Review of: "A Value-Driven Future Approach to Precision Medicine for Health Sustainability in New Zealand: A Perspective"

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Potential competing interests: No potential competing interests to declare.

In this article, the author analyzes the ultimate goal of precision medicine, which is the early diagnosis of communicable and non-communicable diseases and their risks, along with early disease prevention, and treatment with targeted safe drugs with no side effects, within the context of an efficient personalized approach. The manuscript is straightforward, well written, and concise. Definitely deserves to be published and is a valuable contribution to the “Qeios” journal. Some comments need to be addressed, as recommended.

[1] “1. Precision Medicine”, Page 2/14:

“The vision of healthcare driven by precision medicine is to comprehend the biological events of disease prognosis and associated pathogenesis, that enabling the use of targeted treatment modalities for individuals and population groups.”.

The authors should highlight that in the era of targeted therapies, accurate histopathological and molecular classification of tumours is essential, in order to administer the best tailored therapeutic strategy. Classifications based on epigenetic alterations have served this purpose. Indeed, cancer cells are characterized by a massive overall loss of DNA methylation (20–60% overall decrease in 5-methylcytosine), and by the simultaneous acquisition of specific patterns of hypermethylation at CpG islands of certain promoters, which can reversibly or irreversibly alter gene function, thereby contributing to cancer progression.

Recommended reference: Rassy E, et al. New rising entities in cancer of unknown primary: Is there a real therapeutic benefit? Crit Rev Oncol Hematol. 2020 Mar;147:102882.

[2] “1. Precision Medicine”, Page 2/14:

“Patients, the valued participant of the research projects, are deemed to provide the biospecimens for testing along with the information of family history, environmental exposure (life-style), other medications, epigenetic errors, etc.”.

It would be beneficial for the readers to provide the example of BRCA1/2 germline mutations, which are the strongest known genetic risk factors for epithelial ovarian cancers and are found in 6–15% of women diagnosed with that disease. The BRCA1/2 status can be used for patients’ counselling regarding expected survival, as BRCA1/2 carriers with epithelial ovarian cancers respond better than non-carriers to platinum-based chemotherapies. This yields greater survival, even

though the disease is generally diagnosed at a later stage and higher grade.

Recommended reference: Shah S, et al. Epithelial Ovarian Cancer: Providing Evidence of Predisposition Genes. Int J Environ Res Public Health. 2022;19(13):8113.

[3] “1. Precision Medicine”, Page 2/14:

“The analysis of therapeutic efficacy and adverse toxicity effects through genomics and molecular testing will determine the optimized dosing recommended for appropriate clinical use.”.

It is worthy to be provided the example of the cancer of unknown primary (CUP), characterized by aggressive biological behavior and metastatic potential. From the therapeutic point of view, chromosomal instability (CIN) is not a frequent phenomenon in CUP, which may favour immune checkpoint inhibitors (ICI) among patients with CUP. Conversely, these patients present individual gene alterations implicated in immune-evasion and resistance to ICI. Further clinical investigations are needed to provide more information regarding the interplay between CIN, point mutations and the immune system, allowing a better understanding of ICI use in patients with CUP and potentially improving their efficacy.

Recommended reference: Chebly A, et al. Chromosomal instability in cancers of unknown primary. Eur J Cancer. 2022 Sep;172:323-325.

[4] “4. Respiratory Diseases & Personalized Medicine”, Page 5/14:

“Proteomics is the best-selected tool to find specific biomarkers involved in cancer.”.

At that stage, the authors should make a comment on the technologies of mass spectrometry and protein array analysis, which have advanced the dissection of the underlying molecular signaling events and the proteomic characterization of several tumors. Proteomics analysis of ovarian cancer, as well as their adaptive responses to therapy, can uncover new therapeutic choices, which can reduce the emergence of drug resistance and potentially improve patient outcomes.

Recommended reference: Ghose A, et al. Applications of Proteomics in Ovarian Cancer: Dawn of a New Era. Proteomes. 2022;10(2):16.

[5] “6. Precision Medicine Practice”, Page 6/14:

“Theranostic platforms can be adopted to test several biomarkers using various diagnostics to guide appropriate therapy”.

At that point, the authors should mention that exosomes have emerged as a novel source of non-invasive tumor biomarkers. The unique bilayer membrane structure of exosomes offers protection against external RNases and proteases, leading to enhanced stability of the enclosed mRNAs, miRNAs, and functional proteins, thus making exosomes highly sensitive markers for disease diagnosis. The cargo in tumor-derived exosomes, such as the range of miRNAs, can also serve as biomarkers for clear cell RCC in the serum and urine of patients, offering valuable targets for early detection and monitoring of the disease.

Recommended reference: Boussios S, et al. Exosomes in the Diagnosis and Treatment of Renal Cell Cancer. Int J Mol

Sci. 2023;24(18):14356.

[6] “9. New Opportunities”, Page 10/14:

“Early screening tests lower the risks for specific types of cancer or autoimmune disorders. Genetic, molecular, and genomic tests are commonly used terms in regular practice by healthcare providers (American Cancer Society).”.

At that point, it should be reported the recommended colon cancer screening for defective DNA mismatch repair using immunohistochemistry and/or MSI test. There are challenges in distilling the biological and technical heterogeneity of MSI testing down to usable data. It has been reported in the literature that immunohistochemistry testing of the mismatch repair machinery may give different results for a given germline mutation and has been suggested that this may be due to somatic mutations.

Recommended reference: Adeleke S, et al. Microsatellite instability testing in colorectal patients with Lynch syndrome: lessons learned from a case report and how to avoid such pitfalls. Per Med. 2022;19(4):277-286.