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PERSPECTIVE

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Applications of biomarkers of exposure and biological effects in users of new generation tobacco and nicotine products: Tentative proposals

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Abstract

Despite efforts to eliminate smoking, more than 1 billion people worldwide continue to use combustible cigarettes through choice or inability to quit. With an associated 8 million deaths, the provision of noncombustible tobacco and nicotine products that smokers will accept to replace combustible cigarettes can lessen harm. However, most of these products have entered the market only in the past 20 years. Therefore, particularly for some smoking-related diseases, epidemiological studies to test harm reduction potential are only now becoming feasible. For cancer and chronic obstructive pulmonary disease, around two decades of data might be required. In this article, we discuss how the use of biomarkers might be applied to supplement epidemiological research for regulators. We further discuss how health providers and insurers can keep up with the rapid changes in biomarker research and recognize these reduced risks.

KEYWORDS
biomarkers, combustible cigarettes, exposure, noncombustible nicotine and tobacco products, tobacco harm reduction

1 | INTRODUCTION

Combustible cigarettes (CCs) are currently smoked by more than 1 billion people and account for nearly 8 million deaths worldwide. The US Surgeon General Report of 1964 (the Terry Report) can be regarded as the first milestone in the fight against the deadly consequences of tobacco smoking, in particular the habit of cigarette smoking.[1] Smoking cessation and prevention of adolescents starting to smoke are indisputably the most effective and preferable ways to reduce tobacco harm. Despite tremendous efforts, elimination of exposure to combustible tobacco products has not been (and probably never will be) accomplished.[2] Continued use of tobacco and nicotine worldwide, through choice or inability to quit, strongly indicates that a third route is viable: the provision of products to smokers that can replace CCs and lessen harm. This approach was supported by the pioneering 2001 report of the Institute of Medicine *Clearing the Smoke*,[3] which defined tobacco harm reduction products as those that lower total tobacco-related mortality and morbidity even though use of that product may involve continued exposure to tobacco-related toxicants, although largely reduced. The term is also now enshrined in World Health Organization's agreed approach to tobacco control, which it describes as "a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke."[4] Noncombustible tobacco and nicotine products offer a promising way to comply with these requirements. For example, due to the long-established use of snus (oral moist tobacco pouches) in Sweden, male lung cancer and mortality rates have fallen

dramatically and risk has been reduced for individual users and the population.[5] Data from countries where electronic cigarettes (ECs) are widely available suggest that they have a role in helping smokers to quit CCs.[6]

Epidemiology is the most suitable tool for assessing human risks for chronic diseases. However, as most new generation tobacco and nicotine products (NGPs) entered the market only in the past 10–20 years, the use of epidemiology to establish their harm reduction potential, both at the individual and population levels, will not be feasible for these products for around two decades. Given availability, smoking cessation goals, and the recognition in some countries that regulation is more advantageous than bans, the use of biomarkers as a surrogate approach to establish reductions in individual risk has been suggested.[3,7,8] Indeed, this science now forms an important basis for industry submissions to regulatory bodies like the US Food and Drug Administration (FDA). Biomarkers could also inform wider understanding of reduced risk to smokers.

In this article, we discuss how the use of biomarkers might be applied not only to support epidemiological research but also to maximize their role in understanding the benefits of tobacco harm reduction.

2 | NEW GENERATION TOBACCO AND NICOTINE PRODUCTS

The main NGP categories are ECs, heated tobacco products (HTPs), and (tobacco-free) oral nicotine pouches (NPs). In ECs, a mixture of propylene glycol and vegetable glycerol, often with nicotine and flavors added, is aerosolized at up to 350°C and inhaled. In HTPs, tobacco is heated to a maximum of roughly 350°C so that it does not combust but does release an aerosol containing nicotine and some volatile tobacco constituents. Flavors may also be added. Compared with CCs, most toxicants (e.g., aldehydes and epoxides) in EC and HTP are at least 95% lower.[9] NPs are used in a similar way to snus but contain nicotine without tobacco. They are placed between the lip and gum to allow buccal absorption of nicotine over around 30–60 min.[10]

Prevalence of use for HTPs and ECs varies depending on the country, but percentages are all in the single-digit range.[7,8] Consumption of NPs, being newer to the market, is still at least a factor of 10 lower.[11] Despite the small market shares, NGPs are already relevant to public health and will continue to grow. Therefore, a solid evaluation of health risks implicated with the use of NGPs is of paramount importance.

3 | BIOMARKERS FOR SMOKERS AND NGP USERS

In general, two types of biomarkers are used in tobacco/nicotine product research: biomarkers of exposure (BOE) and biomarkers of biological effect (BOBE). BOE are metabolites (or the parent compound) taken up by the user and measurable in body fluids (blood, urine, or saliva), exhaled breath, tissues, cells, or other biological material. Noninvasively obtainable biological matrices, such as urine, saliva, and exhaled breath, are highly suitable for biomarker determinations in field studies. The half-lives of BOE determine whether the short-term (hours to days), medium-term (days to weeks), or long-term (months) use of the products is reflected by the observed levels. Another important property of BOE is the specificity for a product. For most BOE, other sources of exposure have to be considered. Established examples of BOE in cigarette smoke together with some important properties are presented in Table 1. The level of a BOE should reflect the constituent dose at exposure. BOBE, also referred to as biomarkers of risk or potential harm,[7] are heterogeneous and usefulness is highly dependent on the purpose for which they are deployed (e.g., risk prediction, physiological change, and disease outcome surrogate). In the context of this paper, we discuss BOBE indicating early physiological changes caused by smoking or use of NGPs that could, over a long period (usually years), lead to a disorder or disease. Table 2 shows some BOBE, which would meet these requirements. BOBE are by no means specific for use with individual products. The influence of other causes has always to be considered and, if possible, controlled for.

Ideal biomarkers for assessment of tobacco harm reduction will distinguish differences in exposure to compounds between NGP users, smokers, and never smokers. The duration of exposure needs to be known, as some chemicals are removed from the body rapidly (hours to days), whereas others remain for weeks or months. Alternative sources of compounds (e.g., foods, environmental pollutants, or endogenous formation) must be taken into account as these can confound accurate measurement. Additionally, many people use a variety of products (dual or multiple product users). Therefore, distinguishing the effects of different exposures may be challenging. BOE have been widely used in controlled clinical and open field studies investigating exposure to constituents in NGP aerosols. By contrast, BOBE are less widely used. A general problem with the application of BOBE is that they often indicate changes with multiple causes and potential effects (Table 2). Furthermore, the probability of early changes eventually leading to a given disease, reversibility, and (exposure) dose dependency are not well defined.[7,23] Adverse outcome pathways are proposed for the major smoking-related diseases, such as chronic obstructive pulmonary disease,[24] cardiovascular disease,[25] and lung cancer.[26] Despite this, substantial further work is needed before BOBE can be used as surrogate endpoints for disease, and those employed in studies now must be carefully selected.

4 | APPLICATION OF NGP-RELATED BIOMARKERS

NGP-related biomarkers, both BOE and BOBE, can be beneficially applied in a number of ways and in a range of fields. As mentioned above, they have been used to assess the tobacco harm reduction potential of NGPs, particularly BOE but also BOBE,[23,27–32] in cross-sectional, longitudinal, and switching studies.

TABLE 1 Biomarkers of exposure of selected tobacco smoke constituents.

Biomarker (abbreviation)	Biological matrix	Smoke constituent (parent compound)	Half-life ($t_{1/2}$)	Other sources
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	Urine	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	10–45 days	None[12]
3-Hydroxypropyl mercapturic acid (3-HPMA)	Urine	Acrolein	5–9 h	Food (heated fat), combustion exhausts, and endogenous formation[13]
3-Hydroxy-1-methylpropyl mercapturic acid (HMPMA)	Urine	Crotonaldehyde	5–9 h	Traffic exhausts and food[13]
Monohydroxybutenyl mercapturic acid (MHBMA)	Urine	1,3-Butadiene	5–9 h	Traffic exhausts and some workplaces[14]
2-Hydroxyethylmercapturic acid (HEMA)	Urine	Ethylene oxide	<5 h	Exhausts and oxidation product of ethylene (exogenous and endogenous); HEMA also formed from acrylonitrile and vinyl chloride[14,15]
4-Aminobiphenyl (4-ABP)	Urine	4-Aminobiphenyl	15 h	Hair dyes, grilled and fried food, and traffic exhausts[16]
2-Aminonaphthalene (2-AN)	Urine	2-Aminonaphthalene	Unknown	Hair dyes, traffic exhausts, and grilled and fried food[16]
o-Toluidine (o-tol)	Urine	o-Toluidine	12–15 h (in rats)	Ubiquitous occurrence, traffic exhausts, hair dyes, and grilled and fried food[17,18]
1-Hydroxypyrene (1-OHP)	Urine	Pyrene	6 h	All combustions and food[19]
Exhaled carbon monoxide (eCO)/carboxyhemoglobin (COHb)	Exhaled breath or blood	Carbon monoxide	1–4 h (Peck et al., 2018)	All incomplete combustions and endogenous formation
Total nicotine equivalents (Tneq)	Urine	Nicotine	2–17 h (varies by metabolite)	Trace amounts in some edible plants[20]
S-phenyl mercapturic acid (S-PMA)	Urine	Benzene	6–12 h	Mineral fuels and combustions[21]
2-Cyanoethyl mercapturic acid (CEMA)	Urine	Acrylonitrile	~8 h	Some workplaces[22]
N-(2-cyanoethyl)valine (CEVal)	Blood (erythrocytes)	Acrylonitrile	Associated with RBC lifecycle (90–120 days)	Some workplaces[22]

Abbreviation: RBC, red blood cell.

TABLE 2 Biomarkers of biological effect relevant to combustible cigarettes and new generation noncombustible tobacco/nicotine products.

Biomarker (abbreviation)	Indication	Association
High-density lipoprotein cholesterol (HDL)	Lipid metabolism	CVD
Augmentation index (AI)	Arterial stiffness	CVD
Pulse wave velocity (PWV)	Arterial stiffness	CVD
White blood cell count (WBC)	Inflammation	CVD, COPD, and cancers
C-reactive protein (CRP)	Inflammation	CVD, COPD, and cancers
Fibrinogen	Inflammation	CVD, COPD, and cancers
Forced expiratory volume in 1 s (FEV_1)	Lung health	Respiratory disease
Club cell protein 16 kDa (CC16)	Lung health	Respiratory disease
Fractional exhaled nitric oxide (FeNO)	Bronchodilation/vascular tone	Respiratory disease and CVD
Soluble intercellular adhesion molecule-1 (sICAM)	Endothelial dysfunction	CVD
Thromboxane (11-dTx B2)	Platelet activation/coagulation	CVD
Lipid peroxidation: 8-Isoprostance (8-epi-PGF-2α)	Oxidative stress	CVD, COPD, and cancers
Lipid peroxidation: Malondialdehyde (MDA)	Oxidative stress	CVD, COPD, and cancers
8-Hydroxy-2′-deoxyguonosine (8-OH-dG)	Oxidative stress	CVD, COPD, and cancers

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Biomarker data are now forming useful contributions among many lines of evidence indicating appropriateness for the protection of public health in NGP regulatory submissions. In the United States, such studies have been instrumental in the marketing authorizations being granted to selected HTPs, a few ECs, but as yet no NPs. The evidence has been deemed sufficient to show that marketing of these products would be appropriate for the protection of the public health by reduced exposure or risk compared with CCs. This classification has a significant impact on the product choice of potential NGP users because perception plays an important part in the decision to switch partly or entirely away from smoking.[33]

Biomarker data are also of value for the manufacturers of NGPs. Several studies have been conducted by manufacturers on NGPs, including studies on BOE and BOBE as well as nicotine pharmacokinetics. They add supporting information about product efficacy and confirm reduced exposure and favorable changes in biological effects.[34,35] This information may be used to improve future product development (e.g., new iterations of an existing product).[36]

Epidemiology may benefit from NGP-related biomarkers in at least two ways. They may be used to verify objectively compliance of (exclusive) NGP use and no additional use of CCs in the short term (e.g., by measurement of exhaled carbon monoxide/carboxyhemoglobin or cotinine), medium term (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol), and long term (N-[2-cyanoethyl]valine; Table 1). Furthermore, if BOBE can be suitably validated, they could prove (or disprove) the beneficial effects of NGPs in switchers much earlier than classic epidemiological endpoints, such as morbidity and mortality.

Life and health insurance companies have traditionally delineated smokers from nonsmokers to determine premiums. However, in a major review of insurer practices for assessing smoking status revealed issues with risk weighting and detection.[37] Most companies included all current users of nicotine products (including nicotine-replacement therapy) in the smoking risk category, irrespective of the last use of CCs. Furthermore, 91% relied on self-declaration of status. The other 9% measured cotinine levels, but this is an inadequate biomarker for differentiating smokers from users of NGPs.[38,39] To identify the highest risk group, CC smokers, additional (to cotinine) measurement of a biomarker of combustion as a BOE (e.g., acrylonitrile or acrolein) might be more useful to measure. Measurement of 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol would also be feasible. The inclusion of N-[2-cyanoethyl]valine would provide information on long-term smoking behavior. Of note, BOBE are not useful in this context.

5 | OUTLOOK

We suggest several approaches to maximizing the role of biomarkers in the areas indicated. Research on the identification of new and validation of all BOE and BOBE is worthwhile, given their potentially broad applications. Stable-isotope-labeled NGP constituents[40,41] and the use of untargeted approaches in body fluids of NGT users have shown promising results.[42] Relations with innovative biotech and digital health companies should be procured and developed to find new ways to reduce the harm through new technologies. These could range from new device components to personalized monitoring products to assess real-world health outcomes during smoking cessation and product switching. The progress already made in developing and validating biomarkers needs to be extended and widely disseminated to the health and medical community. This should be followed by discussions and consensus on which biomarkers will be most relevant to epidemiological research and the development of guidelines for their use. Ideally, the leading funders, such as the FDA Tobacco Centers of Regulatory Science and National Institutes of Health/FDA programs, should be encouraged to consider evidence for selected biomarkers that is incorporated into research, particularly that required for regulatory approval of NGPs and as part of post-marketing surveillance.

Engagement between leaders in public health and the life insurance industry and its trade organizations, such as LIMRA and LOMA (formerly the Life Insurance Marketing and Research Association and the Life Office Management Association), would be welcomed to ensure adoption of best practices for individuals who choose to quit smoking CCs by switching to NGPs or nicotine-replacement therapy.

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CONFLICT OF INTEREST STATEMENT

Derek Yach was previously employed by the World Health Organization (WHO) where he led the development of the Framework Convention on Tobacco Control (FCTC) and, later, the Foundation for a Smoke Free World (FSFW). He currently provides consulting services to a range of clients, including those working on reduced risk nicotine products. Gerhard Scherer is employed by ABF GmbH, an accredited bioanalytical laboratory focused on analysis of BOEs and BOBEs within clinical and epidemiological studies, which has previously received funding from FSFW for some biomarker development research. DY and GS did not receive any funding to write this article.

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