

Opinion Paper

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A repository for “rare” tumor markers?

Abstract: In 2013, the National Cancer Institute of the USA announced a new program, to catalog “exceptional responders” in cancer trials. This program aims to identify a small number of well-responding patients to new treatments, with the hope that in the future, patients with cancer could be treated with the most effective drugs (personalized therapy). In this paper, I extrapolate on this idea and propose to also catalog cancer biomarkers that only work in a minor proportion of patients, and are currently ignored as clinically useless. Such biomarkers could be used to select optimal treatments, optimal monitoring or for assessing prognosis. The informative biomarkers for these rare patients may also provide the opportunity to identify molecular networks that are altered in cancer and explain why these markers are elevated in these few patients. I provide an example of two kallikreins (KLK6 and KLK10), which are highly elevated in serum of 3%–5% of pancreatic cancer patients at 100% specificity.

Keywords: exceptional responders; personalized cancer markers; personalized medicine; rare tumor markers.

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In April 2013, the US National Cancer Institute (NCI) announced a new program which aims to catalog “exceptional responders” in cancer clinical trials [1]. Exceptional responders are individuals who had favorable responses lasting at least 6 months in a clinical trial, for a drug that was not approved for that cancer because too

few patients overall responded. A few years back, such exceptional responders were not given much attention since there was no way to identify them before initiation of treatment and then link them to clinical response for a particular drug. However now, with whole genome and whole exome sequencing technologies, it may be possible to find out as to why these patients show exceptional responses to specific drugs. For example, while most patients with advanced bladder cancer did not respond to the drug everolimus, one woman went into remission that lasted more than 3 years. Whole genome sequencing of this patient revealed that the woman's tumor carried the mutated version of a gene, *TSC1*, which was linked to everolimus' favorable response [2]. The same group further identified a woman with cancer of the ureter, who responded well to a drug cocktail and later found to have a mutation in the DNA repair gene, *RAD50* [1]. These and other examples suggest that current technology allows identification of the molecular alterations that are associated with rare, favorable therapeutic responses. By extrapolation, it may be possible in the future to link patients with specific whole genome genotypes to specific drug sensitivities, something that has been coined “precision medicine” or “personalized cancer treatments”.

Not all clinicians and scientists agree that this approach will be fruitful in the long-run, since the number of identified patients with specific mutations that are linked to favorable drug responses may be very small overall. Time will show if this new approach for selecting the most likely to work therapies for cancer patients will have a major impact on disease mortality.

Recently, Fishman has also put forward the idea that it is easier to develop effective therapeutics for homogeneous populations of patients with rare diseases, for which the pathogenetic mechanism is known. This approach has the advantage of needing smaller trials, provision of new treatments to rare diseases and, often, expansion of these treatments to subsets of patients with more common diseases [3].

A similar approach could be envisioned in the cancer biomarker field. As I and others have indicated in previous editorials, very few, if any, major cancer biomarkers have entered the clinic the last 30 years [4–7]. Recently, I cited

three reasons which are responsible for biomarker failure to reach the clinic [6]. One, fraud, is rare and should not have a major impact in the field [8, 9]. The two major reasons for biomarker failure are false discovery and discovery of biomarkers with weak clinical performance. False discovery is defined as an erroneous identification of a new biomarker due to pre-analytical, analytical, post-analytical and bioinformatic shortcomings [5]. Biomarkers which fall into the "false discovery" category are not reproducible in other laboratories and represent contamination of the biomedical literature. Some examples of such false discoveries, which sparked initial excitement in the literature and the public media, have been summarized elsewhere [5, 10, 11].

The third category of biomarker failures includes biomarkers which, although legitimately discovered and validated, show rather low specificity, sensitivity or prognostic/predictive value, thus making them unsuitable for clinical decision-making. For example, it is highly unlikely that companies would be interested to market biomarkers with 5%–30% sensitivity, even if the specificity is close to 100% and vice versa.

There are thousands of published biomarkers whose performance was deemed unsuitable for clinical use. There must also be even more biomarkers that have never been published due to very low sensitivity (e.g., <10%), despite very high specificity (e.g., >95%). However, similarly to the so-called "exceptional responders", defined above, there are biomarkers which can clearly discriminate a few patients from normal subjects and patients with benign diseases (but with very low sensitivity; e.g., 2%–5%). Why a biomarker could be informative for one or a few patients but not for the majority of patients? While previously we had no way of investigating as to why this may be happening, the new technologies of whole genome and whole exome sequencing, with their dramatically decreasing costs, may offer the possibility for further investigating these "informative" patients, in hopes of finding molecular alterations that are responsible for the consistent elevations of these biomarkers in biological fluids [12].

To demonstrate my point of existence of low sensitivity/high specificity biomarkers, I here describe an example of biomarkers that have been developed by us in the past, and were deemed unsuitable for clinical use (and

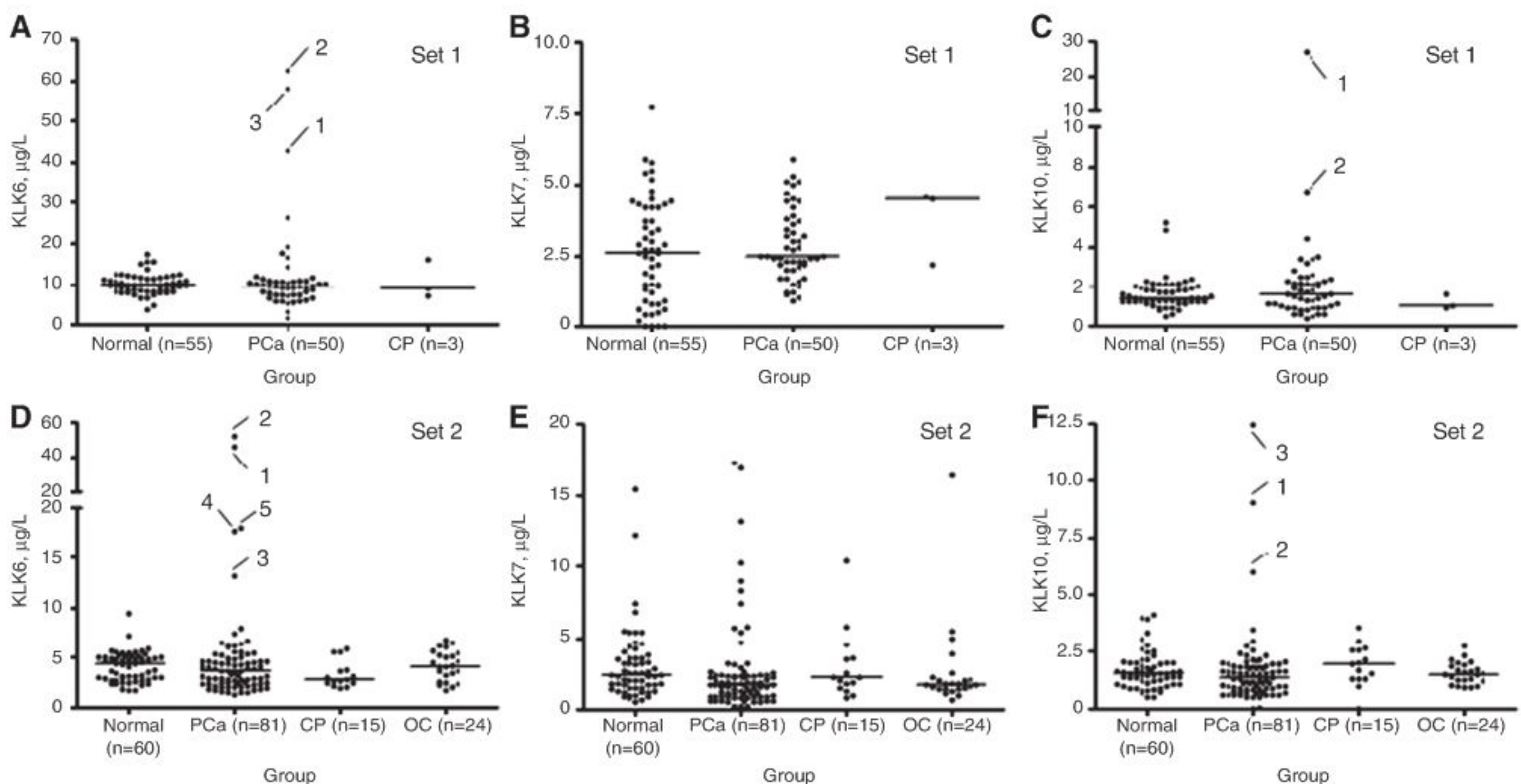


Figure 1 Serum analysis of kallikreins KLK6, KLK7 and KLK10, by using ELISA assays developed and validated in the author's laboratory. The first set of samples (set 1, panels A, B, C) was obtained from Dr. Craig D. Logsdon, University of Michigan, and analyzed in 2003. CP, chronic pancreatitis; PCa, pancreatic adenocarcinoma. The numbers in brackets indicate number of patients. Horizontal lines are medians. Note that among the 50 patients with pancreatic adenocarcinoma, two of them (shown as 1, 2) have serum elevations in both KLK6 and KLK10 and another one (3) had elevations only in KLK6. None of the patients had any elevations in KLK7. Set 2 was obtained from Dr. Randy Haun, University of Arkansas, and was analyzed 3 years later. OC, other cancers (not pancreatic). Note that three patients with pancreatic adenocarcinoma (1, 2, 3) had serum elevations in both KLK6 and KLK10 and another two patients (4, 5) elevations in KLK6 only. None of the patients had elevations in KLK7. For more discussion, see text.

publication), due to low sensitivity. We quantified three kallikreins (KLK6, KLK7, KLK10) in serum of patients with chronic pancreatitis, pancreatic adenocarcinoma, normal males and females and patients with other cancers (set 2 only). The first sample set was obtained from Dr. Craig D. Logsdon, University of Michigan, in 2003 (Figure 1, panels A, B, C). Two out of 50 pancreatic cancer patients had highly elevated levels of both KLK6 and KLK10 (patients 1 and 2), and a third patient (patient 3) had elevated levels of only KLK6. Notice that KLK7 was not elevated in any of the patients. Three years later, we repeated similar analyses in an independent set of patients obtained from Dr. Randy Haun, University of Arkansas (Figure 1, panels D, E, F), and identified three patients with elevated KLK6 and KLK10 (patients 1–3). Two other patients (patients 4 and 5) had elevated KLK6 only. KLK7 was also uninformative in these patients.

This example makes the point that it is possible to identify consistent (e.g., in two independent patient sets) and quite significant changes of some biomarkers (in this case, KLK6 and KLK10) in the few patients (e.g., 3%–5%), at 100% specificity.

While up until a few years ago, such findings were not as easy to explain, whole genome and exome sequencing could now be used to investigate if these few exceptional patients have distinct molecular changes that are responsible for the increased biomarker levels in their serum. If this is true, then, patient subgroups could be identified by biomarker analysis alone. If the biomarker levels correlate with a specific molecular event, we could define subgroups that may be responsive to certain treatments or identify aberrant pathways which may be worth targeting for therapeutic applications. For biomarker applications, it may be possible to use these biomarkers, in these few

patients, for monitoring response to therapy (precision medicine, but here, for "personalized monitoring").

There must be numerous biomarkers that work in a minor proportion of patients (similar to the example presented in Figure 1), which are usually ignored as clinically useless. I believe the project initiated by NCI, to identify "exceptional responders", could be expanded to catalog tumor markers which can be used in small groups of informative patients, to identify optimal treatments, institute optimal monitoring or assess the prognosis of such patients. It will also be interesting to examine if the tumor marker alterations in these patients are associated with specific molecular changes in their tumors, thus providing a mechanistic rationale for their serum elevations.

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