Editorial

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**Biomarker research and leading causes of death worldwide: a rather feeble relationship**

**Keywords:** biomarkers; diagnosis; laboratory testing; mortality; screening.

Laboratory testing is an essential part of the clinical decision-making, wherein results of diagnostic testing efficiently contribute to screening, diagnosis, prognostication, follow-up and therapeutic monitoring of most human disorders. According to the Working Group of the National Institute of Health (NIH), a biomarker (also known as “biological marker”), can be defined as “...a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [1]. According to this definition, almost all laboratory tests should be labelled as “biomarkers”, but a better understanding of the term should also arise from a careful revision of their current clinical application(s). In fact, a biomarker may be measured in a biosample (e.g., blood, serum, plasma, urine, other biological fluids as well as tissues), it may be a physiological (phenotype) recording (e.g., blood pressure, ECG or Holter), or it may be even an imaging test (e.g., echocardiogram or CT scan) [2].

In the last decade, a clear distinction has been proposed between laboratory tests generally used in clinical laboratories and innovative biomarkers that have been instead defined as “the core instrument of translational medicine” [3]. Therefore, while the field of biomarkers application is rather broad, ranging from risk prediction to diagnosis, prognosis, staging and monitoring of diseases, the term “biomarker” more stringently applies to innovative tests, specifically developed for improving current knowledge and practice in biology and medicine.

The introduction into clinical (daily) practice of novel biomarkers is a lengthy and challenging enterprise, wherein results of the bench are finally translated into practical applications for — ultimately — improving patients’ outcome [4]. It is undeniable that several remarkable technological advances that have occurred over the past decades have also made it possible to identify a large number of biological markers, whose assessment in clinical laboratories is now a substantial part of the routine clinical management [5]. It is also widely acknowledged that these spasmodic efforts have been mirrored by an increasing number of publications in the field of diagnostic and prognostic biomarkers, although no definitive evidence has been provided on how this basic research has really impacted on the most frequent human disorders. In both *Clinical Chemistry and Laboratory Medicine (CCLM)* editors’ and readers’ perspective, it may hence be attractive to analyse the current trends of publications in the field of diagnostic biomarkers, since this may also reflect the real impact on management of the leading causes of death worldwide.

As known by most, PubMed is one of the most comprehensive biomedical search platform, including as many as 22 million citations from MEDLINE, life science

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Top 10 leading causes of death worldwide, according to World Health Organization (WHO).</th>
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<tbody>
<tr>
<td>World</td>
<td>Deaths (millions)</td>
</tr>
<tr>
<td>---------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>7.25</td>
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<tr>
<td>Stroke and other cerebrovascular disease</td>
<td>6.15</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>3.46</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3.28</td>
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<tr>
<td>Diarrhoeal diseases</td>
<td>2.46</td>
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<tr>
<td>HIV/AIDS</td>
<td>1.78</td>
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<tr>
<td>Cancers</td>
<td>1.39</td>
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<tr>
<td>Tuberculosis</td>
<td>1.34</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.26</td>
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<tr>
<td>Road traffic accidents</td>
<td>1.21</td>
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journals and online books [6]. In order to establish the current trends in biomarker research, we have hence retrieved the number of citations from years 1982 to 2012 using “PubMed Advanced Search Builder”, which was interrogated with the key words “biomarkers” and any of those listed by the World Health Organization (WHO)

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**Figure 1** Trends of biomarker research in the top 10 causes of death worldwide.
as the top 10 leading causes of worldwide deaths in 2008 [7], as reported in Table 1. Results were further refined for years, by using the search option “results by year”.

Overall, 593,896 cumulative citations were found according to the established search criteria. The number of biomarker items in PubMed impressively increased by nine-fold from 1982 to 2012 (i.e., from 3770 to 34144 citations/year). The trend of total citations according to the different subject areas is shown in Figure 1. A steady increase was observed for all categories, except “HIV”/“AIDS”, which suddenly and rather unexpectedly declined after the year 1998 (Figure 1A). Even more interestingly, when citations were given as a percentage, a dramatic drop could be observed in the number of articles dealing with biomarkers of “ischaemic heart disease” (from 65% in 1982 to 26% in 2012) and “HIV”/“AIDS” (from 55% in 1988 to 20% in 2012), whereas the remaining categories experimented an exponential growth, especially “cancer” biomarker research, which increased from 17% in 1982 to 42% in 2012 (Figure 1B). It is noteworthy that no significant relationship was found between number of deaths for specific diseases and number of related PubMed items (r=0.06; p=0.88).

One of the most important conclusions that can be drawn from these data is that there is a rather feeble relationship between biomarker research and actual causes of death worldwide. It is particularly impressive that <2.0% cumulative citations in 2012 regarded disease such as “lower respiratory infections”, “chronic obstructive pulmonary disease” and “diarrhoea” (listed as the third, fourth and fifth causes of deaths by the WHO, respectively), which cumulatively averaged more deaths than “ischaemic heart disease” or “cerebrovascular disorders” alone. It is also noteworthy that research about “cancer” biomarkers has gradually overcome that about “ischaemic heart disease” or “HIV”/“AIDS”, wherein the percentage of publications in the former area is nearly equivalent to the sum of the others. Interestingly, this is also reflected by the high number of articles that *CCLM* has published on diagnosis and management of malignancies, over the past few years [8].

It has been recently concluded that the biomarker pipeline is becoming dry due to the lack of discovery, whereas the validation of existing biomarkers is also remarkably slowing down [9]. Although it is hence undeniable that some areas of biomarker research are becoming “arid”, others represent appealing perspectives for laboratory diagnostics.

As editors of *CCLM*, we thereby encourage all potential authors to submit basic researches as well as clinical articles in “orphan” fields (including “lower respiratory infections”, “chronic obstructive pulmonary disease” and “diarrhoea”) which represent, however, leading healthcare issues in the third millennium.

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### References


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