New discoveries in the evolving world of genetics: diagnosis and treatment of CP

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Disclosures

- Aeglea
- PTC Therapeutics

Background

Genetic mutations lead to a substantial proportion of CP cases

DEVELOPMENTAL MEDICINE &

Genetic testing in

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CENTER GENOMICS TEAM[1,2,3,

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Open Access

lentified with whole exome
palsy

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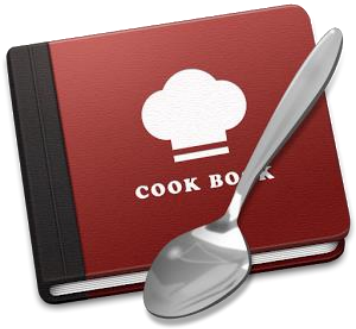
Genetics in a nutshell



Genome

Genes

DNA

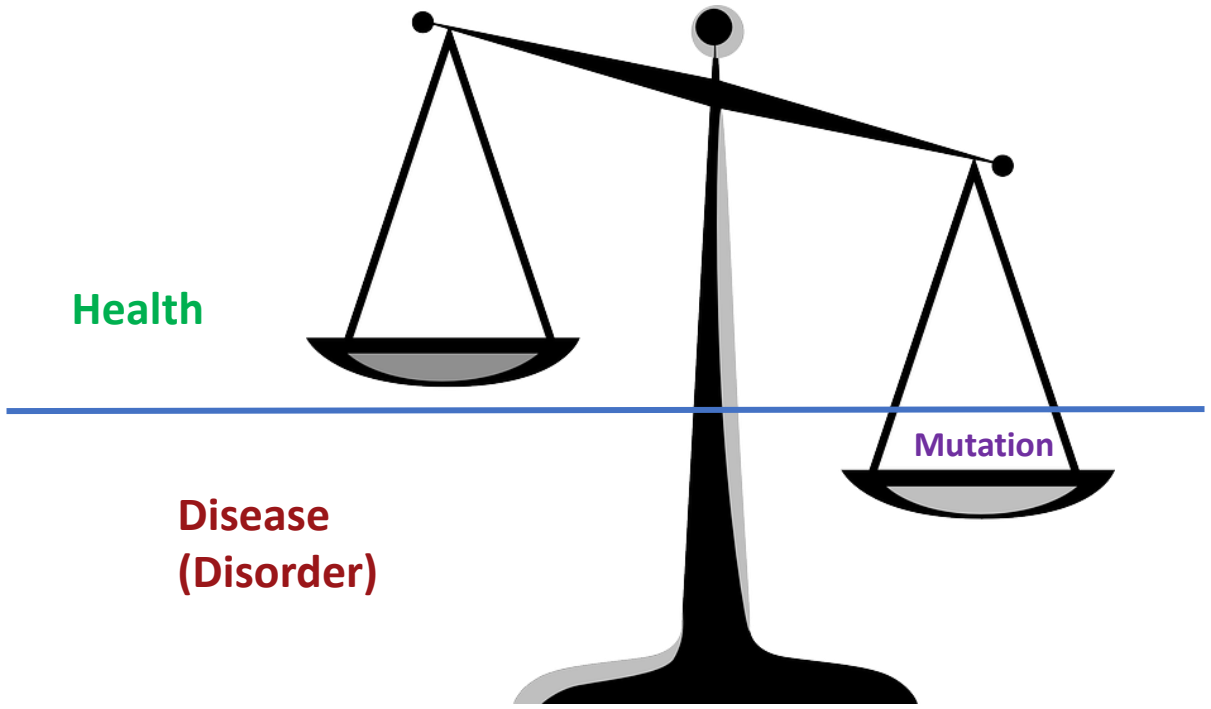
Protein

Mutations

Copy Number Variant (CNV)

Single Nucleotide Variant (SNV)

Genetic risk factors vs. genetic causes



Can genetic findings impact diagnosis & treatment in CP?

Case 1

- A 5 year-old boy with dyskinetic CP is admitted to the hospital with respiratory distress. His respiratory symptoms stabilize with supplemental oxygen and supportive care, but his dyskinesia (chorea) worsens considerably. He is treated with several medications with some improvement in his chorea, but he becomes somnolent and his respiratory drive worsens. He is urgently transferred to the intensive care unit. Rapid whole exome sequencing discloses a *de novo* pathogenic mutation in *GNAO1*. After careful discussion with his parents, the decision is made to place a deep brain stimulator. After surgery, he is able to be weaned from the ventilator. His chorea is controlled and sedating medications are able to be weaned.

Genetic findings can lead to new insights that guide treatment decisions

Case 2

- A 6 year-old girl with a diagnosis of spastic quadriplegic CP was born at 27 weeks estimated gestational age. Her mother becomes concerned that the botulinum toxin injections that seemed to help her hypertonia at first are now making her tighter. She is experiencing daily painful muscle contractions that limit her ability to participate in therapy. A repeat MRI is performed, and shows the appearance of iron deposits in the brain, suggesting she may not have CP after all, but a *CP mimic*. Genetic testing is performed, and identifies pathogenic mutations in the *PANK2* gene. Her tone is re-evaluated and found to represent dystonia, prompting a change in her medications and adjustment of therapy goals. Botulinum injections are continued as a valuable part of her treatment plan.

Genetic results can clarify confusing clinical pictures

Case 3

- A 7 year-old boy was born at 30 weeks gestation and is diagnosed with spastic diplegia just after his first birthday. His MRI shows periventricular leukomalacia. His clinical course is stable, and he shows a partial response to oral medication, botulinum injections, and physical therapy. Genetic testing reveals a pathogenic mutation in the *SPAST* gene – classically associated with hereditary spastic paraplegia, a progressive disorder. Noting his preserved strength and good selective motor control, his CP team proceeds with a selective dorsal rhizotomy, with excellent postoperative outcome.

Genetic results may not change what we already know

The Wh- questions in CP genetics

- Who?
- What?
- When?
- Where?
- Why?

Who?

- Should we test all CP patients or only selected individuals?

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Review article

The evolution of our understanding of the conceptualization and genetics of cerebral palsy: Implications for genetic testing

Michael Shevell *

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY COMMENTARY

All cases of cerebral palsy warrant genomic screening

ALASTAIR H MACLENNAN

The Robinson Research Institute, The University of Adelaide, North Adelaide, South Australia, Australia.

doi: 10.1111/dmcn.14951

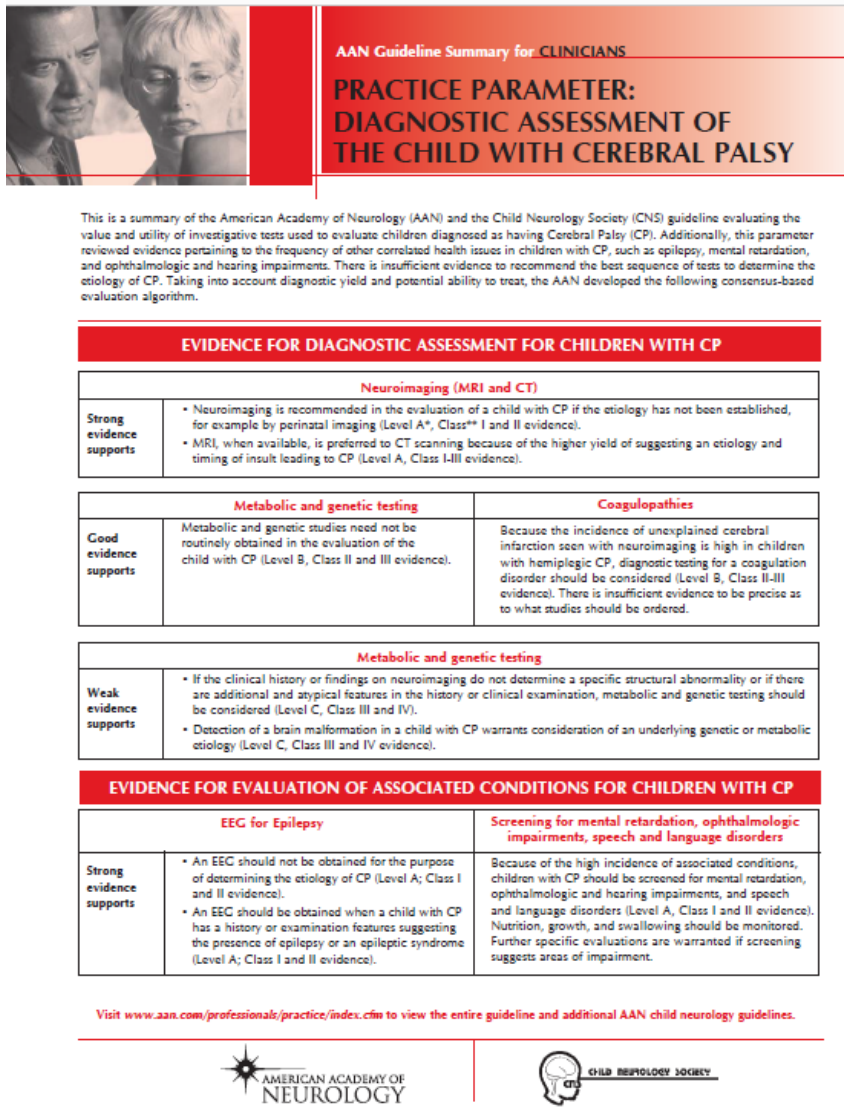
This commentary is on the original article by May et al. To view this paper visit https://doi-org.ezproxy1.library.arizona.edu/10.1111/dmcn.14948.

Genomic studies are now showing that many cases of cerebral palsy (CP) have a genetic causation. May et al.[1] perthem of a sense of guilt and a tendency to blame their obstetric and neonatal carers. (3) A genetic diagnosis greatly negates CP litigation. The legal profession has had much to do with defensive obstetric practice and a huge escalation in caesarean delivery rates.[4] (4) A genetic diagnosis gives insights into comorbidities (e.g. autism, intellectual disability, epilepsy), allowing prediction of future problems. (5) Family planning is assisted by identifying variants with a very low chance of recurrence or occasionally an increased heritable risk.

Research knowledge has advanced faster than clinical standards of care

‘There is no role for genetic or metabolic testing in the diagnostic assessment of the child with cerebral palsy’

Evidence base building



AAN Guideline Summary for CLINICIANS

PRACTICE PARAMETER: DIAGNOSTIC ASSESSMENT OF THE CHILD WITH CEREBRAL PALSY

This is a summary of the American Academy of Neurology (AAN) and the Child Neurology Society (CNS) guideline evaluating the value and utility of investigative tests used to evaluate children diagnosed as having Cerebral Palsy (CP). Additionally, this parameter reviewed evidence pertaining to the frequency of other correlated health issues in children with CP, such as epilepsy, mental retardation, and ophthalmologic and hearing impairments. There is insufficient evidence to recommend the best sequence of tests to determine the etiology of CP. Taking into account diagnostic yield and potential ability to treat, the AAN developed the following consensus-based evaluation algorithm.

EVIDENCE FOR DIAGNOSTIC ASSESSMENT FOR CHILDREN WITH CP

	Neuroimaging (MRI and CT)
Strong evidence supports	• Neuroimaging is recommended in the evaluation of a child with CP if the etiology has not been established, for example by perinatal imaging (Level A*, Class** I and II evidence). • MRI, when available, is preferred to CT scanning because of the higher yield of suggesting an etiology and timing of insult leading to CP (Level A, Class I-III evidence).

	Metabolic and genetic testing	Coagulopathies
Good evidence supports	Metabolic and genetic studies need not be routinely obtained in the evaluation of the child with CP (Level B, Class II and III evidence).	Because the incidence of unexplained cerebral infarction seen with neuroimaging is high in children with hemiplegic CP, diagnostic testing for a coagulation disorder should be considered (Level B, Class II-III evidence). There is insufficient evidence to be precise as to what studies should be ordered.

	Metabolic and genetic testing
Weak evidence supports	• If the clinical history or findings on neuroimaging do not determine a specific structural abnormality or if there are additional and atypical features in the history or clinical examination, metabolic and genetic testing should be considered (Level C, Class III and IV). • Detection of a brain malformation in a child with CP warrants consideration of an underlying genetic or metabolic etiology (Level C, Class III and IV evidence).

EVIDENCE FOR EVALUATION OF ASSOCIATED CONDITIONS FOR CHILDREN WITH CP

	EEG for Epilepsy	Screening for mental retardation, ophthalmologic impairments, speech and language disorders
Strong evidence supports	• An EEC should not be obtained for the purpose of determining the etiology of CP (Level A; Class I and II evidence). • An EEC should be obtained when a child with CP has a history or examination features suggesting the presence of epilepsy or an epileptic syndrome (Level A; Class I and II evidence).	Because of the high incidence of associated conditions, children with CP should be screened for mental retardation, ophthalmologic and hearing impairments, and speech and language disorders (Level A, Class I and II evidence). Nutrition, growth, and swallowing should be monitored. Further specific evaluations are warranted if screening suggests areas of impairment.

Visit www.aan.com/professionals/practice/index.cfm to view the entire guideline and additional AAN child neurology guidelines.

AMERICAN ACADEMY OF NEUROLOGY

CHILD NEUROLOGY SOCIETY

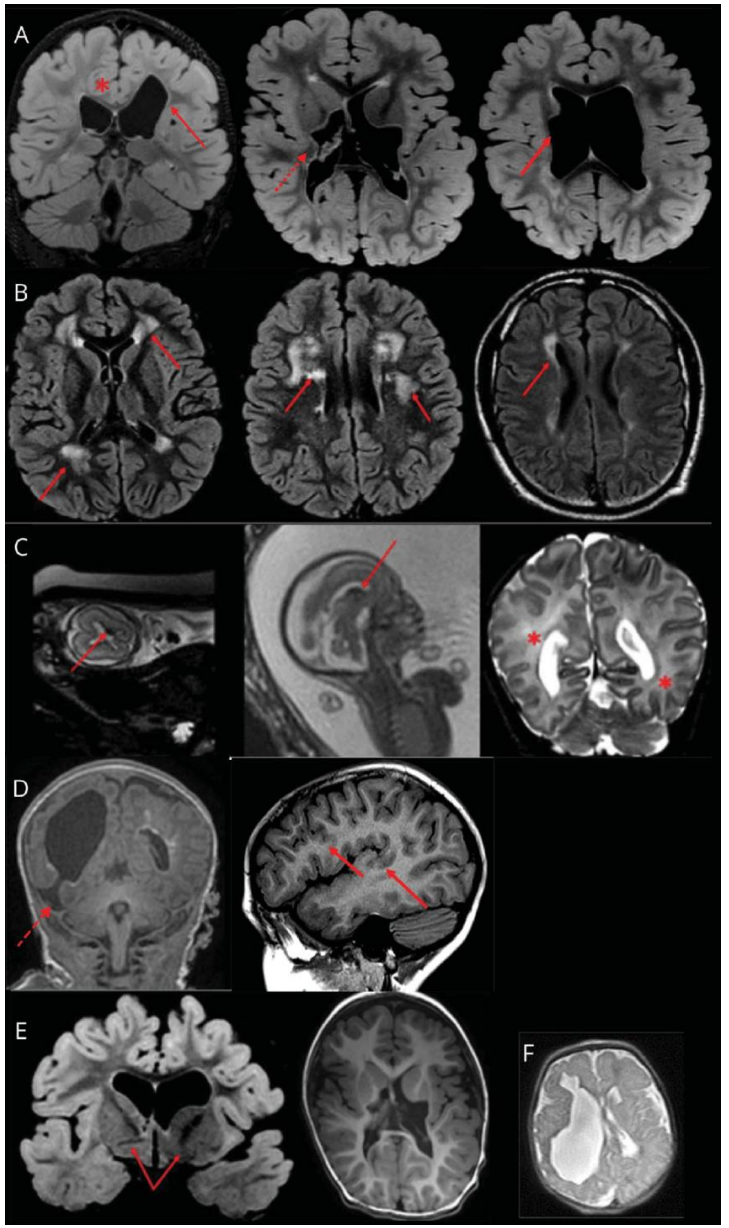
Reaffirmed July 2007

Who should be tested?

- We don’t know
  - Cryptogenic (PMID: 32989326)
  - Comorbid NDDs (PMIDs: 33528536, 34077496)

- Efforts underway to provide additional data to inform practice
- For now, recommend testing if there is not a clear etiology

COL4A1 mutations



PMID: 30413629

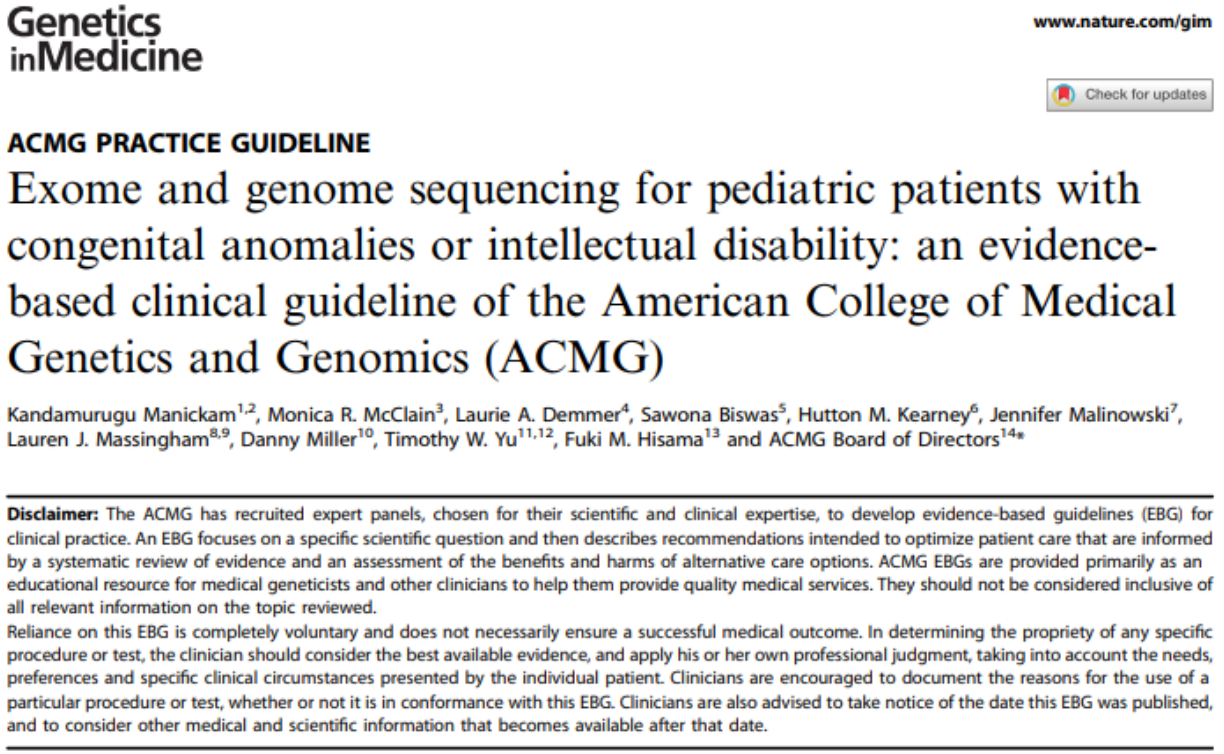
What?

- Single gene sequencing
  - Given that there are likely hundreds of genes that may lead to CP, you'd better be really lucky or really good!
  - Better yield with large-scale unbiased testing

- Chromosomal microarray
  - Can detect genomic copy number variants that lead to CP

What testing should be performed?

- Gene panels
  - Two commercial CP panels are currently available
- Whole exome/genome sequencing



Genetics inMedicine

www.nature.com/gim

Check for updates

ACMG PRACTICE GUIDELINE

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14]*

When should we test?

- Ideally at the time of diagnosis

- For many with an existing diagnosis of CP, testing may be appropriate now

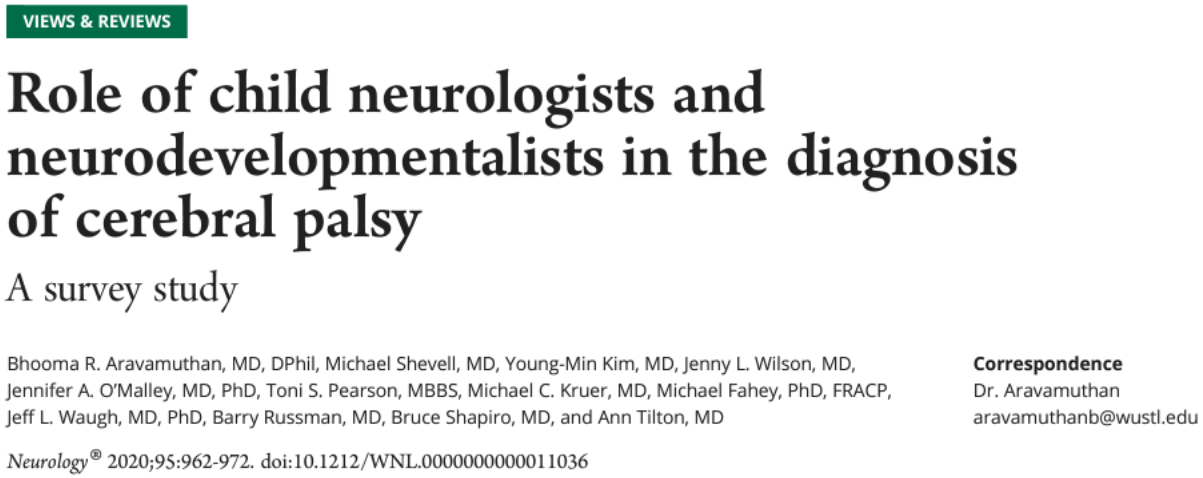
Network Implementation of Guideline for Early Detection Decreases Age at Cerebral Palsy Diagnosis

Nathalie L. Maitre, MD, PhD,[a,h] Vera J. Burton, MD, PhD,[c,d] Andrea F. Duncan, MD, MSClinRes,[e] Sai Iyer, MD,[f] Betsy Ostrander, MD,[g] Sarah Winter, MD,[g] Lauren Ayala, DPT,[g] Stephanie Burkhardt, MPH,[a] Gwendolyn Gerner, PsyD,[c,d] Ruth Getachew, BS,[c] Kelsey Jiang, BS,[f] Laurie Lesher, RN, MBA,[g] Carrie M. Perez, MA, LPA,[e] Melissa Moore-Clingenpeel, MA, MAS,[b] Rebecca Lam, BA,[i] Dennis J. Lewandowski, PhD,[a] Rachel Byrne, PT[i]

Where?

- Clinical Genetics and Genetic Counseling
  - Medical genetics professionals; yet often overwhelmed by growing demand for genetic medicine

- Other specialties may contribute (medical home)
  - Neurology
  - Developmental pediatrics
  - Physiatry
  - Orthopedics
  - Neurosurgery
  - Complex care



VIEWS & REVIEWS

Role of child neurologists and neurodevelopmentalists in the diagnosis of cerebral palsy

A survey study

Bhooma R. Aravamuthan, MD, DPhil, Michael Shevell, MD, Young-Min Kim, MD, Jenny L. Wilson, MD, Jennifer A. O'Malley, MD, PhD, Toni S. Pearson, MBBS, Michael C. Kruer, MD, Michael Fahey, PhD, FRACP, Jeff L. Waugh, MD, PhD, Barry Russman, MD, Bruce Shapiro, MD, and Ann Tilton, MD

Correspondence
Dr. Aravamuthan
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Neurology® 2020;95:962-972. doi:10.1212/WNL.0000000000011036

Why?

BOX 2. KEY BENEFITS, RISKS, AND LIMITATIONS OF GENETIC TESTING IN NDDs

Potential benefits

- End diagnostic odyssey
- Provide a name that unifies child's symptoms
- Enable provision of prognostic information
- Enable tailoring of medical management
- Result in targeted treatment
- Alleviation of negative emotions such as guilt or blame
- Increase access to services and condition-specific support groups
- Enable counseling with specific recurrence risk and reproductive options

PMID: 31501260

A role for personalized medicine in CP?

- If you've seen one patient with CP… you've seen ONE patient with CP

Editorial

Is Cerebral Palsy a Wastebasket Diagnosis?

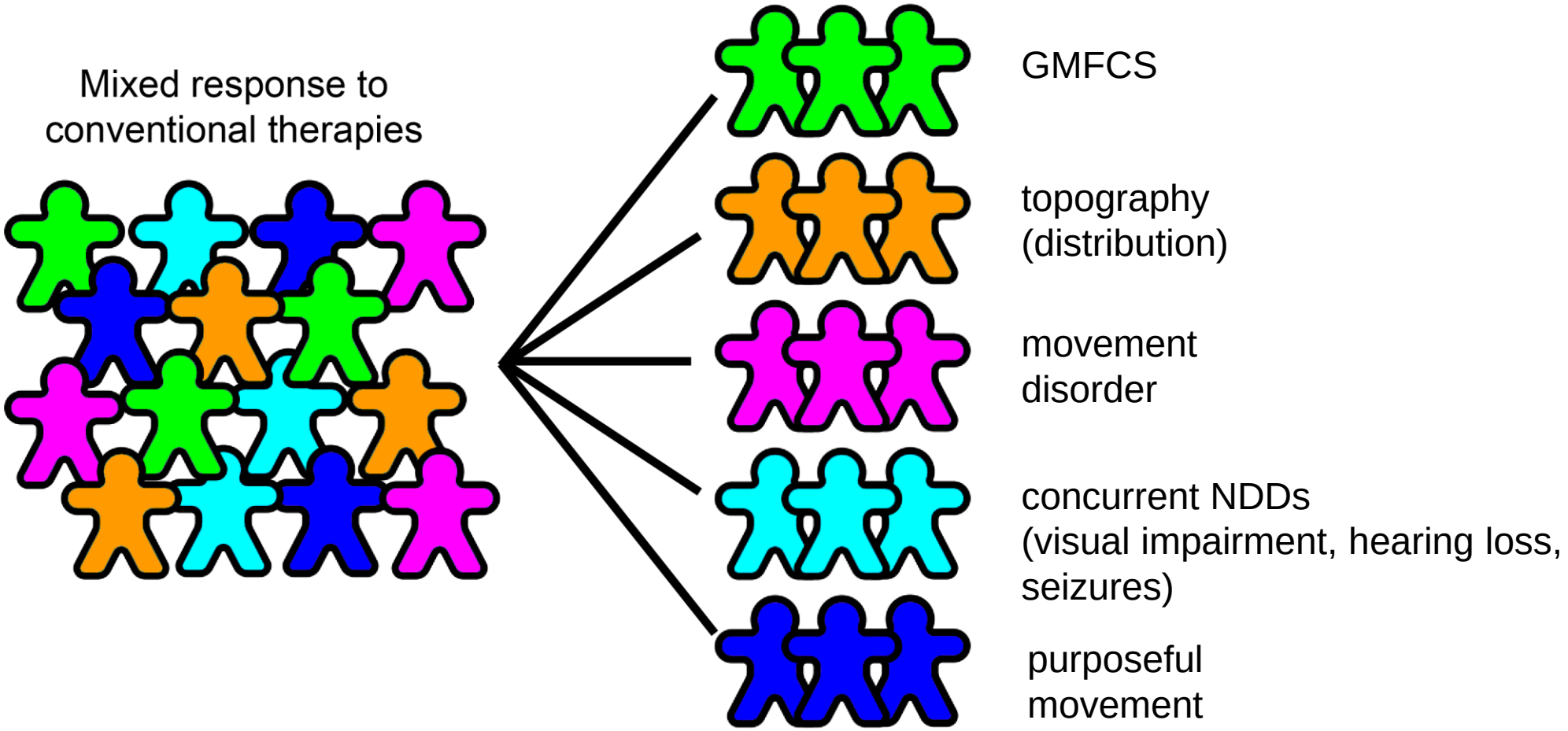
Terence D. Sanger, MD, PhD

Journal of Child Neurology
Volume 23 Number 7
July 2008 726-728

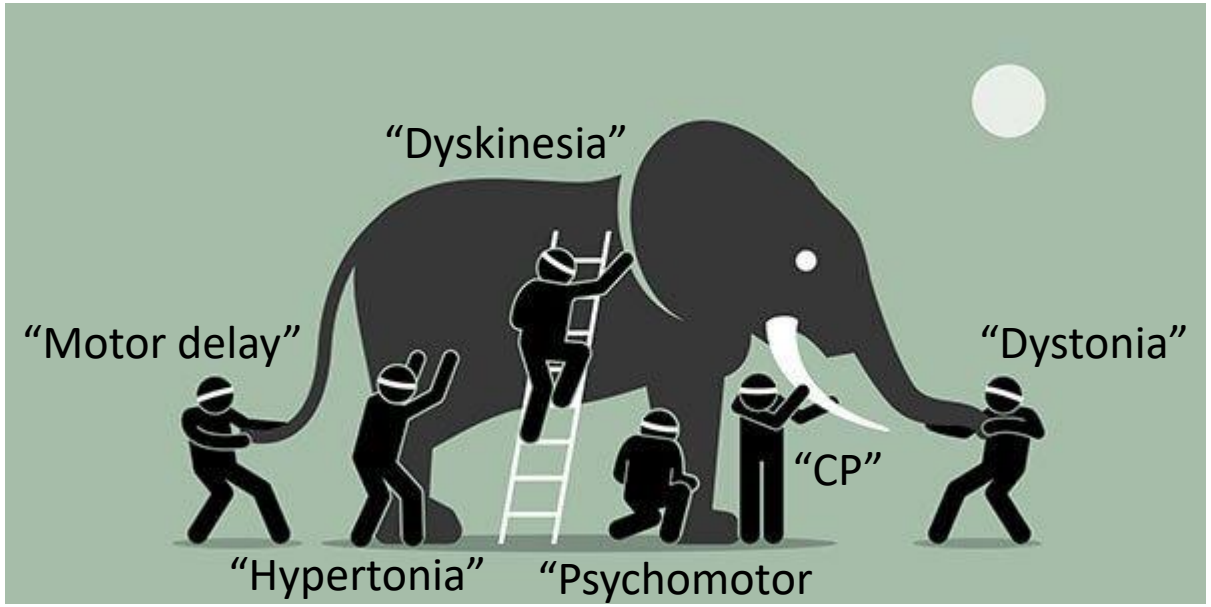
10.1177/0883073808314963
http://jcn.sagepub.com
hosted at
http://online.sagepub.com

- Perhaps this is not true, but nevertheless, a one size-fits-all approach is often not effective

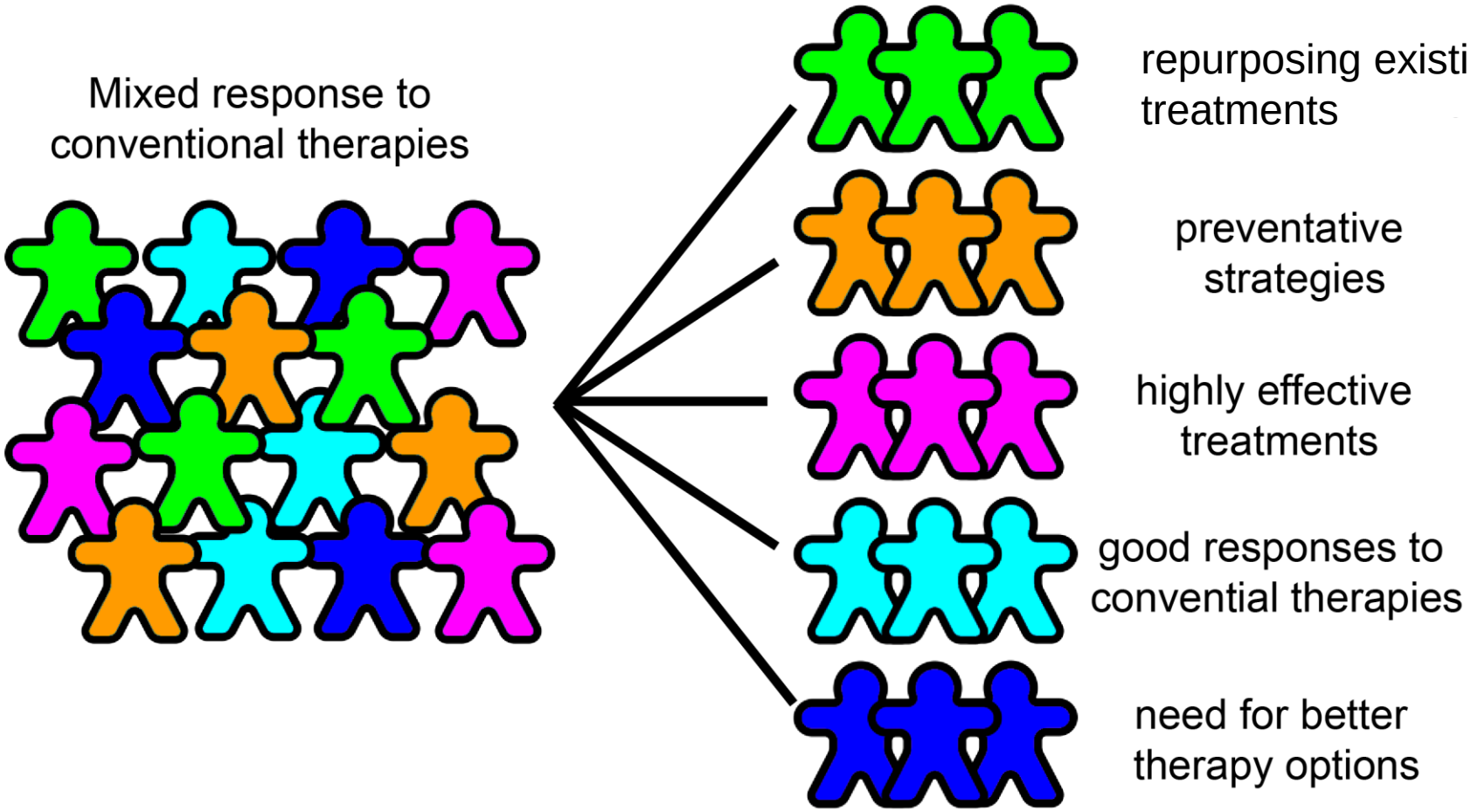
Opportunities for personalized medicine in CP



Seeing the whole picture



Opportunities for personalized medicine in CP



Changing management – Reaching for the best treatment first

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

Letters: New Observations | Full Access

Rationale for dopa-responsive *CTNNB1/ß*-catenin deficient dystonia

Judy Pipo-Deveza MD, Darcy Fehlings MD, David Chitayat MD, Grace Yoon MD, Hana Sroka MSc, Ingrid Tein MD

Changing management – Repurposing existing treatments

Annals of Internal Medicine®

LATEST ISSUES CHANNELS CME/MOC IN THE CLINIC JOURNAL CLUB WEB EXCLUSIVES A

‹ PREV ARTICLE | THIS ISSUE | NEXT ARTICLE ›

LETTERS | 17 SEPTEMBER 2019

Caffeine and the Dyskinesia Related to Mutations in the *ADCY5* Gene

Aurélie Méneret, MD, PhD; Domitille Gras, MD; Eavan McGovern, MD, PhD; Emmanuel Roze, MD, PhD

Sun, Oct 06, 2019

Newsweek

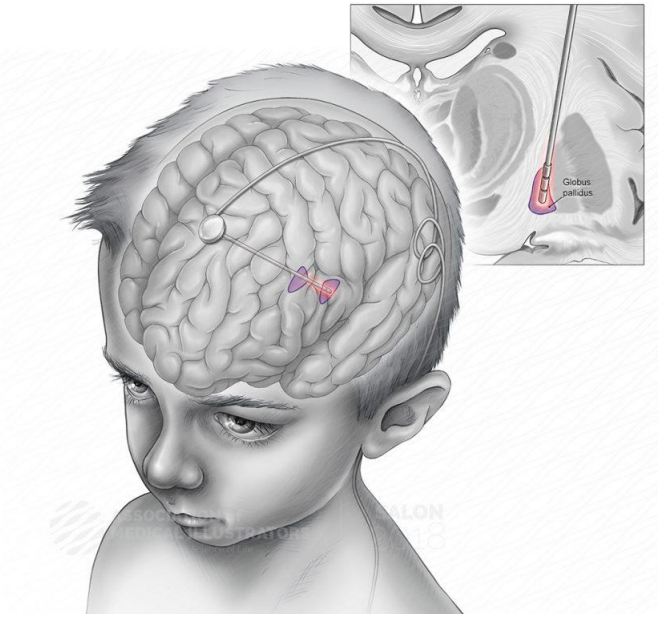
U.S. World Business Tech & Science Culture Newsgeek Sports Hea

HEALTH

DOCTORS USE COFFEE TO TREAT BOY WHOSE LIFE WAS RUINED BY GENETIC DISORDER

BY KASHMIRA GANDER ON 6/12/19 AT 7:06 AM EDT

Changing management – Predicting responders



Changing management – Developing new treatments

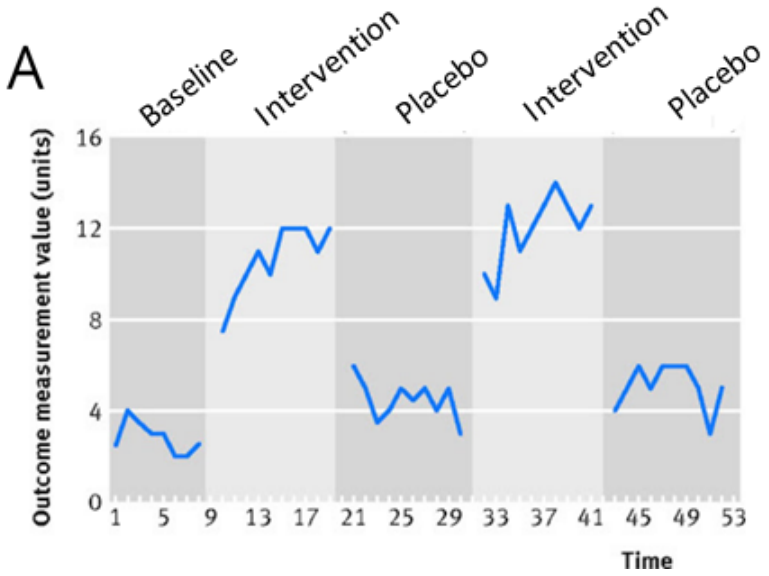
VIEWS & REVIEWS | OPEN ACCESS

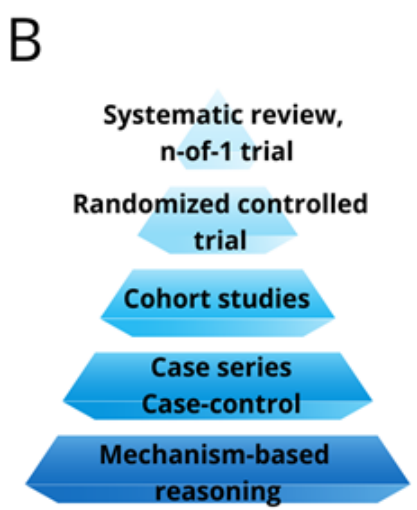
Systematic Review of N-of-1 Studies in Rare Genetic Neurodevelopmental Disorders

The Power of 1

Annelieke R. Müller, MSc, Marion M.M.G. Brands, MD, PhD, Peter M. van de Ven, PhD, Kit C.B. Roes, PhD, Martina C. Cornel, MD, PhD, Clara D.M. van Karnebeek, MD, PhD, Frits A. Wijburg, MD, PhD, Joost G. Daams, MA, Erik Boot, MD, PhD, and Agnies M. van Eeghen, MD, PhD

Neurology® 2021;96:529-540. doi:10.1212/WNL.0000000000011597





Early intervention may increasingly become medical as well as therapy-based

Identifying actionable genes within the CP population

CP patients
- research ES (n=496)
- clinical ES (n=1345)

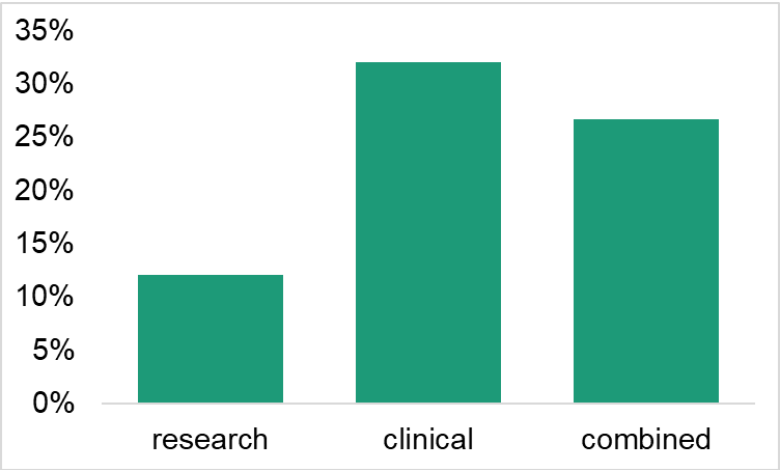
Pathogenic variants
- 243 genes
- 491 patients

Literature search
- Patient(s) received treatment not part of standard of care
- Showed a change in measurable outcome (or Phase II/III trial)
- Matched mechanism of disease between CP cohort + lit

Actionable

Personalized medicine opportunity based on gene finding + literature
61 genes (25.1%), 130 patients (7.1%)

26.7% positive molecular diagnosis in n=1841 patients



Lewis, et al. in preparation

Categories of interventions

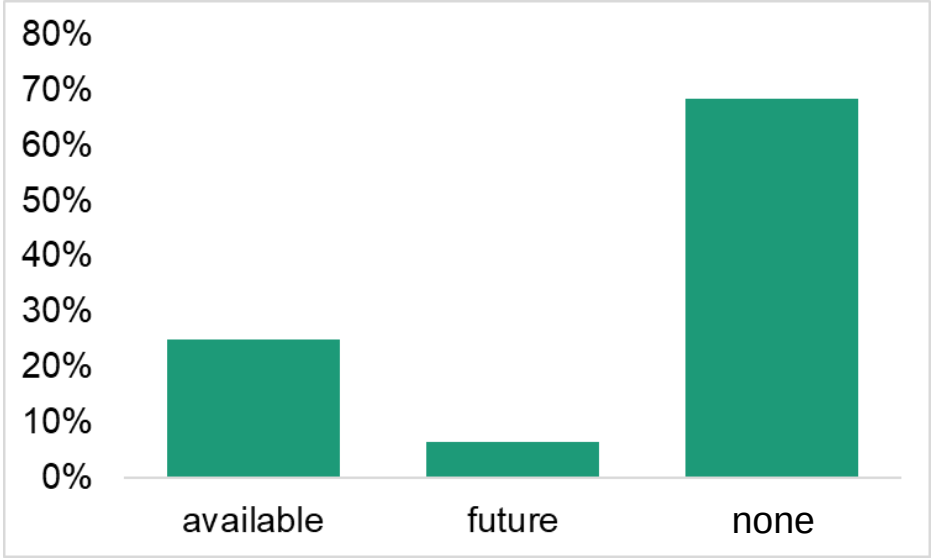
Primary
- Target disease mechanism (ex. replacing biochemical deficiency, gene therapy)
- 20 genes

Preventative
- Avoid triggers that worsen function OR potential complications requiring surveillance
- 19 genes

Symptom
- Identifying an effective treatment with reduced trial and error (ex. candidates for DBS or ketogenic diet)
- 22 genes

Future
- Interventions in development (ex. Phase II/III clinical trials)
- 16 genes

25.1% of genes with pathogenic variants have precision medicine treatments



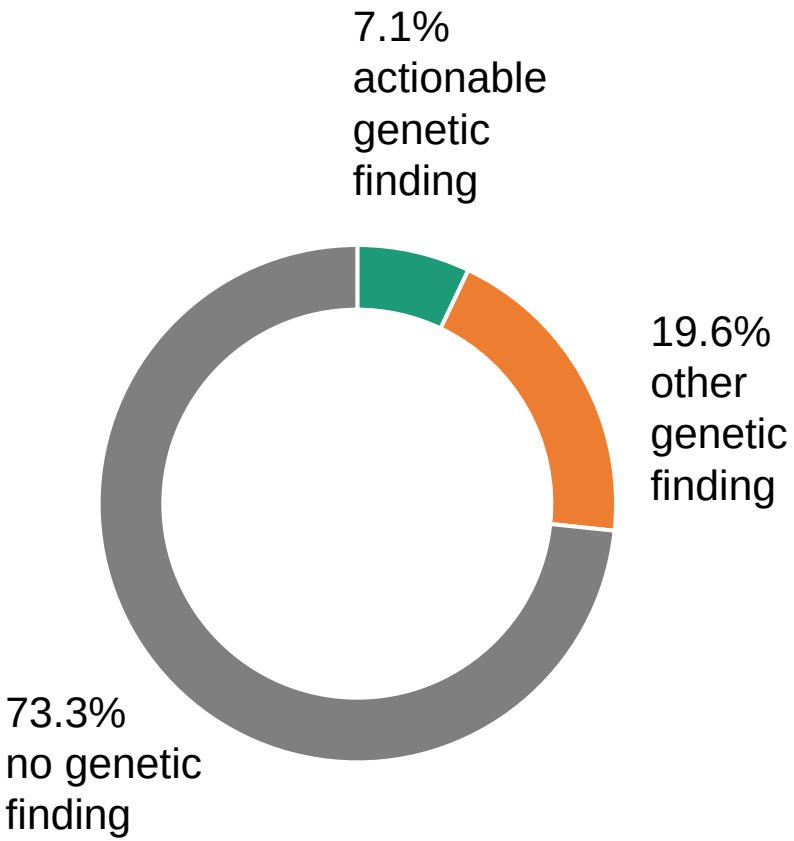
Modified Delphi process for evaluating impact

The team
- Working group including genetic counselors, neurologists, developmental pediatricians, and research geneticists.

Rubrics
- Draft rubrics (evidence, severity, nature, efficacy)
- Modified from ClinGen framework (adapted to CP scenario)

Discussion
- Virtual meetings to discuss approach
- Written rubric revisions/feedback

Consensus
- Individual scoring
- Virtual discussion, scoring consensus



Rubrics for severity of outcome, risk/burden of intervention, and efficacy of intervention

Benefit

Score	Outcome	Intervention risk/burden	Impact of intervention
0	No change	Severe risk	No effect
1	Mild impairments	Moderate risk	Small improvement
2	Moderate impairments	Mild risk	Moderate improvement
3	Severe impairments	No or very low risk	Significant improvement or avoidance of outcome

Benefit of interventions

Benefit

Score	Outcome	Intervention risk/burden	Impact of intervention
0	No change	Severe risk	No effect
1	Mild impairments	Moderate risk	Small improvement
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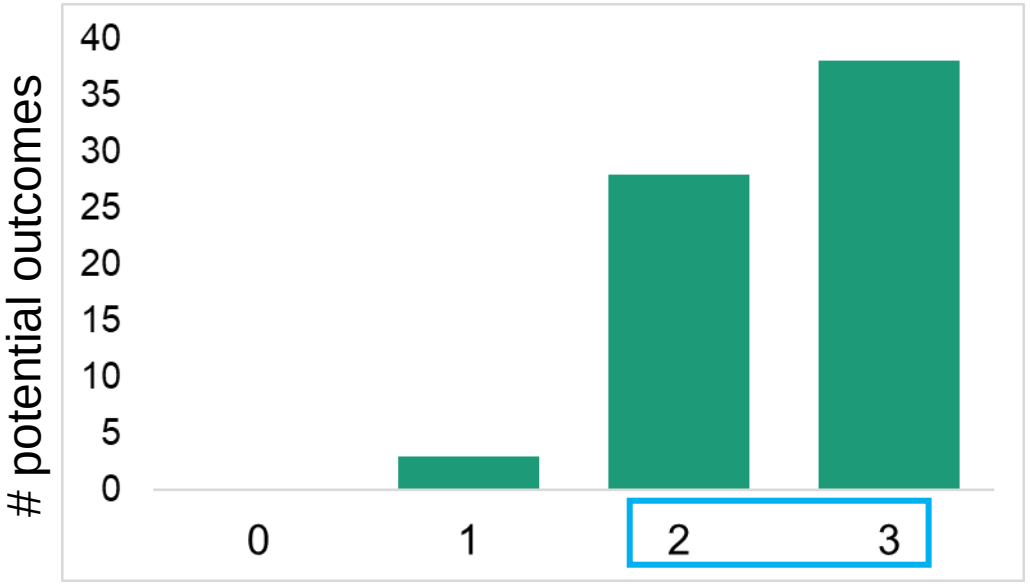
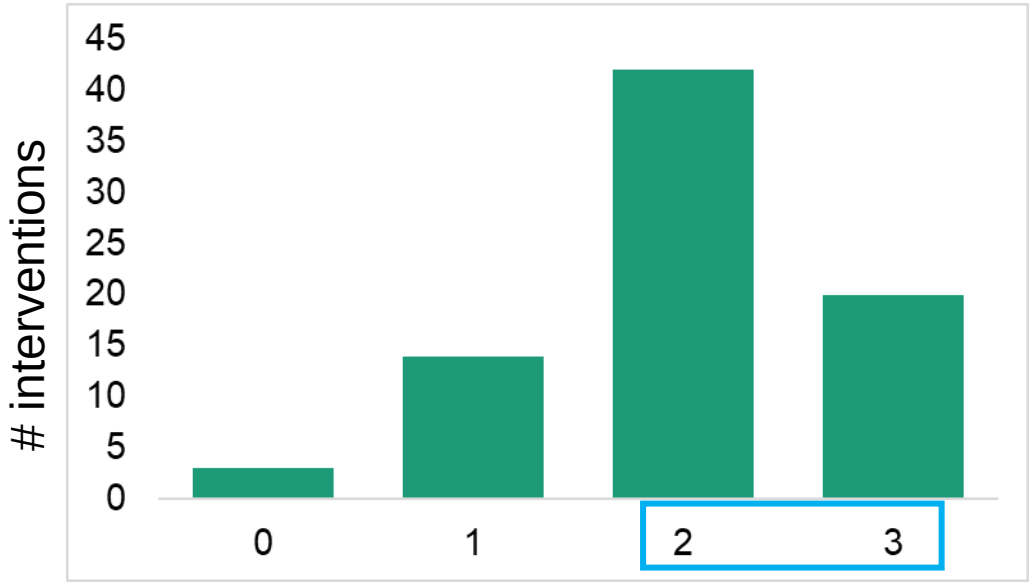
Outcome



Moderate-severe

Intervention risk/burden

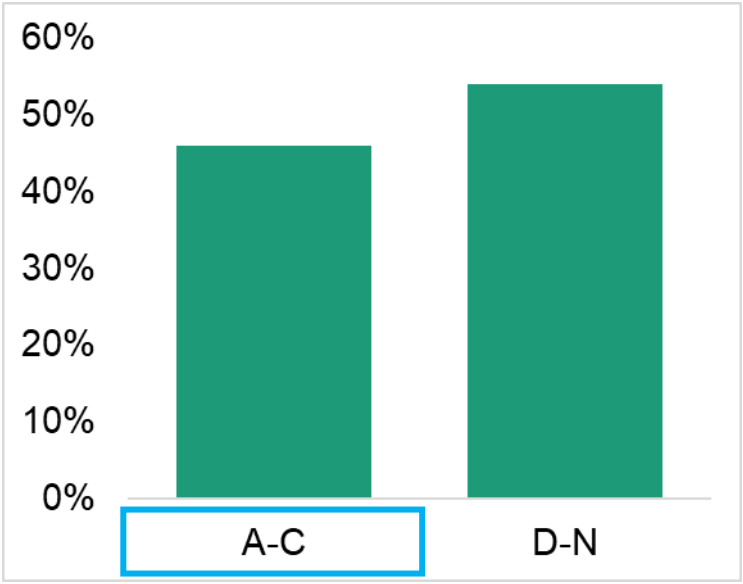


Mild-low risk

Strength of evidence

Grade	Definition	# of interventions
A	Clinical guideline consensus statement/FDA approved for application	17
B	Literature review with multiple case-control studies	38
C	Case-control multi-patient trial with quantitative evidence for outcomes	3
D	Multiple-patient clinical report or expert opinion without further information	42
E	Single-patient clinical report	18
N	Source not found	8

Evidence



Strong

Take home points

- 26.7% of patients had a positive genetic finding
- ~30% of those had a potentially actionable genetic findings
- This is 7% of the total CP population – or 70,000 individuals in the U.S.

- Actionable findings can target primary disease mechanism, create prevention opportunities, or inform symptom management
- In regard to patient impact, most untreated outcomes would be moderate-severe, while most interventions only create mild risk/burden
- Less than half of actionable findings are supported by high quality evidence

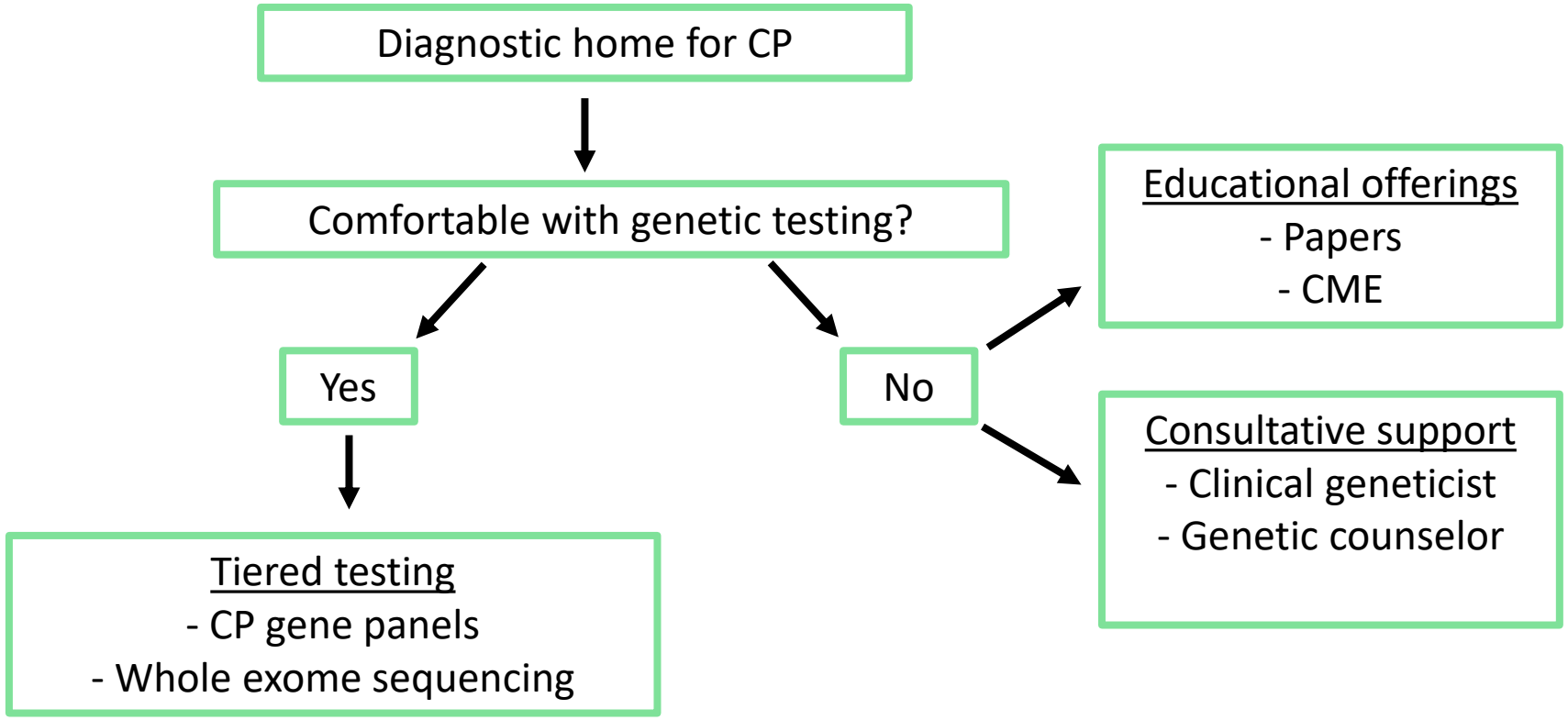
Knowledge transfer –
Practical aspects of implementation

Before you jump in with both feet…

Potential risks and limitations

- Failure to identify definitive etiologic diagnosis
- Genetic diagnosis may not alter medical management or treatment
- Genetic diagnosis associated with limited or no prognostic information
- Possibility of variants of unknown significance, incidental/secondary findings, or unexpected information about familial relationships
- Negative emotional responses to results
- Unexpected diagnosis of parent or relative based on inherited variant
- Concerns about genetic discrimination and privacy of data

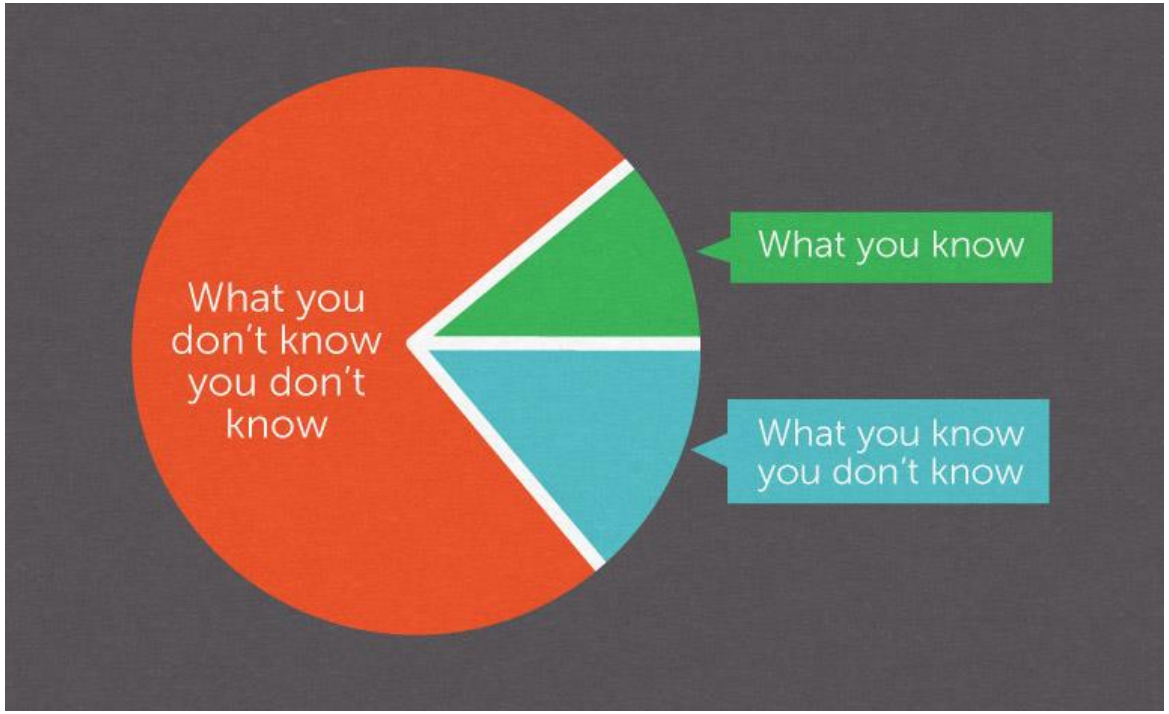
Incorporating genetic testing into your practice – Process Flowchart (implementation)



Variant interpretation

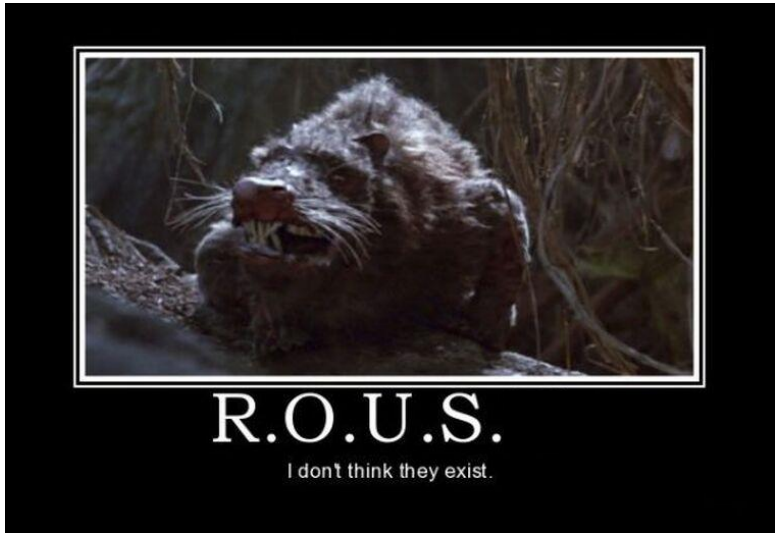
Genetic testing is seldom negative…

- But we fail to find a definite cause more than half of the time
  - Its difficult to conclude “genetic testing is negative”



“Oh no, it’s a Variant of Unknown Significance” (VOUS)

- Many variants are not able to be classified as Pathogenic/Likely Pathogenic or Benign/Likely Benign



Functional assay: Laboratory methods for directly or indirectly assessing the influence of a specific variant sequence on protein conformation or function

Literature evaluation: Case reports and other reports in the literature may provide insight regarding the clinical implications of the genetic change.

Segregation analysis: An analysis that considers whether a variant tracks within a family

Figure 2. Selected Reclassification Techniques

PMID: 25901385

In the end… be family-centered

BOX 3. SUGGESTIONS FOR DELIVERY OF A GENETIC DIAGNOSIS IN NDDs

- Attend to parents' emotions and provide emotional support
- Offer messages of hope and perspective.
- Engage the parents in a dialogue and encourage parents to talk (avoid verbal dominance).
- Check in with parents throughout the discussion and reengage as necessary.
- Limit the use of difficult medical terminology.
- Elicit parental preferences (e.g., asking whether they would like to see a picture of other individuals with the same condition).
- Provide the most up-to-date information possible.
- Provide balanced information (e.g., in addition to describing the features of the condition, point out aspects of the child's health that are not expected to be affected, if appropriate).
- Give written information about the diagnosis and an outline of follow-up plans.
- Give resources such as condition-specific support groups, when available.

Thanks!

- My lab
- Our collaborators
- My family

UCP

PTC THERAPEUTICS™

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