

# The HERCULES Study: Methods and Rationale of Assessing the Health-Related Quality of Life (HRQoL) in Patients Living With Early-Stage Chronic Kidney Disease and Their Carers in the US

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## Objective

- To characterize HRQoL in early-stage CKD, including patient and carer experiences, particularly in individuals with multiple comorbidities (e.g., diabetes and hypertension) that also are serious risk factors for developing CKD

## Conclusions

- The HERCULES CKD program will generate contemporary observational HRQoL insights on the impact of early-stage CKD in patients and their carers
- It will support data-driven segmentation of the CKD population into subgroups with distinct HRQoL profiles using Latent Class Analysis
- HERCULES will support and improve clinical decision-making in early-stage CKD using HRQoL-driven prospective real-world evidence generation

## Introduction

- CKD is a growing global concern and a leading cause of death that places a substantial financial and resource burden on healthcare systems worldwide<sup>1</sup>
- An estimated 800 million people worldwide are affected by kidney disease, whereas CKD is the third fastest-growing cause of death globally and is projected to become the fifth leading cause of death by 2040<sup>2</sup>
- However, CKD is often overlooked in health systems globally because the early stages are asymptomatic, leaving many patients undiagnosed until the disease is advanced<sup>3</sup>
- Even in early-stage CKD when symptoms may not be apparent, HRQoL is significantly affected compared with healthy individuals<sup>4,6</sup>
- The HERCULES study tests the hypothesis that some patients with early CKD experience symptoms that negatively impact their HRQoL. Using a cross-sectional observational design, a comprehensive range of PROMs, and Latent Class Analysis, the study aims to identify symptom profiles across CKD stages based on patient characteristics

## Methods

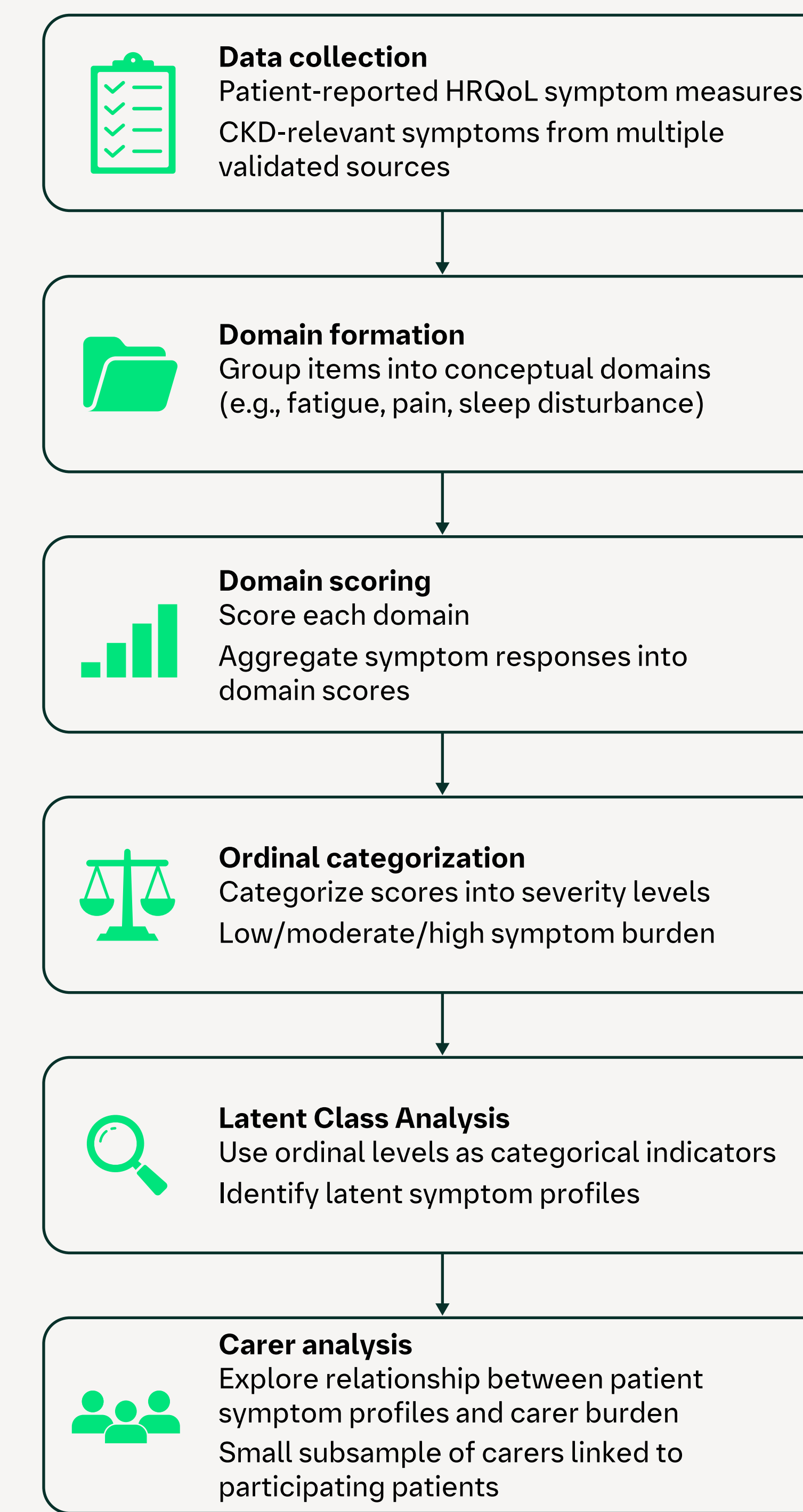
<p><b>Study objectives</b></p> <ul style="list-style-type: none"> <li>Assessment of <b>CKD patients' HRQoL</b>, across CKD stages (G1, G2, G3a, G3b, G4, and G5) to understand how CKD affects health status, social functioning, physical and mental wellbeing, and symptom burden</li> <li>Identify <b>latent CKD symptom profiles</b> using patient-reported HRQoL measures across CKD stages G1–G5</li> <li>Explore <b>carer burden and functioning</b> in relation to patient symptom profile</li> </ul>
<p><b>Study design and population</b></p> <ul style="list-style-type: none"> <li>This is a cross-sectional, patient-centered survey of US adults (≥18 years) with clinician-verified CKD across all stages who complete an English-language online survey</li> <li>A subsample of unpaid <b>adult carers</b> of participating patients will also be recruited to evaluate carer burden and functioning</li> </ul>
<p><b>Sample size</b></p> <ul style="list-style-type: none"> <li>Approximately <b>360 patients with CKD</b> (~60 per CKD stage)</li> <li>Approximately <b>60 carers</b> (~10 per CKD stage, where feasible)</li> </ul>
<p><b>PROMs</b></p> <ul style="list-style-type: none"> <li><b>PROMs</b> include a battery of generic and disease-specific validated state-of-the-art questionnaires:                     <ul style="list-style-type: none"> <li>SF-36v1, EQ-5D-5L, KDQoL-36, OAB-BAT, and the KCCQ</li> <li>De novo item (assessing night-time urination)</li> <li>Demographic, clinical, and psychosocial variables</li> </ul> </li> <li><b>Carers</b>, in addition, will complete the following PROMs:                     <ul style="list-style-type: none"> <li>AC-QoL and WPAI</li> </ul> </li> </ul>
<p><b>Latent Class Analysis</b></p> <ul style="list-style-type: none"> <li>This will be used to identify <b>latent CKD symptom profiles</b> based on shared self-reported response patterns</li> </ul>
<p><b>Statistical analysis</b></p> <ul style="list-style-type: none"> <li>Results will be summarized using descriptive statistics and instrument-specific scoring (total and subscales)</li> <li>Adjusted linear regression models will be applied to support identification of clinically meaningful CKD subgroups</li> </ul>

**Abbreviations**  
 AC-QoL, Adult Carer Quality of Life; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol-5 Dimensions 5 Levels; HRQoL, Health-Related Quality of Life; KCCQ, Kansas City Cardiomyopathy Questionnaire; KDQoL-36, Kidney Disease and Quality of Life-36; OAB-BAT, Overactive Bladder-Bladder Assessment Tool; PROM, patient-reported outcome measure; QoL, quality of life; SF-36v1, 36-Item Short-Form Survey; WPAI, Work Productivity and Activity Impairment.

**References**  
 1. Johnston-Webber C, et al. *Health Policy*. 2025;152:105244.  
 2. Luyckx VA, et al. *Bull World Health Organ*. 2018;96:414–220.  
 3. Kushner P, et al. *Adv Ther*. 2024;41:3757–70.  
 4. Tsaoi T, et al. *PLoS One*. 2025;20:e03119100.  
 5. Pageels AA, et al. *Health Qual Life Outcomes*. 2012;10:171.  
 6. Moximov A, et al. *Qual Life Res*. 2026;35:28.

## Methods (continued)

- The study workflow is presented in **Figure 1**
- Figure 1. Workflow for identifying CKD symptom profiles and assessing associations with outcomes**



## Rationale

### Assessments included in the HERCULES CKD study framework

- The HERCULES study employs a multifaceted approach using a wide range of PROMs, open-ended questions, and carer perspectives to provide a more comprehensive assessment than previous studies (**Table 1**)

**Table 1. Assessments included in the HERCULES framework**

PROM	CKD patients	CKD carers
Patient characteristics, demographics, health information, etc.	✓	✓
SF-36v1 (36-item)	✓	✗
EQ-5D-5L (5-item)	✓	✗
EQ-5D (Visual Analogue Scale)	✓	✗
KDQoL-36 (4-item)	✓	✗
OAB-BAT (2-item)	✓	✗
De novo item* (1-item)	✓	✗
KCCQ-23 (4-item)	✓	✗
AC-QoL (40-item)	✗	✓
WPAI (6-item)	✗	✓

\*De novo item assesses night-time awakening due to urination.

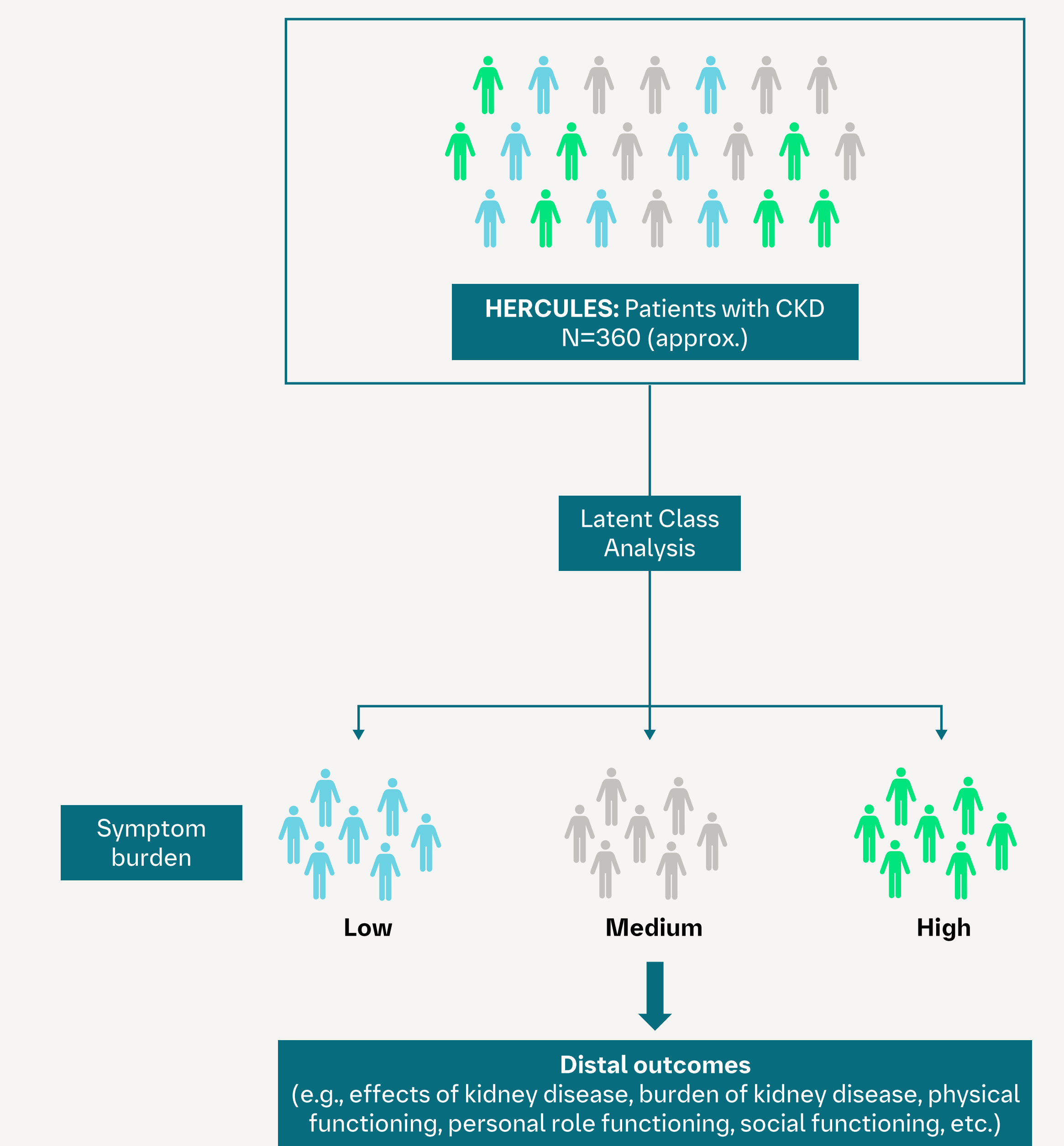
**Disclosures**  
 VWJ, NP, and SS are employees of Boehringer Ingelheim. JFP reports consulting fees from Boehringer Ingelheim. JH, BF, SD, and NJ are employees of Lumina. KFE reports consulting fees from Boehringer Ingelheim.

## Rationale (continued)

### Use of Latent Class Analysis

- The expected outcomes of Latent Class Analysis (**Figure 2**) in this study include:
  - Identification of distinct symptom profiles based on shared PROM-reported symptom patterns
  - Data-driven patient segmentation into subgroups with different symptom burden and severity, described by CKD stage and other characteristics
  - Assessment of any associations with outcomes, i.e., between symptom profiles and disease burden, physical functioning, personal role functioning, and social functioning
  - Enable exploration of the relationship between patient symptom profiles and carer burden and functioning

**Figure 2. Use of Latent Class Analysis**



### Carer analysis

- This study will include an exploratory analysis among CKD carers, examining the impact of caring on HRQoL, work productivity, and financial outcomes, etc.
- These will provide comprehensive measurement of carer outcomes, capturing not only their HRQoL, but also giving insights on stress levels, and work and activity impairment
- In the exploratory analyses, carer burden and functioning will be compared across patient symptom profiles and CKD stages to explore 'spillover' effects (i.e., where the burden of CKD spills over from patient to carer)

## Summary

- The HERCULES CKD program will provide contemporary HRQoL insights to inform clinical practice and improve understanding of the impact of early-stage CKD on patients and carers. It will also provide data-driven segmentation of the CKD population, identifying subgroups with distinct HRQoL experiences
- It is our hope that the findings will offer new insights and perspectives on the burden of early CKD and support a shift toward more proactive approaches, such as systematic early screening and diagnosis, rather than the current reactive 'watch and wait' paradigm

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