AI in Regenerative Medicine: Predicting Product Potency and Enabling Cost-Effective Manufacturing

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SVP Research

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Aspen NEUROSCIENCE

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This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, those concerning the development and commercialization of our product candidates, the potential benefits and therapeutic potential of our technologies, and other statements that are not historical facts.

Words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "should," "target," "will," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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Andres Bratt-Leal is an employee of and stock-holder in Aspen Neuroscience

Parkinson's Disease: a Large Unmet Medical Need

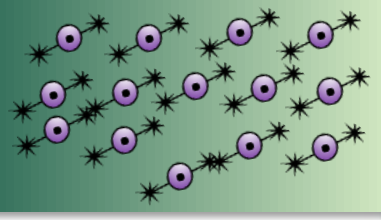
A debilitating condition not adequately addressed with current therapy

Disease Overview

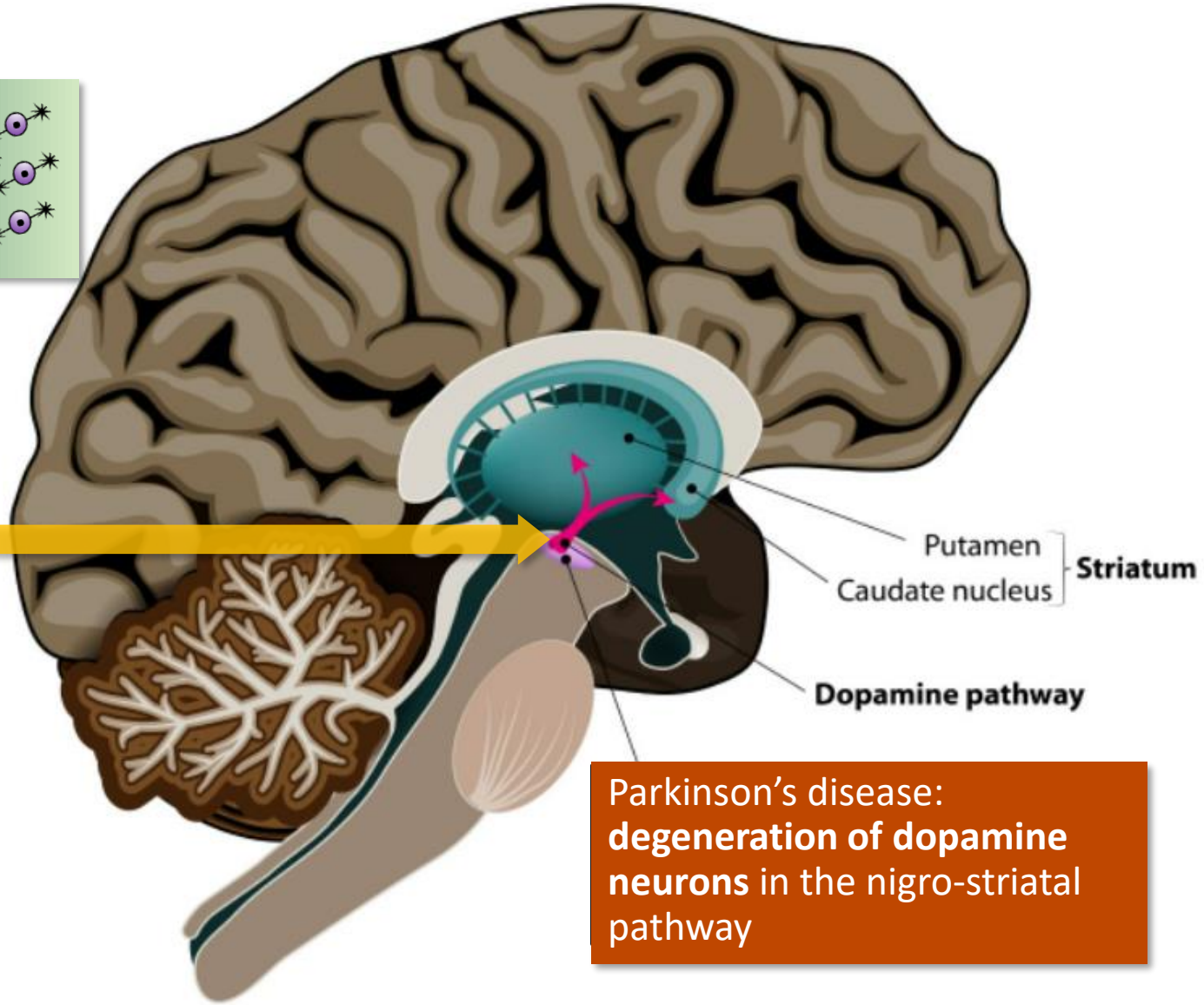
- **Fast growing**, and **2nd most common** neurodegenerative disease
- Loss of dopaminergic neurons in the substantia nigra leads to:
  - **Motor symptoms:** tremor, rigidity, bradykinesia, and falls
  - **Non-motor symptoms:** mood disorders, cognitive impairment
- **High unmet clinical need**:
  - Efficacy of medications decreases over time
  - No drug that halts disease progression

Can Neuron Replacement Therapy Provide Long-Term Benefits?

Target cell type:
Autologous, A9-like
dopamine neuron precursors



>50% of dopamine neurons in the substantia nigra are ***lost before diagnosis***



Parkinson's disease:
degeneration of dopamine neurons in the nigro-striatal pathway

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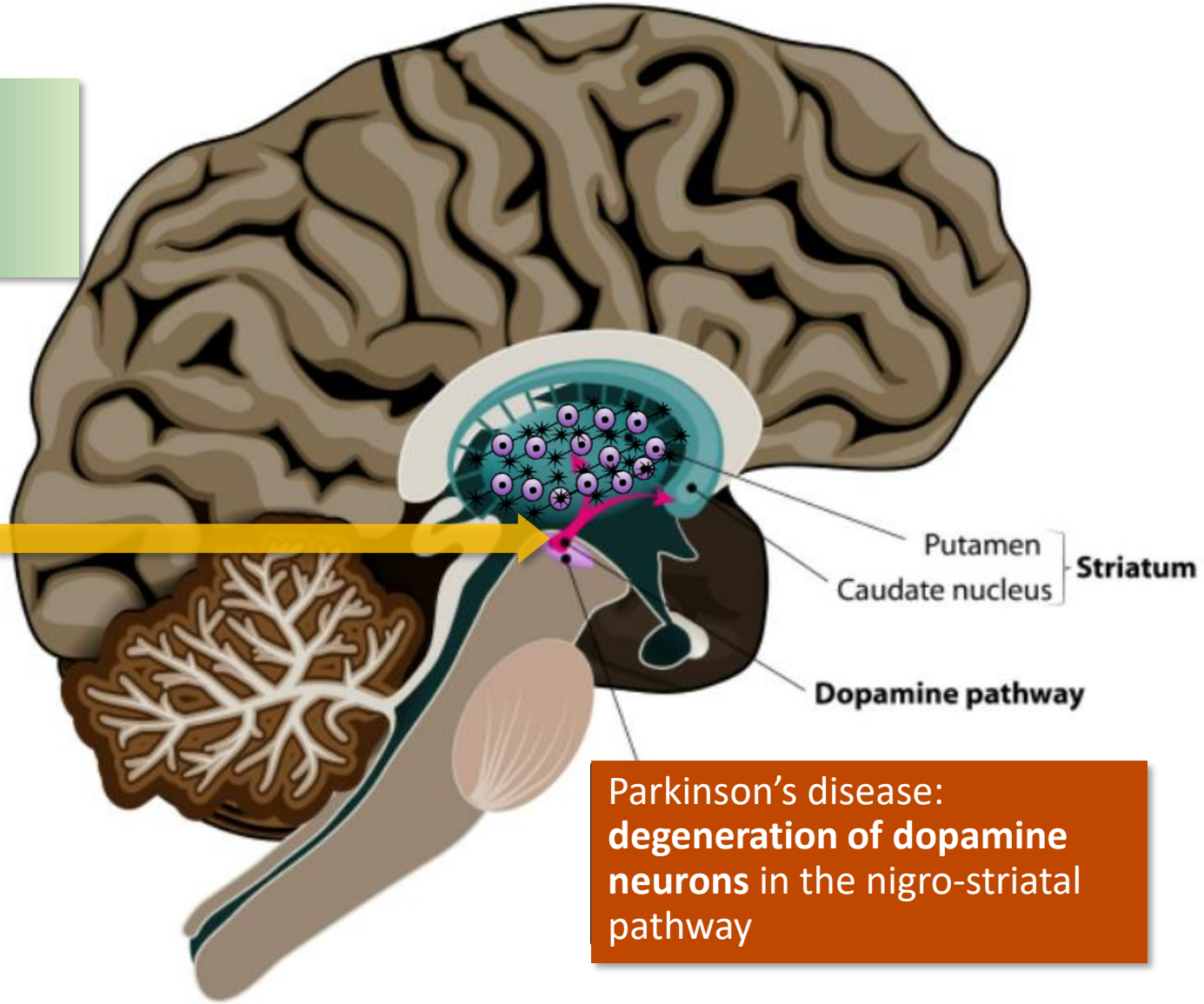

Parkinson's disease:
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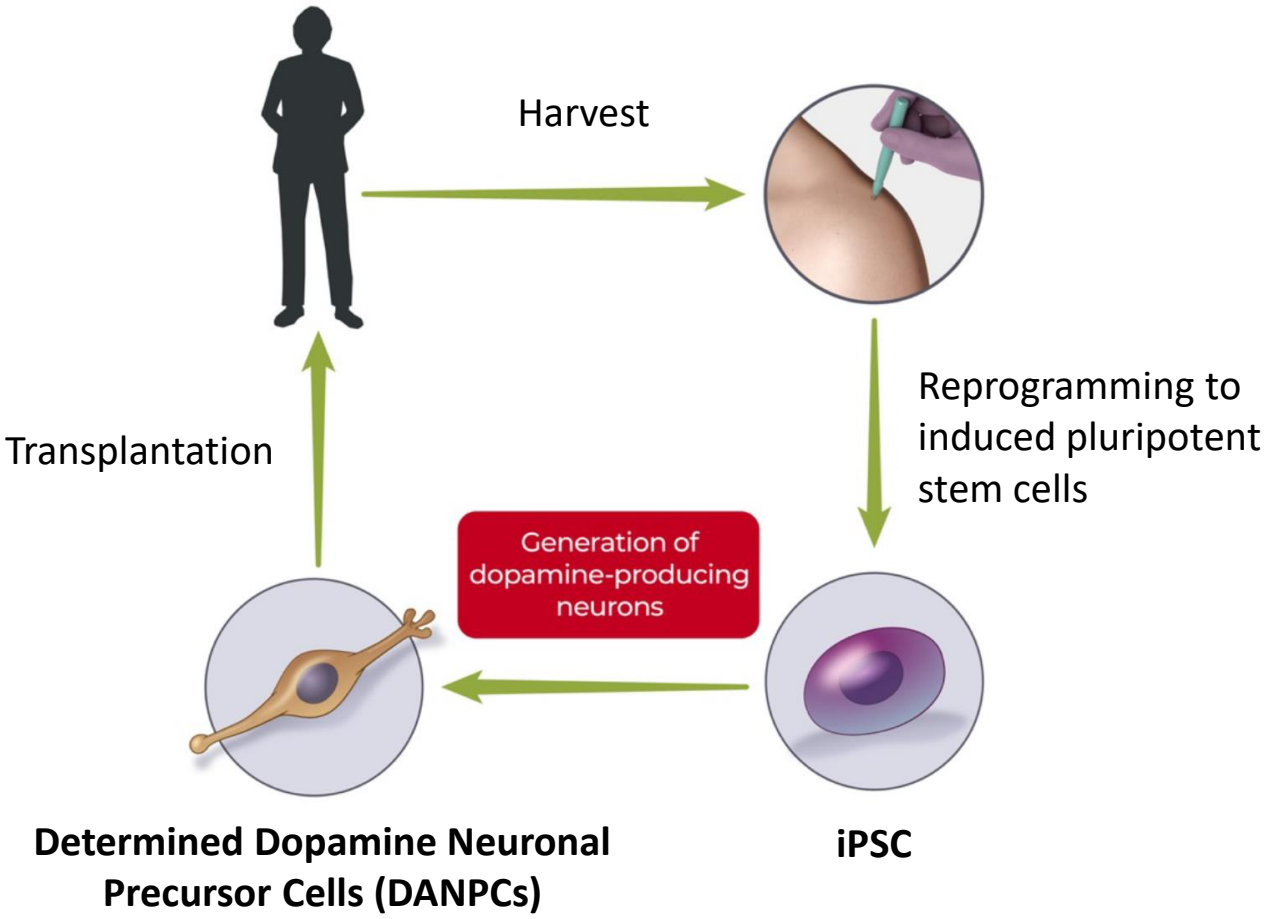
The Aspen Neuroscience Approach to Treat Parkinson's Disease

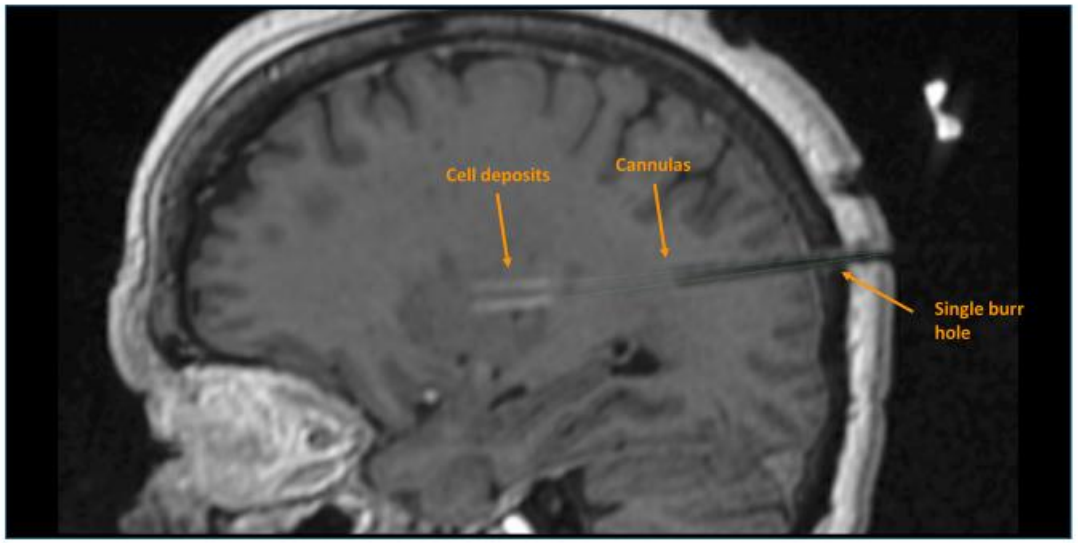


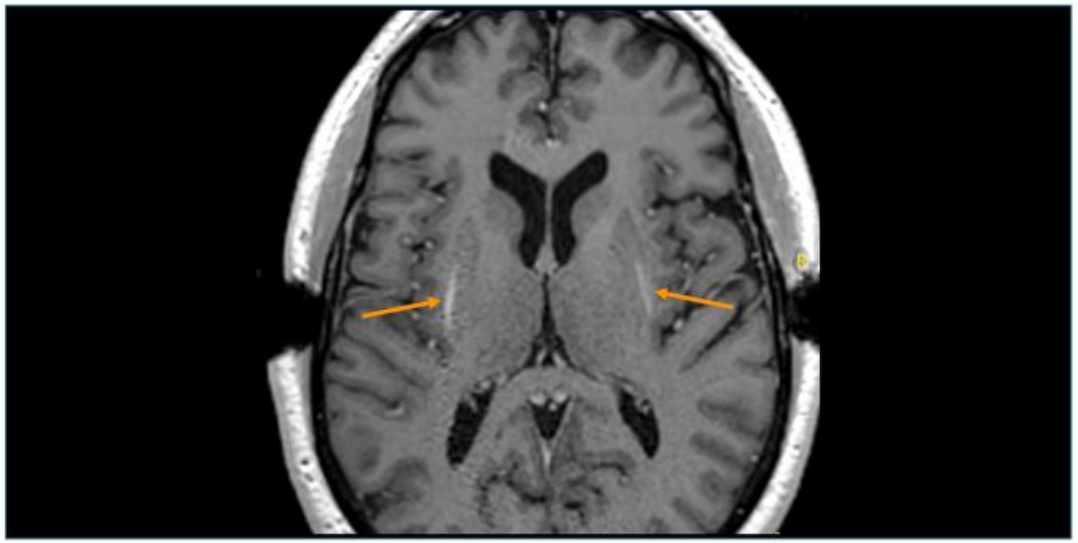
- Aspen Neuroscience is headquartered in San Diego and founded in 2018. We focus on **developing, manufacturing and delivering autologous cell therapies**, which are developed from the patient's own induced pluripotent stem cells (iPSCs)
- ANPD001 is composed of autologous dopamine precursor cells (DANPCs), with the goal of **replacing lost dopamine neurons**
- Cells are administered without immune suppression

International Parkinson and Movement Disorder Society

First in Human Administration of an Autologous Investigational Cell Therapy for Parkinson Disease Using an Intraoperative MRI-guided Posterior Approach

Paul Larson[1,2], Chadwick Christine[2], Nicholas Phielipp[3], Melissa Houser[4], Scott Sherman[1], Edward Wirth III[5]





- Surgical Technique: Bilateral simultaneous delivery to post-commissural putamen using intraoperative MRI guidance
  - Single occipital burr hole, 2 tracts one dorsal, one ventral
- Sagittal MRI showing trajectories for cell placement; Axial MRI showing cell deposits in the intended location

[1]University of Arizona/Banner UMC-Tucson, [2]University of California, San Francisco, [3]University of California, Irvine, [4]Scripps Clinic, [5]Aspen Neuroscience

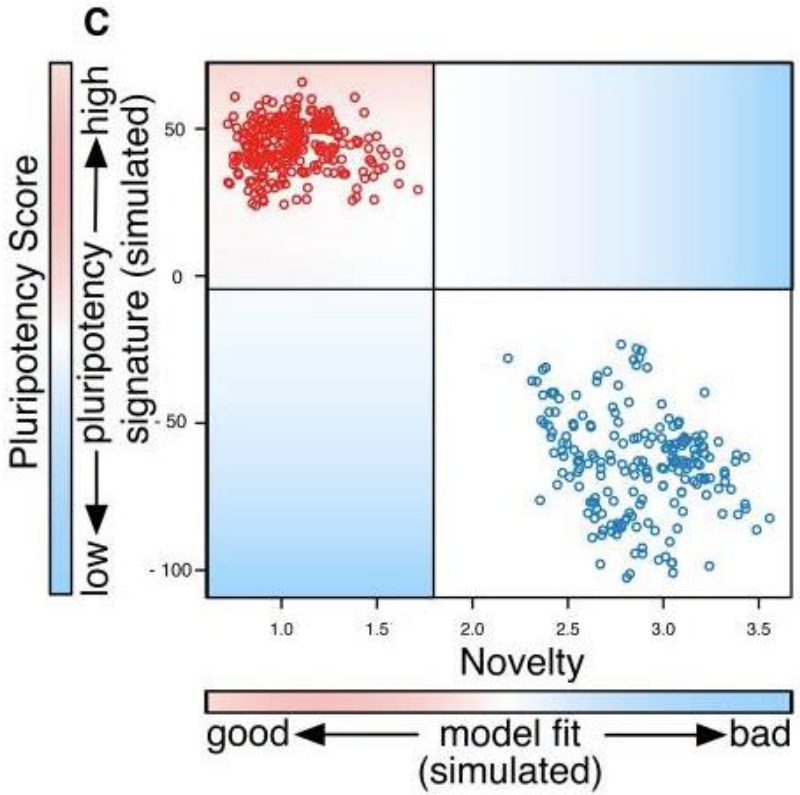
Challenges for Autologous Cell Therapies

- How can we ensure that cells made from each patient are safe and efficacious?

- How can we scale manufacturing and lower cost of goods to ensure patient access?

AI For Supporting Product Quality

Gene Expression Profile as Predictive of Cell State – PluriTest®

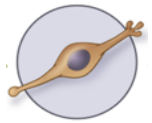


Muller FJ et al. Nat Methods 8(4):315-317 (2011)

Panopoula et al. Stem Cell Reports 8(4):1086-1100 (2017)

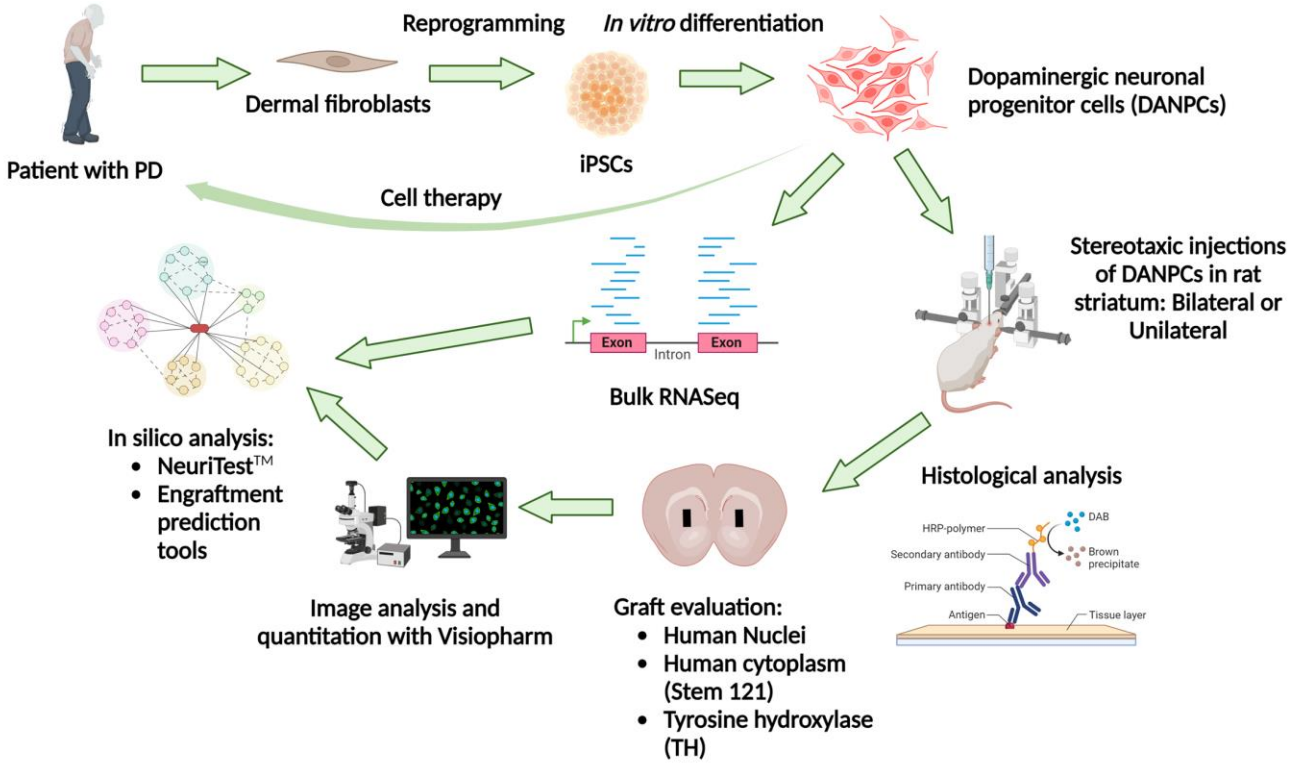
- Aspen Co-Founder Dr. Jeanne Loring led the creation of **PluriTest®** (2011) built using hundreds of gene expression profiles from pluripotent and somatic cells
- First application of machine learning to analyze whole-genome expression data
- Replaces the in in vivo teratoma assay to determine pluripotency of novel cell lines
- Predicts in vivo behavior of stem cells based only gene expression data

Development of Machine Learning Models Predicting DANPCs Biological Outcomes



DANPCs

- *D*evelopment of a predictive model (**GraftTest**) for DANPCs **engraftment**
  - Pairs RNAseq data with graft quantification in rats
- Bulk RNASeq analysis is highly correlated with graft characteristics with >85% accuracy
- Another independent model (**DopaTest**) developed to predict ***in vitro* dopamine release** using bulk RNAseq data from DANPCs



Beauvais et al. SFN (2023)

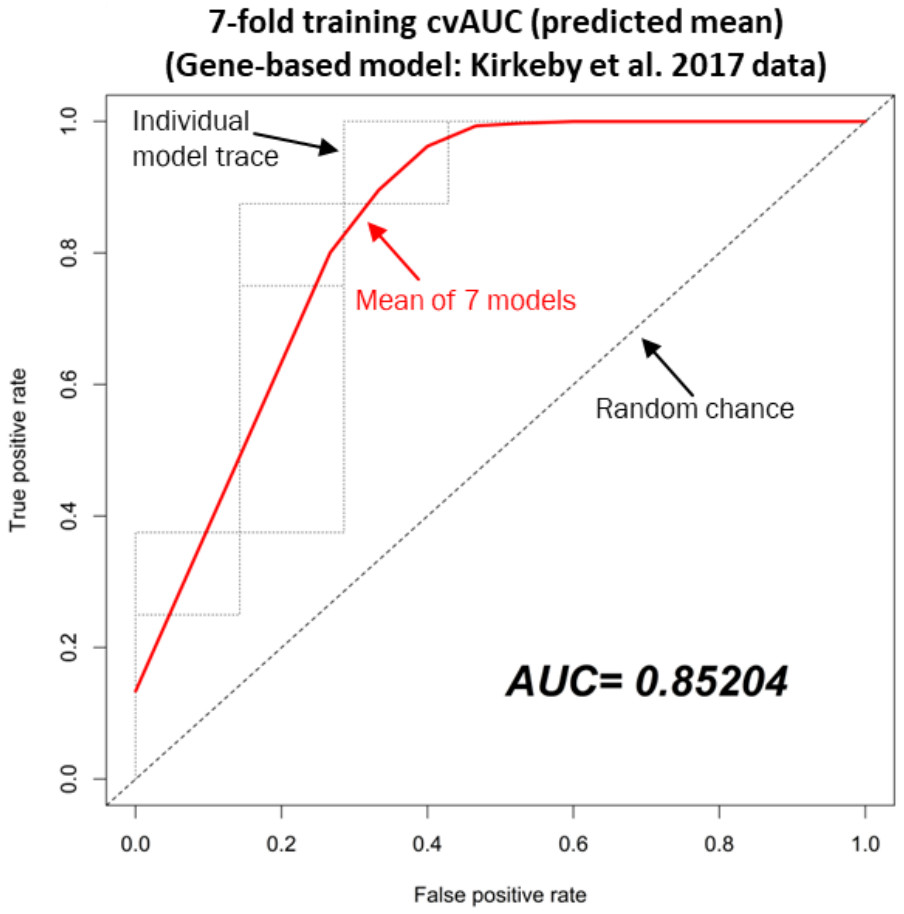
Fremgen et al. Poster #1208, ISCT (2024)

GraftTest – Model Validation With An External Dataset

GraftTest can predict with the same accuracy the engraftment of DANPCs made by a different lab using a different cell line implanted by different people in different types of rats!

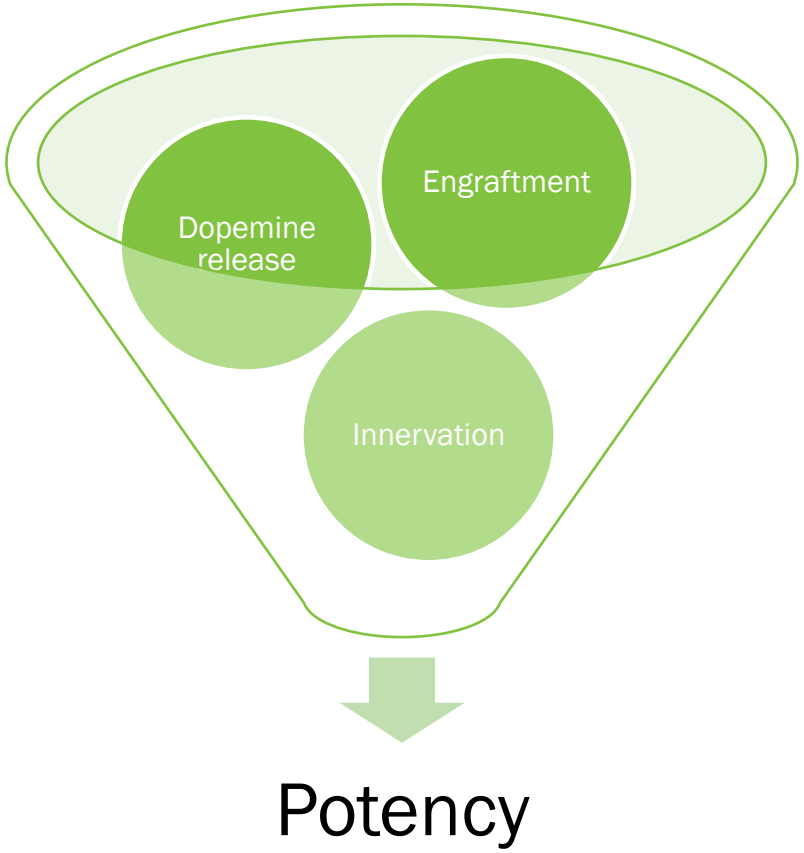
By using diverse cell lines to create a reference data set it may be possible to extract more universal biological insights compared to creating a reference data set with only one cell line.

Out-of-sample data and labels from Kirkeby *et al*. (2017) *Cell Stem Cell* 20 (1): 135-148.



Machine learning-based potency assay matrix

- Breaking down the proposed mechanism of action
  - Cells must survive
  - Cells must differentiate and innervate
  - Cells must release dopamine
- We propose a predictive model to assess product potency for each patient



AI For Autonomous Manufacturing

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Manual iPSC Production Requires Skilled Operators

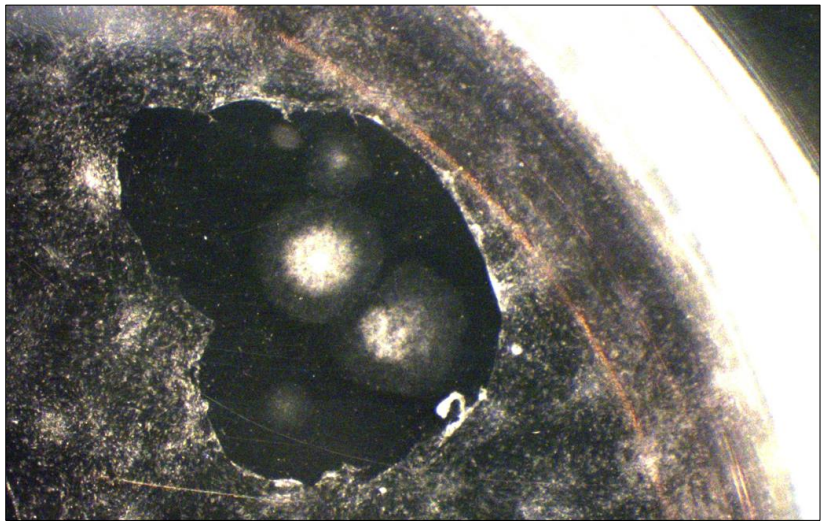
Fibroblasts seeded and treated with reprograming agent

Cleaning of fibroblast from emerging iPSCs

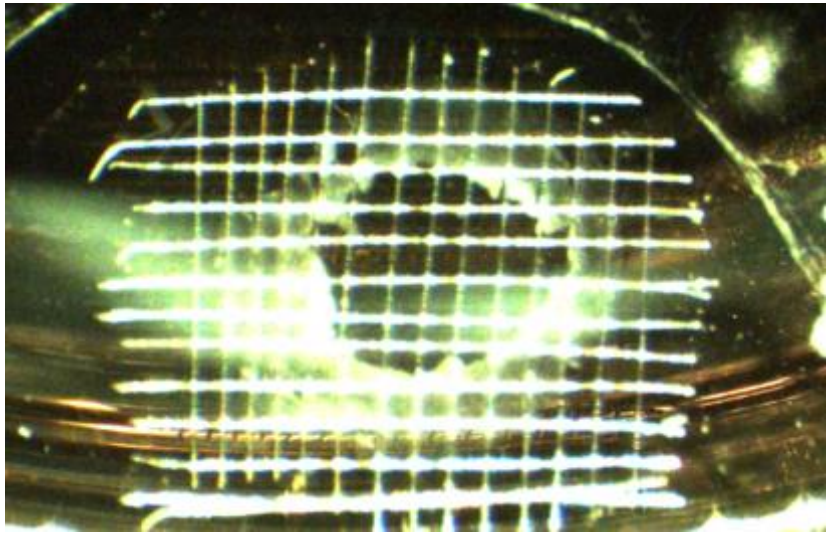
iPSC colony selection and removal / picking

Colony cutting and transfer to new culture

Further passaging and cleaning

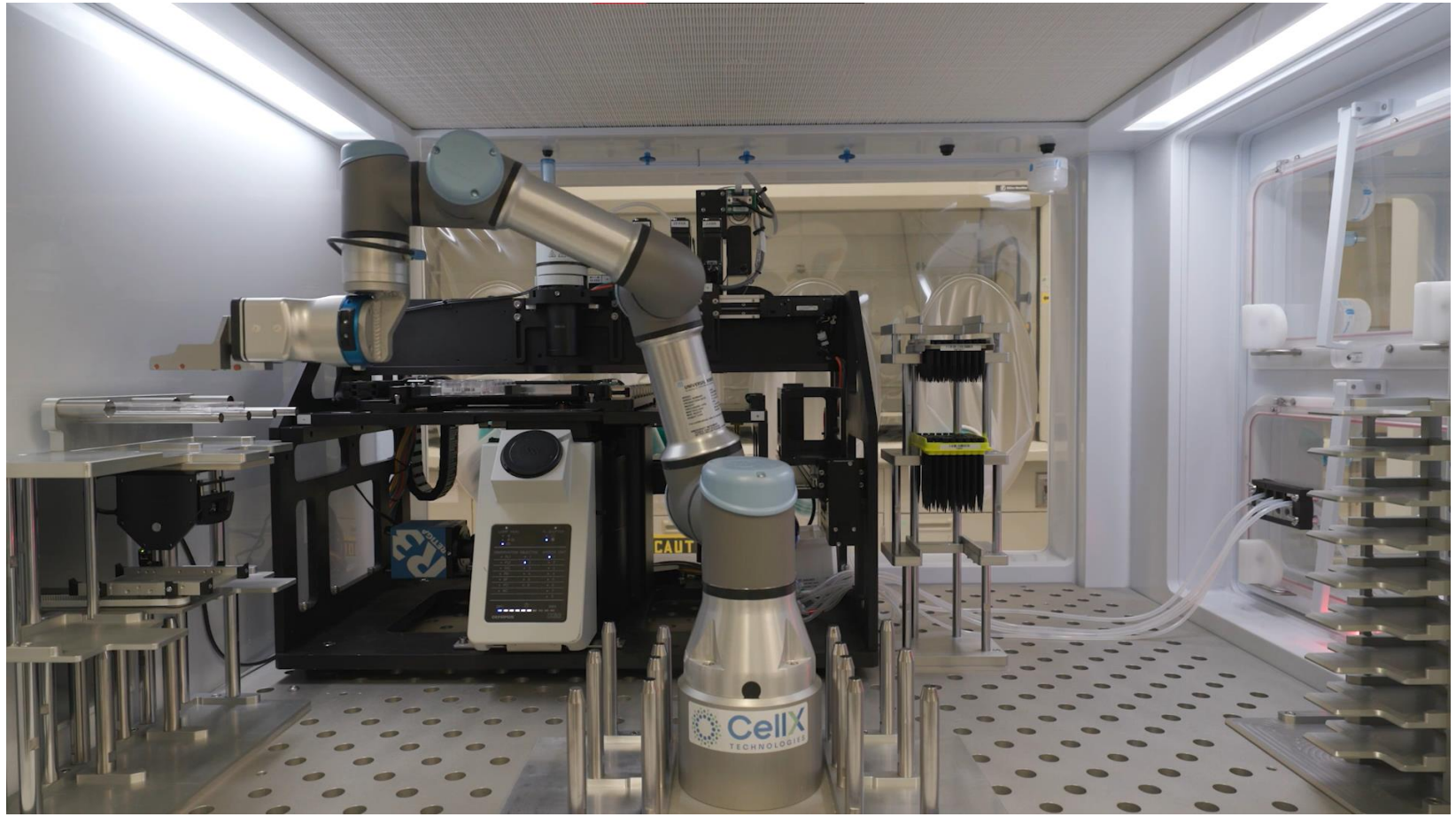


Cleaning fibroblasts away from emerging colonies



Cutting iPSC colonies to transfer to new culture

Aspen's Experience with the Celligent™ Platform for iPSC Production



>22 months
device testing

>6,000
operator hours
spent evaluating

7 cell lines total
6 PD patient lines

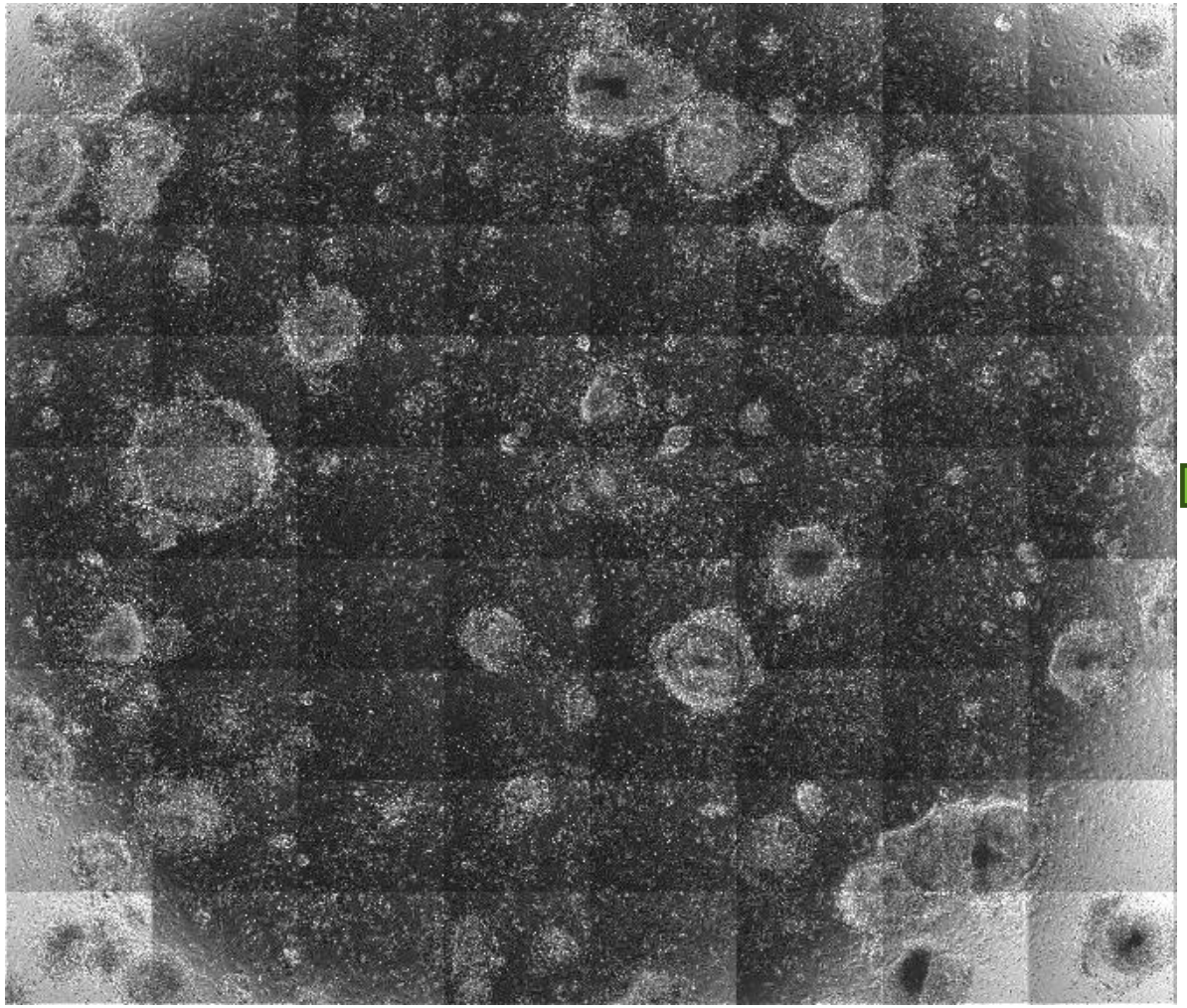
>7,000
passages

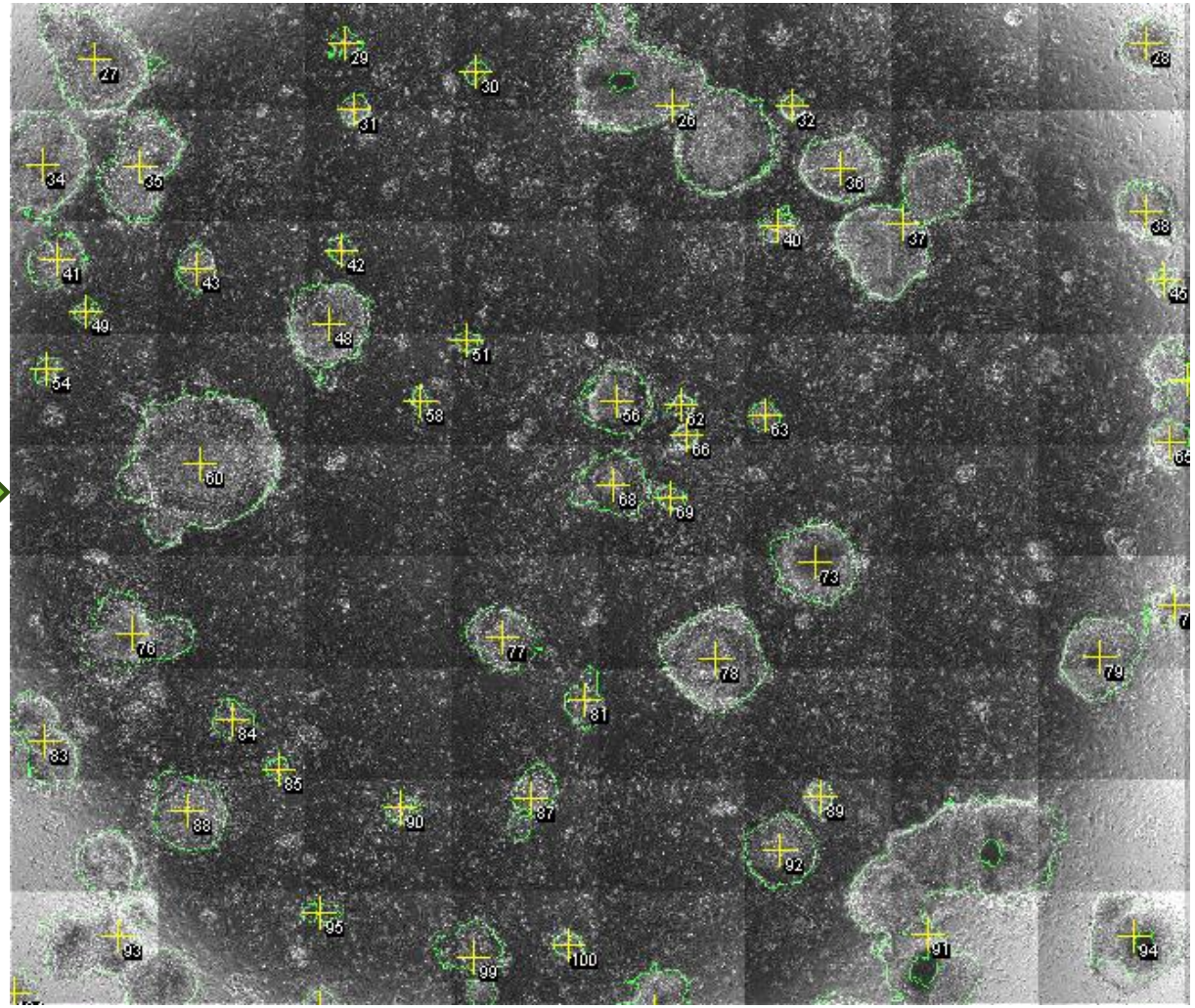
>30,000
clone picks

- Feeding
- Cleaning
- Picking
- Passaging

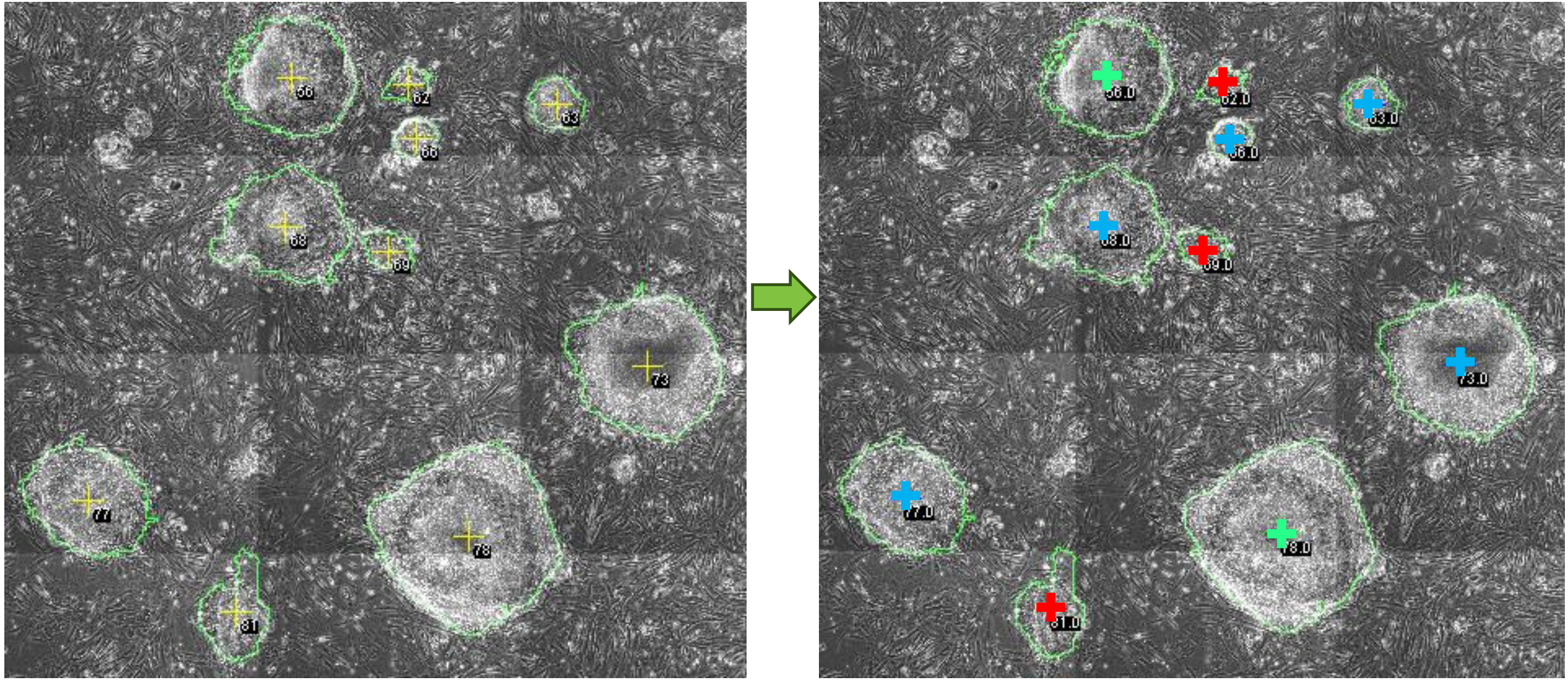
Quality attribute profiles comparable to high quality manually derived cells

Colonyze™ Analysis Enables Segmentation of Emerging iPSC Colonies

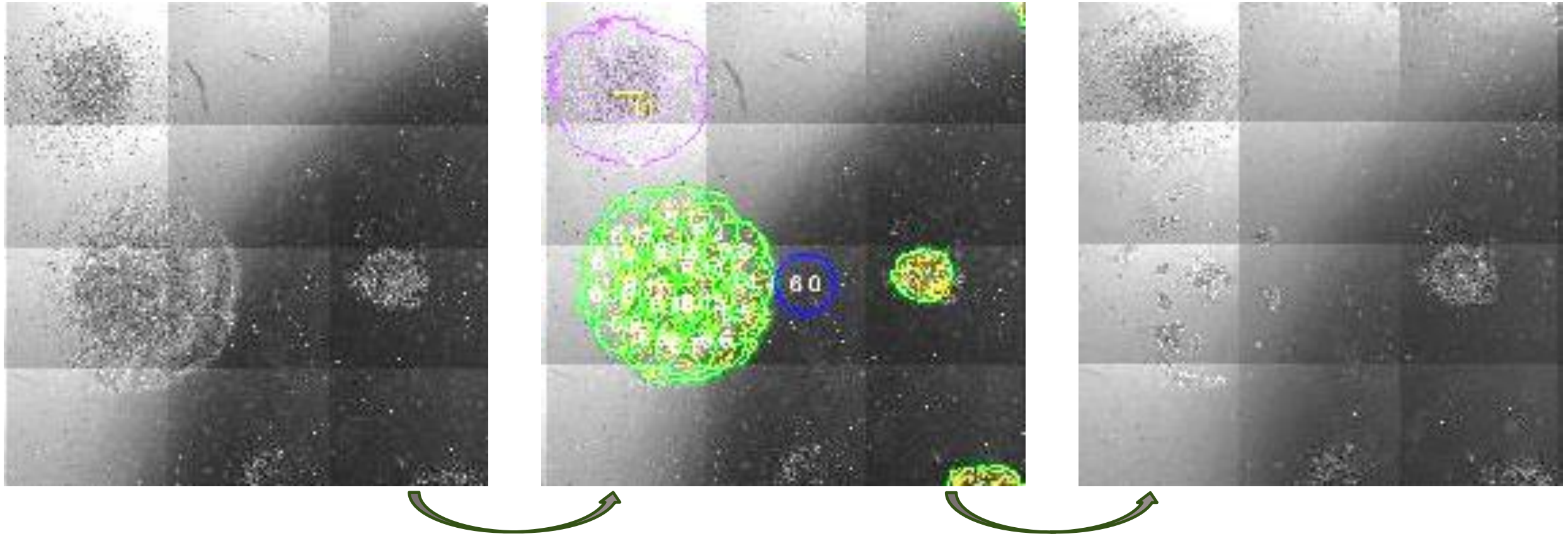




Automated Selection of Preferred Colonies for Further Processing



Automated iPSC Clone Establishment Picking Workflow

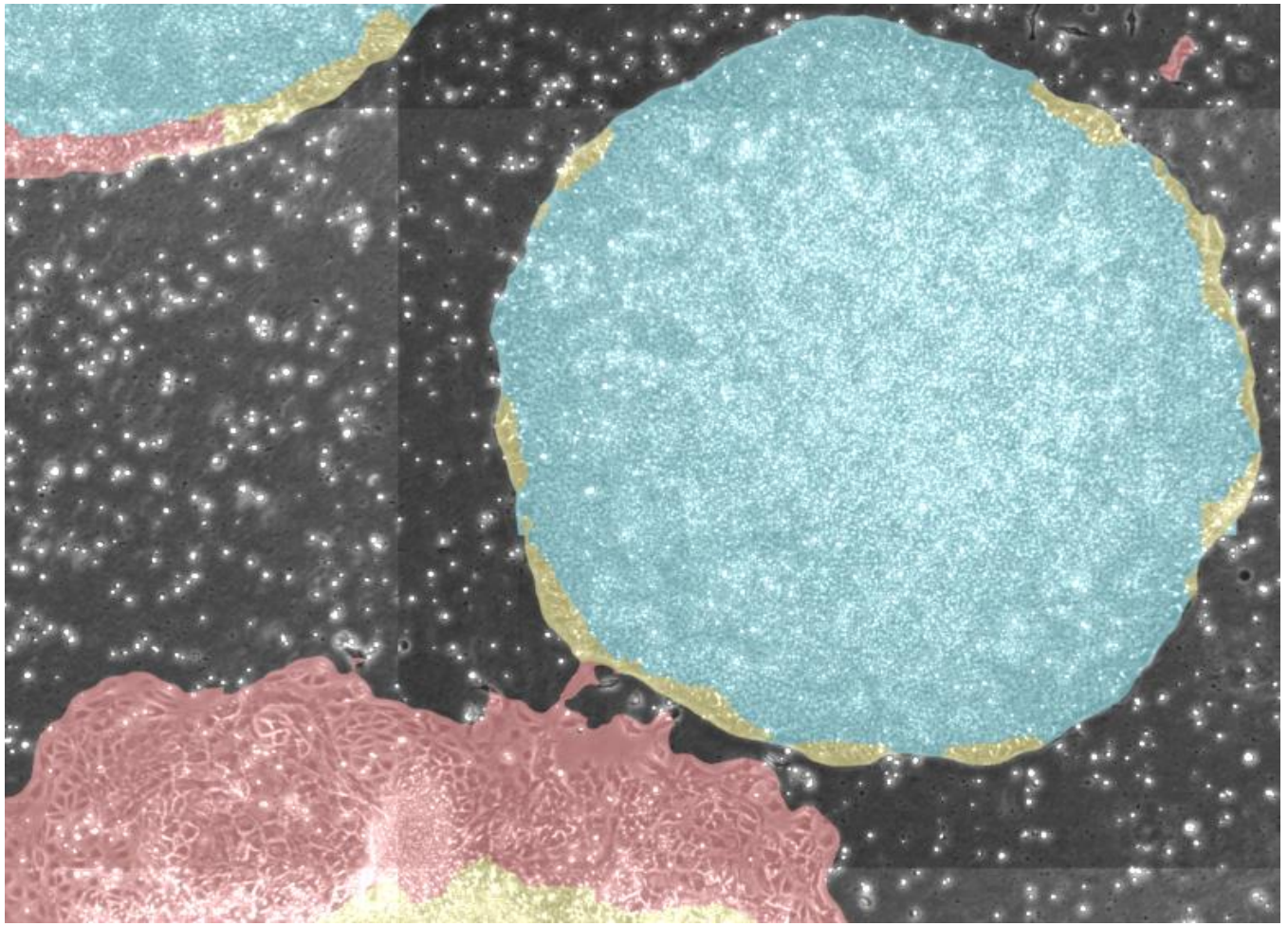


Segmentation, Colony Selection, & Pick Point Suggestions

Picking

Aspen Vision: A Multi-Class Segmentation Algorithm Capable of Discerning High Quality iPSCs

- Aspen team have developed and trained Aspen Vision, the primary basis for autonomous decision-making and robotic control from the P1 plate onward
  - Allows quality metrics to be gathered from in-process iPSCs
- Confluency, morphological quality, and percent of differentiation are used to determine next steps in the process, target robotic interventions, or justify early clone termination

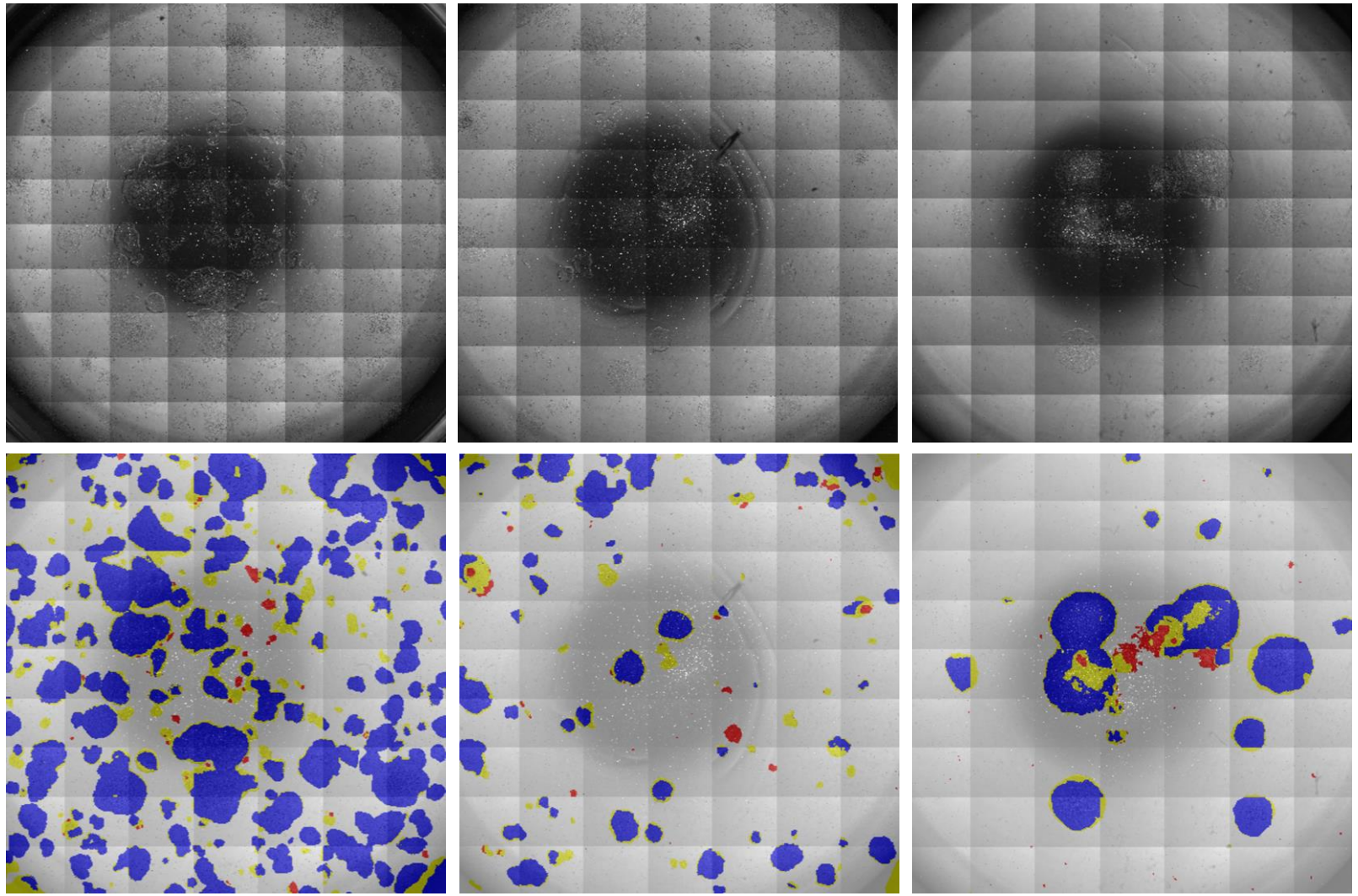


High Confidence iPSC Low Confidence iPSC Differentiation

Automated Ranking of Clones with Aspen Vision

Sample	Confluency	Quality Score
1	43%	79.70%
2	13%	69.80%
3	14%	63.70%

- Samples 1-3 are shown at top right, with corresponding Aspen Vision segmentation maps below
- Using the model output, a quality score is calculated based on the percent of high confidence iPSC areas to automatically rank the clones for use in further manufacturing



Conclusions

- Personalized iPSC-Derived Medicines Platform established
- AI can be used to support development of regenerative medicines by extracting predictive insights from large omic datasets
  - Potency
  - Comparability
- Like autonomous cars, AI can be used for autonomous manufacturing of cell therapy products to reduce cost of goods and increase accessibility

Our vision is to be the ***Leading Autologous iPSC Therapy Company***