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REVIEW ARTICLE

Genes, Brain and Behavior

The collaborative study on the genetics of alcoholism: Sample and clinical data

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Abstract

The collaborative study on the genetics of alcoholism (COGA) is a multi-site, multidisciplinary project with the goal of identifying how genes are involved in alcohol use disorder and related outcomes, and characterizing how genetic risk unfolds across development and in conjunction with the environment and brain function. COGA is a multi-generational family-based study in which probands were recruited through alcohol treatment centers, along with a set of community comparison families. Nearly 18,000 individuals from >2200 families have been assessed over a period of over 30 years with a rich phenotypic battery that includes semi-structured psychiatric interviews and questionnaire measures, along with DNA collection and electrophysiological data on a large subset. Participants range in age from 7 to 97, with many having longitudinal assessments, providing a valuable opportunity to study alcohol use and problems across the lifespan. Here we provide an overview of data collection methods for the COGA sample, and details about sample characteristics and

This is the second paper[a] in a linked series of reviews

[a] The other papers in the series are: 1. The Collaborative Study on the Genetics of Alcoholism: Overview. 3. The Collaborative Study on the Genetics of Alcoholism: Brain Function. 4. The Collaborative Study on the Genetics of Alcoholism: Genetics. 5. The Collaborative Study on the Genetics of Alcoholism: Functional Genomics.

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comorbidity. We also review key research findings that have emerged from analyses of the COGA data. COGA data are available broadly to researchers, and we hope this overview will encourage further collaboration and use of these data to advance the field.

KEYWORDS
alcohol, comorbidity, development, drug, environment, genetics, lifespan

1 | INTRODUCTION

The collaborative study on the genetics of alcoholism (COGA) was designed to identify risk and protective genes for alcohol use disorders and related conditions, with additional objectives to study associations with environmental and neurophysiological factors and their interplay with genes.[1–3] COGA has collected a wealth of data on nearly 18,000 individuals over the past 30 years, creating a national resource for studying the onset, offset, and developmental course of alcohol use disorders and related conditions. COGA data and all assessment instruments are made freely available to the scientific community (details at cogastudy.org). In this paper, we describe how data collection has evolved across the COGA project (Part 1), as well as key areas of investigation and findings that have emerged from the COGA project (Part 2), in the hope of inspiring additional scientists to collaborate and work with this rich dataset.

2 | PART 1: OVERVIEW OF DATA COLLECTION

Since its inception in 1989, COGA has used a family design, recruiting multigenerational families affected with alcohol use disorder (AUD) through probands in treatment for AUD, and a smaller set of community comparison families. To date, there have been 17,878 individuals in 2246 families who have participated in one or more of the assessment waves. Data collection has focused on different participant subsets over time, depending on the research emphasis. There have been four principal data collection waves that may be broadly described as follows: (a) "Wave 1" initial ascertainment and assessment from 1991 to 1999 (initial AUD case and community families); (b) "Wave 2": follow-up of individuals in Wave 1 and other family members not assessed at Wave 1, as well as families from a new research site from 1996 to 2005; (c) the "Prospective wave" from 2004 to 2019 which focused on assessments of youth ages 12–22 (born 1982 or later) in both case and comparison families at 2 year intervals; and (d) the current, "Lifespan" wave, begun in 2019, in which previously assessed participants now in midlife (ages 30–40) and later life (aged 50 or older) are re-assessed. With each phase of data collection, the core assessment interview (SSAGA) was revised to reflect changes in diagnostic criteria or to expand assessment to address newly arising and age-specific research questions. We provide here an overview of the different data collection waves, the research question guiding the focus of the data collection, the numbers of participants assessed at each, and tabular summaries of their characteristics.

2.1 | Wave 1: Initial ascertainment and assessment

At the study's inception, high-risk families were ascertained through probands who were undergoing treatment for AUDs at six sites across the United States. These were the University of Connecticut (Farmington, CT), SUNY Downstate (Brooklyn, NY), Indiana University (Indianapolis, IN), University of Iowa (Iowa City, IA), Washington University (St Louis, MO), and University of California San Diego. Probands were recruited from inpatient and outpatient treatment facilities to ensure a high level of AUD severity that would optimize identification of AUD susceptibility genes and AUD-linked brain dysfunction. Probands were interviewed with a comprehensive assessment created specifically for the project—the SSAGA interview—which was found to be highly reliable and valid.[4–6] Those who met criteria for both DSM-3R alcohol dependence[7] and Feighner alcoholism at the definite level[8] were enrolled. The assessment covered a wide range of health behaviors, substance use patterns and associated problems, and psychiatric symptoms that may have occurred at any point in participants' lifetimes. All first-degree relatives aged 7 or older were sought for interview with developmentally appropriate versions of the SSAGA. In addition, for children ages 7–17, parental corroborating interviews were obtained.[9] In addition to the SSAGA interview, individuals completed personality assessments and were administered a family history assessment.[10] This was considered the core COGA protocol. (See Table 1 for assessments conducted at each data collection wave, including neurophysiological and neuropsychological evaluations.)

From the initial pool of families, a subset of families with at least two affected first degree adult relatives in addition to the proband was selected for intensive study. In these families, data collection was expanded to individuals in other branches of the family. For all available consenting members of these extended, densely affected pedigrees, the core protocol was supplemented with neurophysiological (EEG/ERP) and neuropsychological evaluations and blood was collected for DNA and cell lines (see 4. Genetics and 3. Brain function) (in Table 1, specific components of the brain function protocol in the initial data collection are displayed; additional details about these tests may be found in 3. Brain function.) This approach thus identified densely affected families that were suitable for the planned genetic

TABLE 1 Assessments in each data collection wave.

	Wave 1	Wave 2	Prospective	Lifespan (ongoing)	
				Mid life	Later life
AUD and related					
SSAGA interview	SSAGA-I[a]	SSAGA-II[b]	SSAGA-IV[c]	SSAGA-V[d]	SSAGA-V[d]
Achenbach youth self-report			X		
Achenbach adult self-report			X		
Achenbach teacher report form		X			
Iowa Conners Teacher Rating Scale		X			
Self-rating of response to ethanol (SRE)		X	X	X	X
Drinking to cope			X	X*	X*
Alcohol expectancy questionnaire (adult)		X	X	X*	X*
Alcohol expectancy questionnaire (adolescent)		X	X		
Desires for alcohol (DAQ)		X	X	X*	X*
Ethanol Dependence Syndrome Scale		X	X		
Short Form Health Survey (SF-36)				X	X
Personality and traits					
Tri-dimensional personality questionnaire	X				
Temperament and character inventory	X				
Zuckerman Sensation Seeking Scale	X	X	X		
Russo Sensation Seeking Scale—children		X	X		
Dimensions of temperament survey		X			
Externalizing behaviors		X			
Harter self-perception profile (child & adolescent)		X			
Harter Importance rating (child)		X			
Harter Importance rating (adolescent)		X			
Barrett Impulsivity Scale (child)			X		
Barrett Impulsivity Scale (adolescent)			X		
UPPS-P Impulsive Behavior Scale				X	X
Five Factor Personality Inventory (NEO-FFI)		X	X	X	X
NIH toolbox—Emotional battery				X	X
Borderline Personality Disorder Screener				X*	X*
Environment & family background					
Family History Assessment Module	X	X	X		
Harter Social Support Scale for children	X	X			
Perceived Social Support—Family		X			
Perceived social support—Friends		X			
Important people & activities			X		
Parental bonding			X		
McMaster family assessment			X		
COVID questionnaire				X	X
Daily hassles & uplifts (adolescent)		X	X		
Daily hassles & uplifts (adult)		X	X		
Stressful life events				X*	X*
Experiences of discrimination scale				X	X
Work/employment questionnaire				X*	X*
Neurophysiologic experiments[1]					
Resting-state EEG	X	X	X	X	X
Visual oddball task	X	X	X	X	X

(Continues)

TABLE 1 (Continued)

	Wave 1	Wave 2	Prospective	Lifespan (ongoing)	
				Mid life	Later life
Auditory oddball	X	X	X	X	X
Semantic priming	x	x	x	x	x
Go-NoGo task			X	X	
Monetary gambling task			X	X	
Continuous performance test			X		
Color/Word Stroop			X		
Auditory novel stimuli			X		
Cognitive/affective stroop			X	X	X
Mismatch negativity	X	X			
Bereitschafts potentials	X	X			
Contingent negative variation	X	X			
Object recognition	X	X			
Intertrial interference	X	X			
Neuropsychological tasks[1]					
Tower of London[b]			X	X	
Visual span test			X	X	
NIH toolbox cognitive battery				X	X
NIH toolbox emotional battery				X	X
Porteus maze test	X	X			
TRAILS A & B	X	X			
Wechsler adult & child intelligence scales, rev	X	X			
California verbal learning test adult & child	X	X			
Ravens progressive matrices	X	X			
Wide range achievement test revised	X	X			
Discontinued Jan 2021					

[1]A full list and description of all neurophysiological and neuropsychological measures can be found in the Supplemental Methods section of the companion paper: 3. Brain function.

[a]SSAGA-I included demographics, medical history, tobacco history, suicidal thoughts and behavior, psychosis screener, and diagnostic information for: somatization, alcohol abuse and dependence, cannabis abuse and dependence, drug abuse and dependence (cocaine, other stimulants, sedatives and opiates), major depression, dysthymia, mania, conduct disorder, antisocial personality disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, and eating disorders.

[b]SSAGA-II included demographics, home environment ages 6–13 (e.g., household income, relationship with parents, family tension, parental monitoring, punishment, and consistency), medical history, psychosis screener, suicidal thoughts and behavior, and dDSM-3r, 4 diagnostic information for: somatization disorder, alcohol abuse and dependence, cannabis abuse and dependence, drug abuse and dependence (cocaine, other stimulants, sedatives and opiates), nicotine dependence, and fagerstrom test for nicotine dependence (FTND), major depression, dysthymia, mania, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, and eating disorders.

[c]SSAGA-IV included demographics, home environment ages 12–17 (e.g., household income, relationship with parents, family tension, parental monitoring, punishment, and consistency, sibling and peer substance use), medical history, psychosis screener, suicidal thoughts and behavior, and DSM-3r, IV diagnostic information for: alcohol abuse and dependence, cannabis abuse and dependence, drug abuse and dependence (cocaine, other stimulants, sedatives and opiates), nicotine dependence, FTND, major depression, dysthymia, mania, conduct disorder, antisocial personality disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, and eating disorders.

[d]SSAGA-V included demographics, medical history, social relationships (quality of relationship with spouse/partner, drug and alcohol use/problems of parents, partner, peers, siblings, and offspring), Religiosity, suicidal thoughts and behavior, and DSM-3r and IV diagnostic information for: alcohol abuse and dependence, cannabis abuse and dependence, drug abuse and dependence (cocaine, other stimulants, sedatives and opiates), nicotine dependence; FTND, and DSM-5 use disorders (alcohol, tobacco, cannabis, cocaine, stimulants, sedatives, and opiates), major depression, mania, conduct disorder, antisocial personality disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, and post-traumatic stress disorder.

linkage and association studies (see 4. Genetics). Probands and their relatives constituted "case" families. In addition to the case families, a set of families, called "comparison" families, were recruited from a variety of community sources (e.g., dental clinic admissions and state drivers' registries) and assessed with the identical expanded protocol. Extensions to other family branches in the comparison families were

also allowed as described above, although this was a rare occurrence. For the comparison families, there had to be two living parents and 3 (or more) children aged 14 or older. The presence of AUDs in the comparison families was not used as an exclusion criterion.

In this first data collection wave, 9325 adults aged 18 or older, and 1333 children aged 6–17 in 2246 families were assessed. Interviews occurred from 1991 to 1999 (most from 1991 to 1996). Participants were administered the SSAGA in person, although telephone assessments were conducted when transportation difficulties or distance precluded an in-person visit.[11] Tables 2 (adults) and 3 (children) summarize the participant characteristics, separately for the probands, their relatives, and participants in comparison families. A few points merit comment here. Probands and their family members are racially/ethnically diverse, middle aged, with an unsurprising predominance of men in the proband sample (74.8%) which derived from treatment programs, but a higher proportion of women among the relatives (59%). By definition, probands were affected with AUD; as expected, the prevalence of Alcohol Dependence among their relatives was much higher than that observed among comparison family participants (34.6% vs. 16.6%). There is considerable addiction comorbidity among the probands, particularly for cannabis and cocaine where 44.9% and 48.4% met dependence criteria respectively. Comorbidity

TABLE 2 Characteristics of adults in wave 1 data collection: Initial ascertainment and assessment, by probands, relatives, and comparison participants.

	Probands-case fam ($N = 1247$)	Relatives of probands[a] $N = 7019$	Comparison family participants $N = 1059$
Mean age yrs (sd)	37.7 (10.6)	40.8 (15.1)	36.0 (14.3)
Range	17–77	15–97	17–81
Female (%)	314 (25.2)	4149 (59.1)	548 (51.8)
Male (%)	933 (74.8)	2870 (40.9)	511 (48.2)
Race/ethnicity (self-report)			
Black (%)	262 (21.0)	1321 (18.8)	67 (6.3)
White (%)	946 (75.9)	5513 (78.5)	938 (88.6)
Hispanic ethnicity (%)	87 (7.0)	427 (6.1)	57 (5.4)
Highest years of education			
Mean (sd)	12.5 (2.1)	12.7 (2.4)	14.0 (2.2)
Substance use lifetime disorder (may have more than one): *n* (%)			
DSM-3R dependence			
Alcohol	1246 (99.9)	2426 (34.6)	176 (16.6)
Cannabis	560 (44.9)	997 (14.2)	57 (5.4)
Cocaine	603 (48.4)	773 (11.0)	15 (1.4)
Other stimulants	302 (24.2)	421 (6.0)	7 (0.7)
Opioids	199 (16.0)	212 (3.0)	3 (0.3)
Sedatives	200 (16.0)	205 (2.9)	4 (0.4)
Tobacco—smoked daily for ≥6 mo (%)	1062 (85.3)	4209 (60.0)	357 (33.7)
Non substance lifetime diagnoses (DSM-3R) (*n*, %)			
Major depression	673 (54.0)	2326 (33.1)	242 (22.9)
Panic	104 (8.3)	246 (3.5)	15 (1.4)
Agoraphobia	61 (4.9)	172 (2.4)	15 (1.4)
Social phobia	69 (5.5)	204 (2.9)	16 (1.5)
Conduct (%)[b]	369 (29.6)	804 (11.4)	66 (6.2%)
ASPD (%)[b]	335 (26.9)	470 (6.7)	24 (2.3%)
Somatization (%)	1 (0)	2 (<0%)	0 (0.0)
OCD (%)	49 (3.9)	94 (1.3)	8 (0.8)
Eating disorders (%)			
Anorexia	11 (0.9)	27 (0.4)	2 (0.2)
Bulimia	30 (2.4)	136 (1.9)	6 (0.6)
Suicide attempt	300 (24.1)	674 (9.6)	27 (2.6)

[a]Includes participants in other family types (e.g., Alcohol challenge families $n = 315$).
[b]Includes alcohol- or other substance- induced symptoms.

TABLE 3 Characteristics of children from Wave 1 data collection, by case and comparison families.

	Case families	Comparison families
	$N = 1104$[a]	$N = 229$
Mean age yrs (sd)	11.9 (3.2)	14.3 (2.6)
Range	6–17	7–17
Female (%)	564 (51.1)	113 (49.3)
Race/ethnicity (self-report)		
Black (%)	270 (24.5)	20 (8.7)
White (%)	754 (68.3)	197 (86.0)
Hispanic (see note)	60 (5.4)	7 (3.1)
Education—current grade (SD) Mean (sd)	6.2 (3.1)	8.6 (2.7)
Rearing status		
Live with bio dad (%)	530 (48.0)	220 (96.1)
Live with bio mom (%)	974 (88.2)	227 (99.1)
Substance use		
Ever had a drink (%)	340 (30.8)	102 (44.5)
Mean age first full drink (sd)	12.7 (2.5)	13.1 (2.1)
Ever had seven drinks lifetime (*n*, %)	186 (16.8)	61 (26.6)
Ever intoxicated[b] (*n*, (%)	146 (13.2)	42 (18.3)
Age of first intoxication[b]–mean (sd)	13.9 (1.7)	14.1 (1.5)
Ever used cannabis (*n*, %)	167 (15.1)	35 (15.3)
Mean age first cannabis use (sd)	13.7 (2.2)	14.4 (2.0)
Ever used tobacco (*n*, %)	306 (27.8)	83 (36.2)
Mean age first tobacco use (sd)	11.8 (2.7)	12.5 (2.6)
Diagnoses by either child or parent report: (*n*, %)		
ADHD diagnosis	122 (11.1)	10 (4.4)
Oppositional defiant disorder	139 (12.6)	16 (7.0)
Conduct disorder	161 (14.6)	28 (12.2)
Separation anxiety disorder	139 (12.6)	12 (5.2)
Overanxious disorder	88 (8.0)	21 (9.2)
Depression-lifetime	205 (18.6)	24 (10.5)
Suicide attempt (%)	56 (5.1)	6 (2.6)

Note: Hispanic ethnicity was not asked separately but rather as part of overall racial identity.

[a]Includes other family types (e.g., alcohol challenge families) ($n = 14$).

[b]Only asked of those having seven or more drinks in lifetime.

with other substance dependence is less pronounced among their relatives, where 14.2% and 11% met criteria for dependence on cannabis and cocaine, respectively. The prevalence rates in probands and their relatives were markedly higher than those observed among comparison family participants, where only 5.4% met criteria for cannabis dependence, and 1.4% for cocaine, with rates negligible for the other drugs. In contrast to comparison family participants, prevalence of non-substance disorders comorbidity was elevated among probands and their relatives; for example, prevalence estimates for major depression were 54%, 33.1%, and 22.9% for probands, relatives and comparison participants, respectively, and for conduct disorder 29.6%, 11.4% and 6.2% for proband, relatives and comparison participants, respectively. The children, most of whom were members of case families (i.e., related to probands), were on average about 12 years old and in 6th grade, younger than those in the comparison families, and substance use initiation was not yet a common behavior. The lower prevalence of substance involvement among case family children compared with their comparison family counterparts is probably due to being several years younger, on average. A striking but unsurprising observation is that only 48% of the children in case families were living with their biological father, compared with 96% of children in comparison families. In children from case families, comorbidity with attention deficit-hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD), anxiety, and depression, reported by either the child or parent, was elevated over that observed in children from comparison families.

2.2 | Wave 2: Follow-up

The second data collection wave, which began in 1996 and continued through 2005, targeted Wave 1 probands, members of densely affected families, and comparison family members.[12] In addition, other family members in the Wave 1 families who had not been assessed in the previous wave were assessed in Wave 2. Also in Wave 2, a seventh data collection site, located at Howard University in Washington DC, was added to increase the racial/ethnic diversity of the sample, with an emphasis on Black families. The SSAGA was updated to reflect the change in diagnostic classification system from DSM-3R to DSM-IV,[13] adding new items but retaining the old to preserve consistency across assessment waves. The key elements of the protocol in Wave 2, including the interview, questionnaires, and electrophysiological assessments, remained largely unchanged. Additional neuropsychological tests were included to evaluate participants' decision-making, memory, attention, and problem solving, and, if not previously collected, a blood sample was taken for genetic analyses and cell lines. Children aged 7–17 were also re-interviewed, and additional children in the families were recruited. Altogether, 8799 adults aged 18 and older, and 2646 children, participated in this second wave. In Tables 4 and 5, the demographic and psychiatric characteristics of Wave 2 participants are displayed for adults and children.

As indicated in Table 4, 43.4% of those in case and 36.5% of those in comparison families were newly assessed in Wave 2. There is considerable alcohol and other substance dependence in case families compared with comparison families, with prevalence estimates ranging from 3.4% to 44% (case), compared with 0.4% to 15.7% (comparison participants). Not unexpectedly, prevalence of other disorders in the externalizing domain, such as conduct disorder and antisocial personality disorder (ASPD), is also elevated among those in case families (17.4% and 12.5%, respectively), compared with comparison families

TABLE 4 Characteristics of adults in Wave 2 data collection, by case and comparison families.

	Case families[a]	Comparison families
Number of participants	*N* = 7359 (%)	*N* = 1440 (%)
Mean age (sd)	39.3 (13.3)	37.0 (14.4)
Range	17–96	18–86
Female (%)	4027 (54.7)	795 (55.2)
Race/ethnicity (self-report)		
Black (%)	2003 (27.2)	225 (15.6)
White (%)	5146 (69.9)	1122 (77.9)
Hispanic ethnicity (%)	517 (7.0)	57 (4.0)
Education—highest number of years completed (mean, sd)	12.7 (2.2)	14.4 (2.1)
Interviewed in Wave 1 (%)	4167 (56.6)	915 (63.5)
Wave 2 only (%)	3193 (43.4)	525 (36.5)
Substance dependence (DSM-3R) (may have more than one) (*n*, %)		
Alcohol	3236 (44.0)	226(15.7)
Cannabis	1686 (22.9)	105 (7.3)
Cocaine	1298 (17.6)	33 (2.3)
Other stimulants	544 (7.4)	12 (0.8)
Opiates	362 (4.9)	7 (0.5)
Sedatives	248 (3.4)	6 (0.4)
Tobacco—DSM-4 dependence	2549 (34.6)	211 (14.7)
Non substance dx: (DSM-3R) (*n*, %)		
Major depression	2791 (37.9)	303 (21.0)
GAD[b]	13 (0.2)	2 (0.2%)
Panic[b]	184 (2.8)	17 (1.4)
Agoraphobia[b]	186 (2.9)	15 (1.3)
Social phobia[b]	239 (3.7)	17 (1.4)
Conduct[c]	1283 (17.4)	113 (7.9)
ASPD[c]	922 (12.5)	60 (4.2)
Obsessive-compulsive disorder[b]	83 (1.1)	3 (0.2)
PTSD[b]	388 (6.0)	19 (1.6)
Suicide attempt[b]	695 (10.7)	32 (2.7)

[a]Includes participants from other family types (e.g., alcohol challenge, *n* = 10).
[b]Percent calculated on reduced n, owing to omission of some sections across sites, *n*'s from 6487 to 6505 (case families); 1179 (comparison families).
[c]Includes substance-related symptoms.

TABLE 5 Characteristics of children assessed at Wave 2, by case and comparison families.

Participants	Case families[a] *N* = 2457	Comparison families *N* = 189
Mean age (sd)	11.9 (3.2)	12.6 (3.2)
Female (%)	1219 (49.6)	97 (51.3)
Race/ethnicity (self-report)[b]		
Black (%)	706 (31.5)	29 (16.5)
White (%)	1428 (63.1)	137 (77.8)
Hispanic ethnicity (%)	242 (10.7)	15 (8.5)
Education—current grade		
Mean (sd)	6.2 (3.2)	7.0 (3.2)
% with phase 1 child interview	461 (18.8)	35 (18.3)
Rearing status (ages 12–17)		
Live with bio dad (%)	1273 (51.8)	162 (85.7%)
Live with bio mom (%)	2205 (89.7)	181 (95.8%)
Substance use (may include more than 1)		
Ever had a drink (%)	487 (19.8)	34 (18.0)
Mean age first full drink (sd)	13.4 (2.1)	14.2 (1.9)
Ever intoxicated (%)	296 (12.1)	15 (7.9)
Age of first intoxication—mean (SD)	14.1 (1.7)	14.9 (1.3)
Ever used cannabis (%)	376 (15.3)	15 (7.9)
Mean age first cannabis use (sd)	13.4 (1.8)	13.8 (2.9)
Ever used tobacco (%)	576 (23.4)	28 (14.8)
Mean age first tob (sd)	11.7 (2.7)	12.6 (3.0)
Diagnosis met by either child or parent report:		
ADHD	209 (8.5)	9 (4.7)
Oppositional defiant disorder	147 (6.0)	5 (2.6)
Conduct disorder	193 (7.9)	9 (4.7)
Separation anxiety disorder	52 (2.1)	2 (1.0)
Overanxious disorder	92 (3.7)	3 (1.6)
Depression	299 (12.2)	14 (7.4)
Social phobia	41 (1.7)	7 (3.7)
Suicide attempt	64 (2.6)	2 (1.0)

[a]Includes two participants from other family type.
[b]Based on *n* = 2261 participants in Case, and 176 Comparison, families.

(7.0% and 4.2%). As shown in Table 5, most of the children interviewed in Wave 2 were from case families (2457 vs. 189, 93%), were on average about 12 years old, and in middle school (6th–7th grade). Regardless of family status, most reported modest substance use. Externalizing comorbidity was elevated among the children in case families as compared with comparison families.*

2.3 | Wave 3: The prospective study

In late 2004, the prospective study (2004–2019) was launched to evaluate younger members of the original COGA families who were then between the ages of 12 and 22 (adolescents/young adults). Some had been interviewed in earlier data collection waves, and all had at least one parent who was interviewed in one of the earlier waves of data collection. Participants were interviewed every 2 years,

to study how alcohol use, problems, and related behaviors developed and changed over time. For 12-year-old children, a parent interview about the child was also obtained. Additional children, upon turning age 12, were invited to participate. The assessments administered in this wave were similar to those used in prior waves of data collection, but updated to target the youthful group being studied, such as asking about school behaviors, friendship groups and quality of relationships with parents (see Table 1). The measures also included neurophysiological and neuropsychological tests to assess neurocognitive performance, particularly frontal lobe function across development during this period (detailed in Table 1 under the column heading "prospective"). If not collected previously, blood samples for genotyping were obtained. Many of the participants were one or two generations younger than the original COGA probands (e.g., nephews and grandchildren), but all were drawn from the same family lines of the probands. Youth were also recruited from the original comparison families. Altogether, 3715 individuals participated in the prospective study and were assessed an average of 4 times. In Table 6, attributes of this sample at the baseline assessment are displayed, while lifetime characteristics, as reported at any assessment wave, are shown in Table 7.

At baseline, participants from case families averaged about 16 years of age, with those from comparison families about 1 year younger. Evidence of having initiated substance use was abundant, and more common among those from case versus comparison families, across all types of substances. Alcohol was the most commonly used substance, with about 50% of those in case, compared with about 30% of those in comparison, families reporting ever having a drink. The most common substance use disorders were Alcohol and Cannabis dependence, with higher prevalence of both among participants from case versus comparison families; 4.2% and 6.8% of case family participants, compared with 1.4% and 2% of comparison family members, met diagnostic criteria for alcohol and cannabis dependence, respectively. Likewise, prevalence estimates of non-substance externalizing disorders (Conduct Disorder, ADHD, and ODD) were higher among participants from case families compared with their counterparts from comparison families.

As shown in Table 7, by the time data collection had ended in 2019, the paths of the participants from case families continued to diverge from those of their counterparts from comparison families in numerous domains. This was observed in the substance use realm, where across all types of substances, use began at much younger ages, and prevalence estimates for disorders were 1.4 to over 4 times higher among those in case compared with comparison families. Excess prevalence in participants in case compared with comparison families was also observed for major depression, conduct disorder, and ASPD.

2.4 | Focus on older individuals with AUD: One-year study of those age 50+ with AUD

In 2016–2017, we conducted a one-year study of 2174 participants at least 50 years of age (born 1966 or earlier) who met lifetime criteria for DSM-IV Alcohol Dependence. On average, these individuals had last participated in COGA 22 years earlier.[14] The main goal of the pilot study was to show recruitment feasibility given the long interval between contacts. Participants were interviewed by telephone with a brief, nondiagnostic assessment covering their current living situation, physical health, and current alcohol consumption and problems. In the brief one-year recruitment, 706 were interviewed, 524 were found to be deceased, 28 were unable to be interviewed, and 55 refused; with 861 remaining to be recruited at a later time. Of those interviewed, 99% agreed to be contacted again in the future, and that encouraging finding led to the design of a more extensive investigation of older COGA individuals, ushering in the lifespan study.

2.5 | Wave 4: The lifespan study

In 2019, we began conducting the current lifespan study of COGA, focused on two groups of prior COGA participants. The first consists of individuals from the Prospective Study who would range in age from 30 to 40 by 2023 (born between 1982 and 1993). This sample was chosen due to the lack of studies that have focused on alcohol use and problems in this particular midlife period. The second group is composed of participants who are currently (or will be by the end of 2023) age 50 or older (born before 1974). We are recruiting them now to increase understanding of alcohol use, problems, and disorder during the later life age period which has not been extensively studied. For both groups, the unified protocol includes the SSAGA interview, questionnaires, and in-person laboratory-based neuropsychological and neurophysiological assessments (see Table 1; and also details in the companion paper 3. Brain function). As has been true throughout COGA, the assessment procedures, in addition to being updated when appropriate, maintain continuity with prior evaluations.

The COVID-19 pandemic required changes to the COGA protocol to ensure the health and safety of research participants and staff. These changes included the temporary suspension of all face-to-face evaluations in March 2020, with interviews conducted remotely and questionnaires filled out either via mailed paper versions or online via smartphone, computer, or tablet at a secure website. At several sites, in-person laboratory testing (neurophysiological and computerized neuropsychological assessment batteries of cognition and emotion) resumed during periods when local infection rates were acceptably low. Interviews and questionnaires continued to be administered remotely. Beginning in August 2022, all sites eventually deemed it sufficiently safe, with appropriate screening and safety protocols in place, to resume in-person assessment.

In summary, across all data collection waves and case and comparison families, in the 30+ years of the COGA project, 17,878 individuals have been assessed at least once with a comprehensive protocol including interviews and questionnaires that capture behaviors, psychosocial characteristics, family background, life course experiences and outcomes from both lifetime and current perspectives. A snapshot of their characteristics derived from the deep phenotyping in COGA is provided in Table 8. In addition, the table displays

TABLE 6 Baseline characteristics of prospective study participants in third wave of data collection, by case and comparison families.

	Case families	Comparison/other families+
N	**3203**	**512**
Mean age (sd)	16.2 (3.3)	15.0 (3.2)
% female	1633 (51.0%)	270 (52.7%)
Race/ethnicity (self-report)		
Black	978 (30.5)	41 (8.0%)
White	1936 (60.4)	440 (85.9)
Hispanic	410 (12.8%)	35 (6.8%)
Education—highest years of education completed (mean, sd)	9.9 (2.6)	9.0 (2.7)
Still in school	2626 (82.0%)	466 (91.0%)
Reared by, ages 12–17: (*n*, %)		
Both biological parents	1546 (48.5)	410 (80.2)
Bio mom	1132 (35.5)	60 (11.7)
Bio dad	133 (4.2)	13 (2.5)
Other rearing circumstances	374 (11.7)	28 (5.5)
Substance use (*n*, %)		
Ever had a drink	1592 (49.7)	148 (28.9)
Mean age first drink (sd)	15.0 (2.5)	15.4 (2.6)
Ever intoxicated	1238 (38.7)	97 (19.0)
Mean age first intoxication (sd)	15.8 (2.2)	16.4 (2.1)
Ever had a cigarette	915 (28.6)	66 (12.9)
Smoked 100+ cigarettes	581 (18.1)	27 (5.3)
Ever used cannabis	1147 (35.8)	75 (14.6)
Mean age first cannabis use (sd)	14.9 (2.5)	15.5 (2.6)
Ever used cocaine	218 (6.8)	12 (2.3)
Ever used other stimulants	146 (4.6)	8 (1.6)
Ever used sedatives	179 (5.6)	12 (2.3)
Ever used opiates	208 (6.5)	9 (1.8)
DSM-4 substance dependence (*n*, %)		
Alcohol	133 (4.2)	7 (1.4)
Cannabis	217 (6.8)	10 (2.0)
Cocaine	35 (1.1)	1 (0.2)
Other stimulants	41 (1.3)	0
Opiates	20 (0.6)	0
Sedatives	12 (0.4)	1 (0.2)
Tobacco	277 (8.6)	13 (2.5)
Non substance diagnoses: (*n*, %) (DSM-4)		
Major depression	473 (14.8)	47 (9.1)
Panic	32 (1.0)	4 (0.8)
Agoraphobia	39 (1.2)	0
Social phobia	53 (1.7)	5 (1.0)
Conduct disorder	225 (7.0)	17 (3.3)
ASPD	120 (3.7)	7 (1.4)
ADHD	110 (3.4)	11 (2.2)
ODD	141 (4.4)	7 (1.4)
OCD	12 (0.4)	0
PTSD	45 (1.4)	3 (0.6)
Suicide attempt	99 (3.1)	10 (2.0)

TABLE 7 Prospective study participants: Lifetime characteristics based on summary assessment across all data collection waves.

	Case families	Comparison families
	3203	512
Most recent age, mean age (sd)	23.5 (5.5)	22.5 (5.7)
Education—highest # years completed (mean, sd)	12.8 (2.4)	13.2 (2.9)
Mean # waves	4.1, median = 4	4.4, median = 4
Substance use (*n*, %)		
Ever had a drink	2794 (87.2)	387 (75.6)
Mean age first drink (sd)	15.7 (2.7)	16.3 (2.6)
Ever intoxicated	2533 (79.1)	335 (65.4)
Mean age first intoxication (sd)	16.7 (2.6)	17.5 (2.2)
Smoked 100+ cigarettes	1158 (36.2)	89 (17.4)
Ever use cannabis	2306 (72.0)	258 (50.4)
Mean age first cannabis use (sd)	16.0 (3.0)	17.1 (2.8)
DSM-4 Substance dependence (*n*, %)		
Alcohol	601 (18.8)	45 (8.8)
Cannabis	700 (21.9)	49 (9.6)
Cocaine	125 (3.9)	4 (0.8)
Other stimulants	105 (3.3)	4 (0.8)
Opiates	133 (4.2)	6 (1.2)
Sedatives	55 (1.7)	6 (1.2)
Tobacco	756 (23.6)	46 (9.0)
Non substance diagnoses & suicidality (*n*, %)		
Major depression	1183 (37.0)	144 (28.1)
Conduct disorder	544 (17.0)	34 (6.6)
ASPD	392 (12.2)	15 (2.9)
OCD	53 (1.6)	5 (2.9)
PTSD	163 (5.1)	8 (1.6)
Suicide attempt	272 (8.5)	26 (5.1)

attributes of several key subsets of the entire COGA sample that have been the focus of intense study by COGA. These include the GWAS sample ($n = 12{,}009$), discussed in greater detail elsewhere in this issue (see 4. Genetics); the sample of individuals who have completed at least one electrophysiological protocol administered during COGA's course ($n = 9871$) and who are the focus of the companion paper in this issue (see 3. Brain function); and lastly those participants with genetic, neurophysiologic and comprehensive phenotypic data. The sample is middle-aged, with slightly more female participants, notably diverse with 25%–28% from Black race/ethnic groups and 7%–8% from participants reporting Hispanic background. Over one third (35%–37%) meet criteria for DSM-IV substance dependence on one or more substances, and Alcohol Dependence that is comorbid with other drug dependence is the most common pattern. Non-substance disorders are common, particularly major depression, and both conduct disorder and antisocial personality disorder. The brief overview establishes the COGA sample as well-positioned for continuing on its original path set over 30 years ago to investigate the multifaceted underpinnings and course of AUD, other addictions and related psychiatric disorders.

3 | PART 2: EXAMPLES OF THE QUESTIONS ADDRESSED WITH COGA DATA

With these rich, cross-sectional and longitudinal data, collected within families over decades, a number of critical questions about the causes, consequences, and life course of alcohol use problems and related disorders have been addressed, and more can be studied. Below we provide illustrative examples of areas where COGA data has made substantive contributions to a deeper understanding of the AUD phenotype, its comorbidity with other addictions and with psychiatric disorders, and of the impact of the interplay of genetic and environmental influences on alcohol and other substance use outcomes. We note that COGA data and instruments are made available to any qualified investigator and can be accessed through a variety of routes, including directly from NIAAA, through direct collaboration with COGA investigators, and through dbGAP; details about each of these options are provided at https://cogastudy.org/resources-for-researchers/ with additional details in the companion paper 1. Overview. We welcome collaborations with outside investigators; indeed, some of COGA's most impactful papers have arisen through collaborations with the global community of researchers, such as the Psychiatric Genomics Consortium,[15–20] Externalizing Consortium,[21] and INIA.[22] A complete list of COGA publications can be found at cogastudy.org. COGA is also invested in supporting the development of early career investigators (see 1. Overview) and we encourage the participation of junior faculty in COGA; many of the studies detailed below have been initiated by junior investigators on the project.

3.1 | Familial characterization of AUD and associated comorbidity

The cross-sectional, family-based data gathered early in COGA yielded a rich series of investigations exploring in-depth characterizations of the AUD phenotype (subtypes, withdrawal, and time course), familial aggregation of substance use disorders, comorbidity with other substance dependences and with non-substance disorders like depression, anxiety, eating disorders, and suicidality, to name a few. Among the array of published findings based on COGA data, we highlight several here in acknowledgement of their contributions to some

TABLE 8 Overall table: Characteristics of all participants, those with GWAS data, those with EEG data and those with both GWAS and EEG data.

	ALL	GWAS	EEG	GWAS & EEG
N	17,878	12,009	9871	9076
Mean age, most recent interview (SD)	35 (15)	35 (14)	32 (13)	33 (33)
Female %	52.6	52.7	52.1	52.5
Race/ethnicity (self-report)				
Black %	24.4	26.0	27.7	28.1
Hispanic %	7.4	7.8	8.3	8.2
Highest # yrs of education				
Mean (SD)	13 (3)	13 (3)	13 (3)	13 (3)
Mean number of assessments (SD)	2.0 (1.5)	2.3 (1.7)	2.4 (1.8)	2.5 (1.8)
% with GWAS	12,009 (67.2)	–	9076 (91.9)	–
% with EEG	9871 (55.2)	9076 (75.6)	–	–
Lifetime DSM-IV dependence (%)				
Alcohol	27.5	28.9	27.0	28.0
Cannabis	15.3	17.2	17.3	17.8
Cocaine	11.1	11.7	11.0	11.4
Other stimulants	5.2	5.4	4.6	4.8
Opiates	3.9	4.2	3.7	3.9
Sedatives	2.6	2.6	2.2	2.3
Tobacco—smoked daily for month or more	51.7	51.6	47.2	48.8
Comorbidity among DSM-IV substance dependence disorders				
Alcohol dependence only	12.4	12.7	11.8	12.2
Alcohol dependence + Cannabis Dep	3.4	3.8	3.9	4.0
Alcohol Dependence + other noncannabis drug dependence	5.3	5.4	4.8	4.9
Alcohol + Cannabis + Other drug dependence	6.4	6.9	6.5	6.8
Cannabis dependence only	4.1	4.9	5.3	5.4
Cannabis + Other drug dependence (no alcohol)	1.4	1.6	1.6	1.6
Other drug dependence only (no alcohol or cannabis dependence)	2.3	2.4	2.3	2.4
At least 1 dependence disorder	35.3	37.8	36.1	37.3
No dependence	64.7	62.2	63.9	62.7
Non substance DSM-IV disorders (%):				
Major depression	32.5	34.4	32.8	33.5
Panic	3.6	3.8	3.5	3.5
Agoraphobia	2.8	3.0	2.6	2.6
Social phobia	4.1	4.7	4.4	4.5
Conduct	16.4	18.3	17.6	18.1
ASPD	11.9	13.7	13.0	13.5

Abbreviations: EEG, electroencephalogram data; GWAS, genomewide association study data.

key research questions. An analysis of the large array of alcohol problems collected in Wave 1 contributed to the nosological debate on dimensional versus categorical representations of substance use disorder, finding strong evidence in the full COGA sample that the disorder was best conceptualized on a severity dimension rather than by categories of specific symptoms.[23] Replicating results from a large Australian twin sample,[24] this finding has also been observed in numerous subsequent studies across general population, collegiate and treatment samples.[25–27] In another COGA study, analysis of the early family data led to observations of both common and specific

evidence for familial transmission of alcohol, marijuana, and cocaine dependence and habitual smoking,[28] a finding confirmed in later COGA investigations,[29] as well as in a number of independent twin-family samples analyzed by other researchers.[30,31] In another later analysis of the completed Wave 1 data collected on over 9000 probands, their relatives, and comparison participants, we reported a two-fold excess risk for AUD in relatives of probands with AUD, and observed strong co-aggregation with antisocial personality disorder, other drug dependence, and anxiety and mood disorders.[3] Similar co-aggregation of AUD and other externalizing disorders has been documented in independent twin-family data by other researchers.[32] COGA also found that the presence of a physiological dependence component to alcohol and other substance use disorders implicated a more severe clinical course, that held for alcohol as well as other substances.[33] Other analyses investigated evidence in COGA of a previously established AUD subtype, Type A-B clusters,[34] finding that among affected individuals in COGA, 5 items usefully distinguished the two types with positive clinical applications.[35] Altogether, data on in-depth characterization of a broad range of alcohol and other substance misuse problems, as well as other psychopathology, obtained in the members of the COGA families, have supported numerous analyses in the presentation and familial aggregation of alcohol problems. In this area, COGA not only has provided evidence to support past findings by reproduction of results from prior studies, but also has contributed fresh insights into key issues in AUD nosology and familial transmission that have served as a catalyst for further investigations in other data sources by other researchers.

3.2 | Developmental effects

AUD is, by its very nature, a developmental disorder, which unfolds in a series of stages, from initiation, to regular use, to the development of problems, well argued in the literature to date.[36–38] Further, there is often a pattern of risk-related behavior that precedes the onset of alcohol use.[39,40] Each of the stages of alcohol use is influenced by genetic factors,[38,41–43] as are the premorbid behaviors that comprise the spectrum of preaddiction risk.[44–47]

With the comprehensive and multimodal longitudinal data available in COGA, we can characterize the pathways by which genetic and environmental influences on alcohol-related problems unfold. Consistent with earlier studies in the literature,[48,49] we found that genetic risk for alcohol problems manifests in adolescence and early adulthood as a constellation of clinical behaviors related to impulsivity and behavioral undercontrol, often called the externalizing spectrum.[21,50–54] These childhood behavior problems[42] and traits related to impulsivity, such as sensation-seeking, reflect early manifestations of genetic risk for alcohol and other substance use problems.[55–57] With the greater availability of alcohol as individuals age from later adolescence to emerging adulthood, these same genetic influences begin to impact patterns of alcohol use,[58] the rate of escalation in hazardous use,[59] and the development of problems.[42] Measures of the intensity of response to alcohol are additional early indicators of genetic risk for alcohol problems, and include both a low level of response seen at peak and falling blood alcohol levels and higher stimulation observed at rising blood levels.[60–63] Beginning in 1989, longitudinal studies in COGA focused on the low response across several generations of participants.[61,64] Not only do impulsivity and low level of response to alcohol directly influence risk, they also appear to indirectly amplify risk via environmental pathways and attitudes, through the selection of riskier peers, positive alcohol expectancies, and increased drinking to cope with stress.[64–66] Additional insights into the factors that underlie the transitions in alcohol involvement from use to disorder have been provided by COGA's collection of electrophysiological indicators of brain function across development, as discussed in greater detail in the companion article in this volume (see 3. Brain function).

Other COGA analyses have mapped specific risk factors that impact transitions in alcohol involvement from use, to problems, to disorder. Cannabis use, substance-using peers, externalizing behaviors, and parental history of AUD all increase the likelihood of each stage of alcohol involvement.[67] Nonassaultive trauma is related to early initiation of use, and internalizing disorders such as depression are associated with later stages.[67] We have showed that, consistent with Koob's model of the progression of the addiction cycle,[68] positive reinforcement motives for drinking (e.g., social enhancement) are related to alcohol consumption earlier in the drinking career, whereas negative reinforcement (e.g., drinking to reduce anxiety) predominates once an individual develops AUD.[69] We also showed that alcohol problems cluster and show reciprocal relationships with other disorders and behaviors related to externalizing and internalizing across the lifespan, including suicide attempts and ideation,[70–72] consistent with other studies in the field.[73–75]

Finally, in our latest round of follow-ups of COGA participants approximately 20 years after they were assessed in midlife, we are studying predictors and consequences of alcohol use in later life.[14] Data on outcomes obtained from the brief assessment of older COGA participants with a history of AUD showed that nearly 60% had good outcomes, including 41% abstinent and problem free in the 5 years preceding the follow-up, and 15% were low risk, nonproblem drinkers.[14] However, roughly 30% were current problem drinkers, and another 14% reported high risk drinking. We have also characterized changing patterns of treatment service use for alcohol problems across generations.[76] In the full COGA sample, individuals with AUDs were classified into generations based on their birth year (1928–45, 1946–64, 1965–1980, and 1981–1996), and we found that those in the younger generations used services earlier than their counterparts in older generations, and women across all generations were less likely to use services.[76]

3.3 | Trajectories of use—Initiation, onset, offset, and predictors of patterns across time

The richness of the COGA longitudinal data allows characterization of drinking milestones, transitions across stage of AUD development,

and patterns of use overtime. Consistent with earlier studies in the literature,[77–79] we have shown that age of first drink of alcohol is best predicted by multiple factors. In a multivariate model, we found that best friend alcohol use, a positive family history of having any adult family member in treatment for alcohol dependence, conduct disorder symptoms, and youth externalizing behavioral problems were associated with higher likelihood of earlier alcohol initiation, whereas youth social problems (e.g., friendship difficulties and loneliness) were associated with reduced likelihood of earlier alcohol initiation, underscoring the social component of youth alcohol initiation.[80] In addition, leveraging the multigenerational family-based data, our team has shown that parental AUDs are associated not only with offspring initiation of alcohol use, but also with other risky behaviors, including offspring early involvement with cigarettes and cannabis use, and age at first consensual sexual intercourse.[81] Parental divorce/separation exerted additional effects on the early initiation of alcohol and substance use, with the effect size comparable to that of having two AUD-affected parents.[81] Using COGA's longitudinal electrophysiological data, we have also found that the age of onset of AUD in adolescents and young adults is associated with both genetic and neurophysiological factors, most strongly among those who used substances before the age of 16[82] (see 3. Brain function).

Other COGA analyses have explored heterogeneity in drinking patterns and predictors across time. For example, using latent class growth analysis, we identified four distinct subgroups of trajectories of alcohol intake, characterized by maximum drinks per occasion, across adolescence and young adulthood in this high-risk sample:[64] consistent low drinking, low to high drinking; high to low drinking; and consistent high drinking. This pattern of identified subgroups is consistent with the literature of trajectories of alcohol use across adolescence and young adulthood.[83,84] Group membership was predicted by environmentally-influenced factors (demographics and age of first drink) and genetically-influenced characteristics (sensitivity to alcohol, externalizing behaviors, and personality), that operate together to influence patterns of alcohol use over time. In another study, our team found that after controlling for parent's knowledge of youth's whereabouts and youth's perceived substance use of school peers, close friend substance use was associated with a higher initial heavy drinking status and a greater rate of increase in heavy episodic drinking during the transition between adolescence and young adulthood.[85]

3.4 | Intergenerational transmission of risk

The genetically-informative multigenerational COGA sample, which includes direct assessments alongside information about one's home environment while growing up, can illuminate the mechanisms through which risk for AUD and related disorders is transmitted across generations. For example, consistent with the idea of genetic nurture (a parent's genotype shapes the environment they provide for their children) that others in the field have documented,[86–88] we found that even the risk-increasing alleles for alcohol problems that children did not inherit from their parents (i.e., the nontransmitted alleles) were associated with earlier age at initiation, first intoxication and a greater number of lifetime AUD criteria in offspring.[89] In another example of genetic nurture, we found that parental externalizing polygenic scores (PGS) were associated with adolescent externalizing behavior over and above the effect of offspring's own externalizing polygenic scores, and that these associations were mediated by parental externalizing psychopathology.[90]

COGA has also investigated why some individuals from high-risk family environments are resistant to AUD development. Drawing on the notion of "addiction resistance" proposed by others,[91,92] we took advantage of the high risk family design and deep longitudinal assessments which positioned COGA well for exploring this issue. In one study using COGA data from the prospective study, the only factor found to promote resistance to initiation of alcohol use was high quality of the child's paternal relationship.[93] In contrast, other adolescent social relationship factors, including those involving parenting, peer, and romantic partners, were not associated with resistance to initiating drinking or heavy episodic drinking, or developing AUD.[93] This pattern of largely null effects highlights how little is known regarding potential resistance factors and processes among individuals with high familial and genetic risk for AUD.[91,92]

3.5 | Gene–environment interplay

The depth of phenotypic and environmental information collected on participants makes it possible to study environmental as well as genetic influences on alcohol use outcomes. Importantly, this enables us to study the complex ways in which genetic and environmental risk are intertwined via gene–environment interaction and correlation processes.[57,94,95] It has become clear that genetic influences impact alcohol use outcomes in part by disrupting the family system. For example, genetic risk contributes to hazardous adolescent drinking by adversely impacting parent–child relationships and positive parenting practices,[96] parent–child closeness and parental monitoring,[97] and contributing to lower levels of family support,[98] as has also been found in other samples.[99–102]

Peer influences are also closely intertwined with genetic risk. We have found that individuals with higher externalizing genetic risk[21] show increased affiliation with substance-using peers, in addition to decreased parental monitoring, which then increases future externalizing behavior.[97] Further, parental monitoring of their adolescent offspring along with perceived peer substance use have been found to moderate the association between polygenic scores and externalizing disorders, whereby risky peer groups and reduced parental monitoring exacerbate genetic risk.[103] Conversely, high friend support has been found to attenuate the association between genetic risk, sensation seeking and alcohol use.[98]

Romantic relationships are another important context impacting and affected by alcohol use outcomes. We have found that AUD and other substance use problems are associated with a reduced likelihood of marriage and higher risk of divorce in our COGA families.[104] Further, among those who marry young (average age 21), individuals

with higher genetic risk for alcohol consumption report more heavy episodic drinking, suggesting that early marriage may exacerbate risk for those with higher polygenic load.[105] These findings are in line with other studies that have found environments that are more restrictive tend to reduce genetic influences, whereas environments that promote greater availability or acceptance of substance use increase the importance of genetic effects.[94,106,107]

3.6 | Remission and recovery

A by-product of the high-risk, familial structure of the COGA sample, with its elevated rates of AUD, is an increased number of participants who enter remission from AUD compared with the general population. Thus, the search for the genetics that underpin AUDs has produced a sample that is well-positioned to examine genetic, environmental, and familial influences on remission, an advancement over self-selected samples.[108,109] The genetic and brain function data available from COGA participants can contribute to the evolving field of recovery science, which to date has been based largely on self-selected samples of individuals who consider themselves to be in recovery but which lacks objective measures of recovery and biomarkers.[110]

Of the COGA participants who develop an AUD, a majority have periods of abstinence from alcohol lasting from 3 months to more than 5 years.[111] Individuals with periods of abstinence tend to have more severe histories of AUD, characterized by a younger age at onset, a greater number of symptoms, and co-occurring drug use disorders. They are also more likely to have accessed professional treatment and attended alcoholics anonymous.[111,112] In contrast to abstainers, individuals who no longer have symptoms of AUD but continue drinking at low-risk levels have fewer lifetime AUD symptoms and are less likely to access treatment. Overall, among those who have met criteria for AUD, abstainers in COGA resemble clinical samples in their severity of AUD and high rates of treatment, and low-risk drinkers resemble "natural remitters" from population-based samples in their lower severity and lack of treatment.[113,114]

There appears to be a familial influence on abstinent remission among 1st-degree relatives in COGA. Individuals with AUD who are related to a proband who becomes abstinent are more than 3 times as likely to be abstinent themselves compared with individuals related to a proband with persistent AUD.[115] This suggests that remission might cluster in families, but does not clarify the mechanisms—genetic, environment, or a combination—by which familial influences are transmitted. These findings stand in contrast to a lack of evidence for an association between family history of AUD and probability of remission in a variety of studies.[116–121] The innovation made possible by the high-risk family-based COGA sample is the ability to examine how remission in one family member relates to remission in others, rather than testing AUD-remission associations.

Machine learning models using multiple phenotypes—PGS, neurophysiological information, and behavioral data—have previously been used to identify risk for AUD development.[122–124] When applied to remission and recovery, these models hinted at some improvement in accuracy in predicting remission in COGA participants.[125] Specific patterns in EEG-derived brain network functional connectivity consistently predicted remission across sex and race/ethnic groups, but the addition of a number of PGS related to personality traits, aggression, depression, and alcohol use, along with marital status, medication use, and employment status, further improved prediction, in particular among sex- and race/ethnicity-defined subgroups.[125] This work highlighted the utility of incorporating a wide array of measured indicators, including polygenic, electrophysiological, and psychosocial domains, in the construction of predictive models of remission from AUD.

Data from young adult participants in the Prospective Study have also been used to construct a measure of social recovery capital that reflects the composition of an individual's social network with respect to their drinking habits and support for drinking or abstinence.[126] Social recovery capital influences the development of alcohol problems and recovery from them. While there are other measures of recovery capital,[127–129] none have been collected in samples that include the extensive genetic, physiological, and behavioral measures that are available in COGA data, making this measure valuable for its ability to examine recovery capital in conjunction with biological and psychological factors.

3.7 | Risk prediction and contributions to precision medicine

The promise of genetics is that understanding and characterizing how genetic influences impact alcohol use outcomes will lead to improved prevention, intervention, and treatment.[130] Our efforts to map the pathways by which genetic factors influence alcohol use outcomes via intermediary behaviors and environmental factors have already led to the development of novel intervention approaches aimed at early indicators of risk, such as level of response to alcohol[66,131,132] and externalizing and internalizing characteristics.[133] These interventions target genetically-influenced pathways of risk and can be tailored to an individual's risk profile.

As our gene identification efforts continue to evolve, COGA has initiated efforts to combine genetic information with known environmental risk factors to predict risk for substance use disorders in clinical and population-based samples.[134,135] Although these are not yet ready for integration into clinical practice, we have begun to lay the groundwork for the utilization of genetic risk information by reviewing the current status of genetic feedback for psychiatric conditions,[136] studying public interest in receiving personalized genetic risk scores,[137] and examining how we can return complex risk information in ways that will promote healthy behavior.[138]

It will be critical to carefully consider the benefits and potential harm that could result from the incorporation of genetic risk information into clinical care.[139] To enhance public understanding of the complex ways in which genes influence risk for alcohol use outcomes, COGA investigators have built out resources for the public, available at cogastudy.org. Through videos, graphics, and text, we explain core concepts necessary to understand complex genetics, such as

heritability and genome-wide association studies. Additionally, we have translated key findings from the field into videos and graphical elements in order to make research findings more accessible and engaging to lay audiences. We believe that these tools for enhancing public understanding of complex genetic concepts will help lay the foundation for precision medicine.

4 | SUMMARY AND FUTURE DIRECTIONS

The rich longitudinal family-based data collected by COGA over the last 30 years provides a national resource for the field. With clinical interviews, surveys, environmental information, electrophysiological phenotypes, and genotypic data collected from >17,000 individuals from multi-generational families, COGA enables a wealth of important questions about the onset, developmental course, and consequences of AUD. The genomic data has allowed COGA to make substantive, leading contributions to gene identification for AUD and related substance use and psychiatric conditions (see 4. Genetics). Further, the longitudinal electrophysiological assessments enable study of the neural development that both precedes and follows alcohol use and problems (see 3. Brain function). Integrating these data with our lifespan clinical and environmental assessments has allowed us to characterize the pathways and mechanisms by which risk unfolds and remission takes place, and to translate these findings into personalized prevention and intervention studies (see 1. Overview). The evolving nature of the sample allows us to continually address new questions of interest to the field. As COGA participants age into mid- and later-life, it provides a valuable opportunity to study the consequences of alcohol use across the lifespan. In summary, the COGA study has made substantive contributions to understanding why some individuals are more at risk of developing AUD than others, and as the sample continues to age and evolve, its value only continues to grow.

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CONFLICT OF INTEREST STATEMENT

Dr. Laura Bierut is listed as an inventor on a patent covering the use of certain SNPs in the diagnosis, prognosis, and treatment of addiction.

DATA AVAILABILITY STATEMENT

COGA data are available in dbGaP (phs000125, phs000763, phs000976, phs001208), or via an application to the National Institute on Alcohol Abuse and Alcoholism (https://www.niaaa.nih.gov/research/major-initiatives/collaborative-studies-genetics-alcoholism-coga-study), or a COGA investigator sponsored secondary analysis proposal.

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ENDNOTE

* From 2003 to 2005, a small set of individuals from Waves 1 and 2 was followed up approximately 5 years after their second assessment. This included 200 adults, as well as 272 adolescents and children.

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