



Genetics of INSPPiRE

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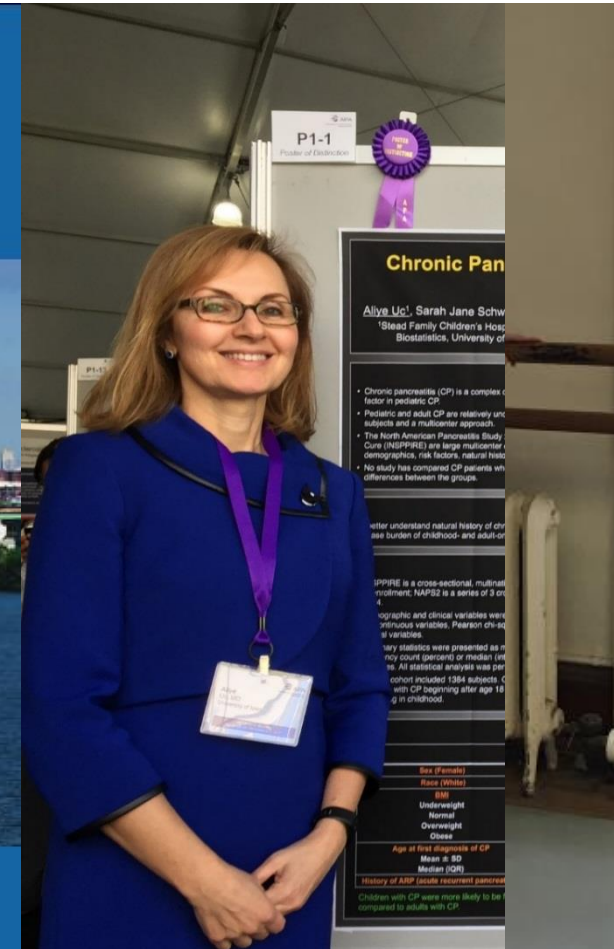
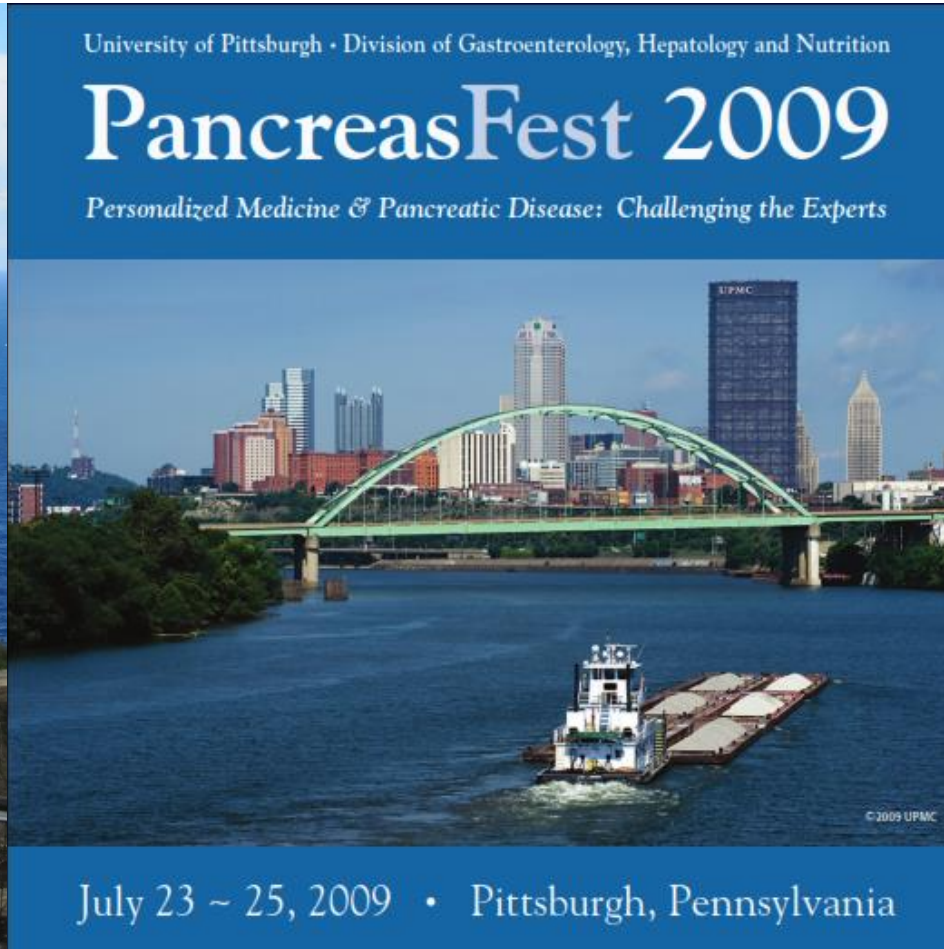
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Author Disclosures

I have nothing to disclose that would
create a conflict of interest.

The Start



INSPPIRE Goals



- To collect longitudinal data from carefully phenotyped children with ARP and CP.
- To create a network of pediatric centers to perform prospective clinical studies.
- To define risk factors that predispose children to ARP and complications: CP, exocrine pancreatic insufficiency (EPI), and early-onset diabetes.
 - Focus on genetic risk factors
- To develop diagnostic or therapeutic guidelines for pediatric ARP and CP.

INSPPIRE Centers to study ARP and CP



- USA

- U of Iowa (main site)
- U of Pittsburgh
- UT Southwestern Dallas
- Baylor Texas Children's
- Nationwide Children's
- Medical College of Wisconsin
- U of Minnesota
- UCSF
- University of Utah
- Seattle Children's
- Cincinnati Children's
- Children's Los Angeles
- MGH Children's
- CHOP
- University of Indiana
- Stanford
- Cedars-Sinai LA
- Washington U of St. Louis

- Canada

- Toronto Hospital for Sick Children
- Montreal Children's

- Israel

- Hadassah Medical Organization, Jerusalem

- Australia

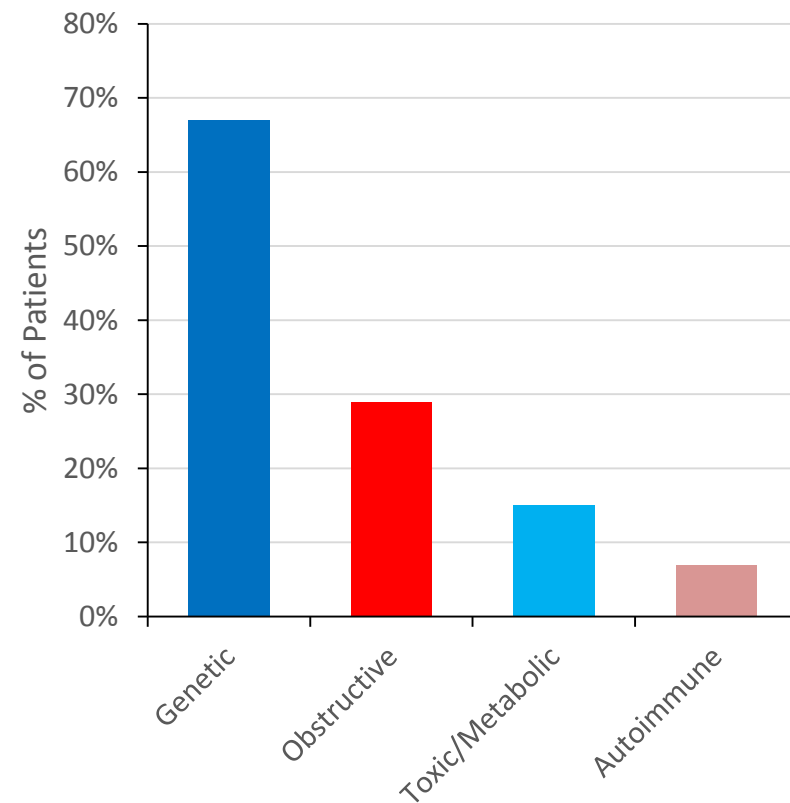
- UNSW, Sydney

Total 22 sites

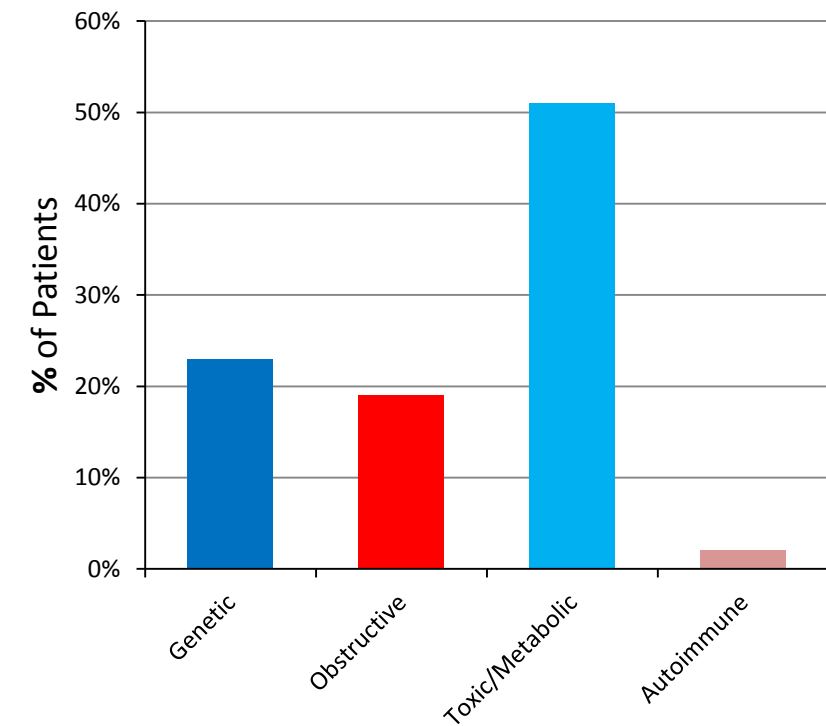
- Funded by NIH/NIDDK R21
- Assembled a cohort of 565 well phenotyped children with ARP and CP
- Built DNA repository with 300 DNA samples

CP Etiology: Kids versus Adults

Kids

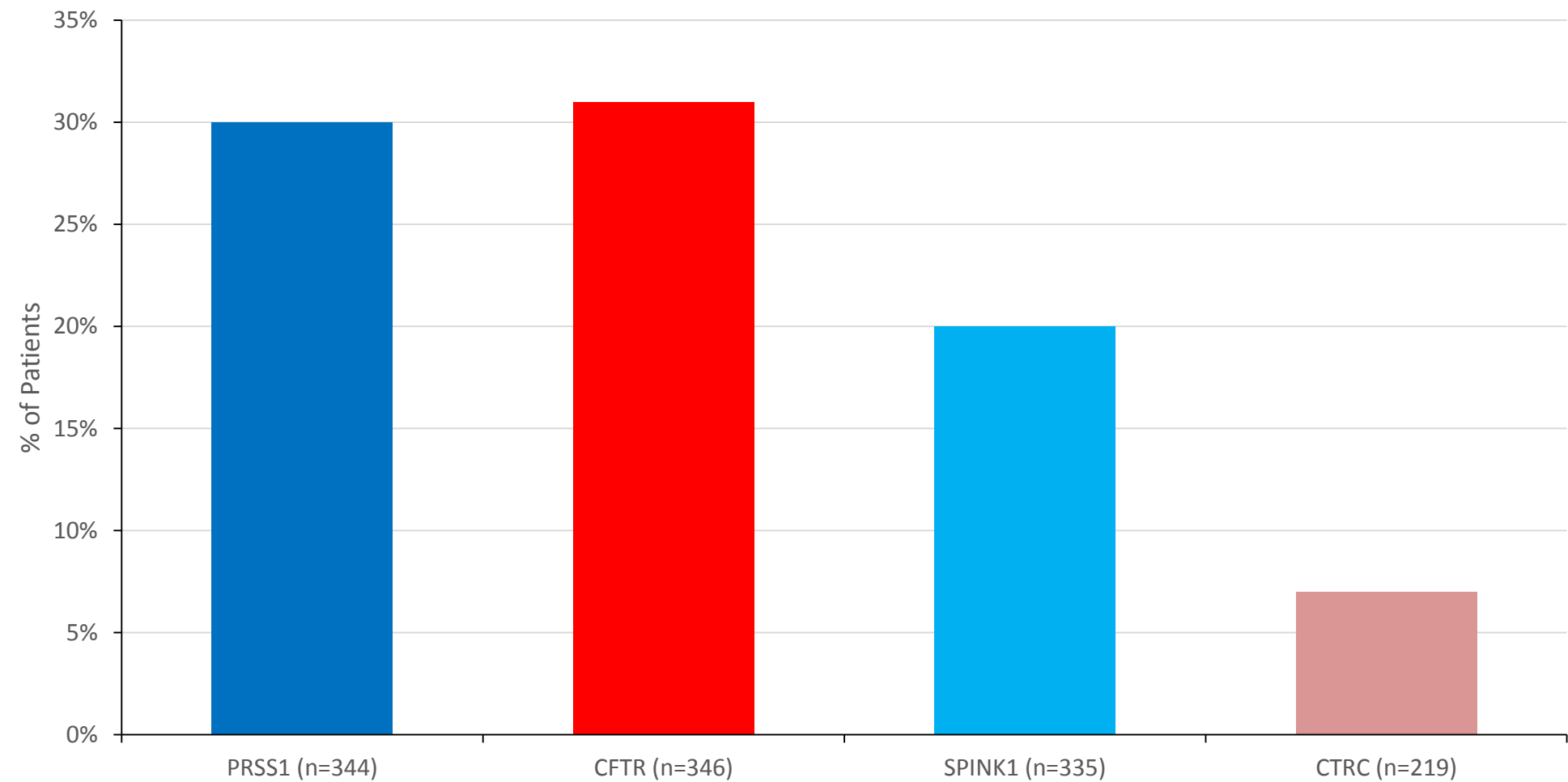


Adults (NAPS2)



Genetic Associations ARP and CP (n=# tested)

Clinical Samples

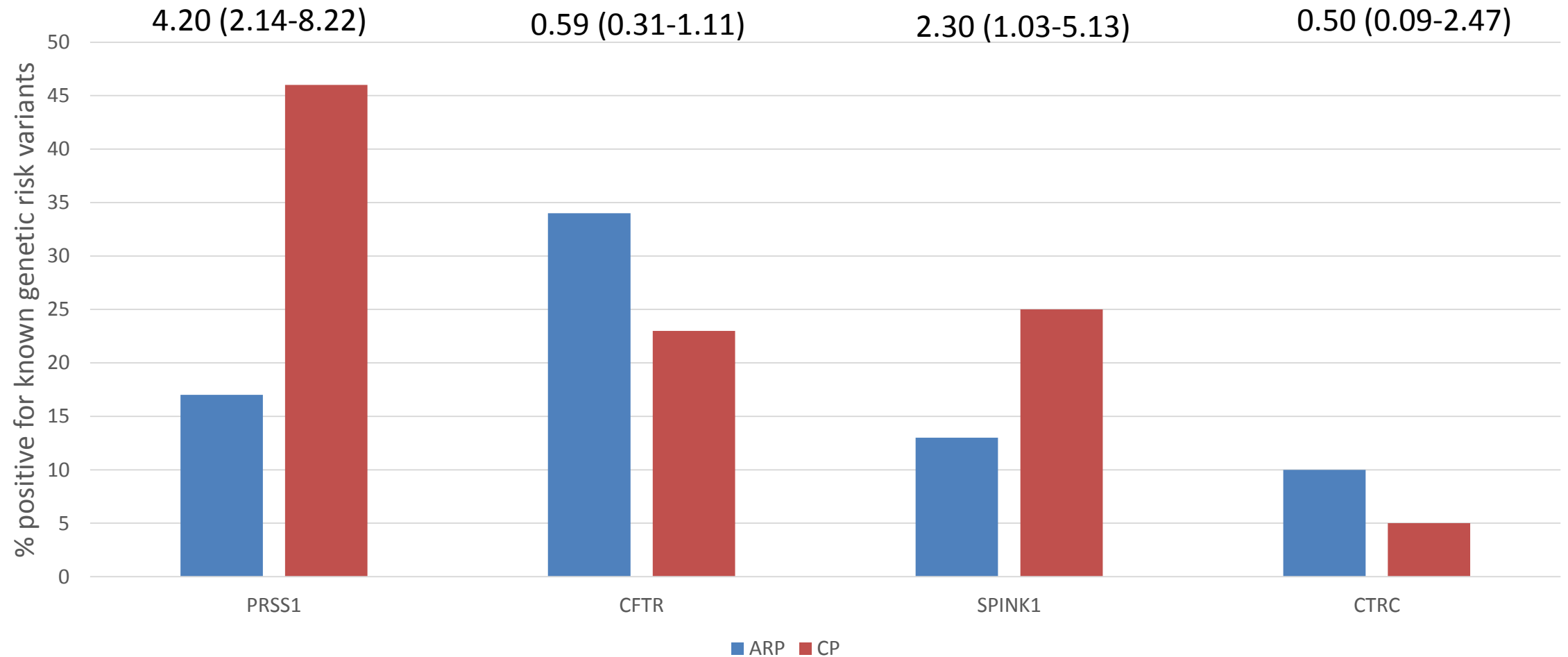


Multiple Genetic Risk Variants

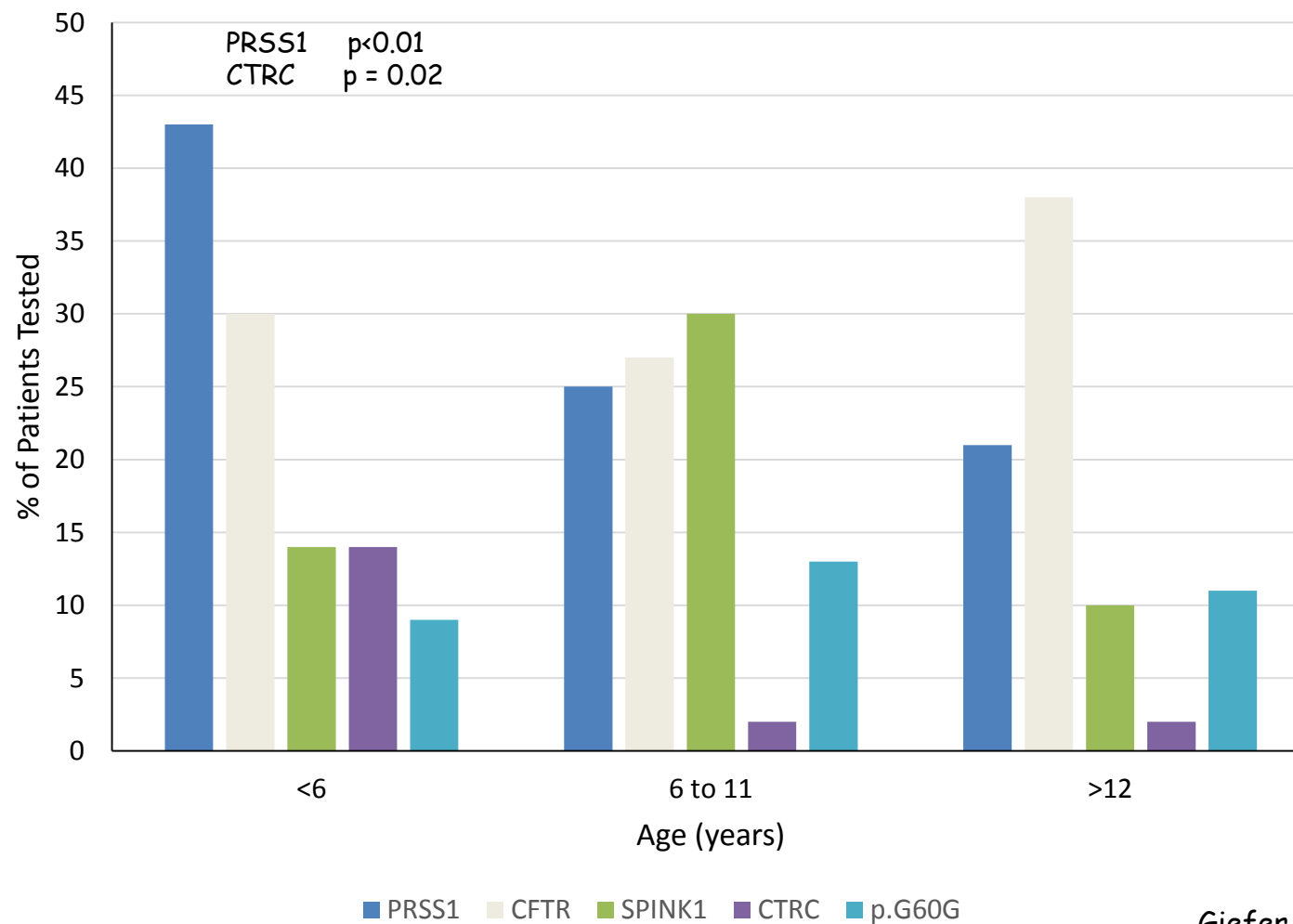
- Of patients who had 3 or more genes tested
 - 10% with ARP had 2 or more risk variants
 - 15% with CP had 2 or more risk variants
- A combination of CFTR with SPINK1 most common
 - 6% with ARP
 - 8% with CP

Genetic Variants ARP & CP

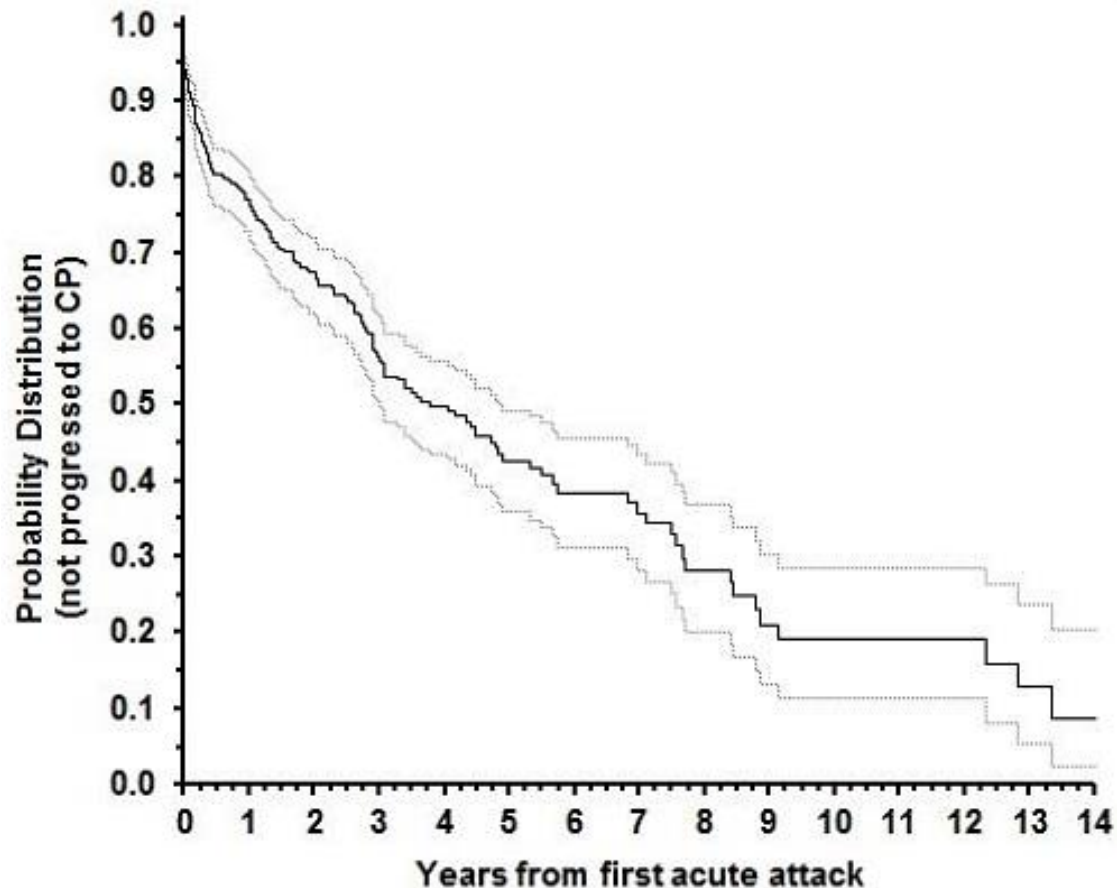
OR (95% CI) of CP



Gene Interactions with Age



Time from first AP episode to CP (n=442)

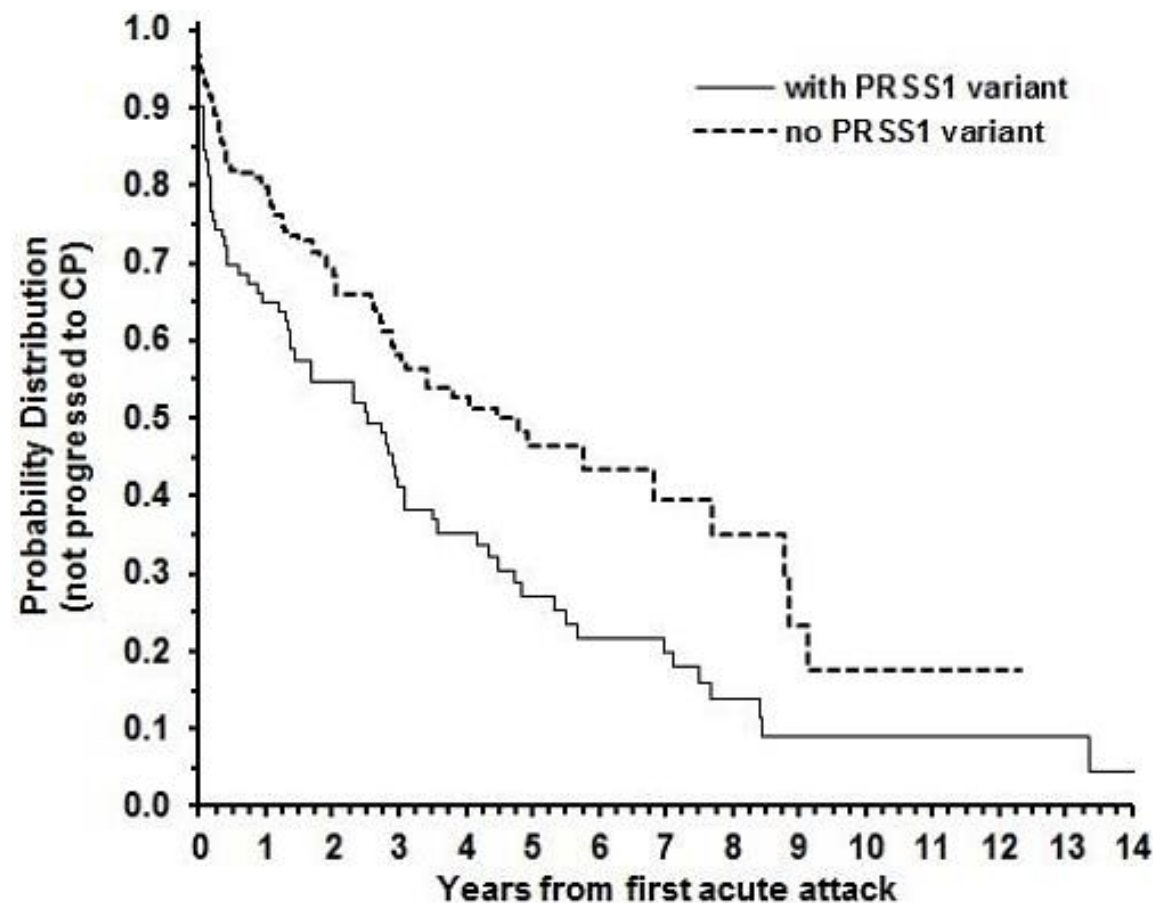


96% of children with CP have prior episodes of acute pancreatitis

Median time to progression from ARP to CP

3.79 years
(IQR: 1.11 – 8.46)

Patients with PRSS1 Genetic Variants



Median time to progression
from ARP to CP

4.48 years
(IQR: 1.25 – 8.87)

**PRSS1
variant
NEGATIVE**

2.52 years
(IQR: 0.25 – 5.50)

**PRSS1 risk
variant POSITIVE**

p-value: 0.001

Pancreas Divisum & Genes

ARP and CP

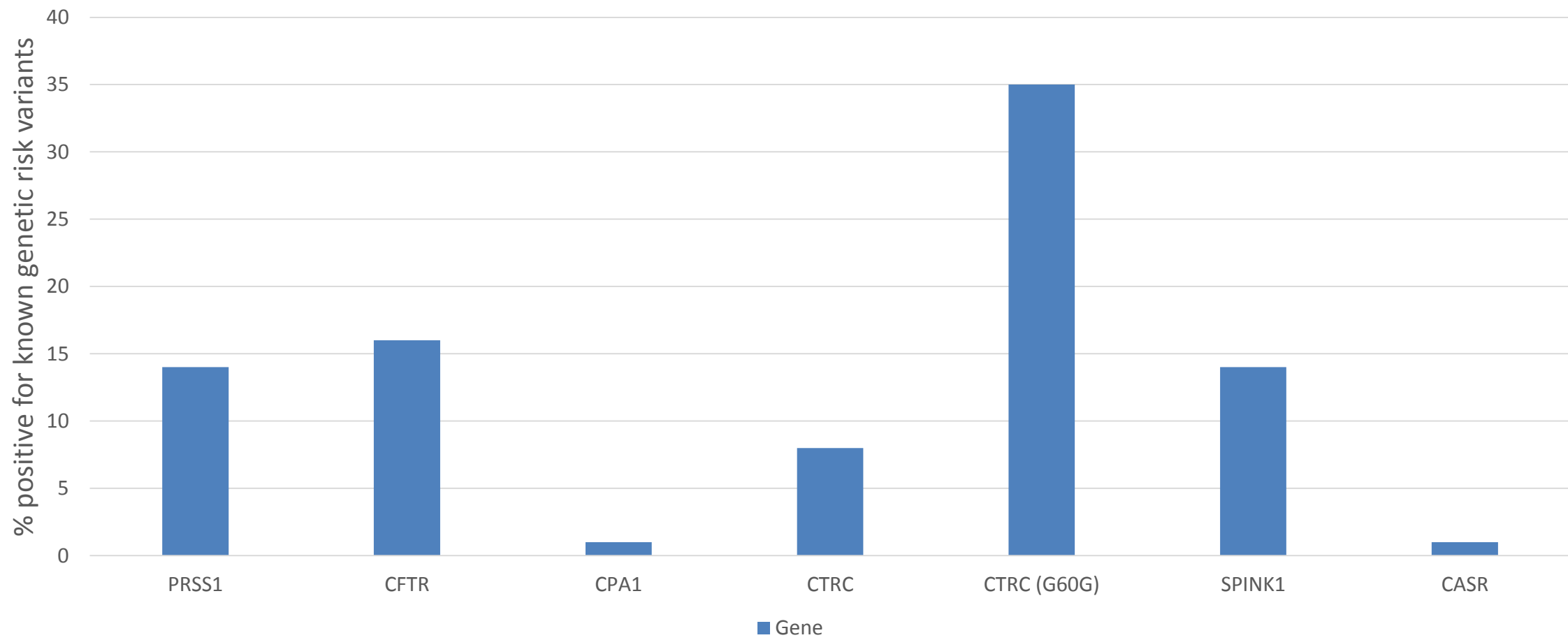
Gene	PD = Yes (N=52)	PD = No (N = 307)	P
PRSS1	4/42 (10%)	79/235 (31%)	< 0.01
SPINK1	12/40 (30%)	44/217 (20%)	0.17
CFTR	15/41 (37%)	66/223 (28%)	0.28
CTRC	3/27 (11%)	9/148 (6%)	0.40

Likelihood of CP

	Genetic Variant	No Genetic Variant	P value
PD	17/22 (77%)	7/21 (33%)	<0.01
No PD	110/161 (68%)	36/99 (36%)	<0.0001
P value	0.541	0.919	

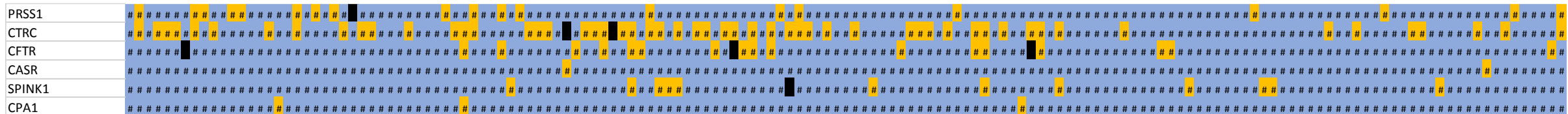
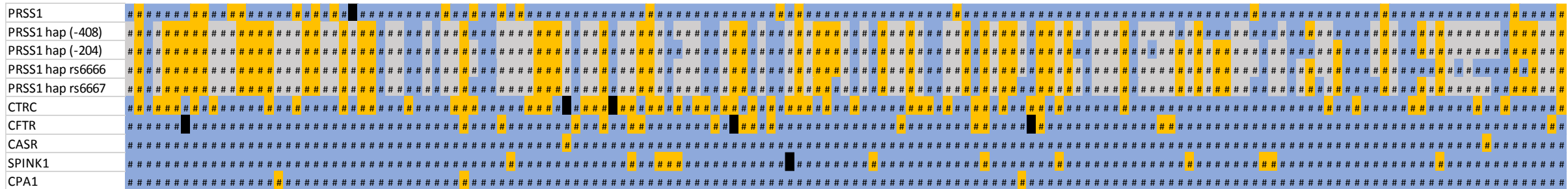
Genetic Variants (155 subjects)

Research Samples



Heatmap of Genetic Variants

Research Samples



Blue = No variants

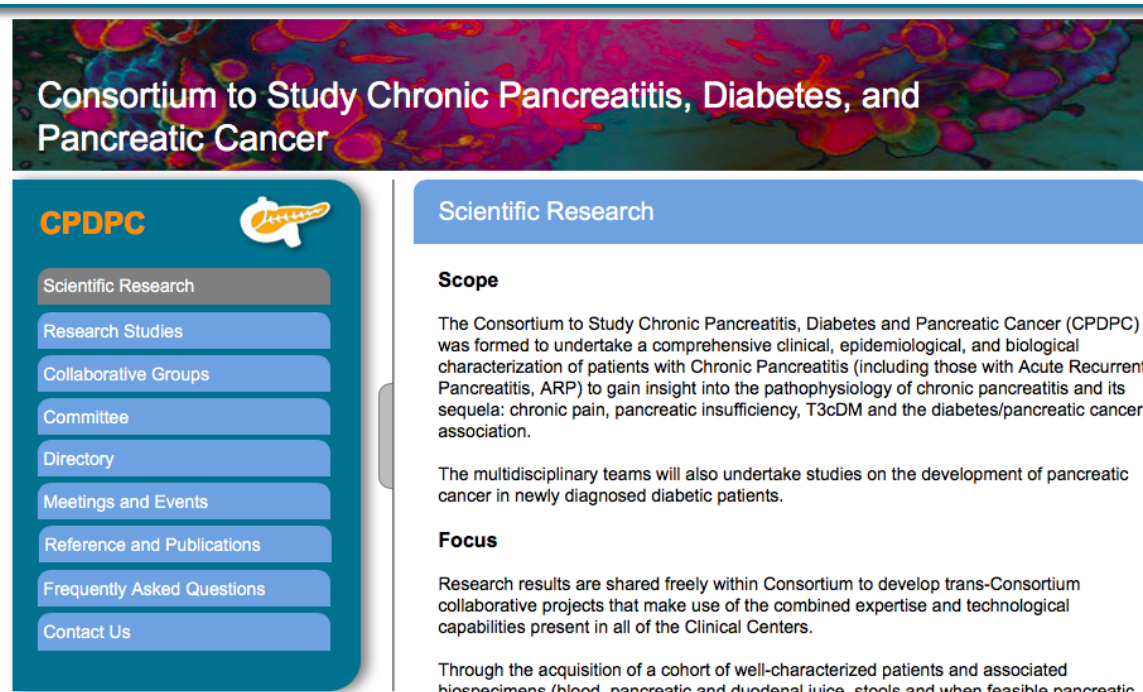
Gold = Known risk variant or high risk haplotype

Black = Two or more known risk variants

Grey = Heterozygous for high risk haplotype

- 24 (15%) have 2 or more risk variants
- 11 (7%) have no known risk alleles or haplotypes

INSPPIRE 2 (2015-20)

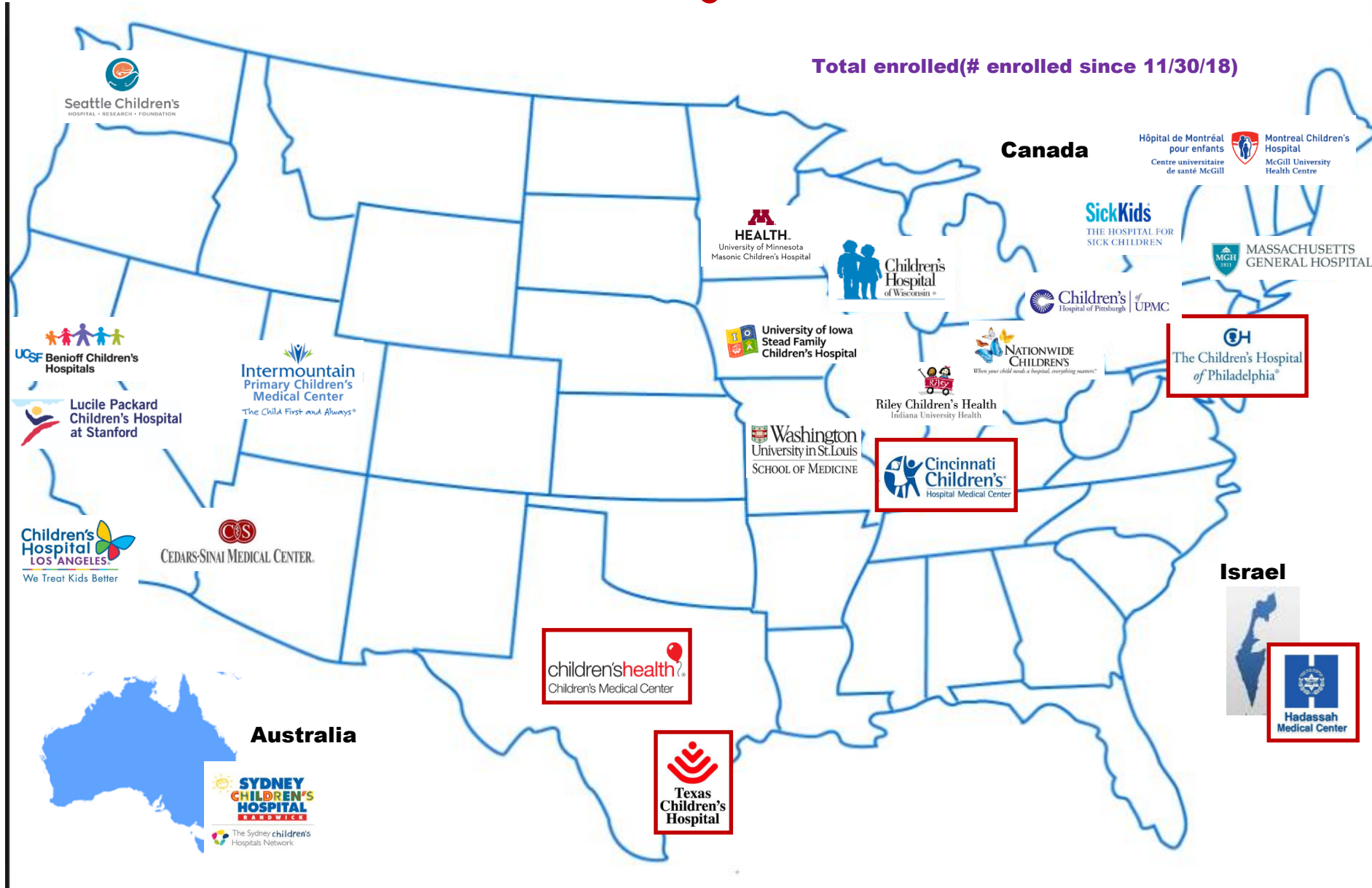


Cpdpc.mdanderson.org

Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) - INSPPIRE 2

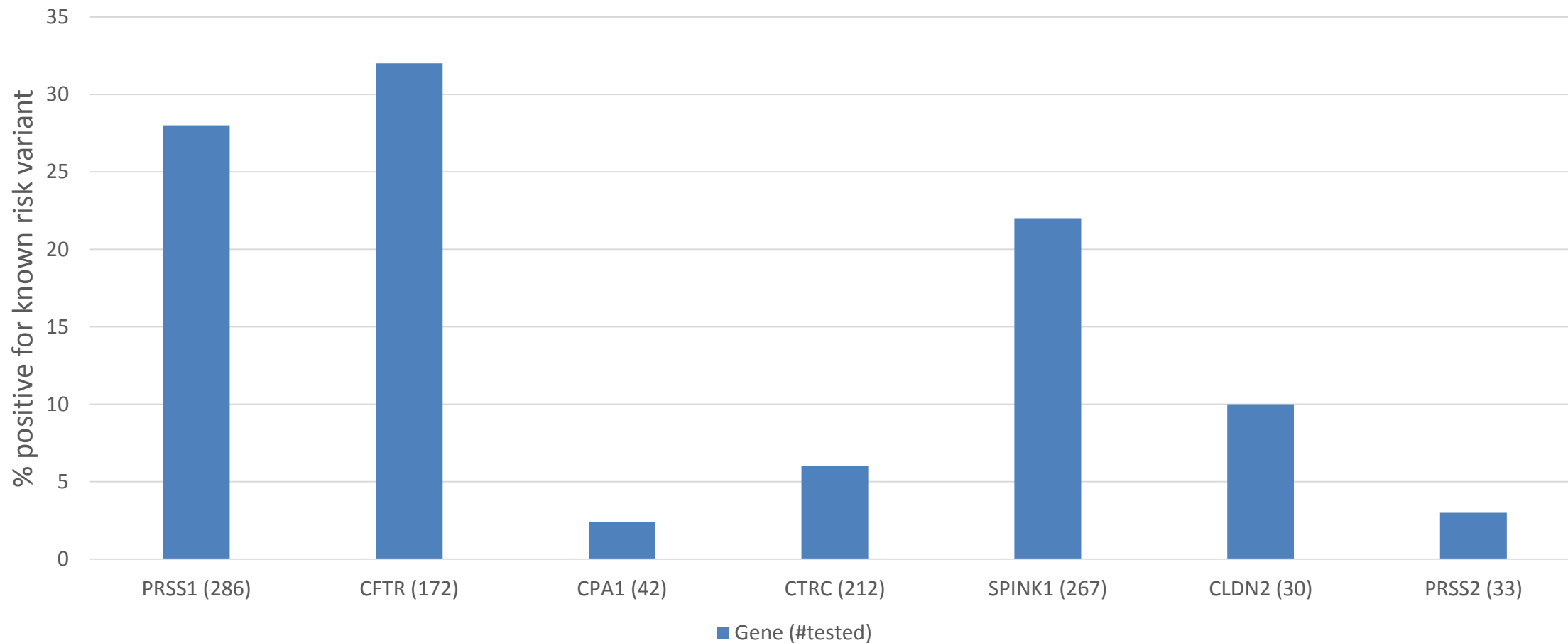
- MD Anderson is the coordinating and data management center
- 9 adult centers
- 1 Pediatric center (**Iowa-the lead site**) with 21 pediatric INSPPIRE satellites (4 international)

INSPPIRE-2: 411 Subjects as of 06/09/19



Genetics in INSPPIRE 2 (389 subjects)

Clinical Samples



Conclusions and the Future

- Children with ARP and CP are likely to have one or more genetic risk variants
- Patients with PRSS1 risk variants present at a younger age and progress to CP faster than patients with other variants
- Need to obtain more samples for DNA analysis
- Need to genotype more alleles in all samples
- Begin analysis of genotypes for co-occurrence and impact on clinical course



Thanks to INSPPIRE Members

- **Aliye Uc (PI)**
- Mark Lowe
- Sohail Husain
- Brad Barth
- David Troendle
- Tanja Gonska
- Doug Fishman
- Ryan Himes
- Steve Werlin
- Cheryl Gariepy
- Steve Freedman
- Veronique Morinville
- Quin Liu
- Sarah Jane Schwarzenberg
- Melena Bellin
- Mel Heyman
- John Pohl
- Michael Wilschanski
- Keith Ooi
- Matthew Giefer
- Maisam Abu-El-Haija
- Joseph Palermo
- Tom Lin
- Zachary Sellers
- Lynette Whitfield Van Buren
- Asim Maqbool
- Maria Mascharenas
- David Piccoli
- Uzma Shah
- Brian McFerron
- Jaimie Nathan
- Emily Perito
- Sue Rhee
- Yuhua Zheng



INSPPIRE study coordinators
Gretchen Cress (Iowa)
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