quality Assurance

- in Molecular Pathology, Royal College of Pathologists. Guidance for laboratories performing molecular pathology for cancer patients. *J Clin Pathol*. 2014;67(11):923–31. <https://doi.org/10.1136/jclinpath-2014-202404>.
23. Guidance for laboratories performing molecular pathology for cancer patients. *J Clin Pathol*. 2014; 67: 923–931.
  24. Capdevila J, Rojo F, Gonzalez-Martin A, et al. Molecular profiling for clinical decision making in advanced cancer: a clinical appraisal. *J Cancer Res Treat*. 2017;5:77–85.
  25. Cochrane DR, Bernales S, Jacobsen BM, Citterly DM, Howe EN, D'Amato NC, et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res*. 2014;16:R7.
  26. Ben-Baruch NE, Bose R, Kavuri SM, Ma CX, Ellis MJ. HER2-mutated breast cancer responds to treatment with single-agent neratinib, a second-generation HER2/EGFR tyrosine kinase inhibitor. *J Natl Compr Cancer Netw*. 2015;13:1061–4.
  27. Azimi NA, Welch HG. The effectiveness of cost-effectiveness analysis in containing costs. *J Gen Intern Med*. 1998;13:664–9.
  28. Cairns J. Using cost-effectiveness evidence to inform decisions as to which health services to provide. *Health Syst Reform*. 2016;2: 32–8.