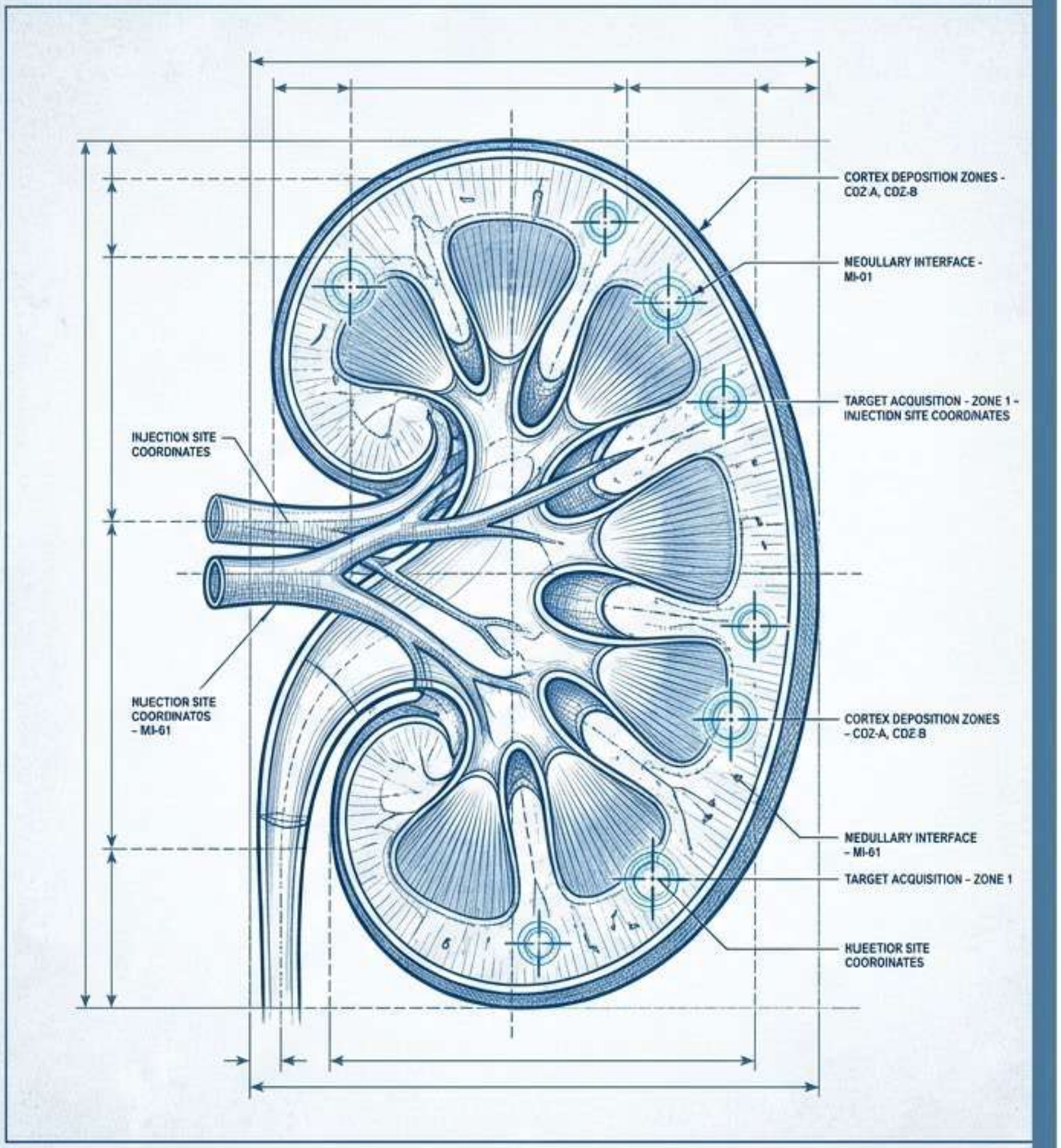


REACT: Phase 2 Clinical Protocol & Precision Delivery

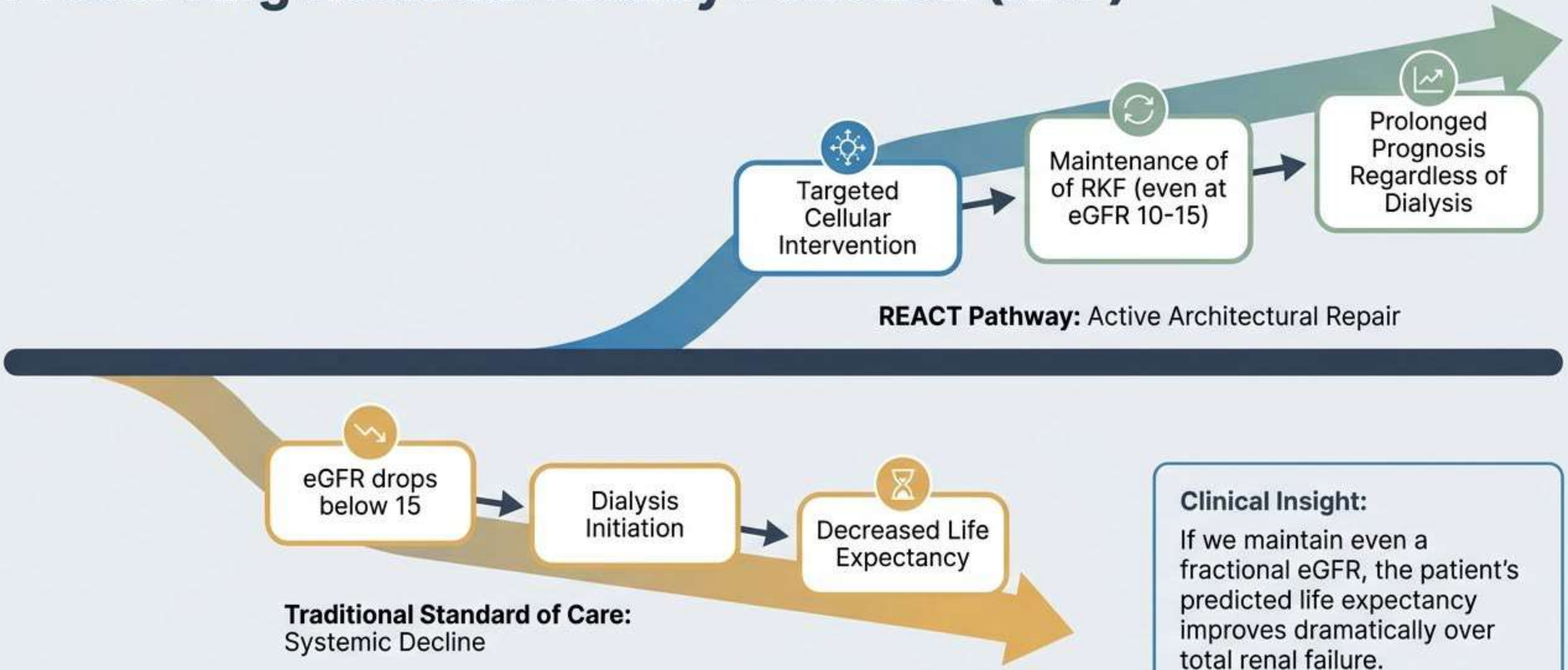
AUTOLOGOUS CELLULAR THERAPY FOR DIABETIC KIDNEY DISEASE

Executive Summary

- **Therapeutic Target:** Type 2 Diabetic Kidney Disease (DKD), addressing the largest patient demographic facing renal failure.
- **Mechanism:** Autologous cellular reinjection targeting the renal cortex to regenerate tissue architecture.
- **Delivery Innovation:** Shifts from blind/endoscopic surgical methods to percutaneous, real-time CT-guided multi-site deposition.

CLINICAL DOSSIER

Shifting the Clinical Paradigm: Preserving Residual Kidney Function (RKF)

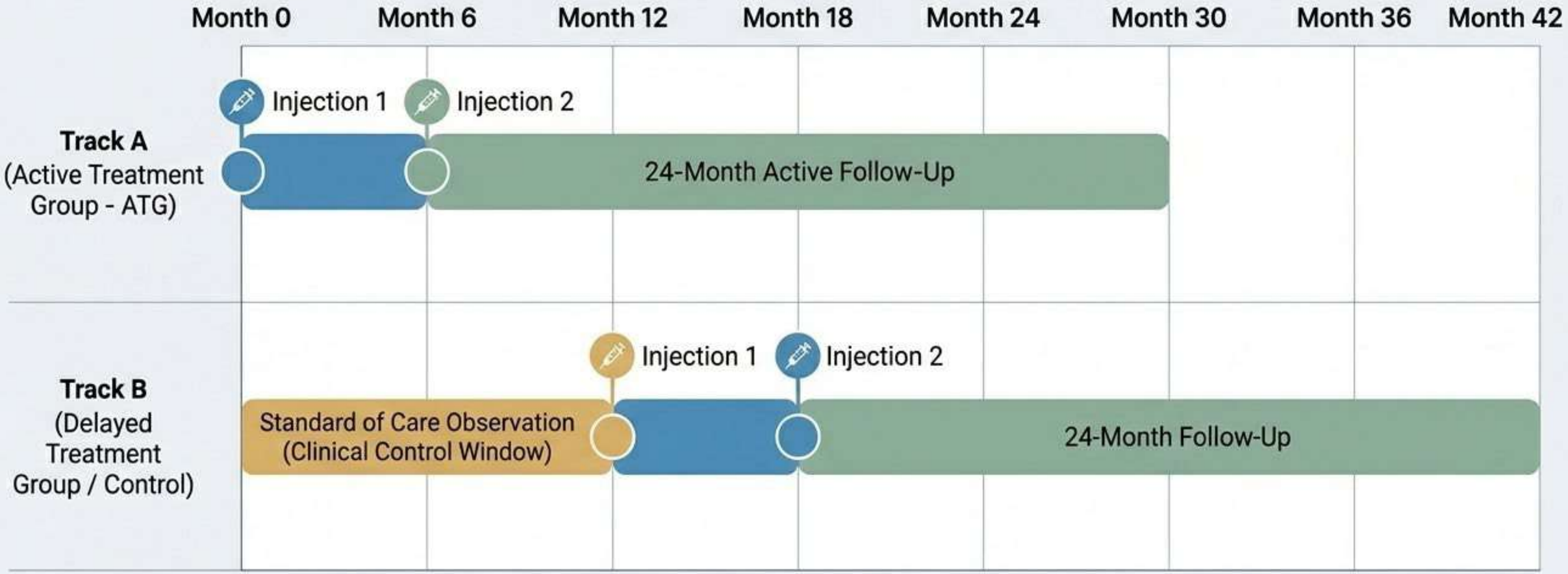


Clinical Insight:

If we maintain even a fractional eGFR, the patient's predicted life expectancy improves dramatically over total renal failure.

CLINICAL DOSSIER

REACT Phase 2 Trial Architecture: Prospective & Multi-Center



Note: Open-label design utilizing blood and urine markers throughout the Standard of Care window as direct comparative controls.

CLINICAL DOSSIER

Patient Qualification Diagnostic Matrix

Inclusion Criteria

- – Age 30–80 with confirmed Type 2 Diabetes.
- – eGFR strictly between 20–50 (CKD Stages 3a–4).
- – HbA1c < 10.
- – Stable blood pressure & stable ACE inhibitor/ARB dosage (>8 weeks).
- – Two prior eGFR/creatinine tests (3–18 months apart) to establish progression baseline.

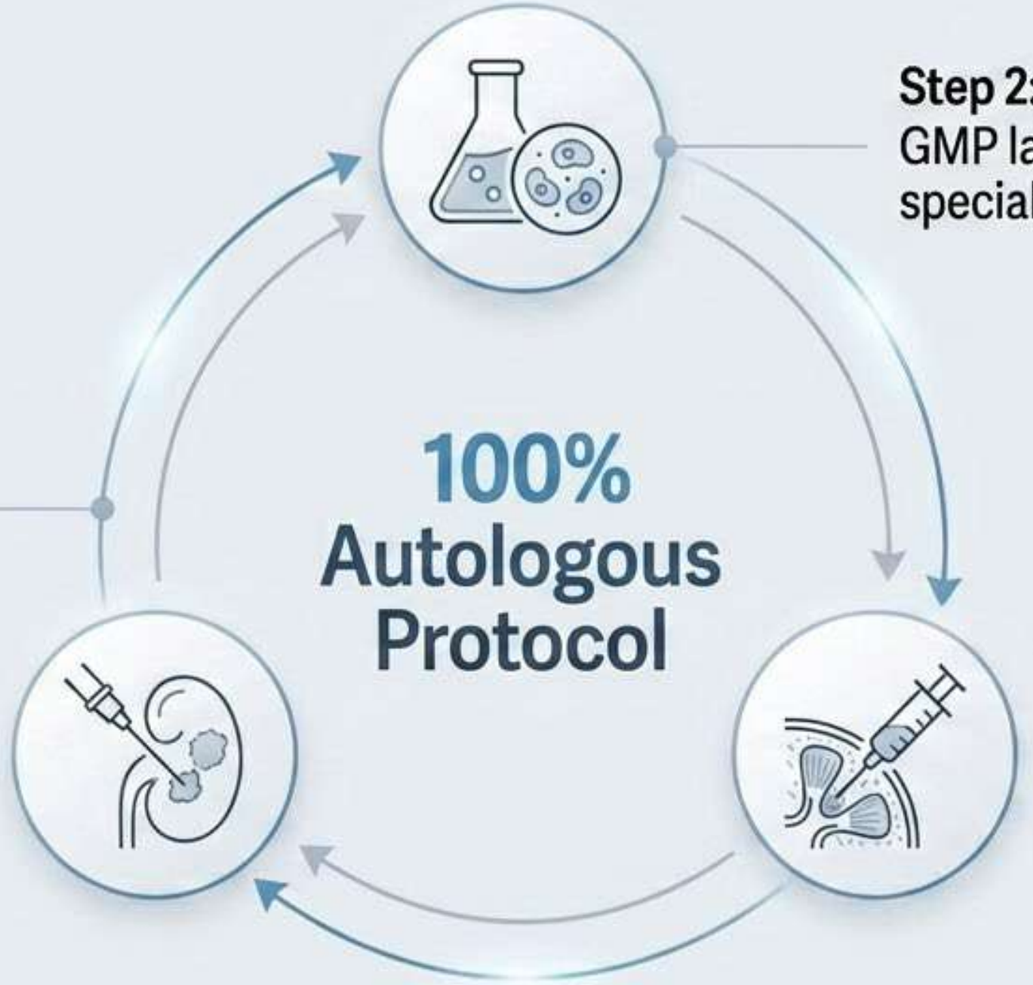
Exclusion Criteria

- – Prior kidney transplant or single functioning kidney.
- – Anatomical barriers: BMI > 45, excessive renal fat, or kidney size < 9cm.
- – Bleeding risk: Active anticoagulant use (e.g., Warfarin).
- – Comorbidities: Active cancer (past 3 years), severs, severe liver disease (ALT/AST >3x), HBV/HCV/HIV, or recent acute kidney injury.

CLINICAL DOSSIER

The Autologous Loop: From Extraction to Deposition

Step 1: Tissue Extraction (Biopsy).
Percutaneous CT-guided harvest of native renal tissue.

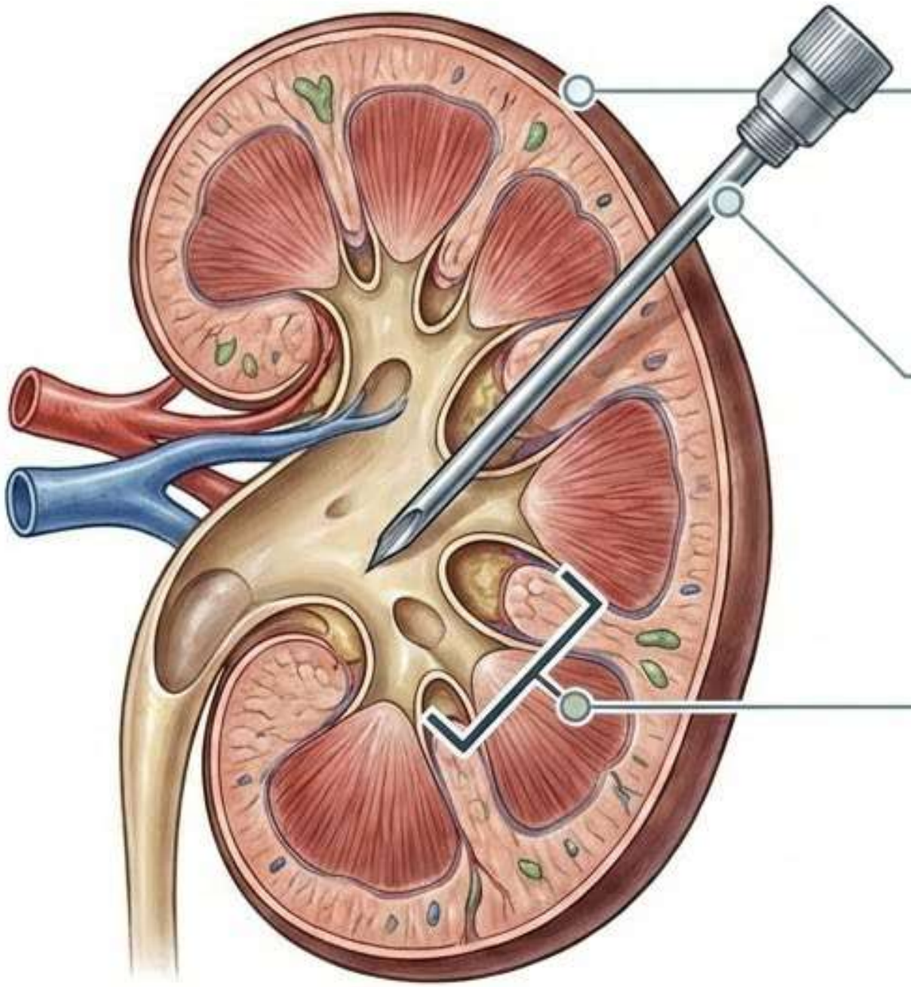


Step 2: Cellular Processing.
GMP laboratory expansion and specialized subpopulation selection.

Step 3: Targeted Reinjection.
Individualized dosing delivered directly back into the native renal cortex.

CLINICAL DOSSIER

Step 1: Precision Tissue Extraction



Guidance: Real-time CT / Imaging Monitored.

Instrumentation: Utilizes 2x 16G needles OR 4x 18G needles.

Depth Marker: Minimum 1.5cm to 1.8cm depth penetration required to secure viable functional tissue.

Immediate Protocol

Immediate stabilization required. Extracted core is transferred directly into transport media for secure shipping to the GMP expansion facility.

CLINICAL DOSSIER

Step 2: Cellular Processing & Selection

A. Enzymatic Digestion
Breakdown of native tissue biopsy.

↓

B. Cellular Expansion
Strict 6-week cultivation cycle.

↓

C. Density Gradient Centrifugation
Selection of specific, viable cellular subpopulations critical for regeneration.

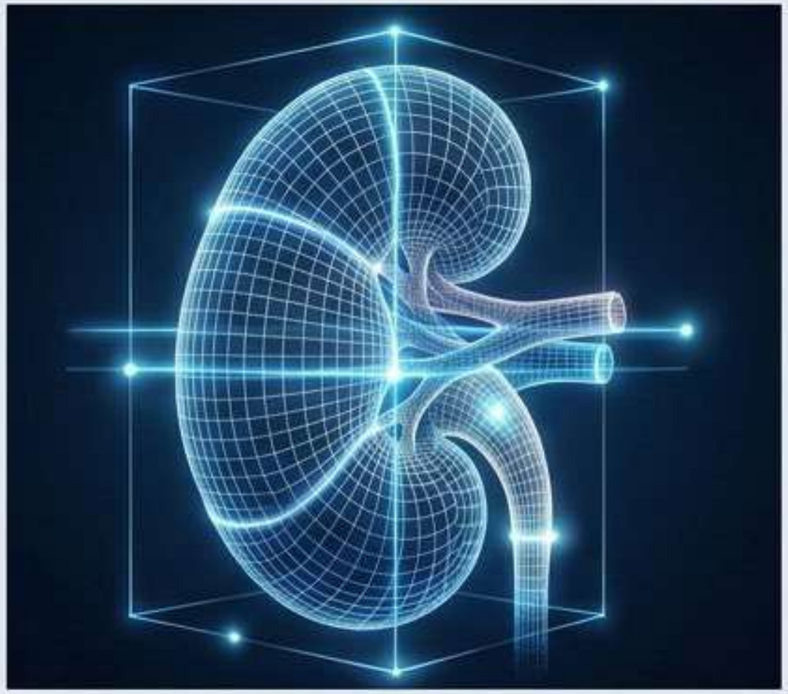
↓

D. Formulation
Integration into a gelatin-based hydrogel matrix.

Critical Protocol: **Strict 72-Hour Clinical Administration Window post-formulation.**

CLINICAL DOSSIER

Step 3: Individualized Dosing Strategy



Organ Mass Baseline
(Determined via MRI Volumetric Image Analysis)

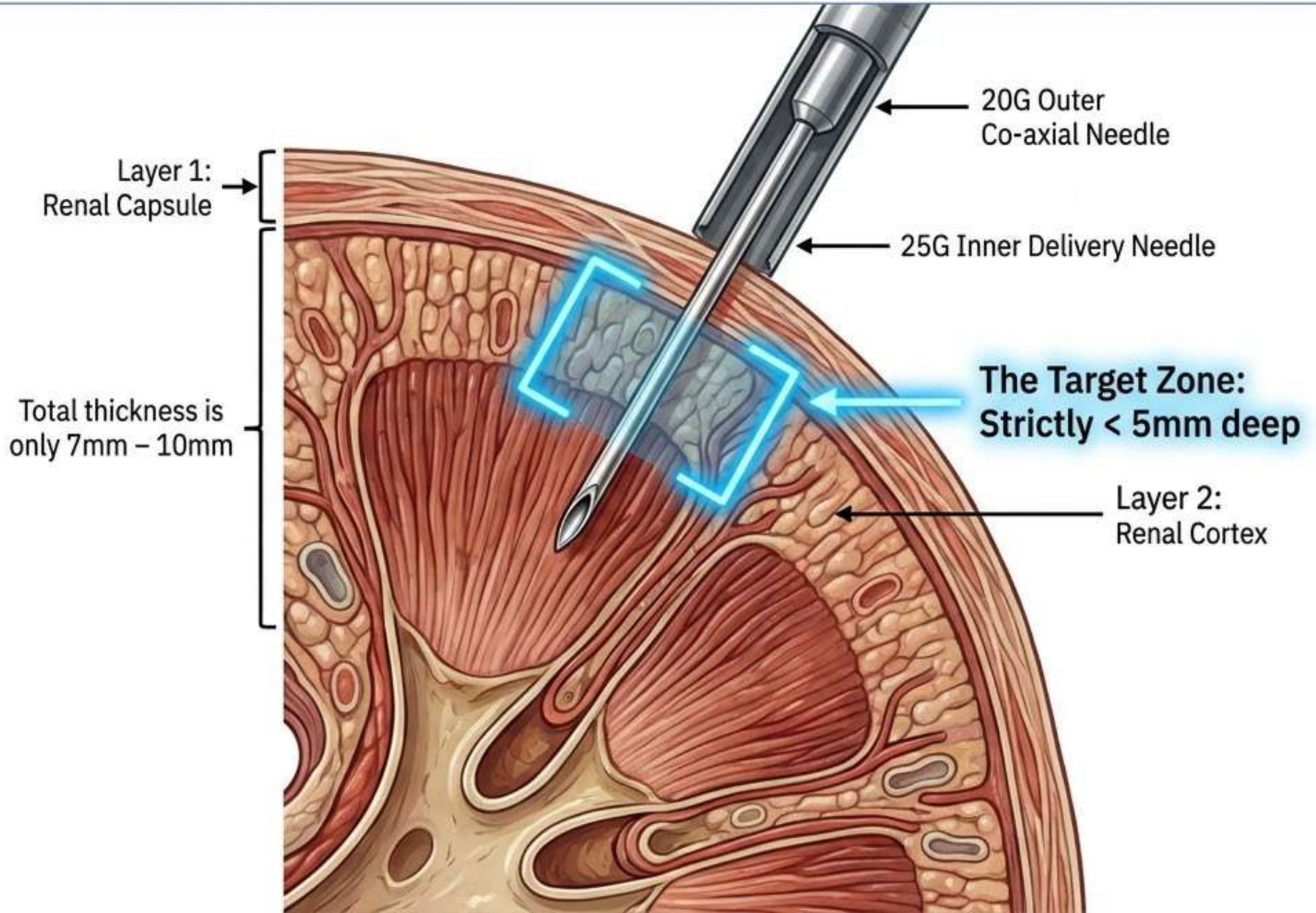
- Male Average: 120g – 170g
- Female Average: 115g – 155g

INDIVIDUALIZED DOSING FORMULA

Volume/ Mass of Kidney × **Targeted Cells per gram** (3×10^6) = **Individualized Syringe Dose**

Insight: Every patient receives a unique cellular volume, mathematically derived before the reinjection protocol begins. This is a personalized biological intervention, not a standardized drug.

The Technical Bottleneck: Renal Cortex Anatomy

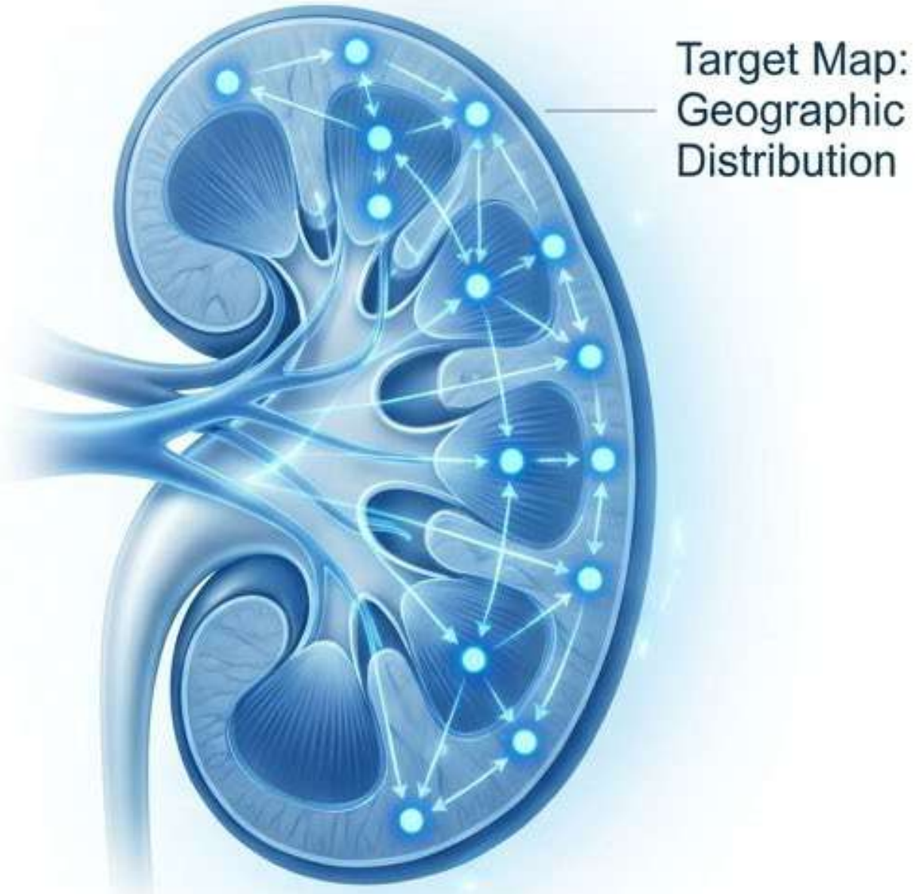


Procedural Reality

The target zone is sub-centimeter.

The outer needle acts as a sheath, while the 25G inner needle must precisely deposit the cells within the fragile interstitial space of the cortex without causing structural damage.

Strategy: Maximized Deposition & Microenvironments



Mechanism Summary

The total calculated cell volume is never delivered as a single bolus.

- Cells are distributed across **multiple mathematically** calculated injection points.
- Ensures delivery to **diverse microenvironments** within the damaged cortex to maximize regenerative signaling.
- Outer needle is **retracted incrementally** (**pull-and-inject method**) to distribute cells safely without pressure blowout.

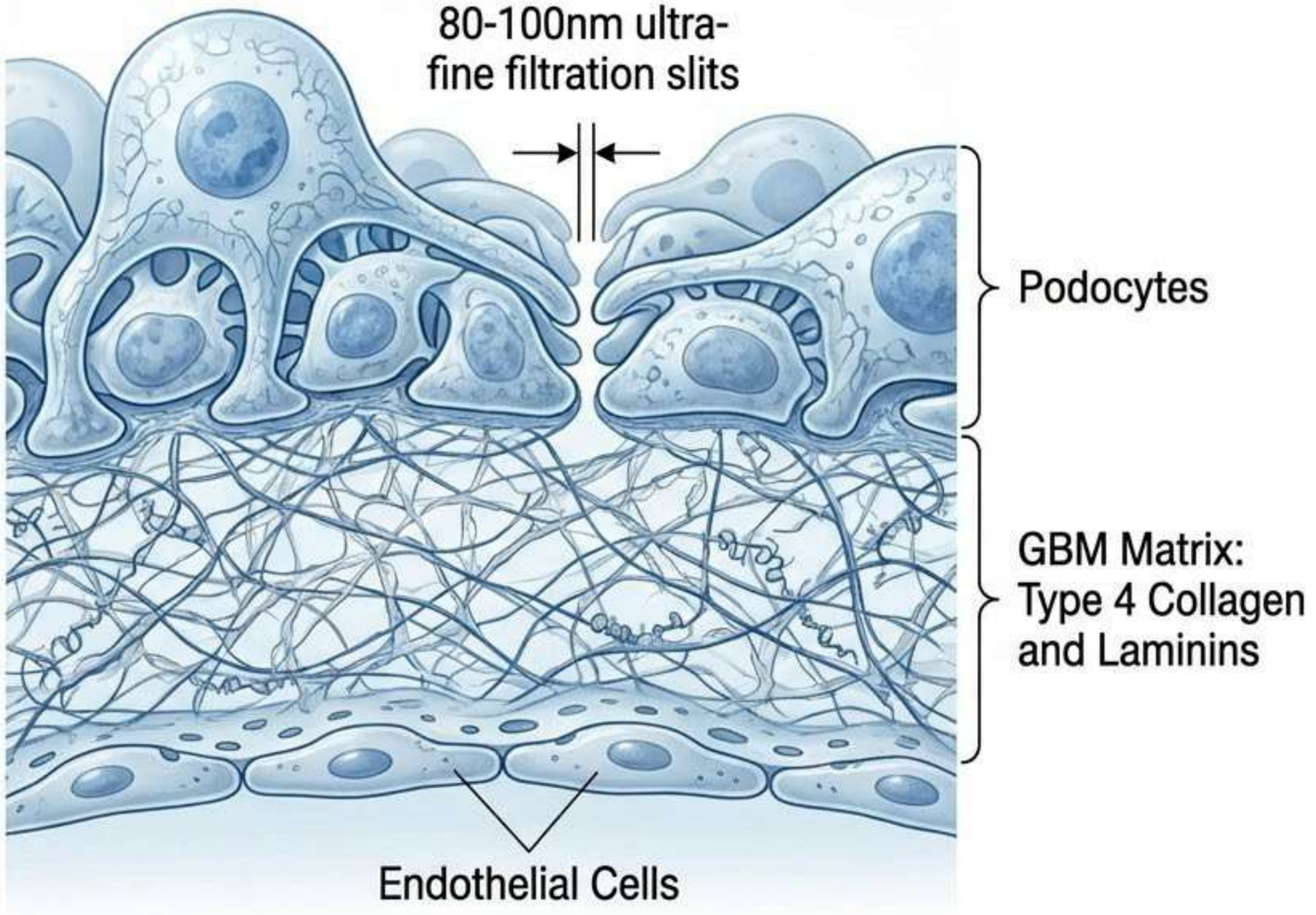
Protocol Mandate:
Requires continuous, real-time CT monitoring to verify spatial distribution during the procedure.

Post-Procedural Care & Longitudinal Monitoring

Acute Local Care (Immediate to 24 Hours)	
✓	Blood and urine clinical baseline assessments.
✓	Immediate Renal Ultrasound (specifically monitoring for procedural complications such as renal hematoma).
✓	Strict 24-hour observation period.

Efficacy Tracking (24 Months)	
✓	Routine serum creatinine level tracking.
✓	Continuous eGFR measurements taken at strict 3-month intervals.
✓	Direct longitudinal comparative analysis against the patient's Day 0 baseline and the Track B Standard of Care cohort.

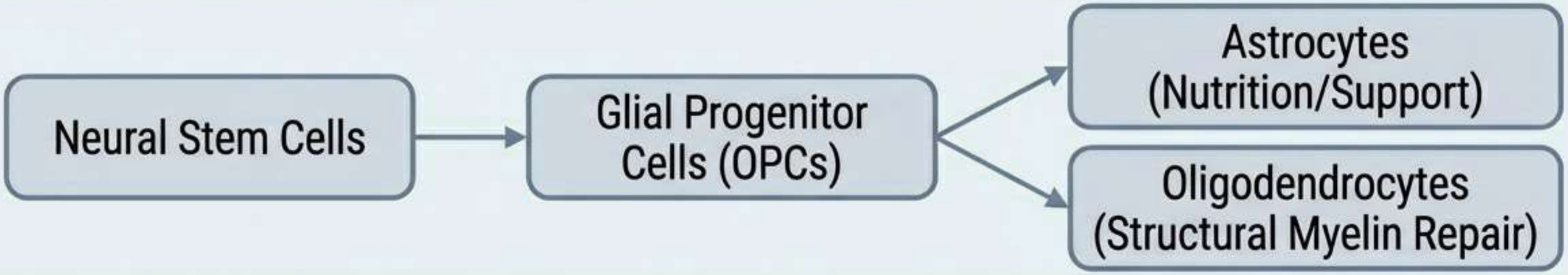
Biological Context I: The Filtration Barrier (GBM)



Physiological Mechanism
This non-dense, highly specialized porous barrier dictates eGFR.
Systemic plasma is filtered through the collagen matrix and podocyte slits, making **structural architectural integrity critical to preserving renal function.**

Biological Context II: Progenitor Cell Differentiation

The Biological Model (Neural Context)



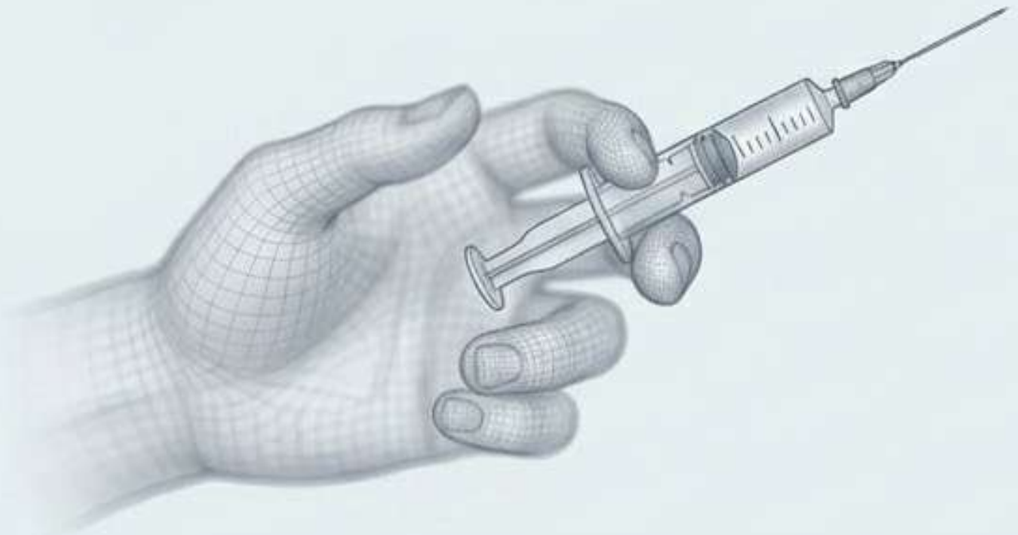
The Clinical Application (Renal Cortex Context)

Mechanism of Action

Just as neural OPCs differentiate based on local chemical markers to repair specific nervous system gaps, the density-gradient selected cells injected into the kidney cortex contain **highly specialized** subpopulations. Once deposited into the interstitial space, they respond to local microenvironmental signals, differentiating to repair specific damaged filtration architecture.

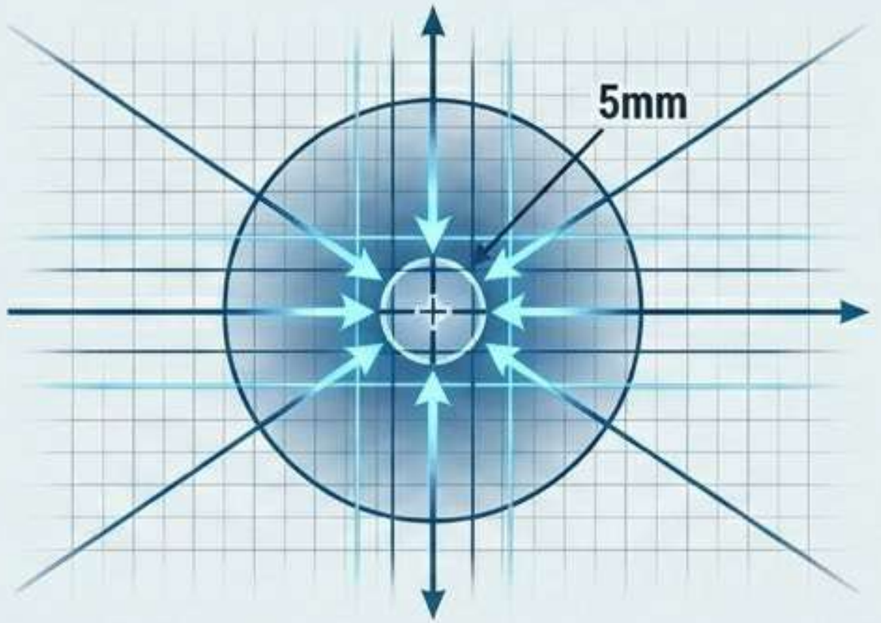
Overcoming the Surgical Blind Spot

THE PROBLEM



The limitation of human touch: The human hand cannot physically feel a 0.5cm anatomical variance deep inside the body. Free-hand surgical variance guarantees inconsistent cellular deposition and potential tissue damage.

THE SOLUTION

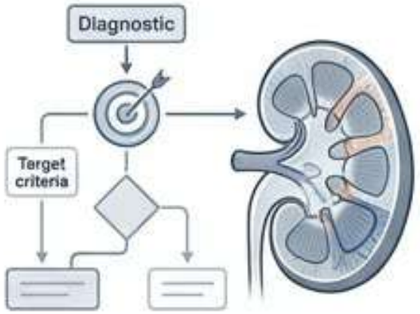


The Mandate for Precision: Computational mathematical modeling and continuous CT guidance are mandatory. We transition from approximated surgery to precision engineering, calculating exact coordinates to deposit cells perfectly into the surviving cortex.

Final Synthesis: The Future of DKD Management

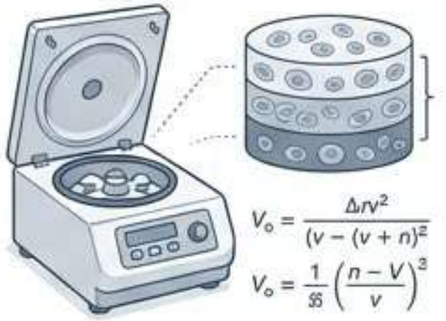
1. Precise Identification

Strict clinical diagnostic matrices ensure we intervene only in Type 2 DKD patients with viable residual architecture (eGFR 20-50).



2. Autologous Regeneration

Utilizing density-gradient selected, mathematically calculated cellular volumes directly derived from the patient's own native tissue.

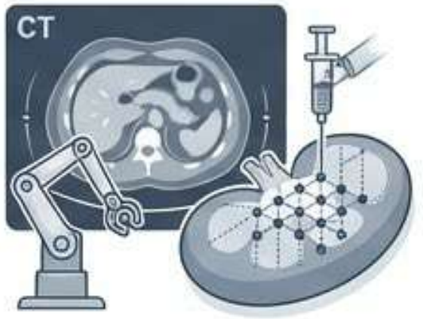


$$V_o = \frac{\Delta r v^2}{(v-(v+n)^2}$$

$$V_o = \frac{1}{\%}\left(\frac{n-V}{v}\right)^3$$

3. Spatial Accuracy

Eliminating human surgical variance through computational, CT-guided, multi-site microenvironmental deposition.



The Paradigm Shift: Transitioning from managing systemic failure to executing localized, cellular-level architectural repair.