Joint Science Subcommittee / Neuro Task Force Meeting

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CIRM
CALIFORNIA'S STEM CELL AGENCY

Presentation Overview

1 Context

2 SAF Overview

3 NTF Background

4 Neuro Survey Results

5 Discussion / Next Steps

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5-Year Strategic Plan (2022-2027)

Advance World Class Science

- Develop shared resources
- Build knowledge networks

Deliver Real World Solutions

- Advance therapies to marketing approval
- Create a manufacturing partnership network
- Expand Alpha Clinics Network
- Create Community Care Centers of Excellence

Provide Opportunity for All

- Build a diverse and highly skilled workforce
- Deliver a roadmap for access and affordability

Background & Rationale

CIRM must allocate remaining resources to maximize its impact by considering available funds and reviewing past strategies

- CIRM has established itself as a leader in stem cell and regenerative medicine, funding basic research, infrastructure, education/training, and regenerative medicine discovery and clinical development
- Since CIRM's inception, the regenerative medicine field has grown exponentially
- CIRM has finite resources
- Demand for CIRM funding exceeds available resources

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SAF Mandate

- September 2023 Science Subcommittee: Prioritization Kickoff Discussion (BM Fischer-Colbrie)
  - **Outcome:** Ask for CIRM staff to develop an approach and recommendations for prioritization
- March 2024 Science Subcommittee and ICOC: Presented SAF and continued process with September 2024 target for recommendations

The **Strategic Allocation Framework (SAF)** is a structured and data-driven approach to prioritize resource allocation and provide recommendations to the ICOC for continued implementation of CIRM's strategic plan

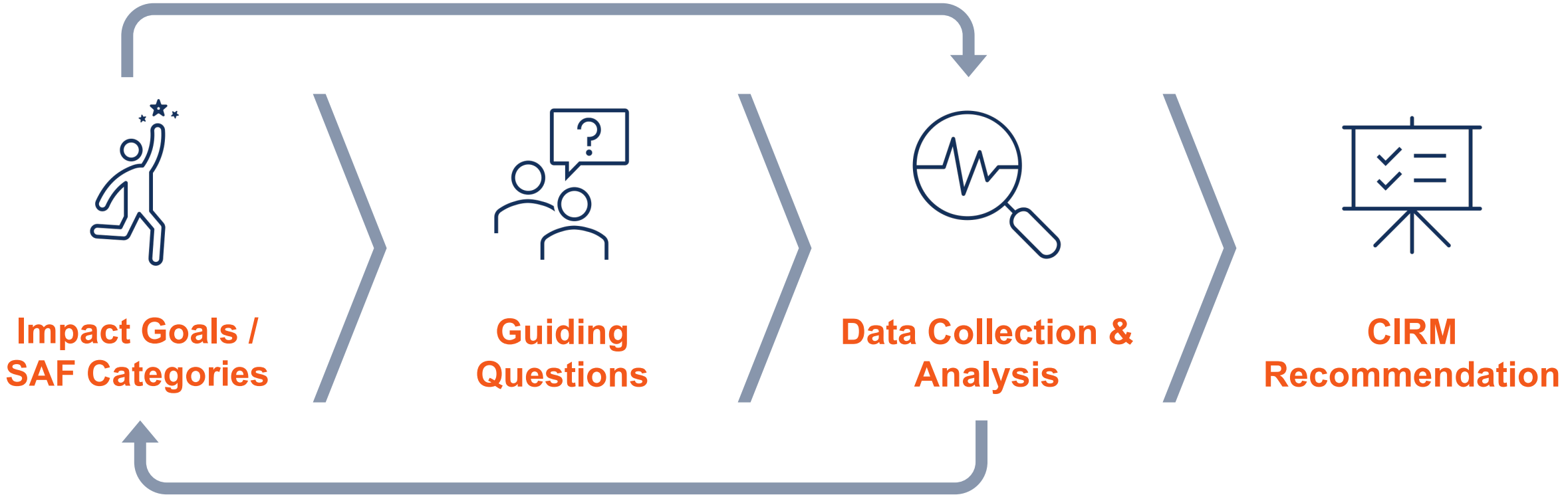
SAF | Design Questions

Determine:

- How can CIRM make the greatest impact on its mission?
- How might CIRM effectively allocate its remaining budget of $3.86B?
  - How might CIRM effectively allocate its remaining Neuro budget of $1.14B?

SAF | Process*

CIRM Staff



*Science Subcommittee, NTF, AAWG will inform specific aspects of the Recommendations

SAF Categories

SAF Categories

1. Cell and Gene Therapy Approvals
2. Accessibility and Affordability of CIRM-Funded Cell and Gene Therapies
3. Discovery of Novel Disease Mechanisms
4. Diverse Workforce Development

*NTF will inform specific aspects of the Recommendations

CIRM Preliminary* Impact Goals

Cell & Gene Therapy Approvals

1. **Advance** at least X rare disease projects to BLA

2. **Propel** X therapies targeting distinct prevalent diseases in California to late-stage trials, including a neurological condition, to significantly reduce morbidity and mortality

Accessibility & Affordability of CIRM-Funded Cell & Gene Therapies

3. **Ensure** that every CIRM funded project completing a late-stage clinical trial has a strategy that enables access and affordability by all California patients, particularly underserved populations

Discovery of Novel Disease Mechanisms

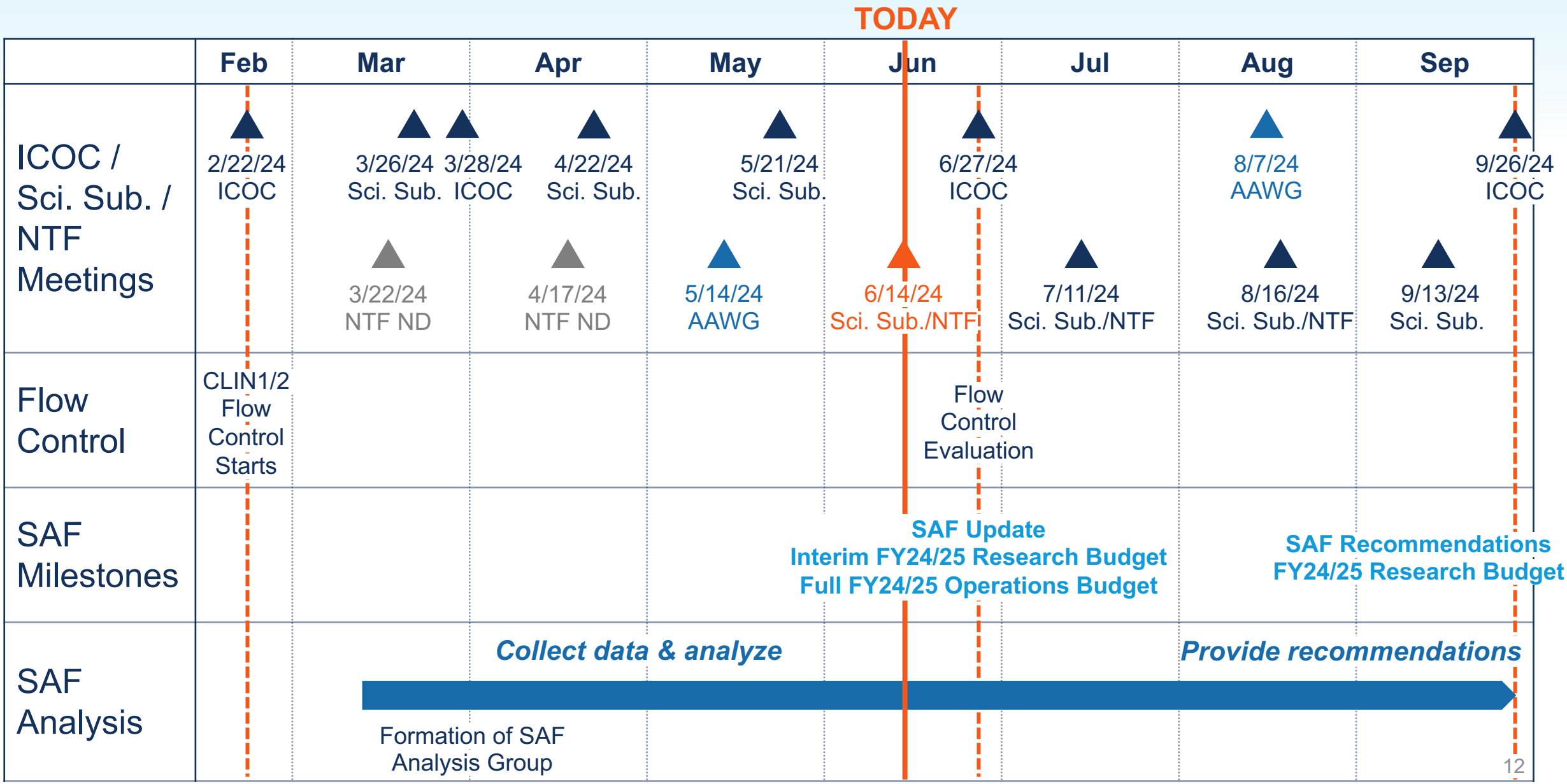
4. **Catalyze** the identification and validation of at least X novel targets and biomarkers, ensuring integration into preclinical or clinical research for prevalent diseases in California

Diverse Workforce Development

5. **Enhance** the integration and real-world application of training programs through strategic partnerships

**Preliminary Impact Goals to be refined through September ICOC*

SAF Timeline



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>27% funding for goals in #1 & #3 will be Neuro

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NTF Educational Sessions

- **Expert Educational Sessions (March-May):** Overview neurodegenerative research, spotlighting innovative approaches and under-explored areas
- **Expert Survey (May):** Across All Neuro - Enables thorough analysis and extensive stakeholder engagement, quickly and comprehensively mapping the current landscape, challenges, and opportunities

Educational Session Design Brief | Intent

1. Identify the bottlenecks/knowledge gaps that would uniquely benefit from multidisciplinary solutions and knowledge sharing
2. Cross-Disease Analysis – discuss how insights from stem cell and genetic research in one ND disease can be applied to others
3. Discuss how insights and innovative tools and techniques can be applied across diseases
4. Discuss a potential role for CIRM in addressing the above points

Survey questions were designed based on the same design brief framework

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Total Survey Responses

679

Neuroscientists* emailed to complete survey

136

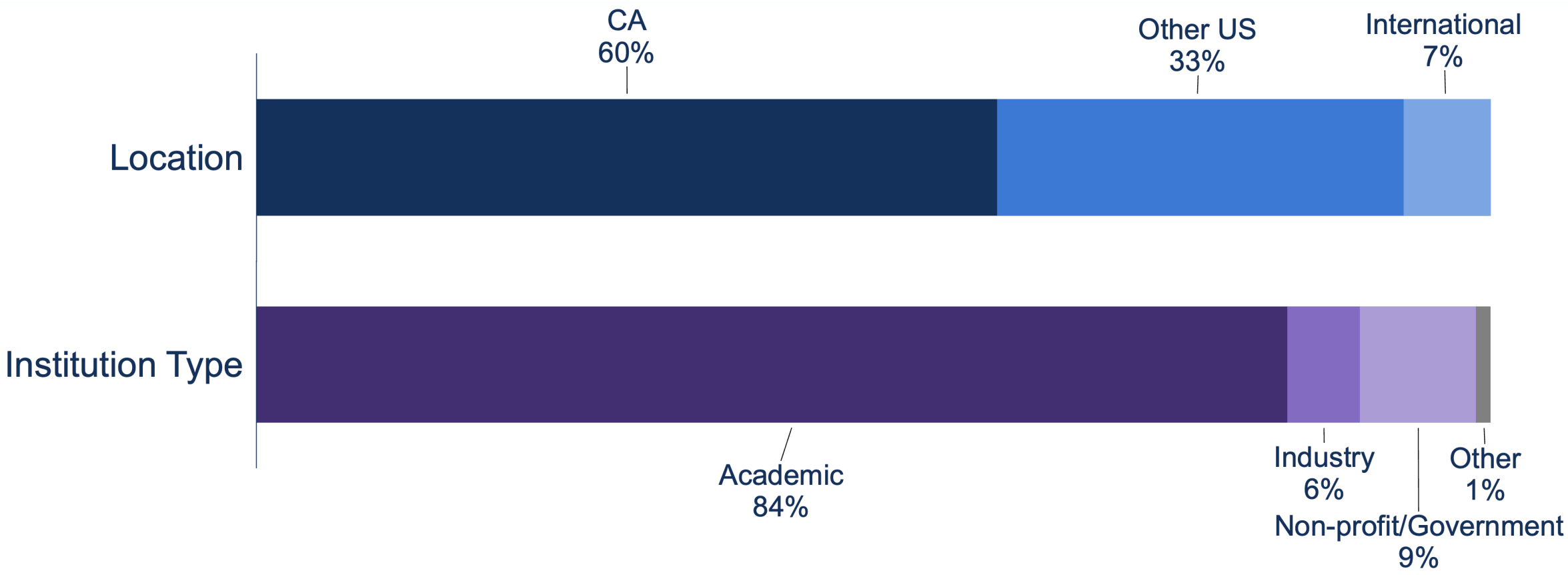
Started survey

111

Responses**

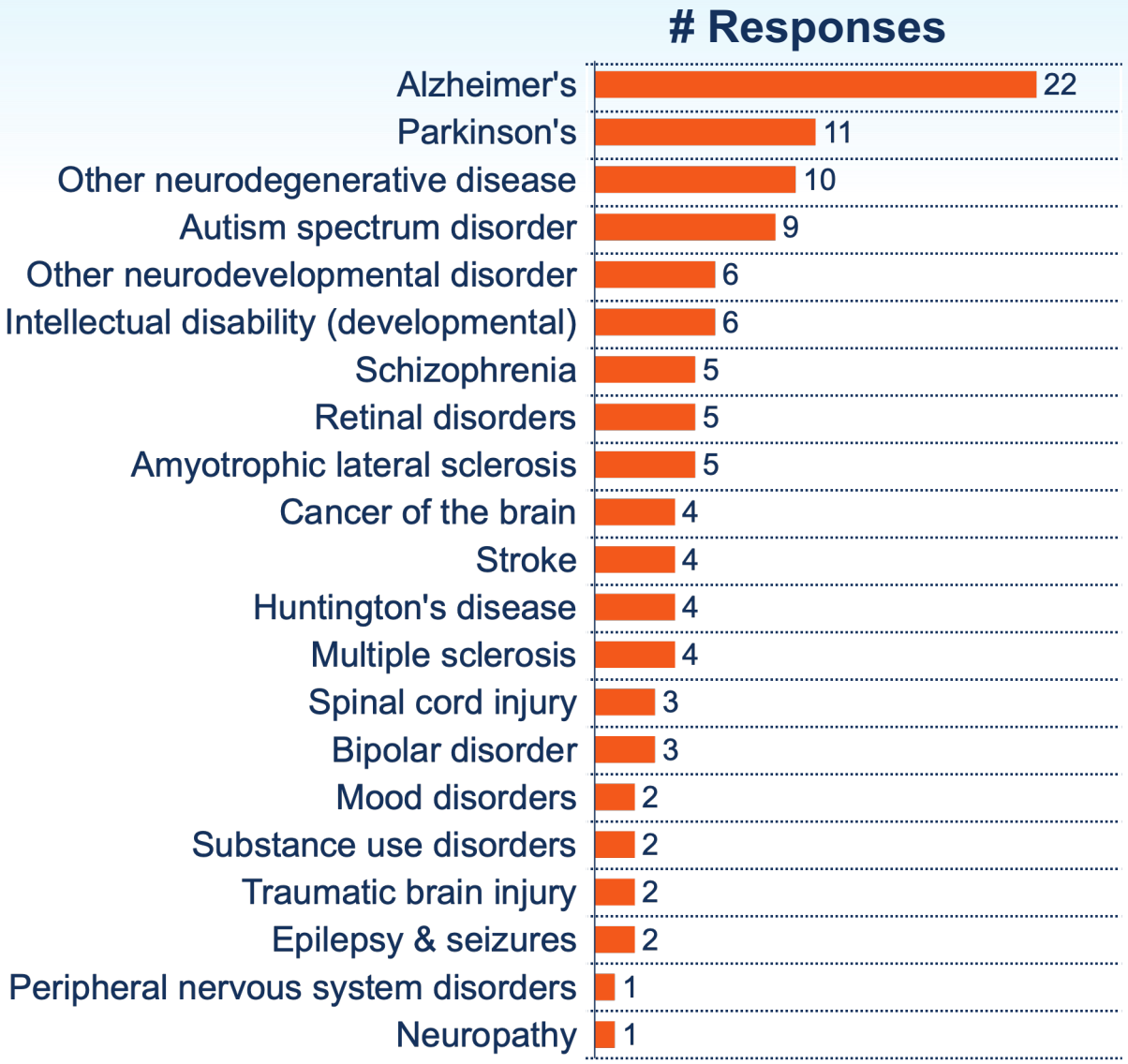
* Neuroscientists were all PhDs and/or clinicians
** Includes multiple responses

Responder Demographics



Source: CIRM Neuro Survey 2024

Neuro Disease/Disorder Response Summary



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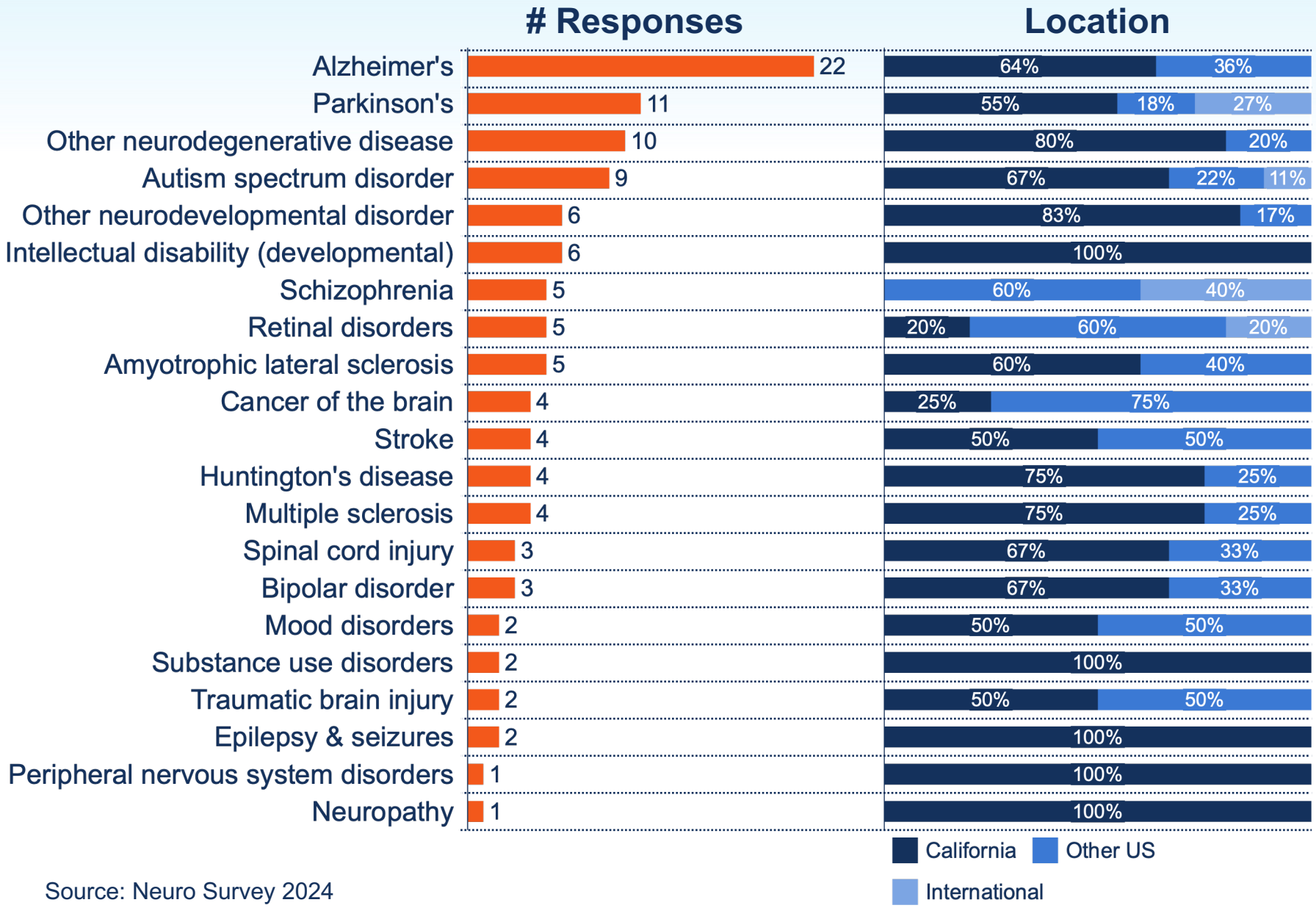
Neuro Disease/Disorder Response Summary



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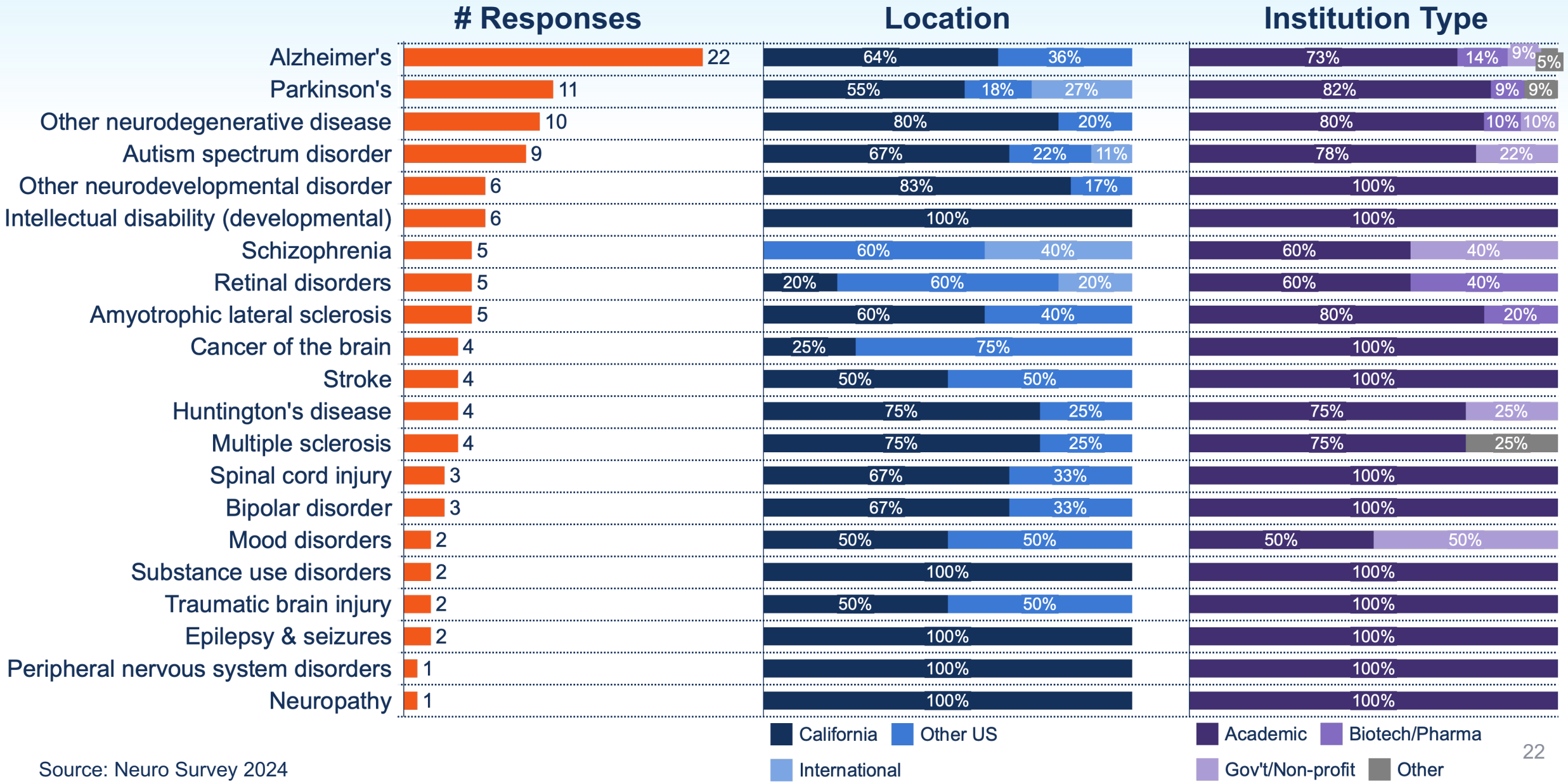
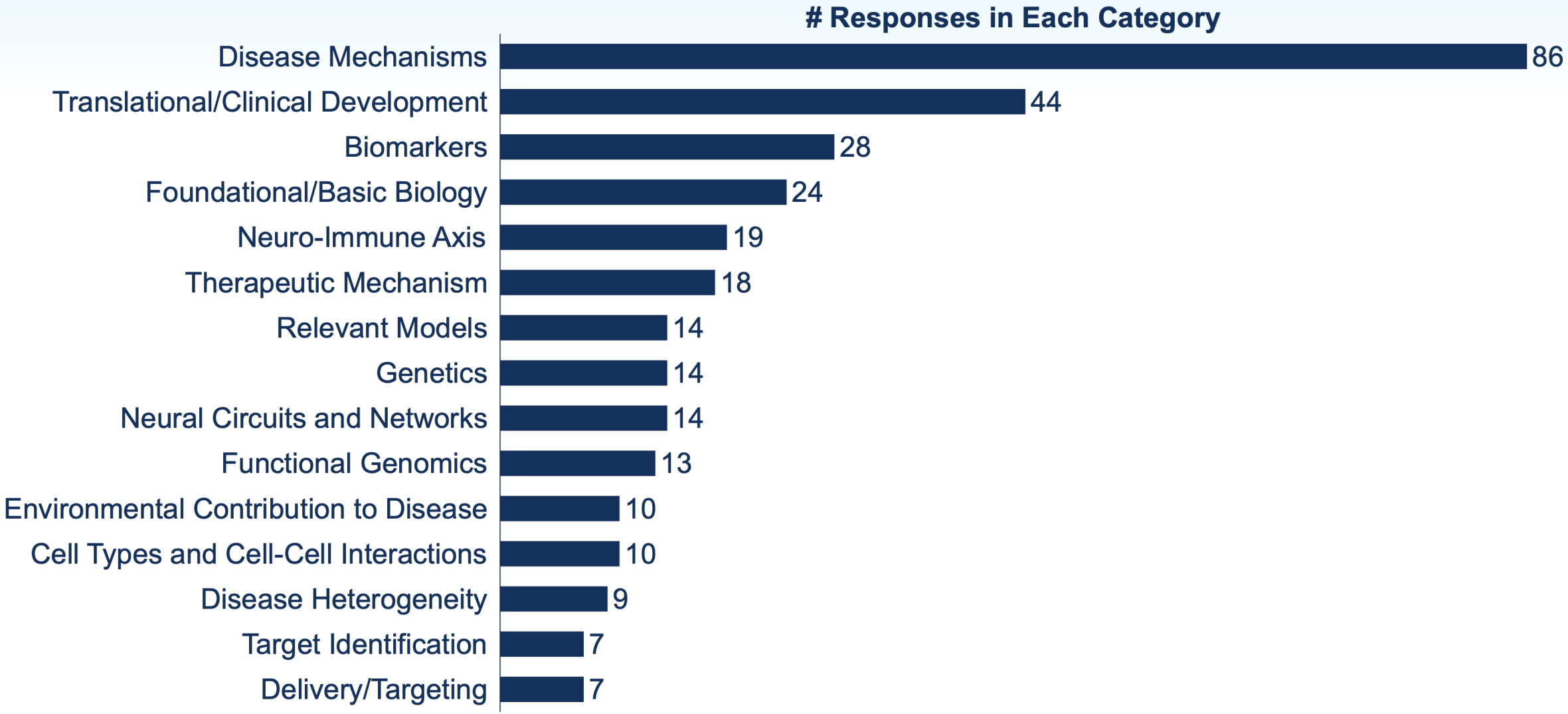


Source: Neuro Survey 2024

Survey Results | Common Knowledge Gaps



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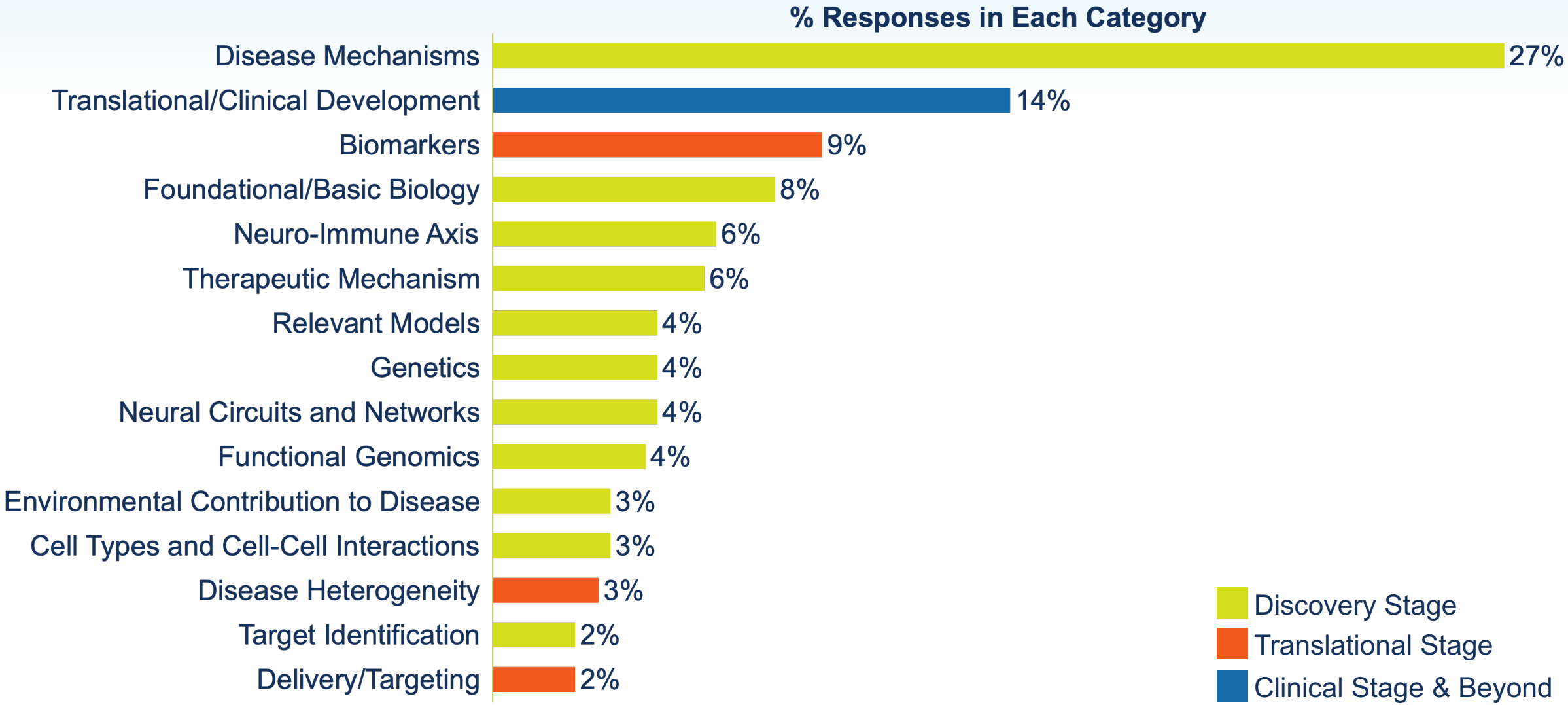


Source: Neuro Survey 2024

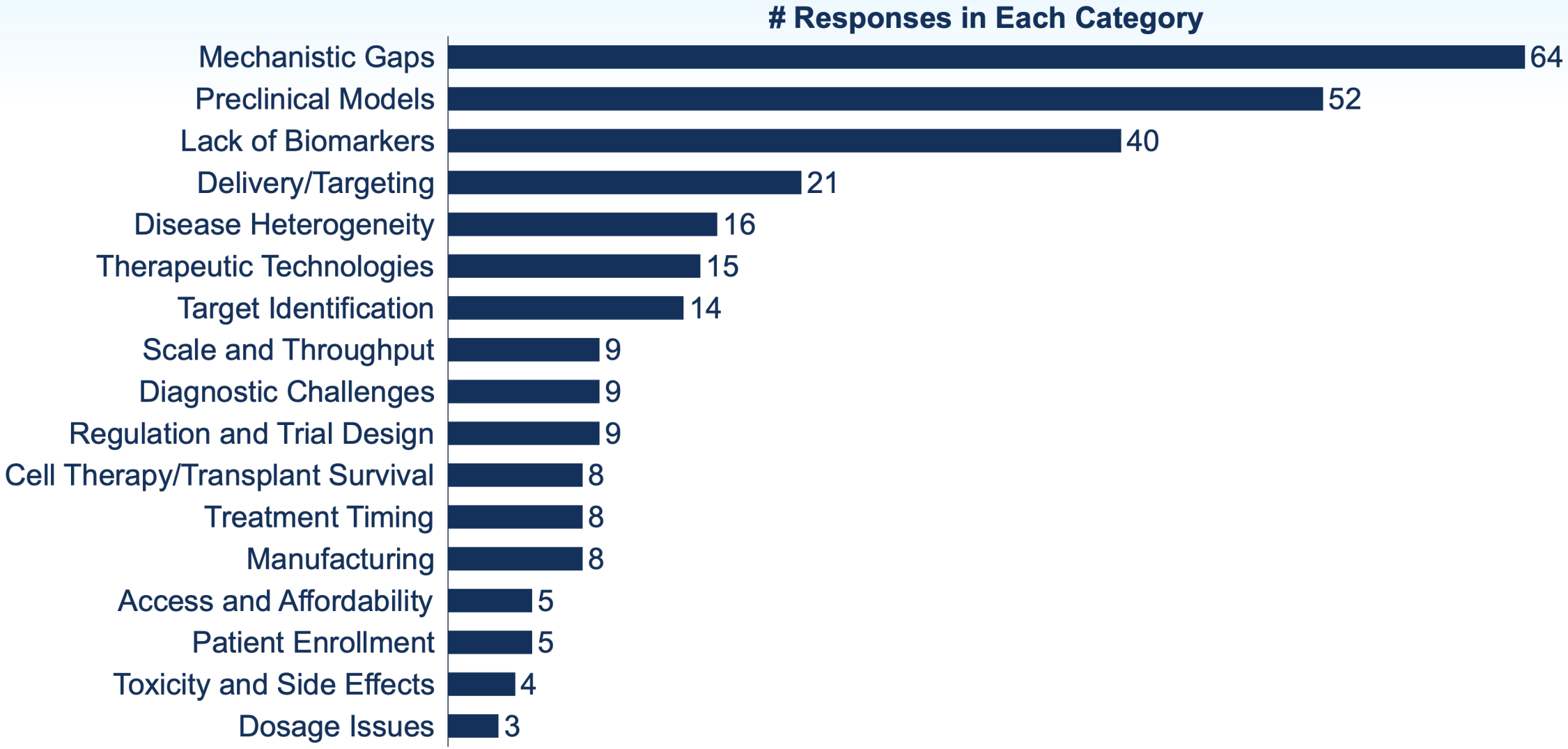
CIRM CALIFORNIA'S STEM CELL AGENCY

Survey Results | Common Knowledge Gaps

Knowledge Gap	Alzheimer's	Parkinson's	ALS	Huntington's	Multiple Sclerosis	ASD	ID (Developmental)	Schizophrenia	Bipolar Disorder	Mood Disorders	Substance Use Disorders	Retinal Disorders	Cancer of the Brain	Stroke	Spinal Cord Injury	Traumatic Brain Injury	Epilepsy & Seizures	PNS Disorders	Neuropathy
Disease Mechanisms	✓✓	✓	✓✓	✓✓	✓✓	✓	✓✓	✓	✓	✓✓	✓✓	✓		✓✓	✓		✓✓	✓✓	
Translational/Clinical Development	✓	✓							✓		✓	✓✓	✓	✓	✓✓		✓	✓✓	✓✓
Biomarkers	✓		✓✓						✓	✓					✓		✓		
Foundational/Basic Biology	✓			✓	✓											✓			
Neuro-Immune Axis	✓				✓								✓		✓	✓✓			
Therapeutic Mechanism				✓	✓								✓	✓	✓	✓✓			
Relevant Models							✓		✓	✓									
Genetics									✓		✓✓								✓✓
Neural Circuits And Networks						✓	✓										✓		
Functional Genomics						✓		✓											
Environmental Contribution To Disease						✓				✓									
Cell Types And Cell-Cell Interactions													✓	✓			✓		
Disease Heterogeneity								✓		✓									
Target Identification								✓	✓										
Delivery/Targeting																			✓✓

Source: Neuro Survey 2024; ALS=Amyotrophic Lateral Sclerosis, ASD=Autism Spectrum Disorder, ID=Intellectual Disability, PNS=Peripheral Nervous System

Survey Results | Common Development Bottlenecks



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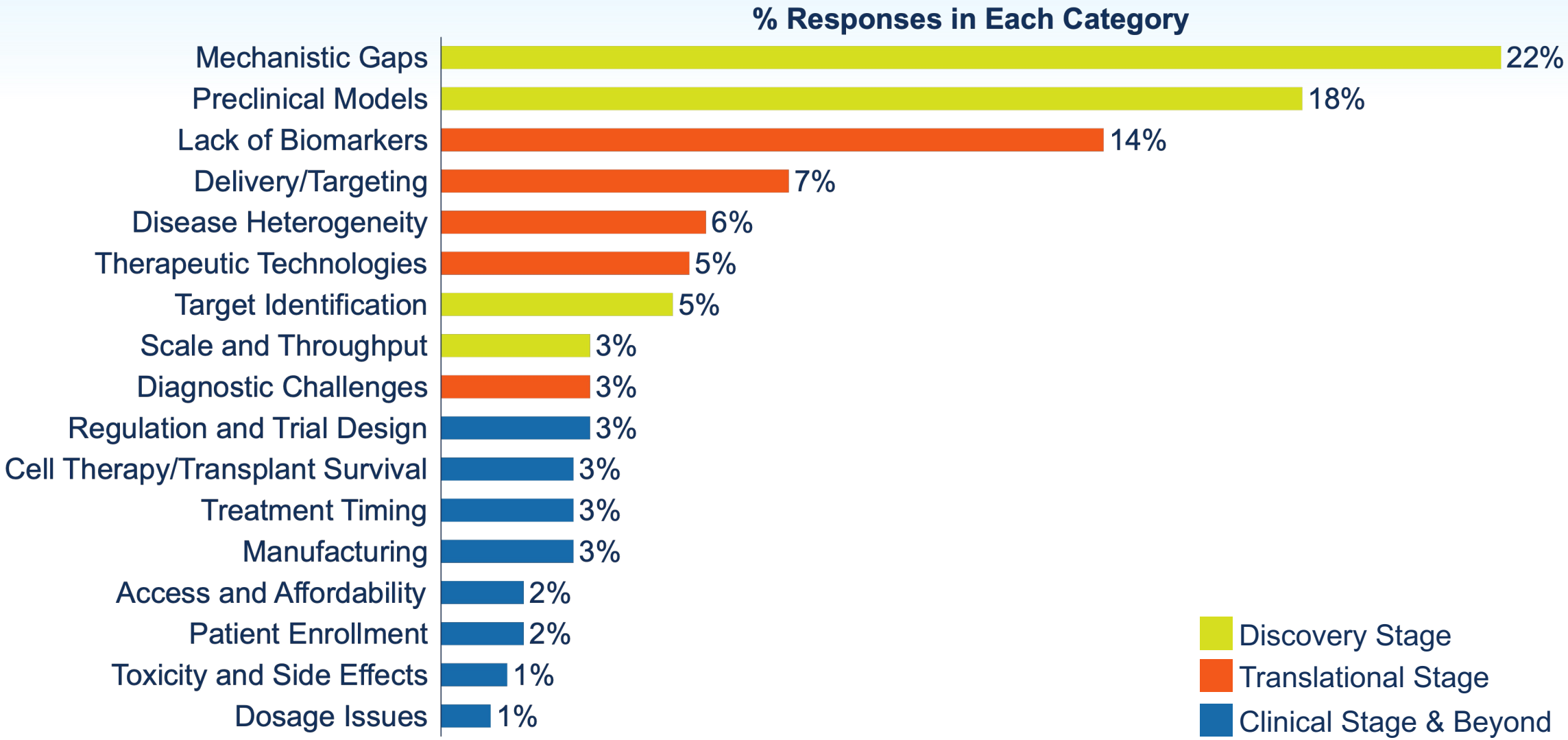
Survey Results | Common Development Bottlenecks



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Survey Results | Common Development Bottlenecks

Development Bottleneck	Alzheimer's	Parkinson's	ALS	Huntington's	Multiple Sclerosis	ASD	ID (Developmental)	Schizophrenia	Bipolar Disorder	Mood Disorders	Substance Use	Retinal Disorders	Cancer of the Brain	Stroke	Spinal Cord Injury	Traumatic Brain Injury	Epilepsy & Seizures	PNS Disorders	Neuropathy
Mechanistic Gaps	✓	✓	✓	✓		✓	✓	✓✓	✓	✓✓				✓		✓	✓✓	✓✓	
Preclinical Models	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓			✓		✓		
Lack Of Biomarkers		✓	✓	✓	✓	✓		✓	✓	✓✓	✓			✓	✓	✓			
Delivery/Targeting				✓			✓					✓	✓				✓		✓✓
Disease Heterogeneity			✓			✓					✓		✓		✓	✓			
Therapeutic Technologies				✓										✓		✓		✓✓	
Target Identification			✓						✓✓	✓	✓								
Scale And Throughput						✓					✓						✓		
Diagnostic Challenges									✓										
Regulation & Trial Design											✓	✓			✓				
Cell Therapy/Transplant Survival												✓			✓	✓			
Treatment Timing							✓												
Manufacturing															✓				
Access & Affordability																			
Patient Enrollment																			✓✓
Toxicity & Side Effects																	✓		
Dosage Issues																✓			

Source: Neuro Survey 2024; ALS=Amyotrophic Lateral Sclerosis, ASD=Autism Spectrum Disorder, ID=Intellectual Disability, PNS=Peripheral Nervous System

Survey Results | Stem Cell Models

Disease/Disorder	Current Use	Current Effectiveness
Alzheimer's Disease	Yes	Effective disease modeling for basic bio but not drug screening
Parkinson's Disease	Yes	Generally effective, but challenges modeling age-related changes
Amyotrophic lateral sclerosis	Yes	Disagreement in SC model effectiveness, leaning towards effective
Multiple sclerosis	Yes	Highly variable
Huntington's disease	Yes	Disagreement in SC model effectiveness
Autism spectrum disorder	Yes	Disagreement in SC model effectiveness, leaning towards ineffective/premature
Intellectual disability (developmental)	Yes	Efffective for neuronal stem cell proliferation/cell survival in early stage, but not curcuit/functions in later stage
Schizophrenia	Yes	Effective for studying bio effects/genetic risks, but no in vitro readout yet
Stroke	Yes	Some positive results, but hard to induce focal ischemia in vitro
Retinal disorders	Yes	Retinal organoids are useful, positive results in animal models, but not yet reproduced in humans
Cancer of the brain	Yes	Unclear if models are effective at predicting patient outcome

Yes No Not Sure

Source: Neuro Survey 2024

Survey - High Level Needs in the Neuro Field

Foundational and Mechanistic Discovery Initiatives:

- Urgent need for deeper understanding of neuro disease mechanisms
- Recognition of the value and need for enhanced human stem cell models
- Identification common areas of potential investment – Broader impact

Efficient Discovery to Translation

- Innovations in CGT technologies and improved understanding of therapeutic mechanisms
- Delivery and targeting to the brain and specific cell-types
- New biomarker identification and validation
- Other bottlenecks in CGT translation and clinical development including:
  - Treatment durability and transplant survival
  - Scale and quality control in manufacturing

Preliminary Recommendations for SAF

1- Foundational and Mechanistic Discovery

Increase research to uncover cross-disease systems and interactions, aiming for breakthroughs in identifying new disease mechanisms, targets, and biomarkers

Potential to accomplish this through ReMIND initiative structure - Promoting collaborative, multidisciplinary innovation in stem cell and genetic research across various disciplines and indications

2- Efficient Discovery to Translation

Enhance investment to address significant common translational needs and bottlenecks across CGT space to accelerate the transition from bench to bedside.

Potential to accomplish this through a revitalized structure integrating DISC2/TRAN/CLIN1 programs to identify and translate new therapeutic and biomarker candidates and address common bottlenecks

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Timeline & Next Steps

Meeting	SAF Topics
June NTF/Science Subcommittee	• SAF Overview - NTF Background • Present Neuro Survey Results – Discussion • Provide a high-level overview of how this fits within Strategic Analysis Framework (SAF)
June ICOC	• Provide an update on the process, aligning with the June NTF/Science Subcommittee • Offer an example of analysis that will inform recommendations
July NTF/Science Subcommittee	• Present four overarching SAF Goals and delve into Goal 4 • Review relevant data associated with Goal 4 • Discuss potential recommendations for Goal 4
August NTF/Science Subcommittee	• Present updates based on feedback received on Goal 4 • Introduce Goal 1 & 2 and discuss associated data • Discuss potential recommendations for Goals 1 & 2
August AAWG	• Present updates on Goal 3 and discuss associated data • Discuss potential recommendations for Goal 3

September Science Subcommittee	• Full SAF presentation:
	  ◦ Present updates based on feedback received on Goals 1,2, & 4
	  ◦ Present Goal 3 (from AAWG feedback) and Goal 5 together, discussing strategies and data relevant to both

September ICOC	• Overall Presentation of SAF recommendations

SAF Timeline