prefer.

PATIENT PREFERENCES

CASE STUDY CATALOGUE

Clinical patient preference studies

We have started three core **PREFER** patient preference studies looking at cancer, rheumatoid arthritis and neuromuscular disorders. Both academic and industry partners are adding more patient preference studies to the PREFER portfolio that will help us cover different disease areas, methods and research questions.

The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federaton of Pharmaceutical Industries and Associations (EFPIA). This booklet and its contents reflects the PREFER project's view and not the view of IMI, the European Union or EFPIA.

imi innovative medicines initiative

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PREFER core case studies

Neuromuscular diseases

PREFER will ask patients and caregivers with two hereditary neuromuscular diseases: myotonic dystrophy type 1, and mitochondrial disorders. The goal of this study is to elicit patient preferences relative importance with respect to met and unmet health needs and assess benefit to risk trade-offs, relative importance, minimum acceptable benefit and maximum acceptable risks for potential future treatment options in neuromuscular disorders (NMD). Hypothetical treatment options will be presented to both patients and people who are caregivers (of patients with NMD). These options will include benefits for unmet health needs identify as more important, and risks identified as feared the most by patients themselves.

Like all neuromuscular disorders, myotonic dystrophy type 1 and mitochondrial disorders are uncommon, serious and debilitating, weakening muscles. They are also progressive, the prognosis is poor and the treatment options (if there are any) are few. Myotonic dystrophy type 1 and mitochondrial disorders have different causes, but the symptoms are similar. In addition to muscle weakness, these diseases affect other systems and organs, including the central nervous system, and can lead to reduced cognitive functions, learning difficulties, daytime sleepiness and fatigue. Symptoms can start showing in early childhood, or later in life. There are no specific cures, and these diseases can affect more than one family member in each generation. People who are affected by neuromuscular diseases sometimes struggle to perform some of their daily activities and some rely on caregivers, which is why PREFER is also asking for their preferences. Very little has been done in the NMD field about studying patient preferences but due to the nature of these rare diseases and how priorities in the field can differ between stakeholders, this is a population in a sensitive stage to perform patient preference studies.

Three different preference methods (Q-methodology, Best-Worst Scaling (BWS) type 2 and Discreet Choice Experiment (DCE)) will be included. The first two have been considered simpler (e.g. less cognitively demanding for the responder) while the last has been considered a more complex method (e.g. more rigorous and in depth).Comparison will allow the identification of suitable preference methods for populations that may present cognitive limitations.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Neuromuscular diseases	Newcastle University	Grainne Gorman Ardine de Wit Cahty Anne Pinto	Pre-discovery	NMD	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Elicit and quantify patient preferences including benefit to risk trade-offs (e.g. relative importance, minimum acceptable benefit (MAB), maximum acceptable risk (MAR)) applicable for future NMD treatments.	United Kingdom	Semi-structured individual interviews Focus Group Discussion Dyadic interviews	DCE Q-method Best-Worst Scaling case 2	June 2019	Q1/Q2-2020

Rheumatoid arthritis

Rheumatoid arthritis (sometimes called “RA”) is a common chronic inflammatory disease that affects around 1% of the population. It is 3-4 times more common in women. In most cases, patients begin having symptoms between 40 to 60 years of age, but it can begin earlier, or later in life. RA affects the joints and causes pain, swelling, and stiffness, but also fatigue. If patients are not treated, the joints can suffer permanent damage, which subsequently can lead to disability. To date, there is no cure, which means that all treatments are long term, with the aim to control the inflammatory disease activity and reduce symptoms.

There is increasing research interest in the idea of treating individuals who are at an increased risk of developing RA to assess whether a relatively short course of therapy will prevent or delay the onset of RA. One such ‘at risk’ group are the siblings and children of patients with RA, who are four times more likely to develop the disease. The presence of RA-related autoantibodies in the blood increases the risk of developing the disease further. This PREFER case study will ask siblings, children and members of the general public about their preferences for preventive treatments. The case study will further look at how participant characteristics, country (UK vs Germany), population (siblings and children vs. general population), knowledge/experience with RA will impact on these treatment preferences. In addition, this case study will evaluate the similarity of two different methods to measure treatment preferences.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Rheumatoid arthritis	University of Birmingham University of Erlangen	Karim Raza Larissa Valor-Mendez Jorien Veldwijk Rachael DiSanto-stefano	Early development & post-marketing	RA	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Assess the preferences of people at risk of RA for preventive treatments. Evaluate the maximum acceptable risk (MAR)/Minimum acceptable benefit (MAB) Characterize preference	United Kingdom Germany	Focus Group Discussion Nominal Group Technique	DCE Probabilistic Threshold Technique	December 2019	Q3-2020

heterogeneity and characteristics that may explain heterogeneity					

Lung cancer

Lung cancer is the most common malignancy in men and the third most common in women. The most frequent symptoms that patients report upon disease presentation are cough, dyspnea, chest pain, fatigue, chest infection, hemoptysis, and weight loss, all of which greatly overlap with symptoms of other common chronic respiratory conditions and are often only present at later stages of the disease. This overlap is one cause of the delay between presentation and diagnosis, which means that lung cancer is diagnosed in late stages in half of all cases. The prevalence of late-stage diagnosis is one of the reasons why lung cancer has such a low survival rate: a 5-year overall survival rate of 18.1% in all lung cancer stages and 4.5% in the metastatic stage.

In recent years, we have witnessed a shift in the treatment paradigm of Non-Small Cell Lung Cancer (NSCLC). Specifically, the inclusion of a new pharmacological approach with the inclusion of Immuno-checkpoint inhibitor therapies that focus on the regulation of the immune system to attack the cancer instead of attacking it directly as chemotherapy does. The approval of the combination of chemo and immunotherapy as first line treatment for advanced NSCLC, while providing a clear benefit for NSCLC patients who are not eligible for mono-immunotherapy treatments (with PD-L1 low/negative), poses a new alternative of care for those patients who can now choose between an immunotherapy treatment, plus a chemotherapy treatment in a subsequent line of treatment, and combined chemo-immunotherapy treatment, that has an increased chance of adverse events and more critical side effects, but can be more effective against more aggressive cancers. Since a direct comparison between the two has not been able to provide evidence of which choice is to be preferred, patient preferences are crucial when choosing between a more “aggressive” approach with a higher toxicity profile or a less intense alternative. PREFER has the objective to identify and evaluate which elements are relevant for patients and should be considered when evaluating the treatment. The study will include NSCLC patients from Italy and Belgium in a different stage to define how preferences evolve according to different stages of the disease. The study will adopt different methods to assess patients’ preferences to evaluate the similarity of the results.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**
Lung Cancer	European Institute of Oncology	Gabriella Pravettoni Serena Oliveri (from January 2020) Eva Katz & Meredith Smith	Post Marketing authorization	Lung Cancer

Clinical Objectives	Patients from	Methods in Qualitative Study	Methods in Quantitative Study	End-date qualitative data collection	End-date quantitative data collection
Identify and quantify patient-relevant benefit-risk attributes of LC treatments Quantify the risk tolerance for experiencing adverse events (Maximum Acceptable Risk) that patients are willing to accept for an increased probability of prolonged survival	Italy Belgium	Focus Group Discussion Nominal Group Technique	DCE Swing-Weighting	October 2019	Q2/Q3-2020

Additional case studies by public partners (academia)

Diabetes

Diabetes is a chronic disease characterized by the body's inability to maintain healthy levels of blood glucose (glycemic control) which is associated with long-term health problems such as retinopathy, nephropathy, peripheral and autonomic neuropathy, cardiovascular symptoms, and sexual dysfunction. Diabetes care is centered around the cornerstone of metabolic control; specifically keeping glucose levels as close to normal as possible through the self-monitoring of blood glucose (SMBG), medication, a careful diet, and physical activity.

Traditionally, SMBG has been done by pricking the finger with a lancet to draw a drop of blood and directly testing the levels of glucose in the blood, sometimes multiples times per day. Recent developments in glucose monitoring devices have led to preference-sensitive decisions where patients have a large variety of choices in regard to function, features, cost, and other factors to consider when choosing which glucose monitor is best for them.

The aim of this study is to determine the preferences and trade-offs of diabetes patients when selecting a device for monitoring their glucose, and to determine whether these outcomes differ by type of preference elicitation method used, the kind of educational tool they are presented with, the way patients are recruited, and patient characteristics, or experiences.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Diabetes	Erasmus University Rotterdam/University Medical Centre Utrecht	Chiara Whichello Ian Smith Ardine de Wit Esther de Bekker-Grob	Early development, HTA/reimbursement, post-marketing	EUR/UMCU	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Which attributes of blood glucose monitoring devices patients consider when deciding on their preferred device What is the relative importance of these different attributes in choosing which devices to use Assess the minimum acceptable benefits needed to justify increased costs	Patient panels and through the patient's primary/ secondary care, and patient organizations	Individual interviews	DCE Swing Weighting	August 2019	Q4-2019/Q1-2020

Multiple Myeloma

Multiple myeloma (MM) is the second most common blood cancer. There are various drugs available for MM. Yet, MM is considered an incurable disease and only half of patients live longer than five years. Numerous clinical trials are currently investigating the benefits and risks of upcoming treatment classes such as CAR-T immunotherapies and bi-specific T-cell engaging immunotherapies. These are often associated with high benefits but also severe risks. In decision-making regarding these therapies, having information from patient preference studies on how patients trade off between their benefits and risks may be extremely valuable.

The clinical objective of this study is to understand how patients trade off between the benefits and risks of multiple myeloma treatments. The methodological objectives are to: 1) compare two preference methods and 2) investigate whether and how patient preferences may be influenced by patient characteristics (e.g. treatment and disease experience). The study consists of two phases: 1) group discussions with MM patients to find out which treatment characteristics they find most important, 2) online questionnaires with MM patients to quantify the trade-offs they are willing to make between hypothetical treatments that vary with respect to these characteristics.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Multiple Myeloma	KU Leuven	Rosanne Janssens, Isabelle Huys	Marketing Authorisation, HTA/reimbursement	KUL - MM	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Identify patient-relevant benefit-risk attributes of MM treatments (including upcoming treatments such as immunotherapy) Quantify trade-offs for benefit-risk attributes of MM treatments (including upcoming treatments such as immunotherapy)	Belgium, Romania, Spain, Finland	Focus group discussions using the Nominal Group Technique	DCE and Swing Weighting	January 2020	April 2020

Hemophilia

Haemophilia is a rare genetic bleeding disorder occurring in 1 of 10 000 births. Two types of haemophilia exist, haemophilia A is caused by an error in the gene for coagulation factor VIII (FVIII) and haemophilia B is caused by an error in the gene for coagulation factor IX (FIX). These errors cause patients to bleed for a longer time compared to people with the correct gene. Bleeds can occur after injuries in mild and moderate haemophilia, but can also occur spontaneously in severe haemophilia. Bleeding can also occur in joints, where it causes joint swelling, pain, stiffness and immobility. Today, haemophilia treatment is based on increasing coagulation factor concentrations through factor replacement therapy to prevent and treat bleeds.

The invasiveness of intravenous injection and the high administration frequency results in a high burden of treatment. Recently, gene therapy for the treatment of haemophilia has been developed. Clinical trial results are promising and gene therapy may be able to cure patients. However, multiple challenges remain. These challenges mainly relate to the fact that it is currently still unknown whether the therapeutic effect of gene therapy will be maintained throughout the full lifespan of patients, and what side effects may occur in the long run. In this case study, we will look at how features of the standard therapy and gene therapy influence patients' choices between these therapies.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Hemophilia	KU Leuven	Eline van Overbeeke Isabelle Huys	HTA/reimbursement	KUL - PAV	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Identify attributes of gene therapy and standard of care that are important to patients Understand trade-offs that patients make when choosing between gene therapy and standard of care	Belgium	Semi-structured interviews	Threshold Technique	September 2019	Q1-2020

Rheumatiod Arthritis

Rheumatoid arthritis (sometimes called “RA”) is a common chronic inflammatory disease that affects around 1% of the population. It is 3-4 times more common in women. In most cases, patients begin having symptoms between 40 to 60 years of age, but it can begin earlier, or later in life. RA affects the joints and causes pain, swelling, and stiffness, but also fatigue. If patients are not treated, the joints can suffer permanent damage, which subsequently can lead to disability. To date, there is no cure, which means that all treatments are long term, with the aim to control the inflammatory disease activity and reduce symptoms.

There is a number of disease-modifying antirheumatic drugs on the market known as DMARDs. These drugs target the inflammation in different ways, and there are some practical differences for the patient: How they take the drug, how often they need to take it, different risks of side effects and tests they need to take. When someone is first diagnosed with RA, they often start treatment with conventional drugs known as ‘synthetics’ (or csDMARDs). If treatment doesn’t work, or if there are too many side-effects, patients often needs to step up treatment to ‘biologics’ (known as bDMARDs), or what is known as ‘targeting synthetics’, also known as JAK-inhibitors (or tsDMARDs). These drugs target specific biological mechanisms that are associated with the start and progression of inflammation. The side effect and the long-term outcomes are well known for older biologics. However, the JAK-inhibitors recently became available so there is still uncertainty in adverse events and the long-term outcomes.

Treatments affect patient’s quality of life. Finding the best treatment for patients with RA that need to change their medication means choosing from a number of drugs with different side effects and practical considerations. Like if patients prefer pills, injections or intravenous treatment. Or how often they are willing to take the drug. We want to explore the preferences of patients with RA to find out what trade-offs they are willing to make for treatments with JAK-inhibitors compared to biologics, to support clinical and regulatory decisions in deciding which treatment is best suited for patients.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Rheumatoid Arthritis	Uppsala University	Karin Schölin-Bywall Ulrik Kihlbom Jorien Veldwijk	Marketing authorization & post-marketing		
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
To elicit RA patients’ preferences	Sweden	Focus groups & nominal group technique	DCE	March 2019	November 2019

To estimate Minimum Acceptable Benefit To explain preference heterogeneity					

Eye Tracking

Attribute attendance is a fundamental assumption of discrete choice experiments, a commonly used technique for investigating individual health preferences. When attribute attendance is not accomplished (also called attribute non-attendance) it presents a serious risk to the validity of the outcomes of discrete choice experiments. One possible method for the assessment of attribute attendance is eye-tracking in which the gaze of a participant is tracked to see where they are looking during a choice task. However, there is limited research that uses eye-tracking to assess attribute attendance during choice task completion, and what research has been done frequently does not use patient populations.

The aim of this study is to investigate attribute non-attendance in different patient populations and disease contexts (i.e. group, disease, previously determined attributes of interest), and how risk attribute presentation formats impacts attribute non-attendance in different patient populations and disease contexts using use eye-tracking techniques.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Lung Cancer, Neuromuscular diseases, Rheumatoid Arthritis	UMCU	Ian Smith Ardine de Wit Jorien Veldwijk	Early development, pre-discovery, HTA/reimbursement, post-marketing	UMCU	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Supplement the research findings of other core case studies in PREFER by assessing attribute	UMCU and local healthcare networks	Cultural validity check	Eye-tracking based DCE	October 2019	Q1/Q2-2020

attendance via eye-tracking					

Additional case studies by private partners (industry)

Chronic Obstructive Pulmonary Disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a common inflammatory disease of the lungs, caused in particular by long-term smoking and resulting in breathing difficulties and other respiratory symptoms. Clinical trials in the past have focused on improving the lung function (breathlessness) or reducing the number of flare-ups (exacerbations), requiring hospital visits, resulting in a number of medications to treat these aspects of the disease.

Whilst there are a number of medications which help with the breathlessness and reduce exacerbations, COPD patients also suffer from other symptoms like chronic cough and excess mucus secretion, which greatly affect their lives and are poorly managed by the current therapies. We have performed qualitative research analyzing social media and online community discussions to highlight the burden of cough and mucus for COPD patients, revealing that these symptoms can lead to disturbed sleep, fatigue, urinary incontinence and social anxiety/embarrassment. The current 5-country patient preference study with COPD patients is designed to show just how important these other symptoms are to patients, compared to breathlessness and exacerbations, and how important it would be to them to be able to alleviate these different consequences of their COPD.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
COPD	Novartis	Nigel Cook	Input to phase III clinical trial design	COPD	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Quantify the relative needs and preferences of COPD patients regarding symptoms, the impact on their QOL, and	Five countries (US, UK, France, Australia, Japan) recruited	Literature review, social media listening, online bulletin boards, qualitative in-depth telephone interviews	DCE for the preferences elicitation Various PRO instruments and other	June 2019	November 2019

evaluate whether preferences vary with certain respondent characteristics.	through patient groups (and in Japan supplemented through patient panels)		questions also included in survey to enable sub-group analyses		

Myocardial infarction

A myocardial infarction (MI), commonly known as a 'heart attack' occurs when a portion of the heart is deprived of oxygen due to blockage of a coronary artery. Without oxygen, muscle cells served by the blocked artery begin to die (infarct). As a heart attack can be fatal, it is crucial to seek emergency help soon after symptoms present. The heart attack or blockage of the artery is due to the buildup of fats, cholesterol and other substances in the body and artery walls, which may also lead to a stroke (due to loss of blood flow to the brain) or fatal events. Clinical treatment guidelines focus on several factors, including the timing of treatment during the course of clinical care, i.e. whether drugs should be administered soon after the heart attack is diagnosed (an acute phase) or at more chronic stages of disease. Treatments for a heart attack may also cause the risk of severe bleeding including risk of bleeding in the skull or other severe bleeding events.

Knowledge of whether patients with acute or chronic disease have different preferences (i.e., willingness to accept higher probability of side effects in exchange for higher efficacy) could inform decision-making by developers, regulators, payers, and clinicians at point of care; it would allow for a patient-centered assessment of which treatment options may be more suitable (i.e., have a more favorable benefit-risk profiles) in these two phases of disease.

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Myocardial infarction	MSD	Cathy Anne Pinto	Post-marketing Pre-marketing: future developments	MSD	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
To compare patient preferences for antithrombotic treatment	United Kindgdom	Semi-structured interviews	DCE Best-worst Scaling case 1	Qualitative pilot completed in	Quantitative pilot completed in

attributes for patients with an acute MI and patients with chronic disease. To assess preference heterogeneity in other relevant subgroups.	Acute MI patients recruited by NHS clinical sites Chronic patients recruited via patient panels			June 2018	July 2018 Ethics approval of subsequent amendment was granted in Dec 2018. Targeted date for completion of quantitative study data collection is October 2019

Chronic pain

Osteoarthritis (OA) and Chronic Low Back Pain (LBP) are two of the most common chronic pain conditions worldwide. Both conditions are associated with substantial humanistic and socioeconomic burdens (Bindawas et al., 2015; Farr et al., 2013; Gore et al., 2012; Gore et al., 2011; Ma et al., 2014). Pharmacologic therapy for OA and CLBP often includes non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, typically in a step-up approach (McAlindon et al., 2014; Qaseem et al., 2017). There is an unmet need for novel, nonopioid treatments for the management of chronic pain conditions because available therapies often have limited effect or work for only some patients (Kissin, 2010). In addition, there are major risks associated with NSAIDS and opioids that limit their usefulness, particularly for patients with comorbidities who are not appropriate candidates for NSAID and/or opioid treatment (Aronson, 2009).

Patient preferences for pharmacologic treatments for chronic OA pain and CLBP have been formally measured; however, existing studies are limited in their ability to provide results that can inform the benefit-risk tradeoffs that patients are willing to make among NSAIDs, opioids, and the long-acting injectable treatments currently being investigated.

Pfizer and Lilly are collaborating on the development of tanezumab, a novel treatment for chronic pain. Tanezumab, a nonopioid analgesic administered subcutaneously every 8 weeks, is being investigated in difficult-to-treat patients with moderate-to-severe pain due to knee and hip OA or CLBP who have taken or tried three or more classes of pain treatment in the past 2 years, for whom NSAIDs

are contraindicated, or who are intolerant of NSAIDs or unwilling to take opioids.

To quantify patients' perspectives of the value of tanezumab compared with other products, Pfizer and Lilly were interested in conducting a DCE in patients with OA only, CLBP only, and concurrent OA and CLBP in the US. Specifically, Pfizer and Lilly hoped to quantify patient preferences for the characteristics of tanezumab relative to those of NSAIDs, opioids, and other NGF-inhibitor products. Separate preference studies were conducted in the US and UK using the same survey instrument. This report contains only the US results because of the limited generalizability of preference data and different data-collection periods across the regions (i.e., UK study was fielded later).

Therapeutic area	**Study led by**	**PREFER leads team**	**MPLC decision point of interest**	**PREFER case study acronym**	
Chronic pain	Pfizer Eli Lilly	Leo Russo Kristin Bullok	Pre-approval & late development	Pfizer-Lilly	
Clinical Objectives	**Patients from**	**Methods in Qualitative Study**	**Methods in Quantitative Study**	**End-date qualitative data collection**	**End-date quantitative data collection**
Quantify patient preferences for pharmaceutical treatments for chronic moderate-to-severe musculoskeletal pain associated with osteoarthritis (OA) and chronic low back pain (CLBP). Understand patients' preferences for, and potential trade-offs among, treatment attributes that are most relevant to them and that correspond to existing and future treatment options	Patients recruited from US and UK online panels maintained by a company called Dynata. Panel members are recruited via partnerships with trusted loyalty programs, as well as through banner ads, pop-ups and messages on websites, television	Focus groups	DCE Best-worst Scaling case 1	US: December 7th, 2017 UK: TBC	US: March 20th, 2019 UK:TBC

(e.g.,. nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anti-NGF mAbs)	advertising, and offline recruiting (e.g., telephone recruitment of targeted populations)				

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