Polygenic Prediction of Substance Use Disorders in Clinical and Population Samples

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Abstract

Genome-wide, polygenic risk scores (PRS) have emerged as a useful way to characterize genetic liability using genotypic data. There is growing evidence that PRS may prove useful to identify those at increased risk for developing certain diseases. The current utility of PRS in relation to alcohol use disorders (AUD) remains an open question. Using data from both a population-based sample [the FinnTwin12 (FT12) study] and a high risk sample [the Collaborative Study on the Genetics of Alcoholism (COGA)], we examined the association between PRSs derived from genome-wide association studies (GWASs) of 1) alcohol dependence/alcohol problems, 2) alcohol consumption, and 3) risky behaviors with AUD and other substance use disorder (SUD) symptoms. Individuals in the top 20%, 10%, and 5% of PRSs had increasingly greater odds of having an AUD compared to the lower end of the continuum in both COGA (80th % OR = 1.95; 90th % OR = 2.03; 95th % OR = 2.13) and FT12 (80th % OR = 1.77; 90th % OR = 2.27; 95th % OR = 2.39). Those in the top 5% reported greater levels of licit (alcohol and nicotine) and illicit (cannabis) SUD symptoms. PRSs can predict elevated risk for SUD in independent samples. However, clinical utility of these scores in their current form is modest. As these scores become more predictive of SUD, they may become useful to practitioners. Improvement in predictive ability will likely be dependent on increasing the size of well-phenotyped discovery samples.

Introduction

Alcohol misuse is one of the leading contributors to preventable mortality and morbidity worldwide ¹⁻³. Identifying individuals at heightened risk for developing alcohol related problems remains an important goal of medical practitioners. One important risk factor for alcohol misuse is one's own genetic liability. Twin and family studies indicate that genetic influences on alcohol use disorders (AUD) account for approximately 50% of the variation in the population ⁴. Genome-wide association studies (GWASs) have identified multiple variants associated with AUD ⁵⁻⁷, alcohol consumption ^{7, 8}, and maximum alcohol intake⁹. Using information from these GWASs, we are now able to aggregate risk across the genome by creating genome-wide polygenic scores (PRS) to predict risk in independent samples ^{5, 6, 8, 10}.

Beyond being useful for research purposes, researchers have begun to examine the clinical utility of PRS to predict risk for medical outcomes. PRS for coronary artery disease (CAD), atrial fibrillation (AF), type 2 diabetes (T2D), inflammatory bowel disease (IBS), and breast cancer (BC) have been found to be as predictive of these diseases as well known monogenic mutations ¹¹. Individuals in the top 5% of the PRS distributions had ~3 fold likelihood of having CAD, AF, T2D, IBS, or BC compared to the bottom 95%. For obesity, individuals in the top PRS decile were on average 13 kg heavier than those in the bottom decile ¹². These studies demonstrate the potential for identifying individuals at heightened risk for various medical conditions using PRS. However, the clinical utility of PRSs for AUD in relation to substance use phenotypes remains an open question.

In the current analysis, we tested PRS in two target samples, a population-based sample and a clinically ascertained sample of families deeply affected by AUD, to evaluate the current state of alcohol-related PRS for possible clinical utility. We use several discovery samples from large scale GWAS to create three PRS: a meta-analysis of two GWASs on alcohol-related problems ^{5, 6}, a recent large-scale GWAS of alcohol consumption ⁸, and a GWAS for risky behaviors, including alcohol use ¹³. We chose to

test PRS based on multiple alcohol-related GWAS because multiple lines of evidence indicate alcohol consumption and dependence have only partially shared genetic etiology^{5, 6, 14, 15}. Additionally, we include a PRS for general risk behavior as there is robust evidence that the genetic risk for alcohol and other substance use disorders is shared with other disorders and behaviors related to reduced inhibitory control. This constellation of behaviors is often referred to as the externalizing spectrum¹⁶⁻¹⁸. We test the association of these PRS with a variety of substance use outcomes (including alcohol, nicotine, and other illicit substance use disorders), based on the robust finding that substance use disorders share an underlying genetic architecture, with the majority of the heritability shared across substances¹⁶⁻¹⁸.

Methods

Samples

The FinnTwin12 Study (FT12) is a population-based study of Finnish twins born 1983-1987 identified through Finland's Central Population Registry. A total of 2,705 families (87% of all identified) returned the initial family questionnaire late in the year in which twins reached age 11. Twins were invited to participate in follow-up surveys when they were ages 14, 17, and approximately 22 (during young adulthood). An intensively studies sample was selected as 1035 families, among whom 1854 twins were interviewed at age 14. The interviewed twins were invited as young adults to complete the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)¹⁹ interview (n = 1,347) and provide DNA samples (see Kaprio 2013 for a full description). The current analysis uses data from the young adult wave (mean age = 21.9; range 20-26), which included retrospective lifetime diagnoses.

The Collaborative Study on the Genetics of Alcoholism (COGA) is a sample of high-risk families ascertained through adult probands in treatment for AUD and a smaller set of comparison families from the same communities. In the first 10 years, probands along with all willing first-degree relatives were assessed; recruitment was extended to include additional relatives. Data collection included the SSAGA¹⁹, neurophysiological and neuropsychological protocols, and collection of blood for DNA. In 2004, COGA began a prospective study of adolescents and young adults, targeting assessment of youth aged

12-22 from COGA families where at least one parent had been interviewed. These young participants were re-assessed every two years. The sample is racially/ethnically diverse (60.6% non-Hispanic White, 24.9% Black, 11.1% Hispanic, and 3.4% other). Most (84%) have GWAS data. A full description of the COGA sample is available elsewhere²¹⁻²³. For the present study, we only focused on COGA participants of empirically assigned (as verified from GWAS data) European ancestry ($n = 7,599$) because each of the discovery GWAS samples were primarily of European ancestry. Ancestral mismatch between discovery and target samples can lead to bias in the performance of polygenic scores²⁴.

Measures

Alcohol Use Disorder (AUD). We used SSAGA interviews to construct lifetime symptom counts of DSM-5 AUD²⁵ in each sample. Because individuals in COGA are potentially interviewed multiple times, we used the highest symptom count ever reported by each subject. In FT12, lifetime symptom counts were measured at the young adult interview. In addition to symptom counts, we created AUD thresholds for those who met criteria for mild (2+ symptoms), moderate (4+ symptoms), or severe (6+ symptoms) AUD²⁵ without clustering. In both FT12 and COGA, individuals who had never initiated alcohol use were coded as missing.

Other Substance Use Disorders (SUD). We constructed lifetime symptom counts of cannabis, cocaine, and opioid use disorders based on DSM-5 criteria. We measured nicotine dependence symptoms using the Fagerstrom Test for Nicotine Dependence (FTND), which assesses six symptoms and has values ranging from 0 to 10 in both COGA and FT12. Because many illicit SUDs were not measured or rare in the FT12 data, we limit analyses of illicit SUD to COGA. Like AUD, these symptom counts represent the maximum reported for each respondent across the course of the study. Symptom counts for each substance were limited to those who indicated ever using the corresponding substance. In the case of FTND, this is limited to those who report smoking 100+ cigarettes in their lifetime.

Polygenic Scores (PRS). We created PRS derived from publicly available large-scale GWASs. Information on genotyping and quality control is available in the supplemental information. We used the

well-established process of clumping and thresholding²⁶. Single nucleotide polymorphisms (SNPs) from discovery GWASs were clumped based on linkage disequilibrium (LD) in the 1000 genomes EUR panel using PLINK²⁷, based on an $R^2 = .25$, with a 500 kb window. SNPs were weighted using the negative log of the association p-values. We then created scores based on differing thresholds of GWAS p-values ($p < .0001$, $p < .001$, $p < .01$, $p < .05$, $p < .10$, $p < .20$, $p < .30$, $p < .40$, $p < .50$). We converted PRS to Z-scores for interpretation.

We used four primary discovery GWASs to create three different PRSs. The first was from a recent GWAS of number of alcoholic drinks per week in approximately one million individuals provided by the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (GSCAN)⁸. We obtained GSCAN summary statistics with all Finnish (which included FinnTwin12) and 23andMe (which are not publicly available) cohorts removed (available $N = 534,683$). The PRS for alcohol problems were derived from a meta-analysis of two GWASs: a GWAS on the problem subscale from the Alcohol Use Disorders Identification Test (questions 4-10; AUDIT-P) in 121,604 individuals from the UK Biobank⁶ and the Psychiatric Genomics Consortium's (PGC) GWAS of alcohol dependence ($N = 46,568$)⁵. Both FT12 and COGA were in the initial AD GWAS and we obtained summary statistics with each cohort removed (meta-analysis results available in supplemental info). Finally, we derived a PRS for risky behaviors from a GWAS of the first principal component of four risky behaviors (drinks per week, ever smoking, propensity for driving over the speed limit, and number of sexual partners) from 315,894 individuals in the UK Biobank¹³. While this PRS does include alcohol consumption and smoking, it captures the shared variance between these substance use measures and the other two risky behaviors. These polygenic scores covered the domains of alcohol consumption (GSCAN DPW), alcohol problems (PROB ALC), and general externalizing (RISK PC).

Analytic Strategy

We identified the most predictive PRS across p-value threshold from each of the discovery GWASs in both COGA and FT12 using the change in R^2 above a baseline model with sex, age of last

observation, the first ten ancestral principal components (PCs), genotyping array, and data collection site (these latter two were only included in COGA analyses). We used linear/generalized-linear mixed-effects models with random intercepts to adjust for clustering at the family level and a pseudo- R^2 for mixed models²⁸. After identifying the most predictive PRS, we estimated the joint effect of all PRS on AUD symptoms to examine whether each PRS explained unique variance. We next divided PRSs at various thresholds (80th, 90th, and 95th percentiles) to determine the increase in likelihood of AUD (using symptom severity thresholds of AUD) associated with being in the top end of split relative to the bottom portion of the split. Because increased risk ratios do not necessarily reflect clinical utility²⁹, we also calculated area under the curve (AUC) of the joint model containing all continuous PRS to estimate sensitivity/specificity (in supplemental information). Finally, we compared mean values of other substance use outcomes for the top 5% in each PRS to those in the bottom 95%.

Results

Table 1 presents the descriptive statistics for each of the samples. Each sample has slightly more female than male participants. COGA has a broader age range and higher mean age. As COGA was primarily ascertained for families with multiple AUD members, the mean number of AUD symptoms (mean = 3.44) is significantly higher than in the population-based FT12 sample (mean = 1.63). Additionally, COGA participants had higher mean levels of FTND symptoms (mean = 4.17) than FT12 participants (mean = 2.57). For other SUD symptoms in COGA, though symptom counts for cannabis, cocaine, and opioid use disorders are zero-inflated; there are a substantial number of participants who report non-zero levels of symptoms (see Table 1).

Predictive Power of PRS

Figure 1 presents the ΔR^2 using each PRS to predict AUD symptom count, in each sample, for each discovery GWAS p-value threshold. Within each sample, we chose the most predictive PRS for each

discovery GWAS in COGA (RISK PC = $p < .10$, GSCAN DPW = $p < .05$, PROB ALC = $p < .50$) and FT12 (RISK PC = $p < .10$, GSCAN DPW = $p < .20$, PROB ALC = $p < .50$). In COGA, the PRS for GSCAN DPW was the most predictive of AUD symptoms ($\Delta R^2 = 1.80\%$). The RISK PC PRS was most predictive of AUD symptom count in FT12 ($\Delta R^2 = 2.10\%$). These PRS were followed by PRS for risky behaviors in COGA ($\Delta R^2 = 1.25\%$) and drinks per week in FT12 ($\Delta R^2 = 1.17\%$), and PRS for alcohol problems (COGA = 1.18%; FT12 = 0.40%).

Increase in Risk across the Polygenic Continuum

In order to estimate whether individuals at the extreme end of the PRS distribution were at elevated risk of AUD, we compared risk of AUD between those above and below a given threshold in the distribution. First, we determined whether each of these PRS contributed to AUD symptoms in a model containing all three, jointly. Figure 2 presents the parameter estimates for the independent and conditional effect of each PRS in both COGA and FT12. In the conditional model for COGA, each of the PRSs remains significantly associated with AUD symptoms, though the associations are attenuated (conditional model $\Delta R^2 = 2.65\%$). In FT12, only the PRS for RISK PC remains significant in the joint model (conditional model $\Delta R^2 = 2.45\%$). We averaged the three PRS into one composite PRS score of genetic risk in COGA and used the RISK PC PRS in FT12 to carry forward in the following analyses.

Next, we divided these PRSs at the 80th, 90th, and 95th percentile in each sample and estimated the odds ratio (OR) for AUD in the top portion of the distribution relative to the bottom portion of the distribution (e.g. splitting at the 80th percentile compares the top 20% to the bottom 80%). Table 2 provides the estimates for all of those models. Across each threshold for AUD severity in COGA, we observed a similar pattern where restricting to the more extreme end of the polygenic distribution resulted in greater odds of meeting criteria for AUD. For example, there was increasing risk for a severe AUD when dividing 80th percentile (OR = 1.948; 95% CI = 1.665, 2.278), 90th percentile (OR = 2.027; 95% CI = 1.655, 2.482), and 95th percentile (OR = 2.126; 95% CI = 1.617, 2.796). In FT12, there was a similar pattern for mild and severe AUD, but not moderate AUD. However, given the small number of cases in

the extreme end for severe AUD, these estimates should be interpreted cautiously. Finally, we assessed the sensitivity/specificity of these PRS by calculating the AUC. AUC from the full model (including both continuous PRS and covariates) for each level of AUD severity ranged from 0.67 to 0.74 in COGA and from 0.65 to 0.75 in FT12. Comparing the AUC for the models with and without PRSs, including the PRS only increased the AUC slightly (see supplemental information).

Examining the Substance Use Phenome of the Extreme End of the Polygenic Risk Continuum

We compared the likelihood of substance-related outcomes in individuals in the top 5% of each of the PRS in COGA and FT12 (adjusted for covariates). Figure 3 presents the mean lifetime symptoms endorsed for a variety of substance use disorders (alcohol, cannabis, cocaine, nicotine, and opioid) for individuals in the top 5% for each PRS relative to the bottom 95% of each PRS. In COGA, individuals in the top 5% of the PROB ALC, RISK PC, and/or GSCAN DPW PRS had significantly higher levels of alcohol (0.25 – 0.33 SD) and nicotine symptoms (0.13 – 0.18 SD) than those in the bottom 95% of the PRS distribution. Those in the top 5% of the RISK PC PRS also endorsed a higher number of cannabis use disorder symptoms (0.14 SD). In FT12, those in the top 5% did not differ significantly for AUD or FTND symptoms.

Overall, individuals in the top 5% of any PRS report greater levels of any substance, though being in the top 5% of the RISK PC PRS is associated with the most other substances. These PRS are modestly correlated with one another in both COGA ($r_{RISK\ PC*PROB\ ALC} = .30$; $r_{GSCAN\ DPW*RISK\ PC} = .37$; $r_{GSCAN\ DPW*PROB\ ALC} = .32$) and FT12 ($r_{RISK\ PC*PROB\ ALC} = .20$; $r_{GSCAN\ DPW*RISK\ PC} = .45$; $r_{GSCAN\ DPW*PROB\ ALC} = .27$). These PRS each seem to capture unique information related to the genetics of substance use problems (and other risky behaviors).

Discussion

Researchers have begun to evaluate the clinical utility of PRS for a variety of medical phenotypes^{11, 12}. In this analysis, we examined the current utility of several PRSs for identifying those at risk for a

variety of SUDs, with a focus on AUD in both a clinically ascertained and population based sample. We were interested in 1) which scores based on available GWASs provide the best prediction for alcohol use disorder and whether these scores predicted unique variance in AUD in a joint model; 2) what the risk of AUD was for those at the upper end of the risk continuum compared to the bottom; and 3) the levels of substance use disorder symptoms for individuals at the top 5% of the polygenic score continuum compared to remaining 95%.

In terms of which polygenic scores were the most predictive, we considered three scores: one based on problematic alcohol use (PROB ALC), one based on alcohol consumption (GSCAN DPW), and one based on general risky behaviors (RISK PC), as twin and family studies have shown alcohol and other risk behaviors to be genetically correlated traits^{6, 14-18}. In the population sample (FT12), the RISK PC PRS was the most predictive. These results support the idea that focusing on the shared genetic etiology towards risk taking, sometimes referred to as externalizing¹⁶⁻¹⁸, may prove useful for identifying those at risk for SUD³⁰. In our more clinically based (COGA) sample, the PRS for alcohol consumption (GSCAN DPW) explained the largest portion of the variance. When we included all of the PRS in one model, all three PRS were associated with AUD symptoms in COGA while only the RISK PC PRS was associated with AUD symptoms in FT12. We ran a series of sensitivity analyses to test whether differences across the samples reflected age differences rather than differences in ascertainment. Restricting COGA to participants under 30 did not fundamentally change the results.

When we divided the PRS at different thresholds, the odds of having an AUD steadily increased from the 80% threshold to the 95% threshold in both COGA and FT12. However, even though the point estimates steadily increased, the confidence intervals around these estimates were relatively large and they did not differ significantly. Additionally, there were only a small number of individuals in the severe category in FT12 and we urge caution in interpreting these estimates. Supplemental analyses evaluating the AUC for each continuous PRS in a joint model revealed the combined effect of all three PRSs only marginally improved the AUC over models with just covariates. Finally, the top 5% of the continuum for

each PRS reported elevated rates of other SUD symptoms (cannabis, cocaine, and nicotine use disorders) compared to the bottom 95%. The RISK PC PRS was the most predictive of these higher mean levels of SUD symptoms, suggesting that risk for externalizing may be particularly useful in identifying individuals at risk for SUDs.

These initial findings suggest the use of genetic data may eventually have utility in a clinical setting for SUDs, but not in their current form. Being able to identify those at heightened risk for SUDs may allow for more targeted early intervention and prevention. Before clinical utility is possible, larger discovery GWAS across substance use phenotypes with PRS that explain greater portions of the variance will be necessary. As GWAS sample sizes for SUDs increase, we will likely see improved prediction³¹. Additionally, using multivariate techniques to model the shared genetic architecture across existing SUD GWAS to include both aspects of externalizing and internalizing (e.g. depression, anxiety) may also improve prediction^{32, 33}. Inclusion of genetic data in a clinical setting will also require that psychiatrists and clinicians receive greater training in genetics and/or that they partner with genetic counselors, so they are both better able to understand what increased genetic risk means and be able convey that information accurately to their patients^{34, 35}. In addition to clinical utility, we must ensure that regulations and protections surrounding the use of genetic information in clinical settings can adequately protect the rights of individuals who are identified to be “at risk.”

This research has several important limitations. First, all analyses were limited to individuals of European ancestry because the discovery GWASs available were conducted in individuals of primarily European ancestry. It will be important to ascertain sizable samples of subjects with non-European ancestries to properly estimate the predictive utility of PRS in non-European samples. This is especially important for racial-ethnic minorities so that health disparities are not further perpetuated³⁶. Second, our use of lifetime diagnoses may obscure the impact of changing genetic influences on the development of AUD across the life course^{37, 38}. Future work should draw on longitudinal data to examine the ways in which the predictive utility of PRS changes with the age of the target sample. Finally, these analyses

examined the marginal influence of PRS, independent of environment. Processes of gene-environment interaction (GxE) are well documented in alcohol misuse using twin and family data³⁹⁻⁴². Incorporating environmental information along with PRS in a methodologically rigorous manner will be an important next step in developing clinically predictive algorithms.

Genome-wide polygenic scores are beginning to have utility in identifying individuals at risk of certain diseases, especially those related to well defined physical health conditions, such as cardiovascular disease^{11, 12}. We examined the current state of PRS for predicting substance use, with a focus on AUD. Each of the PRS analyzed here predicted AUD. However, the overall maximum variance explained was still small (~2%). Individuals at the top of the PRS continuum had elevated rates of multiple substance use problems, but these differences across the PRS continuum are unlikely to be of broad clinical use in their current state. As GWAS discovery samples become larger and we are better able to model the complex relationship between genotype and phenotype, polygenic scores may eventually be useful in a clinical setting.

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Conflicts of Interest

The authors have no conflicts of interest to report.

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Table 1: Descriptive Statistics for FT12 and COGA samples.

Sample	N	Mean/%	Median	% 0	SD	Min	Max
COGA	Female	7,599	52.84%	-	-	-	-
	Age	7,599	36.94	-	14.77	12	91
	DSM-5 AUD symptoms	7,300	3.44	2	28.79%	0	11
	DSM-5 CUD symptoms	5,051	2.37	1	48.19%	0	11
	DSM-5 CoUD symptoms	2,404	3.18	0	50.17%	0	11
	DSM-5 OUD symptoms	1,663	2.05	0	62.96%	0	11
	FTND count	3,701	4.12	4	14.02%	0	10
FT12	Female	1,251	54.40%	-	-	-	-
	Age	1,247	21.94	-	0.77	21	26
	DSM-5 AUD symptoms	1,215	1.63	1	34.57%	0	11
	FTND count	631	2.57	2	21.55%	0	10

AUD = Alcohol Use Disorder; CUD = Cannabis Use Disorder; CoUD = Cocaine Use Disorder; OUD = Opioid Use Disorder;

FTND = Fagerstrom Test for Nicotine Dependence (limited to those who report ever smoking 100 cigarettes)

The N reflects those who report lifetime ever use of that substance. All symptoms counts limited to individuals who had initiated use of that substance. The % 0 represents the percentage of participants who have initiated use and have no reported symptoms.

Table 2: Odds Ratios for Those at Extreme End of the PRS Continuum

<u>Sample</u>	<u>Phenotype</u>	<u>Prevalence</u>	<u>Split</u>	<u>N Cases</u>	<u>OR</u>	<u>95 % CI Low</u>	<u>95 % CI High</u>
COGA	Mild AUD	57.06%	80%	999	1.94	1.68	2.24
	Mild AUD	57.06%	90%	522	1.97	1.62	2.39
	Mild AUD	57.06%	95%	276	2.23	1.69	2.95
COGA	Moderate AUD	37.44%	80%	743	1.97	1.71	2.27
	Moderate AUD	37.44%	90%	401	2.04	1.69	2.46
	Moderate AUD	37.44%	95%	218	2.25	1.73	2.92
COGA	Severe AUD	25.89%	80%	547	1.95	1.67	2.28
	Severe AUD	25.89%	90%	300	2.03	1.66	2.48
	Severe AUD	25.89%	95%	165	2.13	1.62	2.80
FT12	Mild AUD	41.98%	80%	122	1.77	1.22	2.56
	Mild AUD	41.98%	90%	68	2.27	1.39	3.72
	Mild AUD	41.98%	95%	36	2.39	1.21	4.72
FT12	Moderate AUD	13.91%	80%	45	1.80	1.09	2.98
	Moderate AUD	13.91%	90%	22	1.52	0.79	2.92
	Moderate AUD	13.91%	95%	12	1.59	0.66	3.80
FT12	Severe AUD	3.79%	80%	15	2.16	1.06	4.40
	Severe AUD	3.79%	90%	9	2.45	1.05	5.71
	Severe AUD	3.79%	95%	6	3.24	1.11	9.53

All models control for sex, age at last interview, and first 10 principal components. Models for COGA also included data collection site and genotyping array. N Cases = number of individuals who meet criteria for a given level of AUD and are in the top portion of the split.

Figure Captions:

Figure 1: Predictive Power of PRS across Samples

Predictive power of PRS measured using pseudo- R^2 for linear mixed effects models²⁸. Bars represent change in variance explained over models with age, sex, and first 10 ancestral principal components, genotyping array, and data collection site (only COGA for the latter two). Most predictive score outlined in blue. * $p < .05$, corrected for FDR of 5%

Figure 2: Parameter Estimates for PRS in Independent and Joint Models

Parameter estimates from linear mixed models for AUD symptoms regressed on GSCAN DPW, PROB ALC, and RISK PC PRS in COGA and FT12. Independent = model with only corresponding PRS. Conditional = model with all PRS included. Adjusted for age, sex, first 10 ancestral principal components, genotyping array, and data collection site (only COGA for the latter two).

Figure 3: Top 5% of PRS Continuum

Mean levels of SUD symptoms for alcohol, cannabis, cocaine, nicotine, and opioid use disorders for top 5% of each PRS compared to the bottom 50%. Black bar represents mean of bottom 50%. 95% confidence intervals estimated using 1000 bootstrap resampling.

Figure 1

Figure 2

Figure 3