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PHARMACEUTICAL MANAGEMENT SCIENCE ASSOCIATION

2022 ANNUAL CONFERENCE

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Louisville, Kentucky

Building a Machine Learning Model to Find Undiagnosed Patients in Rare Disease

Brett Ramos – Acadia Pharmaceuticals

Griff Vinton – Charles River Associates (CRA)

Presentation Flow

- **Disease Background & Challenge:** Delayed diagnosis of Rett syndrome patients
- **Proposed Approach:** Create a disease ‘fingerprint’ to implement in ML model
- **Define Rett Patients:** Characterize Rett syndrome patients via APLD data
- **Fingerprint Rett Diagnostic Journey:** Explore longitudinal comorbidity mapping
- **Find Undiagnosed Rett Patients:** Demo planned ML process via psoriasis example
- **Expected Impact:** Identify likely Rett candidates for screening
- **Q&A**

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Rett syndrome is a debilitating neurologic rare disease occurring primarily in females

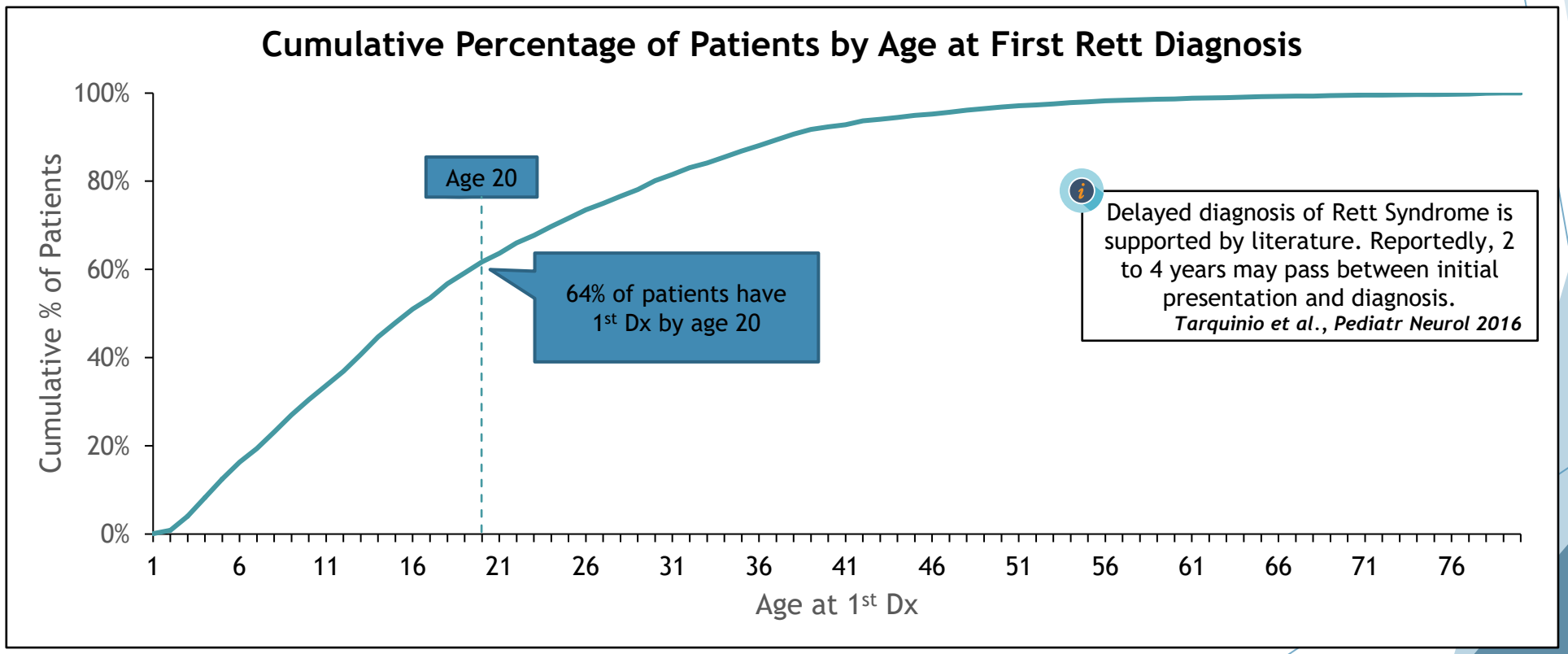
Rett Syndrome		
Epidemiology[1,2]	• Rett Syndrome is a rare disease • Rett has a **worldwide** prevalence of **1 in 10,000 to 15,000** female births • Rett affects approximately **6,000 to 9,000** patients in the **US**	
Disease Impact[1]	• Rett is a **debilitating neurologic disease** occurring **primarily in females** • Rett causes **problems in brain function with rapid decline** commencing around **6 to 18 months of age**	

Symptoms	• Major symptoms include:
	  • Cognitive, sensory, emotional, and motor impairment
	  • Loss of spoken communication, independence, and purposeful hand use	

No FDA-approved treatment for Rett Syndrome		

Rett is not commonly diagnosed until teenage years despite infant onset of brain decline

- Despite decline in brain functions commencing around 6 to 18 months of age, **only half of patients** were **diagnosed** with Rett Syndrome **by age 15**, suggesting <u>delayed diagnosis</u>
- Small patient populations with complex journeys are common in rare disease, where disease awareness may be low, frequently leading to prolonged time to diagnosis



Note: Analysis does not require any washout and includes all patients with 2+ Rett Dx; some patients 1st Dx may reflect a change in coverage
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

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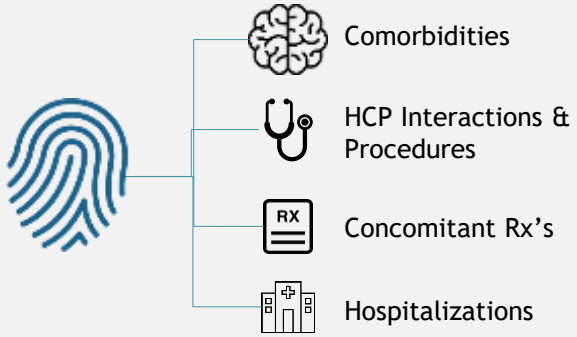
A machine learning approach applied to robust patient level data can identify undiagnosed patients earlier in their journey

Find Patients with Disease X

1 Define

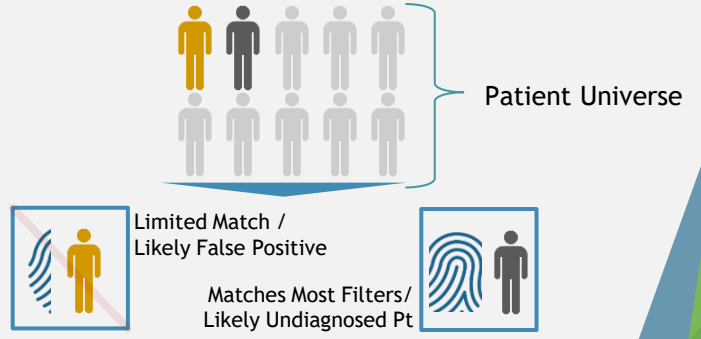
Identify a sample of patients with a **confirmed diagnosis** and determine variables that can **uniquely characterize them leading up to diagnosis**

2 Fingerprint



Focus on key drivers associated with diagnosis and **employ Machine Learning model to develop disease fingerprint**

3 Find



Use disease filters to narrow the predictive modeling universe / minimize false positives and **identify suspected patients with high confidence**

Impact Drivers

Patients mapped to identifiable HCPs for targeted outreach

Diagnosis

Extract **triggers** that can be used **to identify patients earlier**

Publications or other tactics to **communicate evidence-based disease filters with broader audience**

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We defined a confirmed Rett cohort using an ICD-10 diagnosis code among historical APLD data

Total APLD/LAAD* Sample

6,310

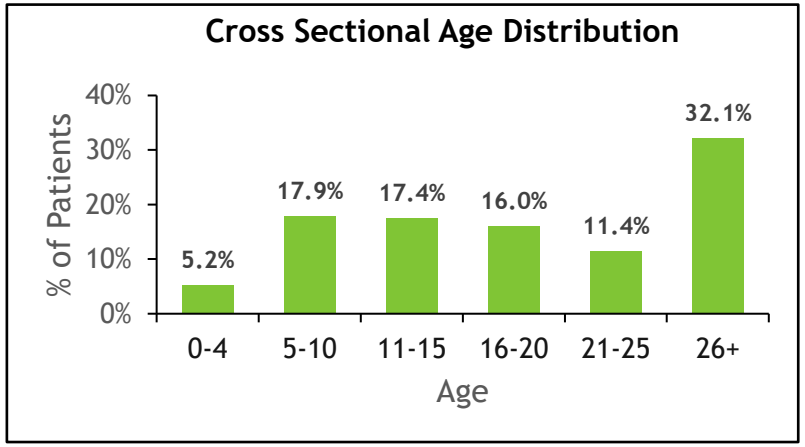
All patients with 2+ Rett Dx codes over the most recent 4-year period (ICD 10: F84.2)

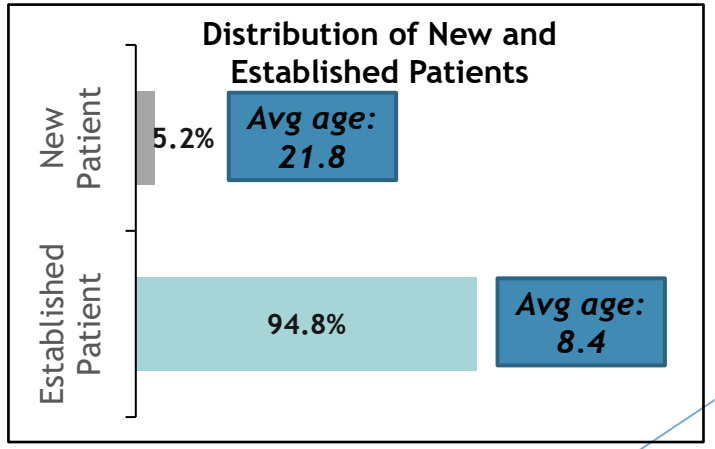
Cross-sectional Market Map Year Patients

3,983

Female patients with at least 1 Rett Dx in the most recent year (11/2018-10/2019)

While ~10% of the sample were male, only females are included in this analysis





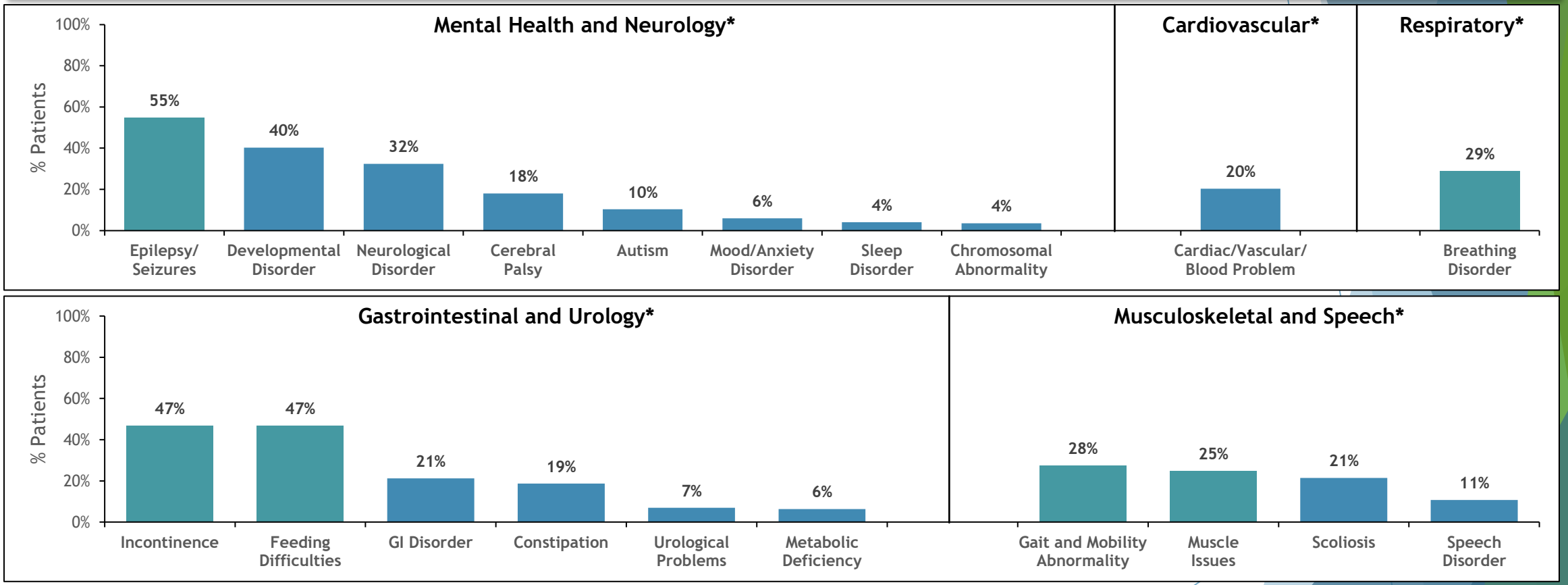
New patients are defined as those that have ***no Rett Dx within 24 months prior*** to the start of the most recent year and are ***≤20 years old***, including patients with insufficient prior history to determine if they have a Rett Dx within 24 months. **Established patients** are those that are not new.

*APLD = Anonymized Patient Level Data
*LAAD = Longitudinal Access and Adjudication Data
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

Characterization of Rett syndrome: Comorbidities (ICD-10)

5 broad categories captured the range of **comorbidities** Rett patients suffer

- Mental Health/Neurology, GI/Urology, Musculoskeletal/Speech, Cardiovascular, and Respiratory

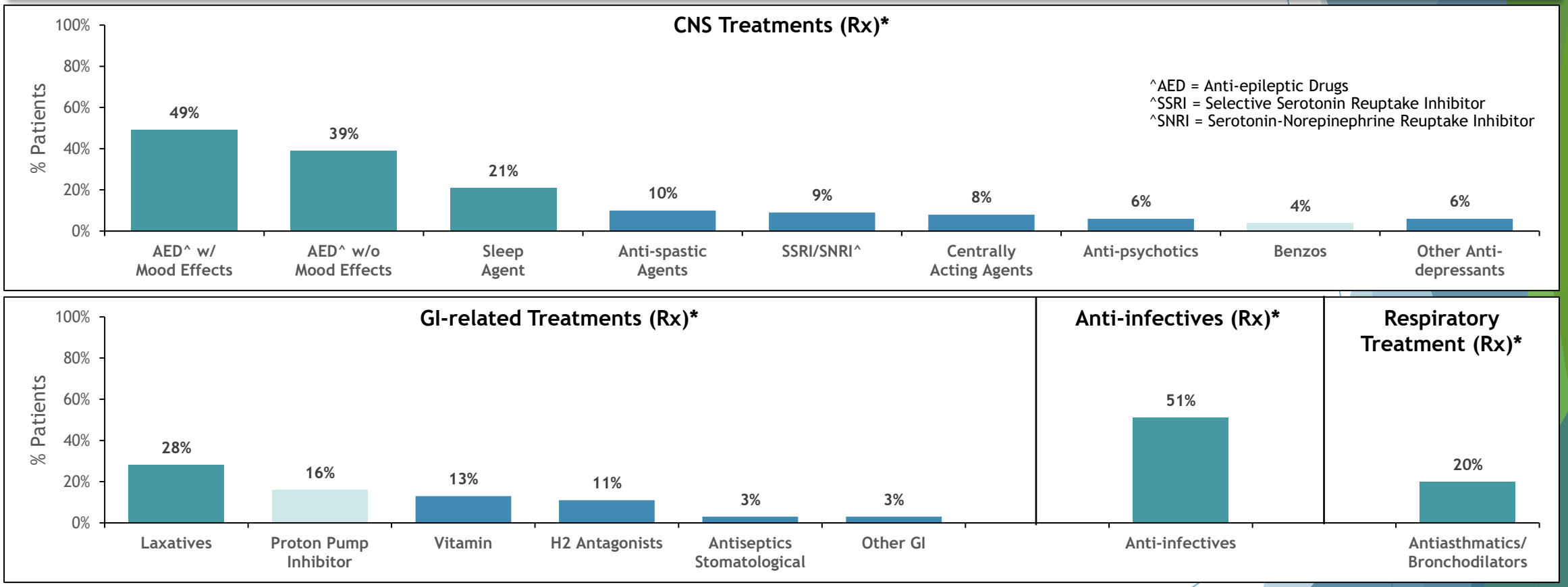


- Seizures, incontinence, feeding problems, breathing disorders and mobility/muscle issues are the most prevalent conditions
- Scoliosis, cardiovascular/blood and speech disorders are also not uncommon

*Note: Patients could overlap among categories so that the sum could be over 100%
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

Characterization of Rett syndrome: Treatment (Rx)

4 broad categories captured the prevalent **treatment modalities** for Rett patients
- CNS, GI-related, Anti-Infectives, and Respiratory

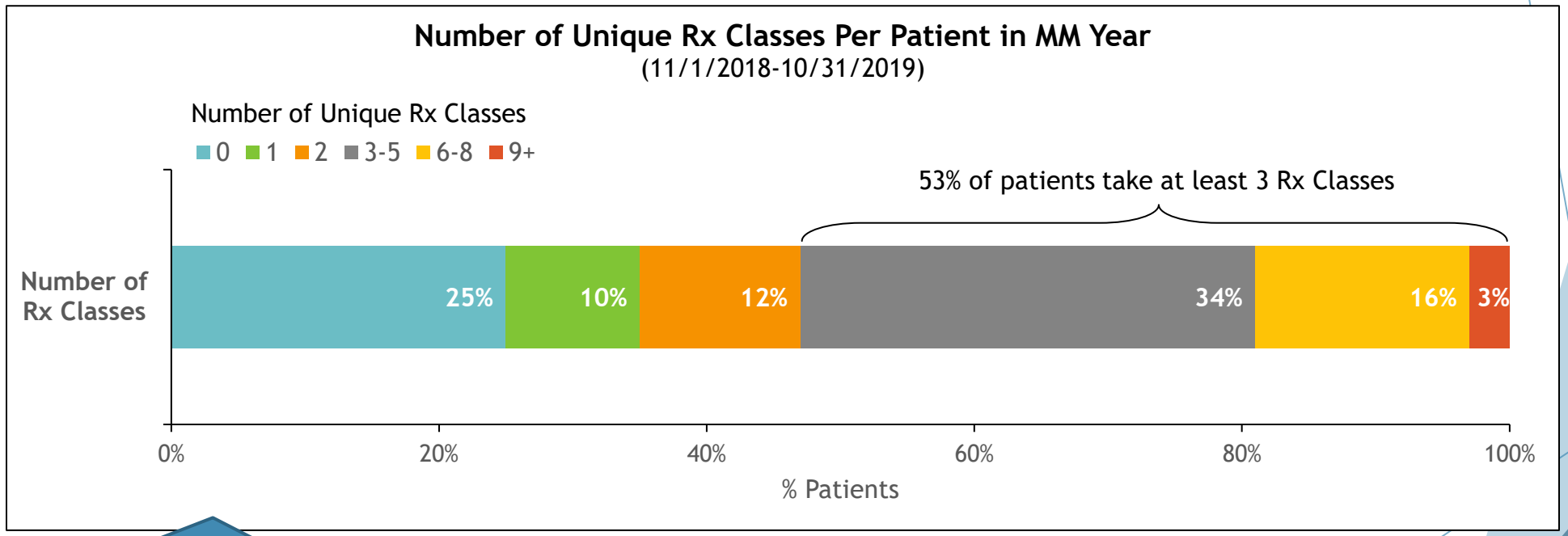


- AEDs, Sleep Agent, and Laxatives were the top Rx classes used within the MM year (11/1/2018-10/31/2019)
- Anti-infectives and respiratory treatments are also commonly used among patients

*Note: Patients could overlap among categories so that the sum could be over 100%
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

Characterization of Rett syndrome: Treatment (Rx classes)

- Over **half of patients** use **at least 3 different Rx classes**
- Approximately 20% of patients are taking 6+ different Rx classes

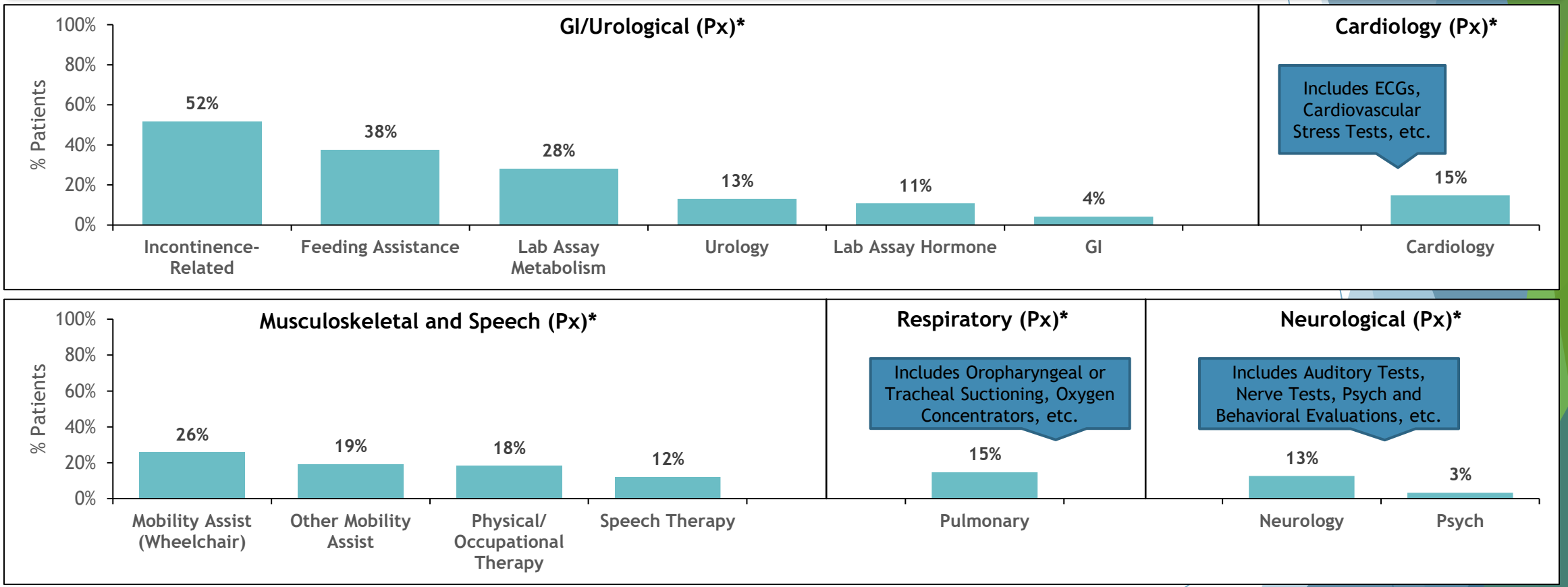


Patients may take multiple drugs within each Rx class, potentially adding further Rx burden

Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

Characterization of Rett syndrome: Procedures (Px)

Procedures are grouped according to the comorbidities they address
- **GI/Urological** and **Musculoskeletal/Speech** are major categories of procedures

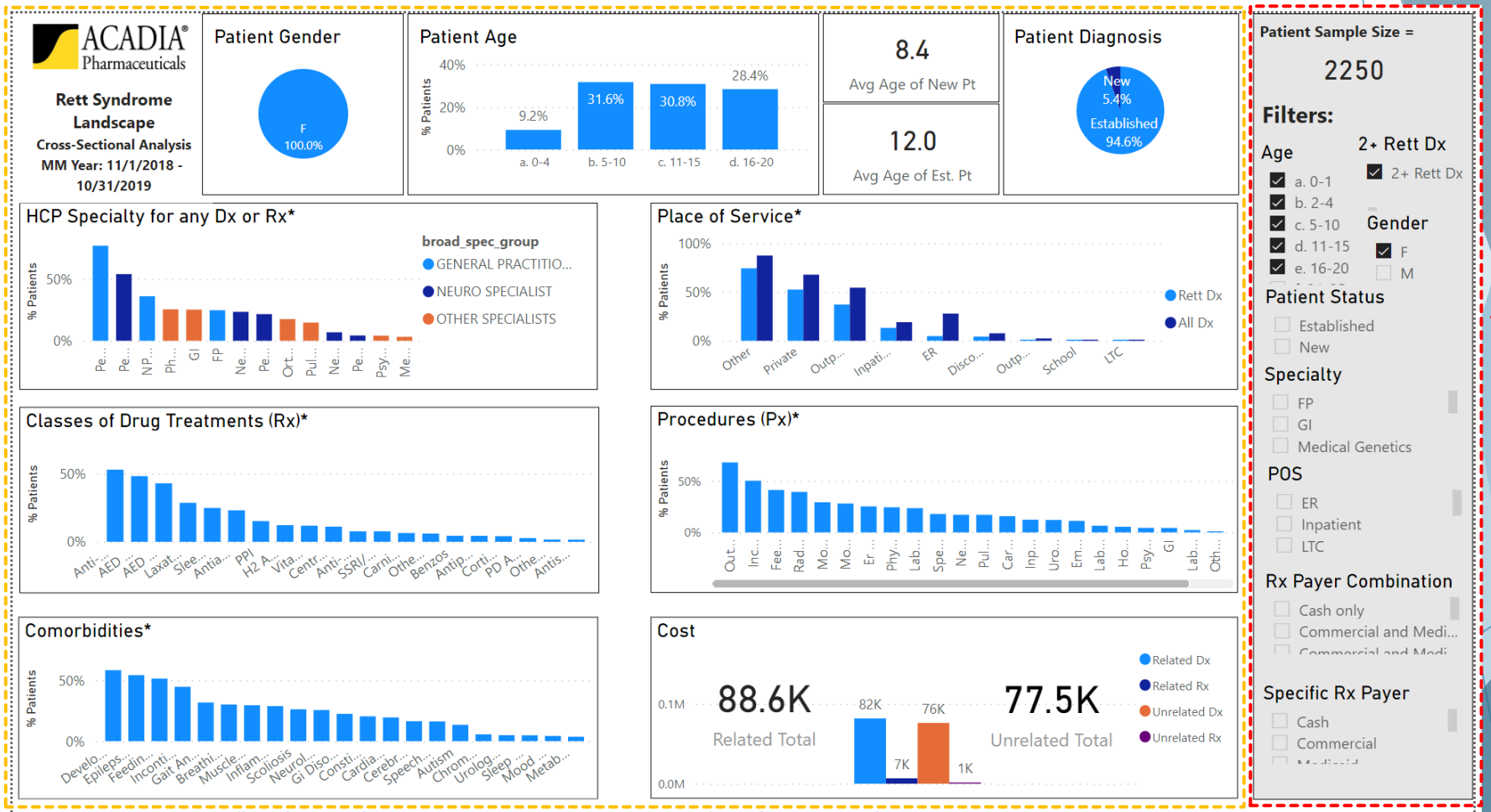


- Incontinence and feeding assistance affect one-half to one third of all Rett patients
- Mobility concerns (wheelchair-related), physical therapy, and speech therapy impact up to 1 in 4 patients

*Note: Patients could overlap among categories so that the sum could be over 100%
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

A comprehensive Power BI database allows Rett complexities to be parsed and visualized for exploration and buy-in

Snapshot overview of patient level data such as treatment, procedures, and comorbidities



*Categories are not mutually exclusive and may sum to >100%. Source: CRA Analysis of APLD/LAAD data (11/01/2015 - 10/31/2019)

Filters (Age, Gender, HCP Specialty, etc.) to select desired patient population with Rett Syndrome

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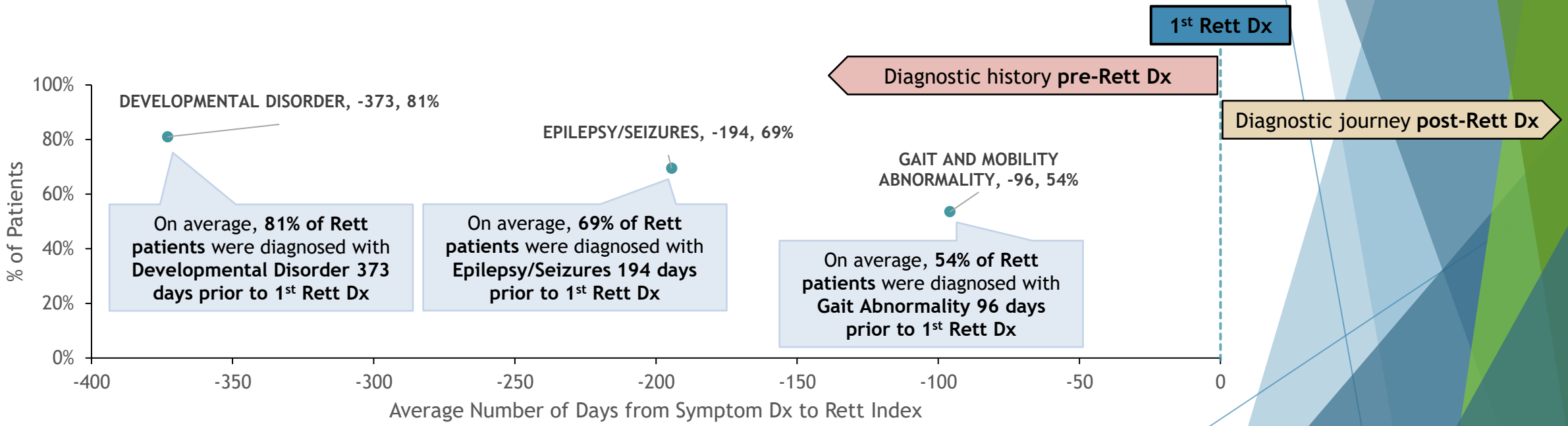
A longitudinal mapping of the patient journey prior to a Rett diagnosis can identify 'fingerprint' characteristics

Rett Dx claims analysis suggested delayed diagnosis

- A comprehensive map of comorbidities/symptoms will enhance **understanding of Rett patients' diagnostic journey**, which **may help in patient identification** and **early diagnosis**

Average Onset of Key Comorbidities Relative to 1st Rett Dx

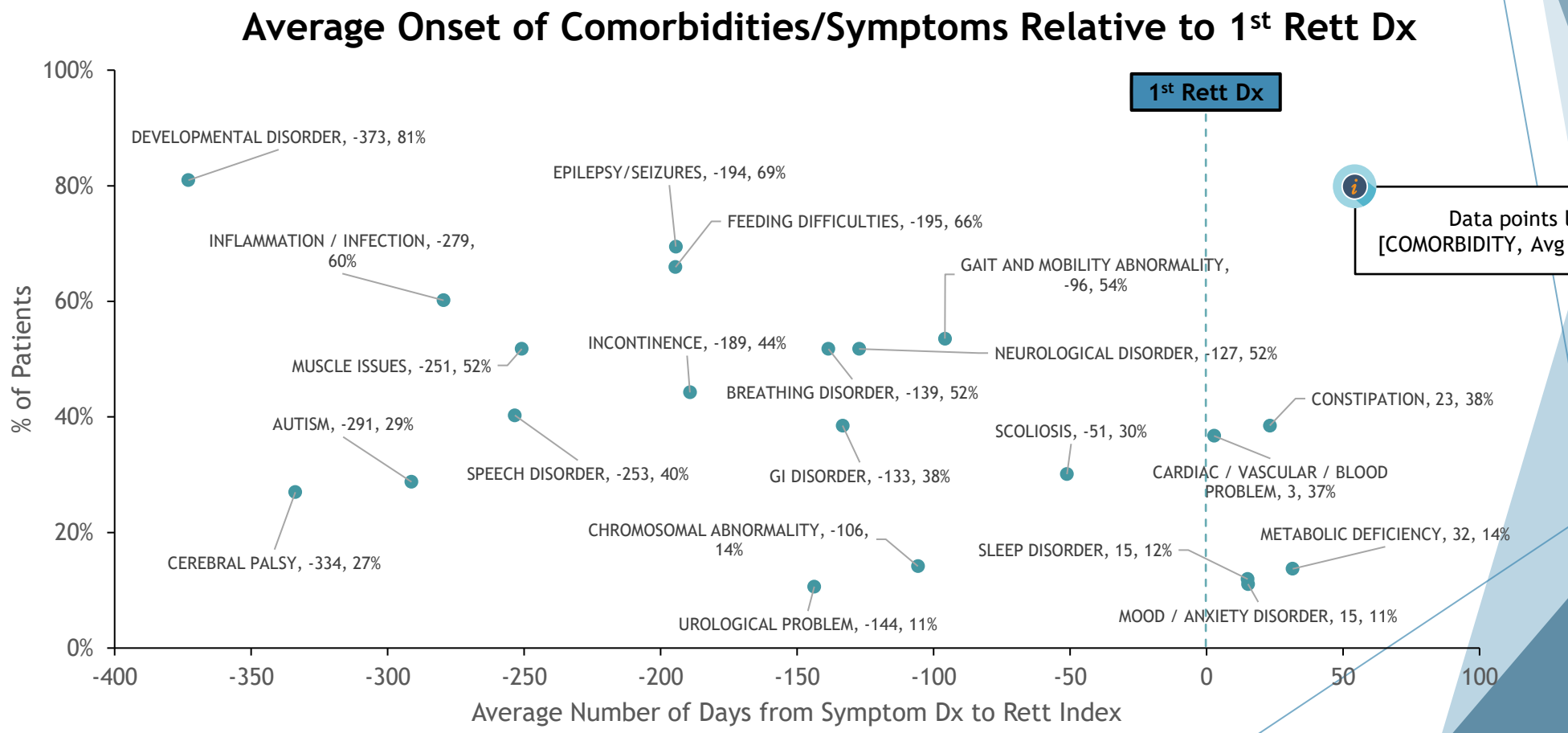


- Major comorbidities such as Developmental Disorder, Epilepsy, and Gait Abnormality were diagnosed approximately 12 months, 6 months, and 3 months, respectively, prior to Rett diagnosis

Note: Analysis does not require any washout and includes all patients with 2+ Rett Dx; some patients 1st Dx may reflect a change in coverage
Source: CRA Analysis of IQVIA APLD/LAAD Data Nov 2018 – Oct 2019

The ML model can leverage the full suite of patient interactions (Dx, Rx, Px) leading to Rett Dx

Common **comorbidities/symptoms**, **average days of diagnosis from Rett** Index Date, and **prevalence** in Rett patients were calculated to map Rett patients' diagnostic journey



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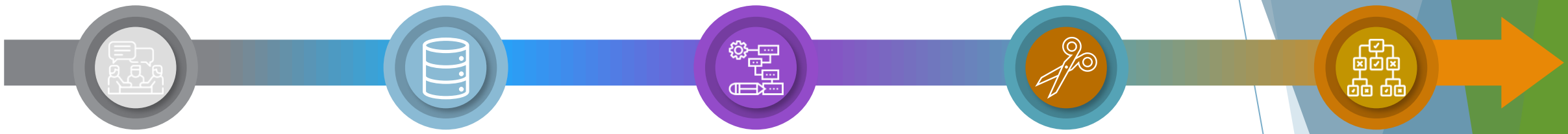
ML modeling to find undiagnosed Rett patients will follow a similar approach as used in a psoriasis case



Define Patient Group	Create Model Database	Model Training and Model Selection	Choose Cutoff	Apply Model to Suspected Group

• Start with a relevant broad patient cohort (e.g., CNS cohort for Rett syndrome)
• For a more accurate model, define 3 groups
  ○ Yes
  ○ No
  ○ Suspected
• Alternatively, define 2 groups:
  ○ Yes
  ○ Suspected
	• Incorporate current and expert understanding of Rett syndrome to include/exclude specific variables
	• Create input variable database for model
		• Generate training and testing data
		• Leverage multiple ML algorithms to build classification models on training data
		• Select the model with highest accuracy
			• Assign predicted probability to each patient in testing data
			• Calculate positive predictive value (PPV) for each cutoff point
			• Determine preliminary cutoff points to classify the testing group into 2 groups:
			  ○ Predicted yes
			  ○ Predicted no
				• Apply the final model to the entire suspected group
				• Compare several cutoff points and select the best cutoff that yields a balance of confidence in prediction and number of patients

Psoriasis Case Study Background

- Subtype-A (ST-A) is a rare form of psoriasis (PsO) and can be under-coded in claims
- In this example, predictive modeling was employed to identify high-likelihood ST-A patients that do not have a formal ST-A Dx, among all PsO patients (Suspected Cohort)
- The model predicted the probability of being a ST-A patient for each of the patients in the Suspected Cohort (from 0 to 1), and positive predictive value (PPV) for each cutoff point

Patient Finding Process: Defining Patient Group

Patient finding process is demonstrated using a previous analysis done in Psoriasis

Define Patient Group → Build Model Database → Model Training and Model Selection → Choose Cutoff → Apply Model to Suspected Group

❖ **<u>Option 1</u>: Create strict "Yes", strict "No", and "Suspected" Groups (recommended)**

➢ Construct the model with strict "Yes" group and "No" group, and apply to the suspected patients

PsO Subtypes	Strict	Loose	Total
1. Subtype-A	1,363	1,306	2,669
2. Subtype-B	1,285	1,282	2,567
3. Subtype-C	2,928	2,714	5,642
4. Subtype-D	32,423	6,962	39,385
5. Subtype-E	30,327	46,125	76,452
6. Subtype-UNK		78,712	78,712
Total	**68,326**	**137,101**	**205,427**

Model Group	Definition	# of Patients
Yes	Strict 1, Loose 1	2,669
No	Strict 2, 3, 4, 5	66,963
Suspected	Loose 2, 3, 5, 6	128,833

❖ **<u>Option 2</u>: Create only "Yes" Group and "Suspected" Groups**

➢ Train the model with "Yes" group and "Suspected" group, and apply to the suspected patients

Patient Finding Process: Building Model Database

Patient finding process is demonstrated using a previous analysis done in Psoriasis

Define Patient Group → **Build Model Database** → Model Training and Model Selection → Choose Cutoff → Apply Model to Suspected Group

- **Select the input variables for the model**
  - Communicate with broader team and determine the predictor variables
    - Input from primary research
    - Provide initial profiling
  - Common variables to include in the model
    - Demographic variables such as gender, age group, etc.
    - Frequency of visit to specialist
    - Occurrence of specific symptoms or comorbidities
    - Treatment type

Patient Finding Process: Training and Selecting Model

Patient finding process is demonstrated using a previous analysis done in Psoriasis

Define Patient Group → Build Model Database → **Model Training and Model Selection** → Choose Cutoff → Apply Model to Suspected Group

Step 1: Generate Training and Testing Data

- Random sampling of 80% of Subtype-A patients and 80% of PsO patients into Training Data
- Allocate the remaining 20% of each Subtype-A patients and PsO patients into Testing Data
- Use up-sampling method to balance both Training and Testing Data

Step 2: Build classification model on the Training Data

- Random Forest
- Conditional Forest
- Neural Network
- GBM

Step 3: Select the model with the highest accuracy

- Apply each model on the Testing Data and pick the one with the best accuracy:

  accuracy=(a+d)/(a+b+c+d)

- Random Forest is selected

		True Indication	
		Yes	No
Model Predicted	Yes	a	b
	No	c	d

Patient Finding Process: Choosing Cutoff

Patient finding process is demonstrated using a previous analysis done in Psoriasis

Define Patient Group → Build Model Database → Model Training and Model Selection → **Choose Cutoff** → Apply Model to Suspected Group

Step 1: Add predicted probability into the balanced Testing Data

Patient ID	True Indication	Predicted Prob
a	No	0.01
b	Yes	0.70
…	…	…

Step 2: Add binary flag using cutoff x, iterative x from 0 to 1 by 0.01

Patient ID	True Indication	Predicted Prob	Cutoff = 0	Cutoff = 0.01	Cutoff = 0.02	…
a	No	0.01	Yes	Yes	No	…
b	Yes	0.70	Yes	Yes	Yes	…
…	…	…	…	…	…	…

Step 3: Calculate PPV for each cutoff points

- PPV (Positive Predictive Value) is calculated as PPV=a/(a+c)

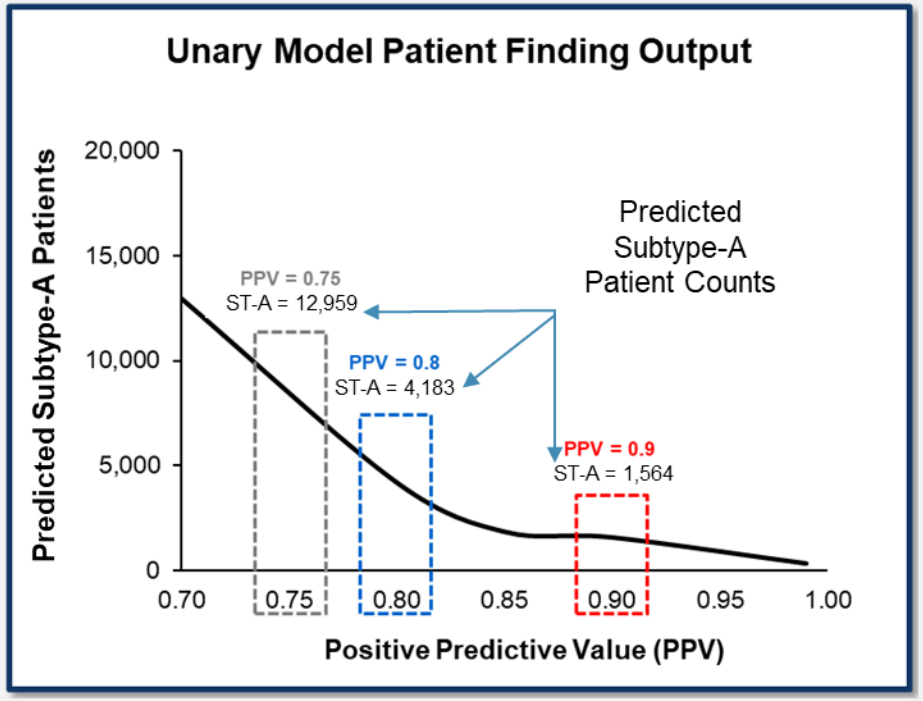
		True Indication	
		Yes	No
Model Predicted	Yes	a	b
	No	c	d

Cutoffs	PPV
0.00	50.0%
0.01	52.9%
…	…
0.91	97.7%
…	…
0.99	100.0%
1	100.0%

Patient Finding Process: Applying Model to Suspected Group

Patient finding process is demonstrated using a previous analysis done in Psoriasis

Define Patient Group → Build Model Database → Model Training and Model Selection → Choose Cutoff → **Apply Model to Suspected Group**



Predicted Subtype-A Patients

	Low Confidence	Medium Confidence	High Confidence
PPV	0.75	0.8	0.9
Subtype-A Patients	12,959	4,183	1,564
Notes	Large # pts, low true positives	Med # pts, high true positives	Low # pts, very high true positives

- We propose a PPV of 0.9, since that generally means for every 10 predicted patients, the model will be correct for 9 of those patients
- In our prior analysis, we chose a PPV of 0.75. However, due to the increased use of the Subtype-A ICD-10 code we propose a more stringent cutoff for the model
- Additionally, the false positives are likely to be severe PsO patients treated by similar HCPs as Subtype-A patients

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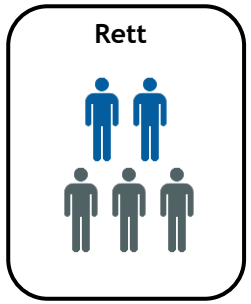
Accelerated diagnosis can better align Rett patients with available treatment resources

Apply model key drivers as selection criteria for testing

Potential **Future value** generation

Test



Maximize *cost effectiveness* of investment in genetic testing program

Provide genetic testing to **high-confidence Rett patient candidates** to validate and confirm diagnosis

Inform/Basis for Additional Workstreams

- Accelerate Dx for undiagnosed/ misdiagnosed Rett patients
- Identify priority HCPs for targeted outreach
- Facilitate Rett patient registry
- Facilitate patient and HCP education
- Influence Rett guidelines to update early screening criteria based on top predictors

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Backup

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Brett Ramos

Senior Director, Commercial Strategy
Acadia Pharmaceuticals

San Diego, United States
o: +1-858-320-8667
bramos@acadia-pharm.com

Overview

Analytic and strategic leader focused on deriving business growth through acquisition evaluation, advanced analytics, strategic recommendations to help launch new products and indications for the organization.

Relevant experience

- 15+ years of experience in research, consulting and analytics for pharmaceutical, biotech, and diagnostic companies
- Commercial leader with in-line, pipeline, and launch experience in Neurology, Psychiatry, Oncology, Hematology & LTC
- Data Scientist and business collaborator leading projects across sales, marketing, IT, medical, finance, and executive functions

Education & Qualifications

- MBA, Anderson, UCLA Graduate School of Business
- BS, Computer Science, University of Virginia
- Minor, Biomedical Engineering, University of Virginia

Griff Vinton
Principal
Charles River Associates (CRA)

Boston, United States
m: +1-585-747-1474
gvinton@crai.com

Overview

Griff is a Principal in the Life Sciences practice who brings 24 years of applied analytics experience across the product life-cycle in pharma, biotech, medical devices and BI platform implementation.

Relevant experience

Griff has led projects and clients in a variety of therapeutic areas, including neuroscience, cardiology, gastroenterology, oncology and rare diseases, while also delivering innovative data visualization solutions in Power BI, Qlik Sense and Tableau. Before joining CRA, Griff held leadership roles at C1 Consulting, ZS Associates, Celltech/UCB, Cognizant, Harris Interactive, Bausch & Lomb and Excellus BCBS.

Education & Qualifications

- MBA, Darden, UVa Graduate School of Business
- MA, French, Middlebury College
- BS, United States Air Force Academy

Acadia Pharmaceuticals

- **Company Profile**
  - Focused on developing innovative candidates in neuroscience areas
  - Developed and commercialized NUPLAZID, the first and only approved therapy for hallucinations and delusions associated with Parkinson's disease psychosis
  - Approximately 400 employees with plans to grow in 2022
  - Offices
    - Corporate Headquarters in San Diego, CA
    - R&D Center in Princeton, NJ
- **Major Milestones**

1993 — Founded by Dr. Mark Brann

2001 — **Pimavanserin (NUPLAZID)** first synthesized by Acadia chemists

2016 — **NUPLAZID** approved by FDA for the **treatment of hallucinations and delusions associated with Parkinson's Disease Psychosis**

2020 — **Trofinetide** received **rare pediatric disease designation** for the treatment of **Rett syndrome**

2021 — **Trofinetide** completed pivotal **Phase 3 in Rett disease**, meeting primary endpoints with high statistical significance

CRA's global life sciences practice has a longstanding **reputation for excellence**

220+
consultants

A dedicated team of life sciences consultants

25+
years

Decades of hands-on life sciences experience

the top
30
pharmaceutical companies

Experience with all of the top 30 global pharmaceutical companies

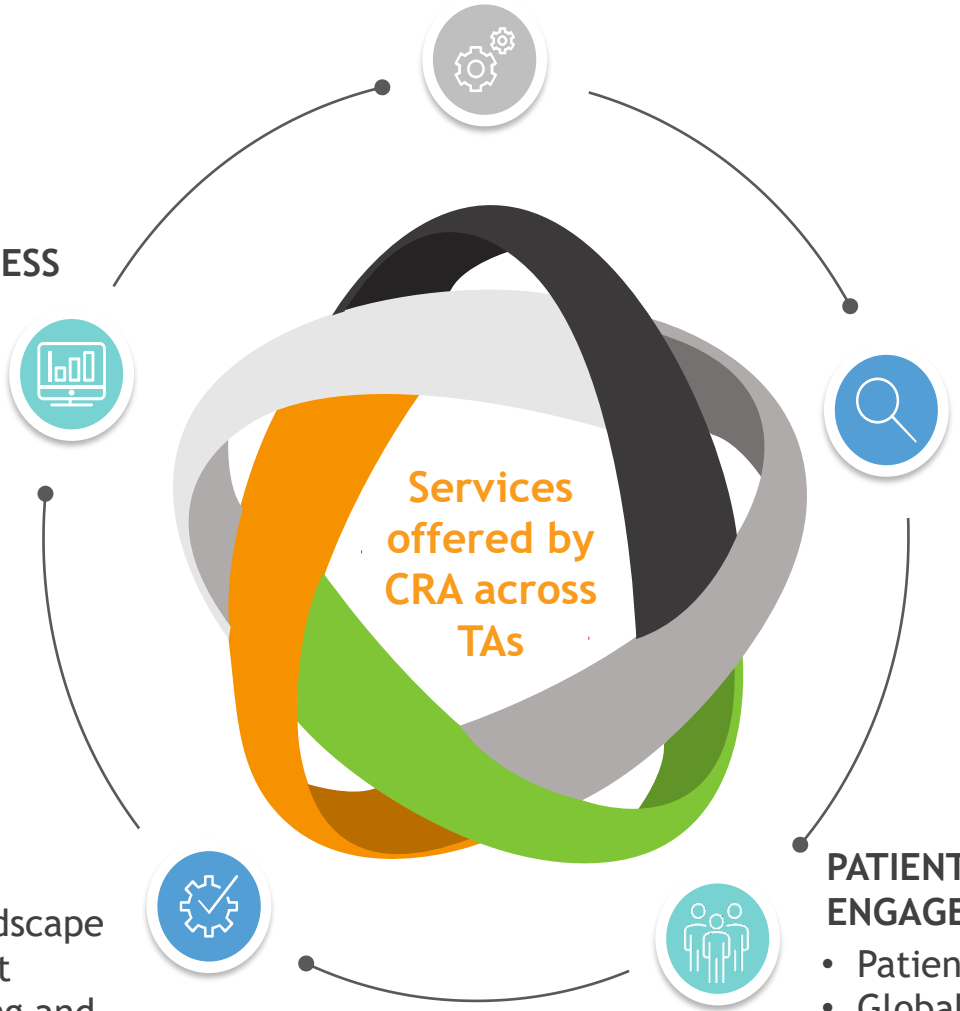
90%
repeat business

Thoughtful, long-term partnerships with clients

CRA Life Sciences offers a **broad range of analytics and advisory services** throughout the **product and market lifecycle**

COMMERCIAL STRATEGY
- Launch Planning
- Brand and Pipeline Optimization
- Forecasting

PRICING AND MARKET ACCESS (PMA) – US and Global
- Evidence Development
- Value Communication
- Pricing and Contracting



MARKET ASSESSMENTS
- Opportunity Assessment
- Competitive Simulation

POLICY
- Policy Landscape Assessment
- Anticipating and Analysing Policy Challenges

PATIENT FINDING & ENGAGEMENT
- Patient Finding Excellence
- Global Epidemiology
- Patient / Patient Advocacy Strategic Planning

CRA has provided strategic and analytic support to over ***250 Rare Disease*** engagements in the past 4 years

Rare Diseases

Genetic disorders	Respiratory
Hematopoietic	Immunologic
Gastrointestinal	Ophthalmic
Neuromuscular	Metabolic
Hepatology	Neurology
Dermatology	Nephrology
Rare Tumors	Psychiatry
Musculoskeletal Disorders	Genitourinary System
Cardiovascular Diseases	Infectious Diseases

Services

- Pricing Strategy
- Market Opportunity Assessment
- Patient Finding Excellence
- Competitive Simulation
- Thought Leader Engagement Planning
- Forecasting
- Brand & Pipeline Planning
- Policy
- Market Access
- Patient / Patient Advocacy Strategic Planning
- Global epidemiology
- Launch Planning
- Patient Journey
- KPI Tracking
- KOL Identification
- Key Behavioral Influence
- Social Listening

Stakeholders

- Physicians
- Patients
- KOLs
- Nurses
- Payers
- Caregivers
- Patient groups
- Policymakers

Not an Exhaustive List of Capabilities