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Facing multimorbidity in the precision medicine era

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ABSTRACT

The clinical picture of multimorbidity is heterogeneous and it is characterized by great complexity. Precision medicine is an innovative approach to provide personalized care focused on individual characteristics and to deliver the right treatments, at the right time, to the right person. The precision medicine approach, which represents an epochal change in the field of chronic diseases, has been poorly implemented in patients with multimorbidity. Several factors can limit this application. First, the precision medicine approach has been successfully applied in the treatment of mono-factorial diseases while multimorbidity is multifactorial. Second, there is lack of understanding of risk factors in the development and evolution of multimorbidity. Third, precision medicine is mainly focused on understanding genetic aspects of diseases and neglects other characteristics contributing to the definition of individual profiles. Finally, individual pathways may lead to the development of different multimorbidity phenotypes. A possible solution to simplify the application of precision medicine to this condition is to reduce its complexity and to find homogeneous patterns of chronic diseases that may work as targets of preventive and therapeutic strategies. This approach can lead to better understanding how these factors interact at individual level and to define interventions that might target multimorbidity.

The world population is aging and the number of individuals with multimorbidity is in a rapid expansion. In high-income countries 20 % of the population before the age of 40, and almost 70 % of those above 60 have two or more chronic diseases, making multimorbidity 'the most common chronic condition' (Tinetti et al., 2012). Low and middle-income countries are expected to present similar figures in few decades (Eyowas et al., 2019). Onset and severity of multimorbidity are determined by a combined effect of lifestyle, behavioural, clinical, and social factors during the entire life-span (Onder et al., 2015). The clinical picture of multimorbidity is heterogeneous across individuals, and it is characterized by a great complexity, which impacts on quality of life, frequency of healthcare use, dependency and survival and challenges medical and care management (Marengoni et al., 2011).

Precision medicine is a new and innovative approach to provide personalized care focused on individual characteristics and to deliver the right treatments, at the right time, every time to the right person. It is defined by the Precision Medicine Initiative as *'…an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person',* in opposition to a one-size-fits-all approach, whereby treatment and prevention strategies are developed for an average person (NIH, 2020). The precision medicine approach will represent, if applied on a large scale, an epochal change in the field of chronic diseases: research and clinical trials performed in the last 30 years, currently driving clinical practice in the treatment of chronic diseases, assess the average effect of a given treatment with little consideration for individual differences. However, so far this approach has been poorly implemented in the multimorbidity field. Which factors can then limit such an application?

First, the precision medicine approach has been successfully applied in the treatment of mono-factorial diseases, in which it is possible to identify a single predictor of disease that can help to target interventions. This may explain the wide application of precision medicine for the treatment of some diseases, especially cancer, and possible difficulties in implementing this approach to the care of multifactorial conditions, such as multimorbidity. Second, there is lack of a clear understanding of risk factors promoting the development and evolution of multimorbidity. A personalized approach to multimorbidity prevention and treatment will require the discovery of reliable biomarkers

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and a more detailed and systematic investigation of potential risk factors. Third, precision medicine is mainly focused on understanding of genetic aspects of diseases and neglects other characteristics contributing to the definition of individual profiles (Khoury and Galea, 2016). Function and living environment, education and social capital, as well as lifestyles, are relevant personal characteristics that should be considered in the individualization of the process of care in persons with multimorbidity (Onder et al., 2015). Preferences and goals of patients for individual wellbeing are also relevant to this aim (Boyd et al., 2019). If a key concept underlying the precision medicine approach is the identification of hazards of diseases that can drive interventions, in the case of multimorbidity, multiple risk factors should be targeted. Forth, precision medicine should be adapted to the overall process of prevention and care of multimorbidity. Nowadays, prevention targeting the most relevant determinants of chronic diseases is based on interventions at population – rather than individual – level (e.g., campaign for smoking cessation or physical activity implementation). Also, some relevant drivers of the development of multimorbidity, such as social, economic and environmental factors, are ubiquitous and cannot be modified at the individual level. Thus, the role of precision medicine will probably be to integrate rather than replace existing programmes for prevention of chronic diseases and multimorbidity. Differently from prevention, the management of persons with multimorbidity follows individual pathways. Key elements of the care of multimorbidity are represented by the comprehensive identification of clinical and non-clinical characteristics of the person that can influence treatment adherence and success, evaluation of individual preferences, development of individual care plans (Boyd et al., 2019; Palmer et al., 2018; Farmer et al., 2016). Assessment and target of genetic aspects are currently not part of this approach. Finally, it should be considered that numerous different individual pathways may lead to the development of different multimorbidity phenotypes. An endless number of combinations of individual factors can determine these phenotypes and a clear understanding of their interplay and interaction might be extremely complex, making the definition of individual and personalized interventions challenging.

Given multimorbidity heterogeneity, a possible solution to simplify the application of precision medicine to this condition is to reduce the dimensionality of its complexity and to find homogeneous patterns that may work as effective targets of preventive and therapeutic strategies. A possible strategy might be to focus on clusters of chronic diseases. This approach aims to identify diseases that co-occur in the same person beyond chance. Diseases can cluster together because they share common risk factors and pathophysiological mechanisms, or one disease directly cause the other one (Marengoni and Fratiglioni, 2011). Knowing how and why diseases cluster together can lead to the development of preventive and therapeutic strategies targeting specific but common pathways. The application of precision medicine to specific clusters of diseases requires the analyses of large datasets collecting epidemiological and biological data and it should investigate the interplay between genetic predisposition to disease and personal and contextual factors such as gender, social and living environments, education, functioning, and lifestyles; all well-known determinants of multimorbidity (Marengoni et al., 2011). The specific factor or combination of factors identified by these analyses might then be systematically assessed in individuals with specific clusters of diseases and they will represent the target for specific treatments. This approach can lead to better understanding how risk factors interact at individual level and to define interventions that might comprehensively target multimorbidity.

The use of Artificial Intelligence is key in studying the complexity of these interactions and their outcomes and the use of machine learning techniques can be used to identify the possible combinations of individual factors underlying multimorbidity clusters. Machine learning algorithms can rapidly search through large datasets and generate probabilistic estimates of patients' likelihoods for different outcomes, such as various disease complications or death within homogeneous groups of patients defined based on disease clusters (Peterson, 2019).Machine learning models may open new possibilities to examine the complex field of multimorbidity by identification of specific risk factors that otherwise would be hidden in traditional analysis methods. This approach can lead to improved clinical diagnosis and prognosis of disease, identify high-risk individuals in a population, or provide information to appropriately monitor risk factors and treat patients with specific clusters of diseases using precision medicine.

In conclusion, if applied on a large scale in future decades, the precision medicine approach will represent an epochal change in the care of multimorbidity. Before that happens, the broad concept of precision medicine should be better expanded to cover aspects that are relevant for prevention and treatment of all chronic diseases and multimorbidity. To do so, population based longitudinal studies collecting information on genetic profile, education and lifestyles, environmental and social factors, and targeting the development of specific clusters of multimorbidity are needed. The use of Artificial Intelligence will be key to support this effort.

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