ORIGINAL ARTICLE

MAYO CLINIC PROCEEDINGS:
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MAYO CLINIC

Evaluation of a Computable Phenotype for Successful Cognitive Aging

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Abstract

Objective: To establish, apply, and evaluate a computable phenotype for the recruitment of individuals with successful cognitive aging.

Participants and Methods: Interviews with 10 aging experts identified electronic health record (EHR)-available variables representing successful aging among individuals aged 85 years and older. On the basis of the identified variables, we developed a rule-based computable phenotype algorithm composed of 17 eligibility criteria. Starting September 1, 2019, we applied the computable phenotype algorithm to all living persons aged 85 years and older at the University of Florida Health, which identified 24,024 individuals. This sample was comprised of 13,841 (58%) women, 13,906 (58%) Whites, and 16,557 (69%) non-Hispanics. A priori permission to be contacted for research had been obtained for 11,898 individuals, of whom 470 responded to study announcements and 333 consented to evaluation. Then, we contacted those who consented to evaluate whether their cognitive and functional status clinically met out successful cognitive aging criteria of a modified Telephone Interview for Cognitive Status score of more than 27 and Geriatric Depression Scale of less than 6. The study was completed on December 31, 2022.

Results: Of the 45% of living persons aged 85 years and older included in the University of Florida Health EHR database identified by the computable phenotype as successfully aged, approximately 4% of these responded to study announcements and 333 consented, of which 218 (65%) met successful cognitive aging criteria through direct evaluation.

Conclusion: The study evaluated a computable phenotype algorithm for the recruitment of individuals for a successful aging study using large-scale EHRs. Our study provides proof of concept of using big data and informatics as aids for the recruitment of individuals for prospective cohort studies.

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Many individuals are living past their expected lifespan.[1,2] People living beyond the age of 85 years represent the fastest growing segment of our population.[3] Most of these people are living independently and free of major diseases. This population provides a foundation of lifestyle, genetic, and environmental factors that can be investigated to determine the influences that increase life expectancy and limit disease burden.[4] Increasing recognition of successful cognitive aging may be critical to methods in preventing and treating age-related cognitive disorders such as Alzheimer disease and related disorders or vascular dementia.[5,6] Defining and identifying successful cognitive aging factors can mold lifestyle, medication, and environmental preventative interventions to decrease disease burden.

Scientist in the field of aging have constructed various definitions of successful aging[7]; however, the most common factors that persists include (absence of) disease status, intact cognitive and behavioral function, and minimal physical disabilities continuing to an advanced age such as age older than 85 years. Moreover, research has reinforced that focusing on physical abilities alone can be insufficient and that cognitive function is a vital pillar in successful aging.[8] For example, the Macarthur model[9] of successful aging describes an all-encompassing life absent or low probability of disease, with high cognitive and physical functioning and engagement in social behaviors. Successful cognitive aging may represent a special (broader or narrower) type of successful aging overall and has been associated with its own specific definitions.[10,11] By identifying factors associated with successful cognitive aging, we may glean insight into factors that could mitigate dementia risk.

Given the risk of cognitive impairments with aging, identifying cohorts of successful cognitive aging presents a unique challenge, especially at very advanced ages. Given the very small numbers of people aged 85 years and older in any community, traditional door-to-door surveys can be expensive and time consuming.[12,13] Using health records and biomedical informatics methods may provide an alternate and efficient approach to identify cohorts of older individuals with intact cognitive function.[14,15] However, informatics approaches present their own challenges. Identifying the appropriate diagnostic and procedural codes and obtaining consent from individuals to be contacted for research purposes in such data sets are difficult.

This study sought to establish, apply, and evaluate a computable phenotype (CP) of factors associated with successful cognitive aging among persons of very advanced age (Figure 1). To accomplish these 3 objectives, we first developed a CP of successful aging on the basis of expert consensus. Next, we used the OneFlorida+ Clinical Research Network[16] to apply the CP to individuals residing within the University of Florida (UF) Health system. Our third aim was to evaluate the CP by contacting, consenting, and briefly evaluating older adults (≥85 years) who met our CP criteria and had previously expressed an openness to participate in research.

PATIENTS AND METHODS

Aim 1: Establish Successful Aging Criteria on the Basis of Variables Routinely Collected in EHRs

A Delphi method involving a panel of experts was used to nominate characteristics that define successful aging in persons aged 90 years and older, with the caveat that these characteristics must be widely accessible in the electronic health records (EHRs). This precluded characteristics that might require direct assessment of cognition, daily function, or informant interview. Rather, the characteristics centered on information such as residential location, and the absence of key diagnostic or procedural codes.

This panel comprised 10 experts in aging, health outcomes and biomedical informatics, epidemiology, gerontology, neurology, neuropsychology, and neuroscience. All experts were individually and separately interviewed by 1 author (D.M.M). From the interviews, the researcher assembled a list of discrete variables. Then the panel members were asked to individually grade the aggregated list of nominated variables as being required, unsure if required, or not required for successful aging for aging older than 90 years. In a post hoc analysis, we elected to apply these criteria to a more traditionally defined "oldest-old" group[17]: those aged 85 years and older.

Aim 2: Develop a Rule-Based CP Algorithm to Identify Successfully Individuals Aged 85 Years and Older From UF Health Using EHRs

The nominated variables were shared with the informatician to assess availability in EHRs using pilot queries over EHRs. Then, the biomedical informaticians (Y.W., J.B.) translated this set of characteristics into a CP on the basis of "machinable" EHR data such as date of birth, zip code, medication records, International Classification of Diseases codes (ninth and tenth versions), and Current Procedural Terminology codes. A listing of these codes is included in Supplemental Table 1 (available online at http://www.mcpiqojournal.org). Then, we implemented the criteria into structured query language (SQL) to include or exclude patients. To ensure the CP algorithm identified a reasonable number of individuals, we iteratively refined the queries according to the query results, for example, how changes in criteria affect the number of identified individuals. Furthermore, we applied the refined CP algorithm to the OneFlorida+ EHR database and identified a "virtual" cohort of individuals who successfully aged to 85 years and older. The OneFlorida+ Data Trust represents approximately 75% of the State of Florida through EHRs from partnering hospitals,

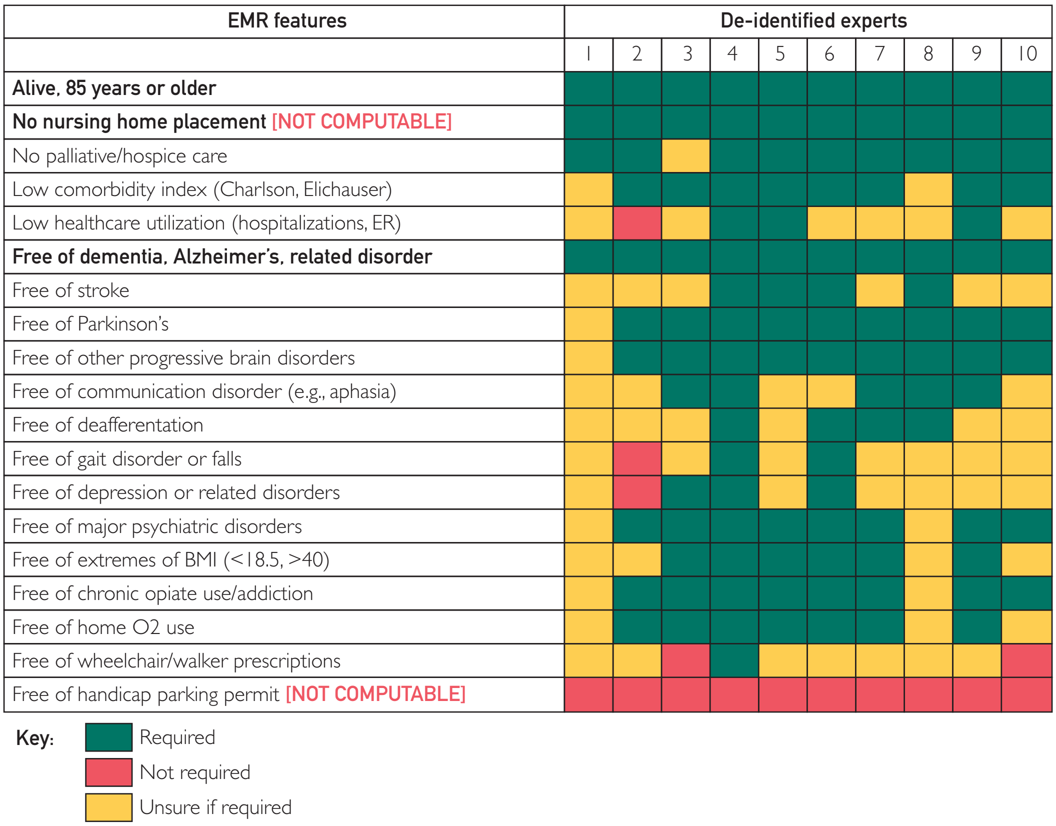

FIGURE 1. Computable phenotype of successful aging.

clinics, and providers, in addition to claims data from individuals enrolled in Florida Medicaid.

All individuals with EHR data in the OneFlorida+ Data Trust are geocoded to their census tract providing information about environmental and community context where these individuals reside. Using this geocoded tracking, our research team could identify individuals residing in the areas of Gainesville, FL, and Jacksonville, FL. This virtual cohort became the targeted recruitment pool for contact and participation in Aim 3.

Aim 3: Directly Assess a Subsample of Individuals Within the Cohort of 85 Years and Older to Evaluate Successful Cognitive Aging Status

Our third aim was to evaluate the CP by contacting, consenting, and briefly evaluating the older adults who met our CP criteria and had previously expressed an openness to participate in research. This consisted of administering the following measures during a remote assessment.

Measures

- Telephone Interview for Cognitive Status (TICS-M)[18,19]: This interview has been used extensively to screen for cognitive impairment in individuals over the telephone. All telephone-interviewed individuals were administered the TICS-M. These scores were adjusted for educational attainment as per the TICS-M validation study.[19]
- Geriatric Depression Scale (GDS)[20,21]: This questionnaire was used to screen eligible and willing participants for depression. This scale has been tested and used extensively within older populations. This short

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form version of the GDS consisted of 15 questions.

- The Barthel Index[22]: This questionnaire was used to establish a degree of independence from any help and establish a level of activity that is performed. This is used as a record of what the participant does regularly. Both participants and proxies (if available) were administered the Barthel Index by the study team during the telephone interviews. Participants were administered the Barthel Index to allow for self-reporting and comparison among participant and proxy responses.
- Functional Activities Questionnaire (FAQ)[23]: This questionnaire was used to measure instrumental activities of daily living, such as preparing balanced meals and managing personal finances. All proxies (if available) were administered the FAQ by study staff.

Validation criteria. A priori criteria were established to define successful cognitive aging. These criteria included the following: (1) a direct interview verification that all components of the CP were met, (2) a TICS-M score more than 27,[19] and (3) a GDS score less than 6.[21]

Recruitment. The process for recruiting and evaluating persons identified by the CP process is depicted in Figure 2. An initial contact letter was sent to potential participants with a return postcard. If this postcard was not returned within a month, a second reminder contact letter was sent. For individuals who returned the postcard, study staff contacted them by phone to further explain the study.

On successful contact, potential participants were informed how researchers were able to identify them as potential successful agers and explained the study opportunity. Consenting persons were enrolled into the study and were administered the following procedures: a telephone assessment and a proxy member telephone interview (if available). During the telephone assessment, the following questionnaires were administered to the participant: self-reported confirmation of CP criteria, the TICS-M, the GDS, and the Barthel Index (Figure 2).

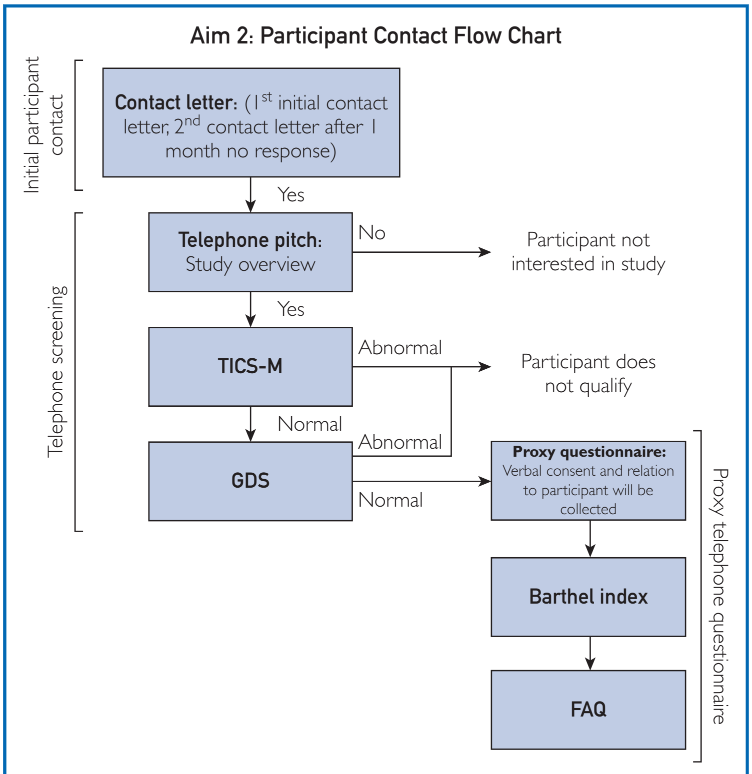

FIGURE 2. Recruitment contact flow chart. FAQ, Functional Assessment Questionnaire; GDS, Geriatric Depression Scale; TICS-M, Telephone Interview of Cognitive Status Modified.

For those participants who successfully completed the telephone screening and were deemed "successful cognitive agers," the research team contacted a proxy member (if available) and administered an additional proxy Barthel Index. The proxy was identified by the study participant as the person knowing best their health and social status. The proxy's name and contact information was collected from the successful ager participant during the initial telephone screening and was not a requirement for study enrollment.

RESULTS

Aim 1: Establish Successful Aging Criteria on the Basis of Variables Routinely Collected in EHRs

At the request of the Delphi Panel facilitator (D.M.M.), the panel of experts, blinded to one another, nominated 19 variables for the CP of successful aging of older than 90 years. Then, the 10 experts were asked to designate

TABLE 1. Successfully Aging Patients in the OneFlorida Data Trust

Characteristic	OneFlorida: older than 85 y		OneFlorida: older than 85 y, successful aging		Older than 85 y, validated successful cognitive aging	
	n	%	n	%	n	%
Total	52,841		24,024		218	
Demographic						
Sex						
Female	33,667	63.7	13,841	57.6	112	51.4
Male	18,993	35.9	10,006	41.7	106	48.6
Unknown	181	0.3	177	0.7	0	0.0
Race						0.0
White	33,719	63.8	13,906	57.9	204	93.6
African American	8184	15.5	2793	11.6	12	5.5
American Indian	58	0.1	20	0.1	0	0.0
Asian	881	1.7	384	1.6	1	0.5
Pacific Islander	33	0.1	21	0.1	0	0.0
Multirace	57	0.1	24	0.1	0	0.0
Other	4377	8.3	2259	9.4	3	1.4
Unknown	5532	10.5	4617	19.2	0	0.0
Ethnicity						
Hispanic	2538	4.8	1128	4.7	2	0.9
Non-Hispanic	41,899	79.3	16,557	68.9	210	96.3
Unknown	8404	15.9	6339	26.4	6	2.8

the 19 variables as required (green), not required (red), or unsure if required (yellow), for successful aging of older than 90 years, again blinded to one another. In addition, a biomedical informatics expert (separate from the panel) determined which of the nominated variables could be captured by the EHR and were computable (Figure 1).

None of the 10 experts agreed completely with any other expert as to which of the 19 EHR variables were required, not required, or unsure. However, all 10 experts agreed that 3 EHR variables were required: alive, 90 years or older; no nursing home placement; and free of dementia, Alzheimer disease, or related disorders. Then, the biomedical informatics team identified computable variables using the OneFlorida+ EHR database and excluded 2 variables that were not computable (no nursing home placement and free of handicap parking permit), resulting in 17 computable EHR.

Aim 2: Rule-Based CP Algorithms to Identify Successfully Persons Aged 85 Years and Older at UF Health

We defined and iteratively fine-tuned the 17 computable EHR variables using International Classification of Diseases codes and procedure codes as summarized in Supplemental Table 1 and implemented the criteria using SQL queries. We took the liberty of applying the CP to persons aged 85 years and older, consistent with standard definitions of "oldest-old," but recognizing that the original Delphi panel specified 90 years and older. Using the SQL query, we identified 24,024 individuals in the OneFlorida+ EHRs (limited to UF Health patients) who met the 17 "successful aging" criteria, comprising the CP (Table 1). This represented 45% of all living persons aged 85 years and older or 70% of the living persons 85 years and older and free from dementia diagnosis. Then, the UF Health Integrated Data Repository gatekeepers provided contact information for patients within the UF Health records system who had indicated openness to research participation. This resulted in 11,898 participants in the virtual cohort for whom Aim 3 researchers obtained contact information. We attempted to recruit and enroll all 11,898 patients identified by the CP.

Aim 3: Evaluate the CP by Direct Brief Evaluation. Approximately half of those meeting CP criteria had previously expressed an openness to be engaged in research and had contact information available. Of the targeted sample (n=11,898), 1111 returned a postcard or called our recruitment telephone line; 3.95% were successfully contacted by telephone (n=470); and of the successfully contacted potential participants, 70.85% consented and agreed to participate in the pilot study (n=333). Our methods of reaching out to the virtual cohort generated nearly a 4% successful contact rate and a 2.8% recruitment rate.

Seventy-five persons (22.5%) who met CP criteria and agreed to participate in the study were excluded for conditions that were intended to be detected by the informatics process. The reasons for exclusion of these individuals are presented in Supplemental Table 2 (available online at http://www.mcpiqojournal.org). Note that in some cases more than 1exclusion criteria were met. Mobility impairments were the major reason for most exclusions (fall or gait disorders, a history of falls, and/or wheelchair/walker use/prescriptions). The CP was fully successful at excluding those with a diagnosis of dementia or AD and largely successful at excluding those with other neurologic disorders.

Only 36 (11%) of those participants who completed the telephone assessment fell below the cutoff on the TICS-M. The mean (and SD) TICS score in this group was 24.3 (2.6). Four participants (1.20%) scored above the cutoff on the GDS. Three of those fell exactly 1 point above the GDS cutoff and none of these 4 participants' TICS-M scores were below the cognitive cutoff. Thus, of the 333 enrolled participants who completed a telephone assessment, the CP was fully "validated" in 218 (65.46%) (Figure 3). The demographic and health attributes of successful cognitive agers are included in Table 2.

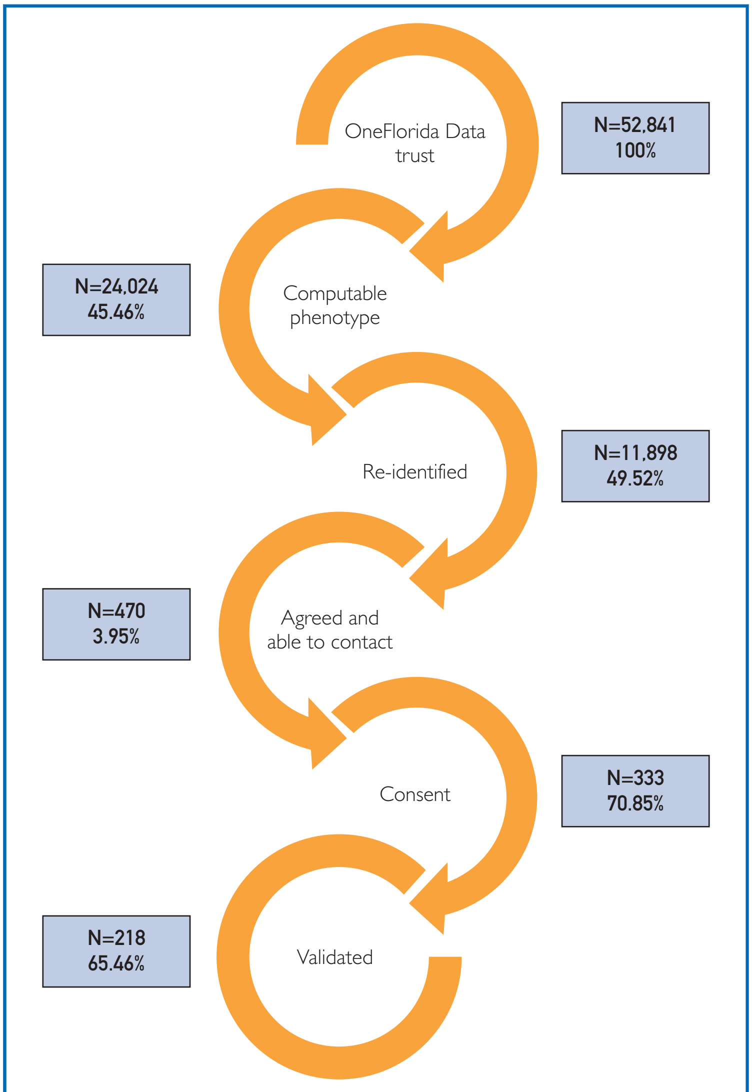

FIGURE 3. Phenotype evaluation flow.

Although functional status was not included in our direct assessment criteria for successful cognitive aging, we note that by self-report, 92% of the participants with normal TICS-M scores disclosed full functional independence, and only 1 person report functioning worse than slight dependence (a score of <90). Proxies were available in only 107 of these cases. Their reports on the FAQ strongly suggested independence in daily living. The mean FAQ was 0.73 (SD, 2.05) and 100 of the 107 participants scored less than 5 on the FAQ. Proxies' Barthel reports

TABLE 2. Additional Demographic Characteristics of Validated Successful Cognitive Aging Participants

Characteristic	Older than 85 y validated successful cognitive aging, n=218	
Annual income at the time of retirement ($/y), n (%)		
<25,000	38	17.43
25,000-50,000	76	34.86
50,000-$75,000	38	17.43
75,000-100,000	9	4.12
>100,000	21	9.63
Unknown/other	20	9.17
Choose not to disclose	16	7.33
Residential area, n (%)		
Urban[a]	132	60.55
Rural[a]	85	38.99
Unknown/other	1	0.45
Marital status, n (%)		
Divorced	19	8.71
Married	80	36.70
Widowed	110	50.64
Never married	5	2.29
Separated	2	0.92
Other	2	0.92
Years of education, n (%)		
<8	4	1.84
8-10	14	6.42
11-15	113	51.83
≥16	87	39.90
TICS-M Score, education adjusted, mean (SD)	33.36	3.54
GDS, mean (SD)	1.18	1.13
Barthel Index (participant), n (%)		
100	181	92
95	10	5
90	5	2.5
<90	1	0.5
Not collected	21	—
FAQ, mean (SD)	0.73	2.05
Barthel Index (proxy)[b]		
100	96	90
95	6	6
90	3	3
<90	2	2
No proxy	111	—

[a]Self-disclosed.
[b]Percentages calculated only on those with available data.
FAQ, Functional Activities Questionnaire; GDS, Geriatric Depression Scale; TICS-M, Telephone Interview for Cognitive Status.

were generally concordant with similarly high frequencies (90%) of reported full independence for those with proxy reports. Where both participant and proxy ratings were available, they were perfectly concordant in 91% of the cases. In 2.5% of the jointly rated cases, the participants rated themselves at 95 whereas the proxy's rated the participants at 100, and in 2.5% of these cases, the converse was true. In only 3% of the cases did the proxy

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rated the more than slight dependence when the participant report full independence.

DISCUSSION

This study found that our CP algorithm, using 17 criteria developed by a panel of experts, can be used to identify participants aged 85 years and older with successful cognitive aging defined as a TICS-M score of more than 27. We found the ability to identify, contact, consent, and evaluate this successfully aged population of individuals aged 85 years and older through brief screening methods. Our CP was validated in nearly two thirds (218/333) of the persons receiving direct full evaluation, and the CP failed to detect cognitive compromise in only 11% of cases.

There are several limitations to our study. We note that nursing home placement, nominated by all 10 experts as an exclusionary criteria, was not discreetly documented in the OneFlorida+ EHR. When processing the CP on deidentified data, we did not have access to full residential addresses but zip codes only. We were able to identify the zip codes of all nursing homes in the State of Florida, and we originally planned to exclude participants who resided within the same zip codes as nursing homes. However, a review of the geographic distribution of nursing homes in Florida indicated that that approach was likely to be overly exclusive, eliminating persons with successful aging over age 90 years who resided in urban areas. Therefore, we dropped the nursing home variable from the CP for this study and determined nursing home status by directly asking participants who consented to participate. In subsequent studies, we plan to explore other approaches to identifying nursing home residence, for example, using nursing home billing codes might enable this important successful cognitive aging criteria to be reintroduced into the CP.

Table 1 reveals an overrepresentation of non-Hispanic White participants in our study. This sampling bias is an indicative of persistent challenges in recruiting underrepresented groups in the research.[24,25] The challenges of recruiting this cohort were amplified by local institutional review board restrictions on the methods of contacting individuals identified in medical records or large deidentified data sets. These restrictions prohibited "cold calling" patients with the CP of successful aging of 85 years and older, thereby requiring eligible individuals to either return a postcard requesting that they be called or call directly, before receiving additional information about the study.

It is also acknowledged that only global cognitive functioning was assessed in this study. A more fine-grained analysis of neuropsychological function across multiple cognitive domains was not completed. Other studies of community-based oldest-old cohorts have shown that normal or superior performance in global measures or in 1 cognitive domain may not extend to other cognitive domains.[26] However, our goal was to demonstrate the feasibility of using a CP of successful aging of older than 85 years to exclude dementia, as "validated" using telephone assessments only, for large and multicenter cohort studies. For this purpose, the TICS-M and GDS measures were fully adequate. In post hoc analyses, we determined that there was a normal distribution of TICS-M scores in the participants aged 85 years and older whom we evaluated, that is, this measure was free from ceiling and floor effects and, hence, appropriate also for use as a continuous measure of cognitive performance (in addition to a categorical measure of cognitive impairment).

Future research could examine whether a smaller set of nominated EHR variables (eg, those for which there is more convergent agreement) has the same validity for excluding patients with dementia or major physical limitations in activities of daily living or whether data driven approaches can produce more accurate CPs of successful aging as compared with knowledge-driven approaches. Similarly, future research could examine whether natural language processing of free text in the EHR might improve the accuracy of our knowledge-driven CP. Future research is also required to determine whether the CP for successful aging of those aged 85 years and older developed at UF is similarly accurate when applied to other EHR registries and patient populations. In addition, future research should engage health systems with greater numbers of underrepresented communities. Equally important, this research should use community engagement strategies not used in this study, to ensure better representativeness and generalizability of this type of research.

CONCLUSION

In summary, this study provides proof of concept for using EHRs to identify cohorts of patients with successful aging of 85 years and older, including participants free of cognitive impairment or major limitations in physical activities of daily living. It also provides benchmark rates for capacity to recontact, recruit, and directly evaluate persons into cohort studies of successful cognitive aging. Our findings suggest that studies seeking to enroll a few hundred successfully aged participants would require a targeted population of tens of thousands with available medical records using our biomedical informatics—based approach.

POTENTIAL COMPETING INTERESTS

The authors have no conflicts of interest to disclose.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CP,** computable phenotype; **EHR,** electronic health record; **FAQ,** Functional Assessment Questionnaire; **GDS,** Geriatric Depression Scale; **SQL,** Structured Query Language; **TICS-M,** Telephone Interview of Cognitive Status Modified; **UF,** University of Florida

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