Specific Aims

This project plans for a new method to help clinicians screen individuals at high risk for substance abuse disorders, in general, and injection drug use, in particular. Currently, drug abusers are identified by either self-report or by clinician-initiated screening. Neither method has led to widespread detection of drug users, as evidenced by a large percent (89.1%) of current drug users not being referred to or receiving treatment [1]. We plan a two-step screening. In the first step, the computer, using existing data in the medical record, will identify likely drug users; in the second step the clinician further screens his/her patients by discussing the issue with them. Because the proposed method works entirely within an existing electronic medical record (no data are reported outside the record) there are minimal privacy or security concerns. Furthermore, because the information is already available, no new data are collected. Patients are not surveyed or asked to describe their drug use. They are screened automatically without either the patient or the clinician initiating the process. Therefore, we anticipate that the proposed method could lead to large increase in screening within primary care settings.

This project tests the claim that it is possible to identify potential drug users from data within the medical record. The project's specific aims are: (1) Construct a set of variables, or composite variables, which are theoretically linked to various drugs, including injectable drugs, such as heroin, cocaine, and methamphetamine. (2) Construct different predictive models to anticipate drug abuse, in general, and abuse of specific injectable substances, in particular. (3) Report the sensitivity and specificity of the predictive models and compare these to published data on substance abuse screening. (4) Report how many days sooner than the current clinical practice will the proposed approach identify potential drug abusers.

To accomplish these aims, the study will use data available through Veterans Affairs Informatics and Computing Infrastructure (VINCI). Through VINCI, we have access to the medical records of 8.7 million veterans in 152 medical centers, including 285 million orders, 158 million procedures, 468 million lab tests, 201 million vital signs (including patient-reported pain levels), and 120 million consults. Our analysis of these data indicate that 870,000 veterans will be identified who have, at some point in their lifetime, been diagnosed or treated for substance abuse disorders. These data suggest that there are sufficient numbers of cases to construct the proposed predictive models.

If the project succeeds, additional studies will be undertaken to examine clinical efficacy of screening based on medical history. Such screening could have many benefits. It may effectively engage primary care providers, a group that has traditionally not screened their patients for substance abuse, in the screening process. Thus it can expand current approaches to screening potential drug users. Furthermore, the screening may be an effective method of preventing diseases related to injected-drugs. In particular, it might provide a strategy for screening for Hepatitis C Virus, a disease with large impact on cost of care and the system for delivery of care. The proposed method of screening may also improve retention in treatment programs as it changes patients' perception about the link between their physical health and their drug use. They may become more aware of health consequences of drug use and therefore may be more likely to seek and stay in substance abuse treatment. Finally, the proposed screening may affect availability, utilization, effectiveness, cost, and quality of prevention efforts by focusing these effort on patients who are high risk for engaging in drug use.

a. Significance

This proposal is in response to the National Institute on Drug Abuse (NIDA) R21 grant application for exploratory/developmental health services research. It is an exploratory/development proposal because it is gathering evidence for a subsequent proposal to test a new method for screening for drug abuse. It is a health services research proposal because it is a hypothesis-driven, theory-based, data analytic retrospective study of existing medical records. As per the RFP, this study develops and validates a new approach for conducting prevention services.

In United States, the rate of drug use is relatively high: each year more than 425,000 people in the US inject drugs [2]. This study focusses on veterans; where the rate of drug abuse among veterans is higher than the general population; 1 in 12 veterans are diagnosed with drug abuse [3].

There has been significant progress in improving screening and referral of patients in primary care settings. Nevertheless, a large percent of drug users are not screened and not referred to treatment programs. The 2013 National Survey on Drug Use and Health reports that 89.1% of current drug users are not in treatment [4]. Screening and referral could reduce the number of patients who are not in treatment. Even in prison, 80%-85% of drug user continue untreated [5,6].

The failure to treat drug abuse has many consequences including continued drug dependence [7,8,9], involvement in criminal justice system [10], and mortality from overdose or from diseases associated with injection drug use [11]. Of particular concern are contributions of injectable drugs to spread of diseases such as Hepatitis C Virus, HCV, or Human Immunosuppressant Virus, HIV [12,13,14,15,16,17,18]. For example, within 5 years from start of injection drug use, more than 90% of drug users will be infected with HCV [19]. It is expensive to treat patients with HCV. The cost of treatment can reach about $100,000 per patient per course of medication, some patients needing multiple courses of medications [20,21].

Prevalence of drug use, mortality from over dose of drugs, blood borne infections as a consequence of injection drug use and the high cost of treatment of these infections have raised the importance of early identification of injection drug use.

b. Innovation

This project will improve scientific knowledge, technical capability and eventually clinical practice in screening for substance abuse, in general, and injection drug use, in particular. Early identification of drug use is difficult. To date, two types of screening have been carried out in primary care settings. In the first method, the patient is asked about their drug use, usually through a questionnaire and usually prior to the clinical visit. Data show that, if surveyed, patients will report their injection drug use [22]. Clinicians fail to survey patients in part because the survey process is time consuming and difficult to maintain over time. Furthermore, patients in denial may not report their drug use accurately. Or, they may do so late in their course of substance abuse dependency and after many consequences of the drug use have manifested themselves. For example, nearly 50% of patients with injection drug use are not identified until they report HCV [23].

A second strategy is to train primary care providers to ask their patients. These efforts are generally achieved through a Screening, Brief Intervention, Referral, and Treatment (SBIRT) process. Among primary care providers (including psychiatrists who are more diligent than general practitioners in administration of the screens), 68% reported that they regularly ask new

outpatients about drug use and 55% reported that they routinely offer formal treatment referral [24]. A sizeable group of primary care providers do not screen for substance abuse, especially injection drug use. Primary care providers who do not screen give various reasons for failing to do so including lack of confidence in obtaining the history of drug use, pessimism about the effectiveness of therapy, concern that patients will object, and time constraints.

This proposal introduces a third method of screening for drug use, in general, and injection drug use, in particular. Within the primary care setting, we plan to use the existing medical history of the patient to predict the possibility of drug use. The approach shifts current paradigms for screening to a solution that addresses and resolves several concerns of primary care providers. In particular, it reduces the time burden as providers do not need to screen everyone. They can focus on patients whose medical histories indicate increased risk of injection drug use. The proposed plan also addresses primary care providers' concern that patients are not truthful about their drug use. Information about drug use is not asked from the patient but inferred from their medical history.

To build a predictive model for drug use, it is important to select a set of variables that increase the risk of drug use. The traditional focus of variables for predicting risk of drug use has been on socio-economic variables, which while predictive may also increase the negative stigma associated with drug use and may make the subsequent conversation between the clinician and the patient more difficult [25]. In contrast, in the proposed screening, we use data on diagnoses and medical treatment to anticipate the possibility of drug use. The primary care provider can focus the discussion on the connection of physical health with drug use and avoid confrontation about drug use itself. Both primary care providers and their patients may find these discussions easier to initiate.

Despite the advantages of relying on medical history to screen for injection drug use, a key issue remains. The sensitivity and specificity of these screening procedures are not known. The current exploratory/developmental proposal is organized to answer concerns about accuracy of using medical history in screening for drug use.

c. Approach

Source of Data: The study will use data available through VA Informatics and Computing Infrastructure (VINCI). VINCI provides a secure environment for both access to the data and analysis of the data. Within this environment, we have access to Standard Query Language and several servers and databases. We also have access to software for analysis of data such as R, Stata, SAS, and others. The data includes near complete longitudinal medical records of 8.7 million veterans. Therefore, it is possible to use early medical history to predict later discovery of drug use.

Measurement of Dependent Variable: There are several dependent variables in this study. These include hospitalization for substance abuse, heroin use, methamphetamine use, and crack/cocaine use. For each dependent variable a separate predictive model will be constructed. These dependent variables can be measured through three different methods. The first method will rely on presence of International Classification of Disease (ICD) code. The ICD codes for drug use include the following: alcohol-induced mental disorders (291-292), alcohol dependence syndrome (303.00-303.02, 303.90-303.92), opioid type dependence (304.00-304.02), sedative, hypnotic or anxiolytic dependence (304.10-304.12), cocaine dependence (304.20-304.22), cannabis dependence (304.30-304.32), amphetamine and other psychostimulant dependence (304.40-304.42, 304.50-304.52), Other specified drug dependence (304.60-304.62),

combinations of opioid type drug with any other drug dependence (304.70-304.72), combinations of drug dependence excluding opioid type drug (304.80-304.82), unspecified drug dependence (304.90-304.92).

The second method will focus on treatment received. Treatment can be inferred from Current Procedural Terminology (CPT) mental health procedure codes 90801-90802, 90804-90815, 90826-90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870-90871, 90875-90876, 99201-99205, 99211-99215, 99217-99220, 99241-99245, 99341-99345, 99347-99350, 99384-99387, 99394-99397, 99401-99404, 99420. Within VA data warehouse, treatment can also be inferred from location of the service, referred to as Clinic Stop codes. These include: outpatient substance use diagnosis individual Session (513), substance use diagnosis home visit (514), substance use diagnosis and PTSD (519), Intensive substance use diagnosis treatment (547), substance use diagnosis group session (560), substance use diagnosis telephone call (545), inpatient substance use diagnosis residential rehabilitation (27), substance use diagnosis domiciliary (86), and high intensity substance use treatment program (74).

The third method relies on diagnoses primarily caused by substance abuse. For example, injection drug use leads to Hepatitis C Virus. These may be identified by diagnoses codes such as Acute Hepatitis C with Hepatic Coma (070.41), Chronic Hepatitis C with Hepatic Coma (070.44), Acute Hepatitis C without Mention of Hepatic Coma (070.51), Chronic Hepatitis C without Hepatic Coma (070.54), Unspecified Viral Hepatitis C without Hepatic Coma (070.70), and Unspecified Viral Hepatitis C with Hepatic Coma (070.71).

Within the VA medical record, providers indicate the type of drug involved (heroin, crack/cocaine, etc.). These will be used to classify the drug of choice for the patient. A separate issue is to understand the preferred mode of transmission. To identify whether the patient is an injection drug user, we will rely on (1) automatic analysis of text of notes of providers among patients classified as substance abusers, (2) reported route of administration (oral, nasal, smoking, non-intravenous drug use or injected intravenous drugs) in the Addiction Severity assessment done on most patients receiving substance abuse treatment, and (3) common modes of using certain drugs such as heroin. We acknowledge that these methods of identifying injection drug use may be contradictory and will design a protocol for how the conflict among these indicators will be resolved.

Measurement of Independent Variables: Since we have access to a longitudinal medical record, we can identify patients who are eventually diagnosed as drug users. The study will report if predictive modeling could identify these patients before the first date of diagnosis of or treatment of substance abuse disorders. The medical history prior to these dates will be used to predict drug use.

The constructs that can be used to predict drug use include the following: First, we will use a set of variables that have limited theoretical linkage to injection drug use but have been shown to be associated with it. These include unemployment and homelessness [26,27,28,29], school dropout [30], gender, race, and age [31]. These variables, while used by the predictive model, are of limited value in the communication between the clinician and the patient as they do not describe a link between physical health and substance abuse.

Second, we will look at some variables that indicate progress from gateway drugs to dependency. These variables may include early-onset substance abuse [32] as measured by non-dependent drug use (ICD codes 305.00-305.02, 305.20-305.22, 305.30-305.32, 305.40-305.42, 305.50-305.52, 305.60-305.62, 305.70-305.72, 305.80-305.82, 305.90-305.92), history of alcohol use as indicated by diagnoses codes or alcoholic gastritis (535.3), alcoholic fatty liver

(571.0), acute alcoholic hepatitis (571.1) alcoholic cirrhosis of liver (571.2), alcoholic liver damage (571.3). Of particular interest is role of prescribed pain medications, a number of investigators have pointed out how prescription pain medications could lead to subsequent drug abuse [33]. We will use length, dose, type of prescribed pain medication and days since the medication was stopped as risk factors for subsequent substance use disorder.

Third, we will look at a set of variables that focus on availability of drugs in the environment by examining the zip code of the patients' home address. Drug users' social and environmental contexts, or "site ecology", contribute to their risk for transitioning to injection drug use [34]. Given the large data set we are analyzing, the patients' home zip code may indicate the site ecology; it may encompass peer support for or pressure to inject [35] and geographic distance from other injectors [36] and access to specific drug markets [37,38,39].

Fourth, drug use and mental illness often co-occur. The association between depression and substance abuse is well established [40]. In addition, a wide range of mental health diseases co-occur with substance abuse [41,42,43]; and 50 to 75 percent of clients in substance abuse treatment have co-occurring mental disorders [44]. These data suggest that presence of certain mental disorders (anxiety disorders, disruptive behavior, mood disorders, oppositional defiant disorder, conduct disorder, attention-deficit disorder, attention-deficit hyperactivity disorder, generalized anxiety disorder, major depressive disorder, and dysthymia to name a few) in the patients' medical history could increase the risk of substance abuse [45].To date several theories have been suggested for why substance abuse and mental illness may co-occur [46]: (1) social isolation that accompanies mental illness may lead to drug use, (2) psychiatric disorders may create biological vulnerability and sensitivity to small amounts of alcohol and drugs, (3) mentally ill patients may self-medicate with available substances to reduce pain and suffering associated with poorly treated diagnoses, or (4) overlapping environmental triggers may lead to dual diagnoses.

Fifth, drug use, especially injection drug use, weakens the body's immune system and this may manifest itself in repeated infections [47,48]. Injection drug users are more likely to have clostridial infections [49], recurrent methicillin-resistant Staphylococcus aureus skin and soft-tissue infections [50]. Risky practices associated with drug use have been associated with spread of infectious diseases. For example, sex and exchange of needle with infected patients may lead to transmission of HIV, Hepatitis B or Hepatitis C [51] as well as sexual infections [52].Repeated drug use may also lead to frequent use of emergency room and longer than normal hospital stays [53].

Sixth, persistent use of drugs have a direct effect on various body systems, especially the skin, heart and the kidney. Injection drug use can cause localized and systemic effects, including granulomata at the site of injection and in the lungs, including eventually systemic amyloidosis [54]. Drug abuse may affect kidney because they are nephrotoxic or may involve other mechanisms that affect kidney operations [55]. Crack cocaine leads to changes in the pulmonary system, including carbon pigmented intra-alveolar macrophages, emphysema and pulmonary arterial changes; opiates/opioids can lead to pneumonitis and hypoxic brain damage due to their respiratory depressant effects [56]. Cocaine and amphetamines have the strongest association with stroke [57]. Injecting heroin can lead to heroin-associated nephropathy [58]. Heroin can cause arrhythmias and non-cardiac pulmonary edema, and reduced cardiac output [59]. All of these studies suggest patterns of diseases from which one can infer potential drug use.

Preliminary Studies: Preliminary studies are not needed for R21 proposals but we have conducted some preliminary analysis that can inform this study. A doctoral student, Reginald

Myron Bruno, working under supervision of the PI, examined the extent to which substance abuse diagnoses could be predicted from age and gender. The data were obtained from Agency for Health Care Research and Quality program on Healthcare Cost and Utilization Project. This Agency provides claims data obtained from different States. The study focused on longitudinal claims data from State of Florida. Presence of substance abuse diagnosis was regressed on gender and age (Table 1). Being male increased odds of substance abuse and older age reduced these odds.

Table 1: Presence of Substance Abuse Diagnosis Regressed on Gender & Age

Source	*B*	*SE*	$\chi^2(1)$	*p*	Odds ratio
Gender	0.16	0.06	7.34	.007	1.174
Age	–0.03	0.00	249.06	< .001	0.973

Methods of Constructing Predictive Models: Separate models will be constructed for different types of substance abuse. Because of the massive size of the data and the large number of independent variables, the traditional Logistic regression or regularized Logistic regression is not practical in our situation. Instead, we will use semi-Markov mathematical model to describe the transition from patient's current state to later substance abuse [60]. Even though we use other information besides diagnoses, for simplicity we describe the inner workings of this approach as if we were using only diagnoses. In this approach, patients are drug free for t_{ij} days, where "i" indicates current physical diagnosis and "j" indicates a later substance abuse diagnosis. After this period, change from state "i" to state "j" occurs with probability p_{ij}. The time before diagnosis of drug use, t_{ij}, are random variables, read from the data, each governed by a probability function $f_{ij}(t)$, called the drug free probability function. The probability of transition from current diagnosis "i" to later substance abuse diagnosis "j" in period "t", $\pi_{ij}(t)$, is calculated as:

$$\pi_{ij}(t) = p_{ij}\, f_{ij}(t)$$

The number of days a patient with diagnosis "i" will remain drug free is calculated as:

$$\mu_i = \sum_j p_{ij}\, t_{ij}$$

Methods of Reporting Accuracy of Predictive Models: The Receiver Operating Curves report both the sensitivity and specificity of the predictions of semi-Markov model. We will report 5-fold [91] cross validated Area under Receiver Operating Curve (AROC). In addition, we will report the number of days that the predictive model could identify the drug user sooner than the current clinical practice.

Methods of Explaining Reasoning behind the Predictive Models: To help patients and clinicians see the reasoning behind the semi-Markov model predictions, for each patient we plan to produce both the risk of substance abuse, number of days till hospitalization for substance abuse and the reasons for the predictions. The reason for the predictions will list the independent variables (e.g. a specific physical health diagnosis) in order of their influence on the prediction model. In this manner, we hope to attract attention away from a specific number and focus attention on why the model has identified the individual to be at increased risk.

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