Received: 22 March 2024 | Revised: 8 May 2024 | Accepted: 13 May 2024

DOI: 10.1111/jgs.19036

SPECIAL ARTICLE

Journal of the American Geriatrics Society

Aging precisely: Precision medicine through the lens of an older adult

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Funding information
Claude D. Pepper Older Americans Independence Center, Grant/Award Number: P30AG067988; National Institute on Aging, Grant/Award Numbers: R01-AG-077163-01A1, R03AG073985; National Cancer Institute, Grant/Award Number: R00CA237744; Conquer Cancer American Society of Clinical Oncology and Walther Cancer Foundation Career Development Award

Abstract

Precision medicine presents an opportunity to use novel, data-driven strategies to improve patient care. The field of precision medicine has undergone many advancements over the past few years. It has moved beyond incorporation of individualized genetic risk into medical decision-making to include multiple other factors such as unique social, demographic, behavioral, and clinical characteristics. Geriatric medicine stands to benefit heavily from the integration of precision medicine into its standard practices. Older adults, compared with other populations, have high clinical and biological heterogeneity that can alter the risks and benefits of different approaches to patient care. These factors have not been routinely considered previously by geriatricians. Yet, geriatricians' ability to address older adults' baseline heterogeneity is increasingly recognized as a cornerstone of delivering quality care in a geriatric medical practice. Given the shared focus of individualized decision-making, precision medicine is a natural fit for geriatric medicine. This manuscript provides, via cases and discussion, examples that illustrate how precision medicine can improve the care of our older patients today. We will share specific and existing tools and evidence, and review the existing multilevel barriers to further incorporate and implement these tools into clinical practice. We propose methods to address these barriers

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and to help realize the full potential of precision medicine for the care of older adults. We conclude with a brief discussion of potential future directions of research of precision medicine in the care of older adults.

KEYWORDS
older adults, pharmacogenetics, precision medicine

INTRODUCTION

The National Institute of Health (NIH) defines precision medicine as a medical practice that, "...uses information about a person's own genes or proteins to prevent, diagnose, or treat disease."[1] Instead of a one-size-fits-all approach, the intent is for patients to receive a more tailored plan of care for treating their medical comorbidities. Initially, this field focused on genomics and proteomics.[2,3] More recently, the field has moved to include an individual's unique social, demographic, behavioral, and clinical characteristics when considering treatment and prevention strategies.[4] The overarching goal is to use novel, analytical, data-driven methods and strategies to potentially lead to improvements in patient care for specific subpopulations and to ensure the right intervention is delivered to the right person.[5]

Geriatric medicine stands to benefit heavily from the integration of precision medicine into its standard practices as older adults are not simply "adults with higher chronological age."[6] Older adults, compared with other populations, have greater clinical and biological heterogeneity that can alter the risks and benefits of different approaches to patient care.[5,6] In fact, a comprehensive geriatric assessment (CGA), routinely used by geriatricians, provides patient-specific details about functional status, neuropsychiatric function and health, nutritional status, comorbidities, and support network, and guide subsequent management. Beyond this, however, older adults' biological and social heterogeneity have not been routinely and systematically considered by geriatricians previously. However, geriatricians' ability to address older adults' baseline heterogeneity is increasingly recognized by the National Institutes of Health as a cornerstone of delivering quality care in a geriatric medical practice.[7,8] Consequently, some geriatric healthcare professionals (GHPs) have already received training in and practiced the basic tenets of precision medicine.[9] Given the shared focus of individualized decision-making, precision medicine is a natural fit for geriatric medicine. GHPs are well accustomed to highly individualized medicine. This creates an ideal environment to take steps to bring precision medicine and genomic information into the fold. This manuscript will provide several examples that illustrate how precision medicine can improve the care of our older adults today. We will share specific and existing tools and evidence, and review the existing multilevel barriers to further incorporate and implement these into clinical practice.

Key points

- Geriatric medicine can benefit immensely from the integration of precision medicine into its standard practices.
- Precision medicine can address the heterogeneity commonly encountered in older adults, ensuring delivery of quality, individualized care.
- The current barriers to the implementation of precision medicine are addressable, and we propose methods to address these barriers.

Why does this paper matter?

Older adults are not simply "adults with higher chronological age." Compared with other populations, older adults have greater clinical and biological heterogeneity, that can alter the risks and benefits of different approaches to patient care. This biological, psychological, and social heterogeneity has not been routinely considered previously. Precision medicine practices provide readily available tools to address this heterogeneity. Given the shared focus of individualized decision-making, precision medicine is a natural fit for geriatric medicine. This manuscript will provide several examples that illustrate how precision medicine can improve the care of our older patients today

Why precision medicine in geriatric medicine?

While precision medicine has taken root in other disease-based specialties such as oncology, its widespread application

in geriatric medicine is still in its nascency. It promises new tools and techniques for clinicians to provide optimal, tailored care to older adults. These include tailoring medication choices based on individual risks of adverse effects and using individual demographics and/or genetic profiles to aid in complex medical decision-making.[10]

Physiologic and genetic heterogeneity characterize older populations.[7] As a person ages, their unique set of genetic and environmental circumstances combined with their individual lifestyle choices (e.g., diet and exercise) generate significant inherent diversity. Thus, even within a given age group of older adults, differences in life experiences lead to a wide variation in physical and mental health, functional status, and cognition. Given this heterogeneity, making individual patient decisions using population averages can worsen the care of specific patients.[11] For example, the decision to screen for colon cancer in a 78-year-old, non-ambulatory smoker with coronary artery disease and chronic obstructive lung disease requiring continuous home O_2 may be very different than the decision to screen a 70-year-old robust, ambulatory, never-smoker with hypertension as their only medical problem.[12] In both cases, accounting for the patients' individual characteristics is imperative in delivering care that is most likely to be beneficial to that specific patient.

With increasing heterogeneity, the management of older adults requires tailoring and individualization to each patient's complex biopsychosocial needs.[8] Patients may have multiple chronic conditions that synergistically produce harm, or where treatment of one condition may antagonize others. Time-to-benefit from treatment becomes a larger concern, as life expectancy may be more limited. Additionally, as life expectancy decreases, compressing the duration of time with disability becomes even more important.[13] Patient preferences may make quality of life a more significant outcome than extension of life. These multiple forms of complexity and competing risks challenge clinicians' conventional decision-making.

This complexity also challenges traditional research design and analytic approaches as well as application of traditional research results to the care of individual patients. When GHPs use data from clinical trials in patient care, they know to consider multimorbidity, individual organ function (e.g., chronic kidney disease [CKD], liver disease, dementia), and social determinants. These factors may not have been considered in the original study.[6] Precision medicine tools, including pharmacogenetic analyses or chemotherapy toxicity risk models, are known to incorporate patient specific factors rigorously tested in the research setting. They provide methods to address clinical heterogeneity and complexity at the patient level, clarifying the science to allow practitioners to focus on the art of medicine. To better illustrate on how precision medicine techniques and tools can be incorporated into geriatric patient care, we present a series of cases with discussion.

Cases

We present three hypothetical patient cases that highlight the potential value of precision medicine in geriatrics. We start with a case that presents a traditional precision medicine, genetic-based approach and conclude with a case that demonstrates the utility of a broader precision medicine approach to geriatric care.

> Case 1. A 69-year-old male with tobacco use disorder, obesity, obstructive sleep apnea, type 2 diabetes, hypertension, hyperlipidemia, gastrointestinal reflux disease, and Barrett's esophagus managed with omeprazole is hospitalized with severe chest pain that has persisted for 24 h. EKG shows ST elevation myocardial infarction and he undergoes percutaneous coronary intervention (PCI) with stenting of the left anterior descending artery. You consider clopidogrel or ticagrelor as an antiplatelet agent post-PCI.

Clopidogrel is a prodrug that requires activation via CYP2C19. Patients who are homozygous for the *2 or *3 alleles of the *CYP2C19* gene, or heterozygous with one copy of each, have loss of function mutations and are less able to convert clopidogrel into its active form. These patients are at higher risk of major adverse cardiovascular events after PCI while on clopidogrel and may benefit from an alternative agent.[14] However, ticagrelor has a higher bleeding risk than clopidogrel and is taken twice daily, increasing pill burden.[15]

In addition to genotype, drug–gene interactions may affect drug metabolism. Omeprazole, a proton-pump inhibitor (PPI), which the patient takes for gastrointestinal reflux disease and Barrett's esophagus, is an inhibitor of CYP2C19, reducing the effectiveness of clopidogrel.[16] Newer PPIs (e.g., pantoprazole, lansoprazole), however, do not have this inhibitory effect.

You genotype the patient for CYP2C19 alleles and discover that his genetics are suggestive of being a normal clopidogrel metabolizer. You can safely prescribe clopidogrel and change the patient's omeprazole to pantoprazole.

> Case 2. A 78-year-old woman with a past medical history of hypertension, type 2 diabetes, liver disease presents for consideration of treatment options after detection of a breast

mass on physical exam during a routine yearly geriatric evaluation. This led to further evaluation via mammography and ultimately a core needle biopsy. Pathology revealed infiltrating ductal carcinoma. The tissue sample has been sent for molecular marker assessment.

The use of molecular targeting for prognostication and treatment decision of breast cancer is a classic example of precision medicine-based oncology. The presence or absence of hormonal receptors for estrogen, progesterone, and HER2 have been used for more than two decades to prognosticate and target breast cancer therapy. More recently, advances in genomic analysis of the tumor have helped with cancer risk assessment to guide the use of adjuvant chemotherapy to reduce the risk of recurrence.[17,18] Usage of hormonal receptor guided therapy allows providers to deliver individually targeted treatment that have the highest likelihood of improving outcomes such as longevity and quality of life, while minimizing the risk of toxicities incurred from less targeted (i.e., broader) chemotherapy approaches.

Importantly, precision medicine is not limited to molecular analyses. In this case, a more complete precision medicine approach includes a CGA. CGA can identify common geriatric issues, such as falls or cognitive impairment, that are associated with worse oncologic outcomes and are frequently overlooked as part of a routine oncologic assessment.[19] These data can then be incorporated into risk models such as the Cancer and Aging Research Group (CARG) Chemotherapy Toxicity Calculator to predict risk of adverse events.[20] Specifically, a CARG-Breast Cancer tool is available for early stage breast cancer with demonstrated utility in predicting the risk of grade 3–5 (severe and/or life-threatening) chemotherapy toxicity, hospitalizations, dose reductions or delays, and reduced overall relative dose intensity receipt.[21] Such information can facilitate shared decision-making to ensure that treatment aligns with the patient's goals and wishes.

Pathology results reveal the presence of HER2 and estrogen receptors, but not progesterone receptors. The patient is determined to have stage IIB disease and her receptor pattern is associated with lower survival than other receptor patterns. A CGA was performed which reveals excellent baseline physical and cognitive functions. The CARG-BC, which incorporates her baseline renal dysfunction, reveals the patient is expected to have a an approximately 45%–54% risk of severe and/or life-threatening chemotherapy toxicity for the recommended regimen. She discusses this with her family, decides to proceed with neoadjuvant chemotherapy and remain vigilant for side effects.

Case 3. An 85-year-old woman is hospitalized after experiencing a right femoral neck fracture due to a fall from her bed. At baseline, she does not have any cognitive deficits and is independent with all activities of daily living (ADLs) and instrumental ADLs (instrumental IADLs). Her fracture was repaired operatively without complication. That night, the patient was noted be restless and agitated. She was frequently calling out and screaming. The inpatient geriatric consult service was contacted to assist with management. The consultant performs a delirium assessment via the Confusion Assessment Method (CAM) and notes that the patient is delirious.[22]

Postoperative delirium is common, occurring in between 20% and 25% of those hospitalized.[23] This syndrome can manifest as agitation, somnolence, or periods of alternation between hyper- and hypoactivity. There are many underlying causes but they include electrolyte abnormalities, adverse effects of medication, infection, and pain.

This patient was noted to be frequently grasping her right hip during periods of agitation. The consultant suspects pain is driving her delirium and starts scheduled three times daily oral acetaminophen along with as needed low dose oral oxycodone for severe pain.

On the subsequent day, the patient is no longer delirious. She complains of severe fatigue but is otherwise back to her baseline cognition. The patient requests that the geriatrics consultant meet with her and her son. They are both concerned about her fall and inquire if she will walk normally again or if this fracture could be an end-of-life event. The patient expresses, "I've lived a good life. If it's my time, it's my time. I don't want to live in a wheelchair and I don't want to live in a nursing home."

Psychological resilience has a strong correlation with improvement in walking capacity after hip fracture.[24] High levels of self-reported psychological resilience after hip fracture are strongly associated with greater recovery of walking distance and speed 4 months after a hip fracture.[25]

The GHP performs a Brief Resilience Scale assessment and finds that the patient's resilience is high. Given the patient's good functional status pre-fracture, good symptom control with as needed oxycodone, great family support, and her individual resilience, the GHP believes she has a good chance of functional recovery. After the GHP shares this information, the patient and her son decide to pursue physical therapy in a rehabilitation facility for the next few weeks with a goal of returning home. After 4 weeks in a rehabilitation facility, the patient regains enough function

to return home, no longer requires pain medications, and will continue outpatient physical therapy.

This case demonstrates how precision medicine approaches include inter-individual clinically relevant multifactorial heterogeneity in terms of function, multimorbidities, frailty, socioeconomic and behavioral factors, and care preferences. Historically, precision medicine has focused on single risk factor such as inherited genetic differences such as those discussed in Case 1. The multifactorial dimensions demonstrated in this final case must be added to the older precision medicine approaches, in order to ensure the best individualized care for each older adult.

BARRIERS TO IMPLEMENTING PRECISION MEDICINE IN GERIATRIC CARE

As illustrated by our cases, many precision medicine approaches are informally employed in geriatric care. However, we argue that there are multiple barriers that must be addressed prior to these approaches being more universally adopted in the care of older adults. Broadly, the barriers to introducing precision medicine into geriatric medical practice can be placed at the patient, health-care provider, health-care systems, and research community levels (Figure 1).

Addressing patient-level barriers

Medical mistrust is an important barrier to accessing medical care in general and specifically, to precision medicine in older adults. Medical mistrust can be magnified among historically marginalized groups, who have often faced medical discrimination.[26] Recording and analyzing an individual's genome raises concerns about privacy, access, and ownership.[27] Patients rightly expect that their data will be protected not only from theft, but from access by unauthorized individuals or organizations such as an employer or insurer. Similarly, patients may wish to control whether their data are used in research or which providers have access to their results. Research based on genomic data that leads to the development of intellectual property raises questions of who owns that property. The ethical issues arising over usage of immortal cancer cells from Henrietta Lacks (HeLa cells) for research purposes provide an excellent example of this potential pitfall.[28] Finally, genomic data may have implications for the health of relatives—who may also be the patient's caregivers—with whom the patient may or may not wish to share results. We have previously surveyed a small number of older adults and their caregivers and found that this was not a significant concern for either group.[29]

Prior research has identified two actions to reduce distrust in genetic testing.[30] They are: (1) denying insurers access to individual test results and (2) having primary care providers offer genetic testing instead of specialists. This research on genetic testing can be extrapolated to reduce distrust in precision medicine, in general. Data collected for precision medicine must not be utilized in a discriminatory manner; the Genetic Information Nondiscrimination Act (GINA) specifically prohibits the usage of genetic information for insurance discrimination.[31] Educating patients and providers on GINA may alleviate some of the fear of discrimination. It will be imperative to extend the protections on genetic data to other precision medicine data such as social determinants of health.

Lack of patient education regarding precision is another potential patient-level barrier. Patient knowledge of precision medicine and its potential is growing but there is a need for greater public awareness and education.[2] A public education initiative with information on precision medicine and its potential benefits will be an integral part of ensuring precision medicine practices become routine care. These initiatives must be offered in media that can reach patients of diverse socioeconomic, racial, and ethnic backgrounds (e.g., television, radio, print).

Addressing healthcare provider barriers

Healthcare provider level barriers include deficits in the evidence base supporting precision medicine, deficits in training in how to contextualize and implement this evidence, and deficits in knowledge of how to utilize the new sources of patient data created by precision medicine.[32] Providing and linking clinical outcome data to provider guidelines could help GHPs adopt and communicate effectively with older adults and their caregivers.[33] Continued research, providing evidence-based precision medicine best practices, will help in overcoming some of these barriers.

In addition to a lack of evidence, significant challenges in precision medicine implementation stem from a lack of education and awareness across healthcare providers, payers, and patients.[34] To address this, precision medicine approaches need to be incorporated early into training in the various medicine disciplines, beginning with medical, nursing, or pharmacy school. Given the natural fit between precision medicine and geriatrics, it is imperative that training in precision medicine be included in geriatric fellowship education. Building on the shared decision-making and individualization skills obtained from training in the CGA

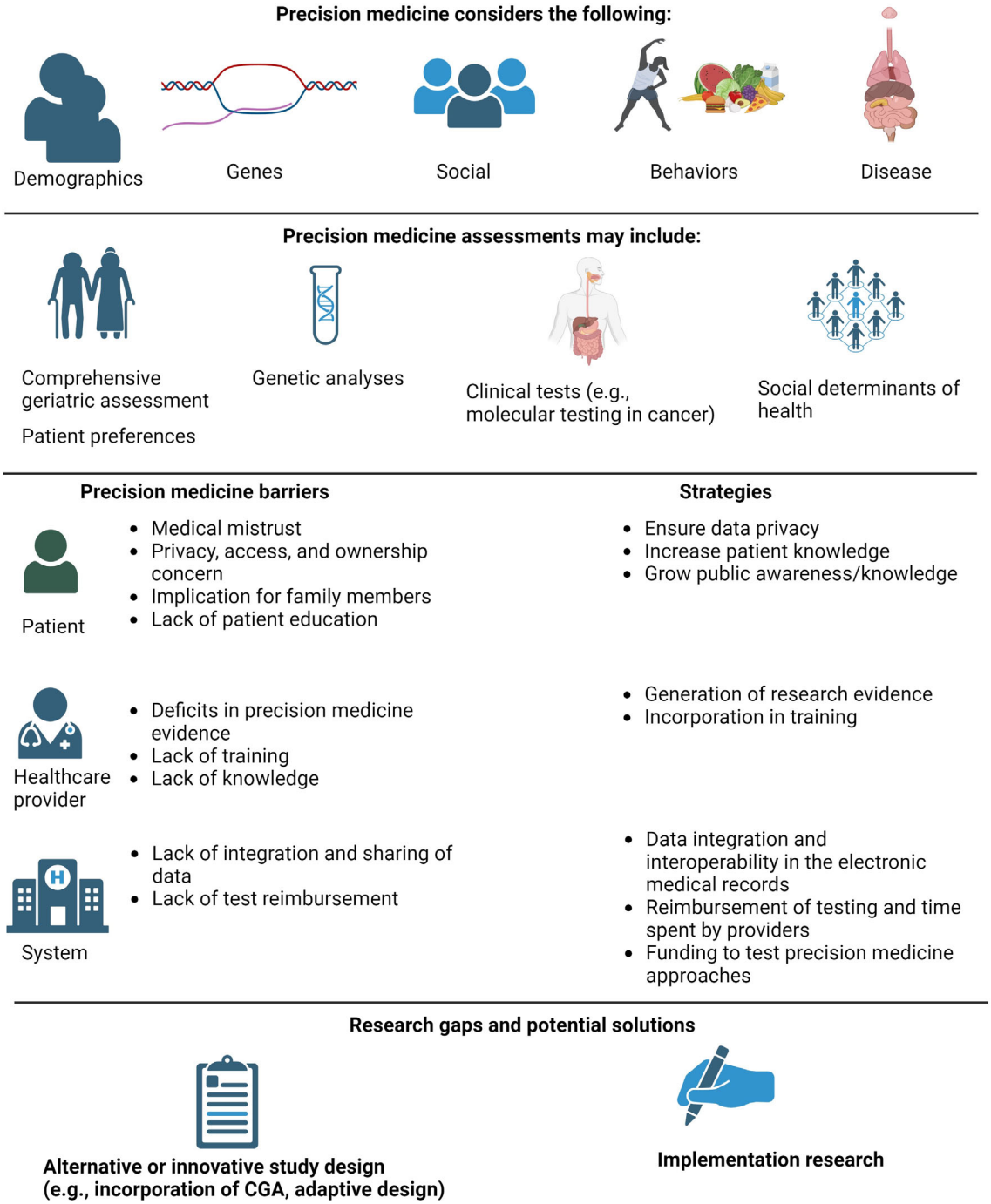

FIGURE 1 Barriers to precision medicine in older adults.

provides a natural method to facilitate training in precision medicine approaches.

Addressing systems barriers

Barriers to precision geriatric medicine at the systems level can be broken down by the different components of the healthcare system: healthcare delivery, payors, and research funders. Within healthcare delivery, a major challenge lies in the integration of appropriate data into care processes, such as laboratory collection and patient intake; documentation in the medical record; and the ability to share data across institutions as appropriate for patient care. However, other components of the healthcare system also need to align with the clinical implementation of precision medicine tools. Commonly used electronic health record (EHR) programs provide a natural platform for integration of this diverse array of information. Key data for geriatric precision medicine, such as

function, frailty, and treatment preferences, are often poorly documented in EHRs or are absent entirely; EHR systems need to be updated to incorporate these data.[35,36] It will also be important to incorporate artificial intelligence (AI) tools into the EHR to help guide precision medicine decisions.[37]

With respect to payors, private insurers as well as Medicare and Medicaid need to reimburse for tests, provider time, and procedures related to precision medicine. For example, if a medication has a differential effect based on pharmacogenetic profiles, then the genetic testing required to determine this effect should be reimbursed. This reimbursement must be provided without disclosure of test results to the payor. More broadly, payors must respect patient privacy concerns, particularly with respect to genomic data and its potential abuse in setting premiums, including following GINA. Payors must also provide reimbursement for time spent by providers discussing precision medicine tests.

Research funders—from public agencies to private businesses—need to support work assessing the value of precision medicine approaches to care, including cost-effectiveness analysis oriented toward common geriatric medicine use cases. For the cases where value is demonstrated, healthcare payors, including private insurance as well as Medicare and Medicaid, need to reimburse for tests and procedures. These ideas suggest a clear way forward: public and private agencies can build partnerships to fund research assessing the value of precision medicine tools and tests for older adults, healthcare systems can partner with EHR manufacturers to improve how these tools are incorporated into workflows, and legislation at state and federal levels can be promulgated to protect patient privacy.

Addressing gaps in research

Broadly, future geriatric research should focus on how to incorporate precision medicine into research design and implementation. As stated above, the vast physiologic diversity among older adults is a significant challenge to running and interpreting clinical trials in this population. Clinical heterogeneity leads to heterogeneity of treatment effects. Traditional trial designs are often meant to compare the mean effect of an intervention to a control. This trial design does not account for the fact that within both groups some participants will improve and others worsen. Delineating the factors that lead to a patient having an extreme response or lack thereof to an intervention could prove immensely useful. Incorporation of CGA into clinical trial design can help better describe population of interest, and more importantly allow differential effects of interventions to be analyzed, through subgroup analyses or other methods.

Adaptive trial designs may make these questions tractable. One such design is the Sequential Multiple Assignment Randomized Trial (SMART).[38] Under this design, participants are initially assigned to an arm of the study. At a prespecified assessment, participants who did not respond can be re-randomized. This design is applicable to many conditions, but particularly to behavioral health where medications are often selected by trial and error. For example, to test pharmacotherapies, participants can be randomized to receive one of several antidepressants, be assessed for response, and nonresponders then re-randomized to another agent. Once ready for analysis not only are average effects estimated, but truly individualized treatment pathways can be identified using reinforcement learning. These research strategies potentially allow for more precise prescribing and better individualization of care to each older adult with their unique type of clinical heterogeneity. These types of designs strongly align with clinical care—if the initial approach does not work, a clinician will change their strategy. In this type of design, one can answer the questions on which is the most effective initial therapy and which sequences work best for which individuals. Furthermore, novel machine learning analytics can be used to evaluate the findings of the trial and create an algorithm to match baseline characteristics to the sequence of choice.

The second broad area of need is in health services and implementation research. Evidence for the use of traditional, genome-centered precision medicine tools with older adults is sparse. This paucity of evidence can slow its adoption into practice.[39] Whether these precision tools are living up to their promise and generating value for patients is not clear, and research on their cost-effectiveness is needed. Further, best practices for implementation, including buy-in from patients, providers, and systems need to be identified. Partnerships between public and private payors may be one way to support these important areas of research. Such an example is the Veterans Affairs Pharmacogenomic Testing for Veterans (PHASER) initiative within the Veterans' Affairs Health System (VA).[40] The implementation of pharmacogenomics testing with VA has led to harm reduction from statin prescribing, among other drug–gene interactions.[41] Incorporation of patients and their families into study designs and research question development is another method to potentially assist with implementation and end-user acceptance.

Conclusions

The care of older adults presents an opportunity to meet the full promise of precision medicine: using the varied characteristics and hopes of our patients to find a plan of care that meets them where they are. Geriatricians—already used to highly individualized medicine—are

well-placed to take the steps to bring precision medicine and the use of genomic information into the fold. Many of the barriers to incorporating precision medicine can be overcome through our own professionalism, education, and partnership with our patients. Others require us to adjust the organizations we work with and for in our practice. These efforts need to be informed by additional evidence that is centered on the concerns of our patients, is adapted to their diversity, and is actionable. Precision medicine is coming for our patients. We are the right professionals to ensure it meets their needs.

AUTHOR CONTRIBUTIONS

All listed authors were involved in manuscript concept, design, and composition.

FUNDING INFORMATION

Dr. John A. Batsis' contribution was funded in part by the National Institute on Aging from the National Institute of Health, Grant number R01-AG-077163-01A1, Dr. Kah Poh Loh's by the National Cancer Institute and National Institute of Aging from the National Institute of Health (R00CA237744, R03AG073985) and Conquer Cancer American Society of Clinical Oncology and Walther Cancer Foundation Career Development Award, and Dr. George A. Kuchel's by the Claude D. Pepper Older Americans Independence Center (P30AG067988).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

SPONSOR'S ROLE

There was no role of a sponsor in the concept, design, or composition of this manuscript.

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How to cite this article: Austin CA, Seligman B, Shan-Bala S, et al. Aging precisely: Precision medicine through the lens of an older adult. *J Am Geriatr Soc*. 2024;72(10):2972-2980. doi:10.1111/jgs.19036