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Development of a Wearable Device for Continuos Monitoring of Levodopa in Parkinson's Patients

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Abstract

Parkinson's disease treatment with levodopa (L-DOPA) is complicated by motor fluctuations, wearing-off periods, and substantial variability in medication response. Treatment decisions still rely heavily on patient recall, symptom diaries, and short clinical visits, while symptoms are also influenced by factors such as medication timing, protein intake, activity, and stress. In this project, we developed a wearable L-DOPA monitoring concept aimed at providing objective information between consultations and supporting more personalized treatment decisions.

L-DOPA detection was based on a differential electrochemical sensing strategy using a tyrosinase-functionalized electrode and an enzyme-free reference electrode. The fully functionalized biosensor showed a linear response between 5 and 40 μM, with a sensitivity of 11.2 nA/μM and $R^2 = 0.9987$.

For translation toward wearable sensing, a disposable patch was developed in which hollow microneedles are used for interstitial-fluid extraction while sensing occurs on a separate two-sided flexible PCB. The PCB integrates the electrochemical electrodes on one side and the pogo-pin interface to the reusable electronics on the other. A magnetically guided docking mechanism was designed to enable repeatable attachment of the reusable readout device. SEM imaging showed open hollow channels in the fabricated microneedles, and agarose experiments demonstrated penetration and liquid transport.

Finally, stakeholder interviews with patients, caregivers, and healthcare professionals were conducted to define the clinical use case and guide the development of the patient and clinician interfaces. Together, these results establish the technical foundation and translation strategy for a wearable system that links longitudinal L-DOPA measurements with symptoms and contextual factors to support more objective and personalized Parkinson's disease management.

1 AP Award: Biosensor Developed for the Eindhoven Testing Event

1.1 Molecular Recognition

Sensing L-DOPA in human serum is challenging due to the presence of electroactive interferents, such as ascorbic acid and uric acid, which can undergo oxidation at potentials similar to those of L-DOPA (Fang et al., 2022). Their contribution to the measured electrochemical signal can therefore interfere with L-DOPA detection and lead to inaccurate concentration estimates. To address this challenge, **selective L-DOPA detection was achieved using a differential enzyme-based strategy with two separate three-electrode chips: a tyrosinase-modified sensing chip and an enzyme-free reference chip. Both chips contained a gold working electrode, gold counter electrode, and Ag/AgCl reference electrode, differing only in the presence of tyrosinase in the outer protein layer.** This sensing mechanism was inspired in the work of Fang et al., 2022 and Cembalo et al., 2023.

The functionalized working electrode consisted of a gold surface modified with Nafion, polyaniline (PANI), and a crosslinked protein layer containing bovine serum albumin (BSA), glutaraldehyde, and tyrosinase. Nafion acts as a permselective membrane to reduce the contribution of charged interferents and to separate the enzyme layer from the conductive gold surface. PANI was used as an enzyme immobilization support, as its porous conducting structure can increase the available surface area for protein attachment. BSA provided a stabilizing protein matrix, while glutaraldehyde was used as a crosslinker to immobilize the protein layer on the electrode surface.

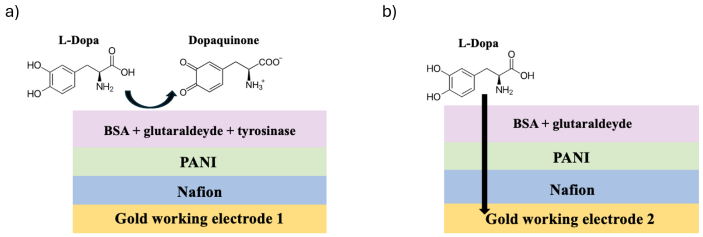


Figure 1: Schematic of the biosensor functionalization layers. (a) Tyrosinase-modified chip. (b) Reference chip.

The working electrodes were prepared through sequential surface functionalization. After cleaning, the gold electrode surface was coated with Nafion and subsequently modified with a PANI layer. A tyrosinase/BSA mixture was drop-cast onto the enzyme-containing chip, while a BSA-only solution was drop-cast onto the reference chip. Both protein layers were then crosslinked using glutaraldehyde, producing a stabilized protein matrix on top of the PANI-modified electrode. Figure 1 shows the final layer configuration. The full surface functionalization protocol, including concentrations, deposition conditions, and crosslinking conditions, is provided in **Appendix A**.

1.2 Physical Transduction

The recognition of L-DOPA is transduced into an electrical signal using square-wave voltammetry (SWV). During measurement, the potentiostat controls the potential of the gold working electrode versus the Ag/AgCl reference electrode and records the resulting faradaic current.

The two-chip configuration enables differential detection. On the enzyme-free reference chip, L-DOPA reaches the electrode surface and undergoes direct electrochemical oxidation, producing

a current peak. In contrast, on the tyrosinase-modified chip, L-DOPA is enzymatically converted to dopaquinone before reaching the electrode, reducing its contribution to the oxidation peak. **The L-DOPA-dependent response is therefore obtained by subtracting the response of the tyrosinase-containing chip from that of the enzyme-free chip**:

$$\Delta I_{\mathrm{p}} = I_{\mathrm{p,enzyme-free}} - I_{\mathrm{p,tyrosinase}}. \tag{1}$$

This subtraction reduces background contributions that are present on both chips. After calibration with known L-DOPA concentrations, the differential peak current is related to analyte concentration. SWV measurements were performed from -0.20 to $+0.60$ V with a 5 mV step, 25 mV amplitude, 25 Hz frequency, and 8 s equilibration time. The analysed oxidation peak was generally observed at approximately $+0.10$ V.

1.3 Cartridge Technology

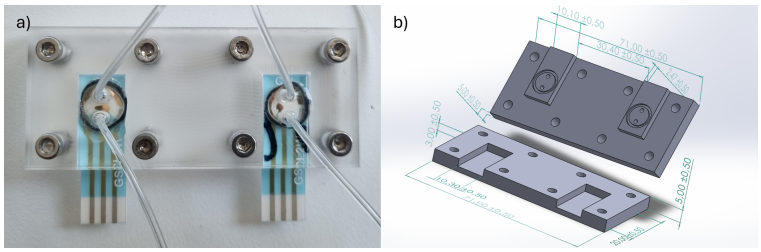


Figure 2: Microfluidic sensing chamber. (a) Fabricated device. (b) CAD model with dimensions in mm.

The microfluidic chamber (Fig. 2a) consists of two poly(methyl methacrylate) (PMMA) sections fastened together with screws. As shown in Fig. 2b, the bottom section contains two recesses for the electrochemical chips, while the top section has protrusions that secure the chips in place. Each protrusion includes a circular groove that houses a rubber O-ring, sealing the chamber and preventing leakage. The sensing chambers have a diameter of $7.5\ mm$ and a volume of $8\ \mu L$.

Since the sensing strategy uses two electrochemical chips, each $100\ \mu L$ sample is split into two $50\ \mu L$ aliquots. The $8\ \mu L$ chamber volume allows $42\ \mu L$ to flush the previous sample while leaving sufficient volume for accurate measurements. Each chamber has an inlet and an outlet connected by tubing. The inlet is immersed in the sample, while the outlet is connected to a peristaltic pump. During operation, the pump draws the sample through the chamber and into a waste reservoir. By immersing the inlet tube in different samples, the chamber contents are seamlessly replaced, resulting in continuous sensing.

1.4 Reader Instrument and User Interaction

Electrochemical measurements were performed using an EmStat Pico potentiostat mounted on its development board and controlled from a laptop running PSTrace software. The electrochemical chips were connected to the board through a PalmSens screen-printed electrode connector using banana-plug leads for the working, counter, and reference electrodes. The reader was integrated into a compact benchtop prototype together with the microfluidic flow cell and peristaltic pump. Before each measurement, the functionalized chips were placed in the flow cell, the PMMA housing was assembled, the electrode leads and tubing were connected, and the in-

let tube was immersed in the sample. The pump filled and flushed the sensing chambers and was stopped during voltammogram acquisition. SWV measurements were initiated in PSTrace, which displayed and stored the current–potential curves. Since the two chips had independent counter and reference electrodes, their responses were acquired sequentially. The data were then exported to a MATLAB script, which extracted the peak currents and calculated the differential response by subtracting the tyrosinase-containing signal from the enzyme-free signal. The laptop interface enabled visualization of the voltammograms and repetition of measurements when required. Future work will focus on translating this benchtop measurement approach into the wearable system described in the next section.

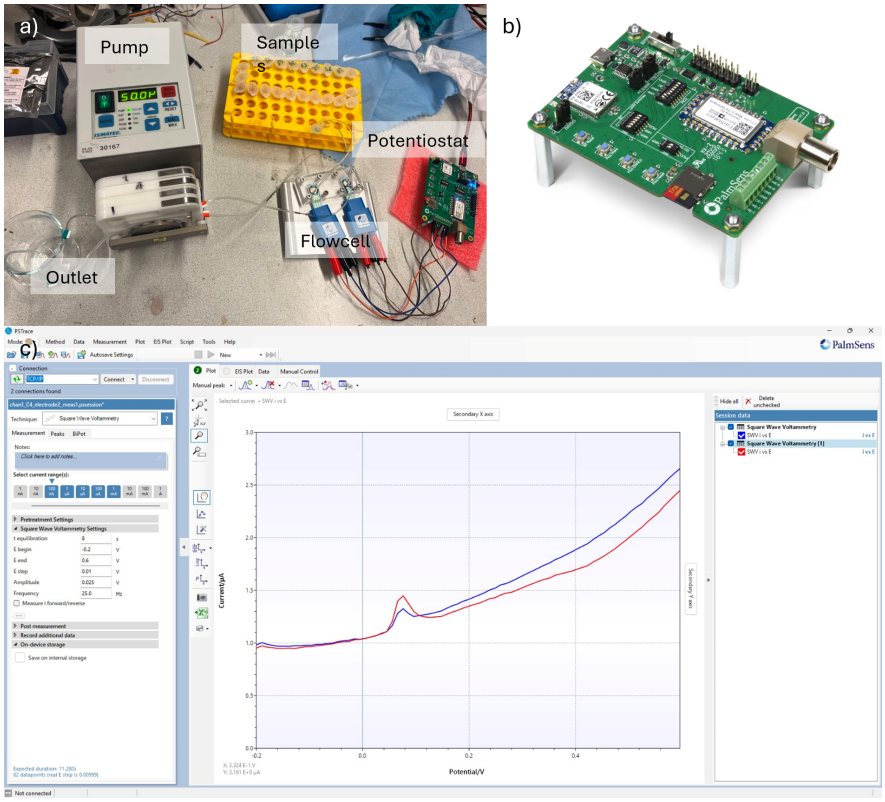


Figure 3: Reader instrument and measurement interface used for electrochemical testing. (a) Benchtop setup including the peristaltic pump, sample tubes, microfluidic flow cell, outlet, and EmStat Pico potentiostat. (b) EmStat Pico development board used as the potentiostat during prototype measurements. (c) PSTrace software interface used to configure SWV measurements and record the current–potential response from the two chips. Around $+0.10$ V, the enzyme-free chip produces the higher L-DOPA oxidation peak, while the tyrosinase-functionalized chip shows a lower peak.

2 IN Award: Biosensor Innovation

2.1 Wearable Sensor

Proposed concept: Our wearable sensor consists of a disposable microneedle patch and a reusable readout device. The patch extracts ISF using hollow microneedles and integrates a two-sided flexible PCB that functions as both the electrochemical sensing chip and the device interface. The reusable device docks magnetically onto the patch, performs the electrochemical readout, stores data on an SD card, transmits the data via Bluetooth, and can be reused with a new patch.

2.1.1 Technological Novelty of Wearable Sensor

Disposable Patch: For the disposable patch (Fig. 4), we decided not to use the microneedles themselves as the direct sensing electrodes similar to glucose monitoring patches. The surface-modification layers required for L-DOPA sensing (see Section 1.1), including the enzyme layer, are not suitable to be inserted directly into the skin. Therefore, the hollow microneedles are used only for ISF extraction from the skin and bring it to a separate electrochemical chip embedded in the patch.

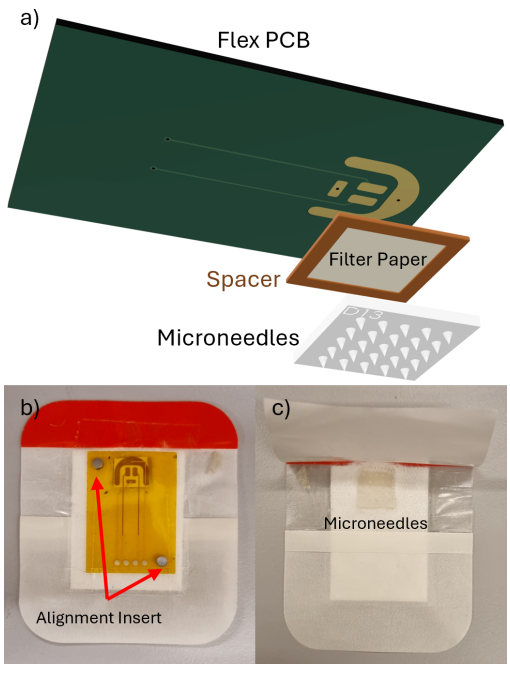


Figure 4: Disposable patch. (a) Exploded view. (b) Top view of the assembled patch showing the electrochemical chip, pogo-pin contact pads, and alignment inserts. (c) Bottom view showing the hollow microneedle array.

During our literature research, we found a recent paper using a similar idea with 3D-printed hollow microneedles coupled to an electrochemical sensing system (Parrilla et al., 2024). The authors kindly provided us with their microneedle 3D design, which we used as part of our patch. The detailed microneedle dimensions and fabrication steps are described in **Appendix B**.

On top of the hollow microneedle array, a filter-paper layer (Whatman qualitative filter paper, Grade 597) and a spacer are added to transfer the extracted ISF toward the electrochemical chip. The filter paper acts as a passive wicking layer; it helps pull fluid out of the microneedle channels by capillary action and spreads it across the working, reference, and counter electrodes. This allows the electrodes to be wetted with a small sample volume and keeps the liquid in stable contact with the sensing surface during measurement. The spacer is made from a double-sided adhesive layer and holds the filter paper in the correct position between the microneedles and the electrochemical chip.

The electrochemical chip itself is implemented as a two-layer flexible PCB, which is a key novelty of the disposable patch. The sensing side contains the electrode layout (two working electrodes, one reference electrode, and one counter electrode) that is wet-

ted by the filter paper, while the opposite side contains contact pads for pogo-pin connection to the reusable readout device (Fig. 5). Traces and vias connect the two sides of the flex PCB, allowing the same disposable layer to function both as the electrochemical chip and as the connection interface to the reusable electronics.

On top of the flexible PCB, two small ferromagnetic alignment inserts are added (Fig. 4b) at positions matching the recesses on the reusable device (Fig. 6b). These inserts are attracted by the magnets inside the device and seat into the recesses, improving repeatable alignment and helping ensure that the pogo pins contact the correct pads on the flexible PCB. The complete patch stack is then covered and held together by an adhesive dressing layer, as shown in Fig. 4b,c.

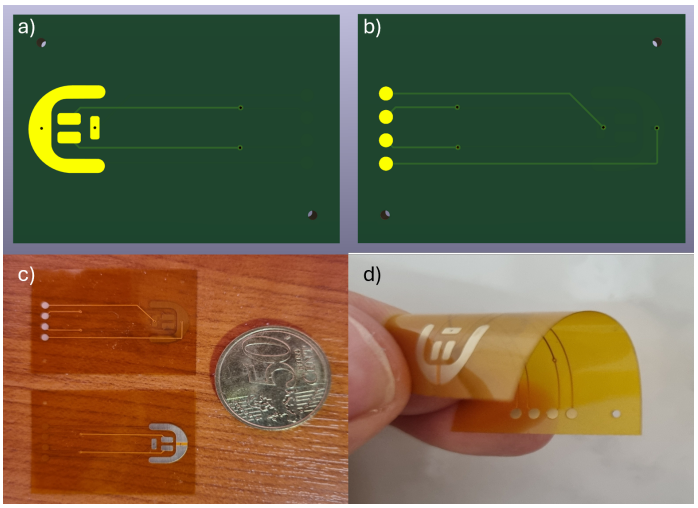


Figure 5: Two-sided flexible PCB used as the electrochemical chip and device interface. (a) Electrode side. (b) Pogo-pin side. (c) Fabricated PCB. (d) Flexibility demonstration.

Reusable Device: The reusable readout device is designed as a compact wearable module with a curved housing for improved ergonomics and comfort on the body (Fig. 6). The current device has a size of $4.3 \times 3.6 \times 1.7$ cm and contains a custom PCB (Fig. 7) with an XIAO ESP32-C3 microcontroller, an SD-card slot, an EmStat Pico potentiostat, and a rechargeable LiPo battery charged through the USB-C connector on the microcontroller module (Fig. 6a). During operation, the EmStat Pico performs the electrochemical readout, while the microcontroller stores the measured data on the SD card and periodically transmits them to the patient's phone via Bluetooth where the L-DOPA data will be combined with other inputs such as food intake. For further details, see **Section 3.2.2** and **Appendix H**. After data transfer, the SD card is cleared for the next measurement cycle. The full schematic of the custom PCB is provided in **Appendix C**.

For further miniaturization, the EmStat Pico could be replaced by a low-power potentiostat analog front-end such as the LMP91000. This would reduce the size and power consumption of the PCB and could allow the LiPo battery to be replaced by a smaller coin-cell battery. However, EmStat Pico was used because it is a ready-to-integrate potentiostat module that already handles the electrochemical measurement control and data acquisition, which makes prototyping faster.

The novelty of the reusable device is the magnetically guided docking interface to the disposable patch. The backside of the device contains four openings for the pogo pins and two shallow cylindrical recesses with a depth of 1 mm and a diameter of 3 mm (Fig. 6b). Small magnets embedded behind the recesses attract the ferromagnetic alignment inserts on the patch during docking (Fig. 4b), while the recesses guide the inserts into position. **This helps align the pogo pins with the contact pads without requiring a twist-lock or mechanical attachment mechanism, which may be difficult for our users with Parkinsonian motor symptoms such as tremor.**

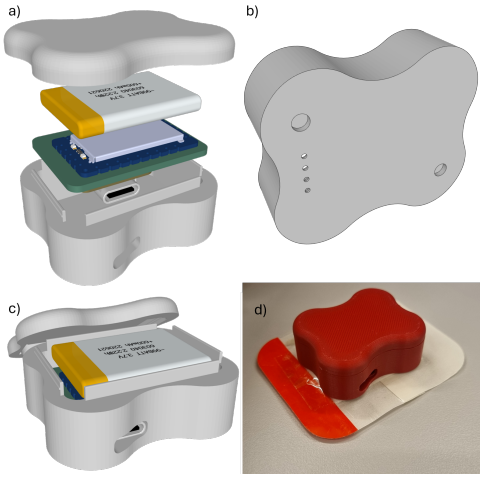


Figure 6: Reusable device. (a) Exploded view. (b) Backside render showing pogo-pin and magnetic docking interface. (c) Render of the assembled reusable readout device. (d) Device docked onto the disposable patch.

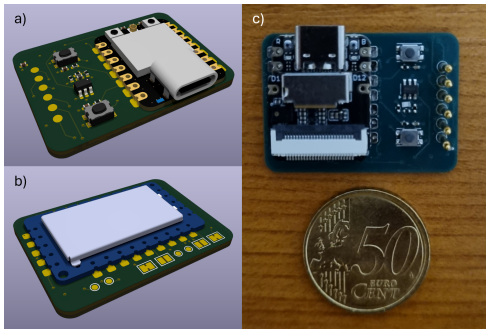


Figure 7: Custom PCB of the reusable device. (a) Top-side render. (b) Bottom-side render. (c) Fabricated PCB prototype shown next to a 50-cent coin for scale.

2.1.2 Technical Feasibility of Wearable Sensor

To verify that the microneedle arrays were fabricated correctly, we first performed SEM imaging of the needle tips. Fig. 8a shows a representative example. The microneedle contains a visible hollow opening, confirming that the internal channels were successfully formed. Some debris and surface roughness can be observed, due to the micro-drilling step used during fabrication (Appendix B). These were not fully removed by an ethanol bath, however, this did not block the channels or prevent the microneedles from functioning.

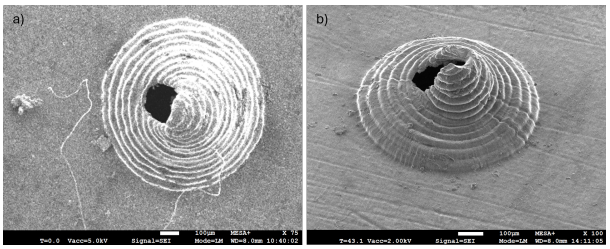


Figure 8: SEM images of representative fabricated hollow microneedles, taken at the University of Twente. (a) Microneedle tip before testing, showing a visible hollow opening. (b) Microneedle tip after the dye-transfer experiment, showing that the channel remained visible although the tip geometry became less sharp.

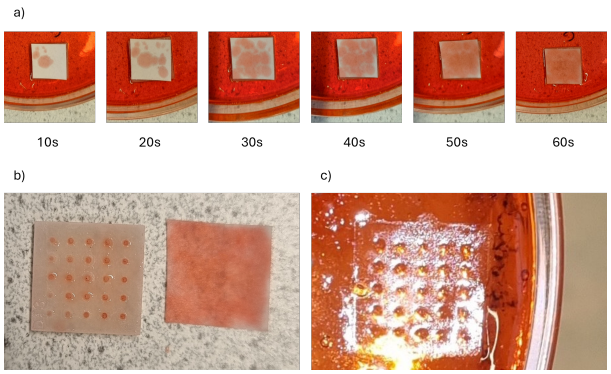


Figure 9: Dye experiment used to evaluate liquid transport through the hollow microneedle array. (a) Gradual appearance of dye on the filter paper. (b) Microneedle array and filter paper after the experiment. (c) Puncture pattern left in the agarose.

To evaluate whether the hollow microneedles could transfer liquid to the filter-paper layer, a simple dye experiment using 2% agarose containing food dye was performed. A filter-paper was placed on the back side of the microneedle array, and the microneedles were pressed into the dyed agarose. Over time, the dye appeared on the filter paper (Fig. 9a and Fig. 9b), indicating that liquid was transported from the agarose into the paper layer. After removing the microneedle array, a pattern of puncture marks was visible in the agarose (Fig. 9c). Post-experiment SEM imaging showed that the hollow opening was still visible, although the tip appeared less sharp after testing (Fig. 8b). Although this agarose model **does not** fully represent human skin or real ISF extraction, the experiment demonstrates the basic feasibility of the proposed sampling principle: hollow microneedles can create contact with a hydrated substrate and transfer liquid toward an absorbent layer inside the patch.

However, the magnetic docking interface still needs to be validated under realistic use conditions. The attachment force must be strong enough to keep the reusable device connected during movement, but low enough to allow easy removal. The impact force during docking should also be evaluated to ensure that snapping the device onto the patch does not break the microneedles or cause discomfort. While this is a general challenge for any device-to-patch attachment mechanism, including established mechanical or twist-lock designs, **the magnetic approach may improve usability because the alignment and attachment force are mainly defined by the device design, reducing the risk that the user applies unnecessary additional force by pressing or twisting the device.**

2.2 Reliability of Sensor Output

2.2.1 Technological Novelty of Reliability Concept

Reliable electrochemical detection of L-DOPA in a wearable platform is challenged by biological variability, electrode-to-electrode differences, biofouling, gradual degradation of the enzyme layer, and non-specific background currents from complex biological matrices. In serum, proteins and other electroactive species can adsorb onto the electrode surface or contribute additional oxidation currents, leading to signal drift during repeated measurements. Fabrication-related variations, such as differences in electroactive surface area and enzyme loading, may further affect the measured current.

The novelty of the proposed reliability concept lies in combining a multilayer enzyme-based sensing interface with a differential electrochemical measurement strategy. While enzyme-based L-DOPA biosensors have previously been reported (Tesoro et al., 2023), **our proposed design uses two independently functionalized electrodes that differ only in the presence of tyrosinase.** Since both electrodes are exposed to the same electrolyte composition, temperature, instrumental noise, and non-specific electrochemical background, common-mode disturbances can be largely reduced by subtracting their responses. In this way, the differential signal is expected to represent the L-DOPA-dependent contribution more selectively than the response of a single sensing electrode.

The multilayer functionalization further contributes to measurement stability:

- The **gold nanostructures** increase the electrochemically active surface area, improving signal intensity and sensitivity.
- **Nafion** acts as a permselective membrane that reduces the contribution of charged interferents.
- The **PANI** layer provides a conductive platform for enzyme immobilization;
- The **BSA/glutaraldehyde** network stabilizes the immobilized enzyme and reduces enzyme leaching, improving reproducibility between measurements.

Together, these layers are designed to improve sensitivity, selectivity, and stability rather than acting as independent modifications. The sequential surface modification was qualitatively verified using SEM, which showed clear morphological changes after each functionalization step (Fig 10), providing evidence of successful layer deposition prior to electrochemical characterization. As an **additional future improvement**, a **polyurethane protective coating** could be incorporated to reduce biofouling and provide mechanical protection during continuous operation.

Although previous tyrosinase-based L-DOPA biosensors have demonstrated operational stability over one to two weeks (Moon et al., 2021 and Fang et al., 2022), and in some cases retained performance over longer periods of 17–28 days or more (Cembalo et al., 2023 and Pinho et al., 2012), **the stability of our own sensor still needs to be experimentally evaluated.**

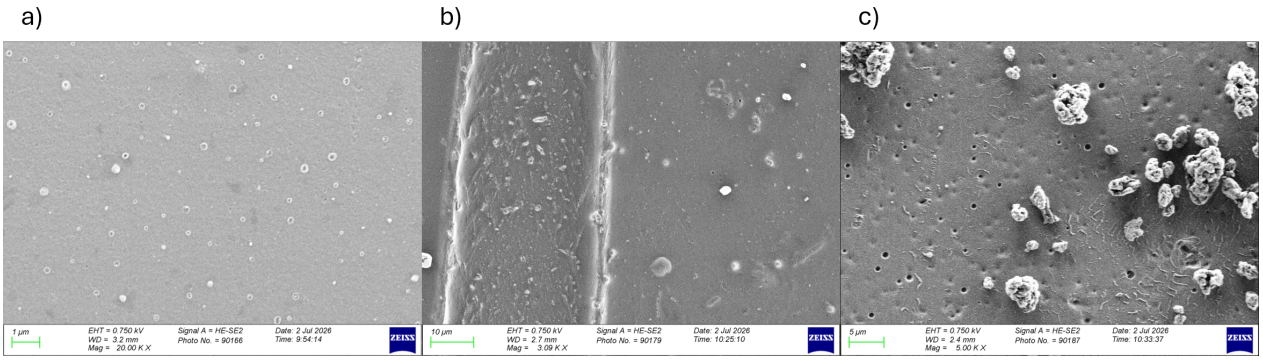


Figure 10: SEM images showing the morphological evolution of the gold working electrode during sequential surface functionalization, taken at the University of Twente. (a). Cleaned bare gold electrode after electrochemical treatment. (b) Gold electrode after Nafion deposition. (c) Fully functionalized electrode after Nafion, PANI, and enzyme.

2.2.2 Technical Feasibility of Reliability Concept

A representative SWV measurement comparing the enzyme-free and tyrosinase-functionalized electrodes is shown in Fig. 11. For each tested L-DOPA concentration, the two electrodes produced different peak-current responses around +0.1 V, with the enzyme-free electrode showing the higher peak current. This demonstrates that the two electrode responses can be experimentally distinguished, making it feasible to calculate a differential signal for calibration.

Calibration measurements were then performed on the fully functionalized biosensor using L-DOPA standards from 0 to 50 µM in PBS containing human serum, corresponding to the con-

centration range defined by the competition. SWV was used, and the peak current around the L-DOPA oxidation potential, approximately +0.10 V, was extracted for each concentration. The analytical signal was calculated as the differential peak current between the tyrosinase-functionalized and enzyme-free electrodes and plotted against L-DOPA concentration.

Although the full 0–50 µM range was tested, **the response was linear only between 5 and 40 µM**. Within this range, the sensor showed a **differential sensitivity of 0.0112 µA/µM** with $R^2 = 0.9987$ (Fig. 12). Therefore, **5–40 µM is considered the linear detection range of the sensor.**

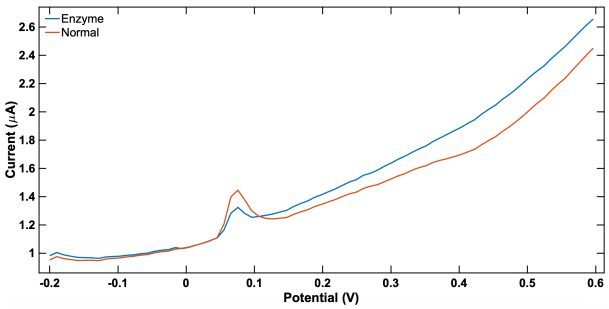


Figure 11: Representative SWV response of the enzyme-free and tyrosinase-functionalized electrodes at the same L-DOPA concentration. The enzyme-free electrode shows a higher peak-current response around +0.1 V, demonstrating the feasibility of calculating a differential signal for calibration.

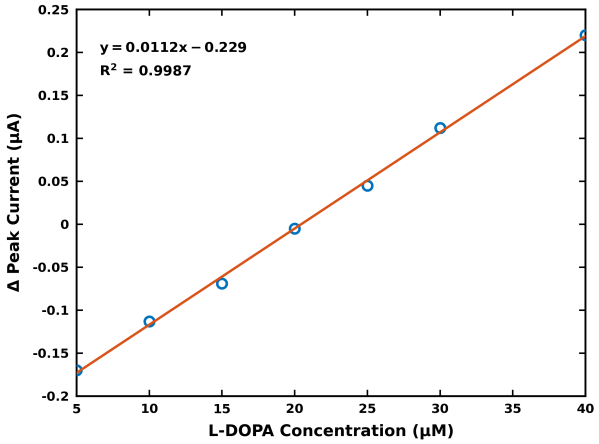


Figure 12: Calibration curve of the fully functionalized biosensor in PBS containing human serum. The differential peak current was plotted against L-DOPA concentration in the linear range of 5–40 µM, showing a sensitivity of 11.2 nA/µM and $R^2 = 0.9987$.

Additionally, the reliability of the wearable interface still needs to be validated under realistic use conditions:

- The current flexible PCB is relatively small (3.5×2.5 cm) and is therefore not expected to undergo severe bending during wear. Still, it may affect signal stability. Previous work has shown that flexible screen-printed electrochemical sensors can maintain their response at bending radii below 8 mm (Cai et al., 2009); however, this should be validated experimentally for our own patch under controlled bending conditions. Future versions could make the PCB smaller and reduce the bending effect by redesigning the docking geometry.
- Calibration of the complete wearable device still needs to be addressed, since the signal may be affected by the patch and ISF transport. One possible approach is batch-level calibration during manufacturing, where representative patches from each batch are tested using known L-DOPA standards. The resulting calibration parameters could be linked to the batch through a calibration ID, QR code, or NFC tag and automatically applied by the device or app.

2.3 Original Contributions

2.3.1 Team Captains

Our team conceived and developed the wearable L-DOPA monitoring concept and its initial prototypes, consisting of a disposable microneedle patch, reusable readout device, and clinician platform. The novelty of the wearable solution lies in its integrated replaceable patch–device architecture, in which a two-sided flexible PCB functions as both the electrochemical sensing substrate and the pogo-pin interface, while magnetic alignment enables repeatable connection to the reusable electronics. The concept was refined through literature research and technical feedback, and its feasibility was evaluated using SEM imaging, agarose penetration tests, and dye-transfer experiments.

For reliability of sensor output, the team developed and tested a differential electrochemical sensing strategy using a tyrosinase-functionalized electrode and an enzyme-free reference electrode. The team selected and adjusted the multilayer functionalization strategy, prepared the electrodes, performed SWV measurements, processed the data, calculated the differential response, and evaluated the calibration performance in PBS containing human serum.

External contributions consisted of supervisory guidance, technical feedback, access to laboratory facilities, support with SEM imaging and flow-cell fabrication, and the hollow microneedle CAD design provided by an external researcher. These contributions supported the project, while the final concept, design decisions, experimental execution, troubleshooting, data analysis, and integration were carried out by the team.

By combining scientific innovation with a clinically informed implementation strategy, shaped through extensive stakeholder interviews, our team developed an integrated L-DOPA monitoring system with the potential to support more objective and personalized Parkinson's disease management.



Amirhossein Zaboli



Jada Heemskerk

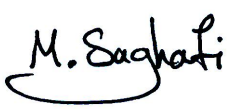
2.3.2 Team Supervisors

The team carried out the project with a high level of independence, taking responsibility for the project strategy, planning, technical decisions, implementation, and experimental work. Mohammad provided introductory training on biosensor development and offered periodic scientific and technical feedback throughout the project. Bahar introduced the team to the electrochemistry laboratory and advised them on practical aspects of electrode cleaning, measurement reproducibility, and the use of appropriate controls for data interpretation, without directing the experimental work. Both supervisors acted as mentors, providing scientific guidance, feedback, and access to laboratory facilities while leaving the project's direction and technical decisions to the students. Throughout the competition, the team retained ownership of the project's execution, troubleshooting, and optimization.

Moreover, Pep provided supervision for the translation potential part, helping the team in structuring their thoughts and to align them into the business side of their clinical translation efforts. They scouted, arranged and executed all the interviews on their own, obtaining valuable insights from the use case that they funneled into their biosensing design efforts, structuring a credible minimal viable proposition. He minimally sign-posted the team into regulatory issues, as some team members had taken specialized courses from their study programmes, and were familiar with such issues. As the team coordinator, Pep structured the course work and the procedure for claiming academic credit, and coached the captains into leadership of teams.



Pep Canyelles Pericas



Mohammad Saghafi



Bahar Atik

2.4 Bonus Criteria: Packaging Strategy for the Disposable Patch

The disposable patch contains both mechanically delicate hollow microneedles and a biologically active tyrosinase layer. Its primary packaging must therefore preserve enzyme activity, protect the microneedles from physical damage, and prevent contamination, evaporation, and exposure to light. Packaging should consequently be considered part of the sensing system rather than only a protective outer layer.

Because the functionalized electrodes were stored in PBS during development, **a logical initial strategy based on the current storage procedure is wet storage in an individually sealed high-barrier pouch**. The sensing region could be maintained in contact with a small PBS-saturated absorbent insert fixed within a rigid or semi-rigid tray. This would confine the hydration source to the sensing region while protecting the microneedles, skin adhesive, and electrical contact pads from direct exposure. The pouch would then be heat-sealed to limit evaporation, contamination, and light exposure.

The tray would include a recessed cavity in which the microneedles can be positioned without contacting the packaging, reducing the risk of bending, fracture, or channel blockage during storage and transport. The skin adhesive would remain covered by a removable release liner. Immediately before use, the patient would open the pouch and lift the patch from the tray, while the PBS-saturated insert remains fixed in the tray. The release liner would then be removed, the patch applied to the skin, and the reusable readout device attached magnetically.

Dry storage with desiccant remains a relevant alternative. Souza et al., 2026 showed that lactate oxidase-modified screen-printed electrodes stored in heat-sealed aluminium pouches with silica desiccant maintained stable electrochemical responses for up to six months, while unpackaged sensors exposed to ambient humidity degraded substantially. However, these results cannot be directly transferred to our tyrosinase-based sensor, which was developed and stored under hydrated conditions. Dry storage should therefore be considered an alternative packaging strategy that requires experimental validation for the current functionalization.

The importance of selecting a high-barrier primary package is further supported by McAlister et al., 2021, who compared different packaging materials for microneedle patches under accelerated storage conditions. High-barrier foil provided better protection against moisture and temperature than polyester packaging and better preserved microneedle functionality. Their study also used double heat seals and dye-immersion testing to evaluate seal integrity, which could be adapted as a simple quality-control method for our packaging prototypes.

A future packaging study should therefore compare wet storage, dry storage with desiccant, and unpackaged controls under room-temperature and accelerated storage conditions. Evaluation criteria should include calibration response, tyrosinase activity, microneedle integrity and channel openness, adhesive performance, electrical contact reliability, and pouch-seal integrity. This would determine which storage strategy provides the best balance between enzyme preservation, mechanical protection, usability, and shelf life for the disposable patch.

3 TP Award: Translation Potential

This section evaluates the developed device's value proposition to reduce uncertainty in mid-stage Parkinson's care by linking daily levodopa levels, symptoms, and contextual factors, and its clinical, business, and implementation potential.

This value proposition is based on 29 stakeholder interviews: 8 neurologists, 3 other healthcare specialists, 16 Parkinson's patients/caregivers, 1 investor, and 1 entrepreneurship specialist. These interviews shaped both the proposed system and its translation pathway.

3.1 Customer Interviews

Stakeholder interviews included three groups:

1. **Patients and caregivers:** to capture lived experience of symptom burden and daily challenges.
2. **Healthcare professionals:** to assess clinical validity and current practice gaps.
3. **Implementation experts:** to evaluate real-world feasibility and adoption barriers.

The interviews revealed three recurring needs: treatment decisions often rely on patient recall during short clinical visits, patients experience fluctuating symptoms and uncertain medication effects between consultations, and clinicians need objective data that connects levodopa response to symptoms and daily context. These insights shaped the whole system and are discussed in more detail in **Appendix D**. These findings also demonstrated the need for a companion app to collect contextual information alongside continuous levodopa measurements.

3.1.1 Identification of Potential Stakeholders

To explore the clinical need and practical context for the proposed biosensor, stakeholders were identified based on their involvement in Parkinson's disease management and potential interaction with our proposed system. Their relevance is summarized in Table 1.

3.1.2 Interview Approach and Execution

Semi-structured interviews were conducted between January and May 2026. Interview guides were developed separately for patients, caregivers, healthcare professionals, and entrepreneurship experts to tailor questions to each stakeholder group while still allowing comparison across interviews. The interview guides and their iterative versions are provided in **Appendices E–G**.

> **Interview focus:** current Parkinson's disease management, levodopa treatment experiences, symptom fluctuations, medication adherence, existing monitoring methods, unmet needs, and views on continuous levodopa monitoring.

Most clinician interviews were conducted online, while patient and caregiver interviews were conducted in person through collaboration with Punt voor Parkinson, a Dutch specialized medical center that brings together all expert care, treatment, and research for people with Parkinson's

Table 1: Stakeholder groups included in the customer interviews and their relevance

Stakeholder group	Reason for inclusion	Key input
Parkinson's patients	Directly experience medication timing, symptom fluctuations, treatment burden, and quality-of-life impacts.	Daily challenges, uncertainty around medication effect, usability needs, and desired patient support.
Caregivers	Often support patients with medication management, symptom recognition, and daily care.	Adherence challenges, observed symptoms, and differences between patient perception and caregiver observation.
Healthcare professionals	Neurologists, Parkinson nurse specialists, DBS nurses, and Technical Medicine professionals are involved in diagnosis, treatment adjustment, and follow-up.	Clinical workflows, current monitoring limitations, treatment decision-making, and the value of objective levodopa monitoring.
Implementation experts	Relevant for real-world implementation and regulatory approval.	Implementation barriers, regulatory requirements, and clinical adoption.
Healthcare financing experts	Relevant for assessing reimbursement and financial feasibility.	Reimbursement pathways and financing.

disease. Interviews lasted approximately 10 to 25 minutes. Participants were informed about the project and the use of their information, and audio was recorded only with their permission.

When recording consent was granted, interviews were recorded and transcribed. If not, detailed notes were taken instead. Patient identities were anonymized using coded identifiers (e.g., Patient 1, Patient 2).

After transcription, findings were organized in a shared analysis matrix and categorized into recurring themes, including current treatment methods, pain points, necessities, implementation barriers, desired features, and validation requirements. Regular team discussions were used to compare findings, identify patterns, and refine questions when new themes emerged. Regular team discussions identified patterns and refined questions as new themes emerged. Detailed stakeholder interview summaries supporting the thematic analysis are provided in **Appendix D**.

3.1.3 Interview Results and Conclusions

Key Findings from Stakeholder Interviews:

1. **Current treatment relies heavily on subjective information.** Treatment decisions are guided by patient recollection, symptom diaries, etc. Neurologists reported that patients often struggle to accurately describe symptom fluctuations, making treatment optimization difficult.
2. **Motor fluctuations and wearing-off periods are major challenges identified by patients and healthcare professionals.** As the disease progresses, levodopa response becomes increasingly unpredictable. Patients are forced to plan their daily activities around their med-

ication schedules. Also, the patients indicated uncertainty on whether the cause of their symptoms is due to insufficient medication, excessive medication, disease progression, or other external factors.

3. **Objective monitoring is a major unmet clinical need.** Current monitoring methods provide limited insight into medication effectiveness and timing. Clinicians indicates that objective measurements could improve treatment personalization, reduce trial-and-error dosing, and support earlier identification of patients who may benefit from advanced therapies.
4. **Factors influencing the symptoms of Parkinson's Patients**
    - **Protein intake:** Protein reduces levodopa absorption.
    - **Activity level:** Physical activity can temporarily improve motor symptoms.
    - **Emotional state:** Stress and anxiety worsen motor and non-motor symptoms.
    - **Medication timing:** Delayed or missed doses increase off periods.
5. **Contextual information is essential for the interpretation of sensor data.** Patients reported that symptom severity and perceived medication effectiveness varied depending on said contextual information such as daily activities, protein intake, and emotional state.
6. **The system should be low-burden and easy to use.** Patients prefer passive monitoring solutions rather than extensive symptom diaries. Neurologists also emphasized that a monitoring system should be suitable for patients experiencing tremor or reduced fine motor control. Suggested features include: large buttons, voice-based input, automated data collection, and integration with wearable devices.
7. **Implementation feasibility is crucial for translation.**

Successful healthcare adoption depends on technical performance, reimbursement, regulatory approval, clinical workflow integration, and acceptance by healthcare professionals. The system should support patient care without increasing workload, requiring clear clinical value and low implementation risk.

> **Key takeaway from interviews:** Current Parkinson's treatment lacks objective and continuous data about levodopa response during daily life. Treatment decisions rely on patient recall, symptom diaries, and short clinic visits, while medication effects are influenced by symptoms, meals, activity, and stress. This gap highlighted the need for objective monitoring.

These findings shaped the device concept as an integrated monitoring system consisting of a wearable biosensor, a patient app, and a clinical platform. The biosensor continuously measures levodopa concentrations in interstitial fluid, while the app collects contextual information such as symptoms, medication intake, meals, and activity. These data are combined in the clinical platform and presented in a structured report, providing patients and clinicians with objective insights to support personalized treatment decisions and improve long-term disease management (See **Appendix H**).

3.2 Validation Study

3.2.1 Selection of the Problem

Stakeholder interviews revealed the main limitations in the current treatment evaluation process: it is largely based on patient self-reporting and periodic consultations, so the assessment might be incomplete and subjective. Having continuous insight into levodopa response and its relationship with factors such as symptoms, medication and protein intake, could support more accurate treatment adjustments and avoid the ”trial and error” phase. Patients also indicated difficulties in accurately remembering symptoms, medication effects and other relevant daily-life factors.

Specific problem to address: The lack of objective and continuous information on levodopa response in daily life and factors that influence it, which limits the ability of neurologists to optimize treatment for PD patients.

3.2.2 Conceptual Design and Use Case

Proposed concept: A wearable microneedle-based sensor that continuously measures levodopa in ISF, coupled with a digital software that combines these measurements with symptoms, medication and protein intake data.

The software is divided into the patient app and the clinician platform:

- Patient app: collects information about symptoms, medication and protein intake via quick pop-ups throughout the day. It also sends reminders to take medication as stipulated by the neurologist.
- Clinician platform: patient information is organized and visualized in a dashboard, showing relevant variables, discovered trends and potential correlations, as shown in Figure 13.

Use case: routine monitoring of mid-stage PD patients treated with levodopa. Between outpatient visits, patients wear the device and interact with the application during daily life. Then, neurologists use the dashboard during follow-up consultations to evaluate treatment effectiveness and adjust medication when necessary.

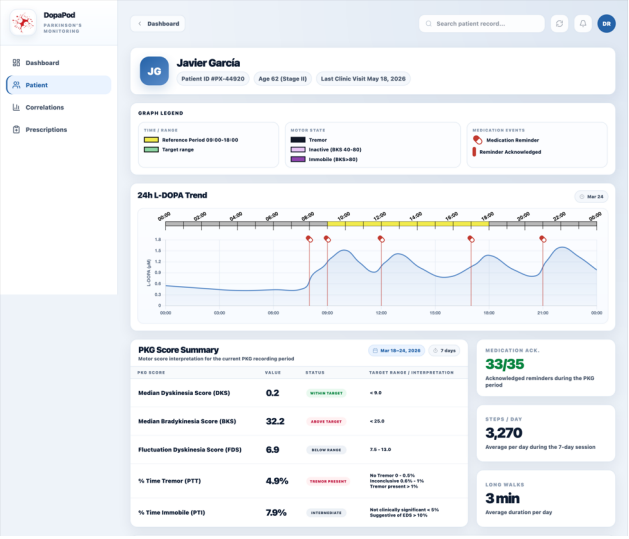


Figure 13: Example of patient report showing L-dopa fluctuations and PKG metrics

This solution provides objective and continuous monitoring of levodopa response, which will help neurologists make personalized treatment decisions. Patients may benefit from better treatment which reduces OFF periods and also removes symptom recall burden thanks to the app. Finally, earlier treatment optimization may reduce unnecessary outpatient visits and inefficient treatment cost. This represents an innovative alternative to the current standard procedure to PD treatment evaluation and adjustment.

3.2.3 Validation Study Design

Objective: to demonstrate the clinical value of continuous levodopa monitoring combined with symptom, medication and nutritional data for supporting treatment decisions. In addition, the usability, comfort and acceptance of the wearable device and patient application, as well as the usability and workflow integration of the clinician platform, will be assessed.

This observational study will be carried out at specialized PD care centers, including Medisch Spectrum Twente and Punt voor Parkinson. The study will be conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki and the GDPR. Participants will consist of 25 PD patients and 10 neurologists meeting the inclusion and exclusion criteria described in **Appendix I**. This sample size is appropriate for pilot and usability studies and will provide enough quantitative and qualitative data, so a hypothesis-testing power calculation was not needed. Future validation studies assessing sensor accuracy and reliability will require other sample size calculations based on those endpoints.

Patients will use the system during a 30-day evaluation period in daily life. Neurologists will evaluate anonymized simulated patient cases using the clinician dashboard. The activities performed by each participant group are summarized in Table 2.

Table 2: Activities performed by each participant group during the validation study.

Participant	Tasks
Patients	Wear the mock-up device according to instructions (charge it every 2 days and replace the patch every week), report symptoms, medication intake and protein consumption through the app, complete usability and acceptance questionnaires, and participate in a semi-structured interview.
Neurologists	Review anonymized simulated patient cases using the clinician dashboard, identify clinically relevant correlations, propose treatment adjustments, evaluate platform usefulness and workflow integration, complete questionnaires and an interview.

The outcome measures and corresponding assessment methods are summarized in Table 3. Questionnaires (quantitative data) will be analyzed using descriptive statistics and interviews (qualitative data) will be analyzed thematically to identify common perceptions regarding usability, clinical value and workflow integration. The findings will be used for further refinement.

Table 3: Outcome measures used in the validation study.

Aspect	Measurement	Method
Clinical value	Perceived usefulness	TAM questionnaire
Patient usability	SUS score	SUS questionnaire
Patient experience	UEQ score	UEQ questionnaire
Comfort	Comfort/burden rating	Likert-scale questionnaire
Clinician usability	SUS score	SUS questionnaire
Workflow integration	Integration rating	Likert-scale questionnaire

To sum up, this study will assess whether continuous levodopa monitoring combined with patient data can support treatment decisions and be integrated into routine PD care. If validated, the system could provide what is currently missing in standard care, thereby, enabling more personalized treatment for a large population of PD patients.

3.3 Bonus Criteria: Market Entry and Clinical Implementation Strategy

Here, we examine four aspects of the market-entry strategy: **market sizing**, **reimbursement feasibility**, **stakeholder adoption**, and **integration into clinical workflows**.

Our team used a top-down TAM-SAM-SOM approach applied to the Dutch market to **size the initial customer market**. The first target population was defined as Dutch mid-stage Parkinson's patients, Hoehn and Yahr stages 2–3, who actively use levodopa, as this group is clinically relevant for treatment adjustment and motor fluctuations (Skorvanek et al., 2017). The Total Addressable Market (TAM) was estimated at approximately 41,300 patients. The Serviceable Available Market (SAM), narrowed to patients experiencing wearing-off, was estimated at 22,800 patients (Wan et al., 2020). For early implementation, a hospital-based rollout through selected Parkinson's treatment centers was considered most realistic, giving a projected Serviceable Obtainable Market (SOM) of about 1,500 to 2,800 patients within the first 3–5 years. These estimates define the clinically relevant first-use population and achievable early adoption pathway; the full assumptions and unrounded values are provided in **Appendix J**.

We explored **reimbursement feasibility** within the Dutch healthcare ecosystem as we considered it to be the first entry market for the biosensor. Since the device supports treatment decisions through remote monitoring linked to hospital care, the most realistic early model is hospital-led implementation rather than direct-to-consumer use. Specialized treatment centers would prescribe the biosensor during monitoring periods before medication-adjustment consultations, aligning it with existing monitoring infrastructure and reimbursement structures (Bruinsma et al., 2025; VGZ, n.d.). An accelerometer for tremor detection was also considered. The most feasible routes are integration with patient-owned wearable devices, such as smartwatches, hospital-provided devices, or dedicated clinical devices covered by insurance if accelerometer data is shown to be essential for clinical interpretation.

We additionally performed a **stakeholder adoption barrier analysis** to assess implementation difficulties. For patients, the main risks were discomfort, excessive daily effort, and unclear perceived benefit; therefore, the system should rely on simple interaction prompts and minimal required input. For clinicians, the main risks were lack of trust, poor interpretability, and increased workload; therefore, the platform should convert raw readings into clinically meaningful and concise reports. For healthcare organizations and insurers, key barriers are infrastructure integration, data safety, training requirements, reimbursement uncertainty, and proof of cost-effectiveness. The stakeholder categories, barriers, and mitigation strategies are summarized in **Appendix K**.

Finally, we identified **clinical workflow integration** as critical for adoption; thus, the accompanying platform should combine levodopa trends with food or protein intake and movement data, and provide actionable insights rather than generic levodopa-level alerts. Examples include wearing off patterns, delayed medication response, and correlations between food intake and symptom fluctuations, as indicated by clinicians. Ideally, these insights would be summarized before or during consultations and integrated into existing systems, supporting clinical decision-making without adding data burden. A mapping of different system functions to clinical workflow roles is given in **Appendix L**.

Together, these different aspects of the market-entry strategy were analyzed to evaluate how the proposed biosensor could move from a technical prototype toward clinical implementation. To conclude, the thorough analyses we conducted further validate the business proposition outlined previously.

4 Team and support

4.1 Contributions of the Team Members

Amirhossein Zaboli (Team captain): Conceptualization of the wearable sensing system; development of the microneedle-based patch and its electrical interface with the reusable device.

Jada Heemskerk (Team captain): Stakeholder interviews; outreach through event organization and promotional content.

Ilaria Vonella: Wearable concept development; fabrication of hollow microneedles; creation of outreach materials; communication support for collaborations and awareness campaigns.

Jasmine Ahmed: Coordination of laboratory activities and tasks; development of functionalization, experimental, and safety protocols; electrochemical biosensor testing.

Francisco Lopes: Design of the flow cell system used for analytical measurements; selection of the sensing method and design of the wearable device.

Ane Gutierrez Martinez: Stakeholder interviews; validation study design; investigation of regulatory aspects; wearable device conceptualization.

Júlia Ribot Calvet: Stakeholder interviews; development of patient and neurologist apps; integration of the device into the clinical workflow; wearable device conceptualization.

Danai Spyridakou: Coordination of laboratory activities and tasks; development of functionalization, experimental, and safety protocols; electrochemical biosensor testing.

Nour Hasnaoui: Surface detection of levodopa; stakeholder interviews; team promotion through event organization and promotional content.

Yilin Chen: Team promotion through social media; creation of outreach materials and promotional content; business interviews with stakeholders.

Mohamed Daher: PCB design assistance; stakeholder recruitment for interviews; interview data processing; entry-to-market analysis.

Isaac Aguirre: Research and laboratory experimentation of the electrochemical chip; PCB design assistance.

Rodrigo Gonzalez: PCB design; 3D modelling of the wearable device; wearable device conceptualization.

4.2 People Who Have Given Support

Dr. Ir. Pep Canyelles Pericas: Supervisor of translation potential award and team coordinator.

Dr. Mohammad Saghafi: Introduction to biosensing concepts; guidance on wearable device design, disposable patch architecture, and practical implementation of the proposed system.

Bahar Atik: Guidance on biosensor chemistry, surface functionalization strategy, and laboratory work.

Dr. Jannis Schlicke: Guidance on biosensor chemistry, surface functionalization strategy, and laboratory work.

Daniël Wijnperle: Flow-cell fabrication and SEM imaging.

Dr. Ir. Jorien Berendsen: Introduction to the flow-cell design that was adapted for our dual-chip setup.

Dr. Marc Parrilla: Provided the STL file for the microneedle design described in his published work.

Vinaya Tennakoon: In charge of managing the team and the board.

Fernando Rodriguez: Guidance on internal team organization.

Andrea D'Silva: Communications and external affairs; Coordination of outreach strategy and sponsor relations.

Deikshi Kumari SN: Secretary and communications.

Matteo Pozzato: Supporting the team's technical systems; assistance with electronics; communication with Benchmark.

Paulo Palomo: Treasure; managing team finances, purchases, bookings, and expenses.

4.3 Sponsors and Partners

TechMed Center and **MESA+ (University of Twente):** University outreach and event visibility.

Benchmark: Workshops on device and PCB design.

Bronkhorst: Technical knowledge on pumps.

5 Final remarks

Biosensing Team Twente brings together BSc and MSc students from a wide range of disciplines, including Electrical Engineering, Biomedical Engineering, Chemical Engineering, Industrial Design, and Technical Medicine, united by a shared goal of developing technology that can contribute to better healthcare. This multidisciplinary structure allowed us to approach the project from complementary technical, clinical, and translational perspectives.

Beyond the technical project itself, the team is supported by a student board that ensures continuity of the organization from year to year. Its responsibilities extend beyond project management and include recruiting new members, managing the team's finances and logistics, coordinating external relations, outreach and sponsorships, and maintaining the broader structure of Biosensing Team Twente. This allows each new team to build on the experience, network, and infrastructure developed by previous generations.

The team is further supported by a supervisory board that provides scientific, technical, organizational, and translational guidance while preserving the students' ownership of the project. The supervisors act primarily as mentors: introducing relevant methods and available university facilities, providing feedback on biosensor development and experimental practice, supporting the translation of technical ideas toward clinical and business applications, and coaching the team captains in leadership and organization. The project strategy, design decisions, experimental execution, troubleshooting, and integration, however, remain in the hands of the students.

Throughout this project, we aimed to move beyond developing a biosensor in isolation and instead explore how continuous L-DOPA monitoring could fit into the daily lives of people with Parkinson's disease and support more informed treatment decisions. By combining perspectives from patients, clinicians, researchers, and professionals across healthcare and innovation, we tried to shape our solution around both the clinical need and the realities of everyday use.

Several steps remain before our solution can be translated into clinical use, and further validation and refinement will be required to establish its long-term performance, reliability, and suitability for real-world use. Nevertheless, we believe we have built a strong basis for further progress. Our device therefore represents not only the outcome of this year's SensUs challenge, but also a starting point for continued work toward more objective and personalized management of Parkinson's disease.

We would like to thank everyone who contributed to the development of our wearable biosensor over the past months for their time, insights, expertise, and encouragement. Hearing the personal stories of people living with Parkinson's disease was one of the most meaningful parts of this project and constantly reminded us of the people behind the problem we were trying to address. We are proud to present a concept that aims to address the unmet need for more objective and continuous monitoring of L-DOPA response in daily life.

With gratitude,

Biosensing Team Twente 2026

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Appendices

A Surface Functionalization Protocol

This appendix describes the surface functionalization procedure used to prepare the differential L-DOPA biosensor chips. The sensing strategy required two separately functionalized three-electrode chips. Both chips contained a gold working electrode (WE), a gold counter electrode (CE), and an Ag/AgCl reference electrode (RE). The first chip was functionalized with tyrosinase and used as the enzyme-containing electrode, while the second chip was prepared without tyrosinase and used as the enzyme-free reference electrode. The difference between the two SWV responses was used as the L-DOPA-dependent signal.

Materials

The main materials used for the surface functionalization are listed in Table 5. All aqueous solutions were prepared using Milli-Q water unless stated otherwise.

Table 5: Main materials used for surface functionalization of the L-DOPA biosensor chips.

Material	Purpose
Gold electrode chip	Electrochemical sensing platform containing gold WE, gold CE, and Ag/AgCl RE
Nafion	Permselective membrane for reducing charged interferent contributions
Polyaniline / aniline precursor	Conductive polymer layer and enzyme immobilization support
Tyrosinase	Enzyme for catalytic oxidation of L-DOPA to dopaquinone
Bovine serum albumin (BSA)	Protein matrix for enzyme stabilization and reference-layer preparation
Glutaraldehyde, 25% in water	Crosslinker for protein immobilization
Polyurethane (PU)	Intended protective and diffusion-control coating
Phosphate-buffered saline (PBS)	Electrochemical testing medium
L-DOPA	Target analyte for calibration and sensor testing
Human serum	Biological matrix component for interference and matrix-effect testing

Overview of Functionalization Procedure

The complete functionalization procedure consisted of the following steps:

1. Electrochemical cleaning of the gold chip.
2. Electrodeposition of Au nanostructures on the working electrode.
3. Nafion coating.
4. PANI layer deposition.

5. Protein-layer preparation, with tyrosinase/BSA on the sensing chip and BSA only on the reference chip.
6. Glutaraldehyde vapour crosslinking.
7. Electrochemical testing using square wave voltammetry.

A PU protective layer was also investigated as a final coating step. However, this layer was not successfully implemented in the final Eindhoven Testing Event prototype and is therefore described as an attempted protective coating rather than as part of the final functionalized chip.

Chip Pre-cleaning

The chips were pre-cleaned by electrochemical treatment using a cleaning solution containing H_2O_2 and $HClO_4$. For a total volume of 10 mL, the cleaning solution was prepared with a target concentration of 0.1 M $HClO_4$ and 3% (v/v) H_2O_2. Based on a commercial $HClO_4$ concentration of 70%, corresponding to approximately 11.6 M $HClO_4$, 86 µL of $HClO_4$ was added. For H_2O_2, 0.1 mL of 30% commercial H_2O_2 was added to obtain a final concentration of 3% (v/v). The solution was prepared by first adding 9 mL DI water, followed by 86 µL $HClO_4$ and 0.1 mL H_2O_2, and mixed gently.

For cleaning, 100 µL of the cleaning solution was pipetted onto the SPE. Electrochemical cleaning was performed using cyclic voltammetry from 0 V to +1.1 V versus Ag/AgCl at a scan rate of 100 mV/s for 10 cycles. After cleaning, the chip was rinsed well with Milli-Q water and dried under nitrogen.

Electrodeposition of Au Nanostructures

The Au nanostructure deposition solution was prepared with 10 mM $HAuCl_4{\cdot}3H_2O$ and 0.1 M HCl in a total volume of 10 mL. For the gold precursor, 39.4 mg $HAuCl_4{\cdot}3H_2O$ was dissolved in 10 mL DI water. For the acid, commercial HCl was assumed to be 37% (w/w), corresponding to approximately 12 M HCl. Therefore, 83.3 µL HCl was added to obtain a final concentration of 0.1 M HCl, and the solution was mixed gently.

The deposition solution was applied to the SPE so that the working, reference, and counter electrodes were fully covered. Electrodeposition was performed using chronoamperometry at 0 V versus Ag/AgCl for 300 s. After deposition, the chip was rinsed with DI water 3–5 times, quickly rinsed with ethanol, and dried using a nitrogen gun.

The gold precursor solution was prepared fresh for each lab session, and bubbles were avoided during deposition.

Nafion Coating

A 1 wt% Nafion solution was prepared from a 5 wt% Nafion stock solution. A total volume of 200 µL was prepared, which was more than required for one chip. First, 160 µL ethanol was pipetted into a tube, followed by 40 µL of 5 wt% Nafion stock solution. The tube was closed and mixed briefly using a vortex. If bubbles formed, the solution was left to sit for a few minutes.

The Nafion solution was then pipetted onto the electrode area of the chip, while avoiding the electrical contact pads as much as possible. The chip was placed in a covered Petri dish and left to dry at room temperature for 90 min.

For other Nafion stock concentrations, the stock volume was calculated using:

$$V_{\text{stock}} = \frac{C_{\text{final}} V_{\text{final}}}{C_{\text{stock}}}$$

For a final volume of 200 µL and a final concentration of 1 wt%, the following volumes were used:

Stock concentration	Stock volume	Ethanol volume
5 wt%	40 µL	160 µL
2.5 wt%	80 µL	120 µL
10 wt%	20 µL	180 µL

PANI Layer Deposition

For the differential sensing strategy, WE1 was functionalized with tyrosinase, while WE2 was kept enzyme-free. First, 1 mL of 0.4 M PANI in 1 M HCl was prepared using 0.92 mL DI water, 0.083 mL HCl, and 0.0365 g PANI. The solution was sonicated for 15 min.

A 100 µL droplet of the PANI solution was applied onto WE1 and WE2. PANI was deposited by applying a galvanostatic current of 0.0031 mA for 300 s. After deposition, both electrodes were immersed in Milli-Q water for 30 min and dried at room temperature.

Protein Layer Preparation

A BSA stock solution was prepared by dissolving 100 mg BSA in 1 mL Milli-Q water, giving a concentration of 100 mg/mL. For WE1, a protein solution containing 2.5 mg/mL tyrosinase and 40 mg/mL BSA was prepared using 100 µL tyrosinase solution, 80 µL BSA solution, and 20 µL Milli-Q water. For WE2, an enzyme-free BSA solution was prepared using 90 µL BSA solution and 110 µL Milli-Q water.

WE1 was immersed in the tyrosinase/BSA solution, while WE2 was immersed in the BSA-only solution. Both electrodes were stored at 4 °C for 24 h. After storage, the electrodes were rinsed with deionized water.

Glutaraldehyde Crosslinking

After protein immobilization, both electrodes were placed in a sealed bottle with 20 µL of 25% glutaraldehyde solution. The sealed bottle was then placed in an oven at 37 °C for 30 min to crosslink the protein layer. After crosslinking, the electrodes were lightly washed with Milli-Q water.

Attempted PU Protective Coating

A 3% (w/w) polyurethane (PU) solution was prepared by dissolving PU in a solvent mixture of 2% dimethylformamide (DMF) and 98% tetrahydrofuran (THF). For a total volume of 50 mL, 1.5 g PU,

0.98 mL DMF, and 47.5 mL THF were used. The solution was mixed using a stirring bar at 60 °C.

The biosensor chip was placed horizontally on a clean, level surface. Using a micropipette, 1–5 µL of the PU solution was dispensed onto the working electrode, ensuring complete coverage of the enzyme/PANI-modified sensing area while avoiding the electrical contact pads. The PU coating was then left to dry under ambient conditions for approximately 2 h.

The intended storage condition for the PU-coated biosensor chips was 0.1 M PBS at 4 °C until electrochemical measurement.

Storage

After functionalization, the biosensor chips were stored at 4 °C until electrochemical testing. If the PU protective coating was applied, the intended storage condition was 0.1 M PBS at 4 °C. L-DOPA standard solutions were stored at +4 °C for no longer than two days.

B Microneedles

Figure 14a shows the main dimensions of the hollow microneedle array used in this project. The design is based on the microneedle geometry described by Parrilla et al., 2024, consisting of a 5 × 5 hollow microneedle array on a 12 mm × 12 mm baseplate, with 2 mm spacing between neighbouring microneedles. Each microneedle has a conical geometry with a hollow channel and a small side opening near the tip, allowing fluid transport while maintaining a sharp tip for insertion. Figure 14b shows the corresponding CAD model of the hollow microneedle array.

Fabrication Process

The hollow microneedle arrays were fabricated using vat photopolymerization (VP) on a Uniformation GKtwo printer with Siraya Tech Fast resin (Fig. 14c). Automatic support structures were generated using the ChiTuBox Pro slicer.

To evaluate print quality, arrays were printed both with and without supports. Unsupported prints resulted in clogged microneedle lumens, whereas supported prints maintained open channels and were therefore selected for subsequent testing. After printing, the support structures were carefully removed manually, using pliers, to minimize damage to the needles.

The printed arrays were then cleaned in two isopropyl alcohol (IPA) baths, including one ultrasonic cleaning step to remove residual uncured resin and debris. Finally, the arrays were UV post-cured for approximately 5 minutes before experimental testing.

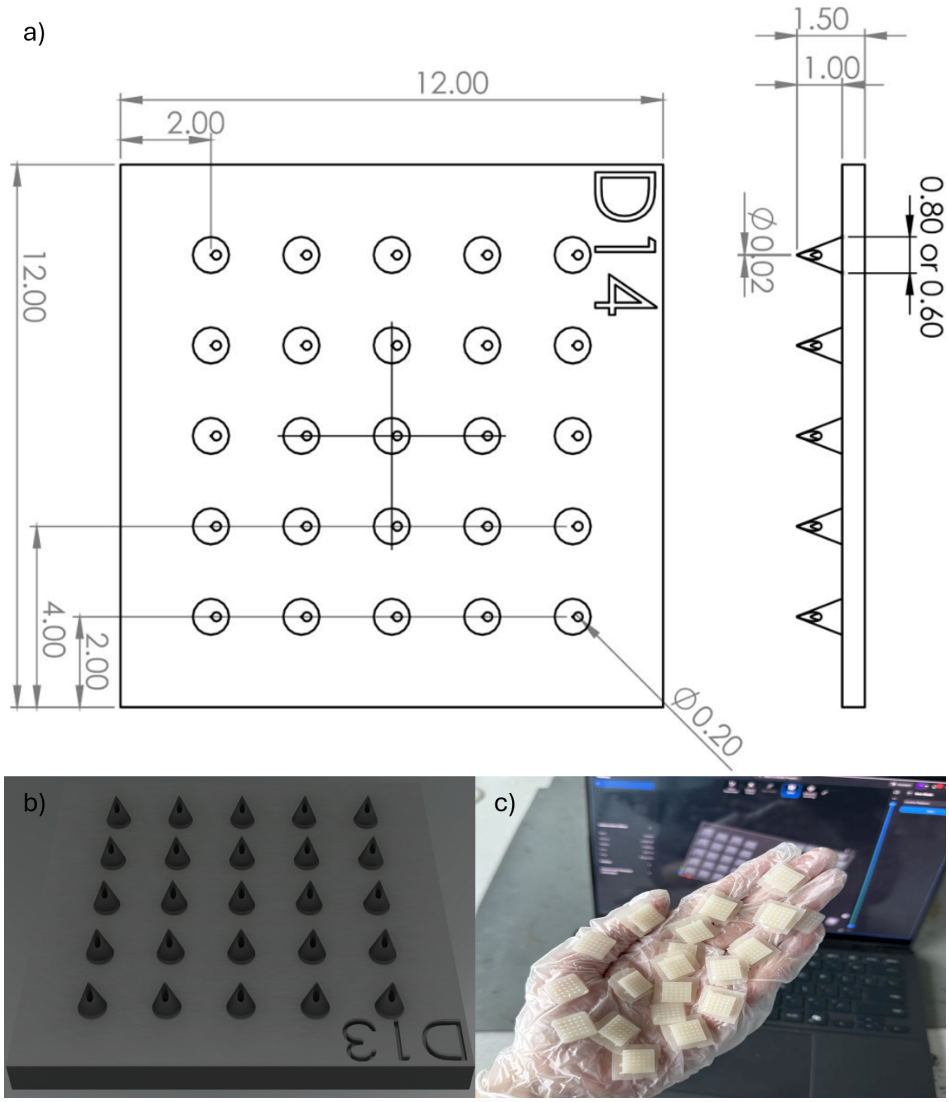


Figure 14: Hollow microneedle array used for ISF extraction. (a) Dimensional drawing of the hollow microneedle array, adapted from the design described by Parrilla et al., 2024. (b) CAD model used to verify the microneedle layout and hollow-channel geometry before fabrication. (c) Fabricated microneedle arrays after vat photopolymerization (VP).

C PCB Schematic

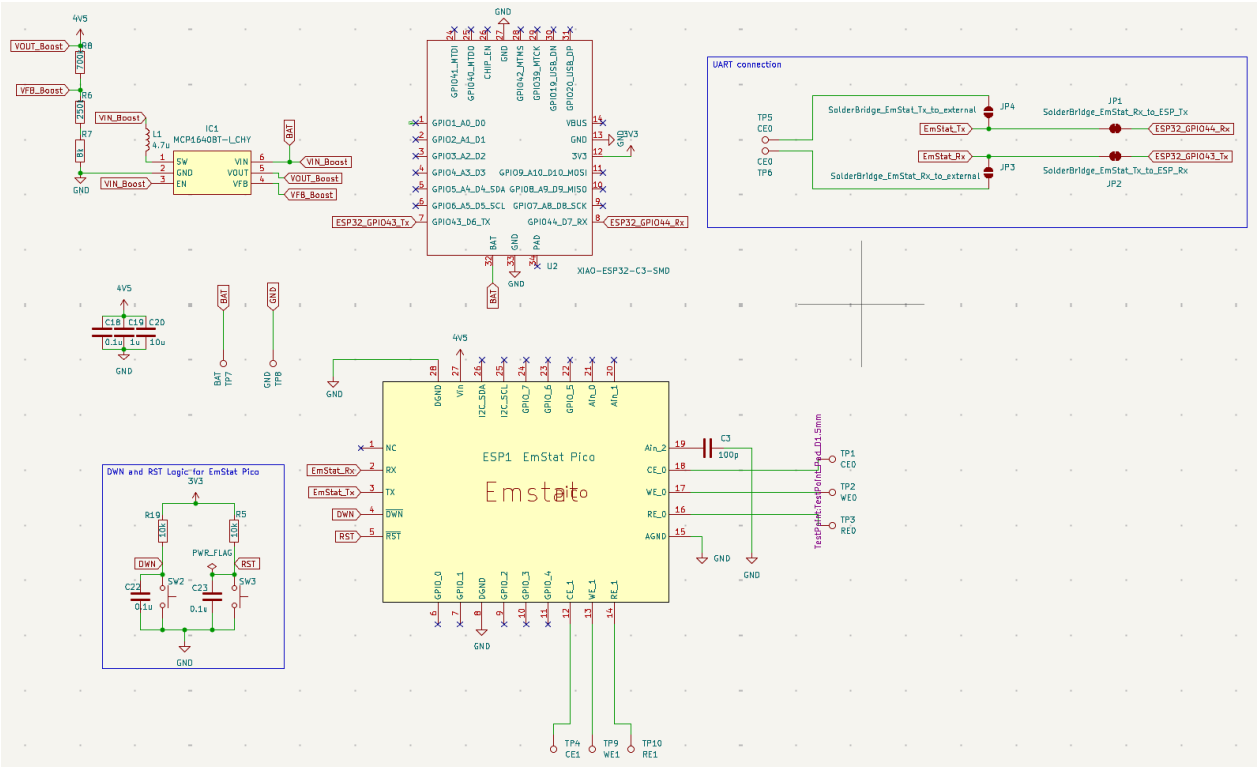


Figure 15: Schematic of the custom PCB used in the reusable readout device.

D Interview Summaries

Name	Stakeholder Type/ Role	Interview date	Main insights/hypothesis
Rick Helmich	Medical Specialist/ Neurologist	April 2nd 2026	Sensor usefulness likely depends strongly on disease stage. Early-stage Parkinson's patients may show poor correlation between blood levodopa and symptoms because dopamine is still buffered in remaining neurons. Later-stage patients with fluctuations may benefit most. Fast measurements (<5 min) are essential. A future closed-loop levodopa delivery system may be clinically valuable. Dopamine agonists are an important confounder because they influence symptoms without being measured by the sensor.

Name	Stakeholder Type/ Role	Interview date	Main insights/hypothesis
Michel van Putten	Medical Specialist/ Neurologist	Not stated	Continuous monitoring may improve levodopa titration, especially when combined with movement data. However, the relationship between interstitial levodopa concentration and clinical symptoms remains unclear and may involve delays or conversion factors. Combining biosensor data with movement metrics (e.g., gyroscope, gait analysis) could provide more clinically useful insights than concentration alone. Compliance and usability are critical: devices must be minimally intrusive, automated, and require little active input from patients. AI-assisted pattern recognition may help personalize dosing schedules.
Martin Sienstra	Business Specialist /Entrepreneurship Expert	Not stated	Need to validate value proposition early with patients. Important to test app concepts and user needs directly with patients. Clinical proof and doctor support are essential before insurers will be interested. Simplicity and usability are very important for Parkinson's patients.
Mark Janssen	Medical Specialist/ Neurologist	March 20th 2026	Continuous levodopa monitoring combined with symptom logging could provide valuable insight for neurologists and patients. System may work best initially as temporary diagnostic optimization tool (e.g. 1 month use) rather than permanent wearable. Strong potential in combining levodopa levels with non-motor symptoms such as sleep and autonomic dysfunction.
Marjolein Brusse-Keizer	Medical professional/ Epidemiologist	April 8th 2026	Monitoring may be useful in both early and late Parkinson stages, but for different reasons: early stage for medication titration and insight, later stage for managing fluctuations. Monitoring should probably come before automatic treatment/pump coupling. Reliability and handling of missing data are critical.
Martijn Beudel	Medical Specialist/ Neurologist	March 20th 2026	Continuous monitoring + personalized microdosing may work better than current generic tablet dosing. Physicians would mainly benefit from linking how the patient feels to levodopa values. Device safety is essential because of MDR regulations.
Dr. Griens	Medical Specialist/ Neurologist	January 30th 2026	A levodopa biosensor appears most clinically relevant for more advanced Parkinson's patients whose symptoms become limiting and whose levodopa response is less predictable. The strongest use case is not early-stage treatment, but detecting declining blood concentration patterns, identifying suboptimal medication strategies, and supporting earlier decisions about advanced therapies such as DBS or pump therapy.
Rob de Bie	Medical Specialist/ Neurologist	April 1st 2026	Main potential value of a levodopa biosensor may be prediction of OFF periods and optimization of medication timing. Relationship between levodopa blood levels and dopamine in the brain is still uncertain and needs validation. Continuous monitoring may be especially useful for patients with unexplained lack of medication effect (e.g., gastroparesis) or patients with severe fluctuations. Feedback-loop systems with levodopa pumps could become interesting in the future.

Name	Stakeholder Type/ Role	Interview date	Main insights/hypothesis
Anne van der Plas	Medical Specialist/ Neurologist	25th March 2026	ISF levodopa/metabolite monitoring could provide major clinical value, especially for detecting malabsorption, optimizing medication, understanding non-motor fluctuations, and supporting diagnosis. Combining ISF measurements with wearables and other biomarkers may provide a much more complete picture than current approaches. Non-motor symptoms may correlate strongly with levodopa fluctuations but are currently very difficult to assess objectively.
Carli and Amy	Medical Specialists/ Deep Brain Stimulation Nurse & Technical Medicine	March 30th 2026	Joy van Meurs (Anna Hospital Geldrop), neurologists, Parkinson nurse specialists.
Mark Kuijf	Medical Specialist/ Neurologist	April 1st 2026	Continuous levodopa monitoring could be especially valuable during fluctuating disease stages and advanced therapies. Combining levodopa levels with movement sensors and patient diaries may provide a much clearer clinical picture than current approaches. Clinical usefulness depends on validating correlations between measurements and patient response.
Annemieke Schipper	Medical Specialist/ Nurse specialist	April 16th 2026	Continuous levodopa monitoring could strongly improve personalized treatment, especially in later disease stages with fluctuations. Measuring levodopa may be more realistic than measuring dopamine directly because dopamine cannot be directly measured in the brain due to the blood-brain barrier. Device usefulness depends not only on measurement, but also on providing actionable interpretation/advice.
WRP 1	End user/ Parkinson patient	Not stated	Medication timing and memory problems create a large daily burden for this patient. Continuous monitoring may especially help patients with cognitive symptoms or medication uncertainty. Real-time levodopa insight may improve confidence, self-management, and treatment personalization.
WRP 2	End user/ Parkinson patient	Not stated	Medication timing and variable levodopa effect create a daily planning burden, even for a patient who feels relatively in control. Continuous levodopa monitoring may be more compelling if positioned as helping doctors tailor treatment and helping patients understand variable medication effect, especially around food/protein timing. Patient interest depends strongly on reliability, comfort, size, and whether the device clearly adds value beyond current self-management.
WRP 3	End user/ Parkinson patient	March 24th 2026	Strong validation that levodopa timing is clinically and personally important but difficult to optimize with current self-reporting and movement-based tools alone. Continuous biochemical levodopa monitoring combined with symptom tracking could help distinguish underdosing, overdosing, and disease progression. A longer-term dataset could be more useful for clinicians than short consultations, especially for personalized dosing and quality-of-life improvement.

Name	Stakeholder Type/ Role	Interview date	Main insights/hypothesis
WRP 4	End user/ Parkinson patient	March 30th 2026	Very short interview. It suggests that this patient still uses levodopa multiple times per day after DBS and experiences day-to-day symptom variability, but there is not enough information about medication timing burden, monitoring interest, wearable preferences, or reimbursement.
WRP 5	End user/ Parkinson patient	March 30th 2026	This interview suggests that for this patient, fall risk and mobility problems are more salient than levodopa-level curiosity. Continuous monitoring may be more compelling if connected to practical outcomes such as fall prediction or understanding when symptoms worsen, rather than only showing levodopa concentration.
WRP 6	End user/ Parkinson patient	March 30th 2026	Very short interview. It confirms that this patient uses levodopa frequently and that levodopa is perceived as helpful, especially for tremor, but there is not enough evidence about monitoring needs, timing burden, symptom tracking, or wearable preferences.
WRP 7	End user/ Parkinson patient	March 30th 2026	This patient validates food/activity effects and the importance of continuous medication routines, but does not personally see strong value in a levodopa-monitoring device while medication feels manageable. The value proposition may need to target patients with more uncertainty or stronger fluctuations.
WRP 8	End user/ Parkinson patient	March 30th 2026	This interview suggests that pill burden and remaining symptoms can be frustrating even when timing deviations do not seem to affect the patient much. The patient did not express a strong personal need for levodopa monitoring, but openness may depend on whether the device clearly works and reduces burden.
WRP 9	End user/ Parkinson patient	March 30th 2026	Very short interview. It strongly indicates high medication burden and possible symptom fluctuation, but does not provide enough information about timing problems, monitoring interest, tracking, clinician follow-up, or wearable preferences.
WRP 10	End user/ Parkinson patient	March 30th 2026	This interview shows that monitoring may be less relevant after successful DBS but potentially valuable before advanced interventions, when medication timing is strict, tremor returns quickly, and higher doses are constrained by side effects. It also supports the idea that late-stage or fluctuating patients may benefit more than patients who are stabilized after surgery.
WRP 11	End user/ Parkinson patient	Not stated	This interview suggests that objective monitoring may need to capture context such as exercise, anxiety/stress, and comorbid conditions, because symptoms may not be caused only by levodopa level. The patient's lack of symptom improvement despite increased medication raises the importance of distinguishing medication-related symptoms from other causes.

Name	Stakeholder Type/ Role	Interview date	Main insights/hypothesis
WRP 12	End user	Not stated	This interview does not validate levodopa-monitoring demand directly, because the patient is not reported as taking levodopa and does not experience daily fluctuations. However, it suggests that objective data and clearer explanations could reduce uncertainty for newly diagnosed patients and caregivers.
WRP 13	End user	Not stated	This interview supports the need for low-burden monitoring because the patient experiences strong fluctuations but is unwilling to manually log unless the benefit is very clear. Mood, stress, and activity may need to be considered alongside medication data.
WRP 14 + spouse/caregiver	End user	May 20th 2026	Patients experience uncertainty about levodopa effectiveness and would value objective continuous monitoring. Real-time alerts may be more useful than retrospective data summaries. Users prefer numerical values with thresholds rather than simple red/green indicators. Contextual factors such as meals should be incorporated into interpretation of sensor data.
WRP 15 + spouse/caregiver	End user + caregiver	May 20th 2026	This patient has developed effective self-management strategies and experiences relatively little burden from medication management. Unlike other interviewees, he does not perceive a strong personal need for continuous levodopa monitoring. However, activity-dependent fluctuations suggest objective monitoring could still provide clinically useful information for treatment optimization.
WRP 16 + spouse/caregiver	End user + caregiver	Not stated	The patient can recognize when medication is wearing off but relies entirely on subjective sensations. Caregiver does not easily recognize these fluctuations. This suggests potential value for objective monitoring, particularly because symptoms are not always visible to others.

E Interview Questionnaires: Initial Version

1. What are the main limitations you observe in current levodopa therapy in daily clinical practice? Which of these limitations have the biggest impact on patient quality of life?
2. In your opinion, where could continuous monitoring add value compared to current symptom-based management?
3. In which patient profiles would a wearable be most useful (e.g. early-stage, advanced-stage, fluctuating patients)?
4. From a clinical or regulatory perspective, what do you think is currently missing for levodopa biosensors to be adopted in practice? What data would practitioners benefit most from receiving from the wearable?
5. What level of accuracy or reliability would you consider clinically useful?

6. How can a wearable improve the daily life of a patient?
7. Do you think the main barriers are technical, clinical, regulatory, or economic?
8. How do you currently assess levodopa exposure or effectiveness in patients?
9. What are the limitations of these methods?

Patient Interview Questionnaire

Block 1: Medication and Follow-up

1. Do you take levodopa? How often do you take levodopa?
2. Are your symptoms predictable during the day?
3. How easy or difficult is it to know when your medication is working? Do you experience on/off periods?
4. How does taking levodopa too early or too late affect your day?
5. What happens when you take too much or too little levodopa? Have you ever taken a dose "just in case" because you weren't sure?
6. What's the most frustrating part about managing your medication timing?
7. Do you track your symptoms or medication in any way (notes, apps, diaries)?
8. Have doctors ever taken blood or other samples to adjust your levodopa treatment?
9. How did you feel about that process (comfort, stress, inconvenience)?
10. How often do you see your neurologist or Parkinson's specialist?
11. Do medication changes often happen during follow-ups? Do they help?

Block 2: Wearable Device

12. Would you be interested in a device that continuously monitors your levodopa levels? Why or why not?
13. Would knowing your medication levels help you feel more in control?
14. Do you think it could help your doctor adjust your treatment better?
15. What would make a wearable device comfortable enough for you to use every day?
16. Where on the body would it feel acceptable to wear it?
17. How often would you be willing to charge it?
18. What would make you stop using it?
19. Would you expect something like this to be paid for by insurance, healthcare system, or personally?
20. What price range would feel acceptable to you?

Closing Questions

- Is there anything else you would like to add?
- Do you know anyone else who may be interested in participating?
- May we contact you again if we have additional questions?

F Interview Questionnaires: First Iteration

Specialist Interview Questionnaire

1. What are the main limitations you observe in current levodopa therapy in daily clinical practice? Which of these limitations have the biggest impact on patient quality of life?
2. Does continuous monitoring add value?
3. Assuming continuous monitoring is used, where would this add the most benefit for:
    - practitioners?
    - patients?
4. What form of wearable solution would patients prefer? Should it be a dedicated wearable, or integration into devices they already use, such as smartwatches?
5. Is a wearable even a solution we should consider?
6. What are the key UI/UX requirements from the patient perspective?
7. How should wearable data be integrated into clinical workflows and existing systems?
8. What data would practitioners benefit most from receiving from the wearable?
9. From a clinical or regulatory perspective, what do you think is currently missing for levodopa biosensors to be adopted in practice?
10. What minimum accuracy threshold (%) would this wearable need to achieve for its measurements to be clinically relevant and usable in practice?
11. Which current problems in the daily lives of Parkinson's patients could be addressed by a wearable solution?
12. Which current problems that practitioners face could a wearable for Parkinson's patients address?
13. How should the most important of these barriers be reflected in the design requirements of a new device?
14. How do you currently assess levodopa exposure or effectiveness in patients?
15. What are the limitations of these methods?

Patient Interview Questionnaire

Block 1: Medication and Follow-up

1. Do you take levodopa? How often do you take levodopa?
2. Are your symptoms predictable during the day?
3. How easy or difficult is it to know when your medication is working? Do you experience on/off periods?
4. How does taking levodopa too early or too late affect your day?
5. What happens when you take too much or too little levodopa? Have you ever taken a dose "just in case" because you were not sure?
6. What is the most frustrating part about managing your medication timing?
7. What are the biggest challenges you experience with your current medication routine and symptom management?
8. Do you track your symptoms or medication in any way (e.g., notes, apps, diaries)?
9. Have doctors ever taken blood or other samples to adjust your levodopa treatment?
10. How did you experience that process (e.g., comfort, stress, inconvenience)?
11. How often do you see your neurologist or Parkinson's specialist?
12. Do medication changes often happen during follow-up appointments? If so, do they help?

Block 2: Wearable Device

13. Would you be interested in a device that continuously monitors your levodopa levels? Why or why not?
14. Would knowing your medication levels help you feel more in control?
15. Do you think it would help during consultations if your treatment data, such as medication intake and symptoms, were presented in a graph?
16. What would make a wearable device comfortable enough for you to use every day?
17. Where on your body would it be acceptable to wear such a device?
18. When a prototype becomes available: what price range would you consider acceptable?

Closing Questions

- Is there anything else you would like to add?
- Do you know anyone else who may be interested in participating?
- May we contact you again if we have additional questions?

G Interview Questionnaires: Second Iteration

Specialist Interview Questionnaire

1. Clinical Decision-Making

1. In which clinical situations do you currently struggle to make treatment decisions due to a lack of objective data?
2. Can you describe a recent patient case where you were uncertain about how to adjust levodopa therapy? What information were you missing?

2. Value of Monitoring

3. At what stage of the disease would levodopa monitoring provide the most value?
4. What specific treatment decisions would change if you had access to continuous levodopa concentration data?

3. Target Patient Group

5. For which type of patients would you actively prescribe or recommend such a sensor?
6. For which patients would this **not** be useful?

4. Data and Interpretation

7. What type of data would be most useful for you?
    - Absolute values
    - Trends
    - Variability
    - Correlations with symptoms
    - Other
8. How would you ideally want this data to be presented?
    - Dashboard
    - Alerts
    - Summary reports before consultation
    - Other
9. What would be the ideal output from such a system?
    - Raw data
    - Treatment suggestions
    - Other

5. Correlation and Trust

10. How important is it to link levodopa levels to:
    - Symptoms
    - Movement data
    - Food intake

11. In which situations would you **not** trust the sensor data?

6. Accuracy and Clinical Thresholds

12. What matters more: absolute accuracy or reliable trends over time?
13. What level of measurement error would still be acceptable for clinical use?
14. Which types of measurement errors would be most problematic in clinical practice, and why (e.g., underestimation versus overestimation of levodopa levels)?
15. Would it be more harmful if the device systematically underestimates or overestimates levodopa levels? Why?
16. How critical is timing accuracy (e.g., detecting changes too early versus too late)?
17. What are the potential clinical consequences of incorrect readings (e.g., incorrect dosing, worsening symptoms, unnecessary interventions)?

7. Workflow Integration

18. At what point in your workflow would you use this data?
    - Before consultation
    - During clinical decision-making
    - Long-term follow-up
    - Other
19. How much time would you realistically be willing to spend interpreting these data?

8. Device Usage Model

20. Do you see this device primarily as:
    - A continuous monitoring tool (similar to glucose sensors)
    - A temporary diagnostic tool (e.g., 2–4 weeks to gain insight)

9. Adoption and Barriers

21. What would prevent you from using such a device in clinical practice?
22. What would need to be demonstrated before you would trust and adopt such a device?

10. Value and Reimbursement

23. Who do you think should pay for this type of device?
    - Hospital
    - Insurance
    - Patient
    - Other
24. In what way would this device create value in clinical practice?

11. Current Apps

25. Do you currently use any applications to support Parkinson's disease management?
26. If yes, which application(s) do you use?

Closing Questions

- Is there anything else you would like to add?
- Do you know anyone else who may be interested in participating?
- May we contact you again if we have additional questions?

Patient Interview Questionnaire

1. Real-Life Challenges

1. Can you describe a recent moment when your medication did not work as expected?
2. What did you do in that situation?

2. Decision-Making and Uncertainty

3. Do you ever adjust your medication timing, or do you always take it at fixed times?
4. If you adjust your medication timing:
   (a) How do you decide when to take your medication or adjust your timing?
   (b) How confident do you feel in those decisions (0–10)?
   (c) When do you feel most uncertain about your medication?

Note: If the participant always takes medication at fixed times, Questions 4–6 can be skipped.

3. Core Difficulties

7. What is currently the most difficult aspect of managing your Parkinson's disease?
   - Timing your medication
   - Knowing whether your medication is working
   - Adjusting your daily activities
   - Other

4. Value of a Monitoring Device

8. In which situations would a device that measures your levodopa levels be most helpful to you?
9. In which situations would such a device **not** be helpful?

5. Trade-Offs

10. What would be most important to you in such a device?
    - Comfort

- Accuracy
- Ease of use
- Other

11. What would be a dealbreaker for you?

6. Effort versus Benefit

12. How much daily effort would you be willing to invest for better medication control?
    - Charging the device
    - Wearing the device
    - Entering data
    - Other

7. Trust and Acceptance

13. In which situations would you **not** trust the advice or data provided by such a device?

8. Control versus Automation

14. Which type of system would you prefer?
    - A system that only shows your data
    - A system that provides treatment advice
    - A system that automatically adjusts treatment (potential future application)

9. Data Sharing

15. Who would you feel comfortable sharing your data with?
    - Doctor
    - Family
    - No one
    - Other

10. Adoption

16. What would convince you to start using such a device?
17. What would stop you from using it?

Closing Questions

- Is there anything else you would like to add?
- Do you know anyone else who may be interested in participating?
- May we contact you again if we have additional questions?

Caregiver Interview Questionnaire

*This interview guide was used for both formal caregivers (e.g., nurses and nurse specialists) and informal caregivers (e.g., family members). Questions marked with * were prioritized when interview time was limited. Questions marked with ** were prioritized when very limited time was available.*

1. Role in Care

* Can you describe your role in caring for the Parkinson's patient(s)? How involved are you in managing their medication?

1. On a typical day, what does medication management look like for you?
2. **Formal caregivers:** How many Parkinson's patients do you currently care for, and how much of your time is spent on levodopa-related issues?
3. **Informal caregivers:** How has your daily routine changed since taking on this caregiving role?

2. Medication Monitoring

** Can you describe a recent situation where you noticed that the patient's medication was not working as expected? What happened?

** How do you currently recognize when a patient's medication is working well versus when symptoms are breaking through? What signs do you usually look for?

* How difficult is it to distinguish medication side effects (e.g., dyskinesia) from symptoms caused by under-dosing?

1. **Informal caregivers:** Has your ability to recognize these signs changed over time? When and how did you learn what to look for?

3. Decision-Making

1. When something seems wrong, what do you do? Do you usually have the authority and/or confidence to act?

* Have you ever felt unsure whether to contact the neurologist or wait? What made that decision especially difficult?

* **Informal caregivers:** On a scale from 1–10, how confident do you feel in your own judgement when something seems wrong?

4. Emotional Burden

* What is the most stressful aspect of managing the patient's medication?

* **Formal caregivers:** How do you communicate a patient's medication status to the patient? How about to the doctor?

1. **Informal caregivers:** How does the unpredictability of good and difficult periods affect your own daily life?

5. Value of a Sensor

** In which situations would a device measuring levodopa levels be most useful to you?

1. Can you think of a specific situation in which having these data would have changed how you acted?

* In which situations would such a device **not** be helpful or even make decision-making more difficult?

6. Data and Interpretation

** What type of output would be most useful to you?

- Real-time alerts
- Daily summaries
- Trend graphs
- Other

** Would you prefer plain-language alerts over numerical data and graphs?

1. Would you prefer the system to suggest actions or automatically alert the doctor?
2. Do you think this device should integrate with existing healthcare systems, or would a standalone application be sufficient?

7. Trust and Control

* In which situations would you **not** use the device's data?

1. What could make you lose trust in the device?

** If the device indicated a problem but the patient appeared to be doing well, what would you do?

8. Effort and Adoption

1. How much daily effort would be acceptable for:
    - Charging the device
    - Wearing the device
    - Logging symptoms

* What would be a dealbreaker regarding the device or its accompanying application?

2. What would need to be demonstrated before you would feel confident using the device in practice? What levels of accuracy and reliability would be "good enough"?

* Who do you think should be responsible for paying for the device?

9. Data Sharing

* Who should have access to the monitoring data?
    - Patient
    - Doctor

- Caregiver
- Family
- Other

1. **Formal caregivers:** Are there any privacy concerns that would make you or the patient hesitant to use such a device?

* **Informal caregivers:** Would you prefer to see the same data as the patient, or a version specifically tailored for caregivers?

Closing Questions

- Is there anything else you would like to add?
- Do you know anyone else who may be interested in participating?
- May we contact you again if we have additional questions?

H Clinician Platform

The platform consists of four main pages: a dashboard, a patient overview page, a correlations page, and a prescription-management page. The dashboard provides a cohort-level overview of monitored patients, including synchronization status, alerts, recent symptoms, and quick access to individual patient records (Fig. 16a). This allows clinicians to identify patients who may need attention without manually checking each record.

The patient overview page provides a detailed view of an individual patient's monitoring session (Fig. 16b). It includes L-DOPA trend, medication events, PKG-derived motor summaries, sleep-related information, dyskinesia and bradykinesia patterns, tremor, immobility, and predose patterns. This page is intended to combine biochemical and movement-related information in one clinical view.

The correlations page focuses on interpretation of L-DOPA response in relation to food intake and motor symptoms (Fig. 16c). It includes an AI-generated summary, food/protein log and dose-response scores. This page was designed to help clinicians identify patterns such as delayed medication response, weaker response after high-protein meals, or worsening motor symptoms despite medication intake.

The prescription-management page allows the clinician to review the current levodopa protocol and prepare an updated medication schedule (Fig. 16d). The interface includes dose frequency, dose timing, dosage selection, notes, and a prescription preview. The intended workflow is that medication adjustments can be reviewed by the clinician and then synchronized to the patient's mobile application, updating reminders and dose timing.

Together, these pages demonstrate how the biosensor output could be integrated into a clinical decision-support workflow.

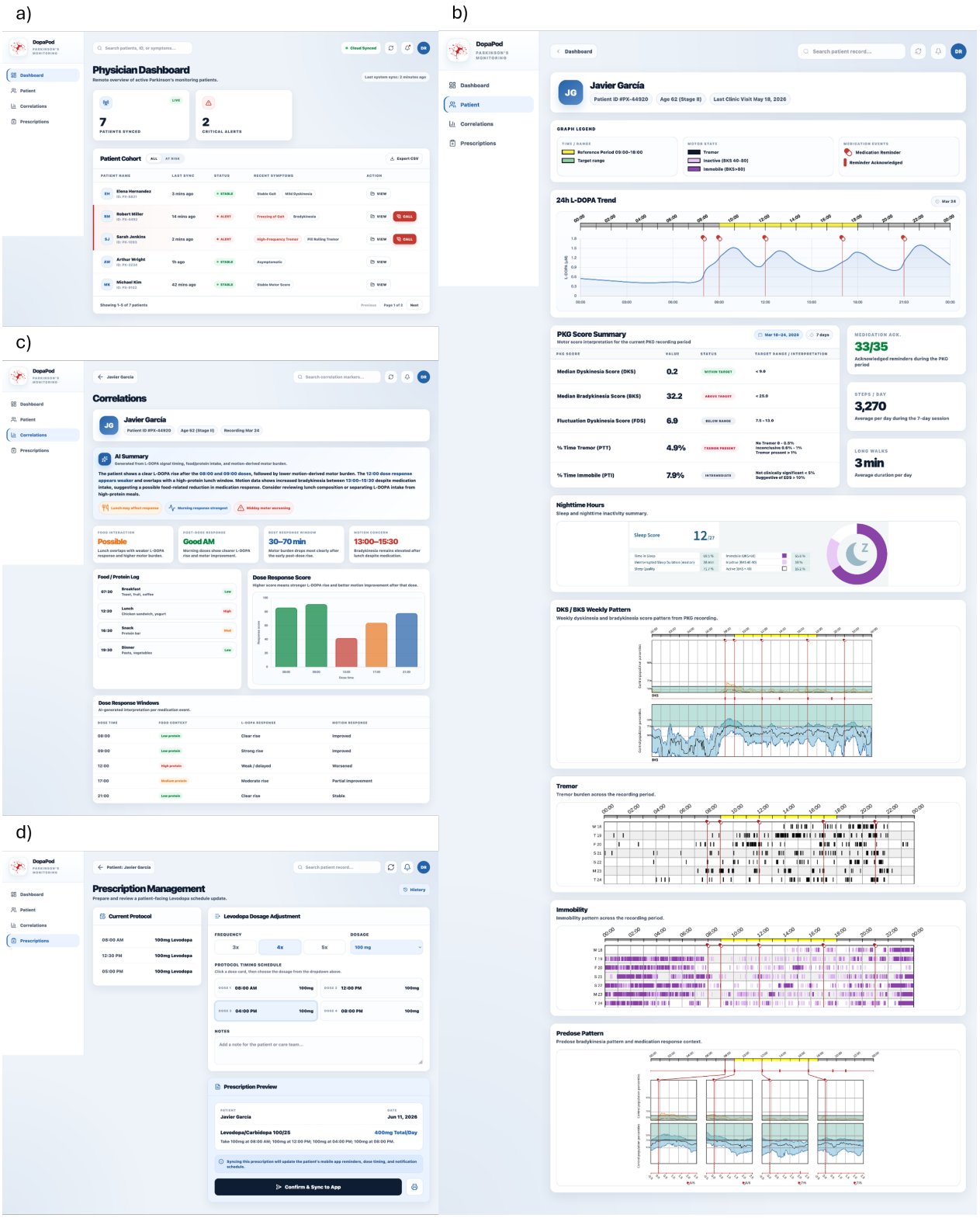


Figure 16: Clinician platform prototype. (a) Physician dashboard with cohort-level patient status and alerts. (b) Patient overview page with L-DOPA trends, medication events, and motor summaries. (c) Correlations page linking L-DOPA response with food/protein intake and motion-derived motor burden. (d) Prescription-management page for reviewing and synchronizing levodopa schedule updates.

I Inclusion and exclusion criteria for Validation Study

This is the established inclusion and exclusion criteria for participants in the validation study, which can be PD patients or neurologists. Each group follows a different criteria.

Patient criteria

Eligible patients must meet the following inclusion criteria:

- Diagnosed with Parkinson's disease in mid-stage progression and currently treated with levodopa
- Aged 18 years or older
- Able to understand the study procedures and provide written informed consent
- Able to wear the device and interact with the patient application

Patient participants will be excluded if:

- Are unable to provide informed consent due to cognitive impairment or other conditions affecting decision-making capacity
- Have a known allergy or sensitivity to the adhesive materials used in the wearable patch
- Have a physical, cognitive or other medical condition that prevents the safe and/or effective use of the wearable device and/or the application
- Are participating in another clinical study or receiving medication that may interfere with the objectives of the study

Neurologists criteria

Neurologists participating in the study must:

- Have a minimum of 5 years of relevant experience in the diagnosis and treatment of PD
- Be currently practicing at one of the participating study centres

J Market Sizing Using TAM-SAM-SOM

The purpose of the used TAM-SAM-SOM model was to identify the first clinically relevant target population for the proposed biosensor.

The TAM for this biosensor was defined as the Dutch Parkinson's patient population for whom levodopa monitoring could be clinically relevant. The estimate starts from approximately 63,000 people living with PD in the Netherlands (Simões et al., 2026). This number was further refined by using the reported levodopa-use percentage of 85.9% (Tolosa et al., 2021) and the proportion of patients in the second and third stages of the disease on the Hoehn and Yahr scale. These two stages were considered to represent the mid-stage population in which medication adjustment and motor fluctuations are especially relevant (Skorvanek et al., 2017).

Next, the SAM was obtained by narrowing the TAM to patients who specifically experience wearing-off, as this is the subgroup that is expected to have the strongest initial need for continuous levodopa monitoring. A reported wearing-off prevalence of 55.1% was used for this estimate (Wan et al., 2020).

Finally, the SOM was estimated using a phased hospital-based implementation model. A network of 57 Dutch Parkinson's treatment sites was identified and used as a practical representation for the specialist center rollout (Frequin et al., 2024). Dividing the previously obtained SAM over these sites gives an approximate 400 eligible patients per site. The 3-year and 5-year cases represent realistic cases that are not too conservative or optimistic. These cases assume adoption by a subset of treatment sites and use by 25% of all eligible patients at participating sites.

Table 7 shows a summary of the information provided above and Figure 17 shows a graphical summary of the projected figures.

Table 7: Market sizing assumptions and calculations for the Dutch implementation pathway.

Market layer	Definition	Calculation	Estimate
TAM	Dutch Parkinson's disease patients using levodopa and belonging to the clinically relevant mid-stage population.	63,000 PD patients × 85.9% levodopa use × 76.3% mid-stage PD	≈ 41,292 patients
SAM	Narrowed to patients experiencing wearing-off, since this group is expected to benefit most from objective levodopa trend monitoring.	41,292 × 55.1% wearing-off prevalence	≈ 22,752 patients
SOM, 3-year	Early hospital-based rollout through selected Parkinson's treatment sites in the Netherlands.	15 sites × 400 eligible patients/site × 25% adoption	≈ 1,500 patients
SOM, 5-year	Expanded hospital-based rollout through a larger group of Parkinson's treatment sites.	28 sites × 400 eligible patients/site × 25% adoption	≈ 2,800 patients

The used model should be interpreted as a strategic first-entry market estimate. The inputs come from a vast set of sources and were combined to approximate the clinically relevant Dutch target population, and thus, commercialization would require that the model be refined using clinical registry data and hospital-specific patient numbers. Additionally, it can be expanded through the consideration of pricing assumptions and willingness-to-adopt data.

K Stakeholder Adoption Barriers

The considered stakeholders were grouped according to their role in the translational pathway in order to support the implementation analysis in Section 3.3. This stakeholder map was then used to identify adoption barriers and possible mitigation strategies for each group.

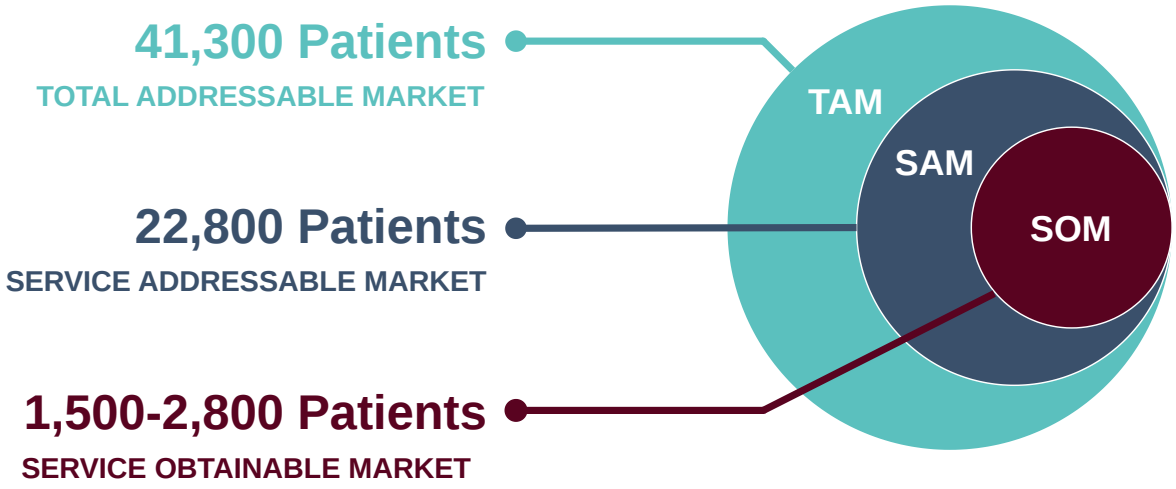


Figure 17: TAM-SAM-SOM Market Sizing Summary

Table 9: Stakeholder categories used for the implementation analysis.

Stakeholder category	Stakeholder type	Role in translation pathway
Direct stakeholders	Patients	Directly benefit from improved treatment monitoring and may use the device during daily life.
Direct stakeholders	Doctors and caregivers	Use the monitoring output to better understand patient status, symptom fluctuations, and treatment response.
Secondary stakeholders	Healthcare organizations	Need to implement the system into clinical infrastructure, workflows, and data-management procedures.
Secondary stakeholders	Insurance companies / payers	Need to evaluate reimbursement, cost-effectiveness, and payer responsibility.
Regulatory stakeholders	Dutch government / regulatory bodies	Responsible for requirements related to patient and device safety and data protection.
Development stakeholders	Device manufacturers	Responsible for scalable production, manufacturability, cost control, and long-term supply.

Dutch home-monitoring reimbursement examples suggest that monitoring equipment and apps may be reimbursed when they are part of hospital treatment for chronic disease management (VGZ, n.d.). Therefore, hospital-provided monitoring equipment appears more realistic than requiring patients to purchase the device themselves. For the smartwatch or movement-monitoring component, reimbursement is less straightforward if the device can also be used for non-medical purposes. A hospital-owned device, or a dedicated low-cost movement sensor justified as essential for clinical interpretation, may therefore be more feasible.

Table 11: Stakeholder-specific adoption barriers and mitigation strategies.

Stakeholder	Barrier	Mitigation
Patients	Discomfort, effort, low perceived benefit, unclear role in treatment.	Passive monitoring, minimal input, clear instructions, simple feedback on treatment relevance.
Doctors and caregivers	Irrelevant, unclear, or untrusted data; increased review workload.	Trends, correlations, concise summaries, confidence indicators, and clear output interpretation.
Healthcare organizations	Infrastructure integration, training needs, data-management responsibility, uncertain cost–benefit.	Workflow-compatible platform, staff training, standardized reports, and evidence on consultation quality and treatment optimization.
Insurance companies	Unclear reimbursement responsibility, uncertain cost-effectiveness, possible increase in healthcare use.	Hospital-led remote monitoring for selected patients, with evidence on efficient consultations and reduced trial-and-error treatment adjustment.
Regulatory bodies / government	Insufficient clinical evidence, device risks, and patient-data protection concerns.	Medical-device pathway, clinical validation, GDPR-compliant data handling, device safety and cybersecurity documentation.
Device manufacturers	Scaling difficulty or unjustifiable production cost.	Scalable production, replaceable components, simplified assembly, early manufacturability assessment.

This analysis shows that the translational potential of the sensor depends on more than its performance alone. The device must be comfortable and understandable for patients while being interpretable and trustworthy for clinicians. Additionally, it should be compatible with hospital infrastructure, acceptable for insurers, compliant with regulatory requirements, and manufacturable at scale.

L Clinical Workflow Integration

The workflow analysis focused on how the system output could support treatment decisions without creating additional burden for clinicians.

Table 13: System functions for clinical workflow integration.

System function	Clinical workflow role
Continuous levodopa monitoring	Tracks levodopa dynamics between consultations.
Medication intake logging	Links levodopa profiles to dosing times and missed or delayed medication effects.
Symptom and ON/OFF reporting	Relates biochemical data to patient-experienced response, wearing-off, and symptom fluctuations.
Food or protein intake logging	Supports interpretation of reduced or delayed levodopa response.
Movement data integration	Adds objective context on motor symptoms and tremor.
Actionable alerts	Flags clinically relevant patterns, such as wearing-off or delayed response, instead of generic alerts.
Pre-consultation summary	Summarizes trends and correlations before outpatient visits.
Clinician dashboard	Combines levodopa, medication, symptoms, food, and movement data for treatment adjustment.

The workflow integration analysis shows that successful implementation depends on converting continuous measurements into concise and actionable clinical insights. The platform should therefore combine levodopa values with external factors to allow clinicians to identify patterns that are difficult to observe during periodic consultations, such as wearing-off, delayed medication response, or correlations between food intake and symptom fluctuations.

To reduce adoption friction, the system should be integrated into existing hospital workflows where possible. Instead of requiring clinicians to review a separate stream of raw sensor data, the platform should provide summarized reports before or during consultations that match the structures and formats already in use. In this way, the biosensor can support personalized treatment decisions while minimizing additional load on healthcare providers.