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What precisely is *precision oncology* and will it work?

Abstract:

Precision oncology is used to describe diverse strategies in cancer medicine ranging from the use of targeted therapy(ies) generally to using data from next-generation sequencing (NGS) to select therapy in a person independent of their cancer type. There is widespread, even extraordinary enthusiasm for precision oncology. But is this enthusiasm justified by biological and conceptual considerations and by data from clinical trials? I describe the challenges of defining precision oncology and applying this concept to treating cancer. Consideration of the complex biology of cancers leads us to suggest caution in estimating the impact of precision oncology in cancer therapy. Exactly which activities and actions fall under the domain of precision oncology is unclear. Some investigators argue blood-typing, targeted therapies and even immune therapy are precision oncology whereas others use the term precision oncology more narrowly, for example, to refer to the use of NGS of cancer tissues to guide targeted therapy. Ironically, imprecise use of precision constitutes jargon as defined by the Oxford English Dictionary: special words or expressions used by a profession or group that are difficult for others to understand. To understand what precision oncology means in current context, Vinay Prasad and I analyzed use of this term in the biomedical literature by searching Google Scholar for precision oncology over three time periods and by classifying 50 articles. Results are depicted in the Figure. Over these intervals use precision oncology has changed. In the earliest interval, precision oncology predominantly described targeted therapies such as VEGF- or BCR/ABL1-inhibitors including bevacizumab and imatinib. Subsequently, precision oncology was used to describe selecting therapy(ies) based on data from analyses of biomarkers. Examples are use of crizotinib in persons with lung cancer with EML/ALK4 rearrangements or using adjuvant chemotherapy guided by results genomic testing such as the Oncotype-Dx® panel in women with breast cancer. By 2016, precision oncology was mostly-used to refer to use of data from NGS to guide therapy(ies). The most paradigm-shifting definition of precision oncology is directing therapy independent of cancer type as currently defined (based on anatomy and histology), and instead by mutation. The practical case against

precision oncology is that it is unlikely to benefit most people with cancer. Data from NGS of persons with advanced cancers indicate fewer than 10 percent have actionable mutations. The only randomized trial of precision medicine, the SHIVA trial tested whether genetic analyses and pathway-directed therapy is better than investigator choice and found no progression-free survival difference between these strategies. This was a phase-2 study without blinding and although these data do not disprove the hypothesis that a mutation profile-based strategy for selecting therapy of advanced cancers might work; this seems unlikely. The biological case against precision oncology is that it contrasts with our modern understanding of cancer. The mutation landscape of most common cancers is highly complex. The least mutated cancers have on average 0.28 mutations per megabase and the most mutated have 8.15 mutations per megabase. Reports of mutation analyses by NGS whole exome sequencing of a moderately mutated cancer like pancreas cancer (mean 2.64 mutations per megabase) indicate very few consistently mutated genes (and even common mutations such as NRAS in only some cases). Although many of these mutations are passenger mutations even driver mutations occur at low prevalence. There are, of course, exceptions such a NPM1 and FLT3 in acute myeloid leukaemia and MYC in lymphomas but this situation is less common in solid neoplasms. Moreover, mutations such as NPM1 and MYC are not currently actionable—we have no drug to halt their activity. Unique amplifications and copy number gains of oncogenes also occur at low prevalence. Because most people with pancreas cancer have unique mutation fingerprints, researchers note substantial diversity of mechanisms involved in pancreatic cancer progression. Precision oncology is based on the notion that in the midst of a shattered genome, identifying and reversing one target, a driver mutation, will dramatically halt the aberrant phenotype that characterizes cancer and ideally restore normalcy. It is as if a city planner studied Rome's rush hour traffic, noting many congested freeways, standstills on crossroads, bloated on-ramps and crawling buses, and thought if only I could build one bridge the traffic problem would be solved. Even at the outset this seems implausible save for rare cancers, such as chronic myeloid leukaemia, where one mutation, BCR/ABL1, is necessary and sufficient to cause the disease. Alternatively, some experts theorize targeting multiple pathways may solve the problem—a series of bridges. The simple reality is drug toxicities are often additive and unpredictable and the history of targeted therapy has failed to validate promising combinations in many settings even when each component drug is effective and safe. When one considers the biological and practical challenges of precision oncology: that we are performing an imprecise sequencing effort that will likely find many alterations in a damaged genome –that we may infrequently encounter an alternation targeted by a drug we already have –that we may give a drug hoping there are limited alternative pathways available for up-regulation –that, all the while, we hope for a sustained and meaningful response; the entire proposition seems uncertain at best.

Precision oncology is seductive and appealing. Who wouldn't want to use a cancer drug that will be effective in people failing other therapy options? But like all seductive notions we must separate evidence supporting a claim from our desire for the claim to be true. In the case of precision medicine we need clear definitions and criteria for success or failure. We hope for success but their remains much imprecision to this strategy.