EXPERT OPINION

HIGHLIGHTS

The article is on a recent approach to Precision Oncology based in the application of a computationally intensive approach to personalized medicine by means of a reverse engineering methodology termed rapid learning that considers individual patients both as a part of a cohort or corpus in an intelligent database and as individuals in an ongoing clinical practice setting. Some of the challenges and shortcomings are discussed.

ABSTRACT

The application of Precision Medicine in the field of oncology has been a long time goal in the search to disentangle the intricacies associated with cancer diagnostics, prognosis and therapy. Indeed oncological research and development have been some of the most active areas in which the paradigm of precision medicine arose. Due to the well known challenges in cancer research, such as molecular and phenotypic heterogeneity and therapeutically resistance/relapse, there is a need to integrate many information resources into models that, at the same time are flexible enough to have a place in the clinical setting. Current trends in Precision Oncology seem to have all the necessary elements to have an impact in the medium to long run, but this would only be possible if firmly grounded programs are established that involve the concerted collaboration of multidisciplinary teams. A recent approach termed Precision Oncology 3.0 is described and discussed, some missing elements are pointed out so that we can envision the way to go towards making it effective in practice.

KEY WORDS

Precision oncology; reverse engineering; translational oncogenomics; intelligent databases

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Cancer is a complex pathology; the molecular onset of this pathology is thought to begin with a few genomic alterations, likely the result of a combination of random and inherited mutations. These DNA variants inside in a number of biological processes: they may lead to deregulation of the control of gene expression that in turn can cause changes in hormone signalling, abnormal metabolism and in general systemic failure. At the cellular level, changes may originate when differentiation and proliferation processes occur in disparate times and disproportionate rates; cells change their morphology in a so-called neoplastic transformation leading to tumor development. The onset of cancer could be driven also by exogenous factors at the organismal level (and even above that level): lifestyle and environmental constraints affect (sometimes on a determinant fashion) the origins, development and outcome of malignant tumors [1]. The combination of these factors adds to the complexity of cancer.

There are important synergistic and cooperative phenomena that are pervasive to this disease in such a way that they have been categorized as hallmarks of cancer [2,3]. However, even when some genomic variants or biological processes are deemed as characteristic features of cancer, there is a big deal heterogeneity in both the causes and the outcomes of neoplastic diseases [4]. Apart from these, the response to anti-tumor therapies is not only vary from person to person, some patients that were initially responding to treatment often present therapeutic resistance and relapse.

A question now arises on how to incorporate (even more, integrate) those complexities and heterogeneities in a strategy to deal with cancer prognostic, diagnostics and therapeutics. In recent times, a new paradigm to face these challenges has been proposed, this is the paradigm of Precision Medicine [5,6]. Precision Medicine represents not only a scientific referent but also has been included in some countries (such as the US) as a well-defined health policy [6,7].

In a nutshell, precision medicine is the application of a multilayered approach to disease based in the analysis of high throughput biomolecular studies (genomics, proteomics, metabolomics and other conforming the so-called panomics) [8,9], individual patient imaging, laboratory tests and electronic health records, as well as (individual) hereditary and (collective) epidemiological information, to formulate hypotheses of the causes that drive the onset of cancer in an individual but more important what are the possible combinations of targeted therapies that may be more effective to treat cancer in that particular individual [8].

Precision Oncology, which is the application of the tenets of Precision Medicine to the study of cancer, is firmly based in the concept of disease networks [10,11] to determine events that may be driving tumorigenesis, metastasis, therapeutic resistance and relapse due to abnormal function of a neoplastic character. Once those networks have been analyzed, a second role of Precision Oncology will be the design of rational tailor-made therapies, often considered as a mixed strategy of novel drug combinations and dosages. The approach has the natural advantage of (usually) resorting to approved drugs that when targeted carefully may produce lesser side effects and be much more effective that broad spectrum chemotherapeutics (commonly of a cytotoxic origin) [8].

One important but definite issue of precision oncology is the fact that it defies not only traditional disciplinary boundaries (as it relies on the collaborative works of clinical physicians, molecular biologists, bioinformaticians, statisticians, and even engineers, physicists and mathematicians) but also it transcends our usual definition of the biomedical research and clinical settings. In some sense, the first step in this direction has already been given within the Systems Biology and Genomics arenas, but the fundamental difference is that the emphasis there is on multidisciplinary collaborative research to understand disease (say cancer) on a fundamentally basic and sometimes clinical research environment.

Precision Oncology, however aims at an application of those systemic integrative approaches but on a much faster way. After all, what is intended is that results may be obtained for an individual patient study within weeks (or at most months) so that this patient could derive some real therapeutic benefits from it.

There are of course many obstacles and conundrums related with the real applicability of such ambitious hybrid research/clinical programs as those delineated by precision medicine and oncology; however there is an optimistic feeling among some sectors of clinicians/researchers that consider that the area has been developed enough as to allow for a so-called third stage of development in precision oncology (termed Precision Oncology 3.0) [8] which is taking benefit of the application of artificial learning techniques from computational intelligence, in particular of a paradigm known as Rapid Learning.
For the proponents of this approach, one can narrowly speaking consider three stages of personalized precision oncology, with the first one, **Precision Oncology 1.0** dealing mostly with the histopathological examination of tumors with some support from low-throughput molecular diagnostics (say to the level of immunohistochemistry and tumor-node-metastases stage profiling).

**Precision Oncology 2.0** in the other hand involves the potential use of high-throughput omic technologies (whole genome gene expression analyses, exome sequencing, etc.) and gives particular emphasis to the molecular causes of disease, sometimes disregarding other sources of information such as the ones related with hystology. **Precision Oncology 2.0** (PO2.0) has however revealed some new light on tumorigenesis and response to drugs as given for instance with the advent of molecular tumor subtypes. In this regard, and in particular in view that gene expression and sequencing are becoming cheaper and somehow easier to carry out, PO2.0 it is becoming the standard of treatment in most medium to high income countries.

**Precision Oncology 3.0** [8], is an emerging paradigm which incorporates high through put omic technologies to a greater extent than PO2.0 and combines this information with suggested combinations of commonly targeted therapies. The shift however (one that is not actually devoid of technical and even ethical challenges) is on considering an individual patient as an additional experiment in the sense that his or her information (clinical, molecular, etc.) is incorporated to an already existing corpus and this data is examined and re-examined continuously to create informs (akin to research reports but also to clinical notes) about any subsequent encounter, either in the same patient (via follow up studies) or in other individuals, already integrated in the corpus.

Once all the information corpus is updated, the information is set up into an intelligent database also called a Global Cumulative Treatment Analysis in which statistical learning techniques are applied both, to generate information useful for therapeutic interventions in the patient and to perform a class of updating of the database (commonly following a form of reverse engineering statistical procedure) to perform what has been called Rapid Learning [12, 13].

To date, initiatives such as the American Society of Clinical Oncology (ASCO) CancerLinQ [14] and IBM’s Watson Oncology [15] exemplify the feasibility of the application of said approach. Some technical limitations and challenges of these approaches have already been discussed [8]. However, there are additional aspects to be considered, in particular regarding ethical and confidentiality issues [16].

**CONCLUSION**

All in all, the elements necessary to establish functional Precision Oncology programs are already developed or very close to being ready. Technical caveats and ethical considerations may be solved on the fly as we become aware of the extent of their influence in the whole program. If these efforts prove to be useful in practice, both the clinical and research settings will result strongly enhanced. Aside from the obvious benefit for the patients (the ultimate goal of both researchers and clinicians), there will be also an additional payoff and a likely lesson for practitioners and users of science in other disciplines, even outside the realms of biomedicine: it will show that academic research and current practice can be tied together for mutual strengthening and enlightenment.

**CONFLICT OF INTEREST**

The authors declare no competing interests.

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**REFERENCES**


