Parkinson's progression marker initiative. Mov Disord 2020;35(8): 1488–1489.

2. Parkinson Progression Marker Initiative. The Parkinson progression marker initiative (PPMI). Prog Neurobiol 2011;95(4):629–635.
3. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inf 2019;95:103208.
4. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42(2):377–381.
5. Monje MHG et al. Toward e-scales: digital administration of the International Parkinson and Movement Disorder Society Rating Scales. Mov Disord Clin Pract 2020. https://doi.org/10.1002/mdc3.13135.
6. Rating Scale Electronic Development Committee. 2020. https://www.movementdisorders.org/MDS/MDS-Rating-Scales/MDS-Rating-Scales-Electronic-Development-Resources/Suggested-Characteristics.htm. Accessed on October 1, 2020.
7. Fuller RL, McNamara CW, Lenderking WR, Edgar C, Rylands A, Feaster T, et al. Establishing equivalence of electronic clinician-reported outcome measures. Ther Innov Regul Sci 2016;50(1): 30–36.

Reply to: "In Support of Electronic Versions of Movement Disorder Society Rating Scales"

We appreciate the reply of Drs. Fuller, Sanchez-Ferro, Goetz, Martinez-Martin, and Stebbins, "In Support of Electronic Versions of MDS Rating Scales,"[1] in response to our letter "Inconsistent Movement Disorder Society-United Parkinson's Disease Rating Scale Part III Ratings in the Parkinson's Progression Marker Initiative."[2] The authors describe the MDS Rating Scales Program's current efforts to create and review electronic versions (e-versions) of MDS-owned rating scales, including the potential for algorithmic correction of inconsistencies during scale completion.

In addition to catching data entry errors, algorithms to identify unusual rating combinations or changes between visits may also prove useful in flagging cases that may not represent idiopathic Parkinson's disease (eg, functional movement disorder or vascular parkinsonism). Similarly, raters could be alerted to unusual patient responses to parts I and II that might suggest atypical parkinsonism; for instance, in PPMI, fewer than 1% of newly diagnosed PD participants rated item 1.11, "Urinary problems," greater than 3 or 1.12, "Lightheadedness," greater than 2 at baseline. Of course, such flags would vary according to the population of interest. Finally, cross-checking ratings between parts I through IV seems worthwhile (eg, correspondence between patient rating on 2.12, "Walking and Balance," and clinician rating on 3.10, "Gait").

A collaborative effort among groups using the MDS-UPDRS may be the most effective means of capturing the full spectrum of PD progression and achieving the aims described in the response letter and expounded on above. In conclusion, we are most pleased to hear that the MDS is developing electronic data capture tools to enhance signal detection in PD research and eager to see the results of future validation studies. ■

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References

1. Fuller RLM, Sanchez-Ferro A, Goetz CG, Martinez-Martin P, Stebbins GT. In support of electronic versions of MDS rating scales. Mov Disord 2021;36(1):270–271.
2. Turner TH, Dale ML. Inconsistent movement disorders society-unified Parkinson's disease rating scale part III ratings in the Parkinson's Progression Marker Initiative. Mov Disord 2020;35(8): 1488–1489.

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Parkin Deficiency Appears Not to Be Associated with Cardiac Damage in Parkinson's Disease

We read with great interest the study "Subclinical Cardiac Microdamage, Motor Severity, and Cognition in Parkinson's Disease" by Choe and colleagues.[1] The authors demonstrated an increase of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with idiopathic Parkinson's disease (IPD) and an association of NT-proBNP and Troponin I with

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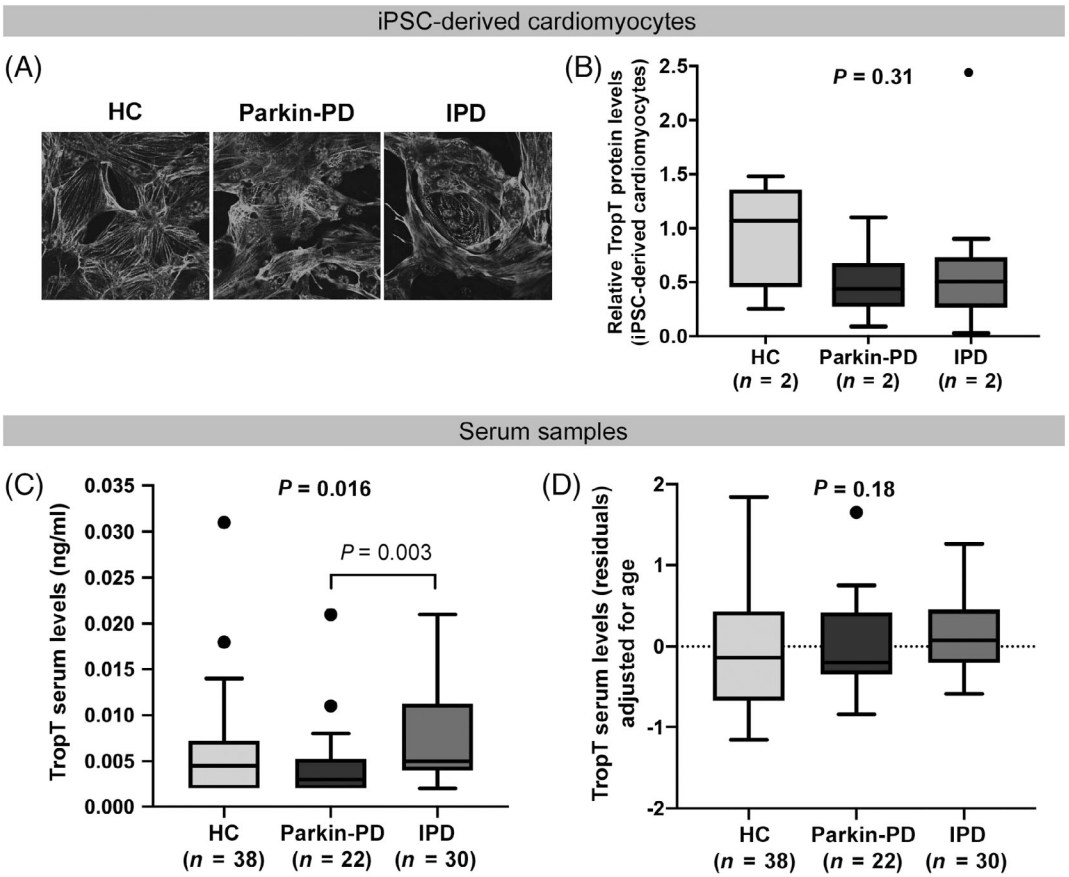

FIG. 1. Troponin T (TropT) levels in cardiomyocytes and serum from idiopathic and *Parkin*-linked Parkinson's disease patients and controls. (**A**) Immunofluorescence staining of iPSC-derived cardiomyocytes from healthy controls (HC), *Parkin* biallelic mutation carriers with Parkinson's disease (Parkin-PD) and idiopathic PD patients (IPD) showing the expression of thin filament-associated cardiac-specific TroponinT2 (green) and the transcription factor Myocyte-specific enhancer factor 2C (red). (**B**) Quantitative analyses of TropT protein expression by western blot revealed no significant difference in Parkin-PD patient lines (n = 2) compared to HC (n = 2) or IPD patient lines (n = 2) after normalization to GAPDH (n = 3 independent cardiac differentiations). Differences between the groups were assessed via Kruskal Wallis test. (**C**) Serum levels of TropT in HC, Parkin-PD, and IPD patients. Compared to HC, TropT was elevated in IPD patients and decreased in Parkin-PD. Differences between the groups were assessed via Kruskal Wallis test. For pairwise comparisons, Wilcoxon rank-sum test was used. (**D**) Because TropT levels increase with age, we performed a sensitivity analysis taking age into account. Therefore, we calculated a linear regression to predict log (TropT) and saved the residuals. Then, statistical analysis was performed as described. This analysis revealed no differences between TropT levels in HC, Parkin-PD, and IPD. [Color figure can be viewed at wileyonlinelibrary.com]

impaired motor and cognitive function. The authors suggested shared pathophysiological mechanisms of PD and heart disease based on overlapping molecular pathways and high energy demand in dopaminergic neurons and cardiomyocytes, pointing to a potential role of mitochondria because their integrity is crucial for proper energy production. Because mutations in *Parkin* cause mitochondrial dysfunction,[2] we aimed to elucidate the impact of Parkin deficiency on induced pluripotent stem cell (iPSC)-derived cardiomyocytes obtained from PD patients with biallelic *Parkin* mutations (Parkin-PD), *Parkin*-mutation-negative IPD patients, and healthy controls (HC, n = 2 per group) (Fig. 1A; Supplementary Table S1). Analyzing cell-specific protein levels by western blotting, we found no significant difference of Troponin T (TropT) levels in cardiomyocytes from Parkin-PD compared to HC or IPD patients (Fig. 1B). Additionally, we investigated TropT levels in serum samples from Parkin-PD (n = 22, Supplementary Table S2), IPD patients (n = 30), and controls (n = 38) (for demographics see Supplementary Table S3). We detected decreased unadjusted TropT levels in Parkin-PD compared to HCs, whereas IPD patients exhibited the highest TropT levels (Fig. 1C). Because TropT increases with age in all groups (Spearman's correlation, n = 90, r = 0.538, $P < 0.01$) and Parkin-PD were younger at examination than IPD and HC, we performed a sensitivity analysis investigating differences in TropT levels taking age into account. We found no differences between the three study groups (Fig. 1D). Data on potentially confounding cardiovascular conditions was limited.

Our study provides evidence for normal TropT levels in *Parkin*-linked PD in cardiomyocytes and sera, suggesting that Parkin deficiency may not be associated with cardiac damage in PD. Therefore, our findings point to mechanisms other than mitochondrial dysfunction that may explain the link between PD and heart involvement in IPD patients.

Supporting this notion, the absence of any acutely deleterious effect of a conditional cardiac-specific *Parkin* deletion in adult mouse hearts indicates that Parkin has a limited role in normal homeostatic cardiac mitochondrial quality control.[3] Our results are in line with studies reporting more severely impaired cardiac autonomic innervation in IPD than in Parkin-PD, possibly indicating no or less α-synuclein deposition in cardiac tissue in Parkin-PD.[4] Interestingly, metabolic syndrome is not only a risk factor for cardiovascular diseases but has been positively associated with the development of IPD.[5] Therefore, our findings indicate that in contrast to IPD, cardiovascular metabolic abnormalities do not appear to play a major role in the etiology of Parkin-PD.

To conclude, we did not find evidence for subclinical cardiac damage in Parkin-PD based on TropT analysis. Further functional studies investigating IPD and cardiac disease are warranted, combined with in-depth epidemiological studies, including confounding factors and appropriate control groups.

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References

1. Choe CU, Niemann L, Englisch C, et al. Subclinical cardiac microdamage, motor severity, and cognition in Parkinson's disease. Mov Disord 2020;35:1863–1868.
2. Pickrell AM, Youle RJ. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Neuron 2015;85(2):257–273.
3. Dorn GW. Parkin-dependent mitophagy in the heart. J Mol Cell Cardiol 2016;95:42–49.
4. De Rosa A, Pellegrino T, Pappatà S, et al. Myocardial 123I-metaiodobenzylguanidine scintigraphy in patients with homozygous and heterozygous parkin mutations. J Nucl Cardiol 2017;24(1):103–107.
5. Nam GE, Kim SM, Han K, et al. Metabolic syndrome and risk of Parkinson disease: a nationwide cohort study. PLoS Med 2018;15(8):e1002640.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Reply to: "Parkin Deficiency Appears Not to Be Associated with Cardiac Damage in Parkinson's Disease"

We appreciate the letter by Trilck-Winkler and colleagues, which sheds light on potential mechanisms of cardiac damage in Parkinson's disease (PD). Trilck-Winkler and colleagues report that unadjusted serum troponin T (TnT) levels are lower in patients with biallelic *Parkin* mutations (Parkin-PD) and higher in patients with idiopathic Parkinson's disease (IPD).[1] Differences were no longer significant after adjustment for age, but further adjustment for additional cardiovascular risk factors was not performed (n = 22–38 per group). TnT protein expression in induced pluripotent stem cell–derived cardiomyocytes was about 50% lower in patients with Parkin-PD and IPD compared with healthy controls, but this difference was not significant (n = 2 per group). Taken together, the unadjusted data suggest increased cardiac microdamage in patients with IPS, but not in patients with Parkin-PD.

Potential mechanisms for cardiac damage in PD involve either intrinsic factors in cardiomyocytes (eg, mitochondrial dysfunction, oxidative stress, energy deficiency) or extrinsic causes (eg, cardiac autonomic denervation). Although Trilck-Winkler et al. did not find any evidence of subclinical cardiac damage in Parkin-PD, several recent animal studies have

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