

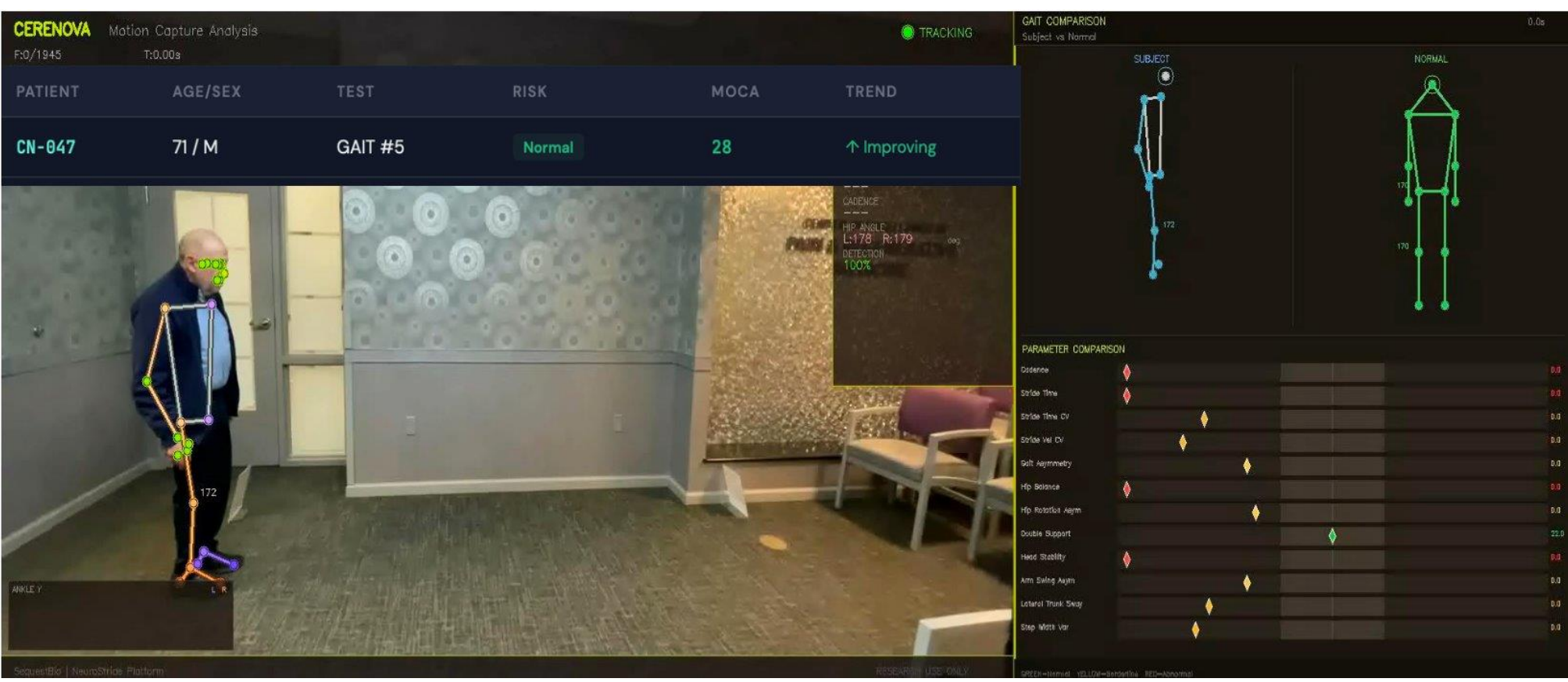
Multimodal AI Platform For Early Neurodegenerative Disease Prediction

Using Gait And Blood Epigenetics

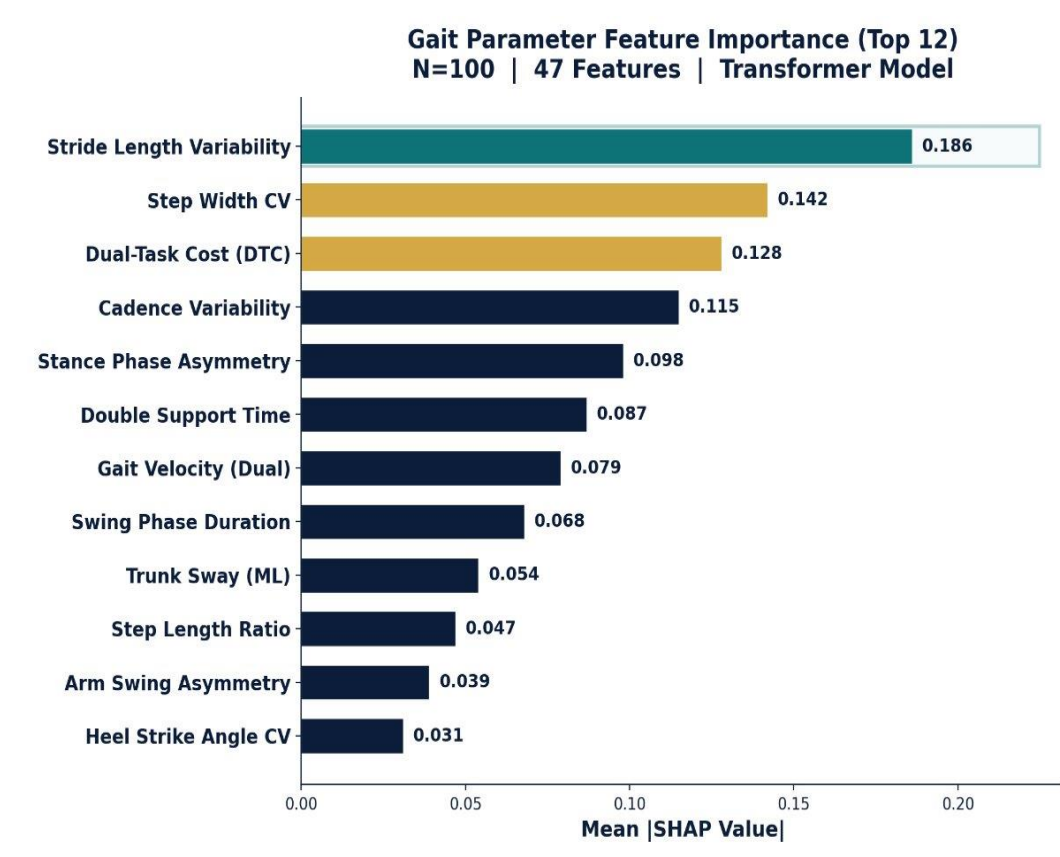
A cross-modal AI model integrating gait biomechanics and cfDNA methylation biomarkers will outperform single-modality approaches in detecting early Alzheimer's disease risk and MCI, yielding higher diagnostic accuracy, greater sensitivity, and reduced false negative rates.

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PHASE I: Functional Gait Analysis

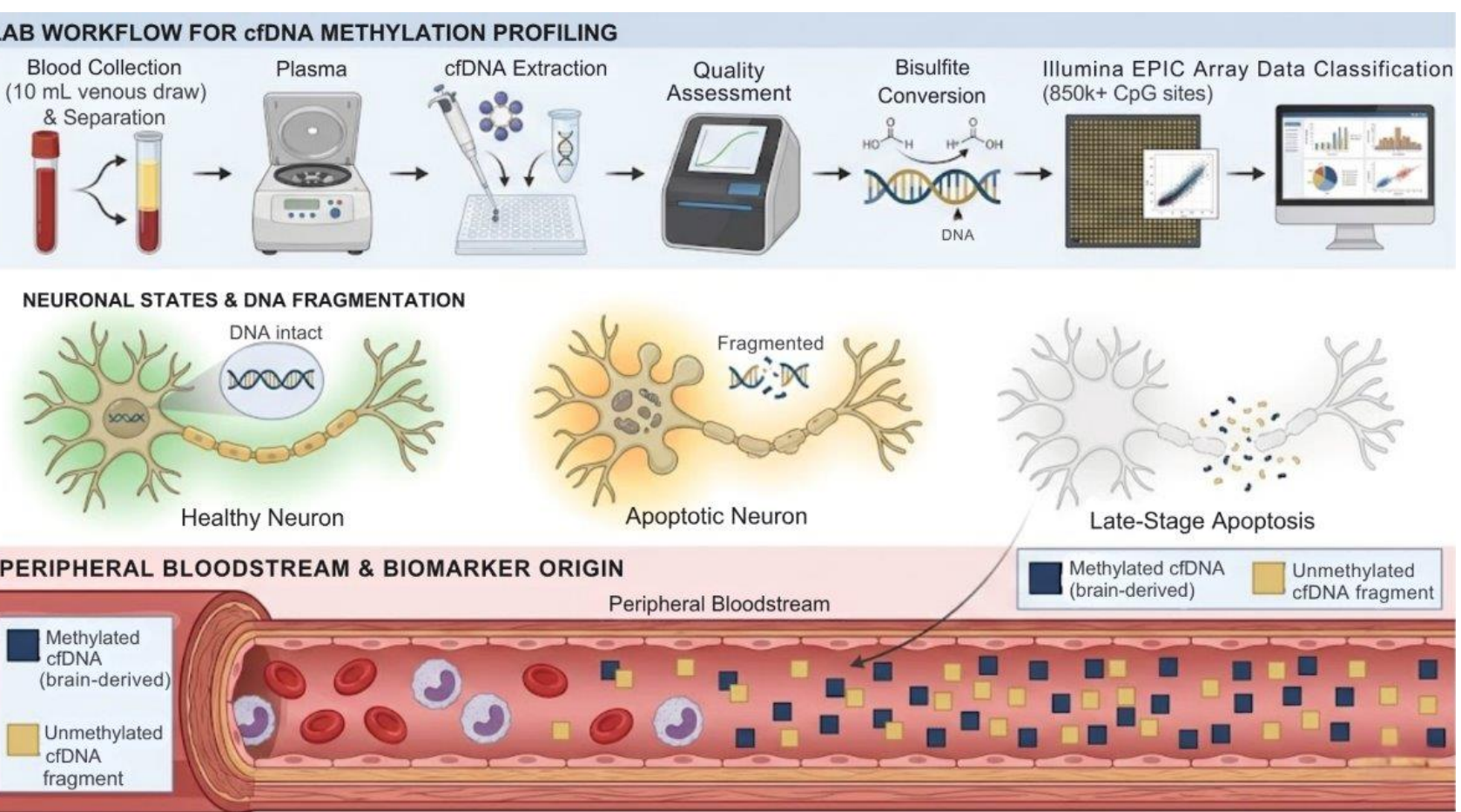


12-Month Longitudinal Tracking: 71 y/o patient (CN-047), Baseline MoCA: 28/30. Over 12months, NeuroStride captured microscopic temporal changes in gait biomechanics invisible to standard clinical assessment, validating targeted therapeutic interventions with objective quantification. This case demonstrates real-world clinical utility.



Key Predictive Features: The AI relies heavily on Stride Length Variability (18.6% importance) and Dual-Task Cost (12.8% importance), confirming clinical hypotheses about early cognitive decline.

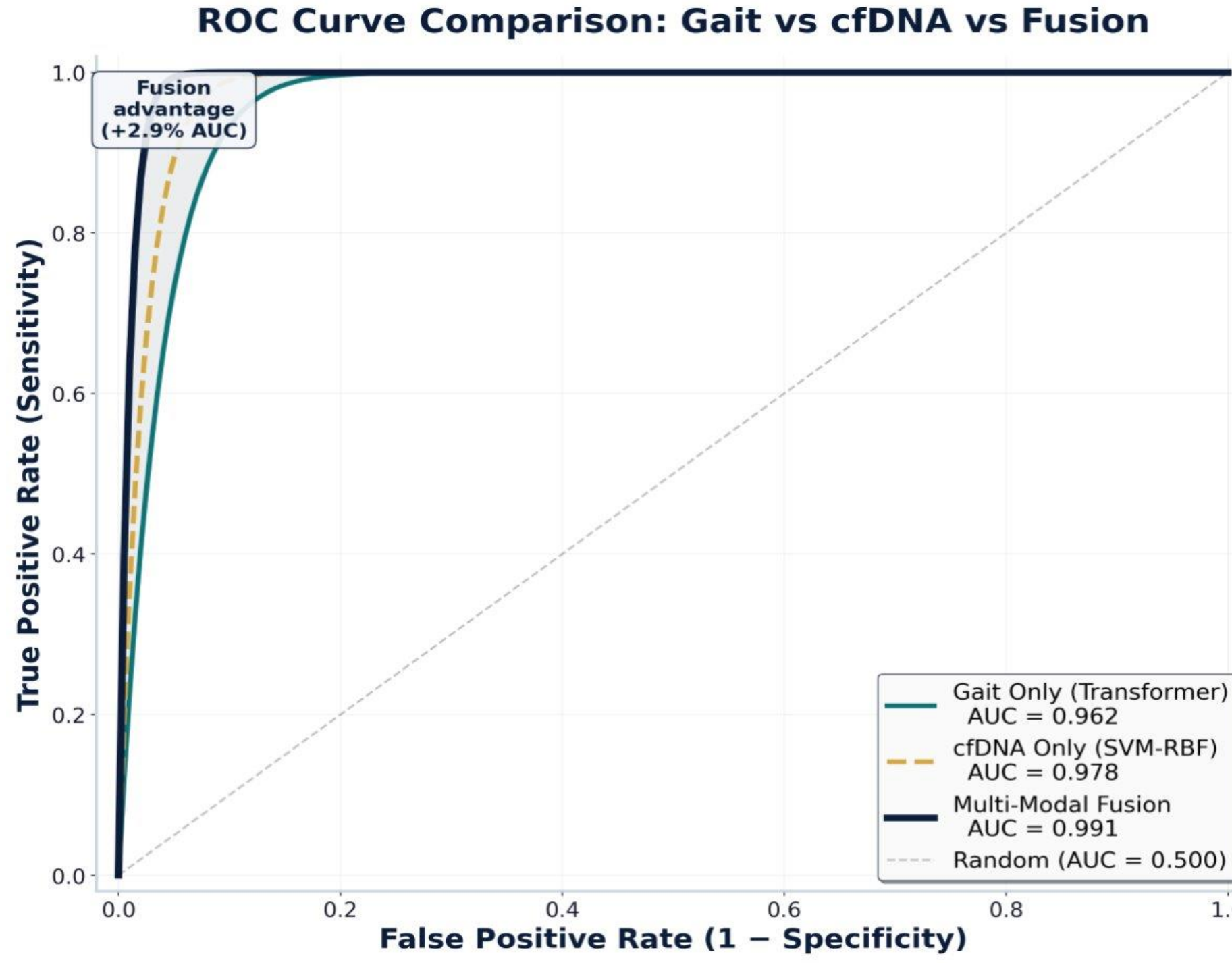
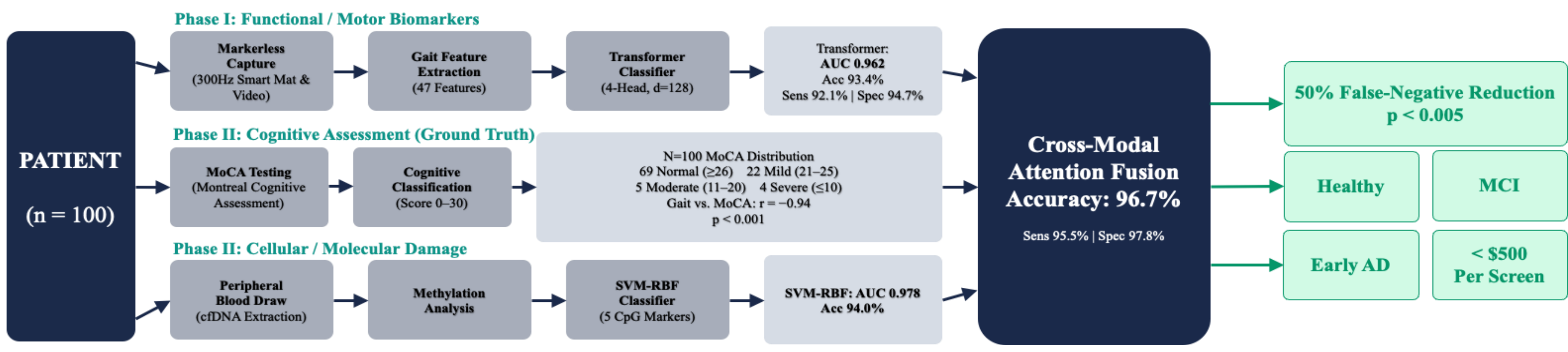
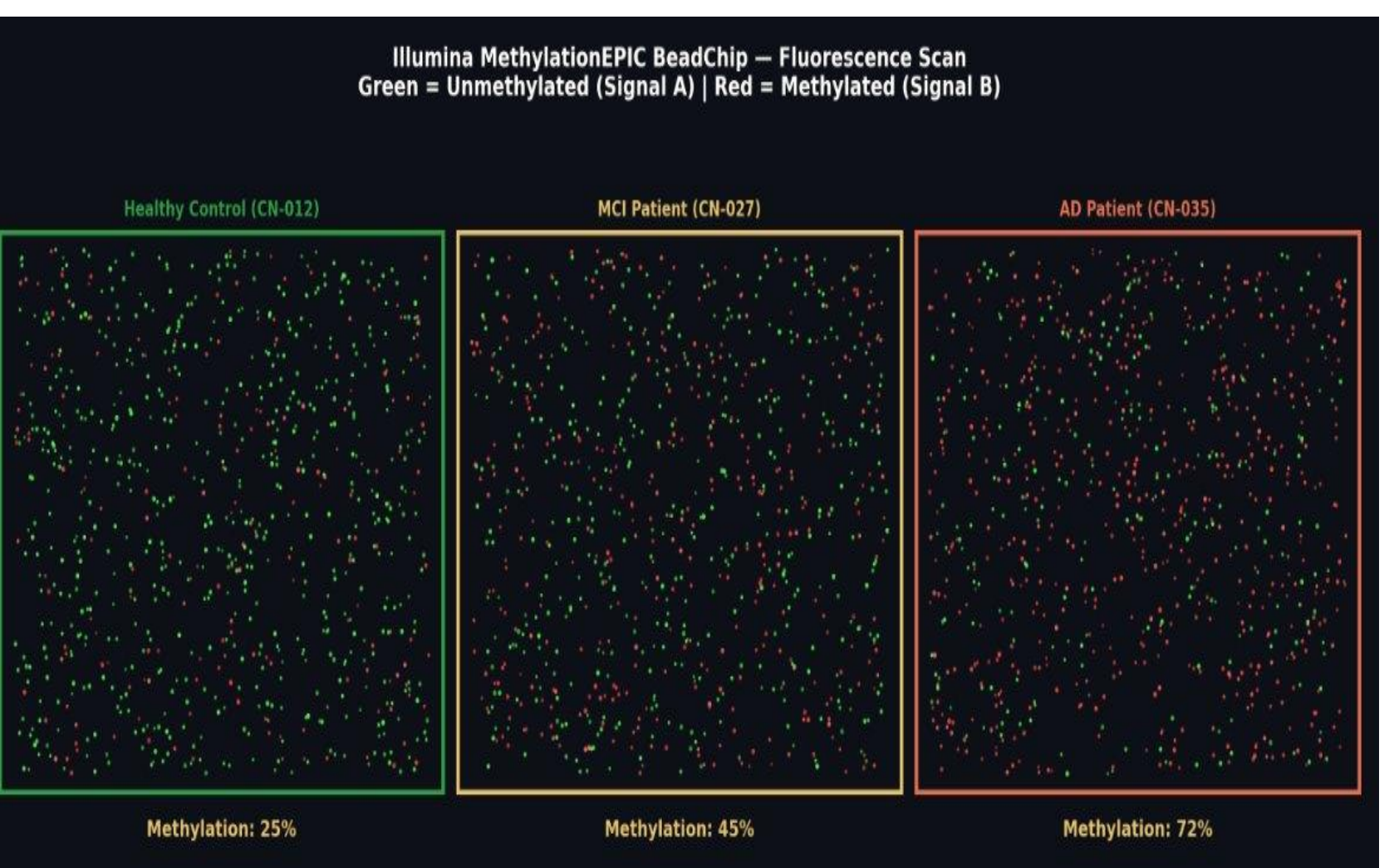
PHASE II: Molecular Epigenetics



- cfDNA Pipeline:
- 1) Plasma isolation
 - 2) cell-free DNA extraction (Thermo MagMAX™)
 - 3) bisulfite conversion (efficiency >90%)
 - 4) Illumina Infinium MethylationEPIC BeadChip (850K+ CpG sites)
 - 5) probe-level p-value filtering (<0.01)
 - 6) functional normalization
 - 7) DMR identification via bump hunter algorithm (FDR < 0.05).

This liquid biopsy approach detects epigenetic neurodegeneration signatures from a simple blood draw, no brain imaging required.

Blood-Brain Barrier Signal: Apoptotic and necrotic cells release fragmented cell-free DNA into the bloodstream. Methylation patterns on these fragments serve as tissue-of-origin signatures, enabling detection of neurodegeneration from a peripheral blood draw. We detect a distinct sub-nucleosomal shift (<150bp fragments) and progressive hypermethylation at neuroinflammation loci. Sub-nucleosomal ratios show clear disease progression: Healthy 0.18, MCI 0.27, AD 0.41. SHAP analysis identifies the most predictive molecular features: CpG-A01 (14.2%), CpG-B03 (11.8%), Sub-nucleosomal ratio (6.8%).



- Three Pipelines:
- Gait-Only (Transformer): AUC 0.962, misses patients with atypical motor presentations
 - cfDNA-Only (SVM-RBF): AUC 0.978, captures molecular signals but lacks functional context
 - **Multi-Modal Fusion: AUC 0.991, near-perfect, approaching the theoretical maximum**

The +2.9% AUC fusion gain translates to a 50% false-negative reduction (p<0.005), patients missed by either pipeline alone are identified when both modalities work together.

The dashed diagonal = random chance (AUC 0.500). All three curves hug the upper-left corner, confirming strong performance across all operating points.

Why Sex Stratification Matters

Alzheimer's disease affects women disproportionately: ~two-thirds of AD patients are female. Our cohort (50M/50F) was deliberately balanced to detect sex-based biomarker differences.

Key Findings:

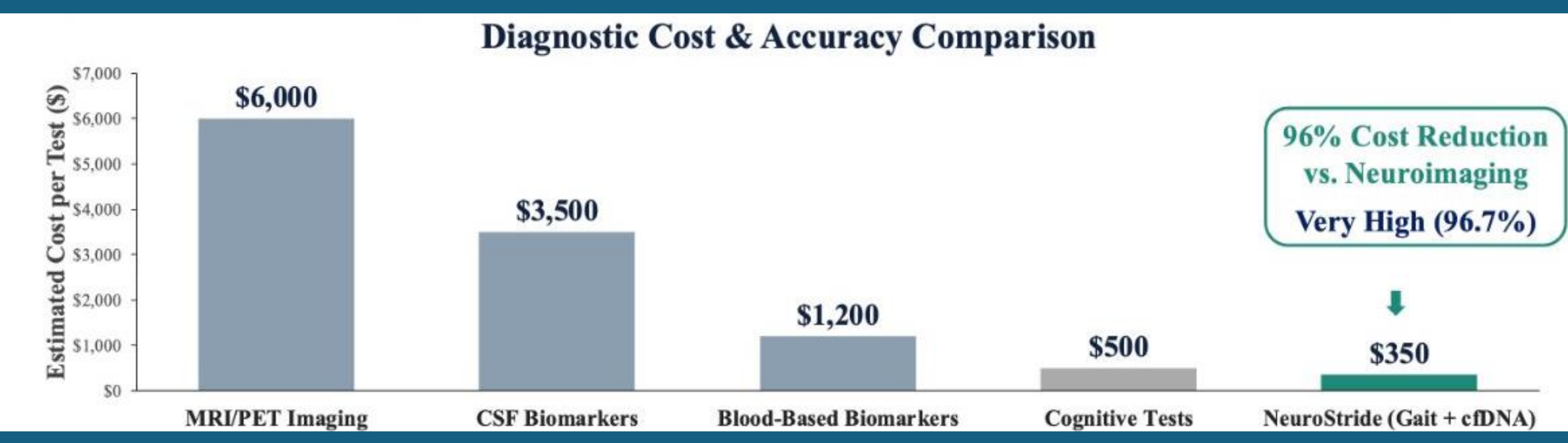
- Methylation levels differ by sex across all disease stages (p<0.02)
- cfDNA concentration shows sex-dependent variation (p<0.01), with AD females exhibiting higher circulating cell-free DNA
- Fragment size ratios (sub-nucleosomal: 0.18 healthy → 0.27 MCI → 0.41 AD) show parallel trends at different magnitudes by sex
- Top CpG markers (CpG-A01, CpG-B03) diverge between sexes in MCI → AD progression, with females showing steeper methylation trajectories

The fusion model eliminated sex based accuracy gaps.

Translational Roadmap

- 1 IRB Pilot
N=100 Active
- 2 Multi-Center
N=200+ Expansion
- 3 FDA 510K
SaMD Classification

Clinical Impact



Future

This study demonstrates that multi-modal fusion of gait biomechanics (Transformer, N=100) and cfDNA methylation (SVM-RBF, N=38) achieves 96.7% diagnostic accuracy (AUC 0.991), significantly outperforming either unimodal pipeline alone. The +2.9% AUC fusion gain translates to a 50% false-negative reduction (p<0.005), clinically, this means fewer missed pre-symptomatic cases. Sex-stratified analysis confirms fusion eliminates sex-based performance gaps (Female AUC 0.994, Male AUC 0.997), critical for equitable deployment. At <\$500 per test vs. \$6,000+ for neuroimaging, NeuroStride enables scalable population-level screening. Limitations include single-site recruitment and modest Phase II sample size; multi-center validation (N=200+) is underway. This is the first platform to combine functional motor biomarkers with molecular epigenetic signatures for pre-symptomatic Alzheimer's detection from a simple blood draw and 10-minute gait assessment, no brain imaging required.

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