UCSF Helen Diller Family Comprehensive Cancer Center

Cancer Research Cancer Research in 2030 Cancer Research

Helen Diller Family Comprehensive Cancer Center Strategic Plan, 2020-2030:

CANCER RESEARCH AT UCSF IN 2030

UCSF Helen Diller Family Comprehensive Cancer Center

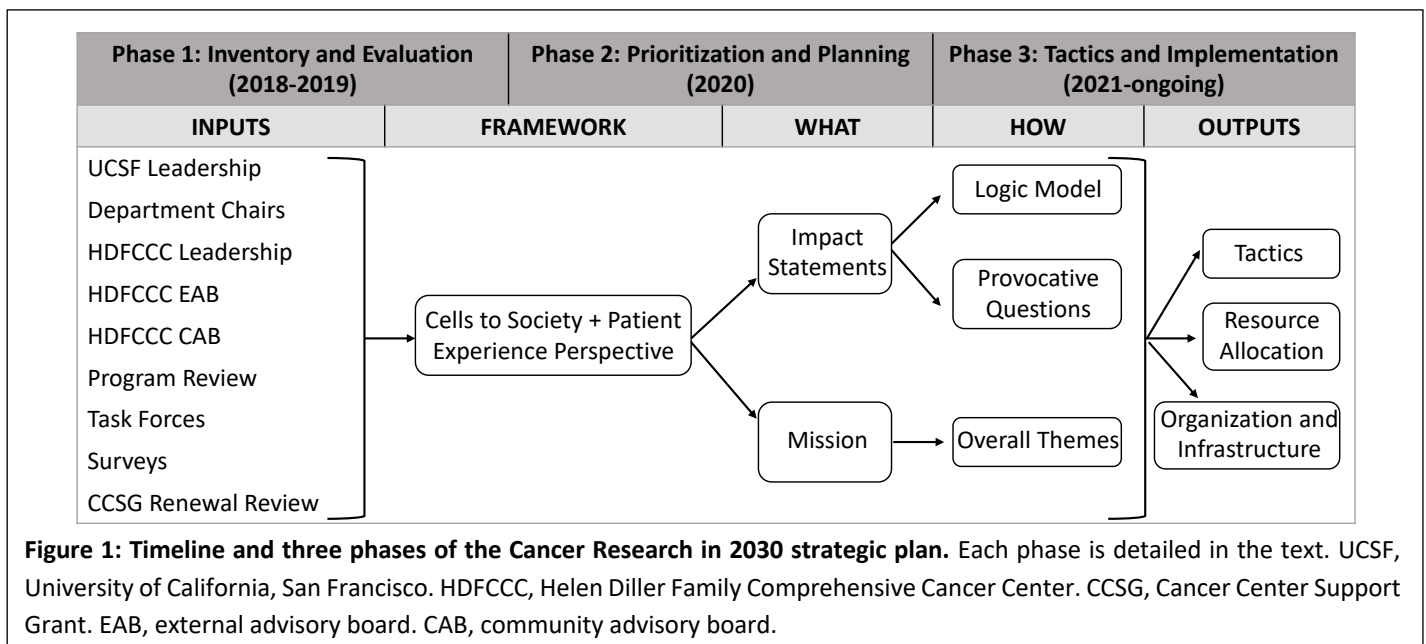Cancer Research Cancer Research in 2030 Cancer Research

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I. APPROACH

In considering a new strategic plan, Senior Leadership of the Helen Diller Family Comprehensive Cancer Center (HDFCCC); the Director, Deputy Director, and nine Associate Directors) developed the theme of "*Cancer Research in 2030*:" that is, what will cancer research look like at UCSF in 2030? This forward-looking focus was intended to encourage creativity unconfined by a particular institutional structure or five-year grant mechanism. Furthermore, the motivation for this strategic planning was not in reaction to a specific problem to solve, but rather to think about where cancer research was going in the near future, and with this vision to define an overall scientific direction, mission, and priorities. Focusing on the science and not the requirements of a funding cycle paved the way for an innovative, actionable, and motivating strategic planning process.

The HDFCCC *Cancer Research in 2030* strategic planning process began in 2018 and was divided into three phases (**Figure 1**). Phase 1, Inventory and Evaluation, captures the logistics of gathering input from a variety of stakeholders and creating a cohesive set of recommendations. Phase 2, Prioritization and Planning, encompasses the development of an innovative framework that defines the Center's philosophy for the next ten years. Phase 3, Tactics and Implementation, involves the creation of a logic model and Provocative Questions.

Figure 1: Timeline and three phases of the Cancer Research in 2030 strategic plan. Each phase is detailed in the text. UCSF, University of California, San Francisco. HDFCCC, Helen Diller Family Comprehensive Cancer Center. CCSG, Cancer Center Support Grant. EAB, external advisory board. CAB, community advisory board.

Phase 1: Inventory and Evaluation

HDFCCC leadership wanted to involve the entire HDFCCC membership in the *Cancer Research in 2030* process, in addition to considering feedback from UCSF leadership, the most recent CCSG review, and HDFCCC advisory groups. To identify areas of focus, a membership-wide Qualtrics-based survey was conducted to which 349 members responded (78% response rate). Senior Leadership defined three broad groups to engage (**Table 1**): (1) the ten extant CCSG Programs; (2) other research aggregations, not funded by the CCSG, such as (a) cancer site committees, which bring together clinical researchers, and (b) established and developing initiatives in research focus areas; and (3) thematic task forces, which were temporary working groups covering the cancer continuum from basic discovery research, to prevention, to diagnosis, treatment, and the delivery of cancer care. These groups,

comprising 214 members in all, participated in organized brainstorming and other focused discussions from August 2018 to September 2019. Internal HDFCCC administration and faculty leaders led these sessions, rather than a hired external consultant, to capitalize on the institutional knowledge and relationships these individuals have developed.

Table 1: Contributing groups to the HDFCCC strategic plan. Groups 1 and 2 were extant groups; Group 3 was convened for the purposes of Phase 1 of the planning process and then disbanded.			
(1) CCSG Programs	**(2a) Site Committees**	**(2b) Other Initiatives**	**(3) Thematic Task Forces**
Breast Oncology	Breast	Geriatric Oncology	Understanding the Mechanisms of Cancer (etiology)
Cancer Control	Cutaneous/Melanoma	Global Cancer	Preventing Cancer
Cancer Genetics	Cancer Control	Integrative Oncology	Detecting and Diagnosing Cancer
Cancer Immunology	Cancer Immunotherapy	Survivorship and Symptom Science	Developing Cancer Cures
Experimental Therapeutics	Experimental Therapeutics	Theranostics	Delivering Heath Care to All
Hematopoietic Malignancies	GI		Developing Tools to Study Cancer
Neurologic Oncology	GU		
Pediatric Malignancies	Gynecology		
Prostate Cancer	Hematopoietic		
Tobacco Control	Metabolic Imaging and Radioisotope Therapy		
	Neurologic		
	Oral, Head, and Neck		
	Pediatric		
	Radiation Oncology		
	Symptom Management		
	Thoracic		

All groups were asked to consider: (1) What cancer research will look like in 2030? and (2) What do we need to do scientifically to get there? Each group produced a brief white paper that outlined the current state of research, their predictions for 2030, what was needed to reach 2030 goals, and a summary of the themes that arose in discussion. The intent of these white papers was to ensure that all areas of current and anticipated cancer research would be represented. The scope was universal, with the focus on what could be accomplished by UCSF and the HDFCCC. HDFCCC Scientific Leadership and our External Advisory Board (EAB) identified the common themes and priorities across all white papers, to inform the next stage of developing a framework for the strategic plan. The intent was to ensure all forms of current and anticipated cancer research would be represented in the strategic planning process (**Figure 2**). The scope was universal, but the focus was internal to what could be accomplished by UCSF and the HDFCCC.

Figure 2: Schematic of Strategic Plan process leading to the overall roadmap: an iterative process with the framework document, provocative questions, and tactics. HDFCCC, Helen Diller Family Comprehensive Cancer Center. CCSG, Cancer Center Support Grant. EAB, external advisory board.
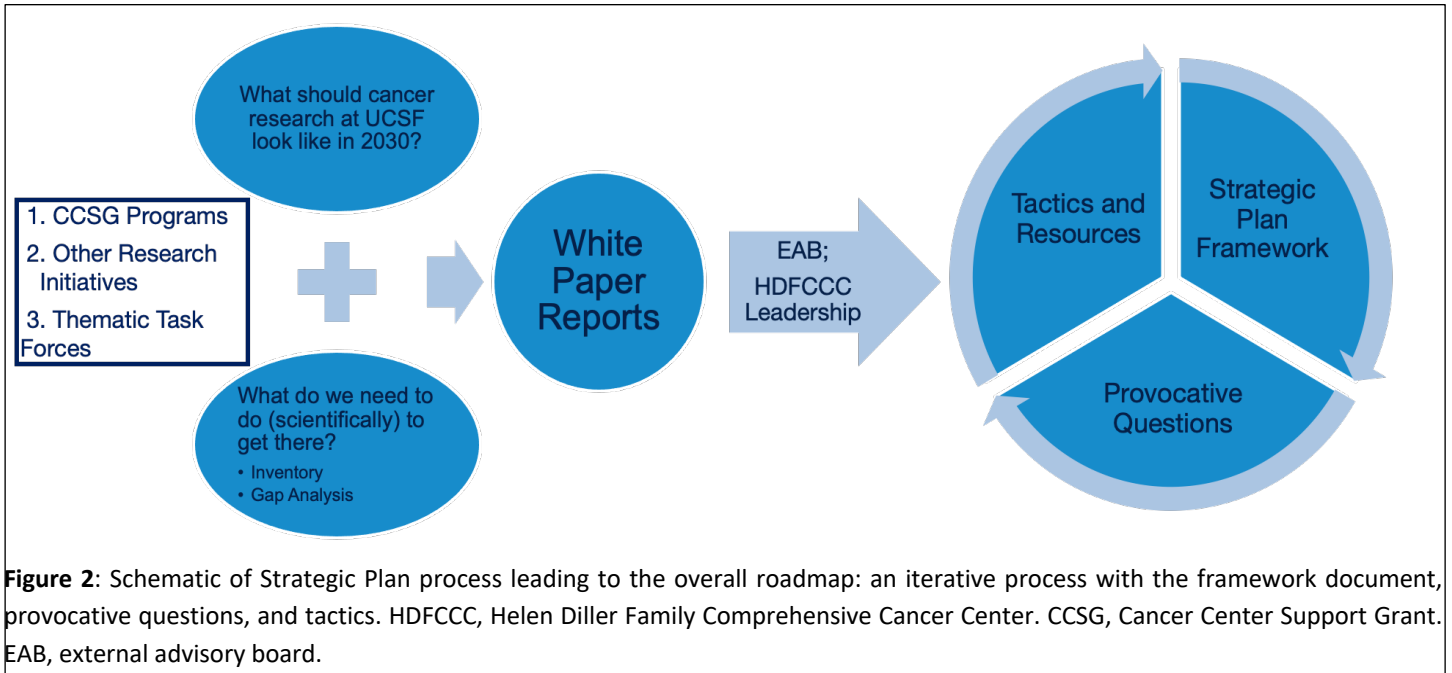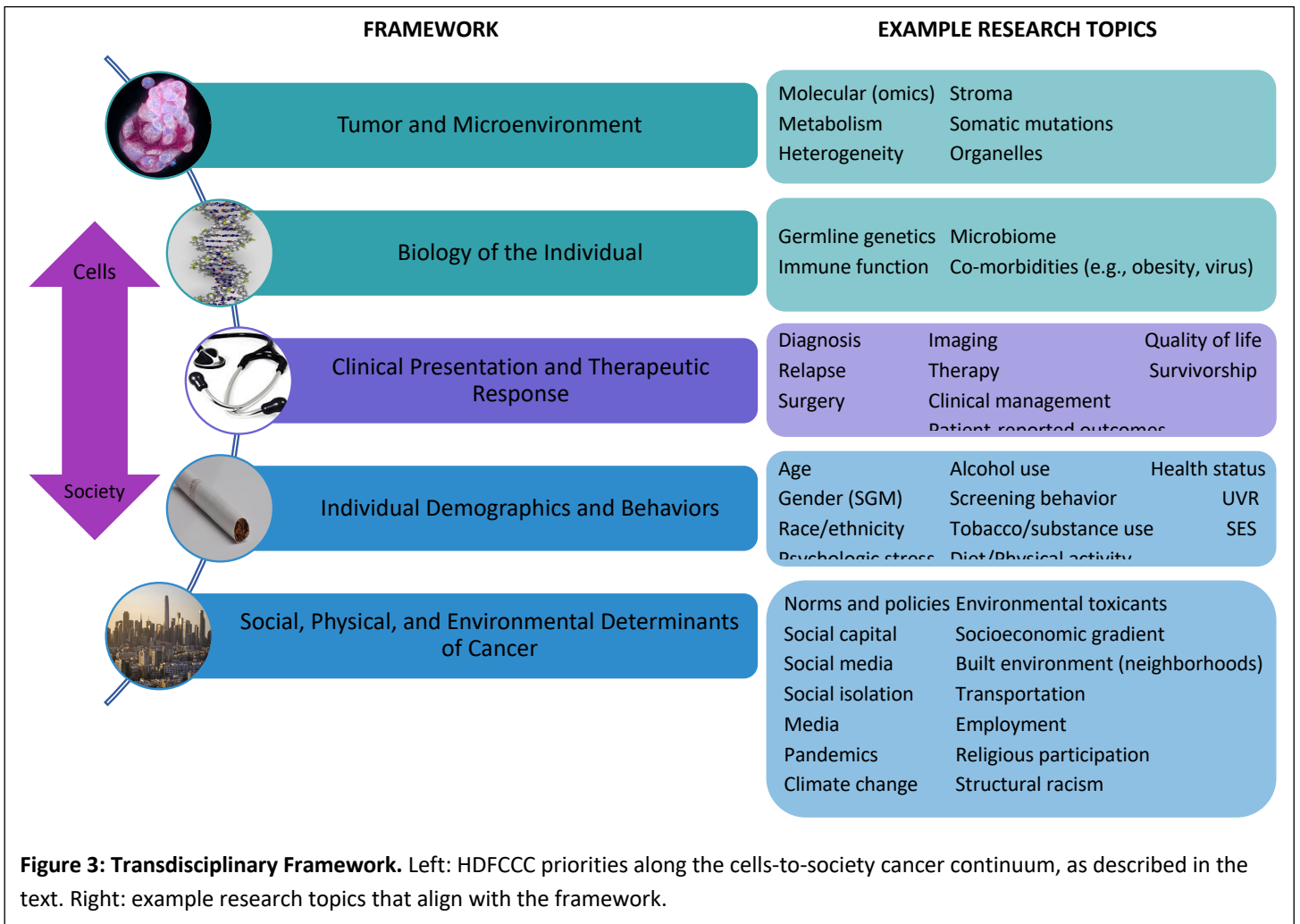
Phase 2: Plan and Prioritization

In order to define Center-wide mission, goals, research priorities, and provocative questions around which to provide institutional support, we developed the (1) **Transdisciplinary Framework** and (2) **Patient Experience Perspective Continuum** around which to organize the common themes and priorities. These are combined in order to drive the development of Provocative Questions, around which RFAs and other galvanizing support can be organized to provide tactics (resources, financial support) to drive research forward.

1. TRANSDISCIPLINARY FRAMEWORK

Transdisciplinary research encourages investigators from different disciplines to tackle critical scientific problems by sharing a common framework and their disciplinary perspectives while being open to the contributions of others.[1-3] Such frameworks, by definition, promote research questions and methodologies that are cross-disciplinary, based on team science, and are aligned with a translational "cells to society" ecosocial model.[4] An additional "society to cells" pathway also exists, by which the etiology of broader societal and demographic factors may be uncovered. This framework does not prioritize one area over another; rather, it shows how all areas are interconnected. Importantly, this perspective also defines pathways by which broader societal and environmental etiologic factors may be uncovered.[4, 5] Furthermore, this framework ensures that understanding and addressing inequities in cancer is woven into all levels across the cancer continuum.[6] **Figure 3** shows the research topics along each step of the framework that were identified in Phase 1.

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Cancer Research in 2030

FRAMEWORK

| Tumor and Microenvironment |
| Biology of the Individual |
| Clinical Presentation and Therapeutic Response |
| Individual Demographics and Behaviors |
| Social, Physical, and Environmental Determinants of Cancer |

Cells ⬍ Society

EXAMPLE RESEARCH TOPICS

Molecular (omics)   Stroma
Metabolism   Somatic mutations
Heterogeneity   Organelles

Germline genetics   Microbiome
Immune function   Co-morbidities (e.g., obesity, virus)

Diagnosis	Imaging	Quality of life
Relapse	Therapy	Survivorship
Surgery	Clinical management	
	Patient-reported outcomes	

Age	Alcohol use	Health status
Gender (SGM)	Screening behavior	UVR
Race/ethnicity	Tobacco/substance use	SES
Psychologic stress	Diet/Physical activity	

Norms and policies	Environmental toxicants
Social capital	Socioeconomic gradient
Social media	Built environment (neighborhoods)
Social isolation	Transportation
Media	Employment
Pandemics	Religious participation
Climate change	Structural racism

Figure 3: Transdisciplinary Framework. Left: HDFCCC priorities along the cells-to-society cancer continuum, as described in the text. Right: example research topics that align with the framework.

2. PATIENT EXPERIENCE PERSPECTIVE (CANCER CONTINUUM)

Although the focus of *Cancer Research in 2030* strategic plan is on research, it is crucial to understand the impact of research on how an individual encounters cancer research, prevention, and care not just in a clinical setting but also in the context of their community, social environment, and across the ecosocial spectrum. An individual progresses through disease prevention, detection and diagnosis, and treatment, and this journey is affected by the social determinants of health encountered by this individual as a member of society. These considerations resulted in a "Patient Experience Perspective" representing the continuum from individual and population health and disease prevention, to disease characterization, to clinical response, to survivorship and end of life (**Figure 4**).

1. **Individual and Population Health:** An individual is living their life, with a certain genetic background, certain biology, in a certain place, and following certain behaviors. Some may be individual risk factors for cancer, some risks are a function of the environment and not the individual, but all are factors that inform a person's eventual risk. In this "pre-tumor" phase, interventions focus on prevention, behaviors, early detection, and improving the environment at a social level in order to allow individuals to live in an equitable and healthy

environment and to make it easier to implement preventive measures and stay healthy. There is a loop here: health –> preventative measures –> change in health (etc.).

→ *Early Detection and Diagnosis* →

2. **Disease Characterization:** An individual may develop symptoms and be diagnosed with a tumor. Now, as a patient, their tumor biology becomes the focus including both the characteristics of the tumor and the microenvironment, and the interacting effects of the tumor and the broader characteristics of a patient (e.g., immune function, microbiome, environmental exposures).

→ *Intervention (Therapeutic and Non-therapeutic)* →

3. **Clinical Response:** Intervention(s) are implemented, targeting the tumor and the microenvironment, or patient biology. Layered on targeted therapies are non-therapeutic interventions (e.g., lifestyle, integrative medicine, diet). Here, data on clinical response, resistance, side-effects, etc. are important to drive clinical decisions. Also a factor here is the environmental framework that allows patient compliance, access to clinical trials, and support during care. There is a loop here: intervention –> response –> recurrence/side effects –> alter intervention –> response (etc.).

Figure 4: Patient Experience Perspective. See text for details.

→ *Quality of Life* →

4. **Survivorship and End-of-life:** The patient is on a quest to live a healthy life after cancer treatment, which may include symptom management, palliative care, monitoring/screening, changes in environment and behavior, integrative medicine, etc. These factors alter the individual biology as the patient re-enters the continuum cycle. This stage also includes accommodations for end-of-life care and wellness measures to provide comfort and dignity to individuals at the end of their life. Inherent in these discussions is an understanding of the patient's environmental framework that may affect decision-making and adherence to interventions.
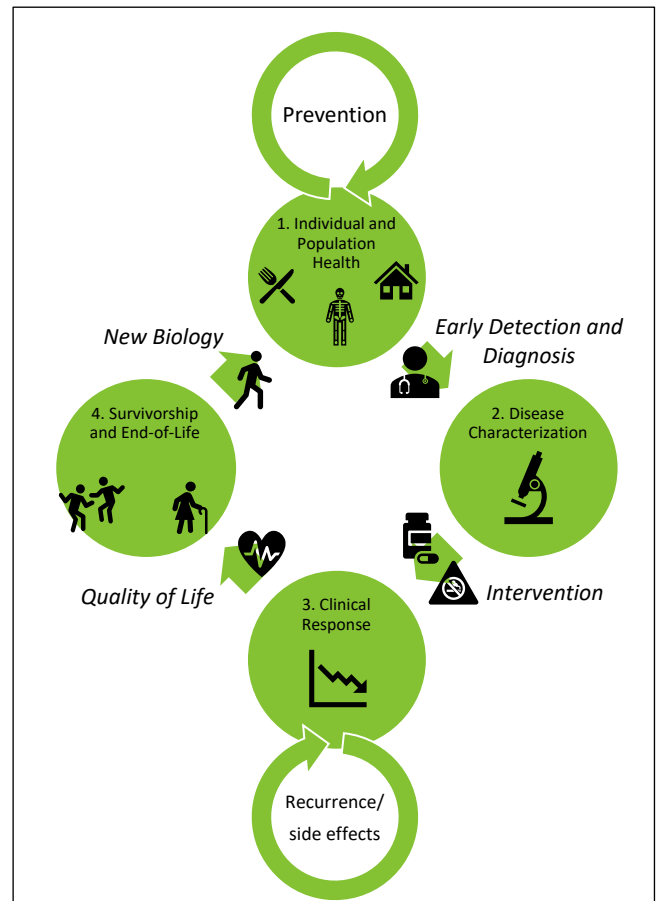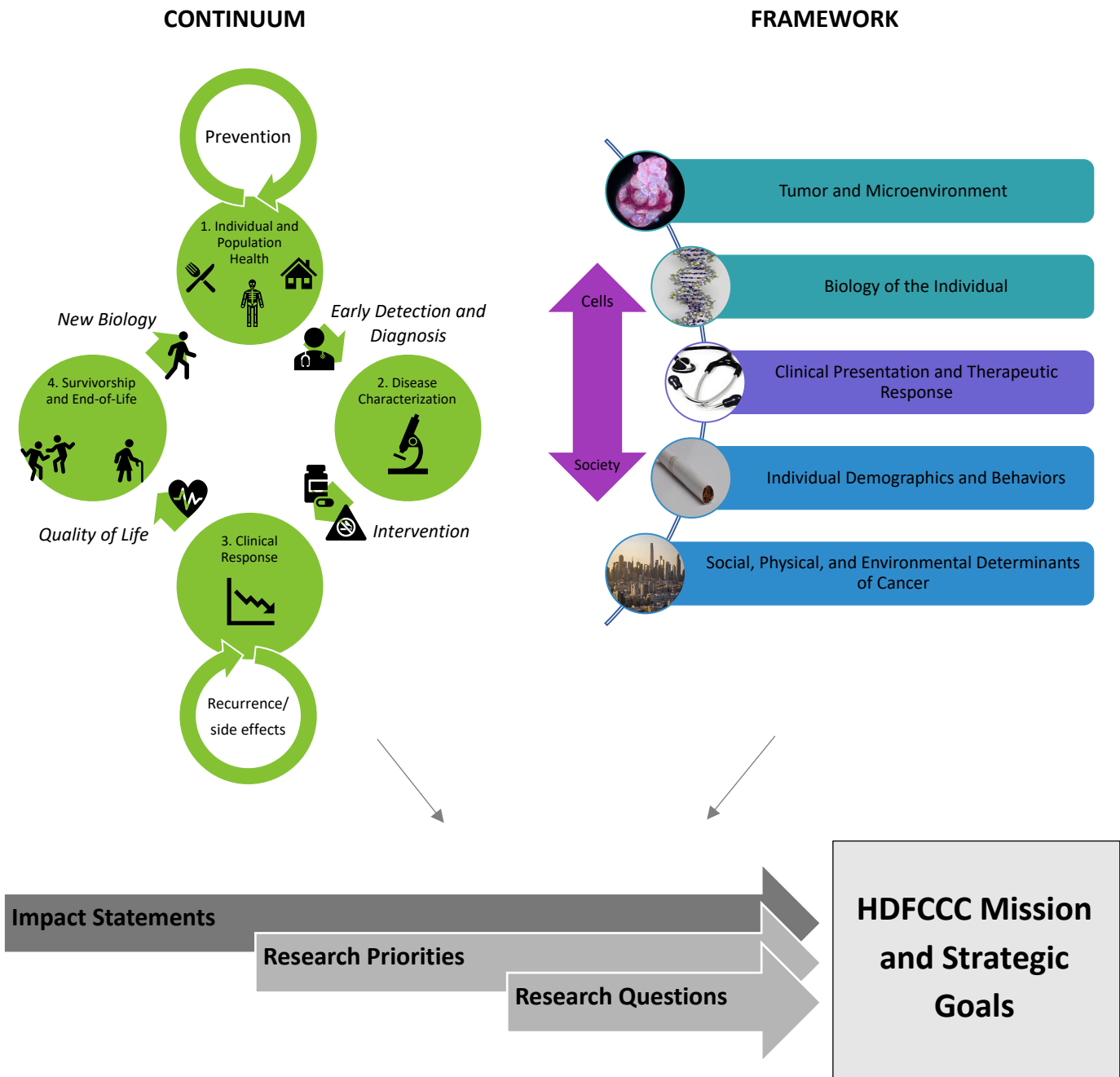
→ *New Biology* → back to (1)

Phase 3: Tactics and Implementation

By combining the Transdisciplinary Framework and the Patient Perspective structures, the HDFCCC defined goals and research priorities that have the highest impact to drive research forward in a way that directly affects patient care and cancer population health. At each stage of the Patient Perspective, research goals and priorities were identified from each level of the Framework. By defining goals at these levels, the HDFCCC was able to identify commonalities and define priority areas for inclusion in a logic model that identifies tactics to achieve goals. These goals and priorities were disseminated at leadership meetings, program meetings, online, and Center-wide Town Halls, allowing broad input and iteration as we finalized this final document.

CONTINUUM

Prevention

1. Individual and Population Health

New Biology

Early Detection and Diagnosis

4. Survivorship and End-of-Life

2. Disease Characterization

Quality of Life

Intervention

3. Clinical Response

Recurrence/ side effects

FRAMEWORK

Tumor and Microenvironment

Biology of the Individual

Cells

Clinical Presentation and Therapeutic Response

Society

Individual Demographics and Behaviors

Social, Physical, and Environmental Determinants of Cancer

Impact Statements

Research Priorities

Research Questions

HDFCCC Mission and Strategic Goals

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Cancer Research *2030*

1. Individual and Population Health

IMPACT STATEMENT

At UCSF in 2030, we will understand the biological, social, environmental, and behavioral determinants of risk, prevention, and disease onset.

RESEARCH PRIORITIES ACROSS THE FRAMEWORK
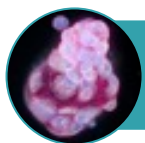
Tumor and Microenvironment

- Link between what happens outside the body with what happens inside the body by understanding the genetic, epigenetic, and developmental origins/predispositions to cancer and we will be able to answer for the patient: What will I get, what am I at risk for, when will I get it, and can you get rid of it before it comes?
- Detection and data collection (markers) of baseline host biology, including immune function/competence, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- Determine the common mechanisms across tissues that promote tumors, and how can these mechanisms be targeted and, perhaps more importantly, prevented?
- Understand the mechanisms of rare and unique cancers to inform how to target disease
    - e.g., cancers dependent on a single pathway; diseases that have changed in etiology or demographics
- Use alterations in tumor and microenvironment metabolism as novel biomarkers and imaging modalities to track tumor growth, plasticity, aggressiveness, and response to therapeutics
- Move from single-cell to systems view (combinations of genes working together)
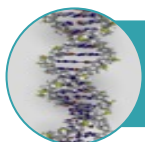
Biology of the Individual

- Link between what happens outside the body with what happens inside the body by understanding the genetic, epigenetic, and developmental origins/predispositions to cancer and we will be able to answer for the patient: What will I get, what am I at risk for, when will I get it, and can you get rid of it before it comes?
- Collect data from a wide variety of sources, including patient-derived data sources, population-level data sets and predictions, and medical records. Incorporate patient-derived data sources (e.g., devices, 23andMe, future tech, etc.)
- Detection and data collection (markers) of baseline host biology, including immune function, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- Determine the common mechanisms across tissues that promote tumors, and how can these mechanisms be targeted and, perhaps more importantly, prevented?
- Move from single-cell to systems view (combinations of genes working together)

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Clinical Presentation and Therapeutic Response

- Collect data from a wide variety of sources, including patient-derived data sources, population-level data sets and predictions, and medical records. Incorporate patient-derived data sources (e.g., devices, 23andMe, future tech, etc.)
  - Building big data - integrated, cells-to-society data resources (e.g., MEC, pathways, EHR linkages, ReSPOND study)
- Detection and data collection (markers) of baseline host biology, including immune function, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- Understand the mechanisms of rare or unique cancers to inform how to target disease

Individual Demographics and Behaviors

- Incorporate germline genetic polygenic risk scores into cancer risk prediction models, including across different ancestral populations
- Innovation in cancer etiology should focus on the root causes of cancer (including social, environmental, and behavioral determinants of health) and specifically tackle prevention as the translational goal (society to cells)
- Correlation of demographics and behaviors with risk stratification and assessment
- Assessment of risk with new behaviors and etiologic factors (e.g., cannabis, genetic, diet and lifestyle)

Social, Physical, and Environmental Determinants of Cancer

- Innovation in cancer etiology should focus on the root causes of cancer (including social, environmental, and behavioral determinants of health) and specifically tackle prevention as the translational goal (society to cells)
- Collect data from a wide variety of sources, including patient-derived data sources, population-level data sets and predictions, and medical records.
  - Incorporate patient-derived data sources (e.g., devices, 23andMe, future tech, etc.)
- Building big data - integrated, cells-to-society data resources (e.g., MEC, pathways, EHR linkages, ReSPOND study)
- There will be a continuing emphasis on acting upon increased knowledge of the origins of cancer inequities (i.e., disparities) at all these multiple levels with the goal of eliminating differences due to malleable causes in etiology, access, and quality of care.

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EXAMPLE RESEARCH QUESTIONS TO BE ANSWERED BY 2030
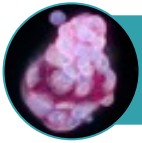
Tumor and Microenvironment

- What innate environments influence tumor development (e.g., metabolism)?
- How do genes elicit complex phenotypes?
- How can we target organelles for prognostic, diagnostic, and therapeutic approaches?
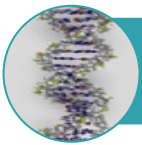
Biology of the Individual

- What general host biology influences cancer risk (e.g., microbiome, immune function)?
- How can measures of lowering risk benefit other disease occurrences?
- How do genes elicit complex phenotypes?
- How does patient microbiota impart its influence and how can microbes be targeted before therapy starts?

Clinical Presentation and Therapeutic Response

- What symptoms of co-morbidities affect cancer risk?
- How do combinations of interventions and prevention measures affect risk?
- How can omics-level measurements be converted to metadata, analyzed by AI, and precisely predict an individual's cancer risk?
- How can tumor antigen/ligand prediction and engineering (e.g., antigen presentation, TCR antibodies, alternate effectors) be standardized?
- Generate hypothesis-driven collection and sharing of data and samples

Individual Demographics and Behaviors

- GWAS studies in ethnic groups to correlate risk
- GWAS studies focusing on risk factors, predictive biomarkers, host determinants of cancer
- What is the influence of microbes on documented cancer social health disparities, and vice versa?
- Understand how behavior change can reduce risk and increase screening compliance
- Do individuals respond to social media messaging promoting screening?

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Social, Physical, and Environmental Determinants of Cancer

- Capacity building
- Implementation science
- Does the flavored tobacco ban influence smoking behavior?
- Ethics of genomic engineering
- What corporate determinants of health are cancer-causing?
- How can screening measures be implemented in different cultural, ethnic, SES, (etc.) groups?
- How do healthcare costs (economics) affect outcomes?
- Implementation science with increased emphasis on application of new knowledge and implementing effective preventative measures (e.g., screenings, interventions, behavior change, policy)
- Better understanding of policy interventions, including smokefree laws, mass media (including the role of industry denormalization), taxation, product regulation, the retail environment, and smoking cessation strategies will continue to develop both for tobacco control and other environmental determinants of cancer, both locally and abroad
- What are the upstream influences on cancer and health in general, including corporate or commercial drivers (e.g., tobacco, sugar, pharm)
- Focus work on the societal and population context that influences cancer. Levels (e.g., patient, family, town, country) have an influence on who develops cancer

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2. Disease Characterization

IMPACT STATEMENT

At UCSF in 2030, we will understand the tumor and the patient through basic research, clinical research, and population research, in order to inform appropriate risk stratification, prevention, screening, diagnosis, and interventions.

RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- A multi-dimensional, translational evaluation will be undertaken for every patient's cancer, including a comprehensive tumor-omics profile (e.g., genomic, epigenomic, transcriptomic, metagenomic, metabolomic), an individualized assessment of the tumor immune microenvironment and microbiome, an evaluation of tumor heterogeneity and plasticity
- Identify biomarkers of tumor and microenvironment characteristics (e.g., heterogeneity, plasticity, metabolism, pathology) + how they interact --> target identification for diagnosis, therapy
- Move from single cell to systems view and combinations of genes working together; increased focus on tumor as a community/network of cells
- Develop new tools (e.g., single-cell profiling, novel imaging and drug delivery systems) and advances in cell culture models to encompass the complexity of human organs and allow the study of how cancer evolves in the context of the tumor microenvironment
- Parallel analysis of high content data from genetically distinct systems will enable even more granular description of heterogeneity, which will be incorporated into artificial intelligence modeling of complexity

Biology of the Individual

- A multi-dimensional, translational evaluation will be undertaken for every patient's cancer, including a comprehensive tumor-omics profile (e.g., genomic, epigenomic, transcriptomic, metagenomic, metabolomic), an individualized assessment of the tumor immune microenvironment and microbiome, an evaluation of tumor heterogeneity and plasticity
- Develop new tools (e.g., single-cell profiling, novel imaging and drug delivery systems) and advances in cell culture models to encompass the complexity of human organs and allow the study of how cancer evolves in the context of the tumor microenvironment

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Clinical Presentation and Therapeutic Response

- Standardize tumor antigen/ligand prediction and engineering (e.g., antigen presentation, TCR antibodies, alternate effectors)
- Use new techniques including single cell analysis and equivalent in silico deconvolution to allow researchers to better define tumor subtypes, to better understand tumor heterogeneity, and to better identify pathways driving processes important in tumor biology and therapy - potentially to be incorporated into AI modeling of complexity
- The biologic, social, and environmental context of the *individual patient* will be an integral component of the treatment paradigm (including immune competence, microbiome, pharmacogenetics, epigenetic and genetic profile, social and environmental determinants of health, symptoms/side-effects/quality of life); the impact of variations in populations will be better understood (e.g., immune response, pharmacogenomics)
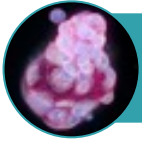
Individual Demographics and Behaviors

- Correlation of demographics and behaviors with tumor development
- The biologic, social, and environmental context of the *individual patient* will be an integral component of the treatment paradigm (including immune competence, microbiome, pharmacogenetics, epigenetic and genetic profile, social and environmental determinants of health, symptoms/side-effects/quality of life); the impact of variations in populations will be better understood (e.g., immune response, pharmacogenomics)

Social, Physical, and Environmental Determinants of Cancer

- Correlation of demographics and behaviors with tumor development
- The biologic, social, and environmental context of the *individual patient* will be an integral component of the treatment paradigm (including immune competence, microbiome, pharmacogenetics, epigenetic and genetic profile, social and environmental determinants of health, symptoms/side-effects/quality of life); the impact of variations in populations will be better understood (e.g., immune response, pharmacogenomics)

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EXAMPLE RESEARCH QUESTIONS TO BE ANSWERED BY 2030

Tumor and Microenvironment

- What are the vulnerabilities not only in the dominant clone of an individual's malignancy, but also in one or more low level subclones that may represent the root cause of eventual acquired clinical resistance?
- How do tumors, host cells, and microbes interact to promote or impede tumor establishment, maintenance, and dissemination? These interactions may be physical, at a distance via secreted products and systemic circulation, and indirectly via somatic effectors such as immune or barrier epithelial cells
- Continued research focused on synthetic lethality and "untargetable" genes/processes
- Single cell analysis and equivalent *in silico* deconvolution to allow researchers to better define tumor subtypes, to better understand tumor heterogeneity, and to better identify pathways driving processes important in tumor biology and therapy
- How does the host environment change upon tumor development (e.g., organelle biology, microenvironment, metabolism) and are these biomarkers for early detection?
- What microenvironment characteristics support tumor development?
- What drives tumor heterogeneity and can it be targeted?
- What are the mechanisms of rare/unique cancers that can inform how to target disease?
  - e.g., cancers dependent on a single pathway; diseases that have changed in etiology/demographics (colorectal)

Biology of the Individual

- What is the effect of host factors (e.g., immune system, microbiome, metabolism) on tumor onset and progression?
- What are the tumor-driven changes in host biology (e.g., immune function, microbiome, metabolism) and are these biomarkers for early detection?
- Develop multimodality data and combine with advanced AI approaches to provide diagnostic, prognostic, and predictive information
- Develop a conceptual framework for defining the immune competence of a cancer patient
- How does host variability influence risk stratification, drug exposure, resistance, and toxicity?
- How do early-stage lesions set into course an immune response?
- How can we restore immune competence in individuals who lack it, such as approaches to rescue the thymus after thymic involution in the elderly?

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Clinical Presentation and Therapeutic Response

- What are the vulnerabilities not only in the dominant clone of an individual's malignancy, but also in one or more low level subclones that may represent the root cause of eventual acquired clinical resistance?
- Develop multimodality data and combine with advanced AI approaches to provide diagnostic, prognostic, and predictive information
- What are the pre-neoplastic conditions that can help with early detection?
- How does host variability influence risk stratification, drug exposure, resistance, and toxicity?
- Single cell analysis and equivalent *in silico* deconvolution to allow researchers to better define tumor subtypes, to better understand tumor heterogeneity, and to better identify pathways driving processes important in tumor biology and therapy
- Evaluation of benefits and risks (costs) of new screening tools (e.g., ctDNA, liquid biopsy, imaging)
- What is the effect of past interventions/prevention measures on current clinical presentation and predicted therapeutic response?
- How can social, physical, environmental, and cultural context inform diagnosis?
- What biologic and -omic processes can be manipulated as biomarkers for early detection?
- How can detection and diagnosis aid in treatment predictions?
- How do competing risks, interventions, prevention measures affect the others?
- Can endogenous microbial analysis provide non-invasive prognostic and predictive information for cancer development, progression, and survival.
- What is the role of non-T cell effectors in cancer immunity?
- Can we use imaging technologies to conduct "virtual biopsies?"

Individual Demographics and Behaviors

- What underlies the etiology of external determinants of health?
  - e.g., how does tobacco and cannabis use cause cancer?
- What are the correlations between demographics and behaviors with risk stratification, tumor development, and tumor progression?
- How does host variability influence risk stratification, drug exposure, resistance, and toxicity?
- What demographics and behaviors affect intervention options and success?
- What behaviors can be changed to improve risk stratification and early detection?
- What genetic variants are associated with disease progression and onset?

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Social, Physical, and Environmental Determinants of Cancer

- What underlies the etiology of external determinants of health?
- Evaluation of benefits and risks (costs) of new screening tools (e.g., ctDNA, liquid biopsy, imaging)
- What social and environmental factors affect intervention options, risk stratification, and early detection?
- What are the societal and political factors that affect intervention options, risk stratification, and early detection?
- How can social, physical, environmental, and cultural context inform diagnosis?
- How is outreach best done to communicate risk, the importance of early detection, navigating a diagnosis?
- Implementation research on polices and infrastructure that seek to improve early detection, seeking treatment, accessing care

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3. Clinical Response

IMPACT STATEMENT

At UCSF in 2030, we will understand the intervention through basic research, clinical research, and population research, and health outcomes research will assure all people receive timely, affordable, and high-quality care, regardless of who they are, where they live, or where they get their care.

RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- Technical advances will make it possible to quickly and accurately identify vulnerabilities not only in the dominant clone of an individual's malignancy, but also in one or more low level subclones that may represent the root cause of eventual acquired clinical resistance, thus improving clinical outcomes
- Use real-time alterations (e.g., of tumor and microenvironment metabolism, compliance to treatment regimens) as novel biomarkers and imaging modalities to track response to therapeutics and iterate future interventions
- Continued focus on "undruggable" targets through chemical biology approaches
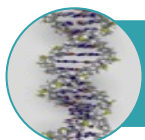
Biology of the Individual

- The biologic, social, and environmental context of the *individual patient* will be an integral component of the treatment paradigm (including immune competence, microbiome, pharmacogenetics, epigenetic and genetic profile, social and environmental determinants of health, symptoms/side-effects/quality of life)
- Research to understand what innate environments and host biology influence tumor development (e.g., microbiome, metabolism) - with the goal of identifying novel biomarkers
- Continued focus on "undruggable" targets through chemical biology approaches

Clinical Presentation and Therapeutic Response

- Interventions will be iterative, based on real-time monitoring of response and compliance to treatment regimens.
- Novel clinical trial designs will consider biomarker-driven trials and molecular subtypes, access to interventions (e.g., distance, cost), alternative outcomes (e.g., patient preferences, PROs, residual disease, resistance), optimization of biobanking, and enhanced integration of technology

- We will design collaborative, multi-dimensional approaches to understand metastatic disease and cancer vulnerabilities and to test individualized therapeutic strategies for each patient, including defining the genetic and phenotypic vulnerabilities of cancer, integrating patient clinical data and tumor -omic platforms, and developing tumor-specific organoids, which can be rapidly tested with targeted therapies.
- Combination therapies

Individual Demographics and Behaviors

- The biologic, social, and environmental context of the *individual patient* will be an integral component of the treatment paradigm (including immune competence, microbiome, pharmacogenetics, epigenetic and genetic profile, social and environmental determinants of health, symptoms/side-effects/quality of life)
- Novel clinical trial designs will consider biomarker-driven trials and molecular subtypes, access to interventions (e.g., distance, cost), alternative outcomes (e.g., patient preferences, PROs, residual disease, resistance), optimization of biobanking, and enhanced integration of technology

## Social, Physical, and Environmental Determinants of Cancer

- The impact of variations in populations will be better understood (e.g., immune response, pharmacogenomics).
- Health outcomes research will routinely report on implementation outcomes, documenting whether key discoveries and evidence-based interventions reach the people for whom they are intended, are adapted to local resources, and are put into practice effectively, safely, and equitably according to principles of patient-centered care.
- Health outcomes research will incorporate a health policy perspective, engaging key community stakeholders throughout the research process and assuring that local, state, national, and international communities and health systems are able to implement key discoveries and evidence-based interventions that are affordable and accessible to the general population, including diverse and vulnerable populations.

EXAMPLE RESEARCH QUESTIONS TO BE ANSWERED BY 2030

Tumor and Microenvironment

- What combination therapy might be developed to target both the tumor and the unique microenvironment to improve response?
- What pathways can be targeted to prevent resistance?
- Are networks of interacting cells the relevant targets for treatment?

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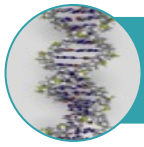
Biology of the Individual

- What combination therapy might be developed to boost patient response to a tumor-directed therapy?
- What patient characteristics might affect susceptibility to toxicity, resistance, other side-effects (e.g., co-morbidities)?
- Why does immunotherapy fail?

Clinical Presentation and Therapeutic Response

- How can datasets (patient characteristics, tumor characteristics, environmental characteristics) be combined in order to make more accurate, precision decisions about interventions?
- How can clinical presentation and response predict resistance?
- How does the interplay of host and tumor genetics (and other sources of host variability like the metabolome, microbiome, etc.) determine the response to therapy?

Individual Demographics and Behaviors

- How do tobacco, other toxins, affect response to interventions?
- What behavior decreases individual compliance to an intervention regimen?

Social, Physical, and Environmental Determinants of Cancer

- What characteristics of a patient's homelife (e.g., isolation, poverty, built environment) affect access to and compliance with interventions?
- What health care policies affect patient's access to and compliance with interventions?
- How do healthcare costs affect outcomes?

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4. Survivorship and End-of-Life

IMPACT STATEMENT

At UCSF in 2030, we will understand the changes in the tumor and the patient over time and following treatment, through basic research, clinical research, and population research, in order to inform appropriate secondary, palliative, and symptom management interventions.

RESEARCH PRIORITIES ACROSS THE FRAMEWORK
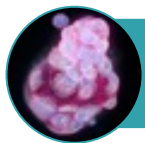
Tumor and Microenvironment

- Long-term and late effects of survivors following new therapies (e.g., targeted therapies, CAR-T therapies; therapies currently in the pre-clinical pipeline)
- Use alterations in tumor and microenvironment metabolism as novel biomarkers and imaging modalities to track tumor growth, plasticity, and aggressiveness
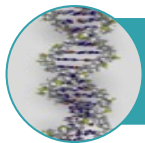
Biology of the Individual

- Cancer research will need to reflect an aging population and a growing number of cancer survivors.
- Late effects and aging of the cancer population will mean that more survivors have multiple comorbidities

Clinical Presentation and Therapeutic Response

- Transdisciplinary, practice-changing integrative oncology research will have a sustained impact beyond UCSF. Our research will lead towards investigating the impact of integrative oncology approaches on survival among cancer patients and cost-effectiveness research.
- The interface between survivors, providers, and technology will be increasingly important and will change in ways that are currently unforeseen. New technologies will provide opportunities for new approaches to research with cancer survivors and new models of care.
- New care delivery models will emerge, as currently there are not enough providers to meet the needs of the rapidly growing survivor population. Within new models of care, a new cadre of providers who are specialized in cancer survivorship care will emerge (e.g., advanced practice providers, nurse practitioners and physician assistants).
- Symptom science (including survivorship), patient-reported outcomes, and patient preferences will be incorporated into study design.

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- New therapies (e.g., targeted therapies, CAR-T therapies; therapies currently in the pre-clinical pipeline) will mean that survivors experience new long-term and late effects that will need to be studied
- Ability to follow, over time, molecule → cell → tissue → organ → organism
- Symptom management across the cancer treatment and advanced cancer trajectory (includes genetics and behavioral science)

Individual Demographics and Behaviors

- Cancer research will need to reflect an aging population and a growing number of cancer survivors.
- The survivor population will reflect broader societal trends, namely the growth and increasing diversity of the US population in general and of California in particular. By 2030, we expect the population of cancer survivors treated at the Helen Diller Family Comprehensive Cancer Center (and, more generally, in California) will be not only larger, but more diverse, and will have more complicated needs.
- Behavioral interventions (e.g., diet, exercise, smoking cessation)
- Individual access to and compliance with intervention regiments (including clinical trials)
- Patient-reported outcomes

Social, Physical, and Environmental Determinants of Cancer

- Emphasis on quality of life and long-term toxicities that impact survivor populations, and an improved understanding of patient values and preferences for care in order to interpret the quality of cancer screening, diagnostics, and treatments.
- The survivor population will reflect broader societal trends, namely the growth and increasing diversity of the US population in general and of California in particular. By 2030, we expect the population of cancer survivors treated at the Helen Diller Family Comprehensive Cancer Center (and, more generally, in California) will be not only larger, but more diverse, and will have more complicated needs.
- Transdisciplinary, practice-changing integrative oncology research will have a sustained impact beyond UCSF. Our research will lead towards investigating the impact of integrative oncology approaches on survival among cancer patients and cost-effectiveness research.
- Health outcomes research will focus on measuring, monitoring, evaluating, and improving health outcomes across the cancer control continuum, with a goal of assuring that all people receive timely, affordable, and high quality care, regardless of who they are, where they live, or where they get their care.
- Real-time characterization of the survivor population as it changes in the face of changing demographics and treatment outcomes. Characterization of the survivorship population should be comprehensive, ranging from molecular characteristics, to survivor behaviors, to social and health system determinants of outcomes.
- Implementation science
- Tools to improve access to and compliance with interventions
- Environmental barriers to access and compliance (e.g., built environment, peer group support)

- Survivorship growth – Larger numbers, new therapies and care delivery models. Need formal Survivorship Program and consider state-wide UCCCC like integration
- Other changes in the survivorship population will result from advances in cancer treatment and access to care (e.g., longer survival, better access for previously underserved populations).
- Health outcomes research will also incorporate a health policy perspective, engaging key community stakeholders throughout the research process and assuring that local, state, national, and international communities and health systems are able to implement key discoveries and evidence-based interventions that are affordable and accessible to the general population, including diverse and vulnerable populations.
- Research that addresses racial/ethnic disparities by striving for equity and the elimination of inequities in survivorship. Multicultural survivorship support, e.g. support groups and peer navigation/coaching, should occur in community engagement, as well as the context of research.
- The interface between survivors, providers, and technology will be increasingly important and will change in ways that are currently unforeseen. New technologies will provide opportunities for new approaches to research with cancer survivors and new models of care.

EXAMPLE RESEARCH QUESTIONS TO BE ANSWERED BY 2030

Tumor and Microenvironment

- Do changes to the microenvironment due to treatment change the long-term side effects or risk of secondary tumors?
- How can imaging be used as a way to understand therapy response and pathways involved in cell fate and disease progression?
- Prevention and therapy of secondary neoplasms
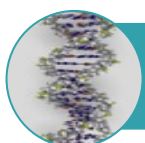
Biology of the Individual

- A precise understanding of the genetics of symptoms and the pharmacology and metabolism of symptom treatments will enable tailoring or symptom management for each individual with cancer, in combination with their cancer treatment (including screening and prevention)
- Challenges in having an appropriately trained workforce to deliver cancer genetic services
- How does age affect long-term side effects of treatment?
- Advanced research using current and future wearable technologies.
- What are the long-term symptoms (e.g., neuropathy, hearing loss)?
- Look across cancer type at co-morbidities

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Clinical Presentation and Therapeutic Response

- What therapeutic uses are there for cannabinoids, including use in supporting treatment of cancer patients?
- What are the costs and benefits of new cancer therapeutic approaches in terms of the length and quality of survivorship for major cancer sites?
- What are the relevant patient-reported outcomes regarding physical symptoms, side effects?

Individual Demographics and Behaviors

- How does supporting patients' end-of-life preferences improve quality of life?
- In what ways do the characteristics of different subgroups (i.e., defined by race/ethnicity, socioeconomic status, or gender identity) influence the length and quality of survivorship for major cancer sites?
- What factors should be considered, and how, in the transition from active treatment to recovery and rehab post-treatment?

## Social, Physical, and Environmental Determinants of Cancer

- What family contexts play a role in survivorship?
- What policies improve survivorship in underserved populations?

## 5. Inequities Across the Framework

IMPACT STATEMENT

At UCSF in 2030, we will understand the inequities in our catchment area related to care, screening, training, leadership, and access to clinical trials that lead to increased morbidity and mortality in different populations, so that all patients have the same chance of surviving and preventing cancer.

RESEARCH PRIORITIES ACROSS THE FRAMEWORK
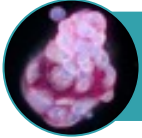
Tumor and Microenvironment

- Mechanisms of how differences in tumor biology lead to different outcomes
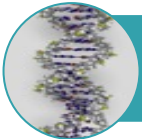
Biology of the Individual

- Mechanisms of how differences in host biology lead to different outcomes

Clinical Presentation and Therapeutic Response

- Ability to follow, over time, molecule → cell → tissue → organ → organism
- Understand what clinical structures (e.g., access to trials, care, implicit bias in medicine) lead to inequities

Individual Demographics and Behaviors

- We will broadly define and adapt to sources of inequity, including race/ethnicity, SES, age, LGBTQ, gender. Diversity increasingly will be understood as multifactorial, including intersections of race, ethnicity, culture, language, geography, sexual orientation, and gender expression.
- Focus our work on the societal/ population context that influences cancer. Levels (e.g. patient, family, town, country) have an influence on quality of care.
- Risk prediction and cancer screening will be available, accessible, and effective for all, particularly underrepresented and minority populations (e.g., with the development of prediction models based on polygenic risk scores for non-European ancestry populations) as well as specific subgroups (e.g., lung cancer screening guidelines for non-smokers).
- Behavioral interventions (e.g., diet, exercise, smoking cessation)
- Individual access to and compliance with intervention regiments (including clinical trials)

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**Social, Physical, and Environmental Determinants of Cancer**

- Health outcomes research will focus on measuring, monitoring, evaluating, and improving health outcomes across the cancer control continuum, with a goal of assuring that all people receive timely, affordable, and high quality care, regardless of who they are, where they live, or where they get their care.
- Implementation science
- Tools to improve access to and compliance with interventions
- Environmental barriers to access and compliance (e.g., built environment, peer group support)
- Health outcomes research will also incorporate a health policy perspective, engaging key community stakeholders throughout the research process and assuring that local, state, national, and international communities and health systems are able to implement key discoveries and evidence-based interventions that are affordable and accessible to the general population, including diverse and vulnerable populations.
- Research that addresses racial/ethnic disparities by striving for equity and the elimination of inequities in survivorship. Multicultural survivorship support, e.g. support groups and peer navigation/coaching, should occur in community engagement, as well as the context of research.
- Our catchment area and unique relationship with our community will allow research to determine the source of inequities, how they affect morbidity and mortality, and the implementation of targeted interventions (including policy) to address them

EXAMPLE RESEARCH QUESTIONS TO BE ANSWERED BY 2030
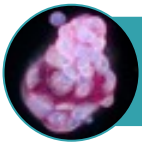
Tumor and Microenvironment

- Genetic basis of tumor differences
- How environment affects biology
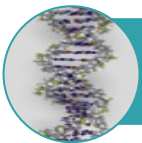
Biology of the Individual

- Genetic basis of response to treatment
- Mechanisms of behavior → cancer

Clinical Presentation and Therapeutic Response

- Is the EHR part of the solution to better understanding of health outcomes or a distraction from the real work of improving outcomes?

Individual Demographics and Behaviors

- Can we show that all population subgroups who present with same stage disease have similar outcomes? (i.e., with equal access and quality of care, do we observe equal outcomes?)
- In what ways do the characteristics of different subgroups (i.e., defined by race/ethnicity, socioeconomic status, or gender identity) influence the length and quality of outcome for major cancer sites?

Social, Physical, and Environmental Determinants of Cancer

- What characteristics of a patient's homelife (e.g., isolation, poverty, built environment) affect access to and compliance with interventions?
- Capacity building
- How are plans and best practices best disseminated to different underserved populations?
- What policies improve mortality in underserved populations?
- Are health outcomes for HDFCCC patients comparable or better than other institutions caring for cancer patients in Northern California? If not, why?

III. OUTPUT: STRATEGIC GOALS ACROSS CENTER
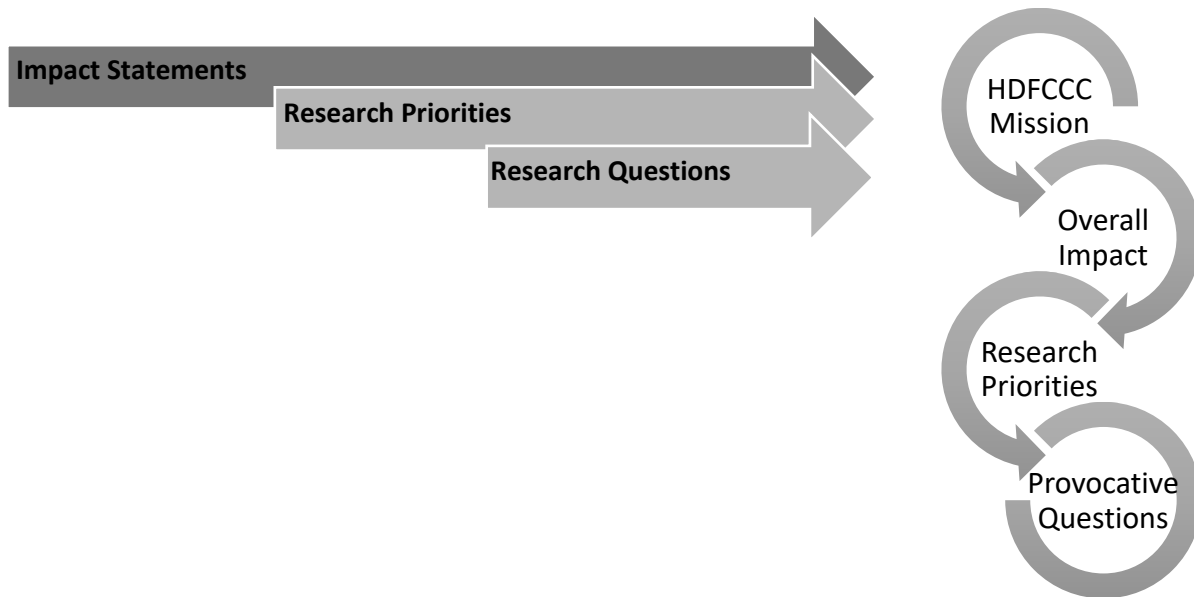
Standard strategic planning roadmaps refer to (1) Vision, (2) Key Aims, (3) Goals, (4) Strategies, and (5) Tactics, which are then ranked by ease of implementation and impact.

We believe our organization along the Translational Framework and Patient Experience Perspective Continuum is better aligned with how our investigators think about their work, collaborations, and impact on cancer research and care. The organization allows for immediate operationalization of scientific research because it is clear what infrastructure and resources are required to address priority areas defined in each step. This organization also allows the plan to be unique and specific to UCSF, tailored to the research strengths, interests, and future directions of our members.

This overlap defines the **HDFCCC Research Mission Statement:**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) seeks to drive scientific discovery and develop tailored interventions to improve cancer outcomes in the catchment area and beyond.

Furthermore, our organization allows for the concept of HDFCCC-wide **Provocative Questions**, to be defined below, around which tactics can be deployed. Finally, the plan can be operationalized into a **Logic Model,** which allows tactics to be identified and progress to be tracked.

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HDFCCC MISSION

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) seeks to drive scientific discovery and develop tailored interventions to improve cancer outcomes in the catchment area and beyond.

This mission statement can further be deliniated into three major thematic areas:

Theme 1 (Innovative Discovery): Advance innovative basic, clinical, and population research, focused on unique characteristics of the individual, disease, population, and community.

Theme 2 (Effective Translation): Translate research to define risk, emphasize prevention, optimize diagnosis, tailor screening and treatment, and improve outcomes.

Theme 3 (Implementation and Dissemination): Reduce inequities in cancer awareness, prevention, early detection and diagnosis, care, treatment, and patient-centered outcomes, through data-driven science and community engagement.

OVERALL IMPACT

- At UCSF in 2030, we will understand the biological, social, environmental, and behavioral determinants of risk, prevention, and disease onset. (1)
- At UCSF in 2030, we will understand the tumor and the patient—by translating discovery, clinical, and population research—in order to inform appropriate risk stratification, prevention, screening, diagnosis, and interventions. (2)
- At UCSF in 2030, we will understand the intervention—by translating discovery, clinical, and population research—and health outcomes research will assure all people receive timely, affordable, and high-quality care, regardless of who they are, where they live, or where they get their care. (3)
- At UCSF in 2030, we will understand the changes in the tumor and the patient over time and following treatment—by translating discovery, clinical, and population research— in order to inform appropriate secondary, palliative, and symptom management interventions. (4)
- At UCSF in 2030, we will understand the inequities in our catchment area related to care, screening, training, leadership, and access to clinical trials that lead to increased morbidity and mortality in different populations, so that all patients have the same chance of surviving and preventing cancer. (all)
- At UCSF in 2030, multi-disciplinary training will shift from individual reward (e.g., fellowships, grants) to greater reward for active engagement in productive teams that are focused on major goals. Meaningful communication with other disciplines beyond medicine will be essential to reap the rewards of cross cutting discovery in other sciences. Cancer research training programs will emphasize new skills in team science and transdisciplinary approaches, engaging a diverse cohort of trainees both in the United States and globally. (all)
- At UCSF in 2030, we will enhance diversity, equity, inclusion, and accessibility (DEIA) in the research workforce, including trainees, faculty, and staff, Center leadership, and advisory boards. To accomplish this, HDFCCC uses an approach that is accountable, engages stakeholders, promotes institutional change that is individual-centered, and aims to provide increasing opportunities for all.

CENTER RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- In general, basic research to understand the tumor (e.g., molecular and genetic mechanisms, metabolism, cell biology) and its context in a patient (e.g., microenvironment, microbiome, immune system) will continue to be a strength at UCSF, and the Cancer Center will be a major mechanism for translating laboratory findings into the clinic, and allowing clinical findings to be studied the laboratory.
- What are the common mechanisms across tissues that promote tumors, and how can these mechanisms be targeted and, perhaps more importantly, prevented?
- Understand the mechanisms of rare/unique cancers to inform how to target disease (e.g., cancers dependent on a single pathway, diseases that have changed in etiology/demographics (colorectal))
- Translate discovery research on tumor biology and host context into the clinic, and translate clinical findings into discovery questions to be studied in the laboratory.
- Identify biomarkers of tumor and microenvironment characteristics (e.g., heterogeneity, plasticity, metabolism, pathology) + how they interact --> target identification for diagnosis, Rx
- Move from single-cell to systems view and combinations of genes working together; increased focus on tumor as a community of cells through single-cell analysis
- Use alterations in tumor and microenvironment metabolism as novel biomarkers and imaging modalities to track response to therapeutics
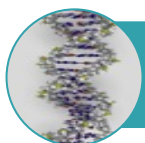
Biology of the Individual

- Incorporate patient-derived data sources (e.g., devices, 23andMe, future tech, etc.)
- Link between what happens outside the body with what happens inside the body
- Detection and data collection (markers) of baseline host biology, including immune function, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- Translate discovery research on tumor biology and host context into the clinic, and translate clinical findings into discovery questions to be studied in the laboratory.
- Look across cancer type at co-morbidities including cardiovascular risk

Clinical Presentation and Therapeutic Response

- Use increasing amount of data to make specific intervention and research decisions (rather than focusing on collecting data for the sake of more data)
- Focus on basic etiology of major cancers with limited prevention and early detection efforts (e.g., pancreas, ovary, prostate, brain)

- Identify biomarkers of tumor and microenvironment characteristics (e.g., heterogeneity, plasticity, metabolism, pathology) + how they interact --> target identification for diagnosis, Rx

- Standardize tumor antigen/ligand prediction and engineering (e.g., antigen presentation, TCR antibodies, alternate effectors)

- Use new techniques including single cell analysis and equivalent in silico deconvolution to allow researchers to better define tumor subtypes, to better understand tumor heterogeneity, and to better identify pathways driving processes important in tumor biology and therapy

- Look across cancer type at co-morbidities including cardiovascular risk

- Etiology of tumor evolution to metastatic disease and changes of tumor in response to treatment

- New techniques including single cell analysis and equivalent in silico deconvolution to allow researchers to better define tumor subtypes, to better understand tumor heterogeneity, and to better identify pathways driving processes important in tumor biology and therapy

- Building big data - integrated, cells-to-society data resources (e.g., MEC, pathways, EHR linkages, ReSPOND study)

Individual Demographics and Behaviors

- Link between what happens outside the body with what happens inside the body

- We will broadly define and adapt to sources of inequity, including race/ethnicity, SES, age, LGBTQ, gender

- Diversity increasingly will be understood as multifactorial, including intersections of race, ethnicity, culture, language, geography, sexual orientation, and gender expression.

- California Neighborhoods Data System (CNDS) - curated collection of social and built environmental data

- Incorporation of germline genetic polygenic risk scores into cancer risk prediction models, including across different ancestral populations

- Implementation science to address disparities in success of interventions

- Correlation of demographics and behaviors with risk stratification

- Correlation of demographics and behaviors with tumor development

Social, Physical, and Environmental Determinants of Cancer

- Link between what happens outside the body with what happens inside the body

- Innovation in cancer etiology should focus on the root causes of cancer (including social, environmental, and behavioral determinants of health) and specifically tackle prevention as the translational goal (society to cells)

- Our catchment area and unique relationship with our community will allow research to determine the source of inequities, how they affect morbidity and mortality, and the implementation of targeted interventions (including policy) to address them

- We will broadly define and adapt to sources of inequity, including race/ethnicity, SES, age, LGBTQ, gender

- Our understanding of social determinants of survivor outcomes will increase and have implications for practice
- We will not introduce inequities with new technologies (e.g., mHealth, telemedicine, device-based interventions, remote monitoring) or treatments
- Transdisciplinary, practice-changing integrative oncology research will have a sustained impact and include cost-effectiveness research
- Our understanding of social determinants of survivor outcomes will increase and have implications for practice
- Correlation of demographics and behaviors with risk stratification
- Correlation of demographics and behaviors with tumor development
- Correlation of demographics and behaviors with tumor progression
- Focus our work on the societal/ population context that influences cancer.
  - Levels (e.g., patient, family, town, country) have an influence on who develops cancer and the quality of care they get.
  - Whether an issue of racial inequality, social inequities, social justice or all of the above, cancer incidence and mortality differ along fault lines. Individual investigators within Cancer Control have taken this on, and it is an exciting (and fraught) idea to have the Cancer Center organize around this.

IV. PROVOCATIVE QUESTIONS (DRAFT)

PROVOCATIVE QUESTION 1

What are the unique independent and interactive contributions of structural, social, molecular, and genetic determinants of cancer among different demographic populations?

Intent: It is becoming clear social determinants of health at a population level greatly affect cancer mortality, for reasons ranging from structural (e.g., access to care, systemic racism), to behavioral (e.g., access to food, tobacco use) and environmental risk factors (e.g., super-fund sites). These social determinants interplay with the underlying molecular and genetic determinants to contribute to overall risk and potential therapeutic response (**Figure 1**). Developing biomarkers, screening strategies, and interventions based on this complex relationship is essential to provide precision prevention and interventions for all individuals.

Background:

- Known problems of resistance, response due to tumor heterogeneity
- Genetic basis of heterogeneity
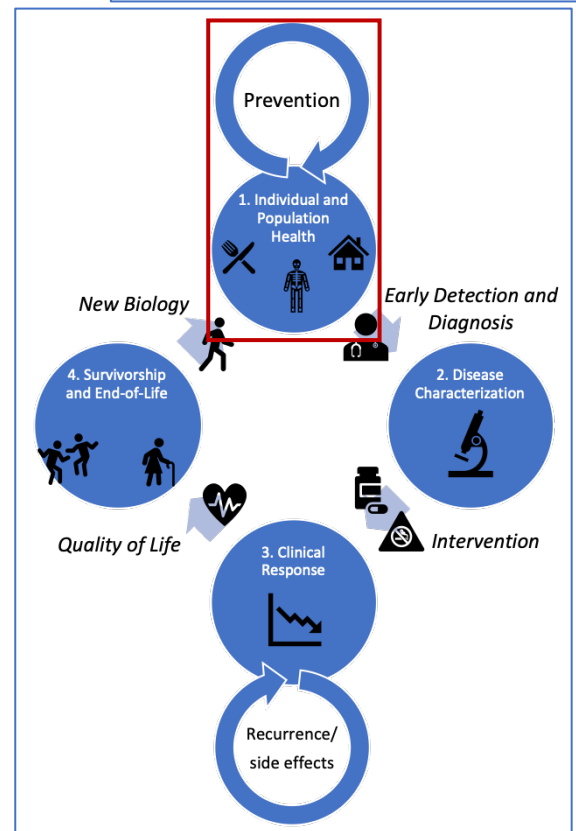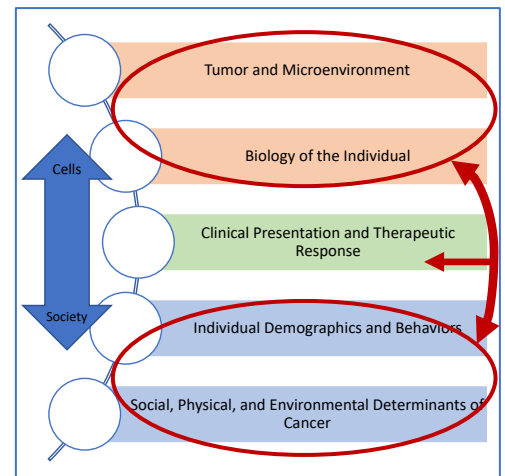- Disparities in response explained by heterogeneity?
- MORE

Alignment with Cancer Research in 2030 Strategic Plan: The Strategic Plan framework includes "Individual and Population Health (including prevention)" as an essential piece of the patient perspective (**Figure 2**). Making treatment and screening decisions based on the complex relationship between external and internal factors driving tumor development is essential in order to meet the 2030 mission of understanding the patient, understanding the intervention, and understanding the tumor to provide precision therapy and prevention strategies to all individuals.

Feasibility: Given that many determinants of health combine to affect risk and response, mechanistic studies of how these factors affect risk and response, alone and in combination, and population-level interventions to increase prevention and lower risk, will be necessary. <<others?>>

HDFCCC researchers are uniquely poised to collaborate with..

Examples of research questions that could be responsive:

- What policy interventions can be introduced based on scientific evidence that the sugar industry marketing tactics are largely responsible for the obesity epidemic and increases in obesity-related cancers (e.g., breast, endometrium, liver)?
- How can we best incorporate germline genetic polygenic risk scores into cancer risk prediction models, including across different ancestral populations?

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- How is the penetrance of cancer susceptibility genes affected by additional genetic variants, environmental factors, genetic ancestry, social economic status, even personality?

- For all major cancers can it be shown that inequities in outcomes (e.g, survival, QoL, and mortality) are similar for all peoples given equal access and quality of care?

- What is the single most effective means of improving access for rural populations to advances in cancer prevention and early detection?

- How does an individual's micro/macro environmental factors (e.g., zip code, air quality, water quality, food desert, proximity to factories, pesticides, etc.) impact their cancer risk through epigenetic factors (e.g., abnormal DNA repair, modifications to oncogenes, and or tumor suppressor genes)? Could this provide insight on which factors contribute to a patient's outcome and mortality, and pave the way for legislative changes to protect vulnerable communities at greater risk?

- What are the key molecular features of cancers in populations exposed to environmental toxicity, radiation and other contaminants, such as those living on top of superfund sites over decades?

- What will be the effect of climate change on cancer prevention and control?

PROVOCATIVE QUESTION 2

How can we overcome intra-tumor heterogeneity (differences within a single tumor) to make cancer therapies work better?

Intent: It is becoming clear that tumor heterogeneity affects response to treatment and development of resistance. Understanding the genetic, molecular, and environmental basis of tumor heterogeneity—both within tumors and between tumors at different sites—will lead to new ways to target the tumor, mitigate resistance, and develop prevention strategies. That is, along the cancer continuum (**Figure 1**), underlying cellular mechanisms and social determinants converge to inform precision therapy for all patients.

Background:

- Known problems of resistance, response due to tumor heterogeneity
- Genetic basis of heterogeneity
- Disparities in response explained by heterogeneity?
- MORE

Alignment with Cancer Research in 2030 Strategic Plan: The Strategic Plan framework includes "Disease Characterization" as an essential piece of the patient perspective (**Figure 2**). Understanding how tumor heterogeneity affects response and resistance is necessary in order to meet the 2030 mission of understanding the patient, understanding the intervention, and understanding the tumor to provide precision therapy to all patients at UCSF.

Feasibility: Given that heterogeneity may arise from multiple sources, addressing this question will involve understanding the various drivers of heterogeneity, including genetic (e.g., germline and somatic genetic differences), biologic (e.g. tumor microenvironment), and environmental (e.g., tobacco use, nutrition); mechanistic studies of how these drivers are altered by cancer and cancer treatment and in turn how cancer and cancer treatment affects those drivers; <<others?>>

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Examples of research questions that could be responsive:

- How does the interplay of host and tumor genetics determine the response to therapy?
- How does heterogeneity of cancer types and microenvironments affect tumor metabolism?
- What are the underlying mechanisms of resistance to standard therapies especially standard chemotherapy or radiation therapy and how can we overcome these differences in cancer response between individuals?
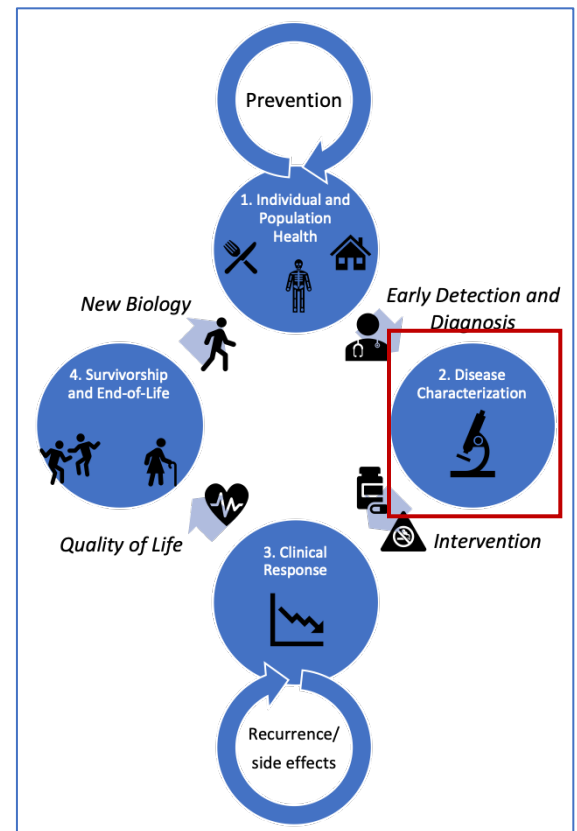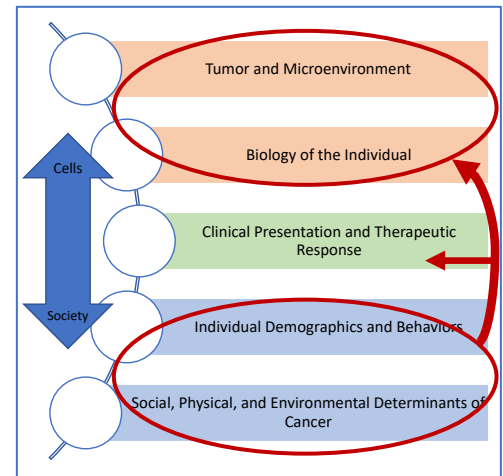
- What are the social determinants of health that play a role in disparities of response to treatment and development of resistance?
- Are there common ways in which tumors of all types become eventually resistant to standard therapies?
- Can in depth profiling of remarkable responders in the UCSF tertiary care population be used to advance cancer therapy?
- Why do germline susceptibility genes have such strong effects on particular tissues? (e.g., mismatch repair gene defects cause colon, uterine and bladder cancer and homologous recombination repair gene defects cause breast, ovarian, prostate and pancreatic cancer?
- How can we use machine learning and deep learning approaches to inform how we combine genetic information to provide the best information about cancer risk?
- Cancer is an evolutionary process. Tumors develop through a process of somatic mutational selection and undergo additional selection under treatment. Can we harness evolutionary principles to better manage/treat cancer?
- How are the multi-cellular networks sustaining tumors qualitatively different than the multi-cellular networks maintaining homeostasis?
- Why are some cancers curable from systemic therapies?
- Why are some cell types within each tissue so much more susceptible to cancer?
- What is the impact of tissue plasticity and evolution in cancer outcomes?

PROVOCATIVE QUESTION 3

What are mechanisms of the biological, environmental, and social determinants of patient and tumor resistance to cancer immunotherapy?

Intent: Cancer immunotherapy is a ground-breaking field out of which many interventions are implemented; however, current therapy is only successful in a small percentage of patients in a small number of tumor types. By 2030, the HDFCCC aims to be at the leading edge of research focused on expanding the proportion of cancer patients who can access and benefit from immunotherapy.

A clear understanding of the mechanisms of treatment response, how the patient immune system predicts response, how patient and tumor genetics can predict treatment response, <more> , and how to provide equitable access to cancer immunology-based care and clinical trials are all key questions to move cancer immunotherapy forward. That is, along the cancer continuum (**Figure 1**), underlying cellular mechanisms and social determinants converge to inform precision therapy for all patients.
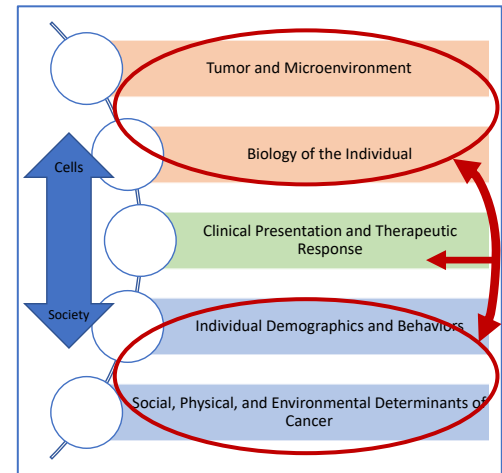
Background:

- Cancer immunotherapy regimens now fall into three categories: Living therapeutics / cellular therapies (CAR T); checkpoint inhibitors; other immune system modulation (e.g., cytokine pathways)
- Cellular therapies are only successful in a handful of cancers (X, Y, Z)
- Cellular therapies and immune system modulation are only successful in fewer than XX% of patients
- Auto-immune disorders, inflammation, and innate immunity are expected to play a role in response to cancer immunology, but the mechanisms by which they individually and together affect response is not fully understood.
- The mechanisms of therapeutic non-response and resistance are not fully understood.
- Cancer immunotherapy is often used in combination with other therapeutic modalities (e.g., chemotherapy) or with each other (e.g., cellular therapy + immune system modulation).
- Cancer immunotherapy is expensive and only available at highly regulated clinics, thereby introducing barriers to access based on distance, SES, insurance coverage, etc.
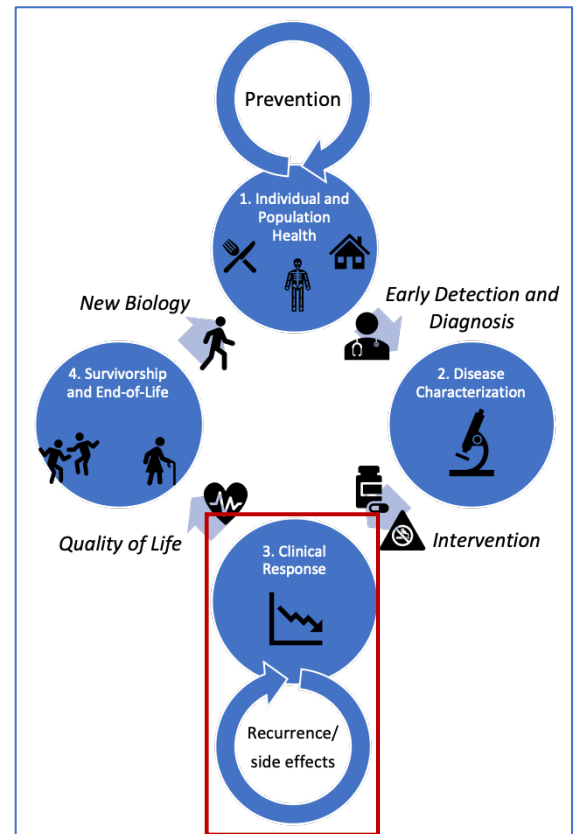
Alignment with Cancer Research in 2030 Strategic Plan: The Strategic Plan framework includes "Clinical Response" (including recurrence and side effects) as an essential piece of the patient perspective (**Figure 2**). Understanding the mechanisms behind response/resistance to cancer immunotherapies is essential in order to meet the 2030 mission of understanding the patient, understanding the intervention, and understanding the tumor to provide precision therapy to all patients at UCSF.

Feasibility: Given that response to the various types of cancer immunotherapy is a multi-factorial issue, addressing this question will involve understanding various measures of treatment response and resistance; mechanistic studies of what drives those measures and how they are altered by cancer and cancer treatment and in turn how cancer and cancer treatment affects those measures; how social determinants of health may affect access to care and therefore drive disparities in response and mortality;; <<others?>> HDFCCC researchers are uniquely poised to collaborate with the strong discovery science in the Department of Immunology, ImmunoX, etc…. to bolster the clinical environment of the Cancer Immunology Program and Clinic…. Etc…..

Examples of research questions that could be responsive:

- What are the genetic or epigenetic components of inflammation and immunity that affect the response of cancer patients to standard (e.g., radiotherapy, chemotherapy), or to more novel (e.g., immune therapy) cancer treatments? Can we modulate these components in patients that do not respond to a particular cancer treatment?

- Can we predict which tumors will respond to immunotherapy more effectively? Can we leverage information from the tumor immune microenvironment using clinical biopsies and FFPE specimens and blood-based biomarkers to understand which tumors will respond? Particularly in cancer types where response is fairly minimal now?

- What is the relationship between obesity and immune surveillance in cancer? Is this organ context-dependent and does it impact response to immunotherapy?

- Can the biology underlying autoimmune disorders inform us about mechanisms underlying immune-related AEs?

- In the era of a lasting pandemic, hundreds of millions of people may get a booster shot every year and hundreds of thousands of people may get infected. Would this have any impact on people's immunity and the effectiveness of immunotherapy?

- Is germline risk for autoimmune disorders a predictor of immune-related AEs during immunotherapy?

- How does immune-genetic make-up influence therapeutic efficacy (immune-modulation and targeted)

- What is the molecular basis for different autoimmune outcomes caused by the various immunotherapeutic treatments?

- How can we reduce cytokine storm and long-term side effects of immunotherapy?

- How do adverse events vary by race/ethnicity and by genetic ancestry? Do the patterns correlate with known differences in autoimmune diseases?

- Can we identify environmental effects on patients' immune system by epigenetic profiling?

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- Can immune profiling of epigenetic changes identify disparities in the immune environment that may be a contributing factor in cancer incidence and outcome?

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PROVOCATIVE QUESTION 4

Does improved quality of life (management of pain, depression, fatigue, etc.) improve cancer mortality, and, if so, how?

Intent: Addressing patent's QOL during and after primary treatment is an important part of their treatment regimen. How QOL affects response to therapy, cancer progression, regression, metastasis, co-morbidities, and ability to thrive can inform treatment decisions, increase patient compliance, decrease mortality. Develop tools to harmonize data related to response to therapy, diagnosis and progression of cancer and co-morbidities, patient-reported outcomes, biomarkers for the effects of QOL. Define QOL as a social determinant of health, and perform research across the cancer continuum to understand the mechanism of how QOL (society) can influence response via the underlying biology in the tumor and patient (cells); and how biology and response may feedback to QOL measures (cells to society) (**Figure 1**).

Background:

- Many treatments have side effects that reduce QOL.
- Growing number of older adults with cancer, or who are cancer survivors.
- Growing number of survivors of childhood cancers.
- Disparities based on social determinants of health may be due to QOL measures.
- Integrated geriatric and palliative care is a relatively unique resource at UCSF for older adults with solid tumors.
- Geriatric assessment-driven interventions have been shown in large, randomized trials to decrease treatment toxicity, improve QOL, and reduce hospitalization and ED visits. However, practical barriers remain in these busy clinics and need to be overcome with novel implementation science approaches.
- Patients with cognitive impairment may be at higher risk for treatment toxicity due to difficulty following complex home medication instructions and treatment and imaging schedules. They are also at risk for both under- and overtreatment given the nuances of shared decision making. Wait lists for formal neurocognitive evaluation at UCSF are quite long and not practical for most older adults with cancer.
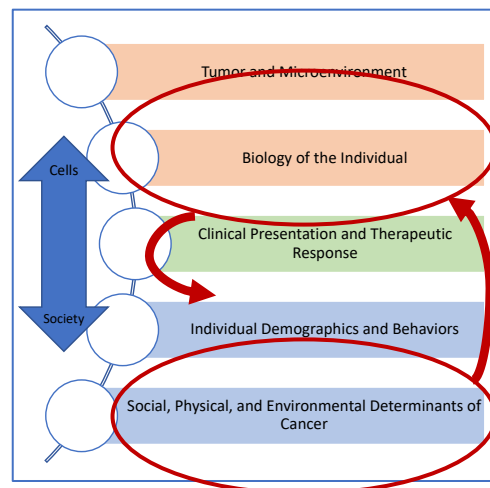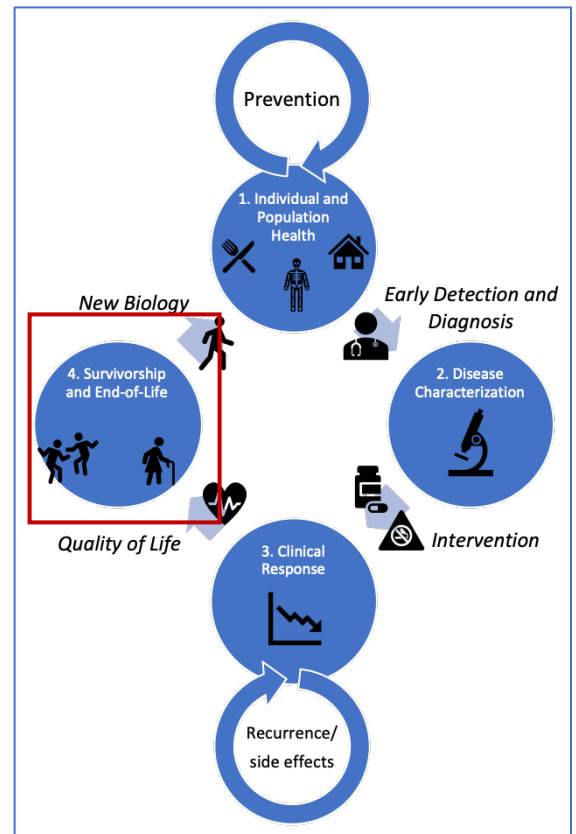
Alignment with Cancer Research in 2030 Strategic Plan: The Strategic Plan framework includes "Survivorship and End-of-Life" as an essential piece of the patient perspective (**Figure 2**), regardless of patient age. While intensive treatment regimens are known to affect QOL, it is equally important to understand how QOL affects patient response to treatment and overall risk and mortality, in order to meet the 2030 mission of understanding the patient, understanding the intervention, and understanding the tumor to provide precision therapy to all patients at UCSF.

Feasibility: Given that QOL is a multi-factorial issue, addressing this question will involve understanding various measures of QOL; mechanistic studies of what drives those measures and how they are altered by cancer and cancer treatment and in turn how cancer and cancer treatment affects those measures; how cultural factors and age (and other social determinants of health) may influence the onset of and patient reaction to to different measures of QOL; how QOL measures can be implemented in the clinic and by primary care physicians; <<others?>>

Examples of research questions that could be responsive:

→ Does integrated geriatric and palliative care synergistically improve outcomes for older adults with cancer beyond what each resource provides individually?

→ What pre- and during-tumor QOL measurements can predict risk, response to treatment, and survivorship QOL?

→ How do cultural factors influence how cancer patients and survivors accept QOL-related side effects? How do these culture factors impact acceptability of QOL-related interventions (e.g., physical therapy, nutrition)?
   o Do cultural factors also influence geriatric assessment-driven interventions?

✓ What is the most effective way to implement geriatric assessment-driven interventions in all UCSF hematology/oncology, surgical oncology, radiation oncology, and neuro-oncology clinics to improve outcomes for older adults with cancer?
   o Can include specific screenings, e.g., neuropathy, cognitive impairment, if results can be generalized/tools used for other conditions

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