

# Bioethics and concierge medicine in aging: exploring complexities

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## Abstract

Concierge medicine emerged as a promising approach to offer exclusive and personalized treatments using genomic tools. In aging studies, concierge medicine has the potential to transform the treatment and prevention of age-associated and related diseases through pharmacogenetics and nutrigenomics; however, its use of genomic data raises important bioethical concerns, including privacy, consent, equity issues and potential misuse of these data for discriminatory purposes. Hence, careful consideration should be given to the biomedical, social, and ethical aspects of concierge medicine in aging contexts. Our review explores the main aspects of age-related pharmacogenetics and nutrigenomics data in concierge medicine, discussing the bioethical concerns involved in its use.

**Keywords:** Aging. Bioethics. Pharmacogenetics. Concierge medicine. Nutrigenomics.

## Resumo

### Bioética e medicina personalizada no envelhecimento: explorando complexidades

A medicina personalizada surgiu como uma abordagem promissora para fornecer tratamentos exclusivos e personalizados para doenças usando ferramentas genômicas. No campo dos estudos do envelhecimento, a medicina personalizada tem grande potencial para transformar o tratamento e a prevenção de doenças associadas à idade e relacionadas à nutrigenômica e à farmacogenômica. No entanto, o uso de dados genômicos na medicina personalizada levanta preocupações bioéticas significativas, incluindo questões como privacidade, consentimento, equidade e potencial uso indevido de dados genômicos para fins discriminatórios. Portanto, é crucial considerar cuidadosamente os aspectos biomédicos, sociais e éticos da medicina personalizada no contexto de condições relacionadas à idade. Esta revisão tem o objetivo de explorar os principais aspectos da medicina personalizada concernentes a doenças relacionadas à idade nos dados farmacogenômicos e nutrigenômicos, abordando as preocupações bioéticas envolvidas no uso desses dados.

**Palavras-chave:** Envelhecimento. Bioética. Farmacogenética. Medicina concierge. Nutrigenômica.

## Resumen

### Bioética y medicina personalizada en el envejecimiento: explorar las complejidades

La medicina personalizada surgió como un enfoque prometedor con el fin de proporcionar tratamientos únicos y personalizados a enfermedades utilizando herramientas genómicas. En los estudios de envejecimiento, la medicina personalizada puede transformar el tratamiento y la prevención de enfermedades asociadas a la edad y relacionadas con la nutrigenómica y la farmacogenómica. Sin embargo, el uso de datos genómicos en medicina personalizada plantea importantes preocupaciones bioéticas, incluidos temas como la privacidad, el consentimiento, la equidad y el posible uso indebido de los datos genómicos con fines discriminatorios. Así, es fundamental ponderar cuidadosamente los aspectos biomédicos, sociales y éticos de la medicina personalizada en el contexto de las afecciones relacionadas con la edad. Esta revisión pretende explorar los principales aspectos de la medicina personalizada sobre las enfermedades relacionadas con la edad en los datos farmacogenómicos y nutrigenómicos al abordar las preocupaciones bioéticas involucradas en el uso de estos datos.

**Palabras clave:** Envejecimiento. Bioética. Farmacogenética. Consejería médica. Nutrigenómica.

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Concierge medicine is a method that uses genomics and biotechnology to develop individualized treatment plans for patients based on their genetic information, as well as on genomic information such as RNA, proteins, and metabolites<sup>1</sup>. In a broader definition, concierge medicine is a health model that incorporates the principles of prediction, personalization, prevention and participation, also known as P4 medicine<sup>2</sup>.

The use of genomic data as the basis for concierge medicine raises concerns about privacy, consent, equity, and the potential misuse for discriminatory purposes. Thus, the careful consideration of biomedical, social, and ethical aspects of concierge medicine in the context of age-related conditions is crucial.

The field of medicine has been transformed: the focus shifted from treating diseases to promoting well-being, which means prioritizing prevention over treatment. This paradigm shift involves the use of personalized patient information to implement proactive measures that prevent diseases before they arise, thus emphasizing a broader and more individualized approach to health care<sup>3</sup>.

Nutrigenomics, pharmacogenomics and other areas have been actively developed to promote greater health among the older population<sup>4-7</sup>. These fields aim to deepen the understanding of the needs of older patients, create targeted interventions to improve their health, and prevent age-related diseases (ARD).

Despite the potential benefits of using genetic data to develop necessary treatment and prevention plans, several concerns arise—especially regarding privacy, prejudice, and resistance to treatment costs<sup>8</sup>. The challenges of storing, sharing, and protecting genetic data must be addressed for their availability. One's genetic information may lead to discrimination, and the possibility of health care providers or insurance companies resisting to cover treatment costs.

The aforementioned concerns emphasize the need for ethical guidelines and policies that balance the potential benefits of concierge medicine while protecting the patient's privacy and rights. This review focuses on these issues and their impact on the treatment of patients with ARD. The bioethical complexities

inherent in concierge medicine, nutrigenomics, and pharmacogenomics will also be examined. This study aims to provide a comprehensive overview of these emerging fields and their potential benefits and challenges, as well as the ethical considerations implied in concierge medicine for older patient care.

## Aging and related diseases

Aging can be defined as the gradual and irreversible decline of physiological function<sup>9,10</sup>. The changes can affect various areas of the body, including cell, organ and metabolism function<sup>11</sup>. The underlying mechanisms of aging are not yet fully understood, but they likely involve a combination of genetic, environmental, and lifestyle factors.

The impact of aging leads to an increased risk of ARD, including cardiovascular, neurodegenerative and metabolic diseases, and cancer, which also poses a significant challenge to the social and economic stability of individuals.

Neurodegenerative diseases, including Alzheimer's disease (AD), are strongly associated with aging. The characteristics of AD include the presence of amyloid plaques outside the cell, neurofibrillary tangles (NFT) within the cell, and the hyperphosphorylation of the Tau protein<sup>12</sup>. Brain aging is characterized by a pro-inflammatory environment, altered signaling and accumulation of senescent glia<sup>13</sup>.

In the case of AD, the main phagocytic cells in the brain, microglia, have their neuroprotective abilities impaired, and low-grade neuroinflammation occurs<sup>13,14</sup>. The presence of reactive astrocytes and the decrease in the number of neural stem cells and in the neurogenesis capacity are also associated with neurodegenerative diseases.

Senescent cells accumulate with aging and may contribute to the development and progression of cancer, promoting an inflammatory state through the expression of the senescence-associated secretory phenotype (SASP)<sup>15</sup>. The NF- $\kappa$ B and p38MAPK signaling pathways are involved in SASP release, which can promote the invasion of cancer cells and epithelial-mesenchymal transition (EMT)<sup>16</sup>.

Epigenetic modifications have been identified as major contributors to cancer development and progression. Aberrant patterns of DNA methylation often seen in aging, such as hypermethylation of the p21<sup>WAF1/CIP1</sup> and p16<sup>INK4a</sup> genes, may lead to cancer development<sup>17</sup>. Histone modifications, including losses in histone acetylation and methylation, are often seen in cancer cells. The role of histone deacetylases (HDAC) in cancer development and progression is well established. The HDAC are closely linked to the progression and prognosis of urogenital, reproductive and gastrointestinal cancer, as well as several others<sup>18</sup>.

Aging affects the cardiovascular system, increasing the prevalence of cardiovascular diseases such as hypertension, atherosclerosis, myocardial infarction and cerebral vascular accident. Cardiovascular tissues undergo pathological changes with aging, resulting in hypertrophy, altered left ventricular diastolic function, reduced left ventricular systolic reserve capacity, increased arterial stiffness, and impaired endothelial function<sup>19</sup>.

In the last decade, the field of aging studies has presented a new hypothesis: a high-calorie diet without physical exercise may have harmful effects by inhibiting the expression of “longevity genes” that facilitate cellular defenses against aging and age-related diseases<sup>20</sup>. This view is opposed to the traditional thesis that cardiovascular diseases result from the accumulation of fatty acids and cholesterol in tissues, stimulating the production of pro-inflammatory cytokines and reactive oxygen species (ROS)<sup>21</sup>.

Metabolic and systemic changes are known consequences of the aging process. Among these alterations, adipose tissue dysfunction is a significant characteristic, resulting in insulin resistance and chronic inflammation, and an increased risk of obesity and type 2 diabetes<sup>22</sup>. Studies suggest that molecular and cellular events that contribute to age-related damage of adipose tissue begin in the subcutaneous adipose tissue due to reduced function of resident antigen-presenting cells, increased inflammation and accumulation of senescent cells<sup>22,23</sup>.

In addition, individuals with type 2 diabetes often exhibit an elevated senescent cell load in

their adipose tissue, evidenced by increased expression levels of markers such as SA-β-gal, p53, p21, and pro-inflammatory SASP components, including IL-1α, IL-1β, IL-6, and TNF-α<sup>24</sup>. Senescence-related hypomethylation is mainly observed in genes that have reduced expression in proliferating cells, but elevated expression in senescent cells. This includes genes encoding p53, p21 and p16 targets, as well as the two primary pro-inflammatory components of SASP, IL-6 and IL-8<sup>15,25</sup>.

Chronic sterile inflammation triggered by aging and obesity can lead to a vicious cycle between senescence and DNA hypomethylation<sup>22</sup>.

## Concierge medicine and age-related diseases

### Nutrigenomics

Nutrigenomics studies nutrients and food structures capable of acting on gene expression, understanding how different nutrients and dietary patterns interact with an individual's DNA, affecting their health and aging process. This approach holds the potential to provide personalized dietary recommendations and interventions based on an individual's genetic makeup to prevent age-related diseases and promote healthy aging<sup>26</sup>.

Single nucleotide polymorphism (SNP) may partially contribute to variations in individual responses to bioactive food components. For example, Zeisel<sup>27</sup>, when investigating SNPs that alter the risk of developing organ dysfunction due to low choline intake, demonstrated that premenopausal women who carry a common SNP (methylenetetrahydrofolate dehydrogenase MTHFD1-G1958A) are 15 times more likely to exhibit choline deficiency symptoms than individuals without this SNP when on a low-choline diet<sup>27</sup>.

Breast cancer risk correlates to certain genetic variants that control homocysteine metabolism, such as methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MTR). This correlation is particularly strong in individuals who have lower intakes of folate and vitamins B6 and B12<sup>28</sup>.

Food can influence the expression of genes and signaling pathways involved in type 2 diabetes and cancer. Naringin, a compound abundant in citrus fruits and some vegetables, has been shown to improve  $\beta$  cell function and reduce insulin resistance, thus acting as a potent hypoglycemic agent through genetic interaction, increasing the activity of peroxisome proliferator-activated receptors (PPAR- $\gamma$ ).

On the other hand, biotin, found in various food sources such as spinach, eggs, sweet potatoes and almonds, increases insulin secretion and islet function through genetic interaction, signaling an increase in the activity of Forkhead Box A2 (FOXA2), HNF-4 $\alpha$ , a nuclear transcription factor and neuroendocrine/brain type calcium channel, alpha-1 subunit (CACNA1D). These findings suggest that specific bioactive compounds in food may play a significant role in regulating the expression of type 2 diabetes-related genes, showing how food compounds are related to gene expression and modulation.

Calorie restriction (CR) increases life expectancy in several organisms, such as humans, mice and non-human primates<sup>29-31</sup>, perhaps due to the induction of sirtuins, especially sirtuin 1 (SIRT1)<sup>32</sup>. Activation of SIRT1 and HDAC1 by caloric restriction induces deacetylation effects that result in changes in gene expression of key aging genes, including p53, Foxo, Ku70, PGC-1 $\alpha$ , and p16<sup>INK4a</sup><sup>33</sup>. The decrease in p16<sup>INK4a</sup> gene expression, resulting from the activation of SIRT1 by caloric restriction, delays the aging process and extends lifespan, since p16<sup>INK4a</sup> is a cyclin-dependent kinase inhibitor linked to the regulation of cellular senescence<sup>34</sup>.

Calorie restriction induces stress defense mechanisms, especially those related to the detoxification of ROS in rodents, a risk factor for cancer and cardiovascular diseases<sup>35</sup>. Because of this, CR has been associated with a reduction in the incidence of age-related diseases<sup>36</sup>. Maintaining a healthy weight and avoiding excessive calorie intake are thus important habits<sup>4</sup>. This approach emphasizes the potential of nutrition to intervene in genomics, with calorie restriction being a possible strategy to promote healthy aging.

The *Drosophila* model was employed in a study to track potentially bioactive compounds

and their effects on aging-related factors in a cost-effective and rapid way, including lifespan and oxidative stress. Evangelakou and collaborators<sup>37</sup> provided examples of bioactive compounds, such as polyphenols, flavonoids, and omega-3 fatty acids, that impacted aging-related pathways in the *Drosophila* model<sup>38,39</sup>. They also noted the potential of combining dietary interventions with exercise or pharmacological treatments to promote healthy aging.

These data highlight how nutrigenomics impacts the health of the older people and the development of personalized nutritional plans. However, nutrigenomics is a complex field, and the interpretation of genetic data requires specialized knowledge and experience. Receiving inaccurate or misleading information could negatively affect an individual's health. Access to accurate and reliable information is necessary, with professionals who can help in the correct interpretation and application of the information.

The potential social and cultural bias must be considered when developing personalized nutrition plans. The genetic makeup of an individual is shaped by genetic and environmental factors, including cultural and social ones. Personalized nutrition plans may be biased toward certain cultures or social groups. Thus, ensuring the development of personalized nutrition plans in a culturally sensitive and inclusive way is important.

### Pharmacogenomics

Precision medicine is advancing through pharmacogenomics (PGx), which involves customizing drug selection and dosing based on a patient's genetic characteristics. Physicians have expressed enthusiasm for several potential advantages of the PGx test: providing guidance on starting new drugs, facilitating shared decision-making, and minimizing the trial-and-error process of finding an appropriate treatment regimen. These advantages are particularly valuable for older patients with comorbidities and polypharmacy<sup>40</sup>.

In addition to genetic variations and changes in DNA methylation and chromatin structure, microRNAs (miRNA), a family of small non-coding RNAs (usually 20 to 24 nucleotides long),

are involved in the regulation of protein translation with a highly precise mechanism that adjusts gene expression in different tissues and cells<sup>41</sup>. This makes miRNAs very important epigenetic modulators, which influence the regulatory networks of genes involved in drug absorption, metabolism, and disposition. MicroRNAs have emerged as a promising therapeutic target.

In a study to identify potential precision drugs for breast cancer patients, Xu and collaborators<sup>42</sup> analyzed the diaphony between different miRNA-mediated risk pathways. Using bioinformatics tools to analyze gene expression and miRNA targets in breast cancer, they identified several miRNAs involved in regulating risk pathways that could be potential targets for drug treatments. Such findings provided insights into the molecular mechanisms of breast cancer—whose incidence increases with aging—and suggested a new approach to concierge treatments.

Warfarin is an oral anticoagulant used to treat various cardiovascular conditions and is affected by SNP in the CYP2C9 and VKORC1 genes. The CYP2C9 gene metabolizes and eliminates S-warfarin and belongs to the cytochrome P450 superfamily. The VKORC1 gene encodes the vitamin K epoxide reductase complex subunit 1, a target of warfarin. The knowledge about SNP in these genes enables concierge treatment with warfarin for cardiovascular patients. Most of the participants were older people, highlighting the contribution of pharmacogenomics to the health of the older population<sup>43</sup>.

The APOE4 gene is associated with an increased AD risk, but its influence on drug effectiveness is still unclear. While initial studies suggested reduced efficacy in APOE4 carriers, later studies reported conflicting results for cholinesterase inhibitors, such as tacrine, donepezil, galantamine, and rivastigmine<sup>44-47</sup>. Associations between polymorphism in acetylcholinesterase, choline acetyltransferase, and CYP2D6, as well as differential responses to treatment, were also evaluated<sup>48</sup>, but studies on adverse drug reactions are limited to tacrine-induced liver damage. The pharmacogenomics approach can help provide a more effective treatment for patients with AD.

Among the bioethical aspects of PGx, emphasizing considerations and principles involved in the use of genetic information to

support drug treatment decisions is important. For example, patients may have concerns about the privacy and confidentiality of their genetic information, or may feel pressured to undergo testing or treatment based on their genetic profile. The cost of pharmacogenomic testing and concierge medicine could widen the gap between the rich and the poor. Unequal access to health care and treatment is also a risk, particularly for marginalized communities, who may not have access to the latest pharmacogenomic technologies.

## Final considerations

Concierge medicine has brought great hope for the prevention and treatment of ARD, associated with nutrigenomics and pharmacogenomics. However, several bioethical concerns surrounding the use of genomic data for concierge medicine in aging studies require attention. One of the main concerns is the privacy of genomic data.

Patients may hesitate to undergo genetic testing for fear of discrimination based on their genetic predisposition to certain diseases. For example, an individual at high risk of developing AD may face discrimination in the workplace or by insurance companies. Thus, ensuring patients' control over their genomic data and establishing measures to protect their privacy is important.

In conclusion, these fields hold great promise for concierge medicine in ARD. Nutrigenomics can provide insights into an individual's unique nutritional needs and how they may be impacted by their genetic makeup, whereas pharmacogenomics can guide personalized drug selection and dosing based on genetic characteristics.

The use of genomic data in concierge medicine raises significant bioethical concerns. Improved education and awareness around the ethical implications of concierge medicine is necessary, both for health care professionals and patients. Therefore, ensuring that patients have a thorough understanding of the risks and benefits and that they can make informed decisions about their care is important.

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