Addiction Breakout Session

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Overview

Tobacco smoke, whether inhaled directly or as secondhand smoke, contains more than 4,000 different compounds, many of which are proven carcinogens (1). Substantial evidence indicates that nicotine plays a pivotal role in mediating the addictive nature of tobacco dependence in humans (2). Most research examining nicotine dependence has focused on males, since initially, a larger portion of the male population smoked (over 50 percent in the mid-1960s) (3). However, by 2001, the gender gap between adult smokers had narrowed such that 24 percent of women smoked, compared with 29 percent of men (4). In light of the overwhelming evidence of the negative health consequences related to smoking, women are still at risk, and an urgent need exists to understand why women become and remain nicotine dependent.

We need to understand the different stages of the nicotine addiction process in women, including initiation, maintenance, withdrawal, and relapse. Women differ from men in their biological responses to nicotine, progression to nicotine dependence, and patterns of intake and have higher rates of relapse and a greater risk of smoking-related health problems (5-12). Thus, the Addiction Breakout Group identified specific areas of needed research, including understanding sex differences in neuroanatomy; the biology of nicotine receptors, particularly in the brain; and the genetic basis of nicotine dependence. Of particular importance was the overwhelming gap in knowledge of the effects of nicotine on the menstrual cycle and on such hormones as estrogen and progesterone.

Other female-related issues regarding nicotine addition have not been studied. For example, the effect of oral contraceptives on smoking rates, relapse, and craving is not understood. Also, very little is known about the effects of menopause and/or hormone replacement therapy on desire for smoking, smoking rates, and relapse. The menstrual cycle, puberty, pregnancy, and menopause should be primary foci of research on nicotine dependence and smoking to determine, for example, whether nicotine has a disruptive effect on hormones and whether hormones can affect craving and rates of relapse in women.

In addition, since a large proportion of smokers report being depressed (13-17), studies are needed to examine whether any gender differences exist in the relationship between smoking and depression relative to other psychological factors, including anger and personality traits. Studies of smoking and depression and the development of interventions must take into account the multiple demands and unique stressors in the daily lives of women. Examining all aspects of nicotine addiction and understanding gender differences will help create prevention and cessation programs that are tailored to the needs of women.

Also discussed was the need to address nicotine dependence using animal models. Animal models complement clinical studies and provide an arena in which various environmental and genetic factors can be teased apart and tested in a controlled setting (18). The self-administration paradigm has been used to examine the reinforcing effects of nicotine in male animals (19-22). Only a handful of studies has examined the reward effects of nicotine in female animals, and very little is known about the effects of the menstrual cycle and gonadal hormones such as estrogen and progesterone on nicotine addiction.

Recommendations

Research

*1. Understand sex differences in the mechanisms and processes involved in all phases of nicotine use and addiction.

The group gave this recommendation the highest priority because of the many gaps in our understanding of sex differences in nicotine use and addiction. An examination is needed of the environmental, behavioral, genetic, molecular, cellular, neurobiological, and hormonal sources of variation and their interactions in animals and humans during all phases of nicotine addiction, including initiation, maintenance, withdrawal, and relapse. This recommendation encompasses a vast array of preclinical and clinical research.

Preclinical. Animal models make it possible to examine the reinforcing effects of nicotine that are highly relevant to tobacco dependence in humans and that cannot easily be studied in human subjects—mainly for ethical reasons. In animals, potential behavioral effects of pharmacological agents can be more fully characterized. Furthermore, these animal models allow the investigation of the basic underlying behavioral and neurochemical mechanisms that are relevant to nicotine addiction (for reviews, see 5, 18).

Behavioral studies of rodents suggest that females are more sensitive than males to repeated nicotine exposure, as demonstrated by a more rapid onset of nicotine-induced behaviors (23). The reinforcing effects of nicotine have been examined in female rats. In one study, female rats self-administered nicotine and, when compared to males, showed a higher motivation to obtain nicotine because they acquired self-administration capabilities of low doses of nicotine, whereas male rodents did not (24). In this study, different stages of the estrous cycle did not affect nicotine self-administration. However, since rodents have drastically shortened cycles (4-5 days in length), heterogeneity within each cycle stage (i.e., animals reaching a stage of the cycle at different times) may have limited the ability of the authors to find a relationship between the estrous cycle and the reinforcing effects of nicotine.

Research should be conducted in animals that have pharmacologically synchronized estrous cycles to reduce variability in hormonal levels, thereby providing a more accurate picture of whether hormone levels can affect nicotine intake. This procedure has been used to establish a relationship between the estrous cycle and ethanol self-administration in rats. In females whose estrous cycles were synchronized, ethanol was found to be more reinforcing during the diestrus phase than during the estrus and proestrus phases (25). The effects of hormones have been examined in a more stable condition; specifically, self-administration of heroin and cocaine has been examined in ovariectomized female animals. When ovariectomized rats were treated with estradiol benzoate, these animals initiated heroin self-administration sooner and consumed greater amounts than ovariectomized rats that did not receive estrogen replacement (26). Animals that were ovariectomized exhibited less response for cocaine, and compared to the intact animals, fewer of these animals acquired cocaine self-administration (27). However, nicotine self-administration has not been examined in ovariectomized female rats.

As illustrated above, the self-administration paradigm can provide a valid measure of the reinforcing effects of nicotine in females and can be further extended to examine the potential role of gene/environment interactions for nicotine addiction. A recent study has shown that male mice lacking a β2 subunit of the high-affinity neuronal nicotinic acetylcholine receptor (nAChR) self-administer nicotine at much lower levels than wild-type mice following cocaine self-administration (28). *Thus, the effects of mutations in nAChR as well as mutations in other receptor systems, such as the dopaminergic system (an important neurotransmitter system that is linked to the addiction process), can be further examined in relation to the reinforcing effects of nicotine in female knockout mice*.

In addition to genetic issues, animal models can be used to examine the effects of environmental factors, such as stressors. Social stressors have been established in animals, and the effect of one such stressor, social defeat stress, further sensitizes cocaine-induced hyperlocomotion, activates cocaine-induced self-administration, and increases the rate of acquisition of cocaine self-administration in male animals (29-31). *The effect of social stressors has yet to be determined in female and nicotine-dependent animals*. Further down the line, the development of animal models of gene/environment interactions in nicotine addiction will provide clues as to whether the interactions can be demonstrated (using the stress and nicotine self-administration model in wild-type and transgenic mice), the magnitude of their effect, the conditions under which the interactions vary in strength, and whether any sex differences exist.

* Recommendations with an asterisk are those identified by the breakout groups as their top three recommendations.

The Addiction Breakout Group also suggested that these animal models be extended to examine sex differences in the neurobiological basis of nicotine addiction. For example, previous research has shown that sex differences exist in dopaminergic function in the brain (32). Finally, different stages of addiction, including acquisition, maintenance, extinction, and relapse, can be studied in female animals using the self-administration model, as has been done in male rodents (33, 34). In adolescence, animal research is needed on all phases of the addiction process, and thus, the development of adolescent nicotine addiction should be examined as well as differences between the sexes. As shown above, much more research is required to understand nicotine addiction in female animals.

Clinical. Naturalistic and epidemiological research in twin, family, and adoption studies has addressed the role of genes and the environment in complex traits such as nicotine dependence. Environmental influences on the development of tobacco dependence are well documented and include peer and familial influences as the strongest contributors in determining how and when cigarette experimentation occurs among young people (for reviews, see 35, 36). However, studies based on twin samples support the hypothesis that genetic influences also underlie the initiation and lifetime use of tobacco (10, 37, 38). Twin studies reveal that approximately 50 percent of the variance in tobacco dependence is attributable to genetic influences (39). Interestingly, the majority of twin studies have been carried out in male twins, and very few studies have examined sex-specific differences. In a recent meta-analysis of twin studies, it was reported that genetic and environmental factors might differentially determine smoking initiation and persistence in male and female smokers (39). *Further studies are needed to fully appreciate genetic and environmental factors in all aspects of nicotine addiction, as well as delineating gender differences.*

In the laboratory, human studies have focused mainly on relapse and have examined responses to drug cues. Few studies have fully examined sex-moderating effects in cue reactivity, even though men and women respond differently to internal and external drug cues. External functions play a greater role in maintenance of and relapse to smoking in women, whereas internal cues are more prominent for males (8). Sex differences in reactivity among the types of cues have also been reported (8, 40).

In humans, although ovarian hormones in females may modulate responses to drugs and could potentially explain different drug responses between males and females, very few studies have examined the role of hormonal influences in women across different stages of nicotine addiction (for a recent review, see 5).

Disparities

This recommendation entails a vast arena of research that could lead to a basic understanding of sex differences in different phases of nicotine addiction. These approaches will identify individual differences that may inform effective interventions.

Partners

Governmental agencies that fund basic addiction research, such as the National Institute on Drug Abuse (NIDA), and other interested funders can help provide funding for the vast arena of projects proposed above.

Impact

With different research groups examining the various aspects of nicotine addiction in both the preclinical and clinical models, we will substantially enhance our understanding of basic biological differences in males and females in 2 to 5 years. This holds promise for understanding susceptibility to nicotine addiction and designing treatments to prevent and help alleviate nicotine dependence.

2. Gender differences in the measurement/definition of addiction, including novel measurements.

Several authors have hypothesized that addiction/dependence is multidimensional and includes physical, behavioral, and physiological components (41-44). Assessment of tobacco dependence has relied largely upon the Fagerström Tolerance Questionnaire (45) and its more recent variant, the Fagerström Test for Nicotine Dependence (FTND) (46) or the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, an approach derived from the need to include tobacco dependence in psychiatric nomenclature and classification and that attempts to adhere to classic definitions of drug dependence (47, 48). The state of the art in the assessment of nicotine dependence is best summarized in a recent paper by Moolchan et al. (44), who directly tested the concordance between dependence as determined by DSM or FTND criteria (≥7). The highest kappa value obtained was 0.21, which is just beyond the upper end of the "poor" range for agreement (49). The authors concluded that multiple instruments should be used to assess nicotine dependence because each may be evaluating separate and independent dimensions. *To date, none of the instruments commonly used to assess nicotine dependence assess all aspects, and their intercorrelation is surprisingly low* (44).

Research is needed on:

- *The definition of nicotine addiction/dependence and the development of measurements to identify differences between men and women and between adults and adolescents*. In most behavior genetic and genetic epidemiologic studies, "smoking" has been assessed as a static phenotype, as if the behavior is a trait that remains constant over time. Not only do reasons and motivations for smoking vary across individuals, but motivations (biological, social, and psychological—individually and in combination) probably vary across different population subgroups, as well as across time and situations (36, 50, 51), making the need for a dynamic definition of nicotine addiction more pressing. A more accurate definition of nicotine addiction will make it possible to better define sex-relevant experimental parameters.
- *Differences in brain neurochemistry between men and women, especially as these differences relate to nicotine dependence*. Sex differences in brain regions and neurotransmitter systems associated with addiction have been observed in smokers and nonsmokers. Women have higher dopamine and serotonin transporter availability than men, regardless of smoking status (52).
- *Gender differences in Fagerström (physiological) and Glover-Nilsson (behavioral) measures of dependence*. The FTND has been used extensively and is thought to be a valid measure for physiological assessment (it can assess a smoker's nicotine intake [53]), whereas the Glover-Nilsson Smoking Behavioral Questionnaire was recently developed to assess behavioral dependence (54). Further studies with a variety of population subgroups, including women and adolescents, are necessary.
- *Biomarkers for nicotine addiction in women versus men that could be implemented in the field*.
- *Sex differences in nicotine metabolism*.

3. Sex differences in genetic influences.

Biometric Studies of Twins and Families

It is known that smoking behavior is influenced by both genetic and environmental factors (18, 55). Twin studies have indicated that heritability rates are as high as 47 to 76 percent for smoking initiation and 62 percent for persistence or dependence (56, 57). Family studies have also been used to assess genetic components of vulnerability to nicotine addiction (58). However, sex differences have not been thoroughly studied (see below).

Measured Genetic Studies

Once it is determined that a complex trait is heritable, linkage analysis can be used to determine whether certain chromosomal regions may contain genes that contribute to the trait of interest. With the advent of the Human Genome Project and advances in molecular genetic technologies, candidate genes that map to the regions identified by the linkage analysis can be tested for association with phenotypic data.

Research is needed on:

- *Genetic studies and microarray technologies*. Several candidate genes may contribute to nicotine addiction. Thus far, research suggests that polymorphisms for genes encoding for cytochrome P450 enzymes are involved in nicotine and cotinine metabolism (e.g., *CYP2A6*) (59) and affect the dopamine system, especially the *DRD2* receptor and enzymes that control dopamine metabolism (a crucial player in the reward effects of nicotine) (60, 61). For example, an association has been reported between variations in genes that influence dopamine metabolism and smoking; this relationship is stronger among whites and women (62). Research in this area with respect to sex differences is lacking, and the advent of newer techniques, such as microarrays, that provide faster screening and detection of multiple gene variations may provide answers in a more efficient and cost-effective manner.
- *Identification of genetic markers and predictors. Several candidate genes are thought to be involved in nicotine addiction*. We can obtain further insight into other novel genes of interest by linkage analysis, which provides analysis of chromosomal regions and localization of genes that contribute to phenotypes associated with smoking. This methodology has provided inconclusive data but has the ability to help identify specific genes involved in nicotine dependence and to further examine sex differences (63).
- *Genetic components and predictors of relapse*. Genetic influences on different stages of smoking, such as initiation, maintenance, cessation, and relapse, may not be identical. A study examining female twins has shown that although risk factors overlap for smoking initiation and dependence, a distinct set of factors was specific for nicotine dependence (64). For cessation treatments, an association between genetic variations in the *CYP2D6* gene and increased incidence of bupropion adverse effects were reported in female patients (65). Data for

genetic predictors of relapse in females and males are lacking.

- *Gene/environment interactions*. As in other fields, such as cancer epidemiology (66, 67), nicotine dependence may also be influenced by gene/environment interactions (68, 69). Nicotine dependence exhibits characteristics of a complex genetic trait (e.g., gene/gene, gene/environment, and genotypic heterogeneity) (70-72). It has been shown that, depending on the nature of the gene/environment interaction (e.g., additive, multiplicative, or synergistic), the potential impact on the prevention of regular tobacco use could be quite high, thereby providing substantial motivation for pursuing an integrative understanding of how genes and the environment interact to increase susceptibility to tobacco use (73).

4. Sex differences in laboratory-based human studies.

Laboratory-based human studies are needed to investigate all aspects of nicotine addiction. These could include cue reactivity studies (e.g., 74), nicotine sensitivity studies (e.g., 75), functional magnetic resonance imaging (fMRI) studies of brain activation (e.g., 76), prepulse inhibition (e.g., 77), and some forms of electroencephalogram-based studies (e.g., 78).

Sex-based research is needed on:

- *Neurobiology of relapse and laboratory-based predictors of relapse*.
- *Risk and protective factors for nicotine dependence/addiction.*
- *Nicotine as a reinforcer and non-nicotine aspects of smoking reinforcements*.
- *An integrated, systematic approach to laboratory-based human studies and field studies*.

5. Human research on gender differences in natural history.

Conducting gender-based studies in naturalistic settings to understand the progression to dependence, quitting, and relapse is important. Thus, gender differences must be examined at different stages of life, taking into consideration biological, brain, behavioral, and environmental factors. The available data suggest that both trajectories of tobacco use and dimensions of adult dependence are strongly influenced by gender. Specifically, girls tended to have greater rates of change than boys in the use of tobacco (79); younger females had greater development of cigarette use than younger males (80) (younger females typically exceeded males in cigarette use [81, 82]); and females had higher initial status than males and increased less rapidly in their use of tobacco (83). White et al. found that while males and females did not differ significantly in frequency or quantity of smoking at most ages, females began to smoke at younger ages than males and at higher rates during adolescence (84).

Based on the results of a factor analysis of 42 items assessing smoking behaviors in 150 French smokers (50 percent male), Gilliard and Bruchon-Schweitzer (85) used principal components analysis and Varivax rotation to identify four factors explaining 52 percent of the total variance: dependence (automatism, lack of control, urge to smoke); social integration (socially acceptable behaviors, impressing other people); regulation of negative affect (management of anxiety, sadness, anger); and hedonism (pleasant smoking-related gestures, seeking relaxation and pleasure). The authors then used multiple-regression analysis to examine—separately for men and women—the relationships among a variety of sociodemographic, personality, and dependence measures. Of note is the finding that correlates of smoking factors were uniformly different for men than for women. For example, being single and being susceptible to boredom were associated with dependence in men, while the use of other psychoactive substances was most strongly related to dependence in women.

Gender-based research is needed on:

- *Natural history of progression to dependence*.
- *Overcoming limitations of current research with adolescents*.
- *Brain imaging in adolescents at multiple timepoints to monitor smoking and other outcomes*.
- *Gender differences in relapse factors*.
- *The menstrual cycle as a primary focus in research on smoking (puberty, pregnancy, postmenopause)*.
- *Sex differences in the rate of maturation of the relevant metabolic and receptor systems*.
- *Gender differences in self-quitting versus treatment-based quitting*.

6. Gender differences in depression, stress, and coping.

People with depression have a higher incidence of smoking (13-17). High levels of depression are associated with higher dependency on smoking (14). Depressed individuals may

self-medicate to alleviate symptoms of depression, and this behavior could be an important factor in tobacco dependence. However, it could also be that a common genetic basis exists for the association of the two conditions (14, 86). *Since females are twice as likely as males to experience mood disorders, depression is an especially important factor to consider with respect to prevention, treatment, withdrawal effects, and relapse*.

Smokers also report that while stress induces smoking behavior, smoking can alleviate stress (2, 87, 88). Women are more likely than men to smoke in response to stress and negative affect (3, 89, 90). A higher level of perceived stress was also identified as a risk factor for smoking in women following physician advice and nicotine replacement therapy (NRT) for cessation, but not in men (91). However, the underlying mechanisms of the relationship between smoking and stress are not fully understood.

Release of glucocorticoid hormones—cortisol in humans and corticosterone in rodents—is one of the final steps resulting in activation of the hypothalamo-pituitary-adrenal (HPA) axis and serves as one of the principal biological responses to stress (92-94). Preclinical studies that examine how nicotine alters the relationship between sex hormones and the HPA axis are lacking. Research has shown that the HPA axis can be differentially regulated in female and male rats in response to alcohol. For example, relative to males, female rats release more corticosterone when they are exposed to alcohol (95). *Thus, research should identify stressors that are unique to women and examine how these stressors affect coping and relapse rates*.

Research is needed on:

- *Depression, stress, and the onset of smoking or differences in smoking between adolescent males and females, and between adolescent and adult females*.
- *The utility of nicotine for young women versus young men*.
- *Hormonal factors in nicotine addiction, especially since phase of the menstrual cycle can affect mood*.
- *Nicotine and stress hormones*.
- *The role of psychiatric comorbidities, including subclinical comorbidities, and how to provide support and treatment*.
- *The relationship between smoking and autoimmune diseases, since stress as well as smoking can affect the progression and severity of autoimmune diseases*.
- *Whether nicotine plays a therapeutic role in depression.*

7. Sociocultural determinants.

We need to understand disparities in smoking prevalence among women by socioeconomic status, race, and ethnicity. For example, certain ethnic groups have a higher prevalence of smoking than the general population (96), and predictors of initiation and persistence of smoking vary across ethnic groups (97). Thus, prevention and cessation programs targeting these particular groups should take into account cultural and potential biological differences, such as nicotine metabolism (98).

Research is needed on:

- *Cultural differences between African Americans and whites in cigarette choice*.
- *Reasons for the high smoking rate among American Indian women, including a better understanding of the social and cultural values adolescents attach to smoking* (99).

In addition, naturalistic observation studies are needed of smoking in people from different cultures as they enter the United States.

Translation

*8. Use evidence from animal studies, pilot projects, and small-scale clinical studies to develop, refine, and evaluate promising interventions.

As illustrated in the above recommendations, animal studies can be used to understand the role of behavioral, hormonal, genetic, neurobiological, and environmental factors in nicotine addiction. These models will help in the development of potential behavioral and pharmacologic interventions for the prevention and cessation of nicotine addiction. For example, treatments based on extinction might be more effective for females than for males.

Research is needed on:

- *Effective treatments from the field of depression and other psychiatric comorbidities*. Pharmacological interventions from these fields can be tested in animal models, and these studies can very quickly provide data to start pilot clinical studies.
- *Menstrual cycle effects on craving and withdrawal symptomatology*. Previous research has shown that when premenstrual symptoms were highest in the late luteal phase of the cycle, women reported an increase in the desire to smoke to alleviate negative symptoms and

minor weight gain following short-term abstinence; thus, women smokers might have better results quitting during the follicular phase of the cycle (100-102).

- *Cognitive behavioral therapy regarding weight gain concerns versus preventing weight gain*. Previous research has indicated that weight gain occurring during an initial short-term period of smoking cessation can constitute a serious barrier to cessation. Weight-concerned women are less likely to seek treatment or attempt to quit on their own (103, 104). Also, weight-concerned women are willing to tolerate only a minimal weight gain, as they expect to gain more weight, and this may hamper their efforts to quit smoking (105). In fact, cognitive behavior therapy that focuses on reducing weight gain concerns improves smoking cessation outcome in weight-concerned women (106).

Disparities

The development of gender-specific treatments should be enhanced, with a view toward targeting priority female subgroups.

Partners

Partners include NIH and private foundations.

Impact

Within 2 to 5 years, we will know the limits and promise of new treatments and have feedback to refine animal models.

Application

*9. Use or modify existing infrastructure (e.g., NIDA Clinical Trials Network) to rapidly evaluate the efficacy of promising treatments and the effectiveness and cost-effectiveness of proven small-scale interventions.

Women are less successful than men at quitting smoking, and those who seek help respond differently to cessation pharmacotherapies (8, 11, 107, 108). For example, in a recent effectiveness trial of bupropion SR (11), the 12-month nonsmoking rate for women (25 percent) was significantly lower than that for men (32.8 percent; $p < 0.01$); women were 45 percent more likely than men to be smoking at 12 months post treatment, after adjustment for other pretreatment characteristics and form of treatment; odds ratio (95 percent confidence interval)=1.45 (1.16, 1.82). This finding is consistent with the report by Dale et al. (109), in which women were 67 percent more likely than men to be smoking at the end of treatment with bupropion SR. The finding that women are more likely to return to smoking following treatment has also come from studies of the effectiveness of unassisted cessation (110-112), community-based interventions (113), behavioral treatment (9, 110, 114), nicotine replacement therapy (10, 114-118), and fluoxetine treatment (119). The basis for lower cessation rates among women remains unknown and may be due to a number of factors, including the presence of undetected subgroups among female quitters that vary with respect to treatment outcome (120). Relatively little work has been done to identify such subgroups, and no published evidence is available within the context of combined bupropion SR and behavioral counseling. *Such information could be useful for understanding whether all, or only certain subgroups of women are at increased risk for smoking following treatment and will help provide the path to cessation therapies tailored to the needs of women*.

Research is needed on:

- *Maximizing the effectiveness of NRT for women*, because gender differences with respect to nicotine sensitivity during withdrawal have been reported. Hormonal effects may alter nicotine sensitivity, but few studies have examined hormonal influences on responsiveness to NRT. Recently, Allen and colleagues (121) reported that women treated with transdermal nicotine patches reported a decrease in craving in the late luteal phase of their menstrual cycles relative to the follicular phase. This indicates that to maximize the effects of NRT, the menstrual cycle should be taken into consideration.
- *Gender differences in non-NRT pharmacotherapies*. In this category, bupropion is currently the only non-NRT pharmacotherapy approved for smoking cessation (for a recent review, see 122). Thus, much work is needed to determine, for example, the dose ranges of effective medications for females. This pharmacotherapy may be especially useful for women, because studies have shown that bupropion may reduce withdrawal symptoms and weight gain—a major concern for women.
- *Combinations of medications and behavioral treatments*. In a study of quit rates following nicotine therapy, women scored higher on behavioral measures of nicotine dependence and lower on physiological measures than men, indicating that, ideally, behavioral therapy should be combined with nicotine treatment and tailored to the individual's needs (107).

- *Applying treatments for other disorders (e.g., depression) to nicotine dependence*, especially since evidence suggests that women smokers who have a history of depression are less likely to quit (9, 115, 123, 124).
- *More-intensive versus less-intensive treatments*. This research could be expanded to include treatments delivered in the "real world."

Disparities

Ascertain efficacy and effectiveness in priority subgroups.

Partners

- NIDA and Veterans Affairs Clinical Trials Network
- NCI's Clinical Cancer Oncology Program
- Substance Abuse and Mental Health Services Administration
- Foundations (e.g., Robert Wood Johnson Foundation)
- Pharmaceutical industry

Impact

Within 5 years, we may have improved the delivery of effective treatments to priority subgroups.

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