Peer Review Plan, Charge to Peer Reviewers, and Consolidated Responses to Peer Reviewers for National Neurological Conditions Surveillance System Technical Report: Prevalence of Parkinson's Disease: Methods and Prevalence Estimates by Age, Sex, and other Demographic and Geographic Characteristics among Adults Aged 35 and Older, United States, 2019

Title: Prevalence of Parkinson's Disease: Methods and Prevalence Estimates by Age, Sex, and other Demographic and Geographic Characteristics among Adults Aged 35 and Older, United States, 2019

Peer Review Plan

Subject of Planned Report: Production of national prevalence estimates for Parkinson's disease (PD) in 2019

Purpose of Planned Report: To present the methods used by CDC to produce national prevalence estimates for PD and key prevalence findings for 2019 by select demographic and geographic characteristics.

Type of Dissemination: Influential Scientific Information (ISI)

Timing of Review: December 2023

Type of Review: Individual

Opportunities for the Public to Comment (how and when): No

Peer Reviewers Provided with Public Comments before the Review: No

Anticipated Number of Reviewers: 4

Primary Disciplines or Expertise: Neurology, neuroscience, Parkinson's Disease, quantitative data analysis, movement disorders, descriptive epidemiologic studies

Reviewers Selected by (agency or designated outside organization): Centers for Disease Control and Prevention (CDC)

Public Nominations Requested for Reviewers: No

Peer Reviewers

Sneha Mantri, MD, MS
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Current Position Title: Director, Program in Medical Humanities, Assistant Professor of Neurology, Parkinson's Disease and Movement Disorders Center
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Caroline Tanner, MD, PhD
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Charge to Peer Reviewers

The document that you will review is a draft technical report of the initial methods used by CDC to produce national prevalence estimates for Parkinson's disease, and key prevalence findings for 2019 by select demographic and geographic characteristics. CDC conducted this work, with input from federal and external subject matter experts, as part of establishing the National Neurological Conditions Surveillance System (NNCSS). The 21st Century Cures Act authorized development of NNCSS, charging CDC with conducting integrated surveillance for neurological conditions, to facilitate further research. CDC chose Parkinson's disease as one of NNCSS's first two neurological conditions in part because it is one of the most rapidly growing neurodegenerative conditions and a significant source of disability.

The report's methods and results are presented in two sections that mirror the iterative steps of the PD demonstration project. Part 1 documents our methods and findings related to selecting PD surveillance case definitions (also known as case algorithms) for use in the types of population-based data sources available to CDC. Part 2 documents our selection of population-based data sources, and our application of the selected PD surveillance case definitions in the selected data sources to estimate PD prevalence.

We request your expert opinion on the following:

- Do the rationale, methods and analyses laid out in Parts 1 and 2 of the report adequately address the objectives of the work?
- Are the findings and conclusions (Parts 1, 2, and overall) appropriate and defensible?
- Is the use of prevalence ranges sufficiently explained and understandable?
- Is there adequate clarity in the explanations and terminology used to describe the lower and upper estimates for the prevalence ranges, and the case definitions that produced them?
- Are there any biases, errors of omission, or limitations that we have not addressed?
- How can the surveillance case definitions and prevalence estimates contained in this report be useful to researchers, clinicians, other healthcare and public health professionals, and others?

We would also welcome any other comments you would like to make.

After receiving comments from all peer reviewers, CDC will compile them and prepare a unified response. The combined peer reviewer comments, without attribution, and CDC's unified response will be posted on the NNCSS website as part of the CDC Peer Review Agenda.

Thank you for your assistance with this review. We recognize and appreciate the commitment of time and energy this will involve.

CDC's Consolidated Responses to External Peer Reviewers' Comments

CDC thanks all peer reviewers for their comments on NNCSS's draft report (referred to hereafter as 'report') and for the time and effort required to provide their feedback.

This section presents peer reviewers' comments and CDC's related responses in three parts:

1. Peer Reviewers' Summary Comments on the Questions Posed by CDC
2. Peer Reviewers' Specific Comments Related to the Questions Posed by CDC
3. Peer Reviewers' Additional Comments

Some comments were edited for brevity. Where a peer reviewer provided comments that related to multiple questions, the comments appear with the question to which they most aligned. Minor editorial suggestions are not included here but have been used in document revision.

Peer Reviewers' Summary Comments on the Questions Posed by CDC

Do the rationale, methods and analyses laid out in Parts 1 and 2 of the report adequately address the objectives of the work?

- Four reviewers said the rationale, methods, and analyses adequately address the objectives. Four reviewers also identified overall strengths of the report and specific items to refine for greater clarity (s*ee comments below).*
- One reviewer stated that there was an issue with the rationale of one part of the report *(see comments below).*

Are the findings and conclusions (Parts 1, 2, and overall) appropriate and defensible?

- Three reviewers indicated that overall, the findings and conclusions are appropriate and defensible, and two reviewers provided overall feedback on these topics *(see comments below)*. Several of these reviewers made specific recommendations or identified minor issues related to the findings and conclusions *(see comments below).*
- One reviewer stated that there were issues with the findings and conclusions *(see comments below).*

Is the use of prevalence ranges sufficiently explained and understandable?

- Four reviewers said the use is sufficiently explained and understandable.

Is there adequate clarity in the explanations and terminology used to describe the lower and upper estimates for the prevalence ranges, and the case definitions that produced them?

- Four reviewers said that overall, there is adequate clarity. They provided overall comments and suggested specific items to address to increase clarity around case definitions *(see comments below).*

Are there any biases, errors of omission, or limitations that we have not addressed?

- Three reviewers indicated that all significant biases, errors of omission, and limitations were addressed. Four reviewers made comments on the overall robustness of the work or comprehensiveness of what was addressed. Two reviewers had suggestions for future exploration or greater context *(see comments below).*
- One reviewer stated that several items were not adequately addressed *(see comments below).*

How can the surveillance case definitions and prevalence estimates contained in this report be useful to researchers, clinicians, other healthcare and public health professionals, and others?

- Four reviewers stated that this is important work with various applications and implications *(see comments below).*

Peer Reviewers' Specific Comments Related to CDC's Questions

Do the rationale, methods and analyses laid out in Parts 1 and 2 of the report adequately address the objectives of the work?

Overall comments:

- [Reviewer 2] stated that the methods and analyses presented in Parts 1 and 2 are clear to follow, and the rationale "is obvious, particularly with regard to the aging of the population and to plan better ways of caring for this growing segment of the population."
- [Reviewer 3] stated there are many strengths of the effort and identified it provides an important foundational step in surveillance for Parkinson's disease (PD) and parkinsonism in the US. The Reviewer further identified that the extensive review to identify case definitions is laudable; the general approach makes sense and is well described; Tables 4 & 5 are clear, detailed, and useful; and the methods for determining prevalence estimates are clearly stated and understandable.
- [Reviewer 4] stated that the systematic review is a significant contribution to the literature. The Reviewer noted that Table 3 provides a useful practical paradigm summarizing the different types of case definitions; Part 1 provides important background information about limitations of definitions, "particularly highlighting the simplicity and practical applicability and advantage of claims and administrative databases as the predominant type of case definition selected;" and Tables 4 and 5 provide a valuable review of population-wide estimates across multiple characteristics.

  CDC thanks the reviewers for their comments.

Specific questions, clarifications, suggestions, and concerns:

- [Reviewer 1] stated that some of the clinical detail may confuse a broader audience.

  Balancing clinical detail and broad understandability of complex concepts is challenging. The level of clinical detail is consistent with that of the literature included in the systematic review. CDC will continue work to explain clearly the important aspects relevant to decision-making and findings.
- [Reviewer 3] wanted the flow of Figure 1 (systematic review structure) to be clarified.

  Figure 1 was modified for greater clarity.
- [Reviewer 1] requested identification of the assumptions used in methods for the risk of bias assessment (pg. 18-19 & Table A2).

  More information on the methods of the risk of bias assessment was added.
- [Reviewer 3] suggested that citations be provided for all information in Table 1.

  References were added to Table 1.
- [Reviewer 1] wanted clarity on why the total population is more than 100%.

  As discussed in the report in Table 6, the final combined population was 102.6% of the size of the 2019 US American Community Survey (ACS) Census estimate for insured adults. The population included all persons with Medicare and Medicaid coverage and the weighted commercially insured population from IQVIA (a healthcare clearinghouse

that provides de-identified data from multiple data sources). Based on the methodology used, CDC did not expect an exact match with the Census estimates. Multiple factors could account for the small difference between this study's overall denominator and the Census estimates, including: 1) the ACS totals are estimates with survey error; 2) weighting factors were used to extrapolate the IQVIA population to the total commercially insured population; and 3) differences in the survey methodology used by ACS to identify insured US adults and the inclusion criteria and aggregation methodology applied within this study. That the combined population is only 2.6% different than ACS estimates of the total population despite these potential sources of variation is a strength of this work.

- [Reviewer 2] inquired whether the predictive algorithm for race/ethnicity in CMS data could cause bias.

  As discussed in the report in the limitations section of the Discussion, the prevalence findings by race/ethnicity may not be representative of differences across the entire population because prevalence by race/ethnicity could only be assessed among persons with public insurance (Medicare and Medicaid data from the Centers for Medicare & Medicaid Services; CMS), and there were varying levels of missingness of race/ethnicity information within the CMS data. The magnitude of the prevalence estimates should be interpreted with caution—especially those calculated among the Medicaid population, which were based on self-reported data. This limitation may also apply to the Medicare data that includes the Research Triangle Institute-derived race/ethnicity variable,[1] which was leveraged in this study. This variable has been shown to have high validity for certain racial/ethnic groups such as non-Hispanic White and Hispanic persons but low validity for others—especially American Indians/Alaskan Natives.[1] Continued exploration of differences by race and ethnicity is warranted since prevalence may be affected by access to care, timeliness to diagnosis, and disparities in receiving neurologist care, surgery, other treatment, and other supportive services, where inequities have been reported particularly for Non-Hispanic Black and Hispanic persons.

- [Reviewer 3] asked how discrepant International Classifications of Diseases (ICD) codes are handled (e.g., when a person receives PD codes initially and then only receives codes for another condition).
  - *For the exclusive (probable PD) case definition, if a possible case meets the inclusion criteria, exclusion criteria are then applied. The presence of exclusionary ICD codes at any point in the three-year case ascertainment period (2017-2019) warrants exclusion, regardless of when they occur in relation to ICD codes for PD.*
  - *As NNCSS is intended for ongoing surveillance, it is likely some persons with discrepant ICD codes in one case ascertainment period will have consistent coding in future periods that either ensures they are identified as a case or not a case based on no longer having discrepant ICD codes.*
  - *Longitudinal analysis of the sequence and order of ICD codes is outside the scope of the current point-in-time prevalence analyses.*

- [Reviewer 3] stated that the rationale for using the 2010 US Census instead of the 2020 US Census is not well justified.

  The use of the 2010 US Census to age-standardize prevalence estimates for appropriate comparison of rates across groups (e.g., states) is consistent with typical ongoing public health surveillance practices, which generally use a long-established and complete Census standard population to standardize estimates. Most major US surveys age-standardize to the 2000 US Census population [e.g., National Health Interview Survey

(NHIS), National Health and Nutrition Examination Survey (NHANES), Behavioral Risk Factor Surveillance System (BRFSS), Medical Expenditure Panel Survey (MEPS)]. NNCSS's use of the 2010 US Census population means NNCSS is using a newer Census population than is typical. Also, the 2010 US Census data were only used for age-standardization while contemporaneous (2019) Census estimates were used for the main rate calculations (discussed more fully in response to another comment below).

Are the findings and conclusions (Parts 1, 2, and overall) appropriate and defensible?

Overall comments:

- [Reviewer 1] indicated the findings are both well explained and important.
- [Reviewer 2] stated the findings and conclusions are appropriate and similar to other cohort studies. The Reviewer stated that the report has "the added benefit of the findings being more comprehensive than geographically based cohorts or prior prevalence estimates."

  CDC thanks the reviewers for their responses.

Specific questions, clarifications, suggestions:

- [Reviewer 2] suggested a log-transformed y-axis as an alternate method for presenting the findings for Figure 4 (combined weighted prevalence).

  Alternate graphical presentation methods were not explored as simple bar graphs are the easiest for broad audiences to understand.
- [Reviewer 3] indicated that tables and figures with estimates should include information on the populations that are less well represented (such as residents of the Western US) in the legend, and the titles should indicate that the information shown represents estimates.

  The tables and figures with estimates are labeled to succinctly describe the type of estimate provided and population included in the estimate. The titles have superscripts on specific words relating to the included population, and the footnotes all contain information on which population is included. The Discussion contains information on potential limitations of CDC's findings, including specific populations that may not be included in the estimates. Additionally, the systematic review included in the report as well as additional literature reviewed to address reviewer's comments do not support the assertion that there is substantial under-representation of sub-groups within the CMS or commercially insured populations. (Please also see CDC responses to peer reviewers' specific comments for the question "Are there any biases…" for additional information).
- [Reviewer 3] noted that the increased prevalence in older age groups may also be due to increased incidence in these older age groups.

  The reviewed literature supports this assertion; therefore, language around increased incidence in older age groups was added.
- [Reviewer 3] asked whether the differences noted in male-to-female ratios between the two case definitions was statistically significant and, even more importantly, if it was clinically significant.

  Consistent with the reporting of prevalence estimates or other ongoing public health surveillance, it is beyond the scope of this report to assess statistical and clinical significance. Instead, the differences in male-to-female ratios between the two case definitions are identified as a starting point for more detailed exploration in future studies by NNCSS or other researchers. This could include further investigation into how sex-based differences manifest across additional demographic breakdowns such as age

group and sex, or race/ethnicity and sex. Also, this could include a greater understanding and refinement of case ascertainment methods, as several of the more prevalent parkinsonism conditions, such as vascular parkinsonism, can impact males more than females compared to PD (as discussed in the report in Table A2).

- [Reviewer 3] noted that the statement about percentage of missed PD cases "… our review of all available evidence suggests that it is no more than 20% of PD cases, and likely less" does not have evidence provided. The Reviewer suggested this may be an underestimation given a 1970's door-to-door study in Mississippi that "found 40% of those with parkinsonism had not been previously diagnosed."
    - *References were added to identify the evidence reviewed that supports the 20% or less statement.*
    - *The 20% assessment was based on information provided in studies that validated Group A case definitions, along with information on healthcare utilization by PD patients, and misdiagnosis data. The studies validating Group A case definitions showed that of the total PD cases assessed in chart review, the percentage of false negatives was generally low, ranging from 2% to 12%,[2-4] although one study found it could be up to 37% depending on the specific Group A case definition used.[4] The percentage of PD cases missed in Group A case definitions is lower than found for case definitions that fall into other Groups. For example, Feldman et al. validated several Group B and Group C case definitions and found that they missed 33% to 77% of PD cases.[5] Given these findings, CDC's estimate was that approximately 20% of cases were likely to be missed by the PD exclusive (probable PD) case definition.*
    - *Given the parameters necessary for a PD exclusive case, a limited number of PD cases may be unable to meet these criteria. Despite the impact of barriers to accessing care, it is likely that persons with PD would see their provider at least twice over the course of three years given the symptomatic impact of PD, age of onset coinciding with Medicare coverage, progressive clinical impairments, and ongoing adjustment of medications with disease progression. This assertion is supported by several recent studies that analyzed Medicare fee-for-service data to identify healthcare utilization of persons living with PD. Pearson et al. found that in 2019, only 10.8% of persons with a PD claim had no visit with a movement disorder specialist, general neurologist, or primary care provider in that year; yet, these patients still had a diagnostic claim for PD in their data from a different provider.[6] Song et al. found that over the course of 14 years, patients with PD remained consistently on levodopa treatment, so persons with PD are likely to have at least two claims for PD medication over the course of three years.[7]*
    - *The last consideration is the likelihood of misdiagnosis of PD patients, such that patients may be mistakenly excluded from the PD exclusive (probable PD) case definition. Several studies that completed chart reviews and autopsies of persons diagnosed with PD found early diagnoses of PD only remain PD over time for 38% to 65% of patients.[8] In studies of persons identified with clinical parkinsonism, the final diagnosis was PD in less than two thirds of the cases.[9,10] In addition, one systematic review of diagnostic errors showed inconsistent evidence of over- or under-diagnosis of PD.[11]*
    - *Taken together, the evidence does not suggest systematic under-diagnosis or under-identification in claims data of PD for the PD exclusive (probable PD) case definition.*
- [Reviewer 3] asserts that "the tone of the current report presents the estimate as overall accurate, and in many places uncritically highlights the lower prevalence in the Western US." Overreliance on the estimates without consideration of the possible biases could result in consequences such as "inappropriate reduced allocation of funds, the unintended systematic

exclusion of certain populations in determination of research priorities, etc." The Reviewer suggests the report should more clearly outline the likely bias of the estimates.

The Discussion section of the report includes a lengthy section describing the limitations of the findings, including outlining specific populations that may not be included or may be underrepresented in the estimates. The systematic review as well as the additional literature examined as part of addressing peer reviewers' comments do not show substantial underestimation in the Western US. (Please see more information re Western US and other possible areas of bias in responses to Reviewer 3's comments on CDC's question "Are there any biases…")

Is there adequate clarity in the explanations and terminology used to describe the lower and upper estimates for the prevalence ranges, and the case definitions that produced them?

Overall comments:

- [Reviewer 1] said the information was well outlined.
- [Reviewer 2] indicated appreciation for the report's careful attention to the challenges of case ascertainment for PD and parkinsonisms and that the PD exclusive and PD inclusive case definitions make good sense.
- [Reviewer 3] stated the use of prevalence ranges is clearly stated and understandable, and use of ranges is a helpful way to frame the inherent uncertainties of these estimates.
- [Reviewer 4] found that the case definitions are reasonable and follow the thorough analysis provided specifying that the inclusive case definition is reasonable and supportable, especially with the point to avoid double counting of conditions; the reference to future surveillance of other parkinsonisms was appreciated and appropriate; and the exclusive case definition is noteworthy as it is a consensus de-novo definition informed by Table 5.

CDC thanks the reviewers for their responses.

Specific questions, clarifications, suggestions, and concerns:

- [Reviewer 1] asked for additional clarity around the selection of Group A and E case definitions and not Group C definitions (described on pg. 21 & in Table 6).

Additional language was added to provide clarity. The systematic review showed the PD case definition groups to be aligned with an ordinal scale, not an interval scale. This is because the exact quantity of PD and parkinsonism conditions identified from case definitions in each group is unknown, and there is likely some overlap between the groups. Group C is therefore not a true mid-point and does not capture a mid-point prevalence. Additionally, the assessment of key attributes of surveillance systems,[12] including measures of accuracy such as sensitivity and specificity, supported selecting Group A and E case definitions rather than Group C.

- [Reviewer 2] suggested that the term "PD exclusive" implies exclusive of PD.

While finalizing NNCSS's PD case definitions and writing the draft PD report, CDC uncovered substantial differences in terminology usage, understanding, and preferences across public health surveillance, clinical research, neurology, and other audiences. No term met the needs of all audiences. Therefore, the section of the report addressing finalization of the two PD case definitions describes them by referring to four parallel sets of terms, which resonate differently with different audiences. The PD case definition at the lower end of the prevalence range is described as "PD exclusive," "probable PD," prioritizing specificity (i.e., "specific"), and the "lower bound." The PD case definition at the upper end is described as "PD inclusive," "possible PD," prioritizing sensitivity

("sensitive"), and the "upper bound." Through most of the remainder of the report text, the terms "PD exclusive" and "PD inclusive" are always used, often in combination with one or more of the other terms. In contrast, presentation of the prevalence findings in the text, tables, and figures uses only "PD exclusive" and "PD inclusive." CDC will add to future publications and communication materials some of the other terms or otherwise adjust terminology and explanations, especially in the tables, figures, and written description of the prevalence findings, to improve clarity for all the audiences listed above.

- [Reviewer 1] stated that the case definitions selected for NNCSS should be included in the text, not just in a table.

  NNCSS PD case definitions were added to the text.

- [Reviewer 3] suggested that the rationale for why the specific case definitions in Table 6 were selected was not clearly stated.

  As discussed in the report in Part 1 Results section "PD Case Definitions that Perform Best on Key Attributes of Surveillance Systems (KQ4)," of the 60 Group E case definitions, the inclusive (possible PD) case definition was the one that was best able to balance and maximize key attributes of surveillance systems—including accuracy (sensitivity, specificity, positive predictive value, and negative predictive value), as well as simplicity, perceived acceptability, perceived cost-effectiveness, reproducibility, and scalability or spreadability (as depicted in Table 4). Of the five Group A case definitions that met the eligibility criteria for the systematic review (Table 5), none were able to balance and maximize these key attributes of surveillance systems. Therefore, several additional potential options for Group A case definitions were developed, based on a review of parameter combinations in case definitions for which validation data were available and all other parameter combinations covered in the systematic review. From these, the case definition that the evidence suggested would be most likely to maximize and balance the key attributes of surveillance systems was chosen as the exclusive (PD probable) case definition.

- [Reviewer 3] asked why the selected case definitions did not use claims-based signs of parkinsonisms, such as exclusions like drugs for drug-induced parkinsonism (e.g., Lee, 2016 and Liu, 2016).

  Exclusions that utilize claims-based signs of parkinsonisms were determined to be best for use in incidence case definitions only as these signs are indicative of onset or early stages of specific parkinsonism conditions. Both example publications[2,3] used exclusions that indicate onset of a parkinsonism condition, such as drugs correlated with the onset of parkinsonism symptoms, to identify incident PD cases. Further, using these indicators to exclude in a prevalence case definition will exclude PD cases unnecessarily. This is because some indications of parkinsonism conditions that occur only prior to or within a year after the onset of parkinsonism symptoms could also occur for a different reason during the course of regular PD (e.g., dementia is common in the older adult population including people with PD, but for dementia with Lewy bodies, dementia occurs within one year prior to or after onset of PD symptoms).

- [Reviewer 4] stated that the inclusive case definition has the potential to underestimate parkinsonisms for those who may not have access to specialists or confidence to code a parkinsonism diagnosis.

  As discussed in the report in the Discussion, one limitation is that the prevalence estimates may miss some persons who are underinsured, or those who have insurance coverage but still have limitations to adequate care, such as those the reviewer

mentioned without adequate access to specialists. Some persons with limited access to care are likely to be included since the case definitions require a limited number of diagnostic or pharmaceutical claims over a three-year period.

- [Reviewer 4] noted that future evaluation will be helpful to validate the exclusive case definition as it is a consensus de-novo definition.

  NNCSS is designed to be iterative and to reassess data sources and methods over time, and one avenue to inform possible modifications is validation. NNCSS is currently using EHR data to validate NNCSS PD case definitions, and any useful modifications will be incorporated in the future.

Are there any biases, errors of omission, or limitations that we have not addressed?

Overall comments:

- [Reviewer 1] stated all were well addressed.
- [Reviewer 2] stated the limitations and associated rationale are well-reasoned and comprehensive.
- [Reviewer 3] said "overall this is a strong effort, with numerous rigorous features."
- [Reviewer 4] indicated that with the limitations associated with administrative data sources being used to estimate national prevalence of PD, "this report remains the best valid report of a national estimate at this time given this limitation."

  CDC thanks the reviewers for their comments.

Specific suggestions and concerns:

- [Reviewer 2] stated that while outside the scope of this paper, urban/rural distribution would be valuable to provide more information on, especially as pesticide exposure is a known PD risk factor.

  This report provides NNCSS's initial estimates of overall national PD prevalence and prevalence within certain demographic and geographic subgroups. Urban/rural differences in prevalence have already been highlighted as priorities for NNCSS's ongoing surveillance of PD, and CDC has explored additional data sources to determine which ones might provide the most thorough information.

- [Reviewer 4] noted that limiting case identification to ICD-10 to indicate a diagnosis could lead to underestimation from both case definitions. The reviewer suggests a case definition that uses medications or symptoms and signs to identify persons with suspected parkinsonisms that do not have an ICD-10 code diagnosis could be considered in the future.
  - *Such a case definition was not supported by the available literature. There are several important considerations as to why.*
  - *Prevalence estimates for PD, by definition, will only include new and existing cases of PD, not those with suspected illness who do not meet the clinical criteria of PD and therefore have not received a related diagnostic code. Both NNCSS's lower bound exclusive (probable) PD definition and NNCSS's upper bound inclusive (possible) PD definition include cases with sufficient claims evidence to identify as PD. The upper bound inclusive (possible) PD definition also includes cases for whom the evidence of PD is unclear due to coding challenges, or incomplete because the diagnostic process of distinguishing between PD and the other parkinsonism conditions is still ongoing (and thus their diagnosis may change). With their focus on identifying PD cases, the two case definitions are not intended to identify all parkinsonism conditions, nor patients that have not met the diagnostic threshold for PD (as proxy for PD diagnosis).*

- *An additional important aspect considered in all decision making was how PD case definitions scored on the key attributes of public health surveillance systems.[12] Using non-specific parameters may adversely impact the accuracy and other attributes of PD surveillance estimates. The literature is generally in consensus that some signs and symptoms and anti-Parkinson medications may be non-specific to PD and in some cases may even be non-specific to parkinsonism conditions as a whole (including PD).[4,13-15] The limited validation studies that present information on this indicate that case definitions using administrative claims data to identify cases of PD or other parkinsonisms tend to have fewer false negatives. For example, Butt et al.[16] validated the case definition selected as NNCSS's PD inclusive (possible PD) case definition based on retrospective chart review, and in their total cohort of 73,003 patients, there were only 51 false negatives, which equated to sensitivity and PPV above 75%, and specificity and NPV over 99%. In another study (Swarztrauber et al.[14]), using indicators of PD diagnostic criteria (e.g., evidence of bradykinesia, tremor, etc.) in addition to diagnoses only increased total cases by 1.7%.*
- *Use of medications, signs, and symptoms to identify prodromal PD in administrative claims data has had notable success in the literature.[17,18] Thus, although it is not appropriate for ongoing surveillance of PD, it could potentially be used if NNCSS undertakes or participates in analyses focused on this pre-PD period.*

- [Reviewer 3] stated that while the rationale of the selection of data sources due to being information easily available to CDC and applicable to future surveillance is pragmatic and understandable, using the selected data sources to produce national PD estimates results in "at least arguably a systematic under-representation of certain geographic areas, notably the Western US."

  As part of NNCSS's 3-stage development process, CDC assessed more than 30 data sources to identify the most appropriate sources for current (and future) NNCSS use. This assessment utilized evaluation criteria first outlined by CDC Guidelines Working Group[19] *and updated most recently by* Groseclose & Buckeridge,[12] *which are used broadly across public health entities to evaluate surveillance systems and their data sources. The four administrative claims databases used for the draft PD Report were selected as the best available at the current time based on their:*
    - *Ability to provide information on large and distinct components of the insured US population and minimize possible double counting.*
    - *Coverage of almost all (93.9%) the US population when used together.*
    - *Overall stability – including being able to track persons longitudinally over multiple years.*
    - *Inclusion of different types of demographic data for use in subgroup analyses and methods to help ensure the data are as representative as possible of the US insured population.*

  While the Discussion of the report identifies several groups that are not included or may be undercounted in the national PD estimates, it is unlikely that there is systematic, significant under-representation of large portions of the US population.
  Please see the sub-bullets below on specific subgroups Reviewer 3 identified as likely under-represented, including the Western US.
  - [Reviewer 3] identifies this is due to the following:
    - IQVIA being the least representative of the Western US commercially insured population.

- *A recent publication[20] estimating the overall US prevalence of MS utilized a similar approach of combining estimates from multiple claims databases representing various sub-groups of the population based on type of insurance coverage (e.g., public, commercial). In selecting which commercial insurance database to use, Wallin et al.[20] completed a sensitivity analysis comparing MarketScan and Optum data alone versus MarketScan, Optum, and Kaiser Permanente data in the Western US. They identified that the difference in the Western US estimates was not statistically significant with or without Kaiser Permanente data. The authors concluded that MarketScan and Optum alone were sufficient to estimate Western US prevalence.*
- *As described in the draft PD report's Part 2 Methods, in the initial selection of data sources, the populations in IQVIA and other commercially insured data sources were compared across age group, sex, and state stratifications to the 2019 US Census ACS commercially insured population. IQVIA was selected for NNCSS use because it required fewer weighting factors than other commercially insured data sources across all groups, and in particular, in the stratified subgroups in the Western US. Then, for all analyses, weighting factors were applied to the IQVIA data based on comparison of IQVIA data to the 2019 US ACS commercially insured population stratified by age group, sex, and state.*
- *CDC's finding that MarketScan required greater weighting factors than IQVIA, particularly in the Western US, provides relative confidence that NNCSS's estimates for the Western US are not subject to systematic under-representation.*

- "Capitation by delegated medical groups limits or obviates reporting of individual level ICD codes to CMS."
    - *CDC's review of relevant literature did not locate any evidence suggesting that NNCSS estimates would be systematically or significantly affected by the potential limitations in reporting to CMS from systems using delegated medical groups under a capitation model.*
    - *Capitation is a system used to represent the costs of care for a group of patients, so that the provider is paid a standard rate per patient, as opposed to per service as in a Fee-for-Service model.[21] Capitation methods vary and often rely heavily on coding optimization.[22]*
    - *CMS uses a risk-adjusted capitation model (Hierarchical Coexisting Conditions [HCC] method) for adjusting the risk of patients.[23] This system groups ICD-10 codes into larger categories (HCCs) based on similarity of disease progression and cost of care.[23-25] This system was adopted by CMS in 2004 to measure and improve quality of care. CDC's review of the relevant literature did not find any evidence of missing or under-reported individual-level diagnostic codes or claims billed from providers in the data reported to CMS.*
    - *Delegated medical groups and independent physicians' associations (IPA) are business entities comprised of physician practices that aim to reduce overhead costs and ease administrative burdens, while reducing costs and improving quality of care for patients. This type of capitation*

currently constitutes only a small portion of payment models in private practice, is most commonly used by HMOs and managed care models and is only seen in specific regions (such as Florida and California).[26] Kaiser Permanente offers an HMO Medicare Advantage plan,[27] which gives patients access to the Kaiser system of medical providers through Medicare coverage. No information is available on how capitation would impact billing to Medicare.

- *Wallin et al.'s[20] finding that including Kaiser Permanente data with MarketScan and Optum was not statistically significantly different than excluding it suggests that substantial differences in claims data due to capitation are unlikely.*
- *The shortcomings of fee-for-service models have again been highlighted by COVID-19, and many primary care providers agree that alternative payment models, like capitation, should be considered.[28] Given the lack of information in the existing literature, further exploration into the impact of capitation on coding could be warranted if capitation becomes more consistent.*

- [Reviewer 3] states that the significance of these limitations is minimized in the report.

  The Discussion section of the report contains detailed information on these and other limitations of the findings, including specific populations that may not be included in the estimates, and evidence and rationale suggesting that substantial portions of the population are not missing.

- [Reviewer 3] states that biased underestimation of PD due to the selected data sources may be compounded by other populations not represented in the report, several of whom may disproportionately reside in the Western US. The reviewer stated that these are important populations overall and lack of inclusion is an additional concern.

  The draft report highlighted the need for attention to groups who may face disproportionate barriers or other challenges to accessing PD care.
  Please see responses to the specific identified populations below.

  - [Reviewer 3]: people receiving care exclusively from the Veterans Health Administration, the Indian Health Services, or the Defense Health Agency, particularly as a number of these populations may experience greater risk factors for PD.
    - *As discussed in the report in the Discussion, missing data from VA and IHS are limitations of the estimates provided. As the report notes, the majority of the ~6.1% missing population is uninsured, so a small portion of the 6.1% is likely persons with VA or IHS coverage and no other insurance coverage. However, as most persons impacted by PD are over the age of 65, and virtually everyone over the age of 65 is covered by Medicare, these groups are unlikely to contribute to substantial underestimation of PD.*
    - *Currently, it is not possible to access Defense Health Agency data. However, reports on various health conditions and situations within these data are published regularly through the* Medical Surveillance Monthly Report (MSMR). *One recent MSMR article[29] identified that among the over 1.1 million individuals in an active component of the US Armed Forces in 2022, only 60 were identified as having PD based on encounters with medical providers billed through the Military Health System (MHS). Inclusion of this population in NNCSS estimates could decrease prevalence estimates somewhat as it would add a much larger*

number of persons to the overall population (denominator) than the number of PD cases (numerator).

- [Reviewer 3]: uninsured persons are not adequately considered.

  As discussed in the report in the Discussion, uninsured individuals make up the majority of the ~6.1% of the total population missing from the PD estimates and highlights this population as important to consider. Nonetheless, the majority of persons missing from the overall population are mostly in younger age groups (i.e., 35 – 44 and 45 – 54 years), which are much less impacted by PD (as evidenced by prevalence estimates reported by NNCSS and others.[3,30-36] As the majority of individuals with PD are over the age of 65, and this corresponds with the age in which persons qualify for Medicare, it is unlikely that inclusion of the uninsured population would increase prevalence. Instead, their inclusion could lead to a small decrease in the prevalence of PD as more persons would be added to the overall population (denominator), with few added to PD cases (numerator).

- [Reviewer 3]: underinsured persons are not adequately considered, and the assertion of persons with PD having "good insurance and access to care due to their eligibility for Medicare may overstate the positive."
  - *As discussed in the Discussion in the report, underinsured persons not accessing care due to Medicaid differences across states is addressed, but it did not discuss barriers for other insured persons. The text has been updated to reflect the broader population with other types of insurance coverage that may face these barriers.*
  - *As discussed in the report, while the importance of the underinsured population should not be minimized, missing people who are underinsured should not be a major source of underestimation. Persons aged 65 and older with cost barriers may have Medicare plus additional Medicaid "wrap around" coverage, which could allow them to receive the services they require. Additionally, the operationalization of NNCSS's PD case definitions requires a limited number of claims during the three-year case ascertainment period. As PD patients experience progressive clinical impairments and typically require ongoing adjustments of PD medications tailored towards their disease progression, it is likely a person who receives PD treatment will see their PD provider at least twice over the course of three years. For example, if a person has an outpatient claim for PD in May 2017, an outpatient claim for PD in April 2019, and no claims for parkinsonisms from 2017-2019, then this person is considered a case. This information has been added to the Discussion section about persons with barriers to accessing care.*

- [Reviewer 3]: those with CMS Part A only; as few people with PD are hospitalized, reliance on hospitalization data may underestimate this group.

  The report acknowledges this population as the seventh listed limitation in the Discussion.

- [Reviewer 3]: residents in rural areas with limited access to general and specialized healthcare.

  As discussed in the report in the Discussion, "Uncertainties around persons with barriers to accessing care, which includes residents in rural areas with limited access to healthcare, may warrant further exploration." It is important to note that the PD case definitions require limited claims evidence to identify a case of

PD. A person living with PD who must travel to receive care, due to living in a rural area, would only need to have two outpatient claims for PD over the course of three years and no claims for any other parkinsonism condition to be identified as a case. As PD patients experience progressive clinical impairments and typically require ongoing adjustments of PD medications tailored towards their disease progression, it is unlikely a person who receives PD treatment will not see their PD provider at least twice over the course of three years. This information has been added to the Discussion section about persons with barriers to accessing care.

- [Reviewer 3]: non-citizen residents in high-risk populations such as farm workers.
  - *Non-citizen residents that are considered "lawfully present immigrants" may be eligible for public healthcare coverage and can receive commercial coverage through the Health Insurance Marketplace.[37,38] Therefore, it is possible some of these individuals may be present in the data sources used.*
  - *As the US Census includes all people – residents and non-residents – who are living in the United States at the time of the census[39] it is likely at least a portion of these individuals are accounted for in 2019 US Census ACS data, and thus would be accounted for in the estimates either as publicly insured (and present in the data sources used), privately insured (and accounted for via the weighting factors used based on the 2019 ACS data), or part of the ~6.1% of the missing population.*
  - *The limitation section of the Discussion has been modified to indicate that non-citizen residents who are not captured in Census data are not included in the denominator and not accounted for in NNCSS's estimates.*
- [Reviewer 3]: non-English-speaking residents or those due to mistrust or other reasons prefer to receive care from community providers that may not include specialists or may be less familiar with PD.
  - *The Discussion has been expanded to include a more nuanced description of groups who may have barriers to healthcare access and thus could be under-reported in the PD estimates, including the group described by the Reviewer in this comment.*
  - *There is a possibility that a portion of this group would be included in the estimates. If these persons are covered by Medicare, Medicaid, or a commercial insurance provider, and community providers bill insurance, then any visit to the community provider would be included in claims data. For example, one study looking at PD care for Medicare beneficiaries found that less than two-thirds (58%) of patients in a three-year period received PD care from a neurologist.[40] It is likely some of the persons in the group the Reviewer identified would be part of this group receiving PD care from providers other than neurologists. Since only two PD claims and no other parkinsonism claims in a three-year period are required for a case, at least some of the individuals in this group are likely included in the PD estimates.*
  - *Data are not currently available to estimate the proportion of people that are not diagnosed with PD due to lack of universal community provider awareness of PD, nor of persons who utilize community providers who do not bill insurance for their PD care. No literature could be found that would enable development of correction factors (or adjustment) for such situations. These persons are likely included in the ~6.1% of the population not included in the estimates. The report*

Discussion states that populations with barriers to accessing care may warrant further research, particularly as these groups may face disparities in diagnosis, access to care, and ongoing services, and a reference is noted (Aamodt, Willis, and Dahodwala[41]).

- [Reviewer 3] asserted that use of the 2010 US Census instead of the 2020 US Census would underestimate PD due to the increase in the population age 65+ from 2010 to 2020.

  US Census American Community Survey (ACS) data from 2019 were used to weight the IQVIA data to be reflective of the entire 2019 US commercially insured population. Further, the 2019 population estimates were used for all crude prevalence estimates. Population estimates from 2010 were only used to age standardize the state-specific findings shown in Figure 5. Thus, the changing age group distribution in the population from 2010 to 2020 may slightly underestimate the state-specific estimates presented in Figure 5 but should not impact any estimates besides those shown in Figure 5. Also of note is that NNCSS's use of the 2010 US Census is atypical since it is a more recent standard population than typically used at the current time for much surveillance by CDC and others. Given the numerous uses of surveillance data, federal agencies and others do not typically move to more recent standards until there has been exhaustive study of the potential impacts.

- [Reviewer 3] stated that the inclusive case definition and resulting estimate is the preferred estimate despite the likely underestimation (underestimation refers to comments from Reviewer 3 discussed above).

  As discussed in the report, CDC's approach of using two case definitions was based on a thorough systematic review of all available evidence, evaluation of over 30 data sources, and NNCSS's mandate to track the epidemiology of multiple neurological conditions, which could ultimately include one or more other parkinsonism conditions in addition to PD. The systematic review revealed that it is not currently possible to identify a single estimate for national PD prevalence due to the challenges from the ongoing diagnostic process of differentiating PD from other parkinsonisms, and ICD code definitions. Since producing a single estimate could create a false sense of precision, CDC chose two case definitions that address diagnosis and ICD code challenges in different ways.
  - *The exclusive (probable) PD case definition is intended to capture only people with PD and to remove people with other parkinsonism conditions. Yet, this case definition may remove some people with PD whose diagnosis is incomplete or unclear. Thus, this case definition prioritizes specificity and has a high diagnostic certainty of PD.*
  - *The inclusive (possible) PD case definition is intended to capture people with confirmed PD as well as people with incomplete or unclear evidence of PD. However, it is not currently possible to ensure these people will be included without also including many people with other parkinsonism conditions whose physical features overlap with PD. This case definition prioritizes sensitivity and has a high diagnostic certainty of parkinsonism. It is important to note that this case definition is not intended to capture all persons with all parkinsonism conditions.*
  - *The report lays out the strengths and limitations of both case definitions and how each of them informs different aspects of research and action to decrease the burden of PD and other parkinsonisms.*
  - *This approach of using two case definitions to identify PD is:*
    - *Supported in PD literature.[13,30,42-45]*

- *Used for other conditions with diagnostic uncertainty.[46-54]*
- *Focused on balancing and maximizing key attributes of public health surveillance systems, particularly measures of accuracy.*
- *Forward looking in preventing anticipated challenges with double counting if other parkinsonism conditions are added to NNCSS.*

How can the surveillance case definitions and prevalence estimates contained in this report be useful to researchers, clinicians, other healthcare and public health professionals, and others?

- [Reviewer 4] discussed specific applications of the case definitions, including other entities using the identified case definitions as standards in other data sources, especially as public health interoperability use cases.
- [Reviewer 2] commented that applications of the prevalence estimates include informing distributions of healthcare resources to address PD patient needs and found the maps particularly useful for considering resource allocation.
- [Reviewer 1] stated this is critical information that can be used to inform research planning, trial design, policy making, regulatory approaches, etc.

CDC thanks the reviewers for their recommendations.

Peer Reviewers' Additional Comments

- [Reviewer 4] stated that the report is a "valuable contribution to the literature because of its systematic review of multiple studies in the literature that have tackled the issue of prevalence of Parkinson's disease and parkinsonism." The Reviewer suggested adding information about how NNCSS case definitions should be validated in independent datasets by independent researchers, as well as about NNCSS being amenable to revisions or updates as new datasets, cohort identification technologies, or PD definitions occur as part of the future, iterative nature of the case definitions.

  NNCSS was designed from its inception to use iterative methods and processes and to reassess data sources, case definitions, and methods over time so that they remain state-of-the-science. Validation of case definitions is an important part of informing possible modifications. Although both of these are discussed in the report, they will be further emphasized moving forward.
- [Reviewer 3] states that PD is now recognized to be one of several phenotypical presentations of neuronally predominant alpha-synuclein disorder, and that as Dementia with Lewy Bodies (DLB) is a common presentation of the neuronally predominant alpha-synuclein disorder and the most common non-PD parkinsonism condition, a surveillance case definition that includes PD and DLB would more accurately represent disease and reflect evolving scientific understanding.
  - *Neuronal alpha-Synuclein Disease Integrated Staging System (NSD-ISS) is an exciting new development that uses biological staging in PD for both clinical and research purposes. We look forward to the future impact of this research on the understanding of neuronal alpha-synuclein diseases and clinical care.*
  - *To identify cases of disease in a population, public health surveillance employs established, international or national standards that are widely accepted and used, and for which data will be available in population-based data sources. For PD, NNCSS utilizes the current, agreed-upon diagnostic criteria and definition dictated by the International Parkinson and Movement Disorder Society—the governing body for PD diagnosis—referred to as the MDS criteria.[55] Although active research and discussion about NSD-ISS is occurring among PD specialists both in the US and internationally, it is not yet broadly*

available, utilized by, or widely agreed upon by clinicians.[56,57] To be eligible for use within US national surveillance of PD, NSD-ISS must be incorporated into or replace the current international standard, and data on NSD-ISS must be routinely available in population-based data sources for all, or the large majority of, patients across the US.

- *Currently, dementia with Lewy bodies (DLB) has its own established, broadly used, and agreed upon diagnostic criteria[58] and is considered a separate condition from PD. Given this, a case definition that intentionally includes both PD and DLB would be beyond the scope of national surveillance by NNCSS until it becomes the new international standard.*
- *NNCSS's iterative approaches involve ongoing review and updating of case definitions and data sources so NNCSS can incorporate changes in established diagnostic criteria over time and remain state-of-the-science.*

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