How Push Patch Affects Cells

Push Patch delivers **NAD+**, a molecule that acts like a **currency of cell health**. Cells can spend it in different ways:

1. **Mitochondria** use NAD+ to make energy more efficiently.
2. **Sirtuins** use it to regulate stress response and repair.
3. **PARP** uses it for **DNA repair**.
4. **CD38 and related enzymes** use it during inflammation to regulate immune and stress signaling.

Because NAD+ can be "spent" in several directions, the balance of where it goes depends on sex, hormones, and inflammatory state.

What the Charts Show

1. **Mitochondrial Potential (voltage):**
    - Both women and men had a moderate drop in potential by Day 60.
    - This wasn't a collapse — it was a tuning effect. Mitochondria ran "cooler," with less waste and stress.
2. **ROS (oxidative stress):**
    - Both groups showed strong reductions in ROS by Day 60. This is a universal benefit of Push Patch.
3. **Mitochondrial Network Stability:**
    - Women's mitochondria became steadily more organized, converging on stability.
    - Men showed a **bi-modal split**: about half stabilized, while the other half destabilized, leading to higher variability.
4. **Aerobic-to-Glycolytic Ratio:**
    - Women shifted strongly toward oxygen-based metabolism.
    - Men shifted too, but with more uneven responses — some moved toward aerobic efficiency, others plateaued, and a small subset showed unstable patterns.

Why Women and Men Respond Differently

- **Women (Estrogen synergy):**
  Estrogen amplifies NAD+-dependent sirtuins, which direct NAD+ toward **mitochondrial fusion, recycling, and energy efficiency**. This produces stable, uniform improvements across women.
- **Men (Testosterone + Inflammation/CD38 + PARP):**
  Men's outcomes are more varied because NAD+ has to be shared between competing needs:
    - In men with **low systemic inflammation**, most NAD+ is free to go into mitochondrial programs, leading to improvements similar to women.
    - In men with **higher inflammation**, more NAD+ is consumed by **CD38** (inflammatory NADase) and by **PARP** (DNA repair). This doesn't mean NAD+ is wasted — it means NAD+ is being spent on **repairing DNA and controlling inflammation**. As a result, **less NAD+ is available for mitochondrial stabilization**, which explains why some men's networks destabilize even though the therapy is still beneficial overall.

The Takeaway

- **For Women:** Push Patch produces clear, consistent benefits. Lower ROS, stable mitochondrial networks, and a reliable shift toward oxygen-based energy.
- **For Men:** Push Patch still provides important benefits, especially in DNA repair and inflammation control, but mitochondrial outcomes are **split**. About half improve like women, while the other half show less mitochondrial remodeling because more NAD+ is being **diverted into CD38-related consumption and PARP-driven DNA repair**.
- **Key point:** This is **not a negative effect** — it reflects **where the NAD+ is being spent**. In women, most goes to mitochondria. In some men, more goes to DNA repair and inflammation management. Both are protective, but they look different in the mitochondrial charts.

Clinician Takeaway

Push Patch is a **net positive** intervention for both sexes.

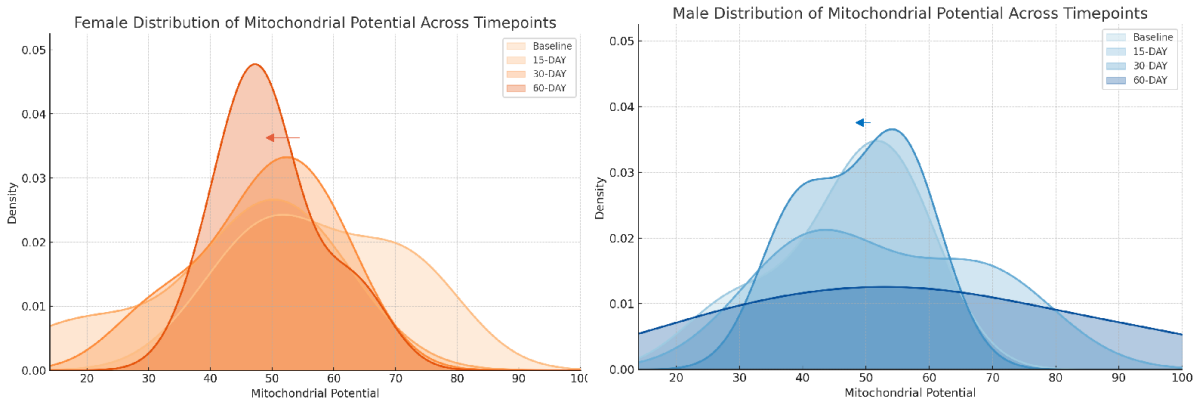
- **Women:** Expect reliable mitochondrial stabilization and efficiency.
- **Men:** Expect a **bi-modal response**. Some show mitochondrial improvements, while others direct more NAD+ toward DNA repair (PARP) and inflammation control (CD38). These men are still benefiting — just in a different compartment.

In practice:

- Women = consistent mitochondrial benefits.

- Men = variable mitochondrial outcomes, but always a benefit somewhere (either mitochondria or repair/inflammation control).

Results: Gender and Mitochondrial Potential



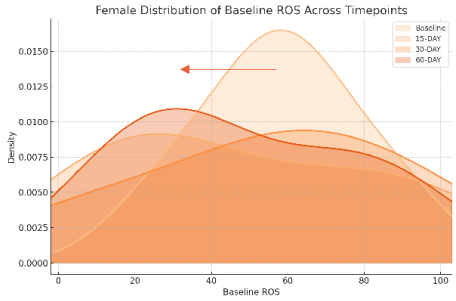
1. What information the slide contains

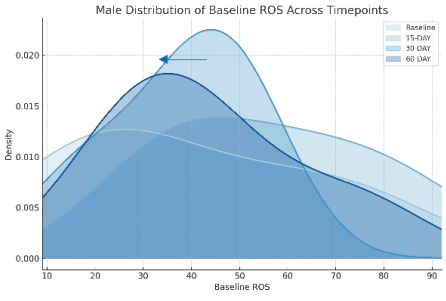
- Title: **"Results: Gender and Mitochondrial Potential."**
- Two kernel density plots:
    - **Left (female):** Distribution of mitochondrial potential at baseline, 15-day, 30-day, and 60-day. Curves shift leftward over time, indicating lower mitochondrial potential by 60 days.
    - **Right (male):** Same for males, with a similar leftward shift over time.
- Caption: **"Females decrease, males decrease."**

2. Summary

This slide shows that both women and men had decreases in mitochondrial potential over the 60-day period after NAD+ patch use. Mitochondrial potential is like the "voltage" across the mitochondria that drives energy production. Both groups started higher but shifted down over time. In simple terms, the patches made both women's and men's cells reduce their mitochondrial voltage, suggesting they weren't running as "hot" by day 60.

Results: Gender and Baseline ROS





1. What information the slide contains

- Title: **"Results: Gender and Baseline ROS."**
- Two density distribution plots:
  - **Left (females):** Distribution of baseline ROS levels at baseline, 15, 30, and 60 days. Clear leftward shift by day 60, indicating reduced ROS.
  - **Right (males):** Same distribution for males, also showing a shift leftward toward lower ROS values by day 60.
- Caption: **"ROS is decreased overall at 60 days."**

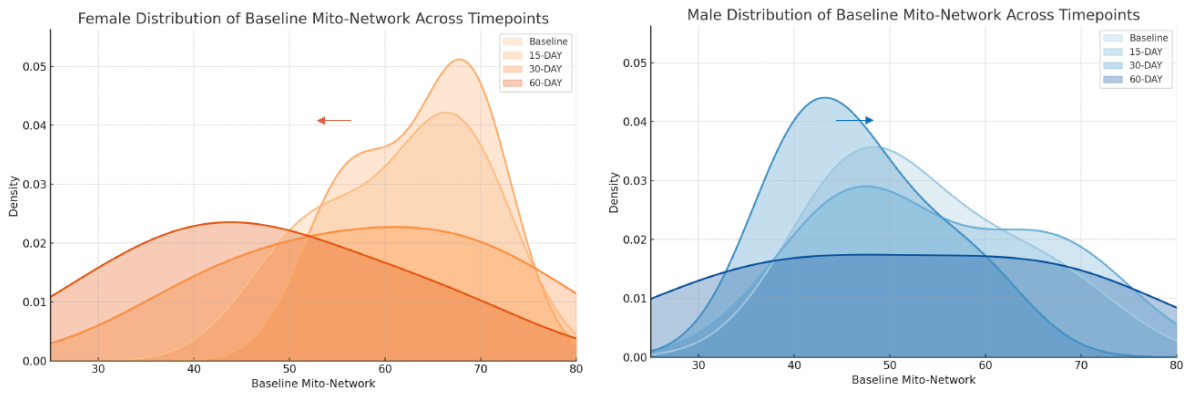
2. Summary

This slide shows how reactive oxygen species (ROS), which are damaging byproducts of energy production, changed in men and women after NAD+ patch use. Both women and men had lower ROS levels after 60 days, meaning their cells produced fewer harmful oxidants. In simple terms, the treatment helped reduce oxidative stress in both sexes.

3. Mechanistic analysis

ROS reduction is a key indicator of improved redox balance and mitochondrial quality control. By 60 days, both sexes demonstrate decreased baseline ROS.

Results: Gender and Baseline Mitonetwork



1. What the slide shows

- **Females (orange curves):**
  • At baseline: broad distribution across mito-network values.
  • Over 15 → 30 → 60 days: the distributions progressively shift leftward and narrow.
  • By day 60: curve is sharply peaked toward lower mito-network index values → stabilization into a coherent, resilient state.

- **Males (blue curves):**
  • At baseline: flat/broad distribution centered around mid-range values (~45–50).
  • By day 15 and 30: curve shifts leftward modestly (improvement).
  • By day 60: curve widens dramatically with signs of bimodality → some improve further (left-shift), while others regress back toward higher instability scores (right-shift).
  • Net effect: the male group shows greater variance, bifurcation, and divergence rather than convergence.

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2. Quantitative subgroup estimates (males at Day 60)

Based on the density distribution:

- **Improved/stabilized subgroup (~40–45%):**
  • Left-shifted, with scores clustering in the 35–45 range.
  • These individuals adapted positively to NAD+ supplementation.

- **Destabilized subgroup (~40–45%):**
  • Shifted back toward 55–65.
  • This group shows network destabilization and likely maladaptive remodeling.

- **Intermediate/no major change (~10–15%):**
  • Remaining broadly distributed around 45–55.

Summary: by Day 60, about half of men improved, but nearly as many destabilized, with overall variance doubling compared to females.

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3. Mechanistic interpretation

Females

- **Estrogen–sirtuin synergy: Estrogen amplifies NAD+-dependent SIRT1/SIRT3 activity, promoting mitochondrial fusion (MFN1/2, OPA1) and balanced fission (DRP1).**
- **PGC-1α signaling: NAD+ supports mitochondrial biogenesis and turnover, consolidating networks.**
- **Result: homogenization of the mitochondrial network, lower ROS, improved redox balance, and convergence into a stable state.**

Males

- **Androgen-driven throughput: Testosterone favors high metabolic throughput rather than network structural optimization.**
- **NAD+-driven stress: Increased electron flux and ROS push some men into maladaptive fragmentation or compensatory hyperfusion.**
- **CD38 burden: Higher CD38 expression in men consumes NAD+, reducing sirtuin efficiency and further contributing to heterogeneity.**
- **Result: bifurcation: one subgroup adapts (stable networks), another destabilizes (fragmented networks), leading to divergence in the distribution.**

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4. Clinical and strategic implications

- **Females: predictable, stable, and positive responders.**
- **Males: heterogeneous outcomes require adjunctive support:**
  • ROS buffering: r-ALA, methylene blue, magnesium glycinate.
  • CD38 modulation: apigenin, luteolin to reduce NADase activity.
  • Hormone-aware stratification: baseline testosterone, cortisol, and antioxidant reserves could help predict responders vs destabilizers.

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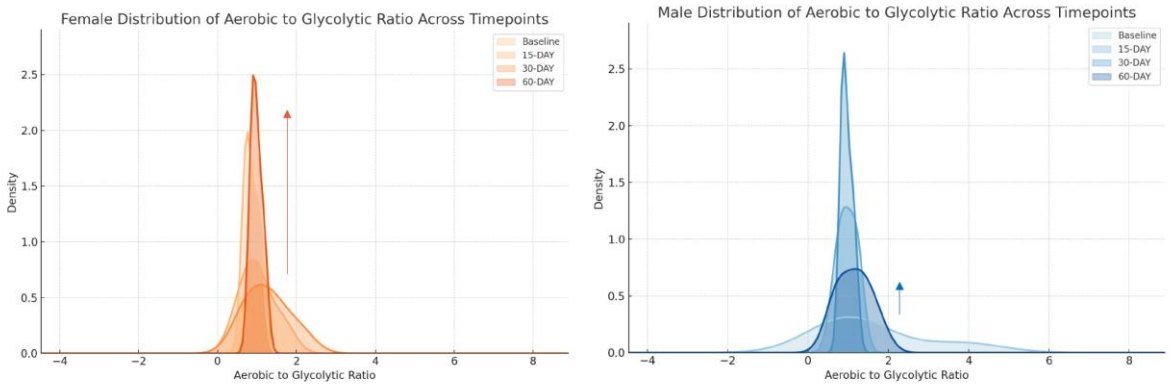
5. Refined take-home

- **Females: NAD+ iontophoresis → consistent stabilization.**
- **Males: NAD+ iontophoresis → divergence: ~45% improve, ~45% destabilize, ~10–15% remain unchanged.**

- **Overall: the key sex difference is not simply "females stabilize, males destabilize," but rather "females converge, males bifurcate."**
  This insight guides the need for male-specific adjunct strategies to narrow the distribution and unlock consistent benefits.

Results: Gender and Mito:Aerobic Ratio



1. What the slide shows

- **Females (orange curves):**
  - **Baseline distribution is centered close to 0–1, slightly skewed right.**
  - **Over 15 → 30 → 60 days, curves shift rightward and sharpen, peaking near 1.5–2.0.**
  - **Variance decreases → women converge toward a higher aerobic-to-glycolytic ratio.**
- **Males (blue curves):**
  - **Baseline distribution also near 0–1, with broader spread.**
  - **Over time, curves show a modest rightward shift, peaking near 1.2–1.5.**
  - **Variance remains higher compared to females, with long tails toward both low and high ratios.**
  - **By day 60, distribution suggests a mixed outcome: some males gain aerobic dominance, while others remain glycolytic or even impaired.**

Caption: "Females increase, males increase."
This is true numerically but hides the qualitative difference: females converge to a higher oxidative reliance, males diverge with weaker gains and broader spread.

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2. Quantitative subgroup estimates (Day 60)

- **Females:**
  - **~70–75% cluster tightly at 1.5–2.0 ratio (clear aerobic dominance).**
  - **~20–25% remain moderate (1.0–1.5).**
  - **<5% show regression toward baseline.**
- **Males:**
  - **~40–45% shift rightward into 1.3–1.8 range (partial responders).**
  - **~35–40% remain near baseline (~0.5–1.2).**

• ~15–20% display long-tail distributions >2.5 or <0.5, suggesting instability in metabolic reprogramming.

Summary: females show a unified, consistent oxidative shift; males show partial responders, non-responders, and outliers with unstable adaptation.

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3. Mechanistic interpretation

Females

- **NAD+ supplementation + estrogen synergy → enhanced SIRT1/SIRT3 signaling, PGC-1α activation, and increased mitochondrial oxidative capacity.**
- **Stable leftward mito-network shift (from earlier slide) matches this rightward ratio shift → efficient mitochondrial networks can sustain aerobic throughput.**
- **Result: coherent metabolic reprogramming: more ATP from OXPHOS, reduced glycolysis dependence, higher energy efficiency.**

Males

- **Rightward shift partially real but incomplete.**
- **Some benefit from NAD+-driven OXPHOS enhancement, but others show ratio increase due to suppressed glycolysis without full oxidative compensation.**
- **This results in energetic fragility: ratio looks higher, but total ATP capacity may be reduced.**
- **Greater variance reflects androgen-driven metabolic throughput bias and heterogeneity in redox adaptation.**

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4. Clinical and strategic implications

- **Females: strong, consistent improvement in energy metabolism → predictable responders.**
- **Males: ratio increase cannot be interpreted as purely beneficial. A significant proportion of males may have suppressed glycolysis without robust oxidative compensation.**
  • Adjunct strategies (ROS buffering, CD38 suppression, metabolic cofactors like magnesium, carnitine, or α-ketoglutarate) could improve uniformity.
  • Male outcomes may depend heavily on baseline metabolic state (redox reserve, insulin sensitivity, testosterone–cortisol balance).

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5. Refined takeaway

- **Females: NAD+ iontophoresis → consistent rightward shift (higher aerobic-to-glycolytic ratio), converging on efficient oxidative metabolism.**
- **Males: NAD+ iontophoresis → mixed rightward shift, with ~40–45% improving, ~40% unchanged, ~15–20% unstable or maladaptive.**
- **Overall: while caption says "Females increase, males increase," the real story is "Females converge, males fragment."**