Intellectual and Developmental Disabilities Research at NICHD: Trends and Future Directions

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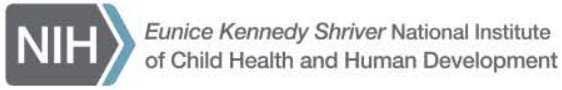
January 18, 2018

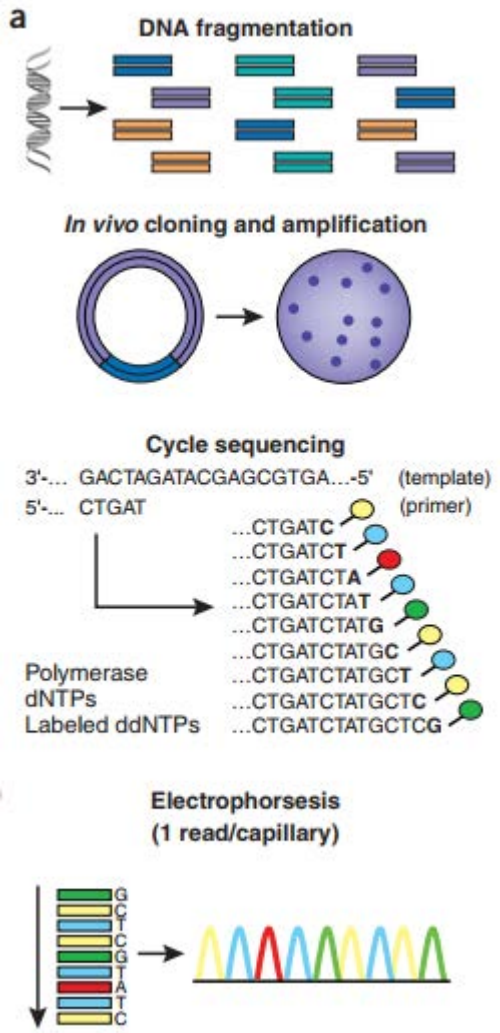


Outline

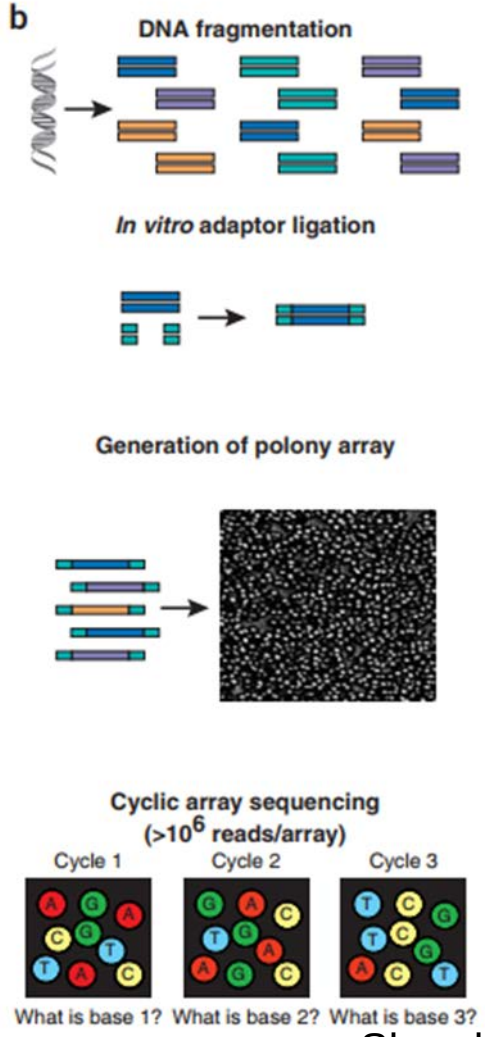
- The Genomics Revolution: unprecedented opportunities and significant challenges
- Progress in the IDDRC program
- Inclusion and informed consent

The Genomics Revolution: unprecedented opportunities and significant challenges

Before (Sanger sequencing)



Now (Next generation sequencing)

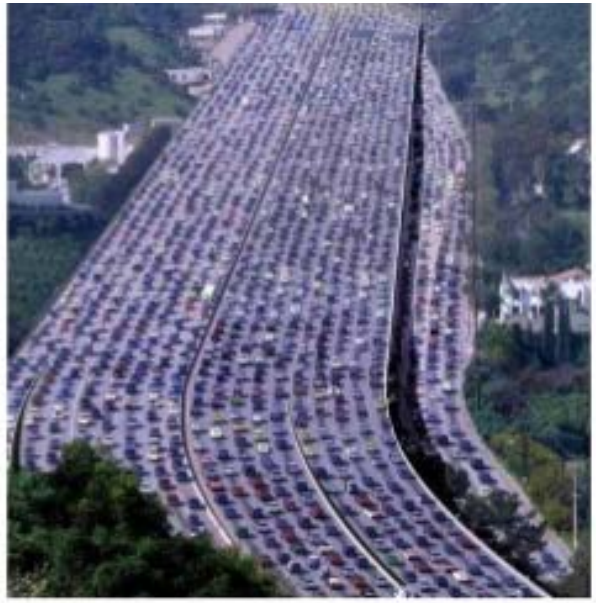


Shendure and Ji 2008

Before (Sanger sequencing)

- 1 read/capillary

Now (Next generation sequencing)

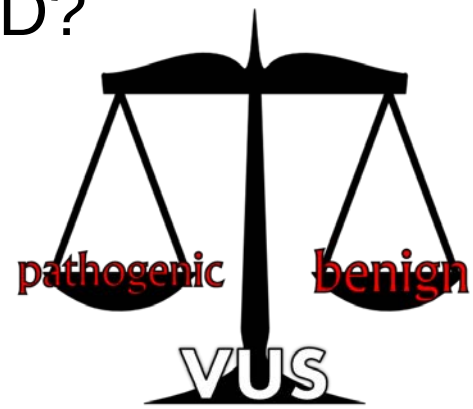


- >10^6 reads/flowcell

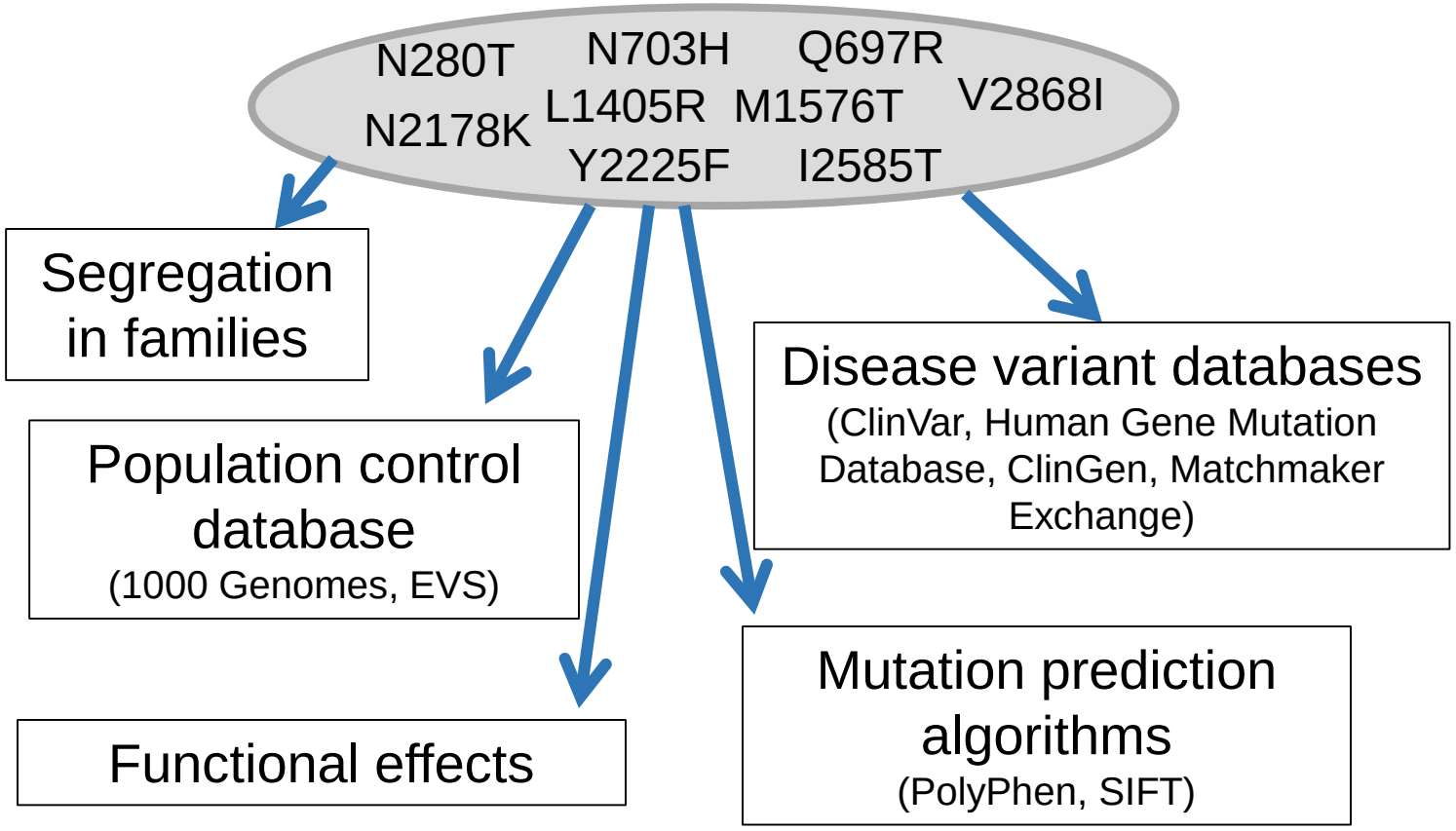
High-throughput sequencing of DNA is no longer the barrier: Data storage and interpretation become the challenges

Practical barriers to implementing the genomic revolution for IDD

1. How can we **apply** genomic testing in the clinic for diagnosis of individuals with IDD?
2. Variant Interpretation Problems:
   a. Too many potentially condition-causing variants. How do I narrow my list down?
   b. After I have identified a “variant of interest,” how do I show functional significance?
3. How can we leverage this effort for new gene discovery?
4. How can we translate these discoveries to develop treatments?



Clinical significance of genetic variation



Compliments of Christina Gurnett, WashU IDDRC. Derived from Richards et al, GIM, 2015

Interpreting the genomic variants identified in the clinic

http://www.stlouischildrens.org/our-services/genetics-and-genomic-medicine

Inventory of Genetic Test Results

Results of inter-disciplinary collaboration:

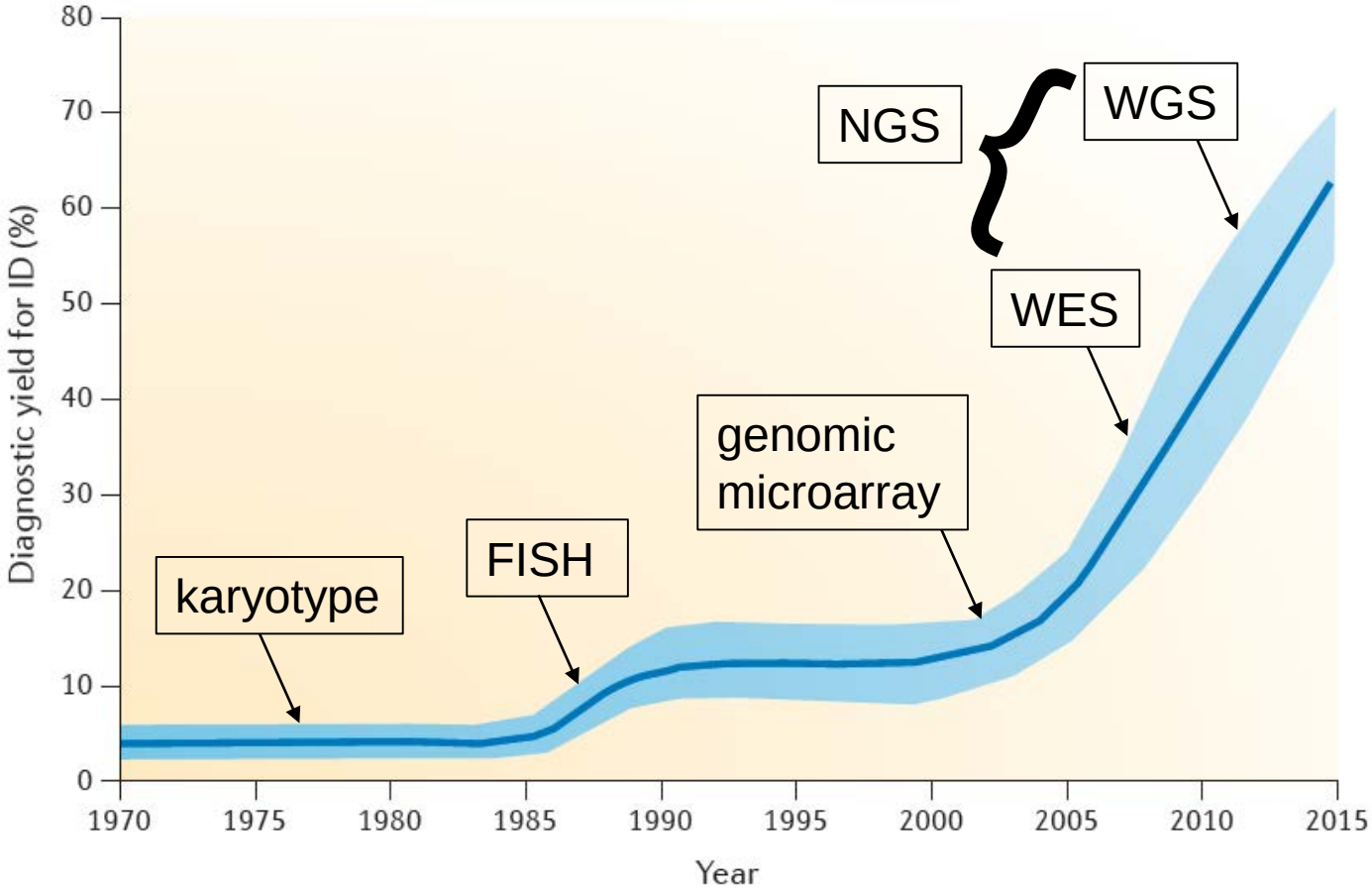
- **Functional analyses** of candidate variants.
- **Biomaterials** for testing investigator's hypotheses.
- Genetics-first **clinical trials**.

http://www.excite.com/education/careers/medical-scientist

Clinical Expertise ⇄ Research Expertise

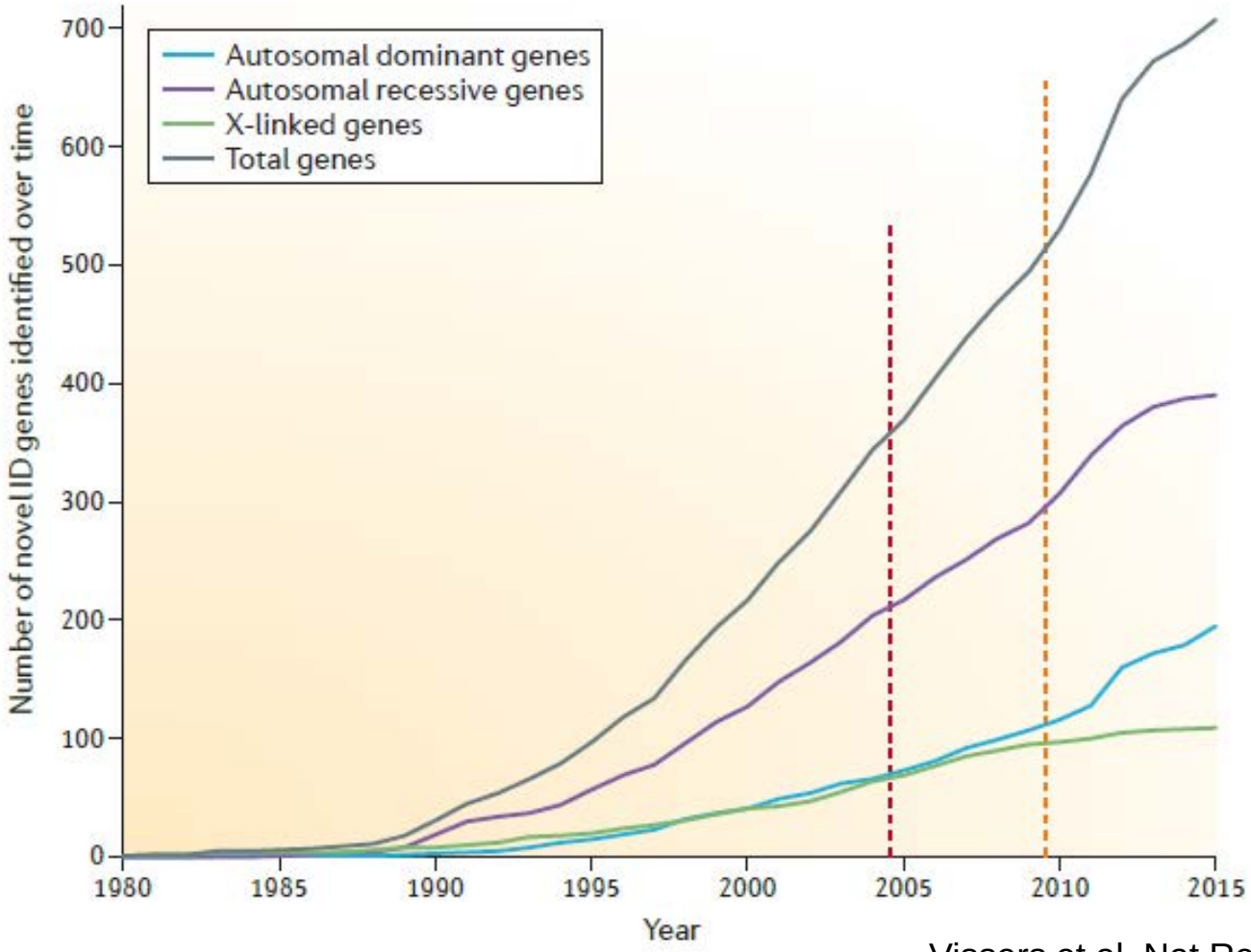
Compliments of Dustin Baldridge, WashU IDDRC

Diagnostic yield for IDD over time



Vissers et al, Nat Rev Genet 2016

Capitalizing on the genomics revolution to identify genes for IDD



Vissers et al, Nat Rev Genet 2016

Challenges to translational science for IDD

- Limited knowledge of biomarkers/target molecules/pathways
- Animal models may not replicate complex human IDD
- Reliability and reproducibility of animal/human measures
- Complexity of comorbid conditions (epilepsy, sleep, mental health problems)
- Lack of natural history studies of rare IDD conditions (small “N”) and broad range of abilities within a known condition
- Lack of understanding of role of environment, epigenetics in complex IDD phenotypes
- Failures of several high-profile drugs in Phase2/3 RCTs by Pharma—hesitant to invest
  - Few drugs developed for IDD outcomes
  - Insensitive or inappropriate endpoints/outcome measures
  - Inadequate stratification
  - Placebo effects
- Lack of dissemination and implementation of treatments into practice

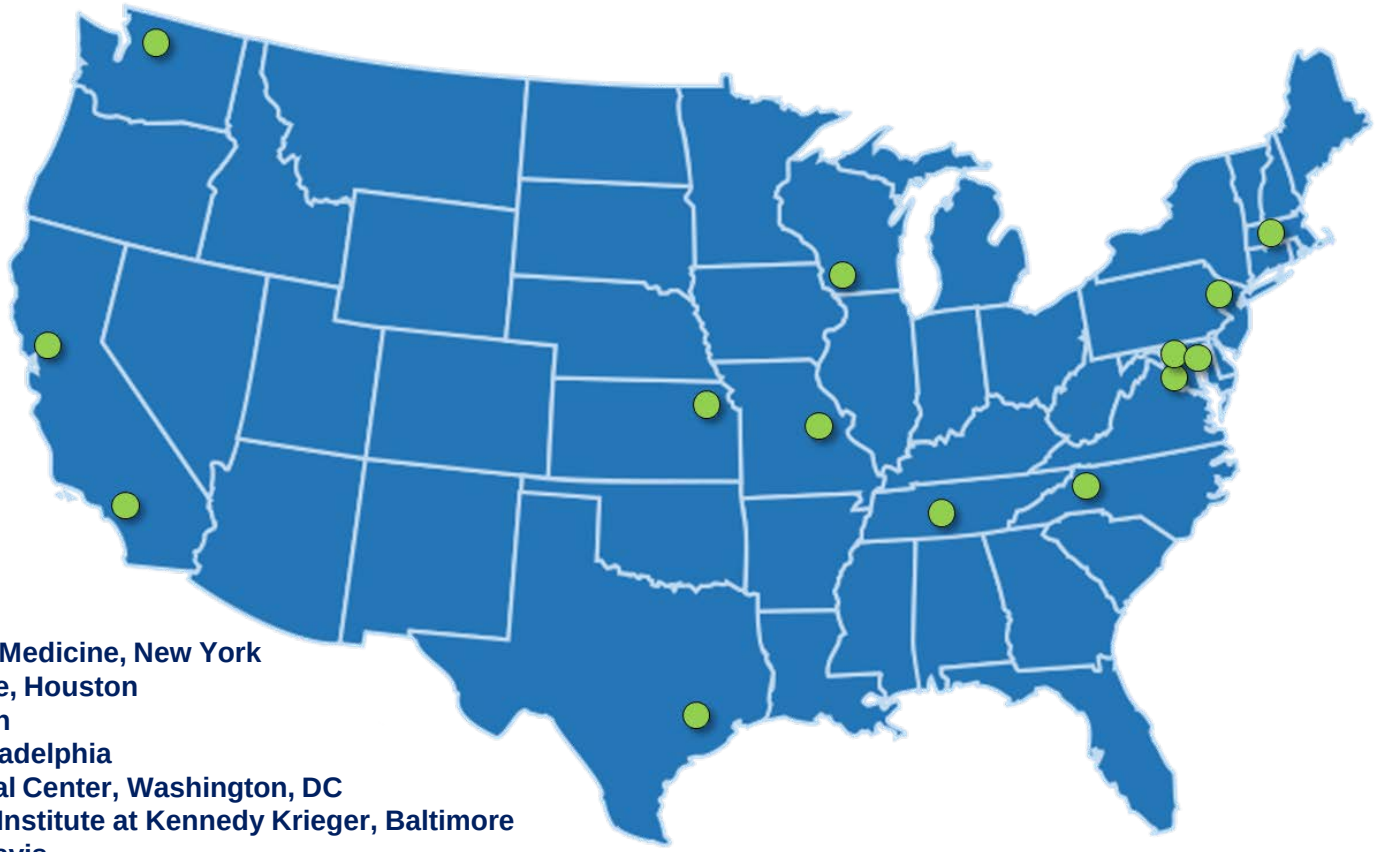
Progress in the IDDRC program

Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRCs)

IDDRCs: History and Goals

- Originally created in 1963 by Congressional mandate: construction of 12 “MR” Research Centers
- 1990s: P30 mechanism: infrastructure cores, encourage training opportunities
- 2013: converted to cooperative agreement with more focused research project, a translational emphasis, and creation of a network
- Multi-component centers that include:
  - Shared resources and facilities in the form of Cores
  - Specific research project funded by Center
  - Additional research projects access Cores that are independently funded
  - Each center supports ~38-70 PIs, 50-100 projects
  - Training role: T32s, Fs, Ks, R13s attract investigators to field
  - Leverage other resources: typically, at least $20 M in institutional support/IDDRC
- Celebrated 50 years of IDD research
- **Goal:** promote collaborative, multidisciplinary research programs to advance development of therapies and interventions for IDD

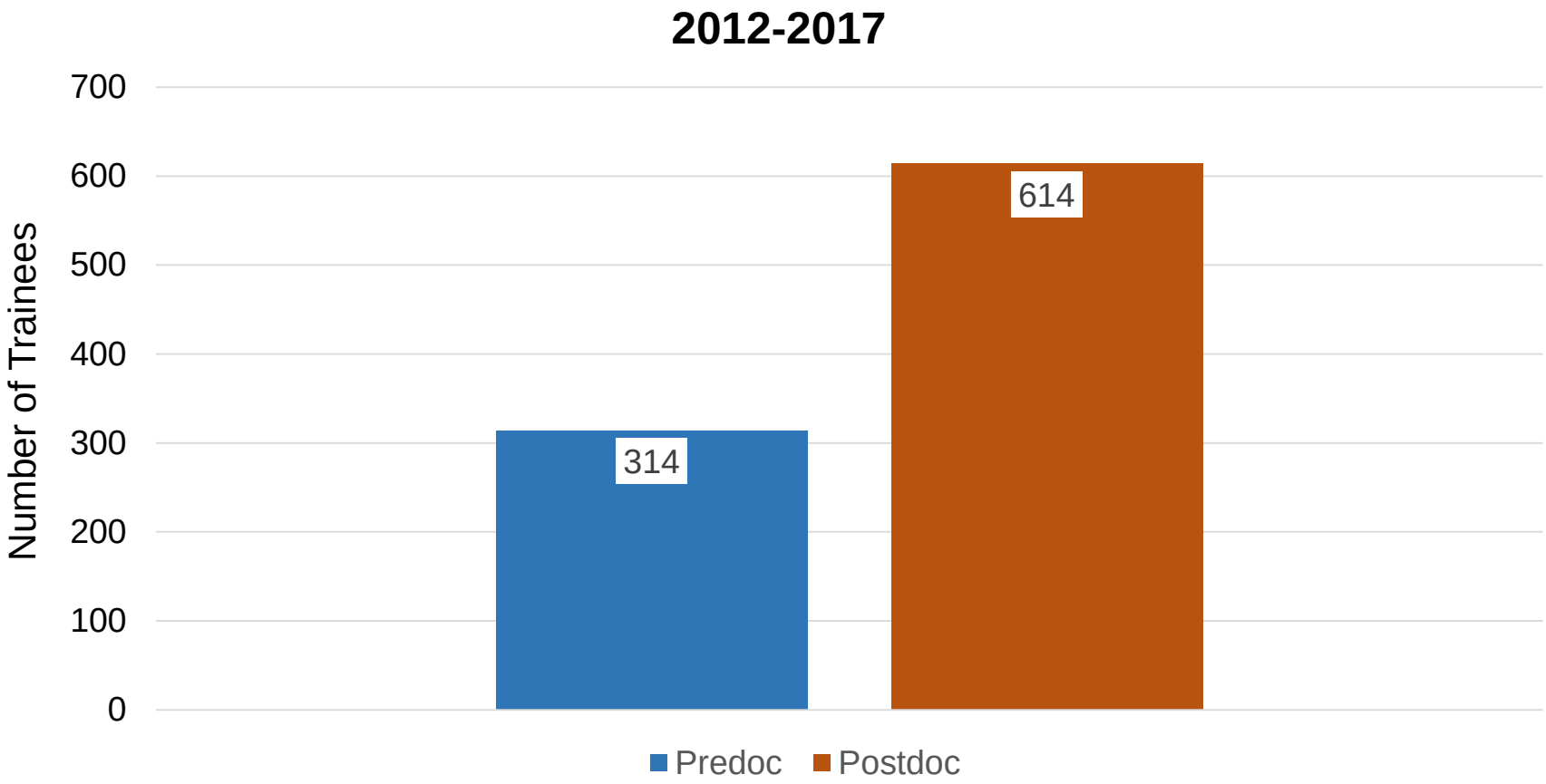
IDDRCs: A National Network



14 IDDRC sites:

- **Albert Einstein College of Medicine, New York**
- **Baylor College of Medicine, Houston**
- **Children's Hospital Boston**
- **Children's Hospital of Philadelphia**
- **Children's National Medical Center, Washington, DC**
- **Hugo W. Moser Research Institute at Kennedy Krieger, Baltimore**
- **University of California, Davis**
- **University of California, Los Angeles**
- **University of Kansas, Lawrence**
- **University of North Carolina, Chapel Hill**
- **University of Washington, Seattle**
- **University of Wisconsin-Madison**
- **Vanderbilt University, Nashville**
- **Washington University, St. Louis**

Training the next generation of IDD researchers



Trainees Supported with NIH Training Grants

Compliments of Len Abbeduto, UC Davis IDDRC

Collaborative workgroups addressing translational challenges

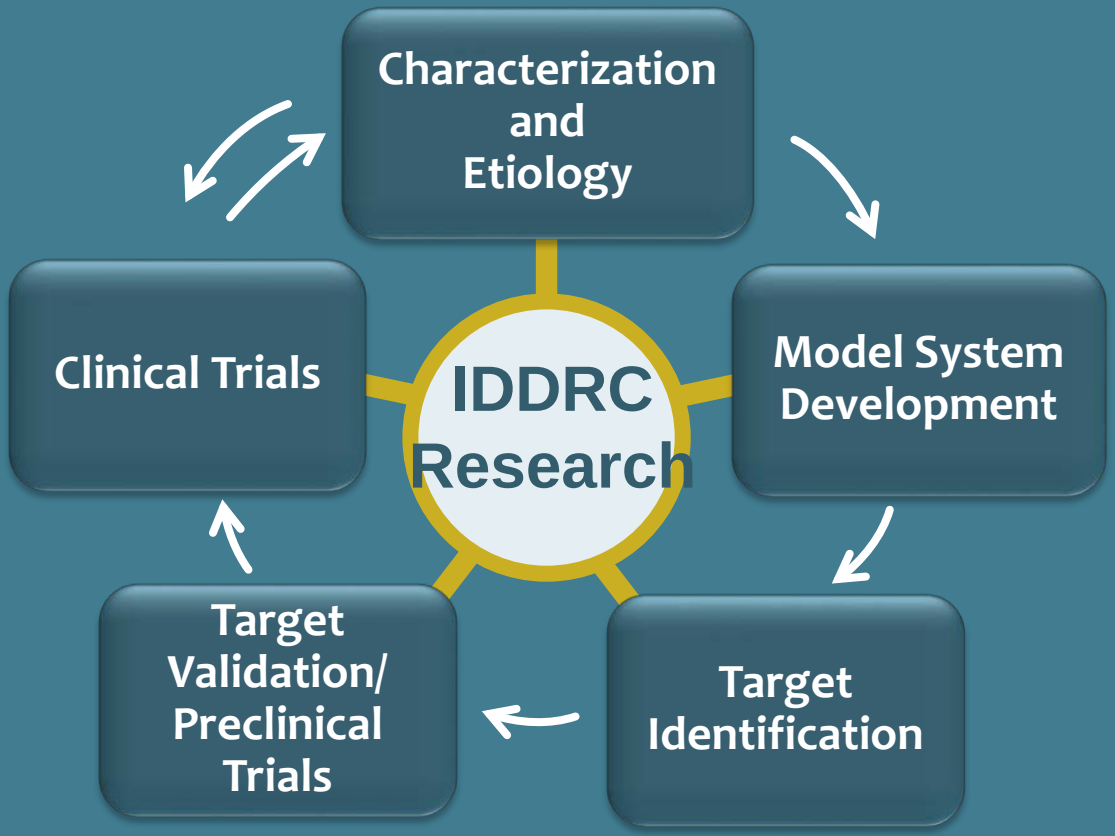
1) Project inventory workgroup
   - Developed an inventory of ~150 projects and resources across all centers, including rare diseases, to increase the "N," for collaborative projects
2) Genomic variants workgroup
   - Developing shared projects to identify, functionally validate, and curate rare/previously unknown genomic variants in individuals with IDD
3) Animal cores workgroup
   - Comparing protocols for a common rodent behavior assay
   - Developing a special issue for Neurobiology of Learning and Memory:

Rigor and reproducibility in rodent behavioral research

Maria Gulinello[a], Heather A. Mitchell[b], Qiang Chang[b], W. Timothy O'Brien[c], Zhaolan Zhou[c], Ted Abel[c,i], Li Wang[d], Joshua G. Corbin[d], Surabi Veeraragavan[e], Rodney C. Samaco[e], Nick A. Andrews[f], Michela Fagiolini[f], Toby B. Cole[g], Thomas M. Burbacher[g], Jacqueline N. Crawley[h,*]

4) Clinical/translational cores workgroup
   - Developing shared phenotyping efforts and tools
   - Exploring ways to leverage informatics, registry resources of the CTSAs
   - Developing "Use Case" for All of Us
5) Developing joint publications to engage families & public

IDDRCs and the Translational Research Cycle

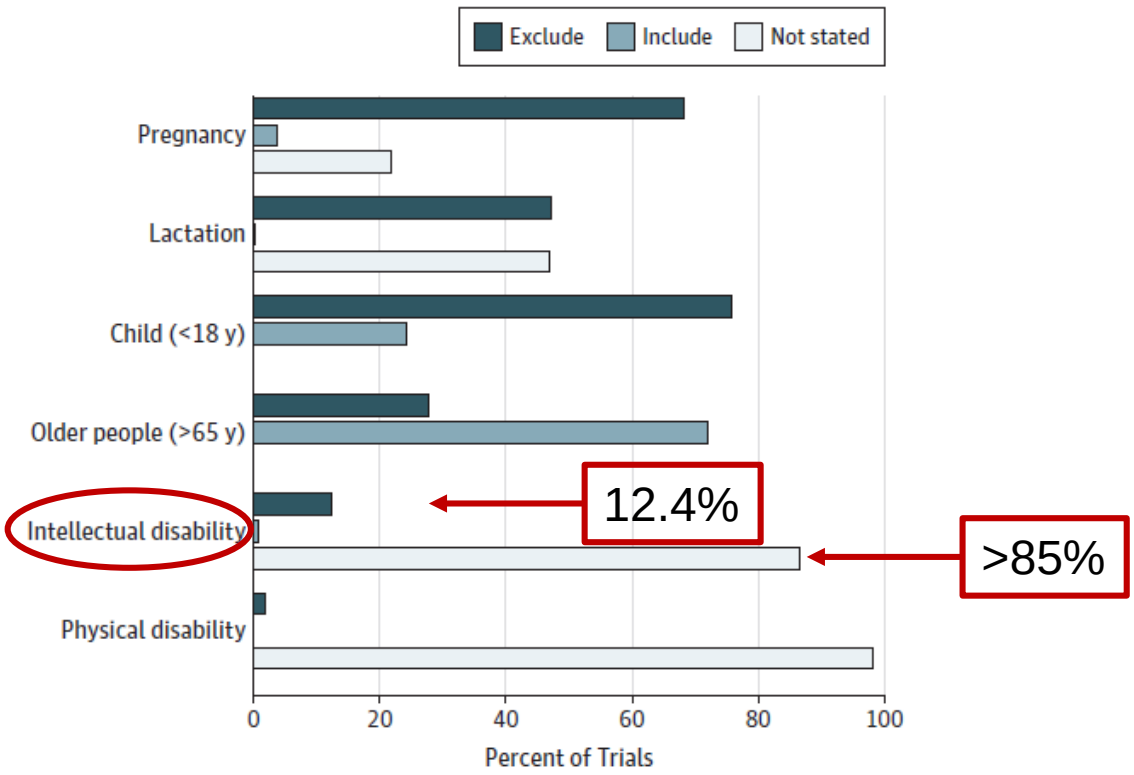


Compliments of Mike Guralnick, Univ WA IDDRC

Inclusion and Informed Consent

People with IDD are often not included in research

Figure. Open NIH-Funded Phase 3 and 4 Studies as of October 19, 2017



Clinicaltrials.gov records (N=338) were reviewed. Exclusion for intellectual disabilities was based on IQ and defined intellectual disability or cognitive impairment; physical disabilities: exclusions for physical disabilities were inability to ambulate, extreme immobility, and paraplegia.

Spong and Bianchi, JAMA online, Dec 28, 2017

The need for inclusion of those with IDD in research

- Alternative drug delivery methods (e.g., gastrostomy tubes) are rarely studied
- Lower threshold for toxicity: (e.g., drugs for children with Down syndrome with acute leukemia)
- Limited PK/PD studies for those with biochemical conditions that alter metabolism
- High rate of psychotropic and other medication prescriptions without knowledge of utility or adverse effects
- We can learn generalizable knowledge about common disorders from people with IDD who are at higher or lower risk of having those disorders

Barriers to Inclusion for those with IDD

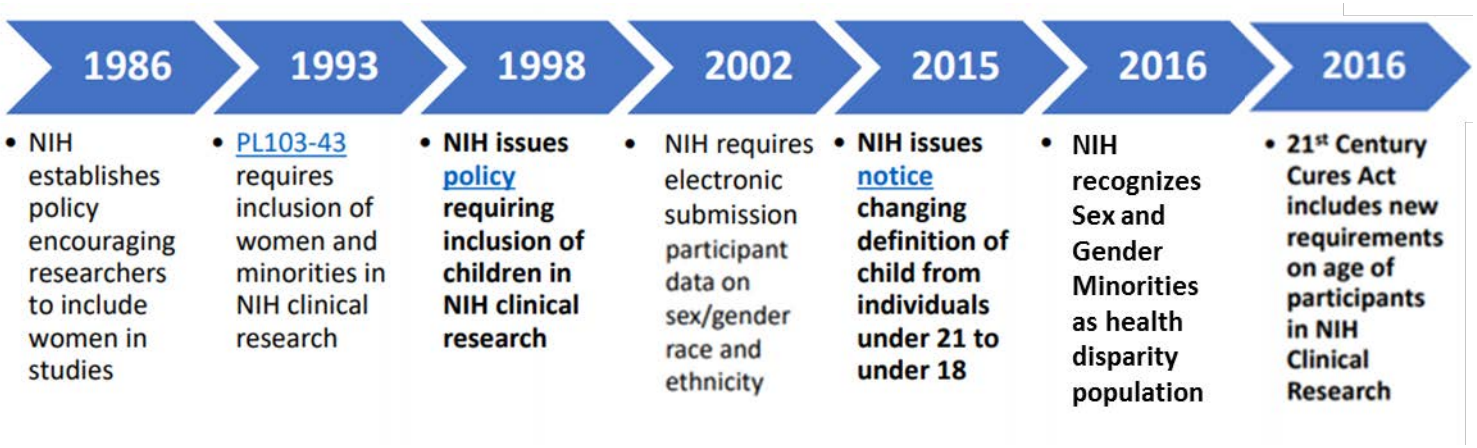
- Scientific requirements require typical cognition or unacceptable risks outweigh knowledge to be gained
- Inability to provide informed consent
  - May take more time to provide consent
  - May be more difficult to ensure understanding, esp. for non-verbal or low-functioning subjects
  - Harder to obtain proxy consent by caregivers or family members
- More difficult to comply with a protocol

But, in a survey of 300 randomly chosen clinical trials published in 6 highest impact medical journals, only 2% clearly included persons with IDD—yet at least 70% could have included these with only minor accommodations or modifications [Feldman et al, JIDR, 2014]

- Ethical concerns: considered “vulnerable” subjects

Inclusion in NIH-sponsored research

- History of inclusion at NIH:
  - Women
  - Racial and ethnic minority populations
  - Sex and Gender Minorities



- Next frontiers:
  - Children and older populations
  - Pregnant/lactating women
  - Those with disabilities

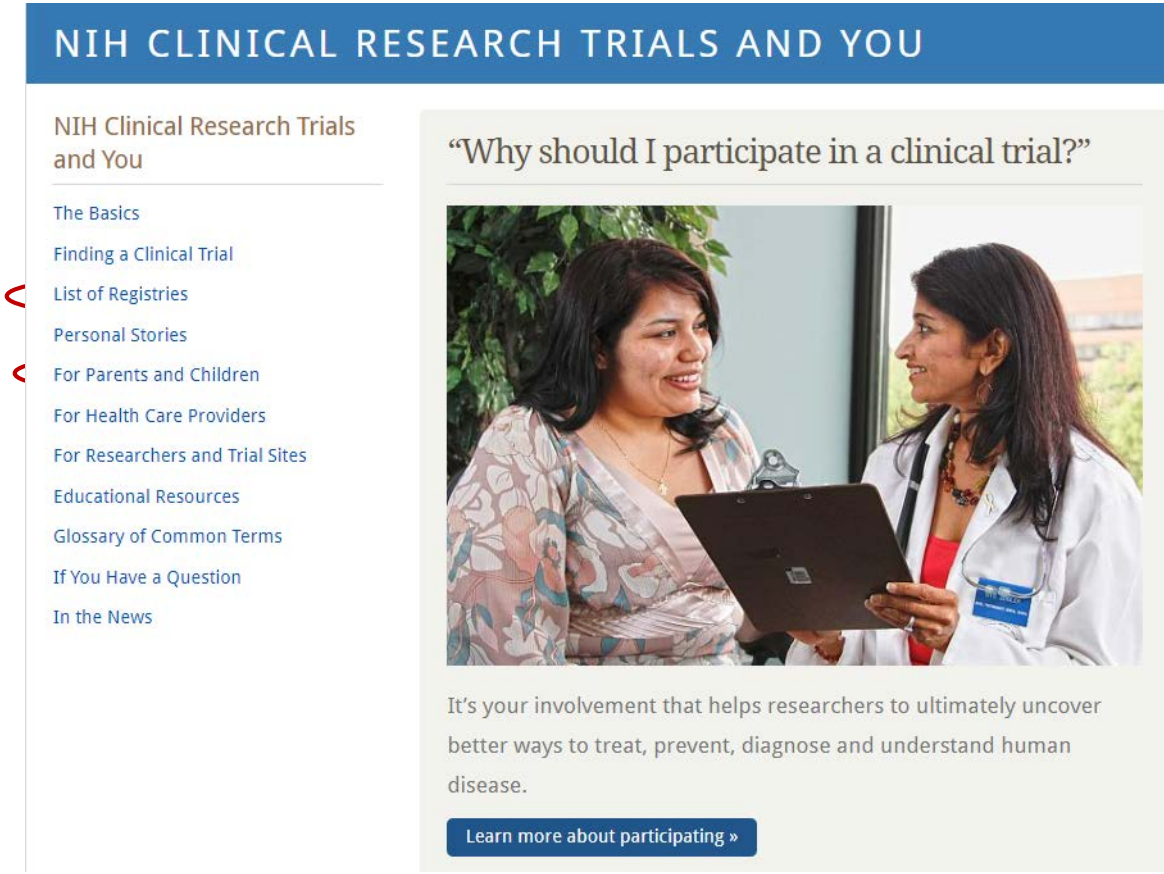
Inclusion of Persons with IDD in Research

- What is NIH doing to include people with IDD in research?
- Resources:

  Registries, such as DS-Connect® and PregSource™

  https://www.nih.gov/health-information/nih-clinical-research-trials-you

- ClinicalTrials.gov



What else is NICHD/NIH doing?

- The 21st Century Cures Act:
  - Workshop held June 2017: inclusion of children and older populations in clinical research.
  - Inclusion Across the Lifespan policy announced Dec 2017 will apply to all grant applications submitted on/after Jan 25, 2019.
- NICHD continues to work with “All of Us” leadership to include people with intellectual and physical disabilities in the initiative.
- The trans-NIH Down syndrome Working Group
  - Met in October to discuss inclusion at a broader scale
  - Working on inclusion of more people with IDD in clinical research.
- Need to engage stakeholders, including families and those with IDD

Nothing about us

without us.

Acknowledgments

- IDD Branch

Sujata Bardhan, PhD

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Danuta Krotoski, PhD

- NICHD Colleagues:
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  - Lisa Freund, PhD
  - Alison Cernich, PhD
  - Cathy Spong, MD
  - Diana Bianchi, MD
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  - Stephanie Sherman, PhD
  - David Egan and Kathleen Egan, PhD
- Many, many Patient Advocacy Groups and Family Organizations