Biomarker Insights

REVIEW

Personalized Medicine in Screening for Malignant Disease: A Review of Methods and Applications

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Abstract: Personalized medicine (PM) is currently a hot topic in the professional world. It is often called the medicine of the future and has already achieved resounding success in the area of targeted therapy. Nevertheless, integration of the concepts of PM into routine clinical practice is slow. This review is intended to give an overview of current and potential applications of PM in oncology. PM could soon play a decisive role, especially in screening. The relevance of PM in screening was examined in the case of four common cancers (colorectal cancer, lung cancer, breast cancer, and prostate cancer). A literature search was performed. This showed that biomarkers in particular play a crucial role in screening. In summary, it can be emphasized that there are already numerous known promising biomarkers in malignant disease. This results in several possibilities for individualizing and revolutionizing screening.

Keywords: personalized medicine, early detection, colorectal cancer, lung cancer, breast cancer, prostate cancer

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Introduction

Personalized medicine (PM) is understood to mean a medical approach to care that is intended to be patient-specific and thus targeted. With the aid of PM, it should be possible to identify those patients who are most likely to respond to a medication and at the same time determine those who will not respond to the therapy. Potential side effects are thus avoided while the effectiveness of a treatment is increased. The aim of PM is thus tailor-made therapy, attuned to the individual patient and therefore highly effective.

With the constantly growing knowledge in the field of molecular medicine, numerous new approaches for the concepts of PM have been developed. Against the background of the future financial viability of the healthcare system and the innovation this will require, PM arouses great interest in all involved in the healthcare system. PM has the potential to improve the efficiency and affordability of the healthcare system, and at the same time to improve the quality of medical care for individual patients.

Especially in screening, PM could soon play a decisive role. The relevance of PM in the context of screening was examined in the case of four common cancers (colorectal cancer, lung cancer, breast cancer, and prostate cancer).

Research Focus

The methods of PM are presented below using four malignant diseases (colorectal cancer, lung cancer, breast cancer, and prostate cancer). The aim of this study is to demonstrate that PM plays a decisive role in early detection of malignant disease and has the potential to revolutionize early diagnosis.

Early detection

Early disease detection is defined as "methods to determine in patients the nature of a disease or disorder at its early stage of progression. Generally, early diagnosis improves prognosis and treatment outcome."[1] This plays a crucial role, especially in the case of oncological diseases. While no investigations are recommended for early detection of lung cancer, there are standardized investigation methods for colorectal, breast, and prostate carcinoma which are intended to serve for early detection. These investigations are organ-specific and are repeated at an interval of one to two years, depending on the guidelines in the respective countries. Screening investigation methods include the fecal occult blood test (FOBT), colonoscopy, mammography, and prostate specific antigen test (PSA).[2–5] These standardized investigations can be supplemented or optimized with the aid of the scientific knowledge of recent years and/or the new methodology of individualized medicine.

Biomarkers

The use of biomarkers for early detection is a promising approach. Since the discovery of carcinoembryonic antigen (CEA), the first biomarker, in 1965, numerous other biomarkers have been identified that can be employed for the diagnosis of cancer.[6] Biomarkers offer the possibility of a non-invasive early detection method and can be obtained from samples, such as blood, saliva, and lacrimal fluid.

Biomarkers can be employed in several ways in early detection. On the one hand, they can be employed as a screening tool for a single tumor entity. The CEA has already proved itself in the diagnosis of colorectal carcinoma. Yang et al have found numerous other biomarkers, which have the potential to be unique and thus seminal for a certain type of cancer. These include, for example, MMP-1 (matrix metalloproteinase-1), BRCA1, BRCA2, PSA (kallikrein III), ErbB2 (Her2/neu) and IGF-II for breast cancer.[7–10] The glycoproteins CD44, VSX2, BEND4, NPTX1 and ALX3 can be found in colorectal cancer.[7,10–12] Biomarkers for prostate carcinoma include, for example, ErbB2 (Her2/neu), BRCA1, BRCA2, MCT2 and PSA (kallikrein III).[7,10,13–16] BRCA1, BRCA2, ErbB2 (Her2/neu), PSA (kallikrein III), HABP2 and IGF-II are found with lung cancer.[7,10,17] It can be seen that many biomarkers overlap. Fan et al have indicated the urgent need for a non-invasive early detection method for breast cancer.[18] They have likewise succeeded in defining several biomarkers. They identified a set of protein peaks from serum samples which could distinguish breast cancer from non-cancer controls. These include apolipoprotein C-I, the C-terminal-truncated form of C3a, and complement component C3a. By this means, they succeeded in differentiating cancerous tissue from normal tissue in their model with a sensitivity of 96.45% and a specificity of 94.87%.[18] The sensitivity of the previous screening methods could be improved by the additional measurement of such biomarkers.

MicroRNA (miRNA) is a new class of biomarker. The first miRNA was discovered in *Caenorhabditis elegans* in 1993.[19] MiRNAs are small, non-coding RNAs with an average length of approximately 22 nucleotides. They regulate the activity of mRNAs (messenger RNAs) and can thus act both as an oncogene and as a tumor suppressor gene. Judging from estimates, over one third of the genome is regulated by miRNA.[20] There is a central database for miRNA named miRBase in which 1084 human miRNAs have been registered on it to date. MiRNAs have numerous prerequisites that predispose them for use as biomarkers, including that they can be obtained easily from the blood and are extremely stable. Additionally, while free DNA and RNA are easily decomposed, miRNAs are almost resistant to the RNases present in the plasma. Moreover, they remain stable under unfavorable environmental conditions such as high temperatures or low pH.[21]

Studies have shown that numerous types of cancer have their own miRNA profiles. For example, miR-195, miR-148b, miR-409-3p, miR-801 and let7a occur in breast cancer;[22–28] miR-92a, miR-17-3p, miR-29a, miR-601, miR-34b and miR-760 are found in colorectal carcinoma;[12,29–36] miR-21, miR125b and miR-210 occur in lung cancer;[37,38] and miR-141 in prostate carcinoma.[39,40] Some miRNAs overlap, that is an miRNA occurs in several tumor entities. For example, miRNA-21 plays a role in several forms of cancer such as breast and lung cancer but also in ovarian carcinoma and pancreatic carcinoma.[21,41–43] However, all biomarkers have this problem in common and it can be considered in two different ways. On the one hand, a screening test can be developed which only contains biomarkers to which a tumor entity is clearly assigned and is thus unique for this. On the other hand, it may allow general screening for oncological diseases. Yang et al pointed out that less than 20% of tumor markers are specific for one type of cancer. The majority of biomarkers are raised in several cancers.[10]

Estimation of the disease risk (low/high-risk groups)

Besides blood samples, tissue samples could also serve to improve the early detection of oncological diseases. In this connection, colorectal carcinoma with its marker lesion, the adenoma, is a good example. It is known that the development of colorectal cancer is based on the adenoma-carcinoma sequence, therefore adenomas that are discovered on colonoscopy are removed completely and investigated histopathologically. It is known that patients with a number of adenomas have an increased risk of developing colorectal carcinoma.[44] Of these adenomas, however, less than 10% degenerate.[45] The question is thus how to recognize these high-risk adenomas and how to manage patients who are prone to adenomas. Tang et al considered this point.[46] They detected markers that change during the process from the normal mucosa via an adenoma to a carcinoma. It should thus be possible to recognize adenomas that have a higher probability of malignant degeneration. Up to now, this has only been possible visually, for example, from the size of the adenoma or a villous growth pattern.[47] Patients in whom such "risk adenomas" occur in large numbers need closer colonoscopy monitoring. It is important to recognize these patients early and to submit them to a special screening procedure adapted to their risk profile.[44]

Another way of optimizing screening consists of adding measurement of the biomarkers to the customary screening methods. Thus the patients to be organized into a low- or high-risk group at the start. The patients can therefore be assigned to a screening programme which is adapted to their individual risk of disease. Marshall et al proposed a biomarker panel, which is intended to establish the respective risk of colorectal carcinoma.[48] Only patients whose risk profile is estimated as high would then be subjected to the often unpleasant procedure of colonoscopy. Pharoah et al have also adopted the same approach.[49] They followed the principle of low/high-risk groups with breast cancer. They criticized the fact that the age of the patient decides when a preliminary screening investigation is carried out. On the contrary, the patient's personal and family history and genetic risk should determine these measures. In their opinion, it could also be possible for women with a particularly high disease risk to receive MRI-based screening investigations. Familial breast cancer, that is, evidence of BRCA-associated breast cancer, entails an increased disease risk.

The general principle that both methods have in common consists in a basic risk group formation, which establishes the further action with respect to

early detection measures. This offers advantages not only to the patient: the physician can thus better estimate the individual disease risk of a patient and choose the necessary screening investigations. The decision-making is thereby objectified and thus standardized.

Breath test

Peng et al introduced a completely new method of early detection: they carried out analyses of the expired breath of various subjects.[50] Among them were both healthy subjects and patients with lung, colorectal, breast, or prostate carcinoma. However, only tumor patients who had received no oncological therapy (chemotherapy, radiation therapy, etc) were included. The discoveries which the group made in the analysis of volatile organic compounds (VOC) have the potential to fundamentally revolutionize the screening programme. Peng et al found out that cancerous breath differs from healthy breath in its VOCs.[50] Thus it is possible, in their opinion, to screen the population for the above-mentioned cancers by means of a simple breath test. The analysis of the VOCs was carried out by of a gold nanoparticle sensor array (GNP sensor). It was possible not only to differentiate between cancerous and healthy breath, but at the same time specific clusters of VOCs. By means of these clusters, it is possible to determine the type of cancer from which the patient is suffering. However, the VOC clusters overlap between healthy subjects and patients with a stage 1 tumor, especially stage 1 prostate cancer. The reliability of the breath test in the early stage of a malignant disease must therefore be regarded as limited.[50]

Further series of tests will show whether this method produces sufficient evidence to allow it to be adopted for clinical use. An early detection method could thus be provided that is cost-effective, non-invasive, and easy to carry out thereby making it possible to carry out effective mass screening.[50] By means of mobile units, it would also be possible to reach the population outside peak population centers and thus reach all levels of the population.

Discussion

The aim of personalized medicine is to offer a tailor-made therapy. Side effects could be avoided so that the patient derives optimal benefit from a therapy. Medical resources should thus be optimally deployed and potential side effects avoided. However, more is now expected of PM. PM should allow not only determination of the response to therapy but also estimation of the disease recurrence risk. Against the background of the future financial viability of the healthcare system and the innovation this will require, PM arouses great interest in all involved in the healthcare system. PM has the potential to improve the quality of medical care for individual patients, and at the same time to improve the efficiency and affordability of the healthcare system. Thus PM offers new opportunities for patients, physicians, insurance companies, politicians and industry. Despite the highly promising approaches, PM is finding its way only slowly into everyday clinical practice and healthcare.

The relevance of PM in early detection was examined in the case of four common cancers (colorectal cancer, lung cancer, breast cancer and prostate cancer). Our results show that the methods of PM play a decisive role especially in screening.

This article shows possible ways of using PM in screening. As these merely provide food for thought and are not detailed concepts, the potential uses proposed here certainly leave room for critical enquiry. Questions remaining include validity of biomarker use in screening, practical and financial applicability of mass screening, cut-offs of low- and high-risk groups, and patient profitability through application of these methods.

The pitfalls in measuring biomarkers must also be pointed out and standardized sample treatment must be ensured so that comparable results are obtained. Moreover, the half-lives of most markers have not yet been defined precisely. The problem of specificity or allocation of biomarkers to their respective malignant diseases was alluded to above. The list of unanswered questions on the topic of PM in the context of screening is certainly a long one. Nevertheless, PM in the area of screening is promising and to date has been used too little.

In summary, it should be emphasized that numerous promising biomarkers are already known in malignant diseases. This results in several possibilities for individualizing and revolutionizing screening.

Personal view and outlook

Despite numerous unanswered questions regarding the feasibility and use of biomarkers, we regard their

use in screening for malignant diseases as the medicine of the future. Use of biomarkers can improve the early detection of malignant disease decisively. Even though the examples mentioned here, such as the breath test, are still immature ideas that leave much room for criticism, these examples indicate future possibilities in medicine.

In future, biomarkers will play a crucial role not only on the treatment level but also on the diagnostic level. Target-specific therapy will therefore be preceded by a biomarker-oriented screening programme. PM thus consists of individual screening and target-specific therapy.

Summary

The basic principles of early detection are presented: early detection can be by means of a blood test using numerous biomarkers (eg, MMP-1, CD44, miRNAs). The blood tests can be carried out before the customary screening methods, but the approved screening methods can also be replaced by a blood test. If the blood test is carried out before the customary screening methods, it is possible to differentiate between organ-specific and general oncological screening. Organ-specific screening could help to define risk groups and to develop an individual prevention programme. Mass screening offers a general test for malignant diseases which could be carried out not only by means of a blood test, but also by a breath test. This test could be introduced as a quick test for malignant diseases. Another approach for improving early detection is to build further on the previous screening methods. On the one hand, if marker lesions are identified, further investigations can be added in order to select patients at risk. On the other hand, the previous screening methods can be extended by biomarker measurement.

Author Contributions

Conceived and designed the experiments: FS. Analysed the data: FS, PKR. Wrote the first draft of the manuscript: FS. Contributed to the writing of the manuscript: FS, PKR. Agree with manuscript results and conclusions: FS, PKR. Jointly developed the structure and arguments for the paper: FS, PKR. Made critical revisions and approved final version: FS, PKR. All authors reviewed and approved of the final manuscript.

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