Redefining Precision Cancer Prevention to Promote Health Equity

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Abstract

Precision cancer prevention as it is currently envisioned is a targeted, molecular-based approach to intercept carcinogenesis before cancer develops or before it becomes untreatable. Unfortunately, due to systemic biases, current precision cancer prevention interventions may not be effective in all populations, especially in minoritized communities. In addition, not all cancer risk is attributable to genetic or even biological factors but includes social determinants of health. Here, we propose a broader framework for precision cancer prevention, anchored in optimizing the benefits to harms for all people. We propose that precision cancer prevention considers not just what is being delivered but for whom, how, when, and where, with a goal of achieving cancer prevention health equity.

Keywords: Precision Cancer Prevention; health disparities; Health Inequities

Introduction

Over the last several decades, as precision oncology has entered mainstream medicine, there has been an increased interest in applying the same approach to cancer prevention, i.e., "precision cancer prevention." Seen through the lens of precision oncology, precision cancer prevention is a targeted, molecular-based approach to prevention based on knowledge of the natural history of cancer, carcinogenesis, and individual susceptibility. Rebbeck *et al.* [1] wrote "a precision prevention and early-detection (PPED) strategy can be defined to consider the mechanistic underpinnings of the carcinogenesis process, as well as the corresponding inter-individual variation in risk and response to preventive interventions."

While such an approach applied to cancer prevention, including early detection, is potentially transformative, it considers only the biological basis of cancer risk. That is, it assumes that all risk can be measured through using biospecimens to assess inherited or acquired genomic susceptibility and biomarkers of risk. Indeed, a 2017 survey found that of 108 precision medicine programs identified, 84% relied on data derived from biospecimens [2]. Yet, much of the individual variation in cancer risk, even those with family history of cancer, has yet to be explained by specific, known genetic variants [3-6]. Moreover, most epidemiology and genomic studies of cancer are not representative of the general population and lack sufficient statistical power to examine biomarkers of cancer risk in important sub-populations, such as racial and ethnic minority groups, who are disproportionately burdened by cancer [7-9]. For example, The Oncotype DX Breast Recurrence Score test has lower prognostic accuracy in *African American women* than in *White women*, likely the result of structural biases in its development [10]. Therefore, risk models and mechanistic underpinnings for targeted prevention, as they are often currently developed, have the potential to exacerbate rather than close gaps in health inequities.

Here we posit that an underpinning of precision cancer prevention is advancing health equity, given its goal to identify and serve populations with disproportionate cancer burden or excess exposure to deleterious cancer risk factors. Advancing health equity in the context of cancer prevention is defined as preventing differences experienced by historically underserved individuals and communities vs. those who are well served. This way targets the most effective interventions to the right population and reduces harms—the fundamental goal of precision cancer prevention.

Expanding the Definition to include Social determinants of health

Social determinants of health (SDH) has long been a major driver of cancer disparities and must be incorporated into a precision cancer prevention paradigm. SDH helps define the elements of who, what, when, where, and how cancer prevention and early detection approaches can be focused to lessen cancer burden and improve health equity. SDH include data that influence personal cancer risk, often more strongly than inherited risk, and facilitate major cancer risk factors such as smoking, obesity, and infection. Where these factors congregate, e.g., in distressed communities with contaminated air and water, poverty, low levels of education and social support, high levels of childhood adversity and psychosocial stress, and limited access to quality medical care, "high risk" can be delineated even without a full understanding of how these factors promote the "under the skin" effects on carcinogenic pathways. Community-based interventions could be deployed in these areas using existing or new facilities that focus on preventive care and risk reduction.

Precision cancer prevention activities should proceed with a clear eye to overcome rather than aggravate existing health disparities. There are numerous examples of precision medicine

78 modalities and technologies implemented inequitably across socioeconomic status,
79 race/ethnicity, geography, and health insurance type [11-15]. Similar problems already exist for
80 current cancer prevention strategies [16,17]. For example, current prophylactic human
81 papillomavirus (HPV) vaccines do not target HPV35, which causes more cervical precancer and
82 cancer in *Black women* than in *White women* due to that specific viral variant [18-25].

83 Moreover, socioeconomic disparities in cancer mortality in the US are widening, especially for
84 cancers deemed most amenable to prevention (e.g., lung, liver, cervix, and colorectal) [26]. Thus,
85 precision cancer prevention is tasked with making up lost ground and devising focused strategies
86 that draw from best practices in implementation science that can overcome bias, cost, physician
87 and patient education, and inadequate access to the right intervention in the right place at the
88 right time. If we use a broader definition of precision cancer prevention that considers the
89 continuum of care, we can provide better approaches for precision cancer screening and
90 prevention to reduce health inequities:

91 *"Precision cancer prevention is the equitable provision of a targeted, preventive*
92 *intervention to mitigate one or more biological, demographic, or social determinants of*
93 *cancer risk while minimizing its harms."*

94 Rather than focusing on one component of cancer risk, we can consider all genetic and non-
95 genetic determinants of cancer risk [27], as well as each step in the delivery continuum for
96 cancer prevention, as an opportunity to be more "precise" and inclusive. In this way, we can
97 incorporate strategies that increase equity in cancer prevention for all groups and individuals.

98 To achieve better precision cancer prevention, we must develop "products" that more people
99 want and can use and have a "product profile" that improves the overall health of the population.

To better understand the wants and needs of the consumer of the prevention “product”, we need to engage people through a variety of community outreach activities such as representative advisory panels. The oft-cited African proverb: "If you want to go fast, go alone; but if you want to go far, go together." might aptly fit here. Otherwise, we may develop underused and thus, ineffective, cancer prevention interventions.

Maximizing the Benefits-to-Harm Ratio

A second fundamental, organizing principle of precision cancer prevention is optimizing the benefits-to-harms ratio (B:H), at both the individual and *population* level. Benefits are the delay, prevention, or early detection of cancer and prolongation of disease-free living. Harms include, but are not limited to, identification and treatment of clinically irrelevant cancer that would never cause death; false-positive tests that induce anxiety and result in unnecessary, sometimes invasive procedures to confirm falseness; adverse events from preventive interventions; and costs to the individual and the health system.

By our working definition, precision cancer prevention strategies are those that maximize B:H by recognizing that cancer risk, and its mitigation, is multidimensional and not just biological. Tailoring interventions that increase access to proven cancer preventive interventions is another form of “precision” that increases *population* benefits. Thus, we can consider not just “what” but also the “who”, “how”, and “where” the cancer preventive intervention is being delivered as an opportunity to improve its precision (Table 1 and Figure 1).

In this framework, “what” is the targeted, molecular approach based on the mechanistic understanding of carcinogenesis. In its simplest conception, a biomarker of risk is measured, neutralized directly, and monitored for enduring risk reduction. As noted above, limitations and

biases in how we have developed a mechanistic understanding of cancer development impedes our ability to deliver an effective preventive intervention to all.

The "who" represents which individuals or populations need the intervention, i.e., their risk, which is a measure of B:H. Typically, the focus is on those who are at higher risk for cancer due to genetic susceptibility (i.e., high-penetrance, germline mutations such as BRCA1/2 or Lynch syndrome) or due to evidence of predisposing condition (e.g., precancer/precursor), defined as the "high-risk approach" [1]. The higher the risk, the greater the benefit per individual. Consequently, assuming that harms are similar across sub-groups (which may or may not be valid), those sub-groups at higher risk "on average" experience a better B:H. However, what places an individual or population at a higher risk and the strategy to reduce that risk often, albeit not always, are related biologically. Moreover, not all prevention is done in the context of high risk but in the general or average risk individuals, in whom most cancers (in absolute numbers) occur ("Prevention Paradox") [28]. Whether a preventive intervention use is justified in the general, average-risk population depends on the B:H as, on a population basis, fewer will benefit and incrementally more will be harmed. Finally, increased risks are not always biologically driven but influenced by or related to SDH , thereby underscoring the need to view cancer prevention through a health-equity lens.

A risk-decision model for interventions, which can incorporate biological, demographic, and social determinants of risk, can be used to decide who needs prevention while accounting for health inequities. Importantly, risk-based model for inventions can promote "equal care for equal risk" [29] across different populations. For example, established individual-level non-modifiable risk factors for prostate cancer might include age, family history, genetic susceptibility, and African ancestry. Thus, precision cancer prevention should place a focus on understanding

cancer-site specific etiology within special populations in hopes of identifying factors that would allow for the development of interventions to reduce disease morbidity and mortality. Decisions to intervene (or not) and subsequent steps are dictated by clinical action thresholds (CAT), which should be determined by B:H and societal acceptance of those tradeoffs. For example, in the case of screening, who gets screened, how they are followed up in relationship to their screening result, who among the screen positives get biopsied, and how the disease is managed is guided by CATs (Figure 2). Risks are updated (*post-hoc* risks) based on the results/effectiveness of the intervention and *a priori* risks. New metrics of benefit, such as quality life years gained rather than the traditionally used mortality [30], might move us closer still towards equity.

While higher-risk populations warrant greater attention, lower-risk populations need less, thereby increasing the population B:H. Lung-cancer screening by low-dose computed tomography is only recommended for those at highest risk, heavy smokers (a ≥20 pack-year smoking history and currently smoke or have quit within the past 15 years)[31], whereas it is not recommended in the lower-risk populations, despite more lung cancers occurring in this group. Women who screen negative for HPV are at much lower risk for cervical precancer and cancer than those negative by Pap testing and therefore can be screened safely at longer intervals, with lower potential harms of screening [32]. Those who have a negative HPV screening preceding a positive screen are at much lower risk than those who do not and therefore need less aggressive management [33,34].

We should not limit precision cancer prevention to biological and population measures of risk. How and where we deliver the preventive intervention can also improve precision while increasing health equity. Differences in cancer risk are also due to SDH that characterize "where" high-risk populations reside i.e., socioeconomic, geographical, occupational,

168 environmental, etc. For example, “hot spots” in cancer burden may suggest geographical (e.g.,
169 rurality) or environmental factors in cancer risk, which are not typically incorporated into risk
170 models. Notably, persistent poverty is an important risk factor associated with cancer mortality,
171 especially those cancers that are preventable [35]. First- and second-generation immigrants from
172 high-cancer burden countries continue to experience excess cancer morbidity and mortality [36-
173 40]. Social factors can superimpose on top of genetic determinants of disease e.g., Lynch
174 syndrome individuals living in Asian countries have a much higher incidence of gastric cancer
175 that is not apparent in individuals with European ancestry [41]. Strategies that target those spatial
176 determinants of cancer risk, such as geographically targeted interventions to improve
177 participation in routine cancer screening, can be cost-effective and increase health equity.

178 In addition, novel delivery strategies have the potential to improve B:H through increasing
179 access and adherence to a preventive strategy (increasing B) and/or limiting toxicities
180 (decreasing H). As an example of the former, there is strong evidence that human papillomavirus
181 testing of self-collected cervicovaginal specimens is an effective method of screening that
182 approaches the performance of provider-collected specimens [42]. This approach offers several
183 benefits including ease of collection at a time and place of women’s choice without need for a
184 clinic appointment and a pelvic exam using a speculum, thereby overcoming barriers related to
185 access and stigma. Indeed, HPV testing of self-collected specimens has been shown to increase
186 screening participation in underscreened or underserved populations and is preferred over clinic-
187 based screening [43-47]. Likewise, mailed, home-based fecal immunochemical testing (FIT) can
188 increase colorectal cancer screening of underserved populations [48,49]. That is, by bringing
189 specimen collection or testing into the home, individuals do not need to take off work and/or get

childcare—costs that constitute harms (i.e., financial toxicity)—to participate in cancer prevention activities.

It is important to note that developing a new prevention/screening method that might be more broadly adopted by the population without addressing the underlying disparities in healthcare delivery, including follow-up care (diagnosis and treatment) for screen positives, may worsen rather than reduce those disparities [50-58]. Point-of-care tests may allow additional diagnostics and care to be provided at the same encounter, which might reduce differential losses to follow-up. The COVID epidemic provided to the cancer prevention field an important reminder about the profound disparities in healthcare delivery of interventions for primary and secondary prevention, despite the development of effective vaccination and screening methods, respectively [59-63].

Finally, the unequal burdens of preventable cancers tend to cluster in the same populations due to the same causes. For example, high cervical cancer burden has long been recognized as "a marker for low access to health care in poor communities" [64]. Thus, bundling preventive interventions may address cancer and other health disparities concurrently, which might increase their effectiveness and cost-effectiveness, factors that are important in resource-limited settings and for the economically disadvantaged. There are data indicating that there are racially associated differences in adherence to medications [65-67], which might be reduced by local delivery or controlled release. One example, if effective, could include the topical application of tamoxifen derivatives in the prevention of breast cancer in high-risk individuals (e.g., atypical ductal hyperplasia and ductal carcinoma *in situ*), which might reduce systemic side effects (e.g., blood clots, stroke, endometrial cancer, hot flashes, nausea, fatigue, loss of libido, etc.) vs. taking tamoxifen orally. If continued dosing is needed, controlled release may result in fewer adverse

reactions by effectively delivering a dose within the "pharmaceutical window." Data suggest that there are racially associated differences in adherence to medications [65-67], which might be reduced with the use of controlled release. In addition, both approaches might increase adherence especially if they reduce side-effects from use of preventive agents that contribute to financial toxicity due missed work and lost wages by the economically disadvantaged.

Concluding Remarks

In conclusion, an alternative, working framework for precision cancer prevention rooted in community engagement and inclusivity as well as *population* B:H is needed to ensure that everyone benefits equitably from innovations in cancer prevention rather than exacerbating cancer health disparities (see Outstanding Questions). Such a framework could build from a recently published framework to address racism and rural cancer disparities [65]. Populations disproportionately burdened by cancer are likely to glean greater benefits, and therefore experience better B:H, from precision cancer prevention strategies than the general population. Like those with heritable cancer syndromes, they should be prioritized for precision cancer prevention interventions.

Outstanding Questions Box (2000 characters, including spaces, required)

1. Can a conceptual framework be developed to achieve greater precision and inclusivity for cancer prevention?
2. Can an equity lens for cancer precision prevention be used to overcome structural inequalities that have been linked to multiple poor health outcomes?
3. How can biological and social determinants of health disparities be best integrated to improve cancer prevention?

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Table 1. Tailoring interventions to improve equity in precision cancer prevention

Principle	Example
What	Removing biases that impede molecular, targeted approaches to understand the basic biology of carcinogenesis that may define a biomarker of risk.
Who	Identifying populations at greatest risk through biological factors and social determinants of health.
Where	Incorporating socioeconomic, geographical, occupational, and environmental factors.
How	Novel delivery strategies that increase access and adherence to a preventive strategy and/or limit associated toxicities.

Figure Legends

Figure 1. Precision cancer screening and prevention strategies. Great precision in cancer prevention can be achieved through considering population risk (who), which is determined by risk factors such as age, genetic, social determinants of health, and carcinogenic exposures e.g., environmental, smoking, alcohol, and infectious agents, biological risk (what), and how and where the intervention is delivered.

Figure 2. A generalized schema for risk-decision model for screening and management. Clinical action thresholds (CATs), based medical/societal/cultural-acceptable benefits-to-harms ratios, can be used to standardize care to achieve "equal care for equal risk". Risks are updated with each intervention in the care delivery continuum determine the subsequent care.

Figure 1

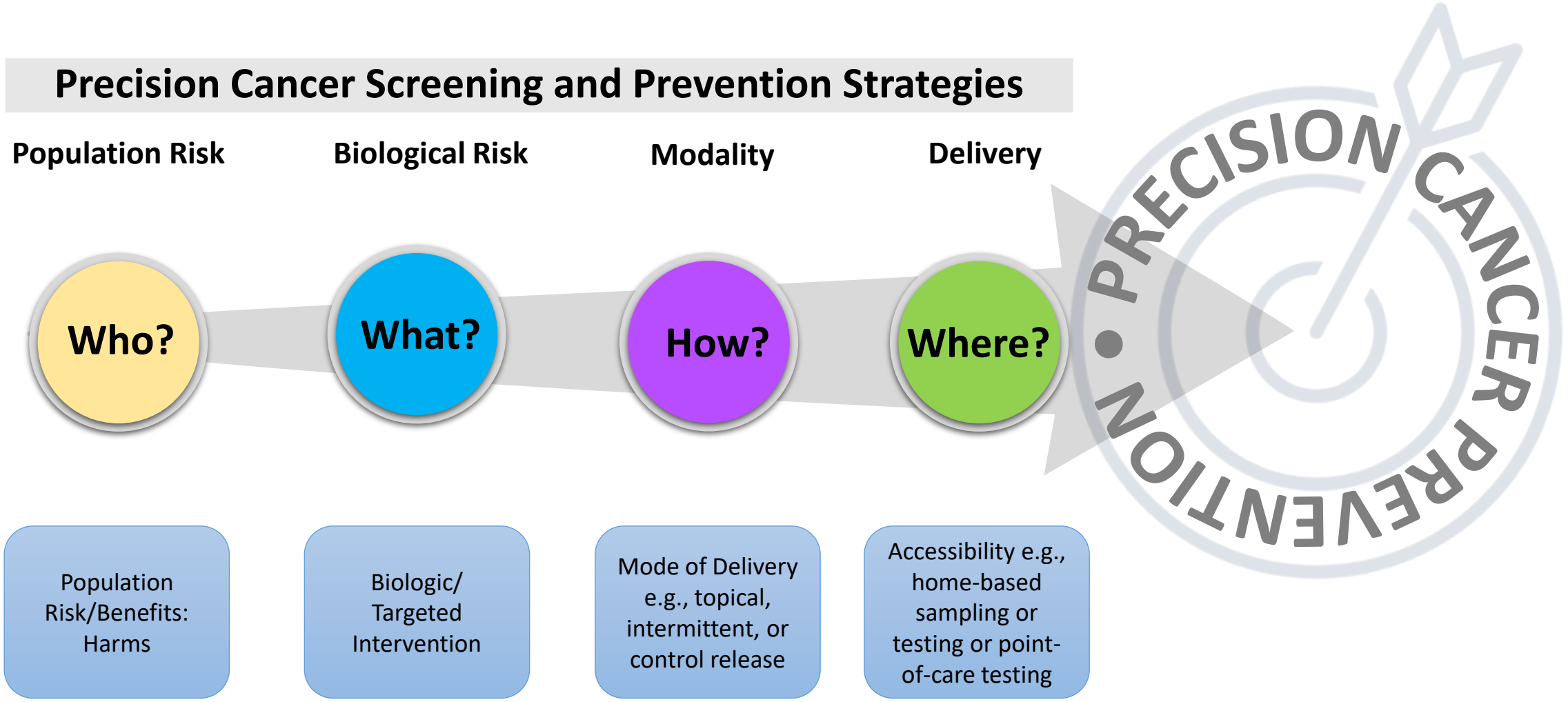
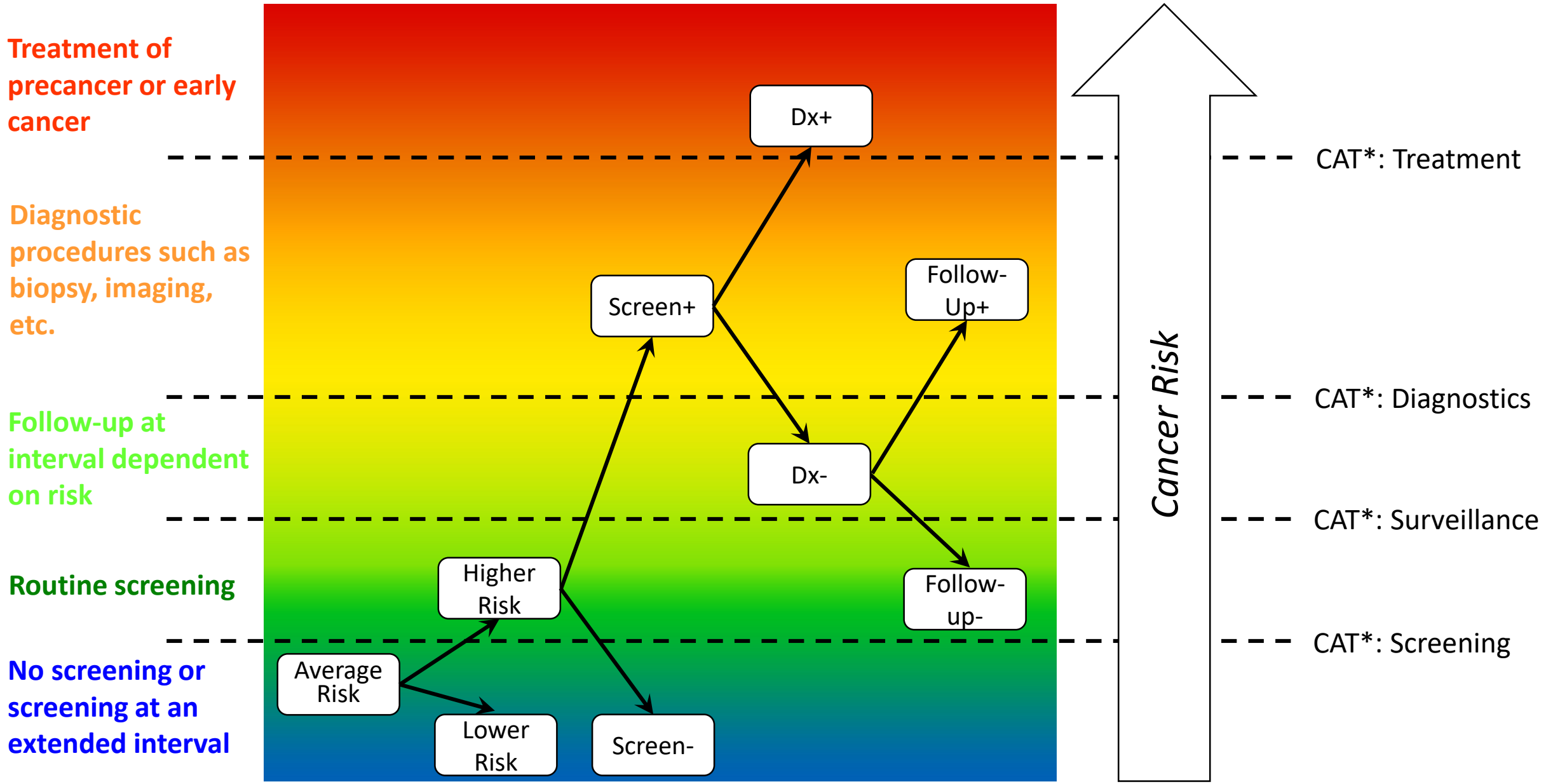

Precision Cancer Screening and Prevention Strategies
Population Risk
Biological Risk
Modality
Delivery
Who?
What?
How?
Where?
Population Risk/Benefits: Harms
Biologic/ Targeted Intervention
Mode of Delivery e.g., topical, intermittent, or control release
Accessibility e.g., home-based sampling or testing or point-of-care testing
PRECISION CANCER PREVENTION

Figure 2


Treatment of precancer or early cancer
Diagnostic procedures such as biopsy, imaging, etc.
Follow-up at interval dependent on risk
Routine screening
No screening or screening at an extended interval
Dx+
Screen+
Follow-Up+
Dx-
Follow-up-
Higher Risk
Average Risk
Lower Risk
Screen-
Cancer Risk
CAT*: Treatment
CAT*: Diagnostics
CAT*: Surveillance
CAT*: Screening