Biomarker Sub-Group Report

Monday, 9 October 2023

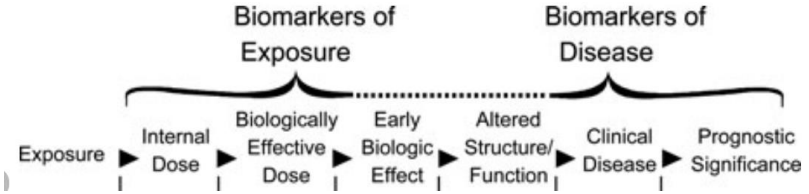
Cancun, Mexico

Vision and Objectives

VISION: “Identify and assess fit-for-purpose biomarkers for tobacco product research.”

OBJECTIVES

1. To develop a robust understanding of mechanistic pathways and clinical outcomes for smoking-related diseases to better identify fit-for-purpose biomarkers.
2. To review and summarize published literature on biomarkers that are fit-for-purpose in the assessment of potential reduced risk tobacco products (PRRPs).
3. To evaluate and recommend guidelines and best practices for utilizing fit-for-purpose biomarkers in studies assessing PRRPs.



Adapted from DeBord et al, J Occup Environ Hyg. 2015;12 Suppl 1(sup1):S41-54.

Biomarker Sub-Group

- **Leadership**
  - **Coordinator & SC Liaison Member: Mohamadi Sarkar**
  - **Secretary: Kirk Newland**
- **Current roster includes 35 members**
  - **Membership represent 11 countries and 18 CORESTA member organizations**
- **Meetings**

Date	Meeting	Chair / Secretary
19 April 2023	Spring meeting	M. Sarkar / K. Newland
7 Oct 2023	Fall meeting	M. Sarkar / K. Newland

Achievements

Project No.	Activity	Leader	Publication date
BMK-186 and BMK-249	Conduct meta-analysis of published literature on urinary nicotine equivalents, carboxyhemoglobin and NNAL to establish a population level estimate. **Implications:** Baseline level for comparisons against changes in exposure for reduced-risk products	Felix-Ayala Fierro	05/22
BMK-273	Definition of use behaviour and exposure terminology across product categories – **Collaborative Project between PUB and BMK**	Lesley Giles (PUB) and Dai Yuki (BMK)	Final version published 10/22.

- **Observations**
  - **Publish technical reports in open access platforms for broader visibility**
  - **Collaborations across subgroups is important**
  - **Virtual meetings lead to greater efficiencies**

Achievements

2,637 397 25

Article rating

3.64 | 22 reviewers

Review this Article

Article May 25, 2022

Qeios ID: ZJJ66O.2

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https://doi.org/10.32388/ZJJ66O.2

Population estimates of biomarkers of exposure to carbon monoxide, nicotine, and NNK in smokers and non-smokers Preprint v2

Felix Ayala-Fierro[1], Thomas Verron[2], Pavel Lizhnyak[3], Robert Freeland[4], Kimberly Frost-Pineda[4], Ashraf Elamin[5], Gaddamanugu Prasad[4], Mohamadi Sarkar[3]

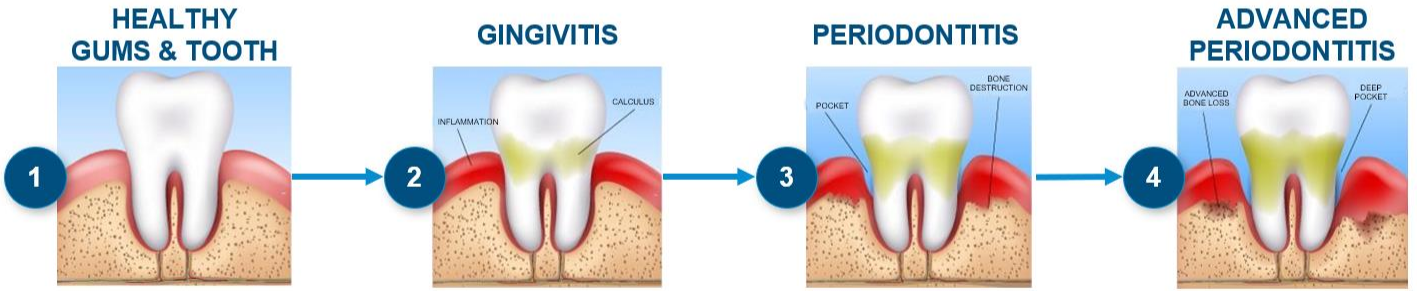
Biomarkers of Oral Health Outcomes

Smoking is a major risk factor for periodontitis
(NHANES III[a])

Gingivitis is the early stage leading to periodontitis

Subgingival microflora of smokers with gingivitis is preceded by an **increase in abundance of periodontal-pathogens**

Stages of Gum Disease



Calculus builds up on teeth and gums are inflamed (red).

Inflammation causes gums to separate from tooth, forming pockets. Early to moderate bone loss.

Severe bone loss, deep pockets. Tooth is in danger of falling out.

a Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. J Periodontol. 2000 May;71(5):743-51. doi: 10.1902/jop.2000.71.5.743. PMID: 10872955.

On-going Projects

Project No.	Activity Report	Leader	Deadline
Not assigned	**Tobacco Data Standards** • The project is already underway with the development team beginning with scoping • BMK will continue to lead the effort within CORESTA to include other disciplines and create collaborative opportunities across BMK, PUB, IVT and SA subgroups.	Allan Rees (ALCS)	4Q 2024

- **Summary of Progress in 2022**
  - **Scoped and modeled concepts for a new v 1.0 Tobacco Implementation Guide**
  - **Developed standards for four key areas inherent to tobacco studies**
    - Product Description
    - Nonclinical
    - Clinical – Product Impact on Individual Health
    - Product Impact on Population Health
  - **Drafted standards to support approximately 25 use cases, with ~50 examples and ~30 supporting domains/datasets**

Introduction to the Tobacco Implementation Guide (TIG)

Christine Connolly, Head of Standards Projects, CDISC

07 October 2023

Tobacco Implementation Guide (TIG)

- Supports the CTP Data Standards Strategy 2021-2025 through provision of standards and terminologies to facilitate tobacco research, scientific review, harm reduction, and information exchange
- Is a collaborative initiative with FDA-CTP, CDISC, and industry stakeholders
- To develop non-proprietary, consensus-based, vendor-neutral, platform-independent submission data standards for tobacco product data
- Will develop a set of standards, collectively referred to as TIG v1.0, to be freely available on the CDISC website in 2024

Without Data Standards

Name for Subject ID is not the same

Name for dataset varies

Gender or Sex - do these mean the same thing!?

Study #1 – demog.xpt

SUBJID	SEX
0001	M
0002	F
0003	F
0004	M
0005	F

Study #2 – dmg.xpt

ID	GENDER
A1	Male
A2	Male
A3	Female
A4	Female
A5	Male

Study #3 – dmgph.xpt

PTID	GENDER
0001	1
0002	1
0003	2
0004	2
0005	1

Study #4 – axd222.xpt

USUBID	SEX
00011	0
00012	1
00013	1
00014	0
00015	1

Is it Male or Female, M or F, 1 or 2, or 0 or 1?

What do these numeric codes mean?

With Data Standards

Study #1 – dm.xpt

USUBJID	SEX
0001	M
0002	F
0003	F

Study #2 – dm.xpt

USUBJID	SEX
A1	M
A2	M
A3	F

Study #3 – dm.xpt

USUBJID	SEX
0001	M
0002	M
0005	F

Study #4 – dm.xpt

USUBID	SEX
00011	M
00012	F
00015	F

Study #1 – demog.xpt

SUBJID	SEX
0001	M
0002	F
0003	F

Study #2 – dmg.xpt

ID	GENDER
A1	Male
A2	Male
A3	Female

Study #3 – dmgph.xpt

PTID	GENDER
0001	1
0002	1
0005	2

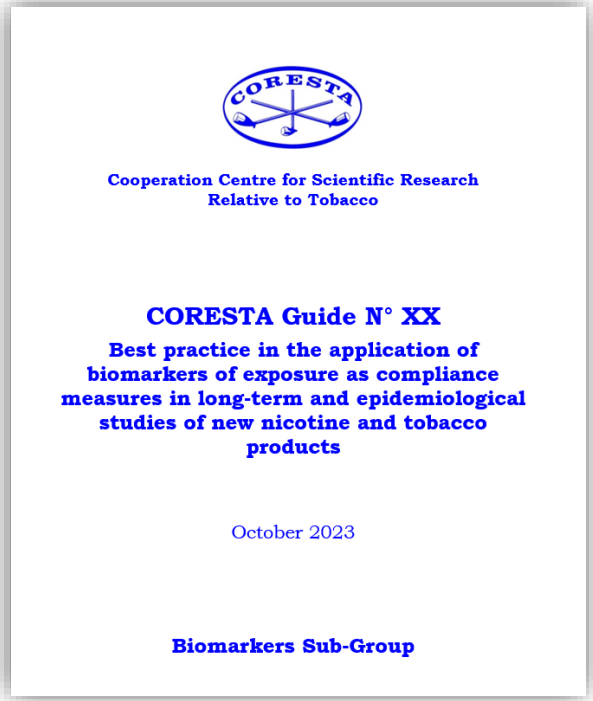
Study #4 – axd222.xpt

USUBID	SEX
00011	0
00012	1
00015	1

Ongoing Projects – NWIP 362

Project Description	Obj. #	Team Members	Company
Identification of specific biomarkers of exposure fit-for-purpose as compliance measures in long-term ambulatory studies to discriminate various tobacco product use states. A. The scope of this project will be to identify suitable candidates as compliance measures in long-term ambulatory studies to differentiate various behavioral states, e.g., dual use, complete switching to a PRRP by literature search in peer-reviewed journals.	#1, #2 & #3	Nikola Pluym Kirk Newland Mike McEwan Mohamadi Sarkar Ben Blount (External Advisor)	ABF Celerion BAT ALCS CDC

Draft Guide



Cooperation Centre for Scientific Research Relative to Tobacco

CORESTA Guide N° XX

Best practice in the application of biomarkers of exposure as compliance measures in long-term and epidemiological studies of new nicotine and tobacco products

October 2023

Biomarkers Sub-Group

- BoE with long half-lives, high detection rate and specificity are preferred.
- **CEVal*** is preferred BoE as compliance measure
- **2CyEMA** is suggested as an alternative.
- **eCO** is a rapid and cost-effective BoE.
- **PG** in urine is a specific BoE to vaping, however needs further verification.
- TSNAs e.g. urine **NNAL, and minor alkaloids** can be used to distinguish HTP use.
- No specific BoE for nicotine pouches.

*CEVal=N-(2-cyanoethyl)valine; 2CyEMA=2-cyanoethylmercapturic acid

Ongoing Projects – NWIP 363

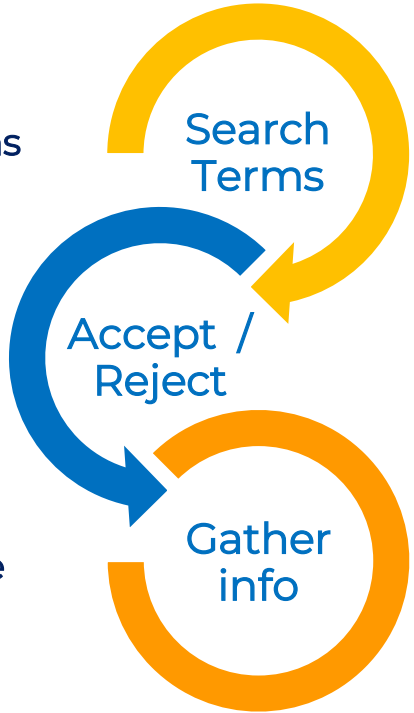
Project Description	Obj. #	Team Members	Company
Develop robust understanding of mechanistic pathways and identify clinically relevant biomarkers for COPD A. Scoping and clearly identifying objectives and deliverables B. Identify biochemical and functional end-points C. Build comprehensive knowledgebase of biomarkers for COPD sensitive and specific for adult smokers switching to PRRPs (e.g., ENDS, HTPs and Oral Nicotine Products) D. Identify fit-for-purpose biochemical and functional end-points that are sensitive to detect clinically relevant early changes in the pathophysiology of COPD	#1, #2 & #3	Patrudu Makena (Lead) Jeff Edmiston Mike McEwan Dai Yuki Ashraf El Amin Mohamadi Sarkar	RAI ALCS BAT JT PMI ALCS

Work in Progress – NWIP 363

- Initial Search: 230 publications

- Accept: 118
- Reject: 112

- Create Evidence Table

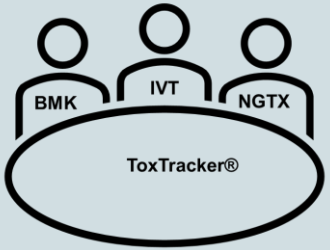


- SCOPUS SEARCH (June 9, 2023)
- Search Terms: copd AND gold OR moderate OR mild AND tobacco OR smok* AND clinic* OR human AND imag* OR ct OR mri (limited to >2012 years, English, and articles) =

- Imaging Technique used
- Endpoints
- Study Groups
- Study Design
- Sample Size
- Imaging parameters Associated with other biomarkers

- Relation to Disease
- Demographics
- COPD Stage
- Key Findings
- Limitations

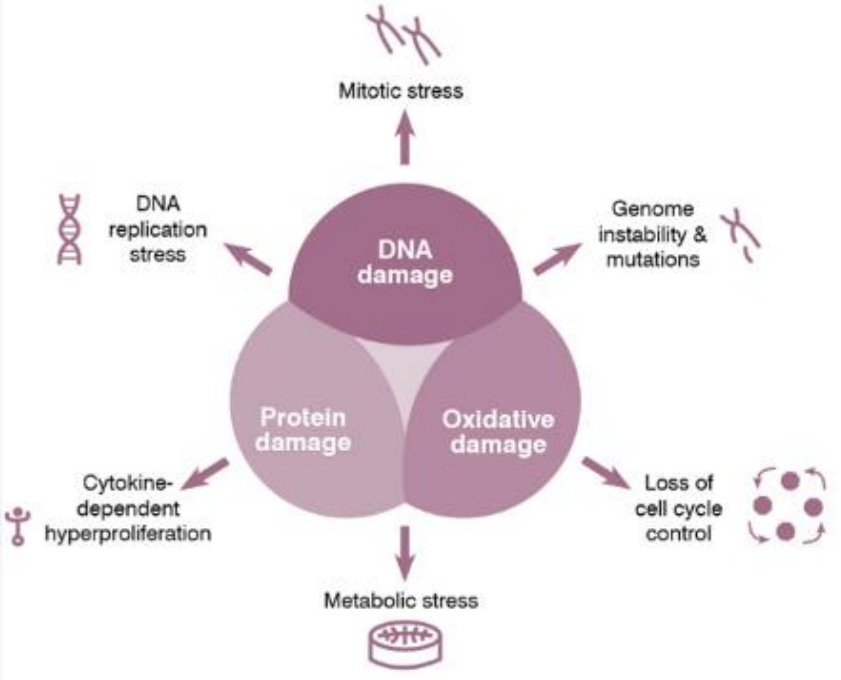
Ongoing Projects – NWIP 367

Project Description	Obj. #	Team Members	Company
Evaluation of ToxTracker[1] assay for applicability for tobacco related clinical research (BMK-NGTX-IVT Collaboration) **Objective:** • To determine if ToxTracker® Assay can be applied on samples collected from human clinical studies. • To assess biomarkers of DNA damage, protein misfolding, and oxidative and cellular stress.	#1 & #2	Kirk Newland (Lead) Marianna Gaca Damian McHugh Liam Simms Michael Hollings Katarina Aleksa 	Celerion BAT PMI Imperial LabCorp LabStat

What is ToxTracker®?

TOXTRACKER®

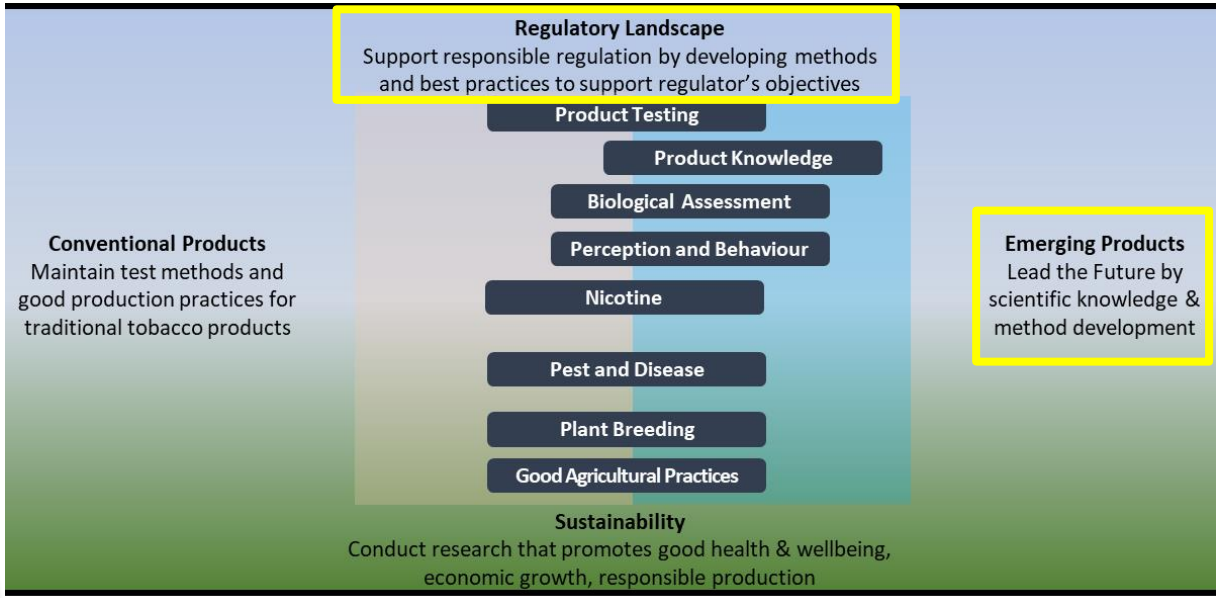
Predict and understand genotoxicity



Proposed Plan

- **Phase 0: (Q4 2023)**
  - **Develop and Finalize Testing Plan** ✓
- **Phase 1: (Q1 2024)**
  - **To determine the feasibility of the assay using concentrated urine from users of combustible cigarettes.**
- **Phase 2: (TBD – based on success of Phase 1)**
  - **To establish sensitivity and selectivity by conducting comparative analysis between urine samples from participants who have never smoked and those that smoke combustible cigarette users**
- **Phase 3: (TBD – based on success of Phase 2)**
  - **To evaluate a broad range of samples from studies with different products (HTPs, EVP and OTDN products).**

Upcoming Proposals: 5-year Strategy



Key Focus Areas – top 5

- **Risk Reduction to Harm Reduction**
- **Real world evidence** in PRRPs in the context of global regulations
- Supply chain considerations in THR
- Developing and applying **new methods/techniques/models to assess PRRPs** across all science areas
- Nicotine Science - Heath effects and misperceptions

Upcoming Proposals: 5-year Strategy

FDA U.S. FOOD & DRUG ADMINISTRATION

GUIDANCE DOCUMENT

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products

Draft Guidance for Industry

SEPTEMBER 2021

Upcoming Proposals: 5-year Strategy

	Projects	Obj. #	Team Members	Company
1	**Develop guidelines and best practices for collecting and analyzing Real World Data**	#3	Members of workstream to be determined	
2	**Develop robust understanding of mechanistic pathways and identify clinically relevant biomarkers for Cardiovascular Disease**	#1, #2 & #3	Tryggve Ljung Members of the COPD workstream	SWD Match

Note: The BMK SG will stay vigilant to identify emerging issues and develop new workstreams or modify/reprioritize proposed work streams