Update on “PROGRESS”

(PSC Resource of Genetic Risk, Environment and Synergy Studies)

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Rationale for "PROGRESS"

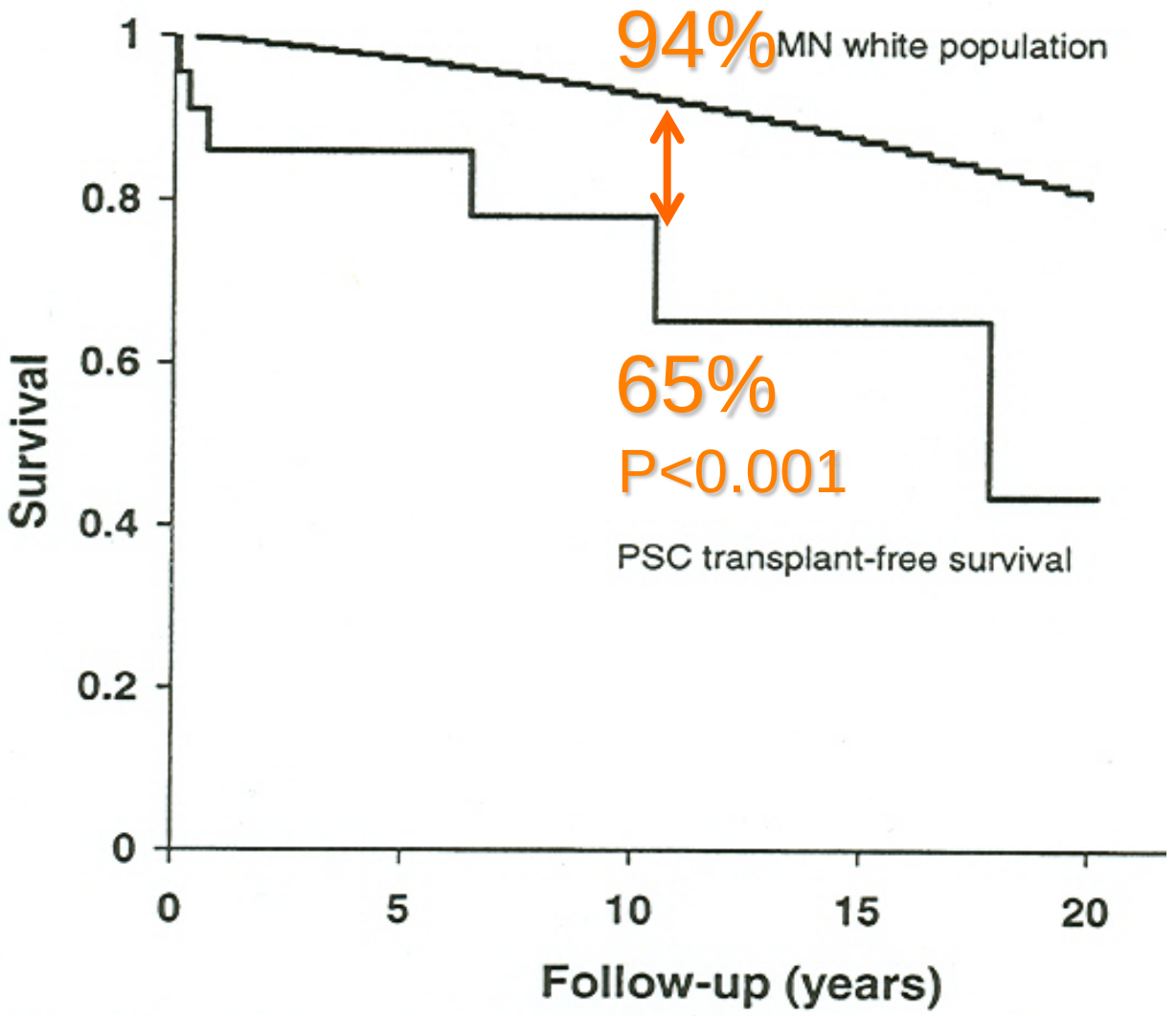
PSC:

- Unknown etiology
- No medical therapy is available
- Leads to shortened survival

PROGRESS aims to:

- Improve knowledge of causes of PSC
- Better diagnose, predict and treat PSC and its complications to expand survival

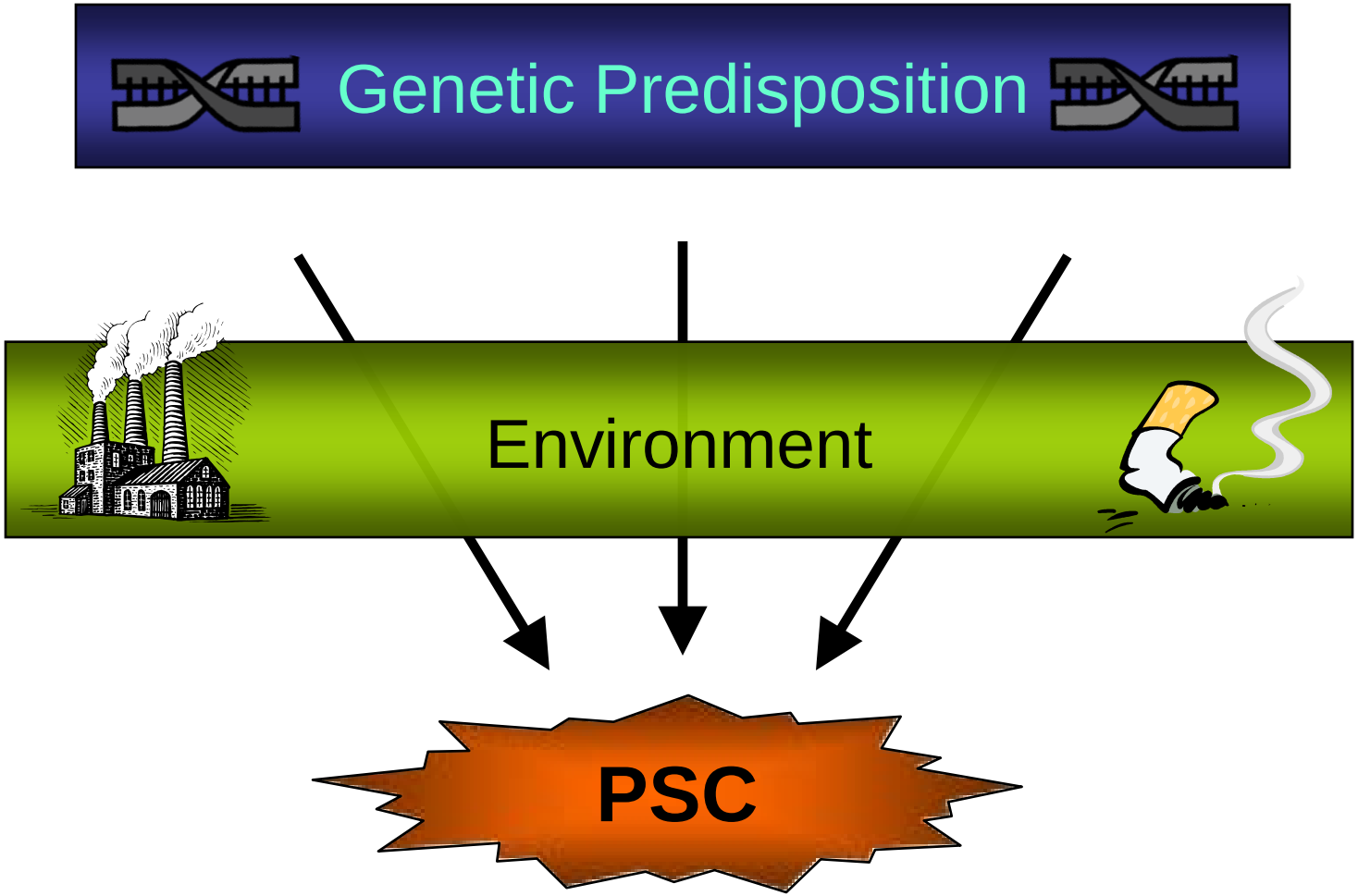
Survival of PSC Patients is Shortened



Bambha K et al., Gastroenterology 2003

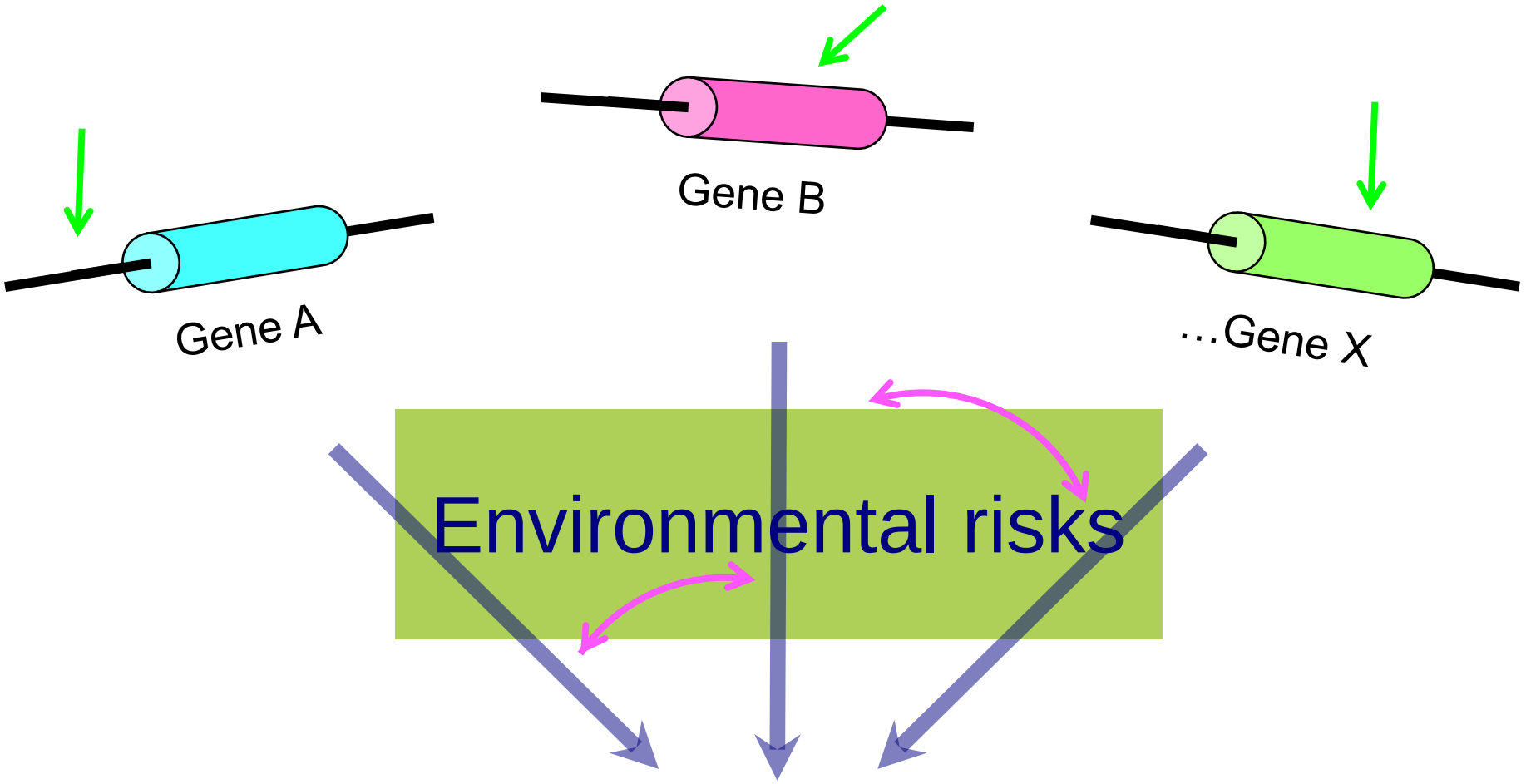
What are the causes of PSC?

Pathogenesis of PSC



How can we find the causes of PSC?

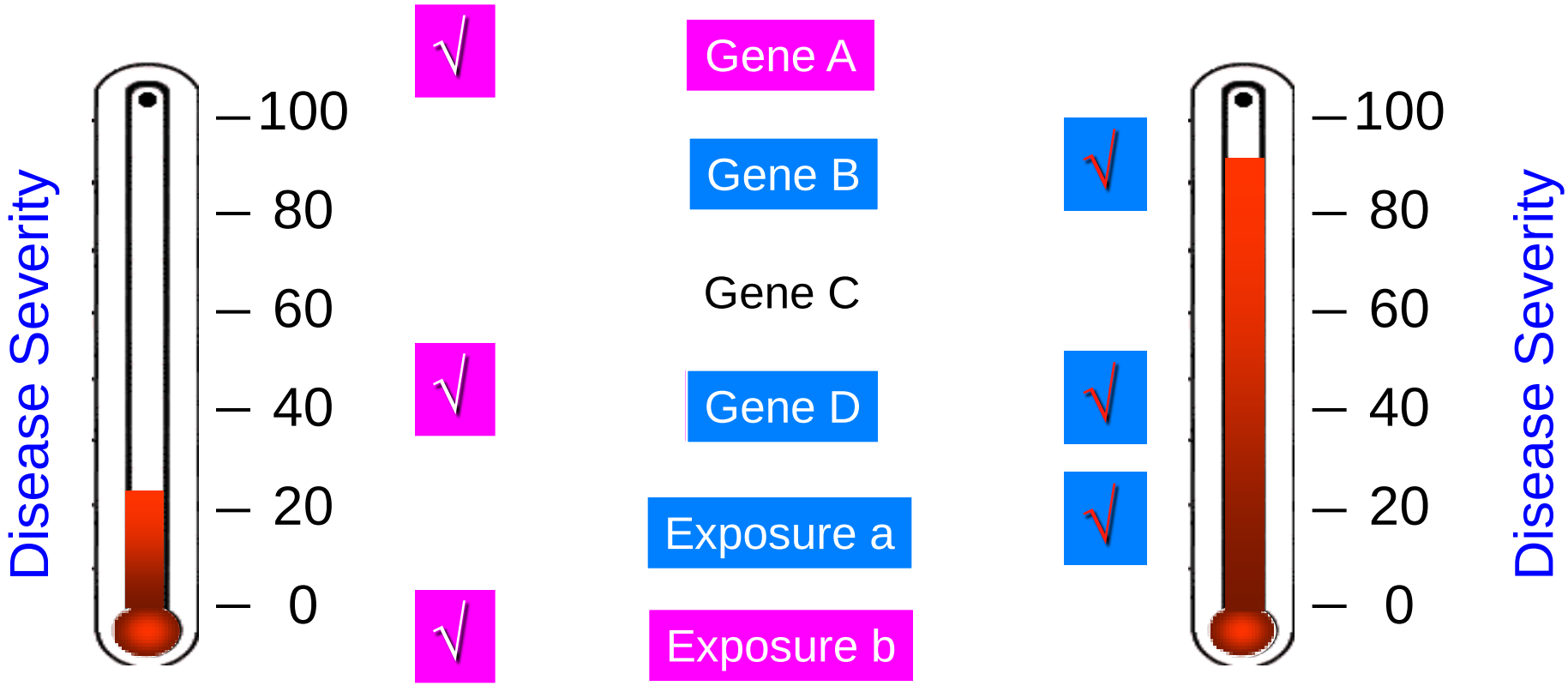
PSC is a Complex Disease



PSC is a Heterogeneous Disease

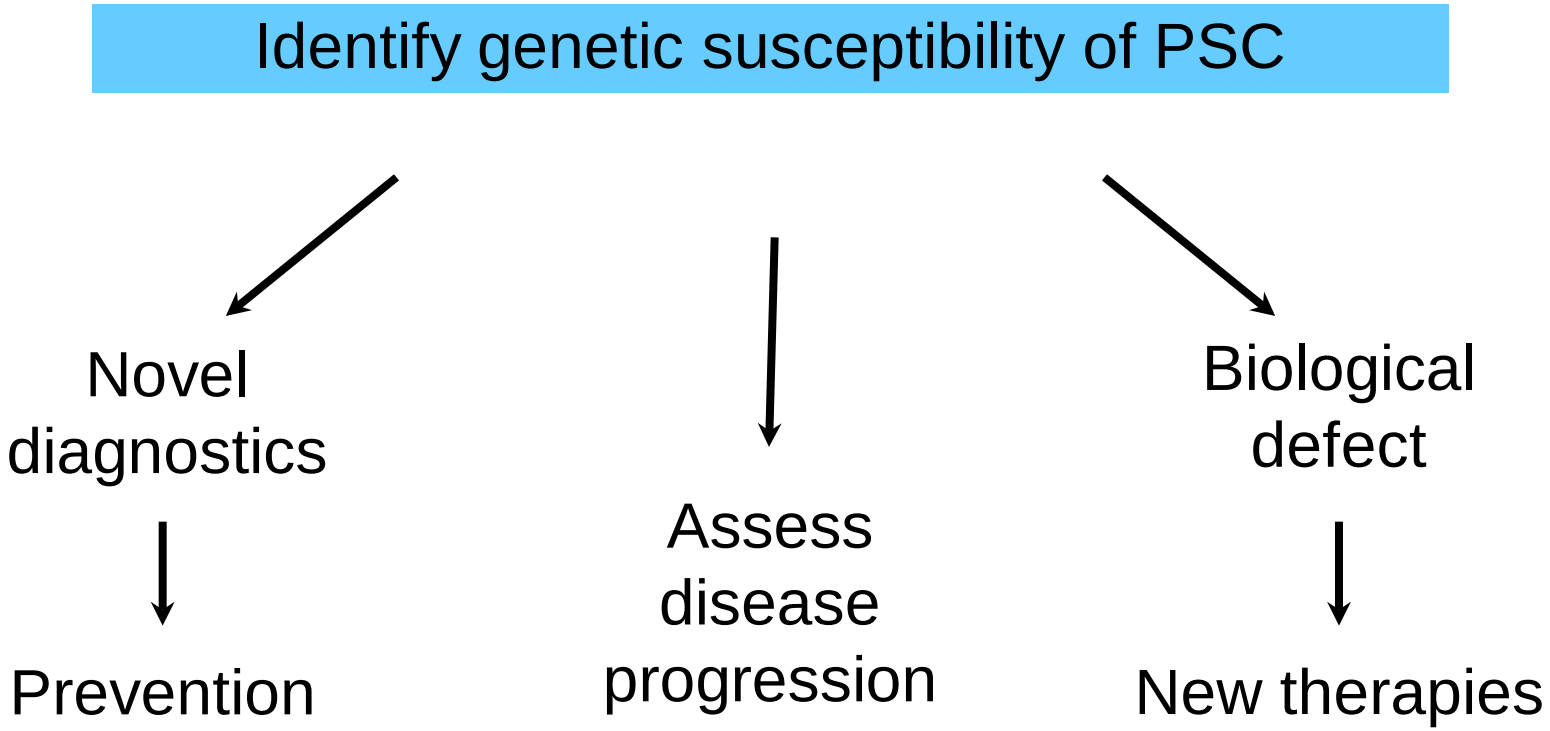
Individual A
"slow progression"

Individual B
"fast progression"

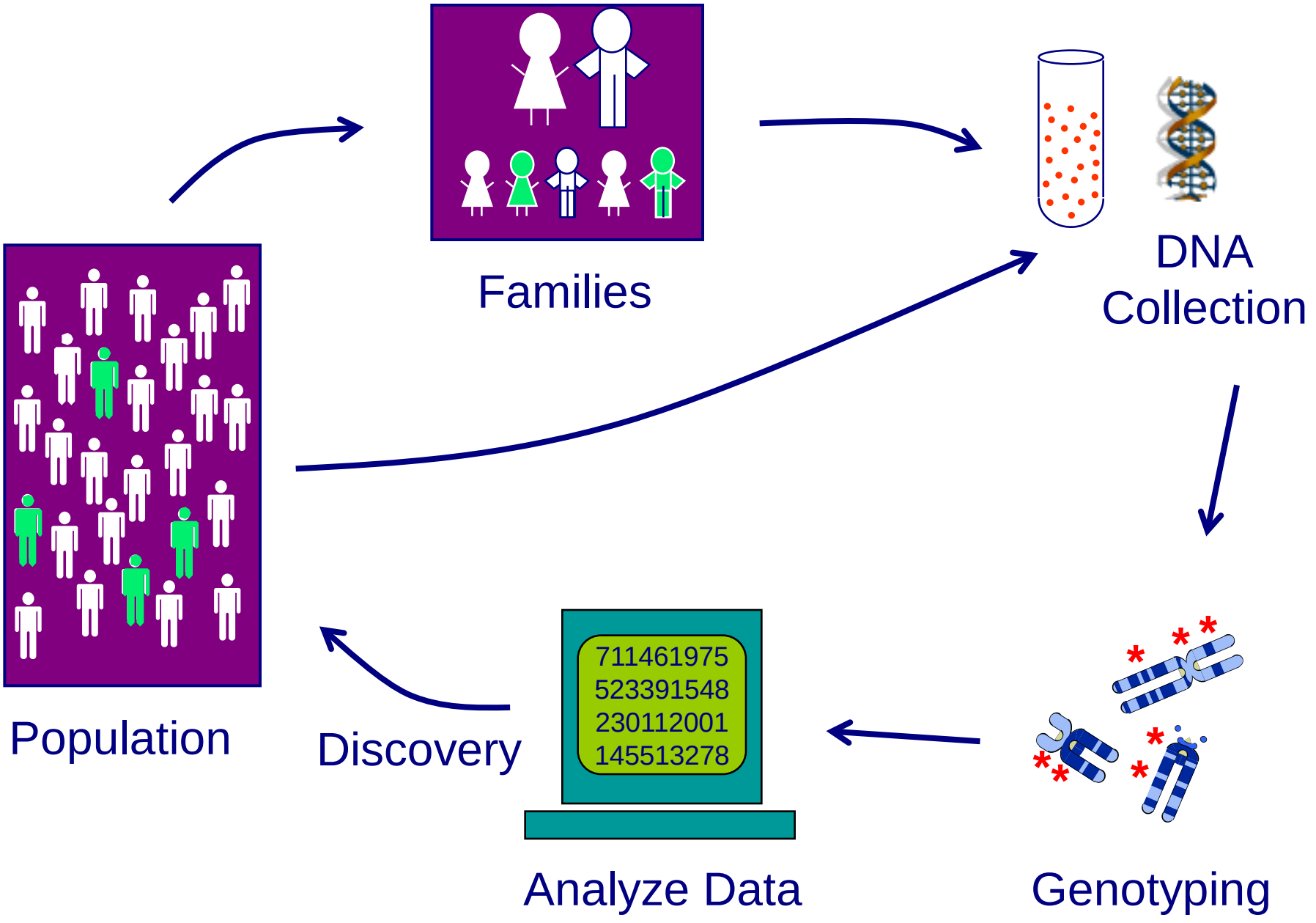


Rationale for Studying Genetic Predisposition to PSC

- Strong genetic component



How to Identify the Genes Predisposing to PSC



Establishment of "PROGRESS"

In 2005

- Need for a PSC registry and repository
- Retro- and pro-spective PSC registry
  - patients
  - first-degree relatives
- Individually matched controls
  - age (±2.5 years)
  - sex
  - race
  - state of residence

“PROGRESS”

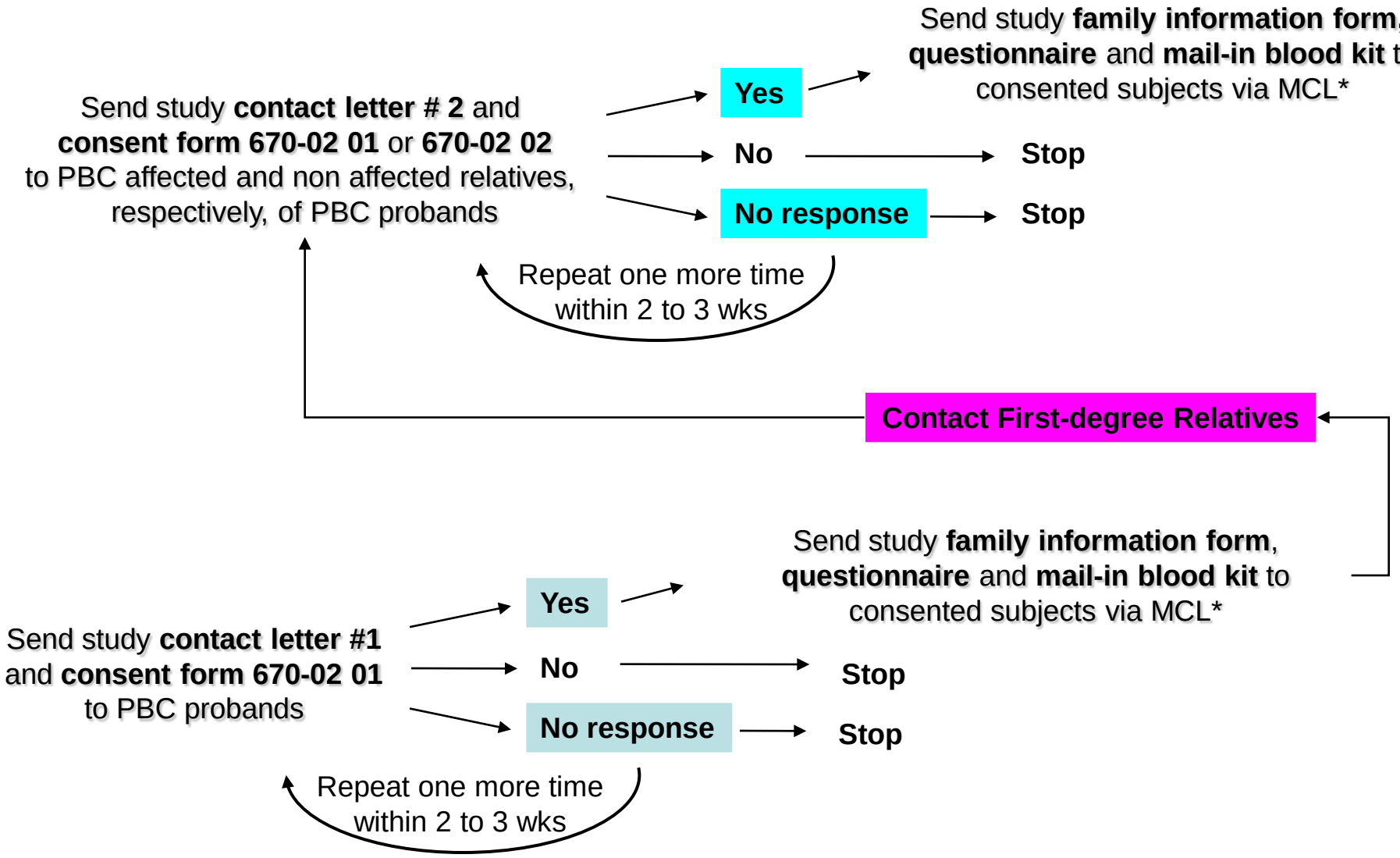
What is Involved with this Study?

- Read and sign a consent form
- Complete a questionnaire and a family information form
- Provide a sample of your blood
- Recipients of liver transplant are not excluded
- This is an one time participation
- No need to visit Mayo Clinic to participate

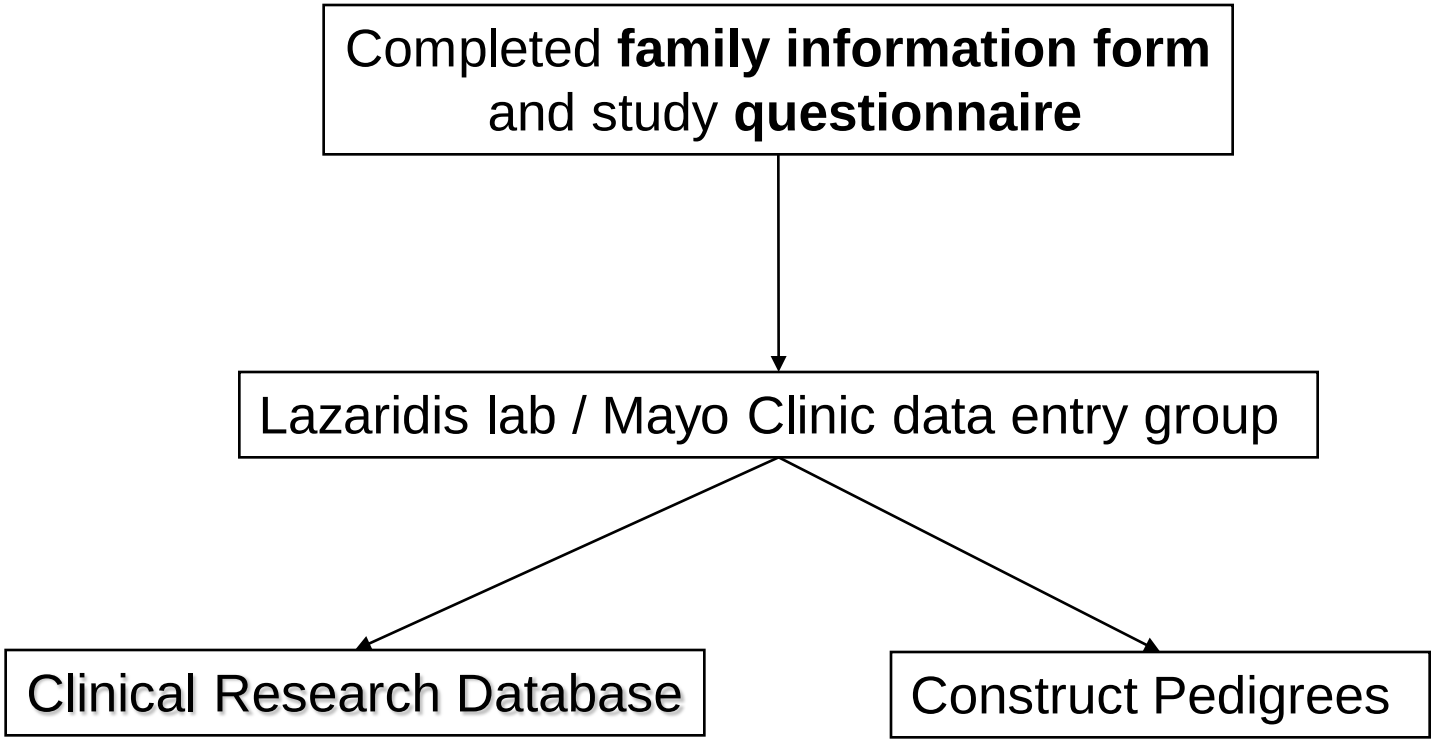
Historic Cohort of PSC Patients at Mayo Clinic

Patient population	N
Pts seen 1967 - 2008	~3,500
New patients per year	~150

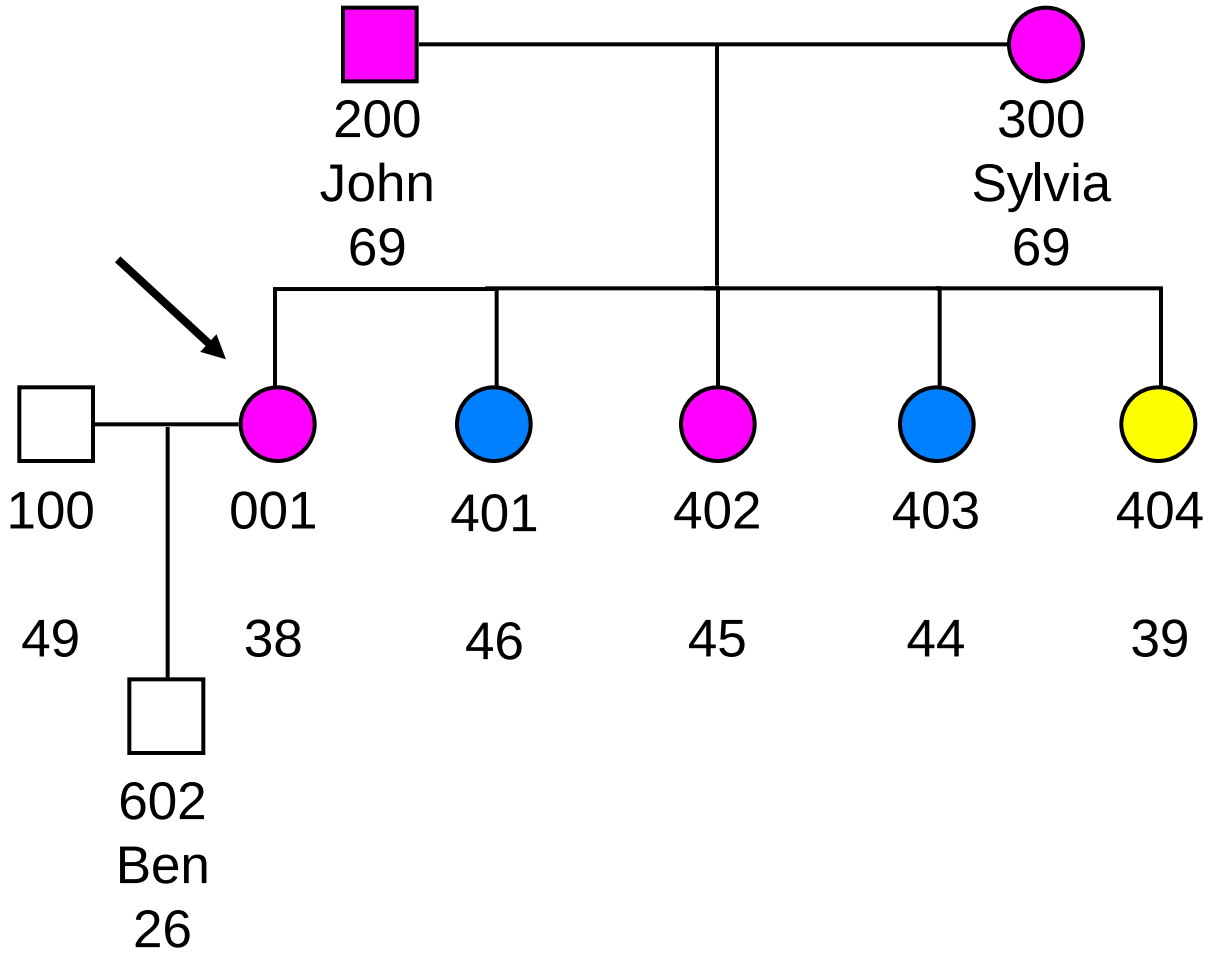
"PROGRESS": Enrollment Strategy



“PROGRESS”: Study Instruments



Pedigree # 5230



Blood kit | Consent sent | Consented/no kit | Refused/Excluded

“PROGRESS”: Mail-in Blood Kit

“PROGRESS”: Study Instruments

Mayo Medical Questionnaire for Adult Chronic Cholestatic Liver Diseases

Instructions for Answering the Questions

- Use a No. 2 pencil only
- Mark your answer to each question with an X ☐
- Erase all changes completely

Please state the person(s) who has completed this questionnaire

- ☐ Patient or study participant
- ☐ Relative of patient or study participant
- ☐ Friend of patient or study participant
- ☐ Other (please specify): _____

Please return this questionnaire in the enclosed, prepaid, self-addressed envelope

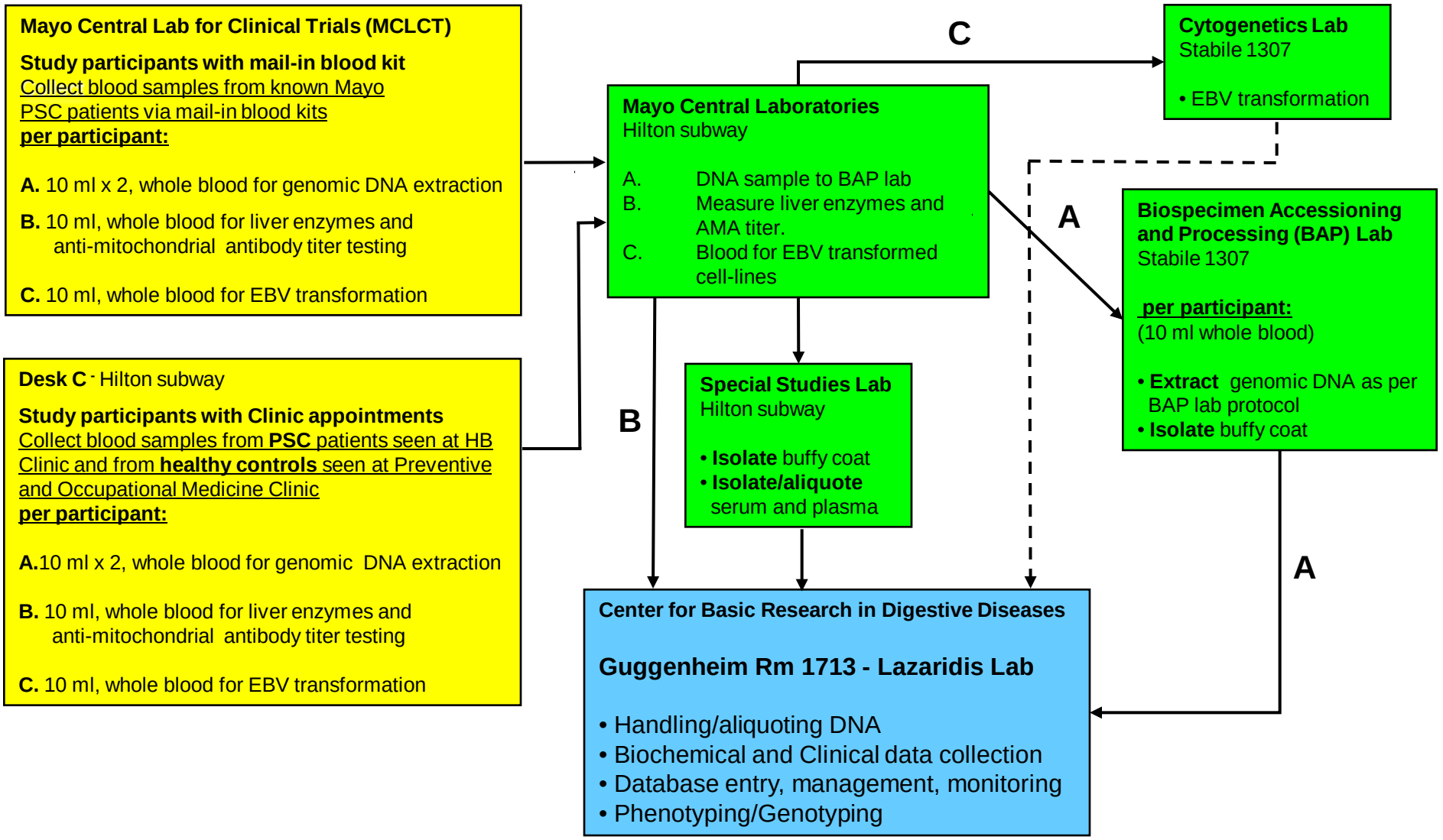
Family Information Form

All information provided will be kept confidential

Instructions for Completing the Family Information Form

- Provide your family information in the appropriate spaces
- Mark your answer to each question with an X ☐

Blood Sample Collection, Processing for Genomic DNA Extraction Development of Cell-lines and Biochemical Testing



“PROGRESS”: Specimen Storage

“PROGRESS” STATUS

Registry and Biospecimens

	Consented	Questionnaire	DNA	Specimens*
Patients	487	325	395	3,191
Controls	216	155	165	1,434
FDRs**	121	106	82	661

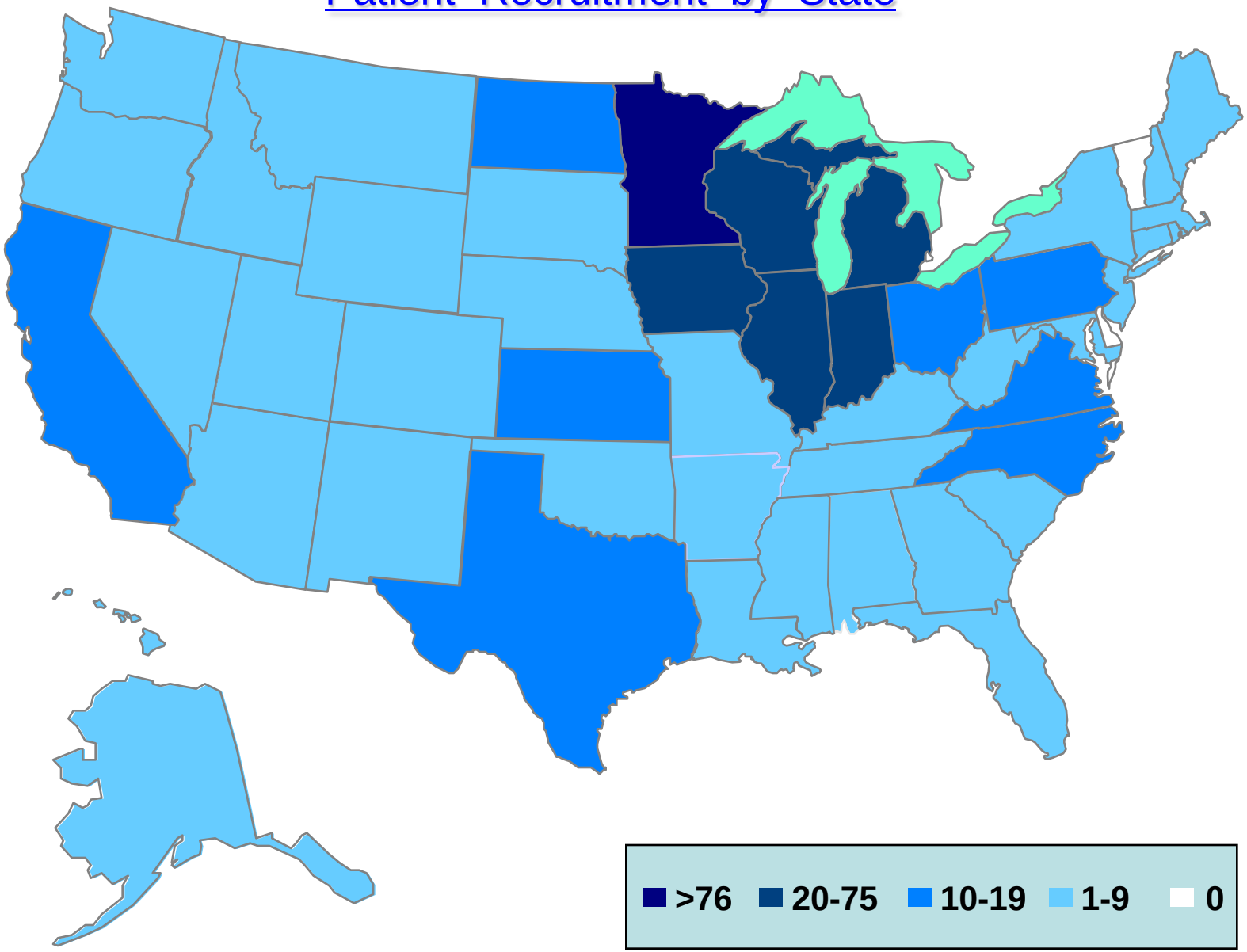
04/29/09

* Primary DNA, Buffy Coat, Serum, Plasma, EBV-transformed Cell lines

** First-degree relatives

“PROGRESS” STATUS

Patient Recruitment by State



“PROGRESS” STATUS

Demographics (n=324)

	(%)
Sex	
Male	63
Race	
White	97

	Years (range)
Age at recruitment	52.7 (5 - 83)
Age at Dx	40.5 (14 - 75)
Duration of PSC	12.2 (0 - 42)

“PROGRESS” STATUS

Clinical Data (n=324)

	(%)
Inflammatory bowel disease (IBD)	79
Type	
Ulcerative colitis	81
Crohn’s disease	9
Indeterminate IBD	10
Colectomy	37
Cholangiocarcinoma	7.7
Liver transplantation	28.1
Sibling relative risk (λs)	30

“PROGRESS” STATUS

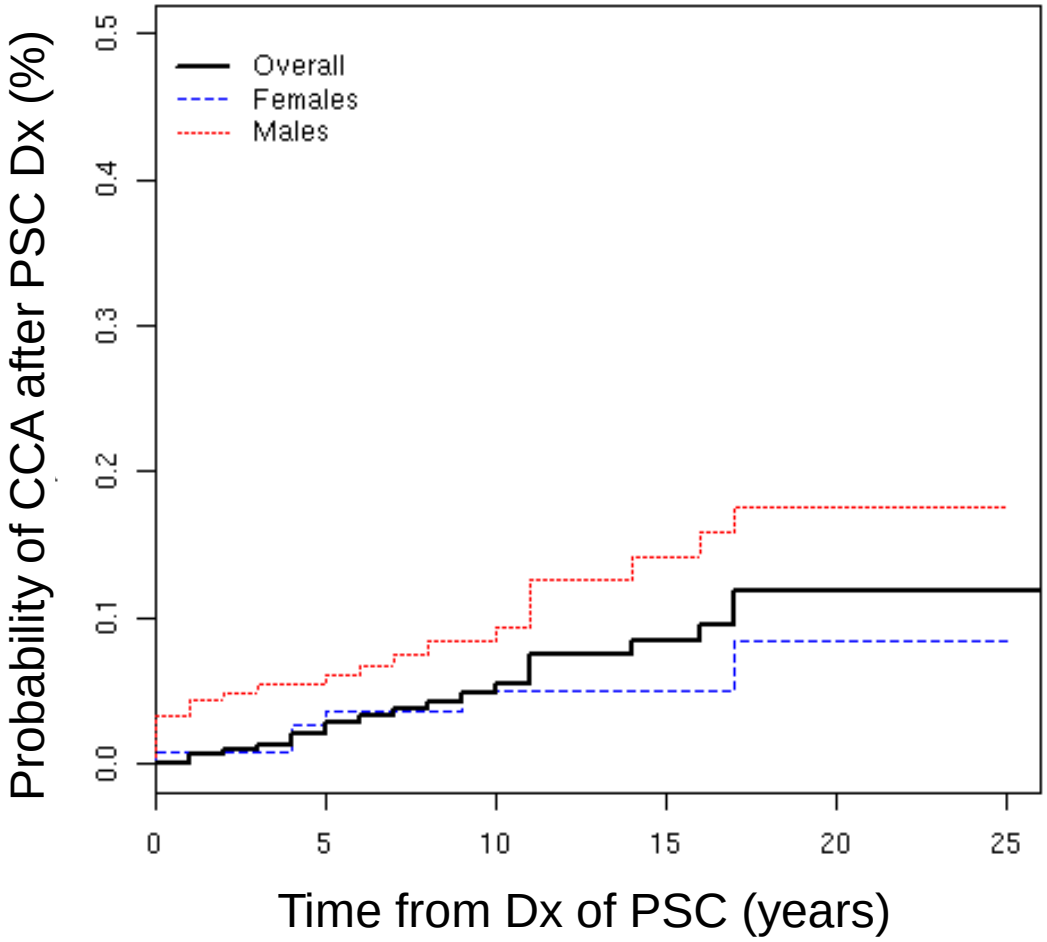
Disease Presentation (n=324)

	(%)	Time lapsed in years (range)
IBD → PSC	67	14 (1 - 42)
IBD / PSC	17	0
PSC → IBD	16	7 (1 - 26)

“PROGRESS” STATUS

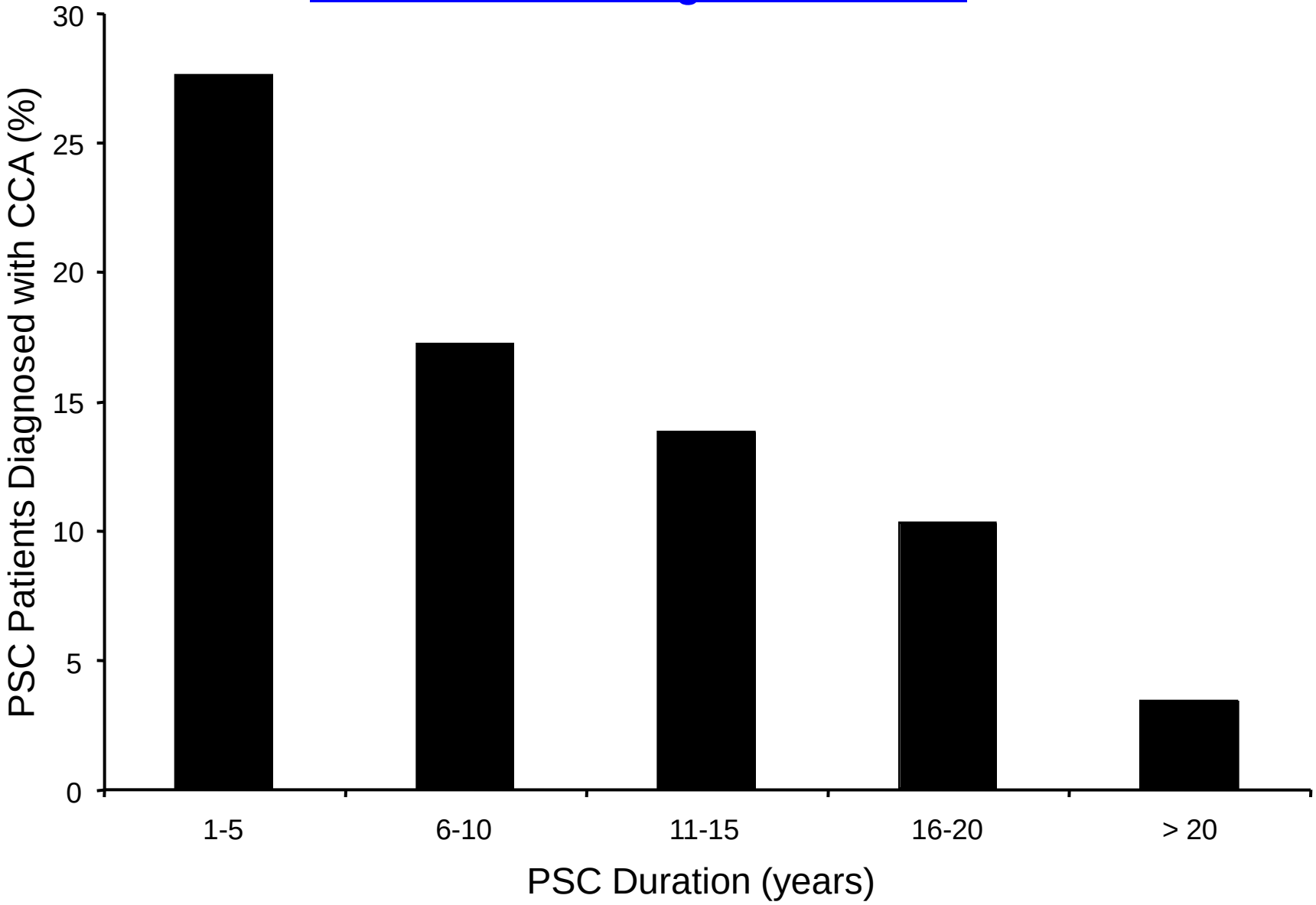
PSC and Cholangiocarcinoma

P value = 0.0397



“PROGRESS” STATUS

PSC and Cholangiocarcinoma



Future Plans for “PROGRESS”

- Continue recruitment of PSC patients
- Begin analyzing environmental data
- Start performing large genetic studies for PSC

Ancillary RO1 with IBD Genetics Consortium

- Genome-wide association of PSC (healthy, IBD controls)

- Evaluate outcome of PSC
  - progression to liver transplantation
  - development of
    cholangiocarcinoma, and
    colon cancer

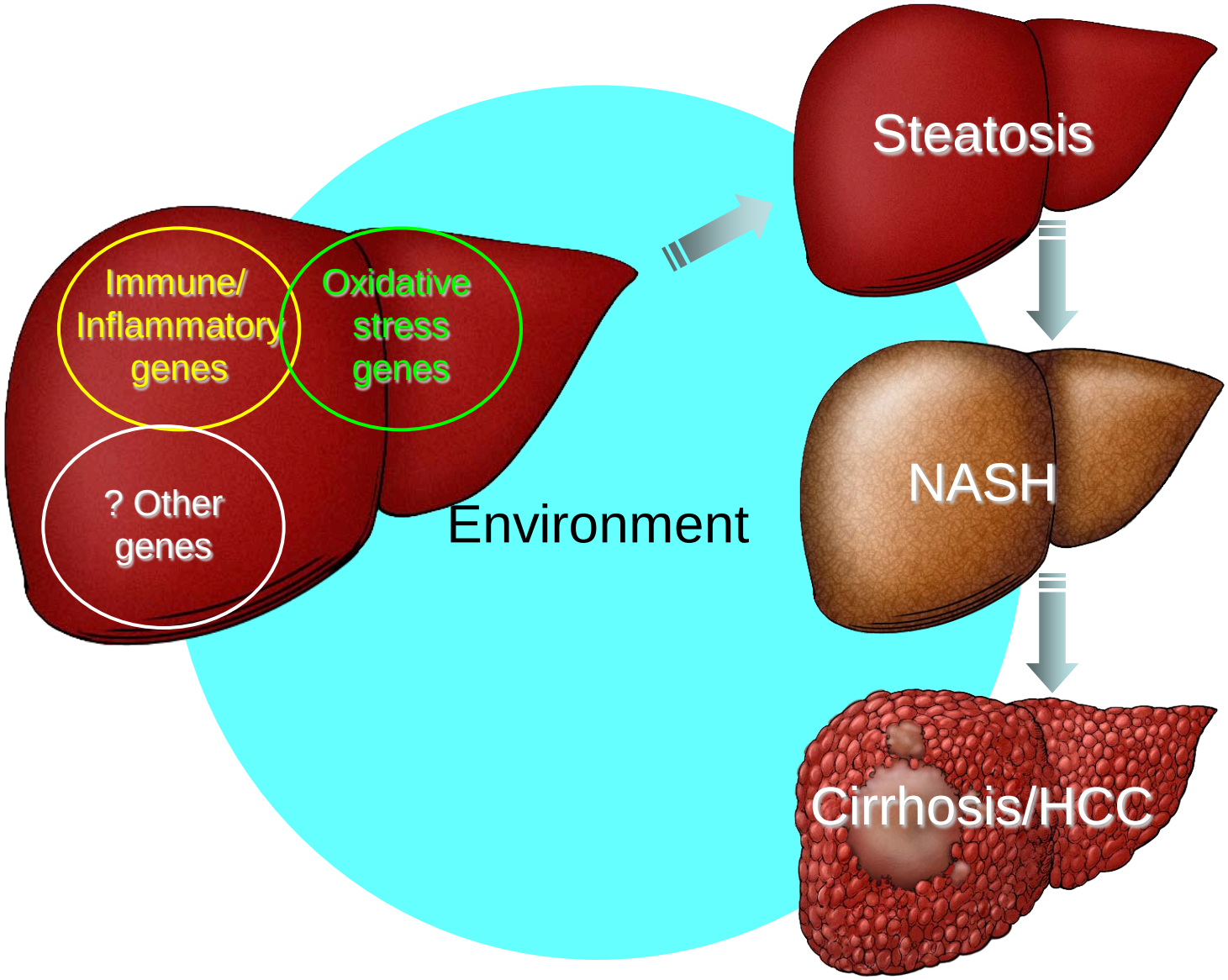
- Assess
  - environmental risks of PSC
  - genetic **x** environment interaction in PSC

Study Support

- Musette and Allen Morgan, Jr. Foundation for the Study of PSC
- A. J. and Sigismunda Palumbo Charitable Trust
- Division of Gastroenterology and Hepatology - Mayo Clinic

Thank you...

NAFLD: A Complex Liver Disease



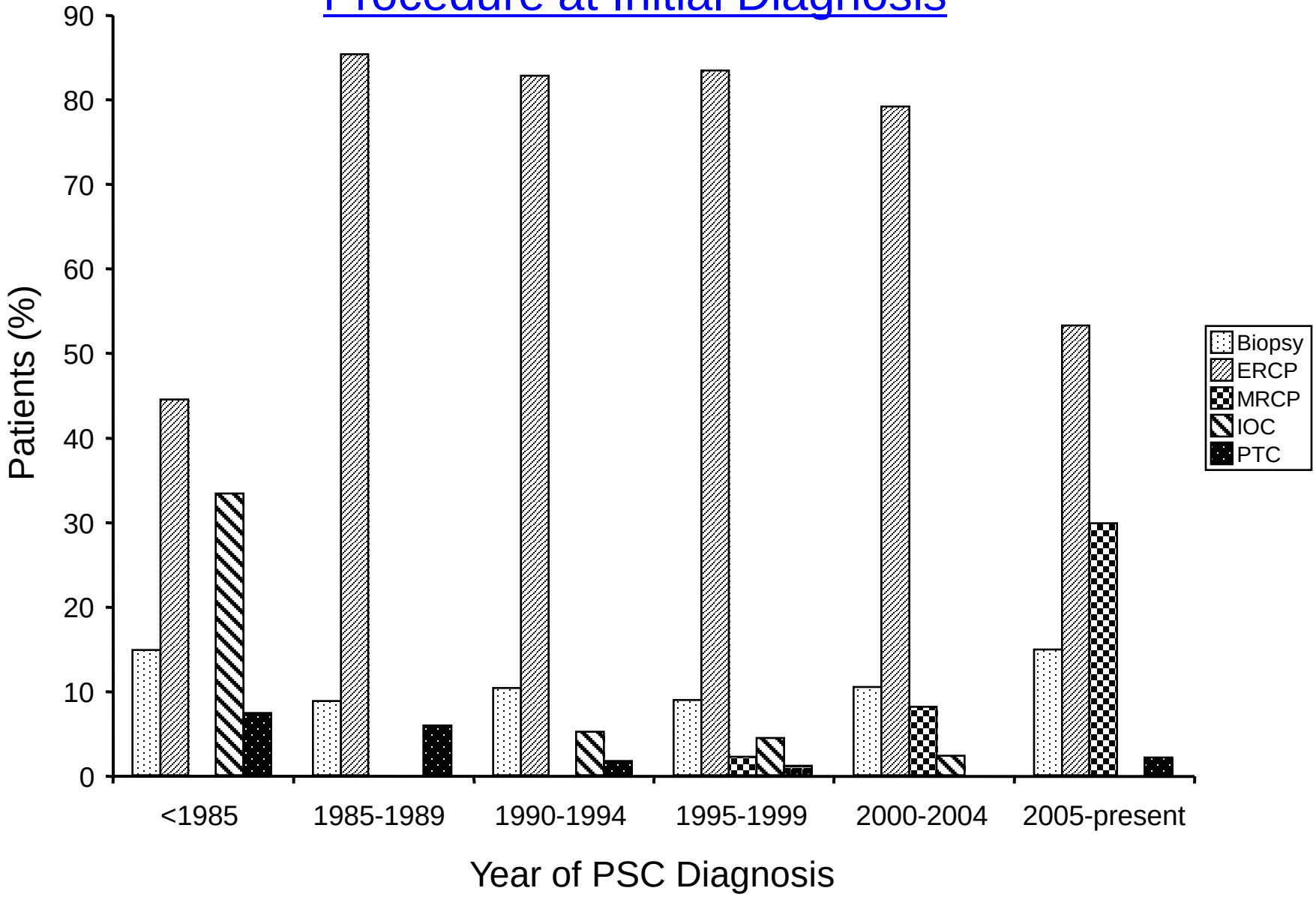
PSC is a Complex Disease

- Individual genetic variants and environmental exposures are neither necessary nor sufficient for disease development...

- Instead are risk factors for disease development...

“PROGRESS” STATUS

Procedure at Initial Diagnosis



Epidemiology of PSC

Prevalence (2000)	1 : ~7,500 *
Cases in USA	~29,000 *
Male	68% *
Mean age of Dx (yrs)	40 (34 - 50) *
IBD	73% (75% UC) *
Sibling relative risk (λs)	~80 #

* Bambha K et al., Gastroenterology 2003

Berquist A et al., J Hepatology 2005

Natural History of PSC

CCA prevalence	~15% *
CA absolute cum. risk (PSC/UC)	10% at 10 yrs # 31% at 20 yrs # 50% at 30 yrs #
Progression to OLT	~20% ‡
Recurrence after OLT	6 - 37% ‡

* Lazaridis K et al., Sem Liv Dis 2006

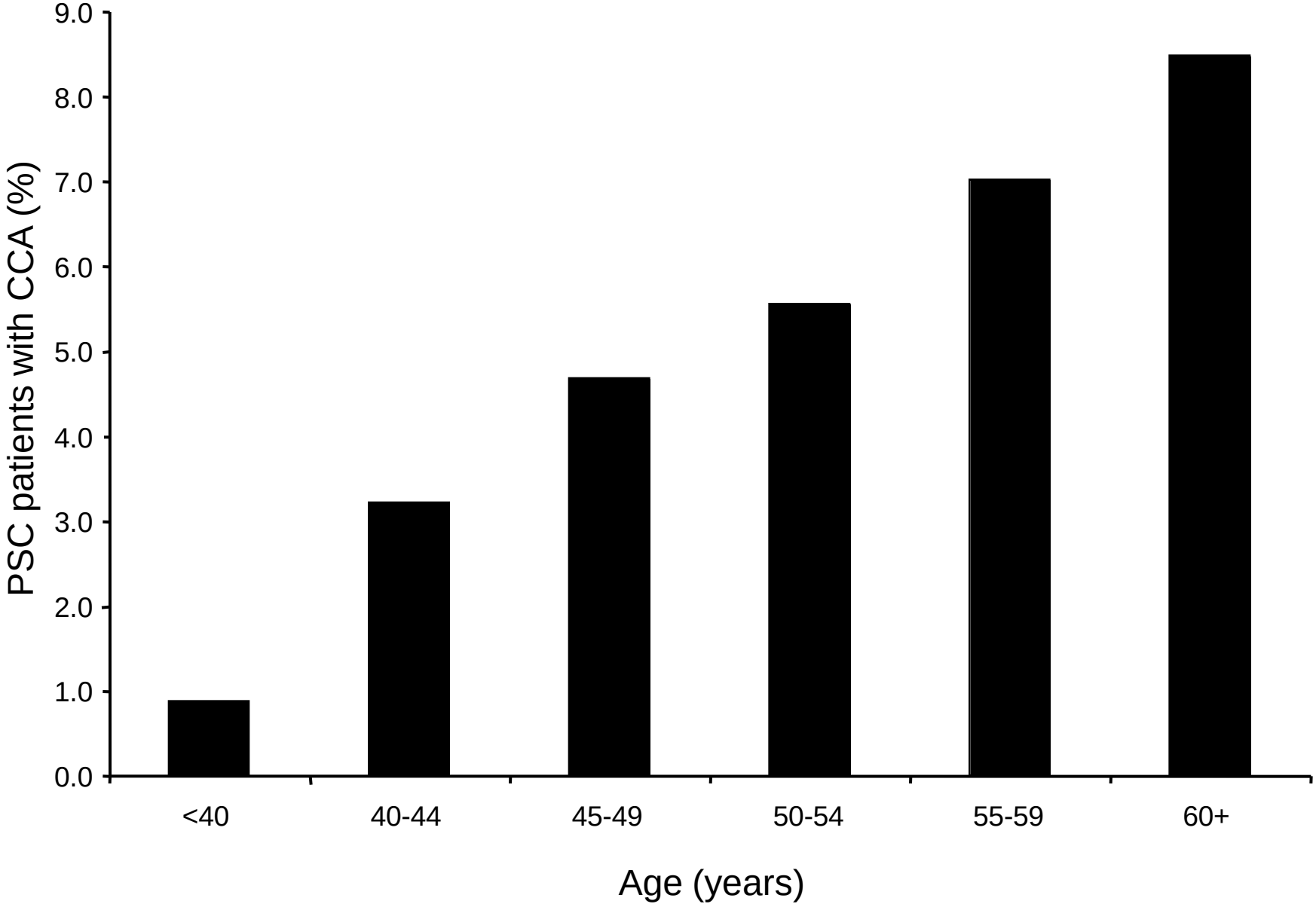
Broome U et al., Hepatology 1995

‡ Levy C et al., Sem Liv Dis 2006

North America PSC Registry and Biospecimen Repository

	Consented	Questionnaires	Samples
PSC probands	423	257	202
PSC controls	97	77	83

PSC complications		Years (range)
CCA	67 (16%)	50 (32 - 69)
CA	42 (10%)	51 (27 - 71)
OLT	89 (21%)	48 (17 - 70)


9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PSC patients with CCA (%)
<40
40-44
45-49
50-54
55-59
60+
Age (years)

“PROGRESS” STATUS

PSC (n=324)

Location of PSC at Dx	%
Intra-, Extra-, hepatic	70
Intra- hepatic	20
Extra- hepatic	5
Small duct	5

“PROGRESS” STATUS

	IBD (+)	IBD (-)
% (n)	79.1% (258)*	19.6% (64)*
Male / Female	78.4% / 80.3%	19.6% / 19.7%
Age at recruitment	52.6 (19 - 83)	52.3 (23 - 81)
Age at PSC Dx	40.2 (14 - 75)	41.0 (19 - 70)
Duration of PSC	12.5 (0 - 42)	11.0 (0 - 27)
Age at IBD Dx	32.2 (8 - 72)	---
Duration of IBD	20.4 (0 - 56)	---