DOWN SYNDROME REGRESSION DISORDER

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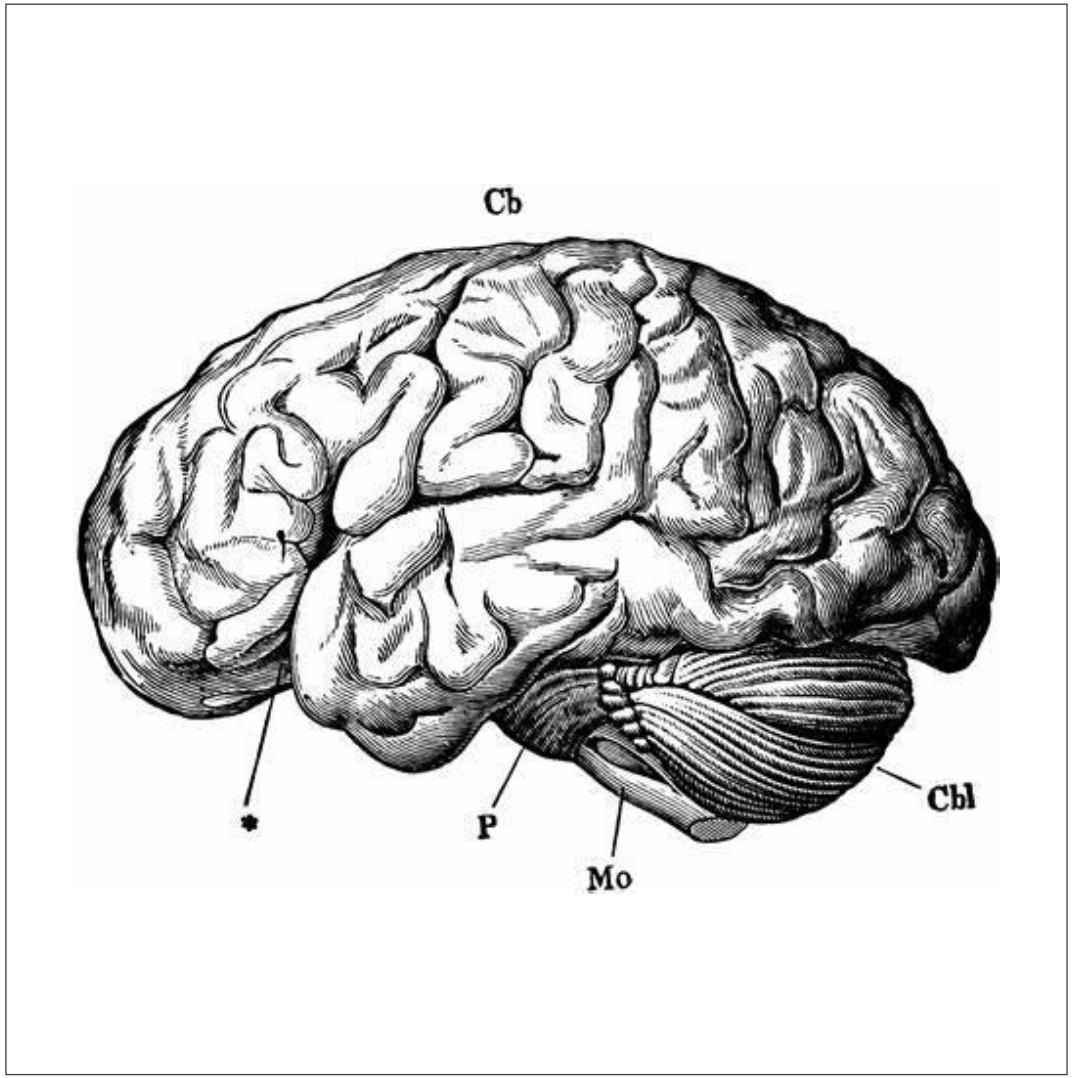


What is Regression?

- Regression is a term for the **loss or previously acquired developmental skills** in an individual.
- This can be activities (toileting, dressing oneself, or eating independently), language (loss of words, loss of ability to community, changes or regression in word structure), motor function (inability to walk, climb or run as previously able), or social interaction.
- ***Regression can be caused by many things.***

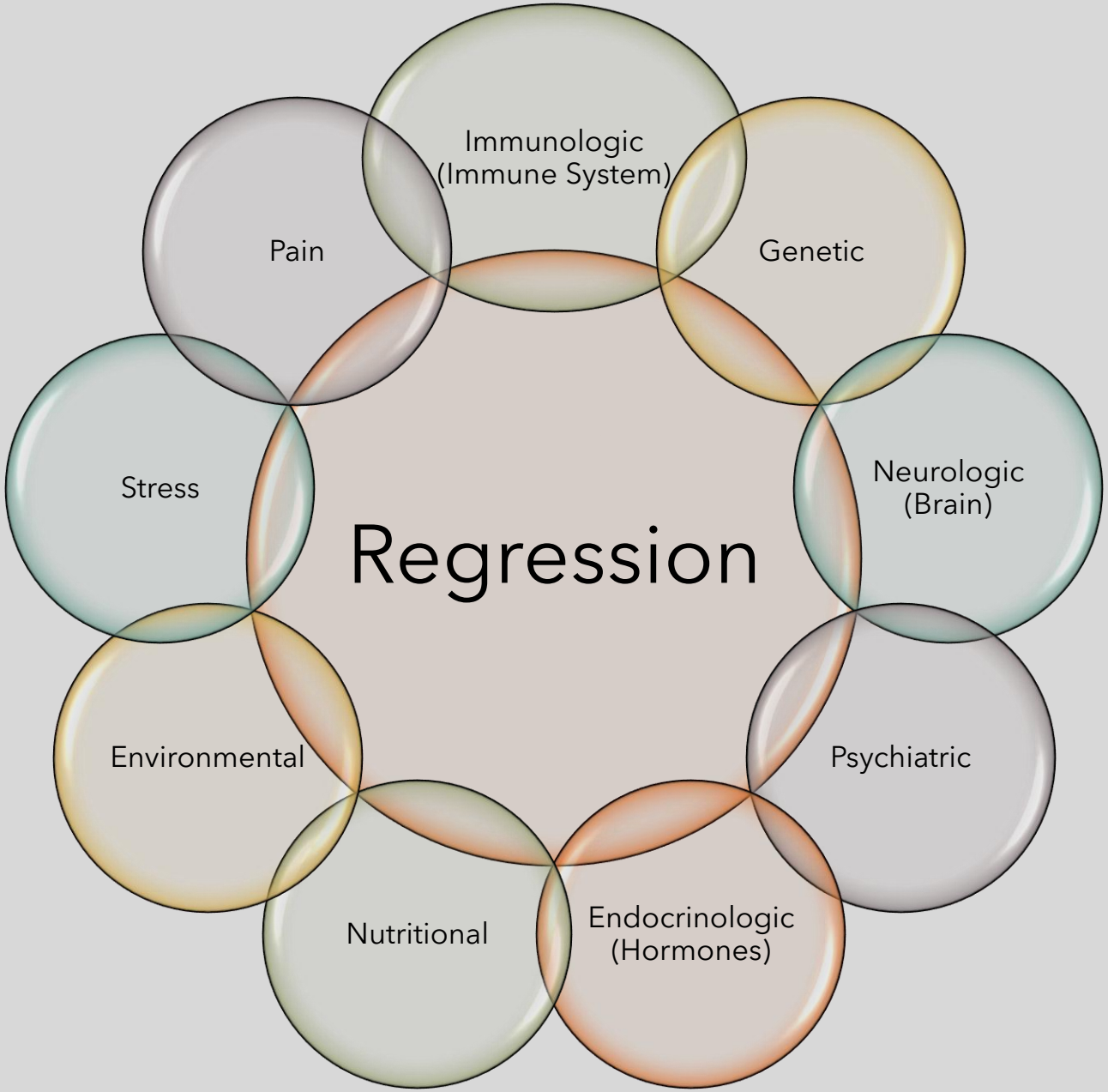
Is Regression Common?

- It is difficult to know as it is very likely that persons experiencing symptoms of regression can go undiagnosed in the community setting.
  - Frequent alternative diagnoses are “late onset autism”, “early onset Alzheimer’s disease” and other primary psychiatric diagnoses like depression.

- Currently, we think **regression is relatively rare**, effecting <5% of all individuals with Down syndrome who are older than 10 years old and younger than 30 years old.

What Causes Regression?

- At this time, it appears that **there may be several causes of regression** in persons with Down syndrome.
  - Traditionally, this condition was thought to be psychiatric although we are learning there are a variety of causes.
- As regression is a description of the symptom (what is happening), this label does not always describe the cause.
- ***Timing matters!***
  - Acute (sudden) or sub-acute (few weeks) from the start of symptoms may be different then chronic or slowly changing symptoms


Immunologic
(Immune System)
Pain
Genetic
Stress
Neurologic
(Brain)
Regression
Environmental
Psychiatric
Nutritional
Endocrinologic
(Hormones)

Symptoms of Regression (Part I)

Mental Status Changes or Behavioral Dysregulation

- Confusion, disorientation
- Inappropriate laughter and laughing at things that are not present
- Being “off in your own world” for extended periods of time
- Increased or decreased eating with corresponding weight loss/gain

Cognitive Decline

- Apathy or lack of interest in things going on around them
- Avolition or limited interest in initiating activity
- Memory impairment or difficulty with recall

Insomnia or Circadian Rhythm Dysregulation

- Inability to sleep or sleeping >16 hours per day
- Reversal of sleep patterns (sleeping all day, up all night)

Symptoms of Regression (Part II)

Developmental Regression

- Social withdrawal
- Loss of previously acquired developmental milestones
- Inability to perform activities of daily living (e.g., toileting, brushing teeth, eating, dressing self)
- Decreased eye contact
- Rigidity around routine changes (extreme inflexibility)
- Stereotypy or repetitive motor behaviors

New Focal Neurologic Deficits

Movement Disorder (excluding tics)

- Catatonia or muscle stiffness
- Bradykinesia (slow movements) or freezing behavior (stuck in place)
- Gait disturbance or inability to walk normally

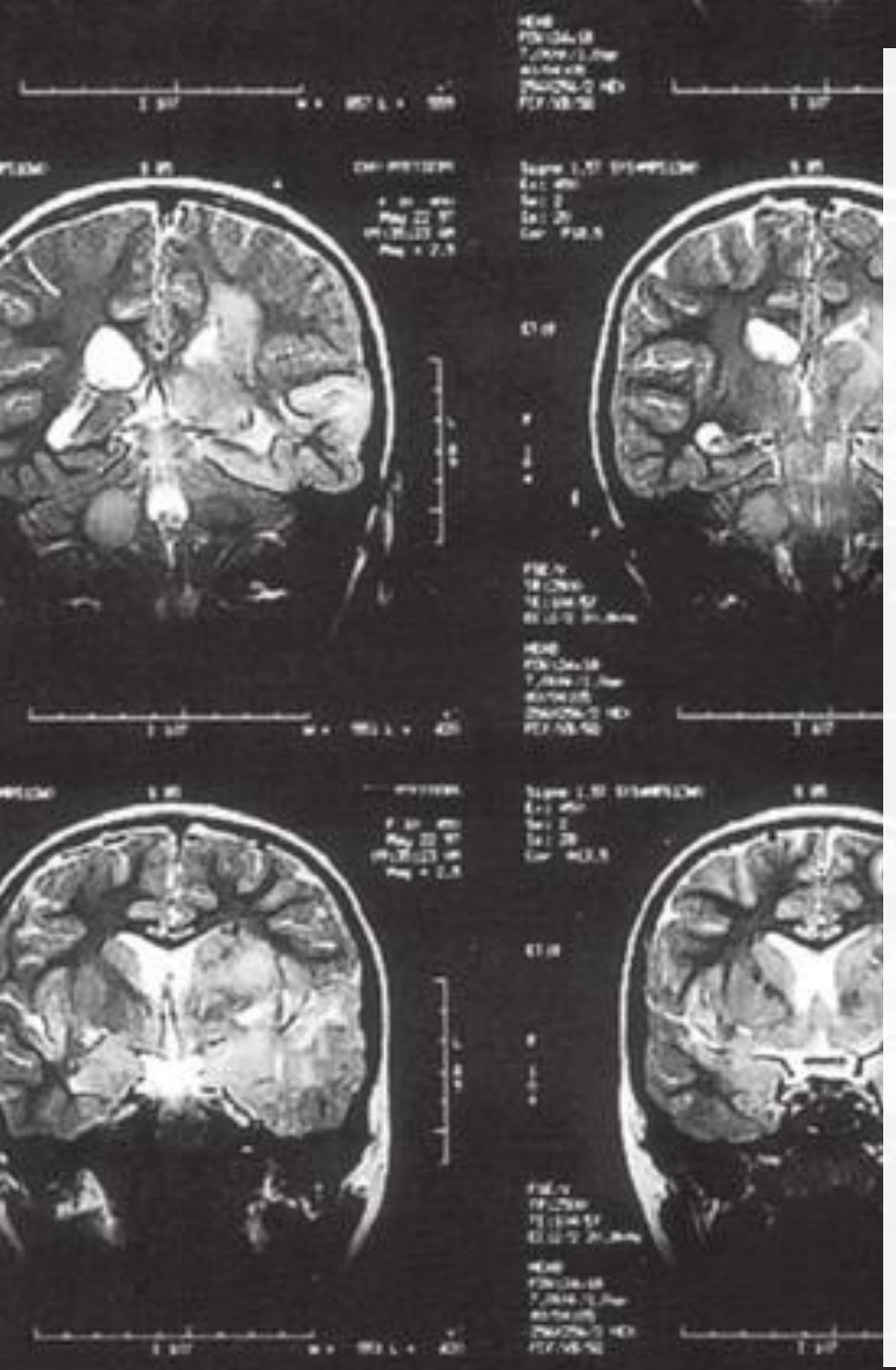
Symptoms of Regression (Part III)

Language Deficits

- Expressive and/or receptive aphasia (e.g., decreased speaking and/or decreased ability to understand speech)
- Whispered speech
- Neologisms (using new or garbled words)
- Global aphasia (mutism)

Psychiatric Symptoms

- Anxiety
- Delusions or hallucinations
- Derealization or depersonalization (belief that you are in a dream or not in reality)
- Obsessive compulsive tendencies (new)
- Aggression/agitation



Our Current Understanding…

- Persons with Down syndrome are at risk for a variety of psychiatric, neurologic, and immunologic disorders
- Regression may be caused by one, multiple, or all of these causes and each case is very unique
- We advised a **broad work up** prior to the diagnosis of regression to make sure there is not another medical explanation for the symptoms.
- At present, regression is a “diagnosis of exclusion”

How to Make the Diagnosis?

There is not one specific test used to diagnose regression.

Rather, we use multiple tests to rule out other medical explanations for this condition.

Blood Work: helps rule out metabolic, gastrointestinal, nutritional, infectious, and some inflammatory disorders that can mimic the symptoms of regression.

MRI: helps determine if there is a structural cause (brain anatomy) that can explain regression or determine if there is stroke, inflammation or other causes to symptoms.

EEG: is used to determine if seizures are a potential cause to symptoms and also evaluate if there is slower than expected brain activity.

Lumbar Puncture (Spinal Tap): helps determine if there is inflammation or infection in the brain

Beyond Diagnosis…

- Arriving at the most likely reason for regression in a person with Down syndrome is very important as the therapies that can be offered vary widely on what the explanation is.
- We encourage discussion with other families about regression but please be aware that no case of regression is exactly like the next.
- If a therapy is not working or providing only partial or temporary results, it is OK to ask your doctor why and if additional testing should be done.
- We as a medical community are still learning the best ways to test and treat persons with Down syndrome and regression and an open dialogue between you and your doctor is the best way to optimize care.

Is there a treatment?

- Right now, **there is no one singular treatment for persons with regression**. However, once a source (or reason) is found for regression, your doctors can work together to provide the best treatment options.

- Given the overlap between psychiatric and neurologic disease, working with a multi-disciplinary team of doctors with expertise in regression is very important!

- Many different treatments have been used, all with some aspect of success although prediction of who will respond to what therapy best is very difficult.


Antidepressants
Benzodiazepines
Antipsychotics
Down Syndrome Regression Disorder
Cholinergic Agents
Electroconvulsive Therapy
Immunotherapy

QUESTIONS?

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Clinical Trial for Mechanistic Investigation of Therapies for Down syndrome Regression Disorder

October 6th, 2022

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ANSCHUTZ MEDICAL CAMPUS

LINDA CRNIC INSTITUTE for DOWN SYNDROME

University of Colorado Anschutz Medical Campus

Children's Hospital Colorado

Children's Hospital LOS ANGELES

Keck Medicine of USC

GLOBAL DOWN SYNDROME FOUNDATION

Clinical trial for mechanistic investigation of therapies for Down syndrome Regression Disorder

A collaboration between the Crnic Institute, Children's Hospital Colorado, and Children’s Hospital Los Angeles.

Principal Investigators:

Santoro

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Co-Investigators:

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Kammeyer

Galbraith

Consultants:

Sanders

Tartaglia

Charoensook

Funded by: NIH THE INCLUDE PROJECT NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Clinical trial for mechanistic investigation of therapies for Down syndrome Regression Disorder

Three goals:

1. To define the relative **safety** profile of Lorazepam, IVIG, and Tofacitinib in DSRD.

2. To compare the **efficacy** of Lorazepam, IVIG, and Tofacitinib in DSRD.

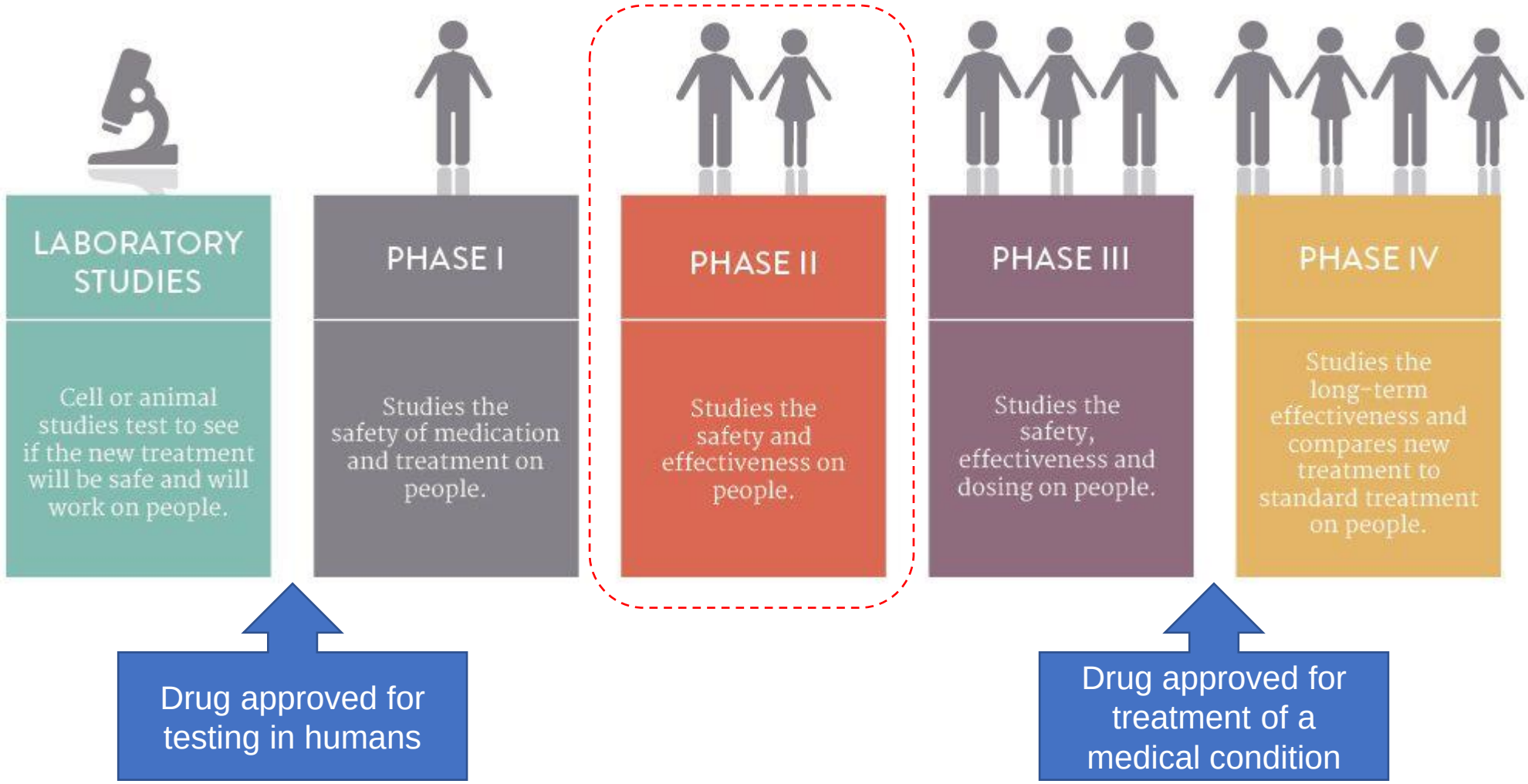
3. To investigate potential **mechanisms** underlying DSRD and its response to therapies.

Is it safe?

Is it effective?

What is the mechanism?

A Phase II, three-arm, open-label, research intensive trial



All three medicines studied in this trial are already FDA-approved for treatment of **other** medical conditions

A Phase II, three-arm, open-label, research intensive trial

Lorazepam
Brand name: Ativan
Benzodiazepine

IVIG
Brand name: Gammagard
Intravenous Immune Globulin

Tofacitinib
Brand name: Xeljanz
JAK inhibitor

All three medicines studied in this trial are already FDA-approved for **other** medical conditions

The power of ‘drug repurposing’: this study benefits from extensive available data for all three drugs

Open label: participants will know which medicine they are taking

No placebo arm

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All three medicines studied in this trial are already FDA-approved for **other** medical conditions:

Lorazepam is a benzodiazepine approved for anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

Lorazepam modulates ‘brain chemistry’ through binding to ‘GABA receptors’ in neurons

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IVIG is approved for primary humoral immunodeficiency, multifocal motor neuropathy, B cell chronic lymphocytic leukemia, immune thrombocytopenic purpura, Kawasaki syndrome, and chronic inflammatory demyelinating polyneuropathy.

IVIG modulates the immune system by ‘flooding it’ with immunoglobulins, a.k.a. antibodies

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Tofacitinib is approved for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.

Tofacitinib lowers inflammation by inhibiting a class of enzymes known as **Ja**nus **k**inases (JAKs)

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All three medicines have well characterized safety profiles (in the general population):

Potential side effects of Lorazepam: sedation, dizziness, weakness, unsteadiness, physical and psychological dependence, fatigue, drowsiness, amnesia, memory impairment, confusion, disorientation, depression, others.

Learn more: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017794s044lbl.pdf

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All three medicines have well characterized safety profiles (in the general population):

Potential side effects of IVIG: Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting, or dizziness, bad headache with nausea, vomiting, stiff neck, fever, sensitivity to light, others.

Learn more at: https://www.fda.gov/media/70812/download

A Phase II, three-arm, open-label, research intensive trial

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Brand name: Xeljanz
JAK inhibitor

All three medicines have well characterized safety profiles (in the general population):

Potential side effects of Tofacitinib: increased risk of infections, nasopharyngitis, diarrhea, headache, elevated cholesterol levels, increased risk of cardiovascular events, thrombosis and malignancies relative to TNF-blockers, others.

Learn more:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf

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All three medicines have benefited <u>some</u> individuals affected by DSRD!

Study doctors have safely administered these medicines to those affected by DSRD!

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What causes DSRD?

Who will benefit the most from which medicine?

A lot of research will be needed to answer these questions

Summary of Study Design

- Only individuals with Down syndrome Regression Disorder
- Ages 8-30
- 12 weeks (3 months) of treatment with one medicine
- 60 participants total, 20 on each medicine
- Two sites, Denver and Los Angeles, 30 participants each

Anschutz Medical Campus

Children’s Hospital Los Angeles

Summary of Study Design

- Primary endpoint: **safety!**
- Secondary and tertiary endpoints: improvements in various symptoms of DSRD.

Global Neurological Health

Catatonia

Movement & Visuomotor Function

Language

Quality of Life

Sleep

Behavior and Social Interaction

Executive Function & Cognitive Ability

Summary of Study Design

Schedule of activities

	Enrollment Period						
	Treatment Period						
	Screening Visit 1 (-4 weeks)	**Baseline Visit 2** (0 weeks)	**Visit 3** (2 weeks)	**Visit 4** (4 weeks)	**Visit 5** (8 weeks)	**Endpoint Visit 6** (12 weeks)	**Follow-up Visit 7** (14 weeks)
Informed consent	x						
Screening labs	x						
Safety monitoring		x	x	x	x	x	x
Psychiatric exam		x	x	x	x	x	x
DSRD diagnostic work-up	x					x	
Pharmacy visit		x		x	x		
Neurological exam		x				x	
Endpoint measurements		x				x	

A lot of important work!

Why compare these three medicines?

- A subset of DSRD cases are associated with signs of immune dysregulation affecting the central nervous system (CNS).

- Is DSRD an autoimmune condition, akin to autoimmune encephalitis?

- What is the value of immune therapies relative to psychiatric medicines?

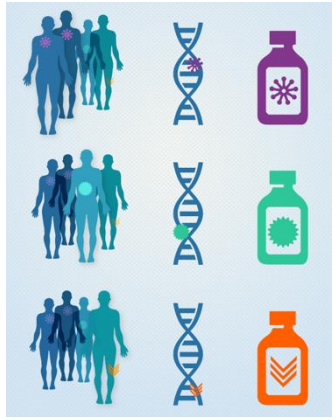
Why compare these three medicines?

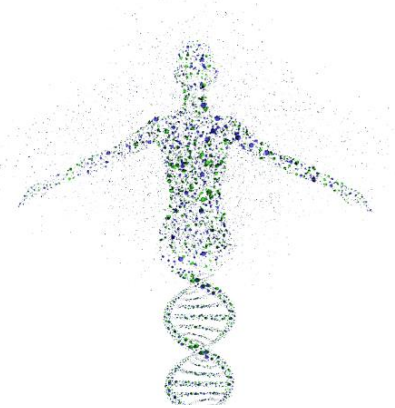
Who would benefit the most from which medicine?

What are the diagnostic characteristics that could predict a good response?

Are there ‘biomarkers’ in the blood or cerebrospinal fluid that could match each participant to their best therapeutic option?

Developing a personalized medicine approach for the treatment of DSRD





A research-intensive clinical trial

- Blood samples and cerebrospinal fluid samples will be collected for deep analysis using cutting-edge technologies.
- Each participant will undergo significant testing to monitor for potential improvements in diverse areas of brain function.
- A multidisciplinary team with expertise in psychiatry, neurology, psychology, immunology, genetics, and molecular biology will analyze the data.

Important facts

- Recruitment will start sometime in 2023 after obtaining all required regulatory approvals and oversight (in progress).
- An interim analysis will be completed after recruitment of the first ~20 participants, before scaling up to ~60 participants.
- Travel and lodging assistance will be provided.
- Participation in the trial will not prevent participants from receiving other medicines (including those tested in the trial) after the trial.
- Stay tuned!

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Thanks to GLOBAL, today is a new age in Down syndrome research, with new NIH funding opportunities, new cohort studies, new clinical trials, and new big data science efforts. The future is bright!