UCSF Helen Diller Family Comprehensive Cancer Center

Cancer Research in 2030

CANCER RESEARCH AT UCSF IN 2030: THE STRATEGIC PLAN

HELEN DILLER FAMILY COMPREHENSIVE CANCER CENTER

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I. APPROACH

The Cancer Research at UCSF in 2030 Strategic Planning process began in late 2018, following the CCSG Site Visit (January 2018). Senior leadership defined three broad groups from which it would be important to coalesce and gather information from: (1) the ten extant CCSG programs; (2) other research initiatives, not funded by the CCSG, some of which were defined during this planning process, but also including important aggregations of researchers such as (a) site committees and (b) developing initiatives; and (3) thematic task forces, which we convened in brainstorming sessions as a new way of aggregating people into task forces that covered the cancer continuum from basic research to prevention to diagnosing to treating to delivering health care.

(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		

From August 2018 to September 2019, HDFCCC administration supported membership-wide surveys and brainstorming and information-gathering meetings of the groups described above. Each group produced a brief White Paper report that outlined (1) predictions for 2030, (2) scientific gap analysis (current state of research at UCSF and what is still needed to reach 2030 goals), and (3) summary of themes.

HDFCCC Scientific Leadership identified the common themes and priorities across all White Papers, which are reflected in the overall framework document. The intent was to ensure all current and anticipated research at UCSF would be represented in the strategic planning process. Importantly, throughout the process, additional inputs included UCSF leadership, department chairs, HDFCCC leadership, the HDFCCC external advisory board, and program advisory boards.

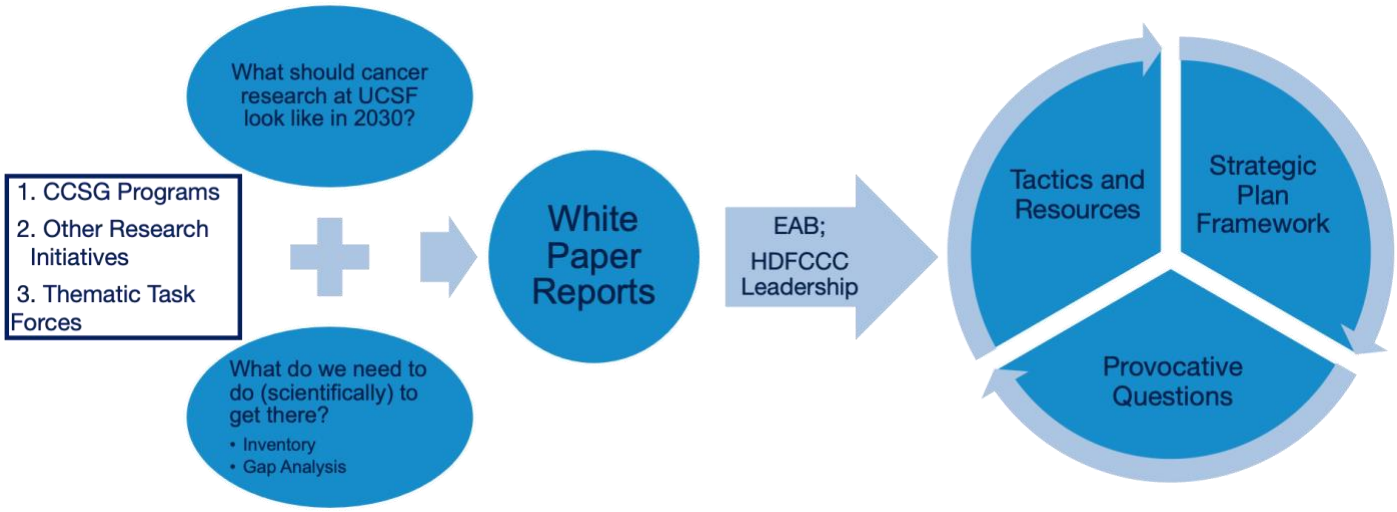
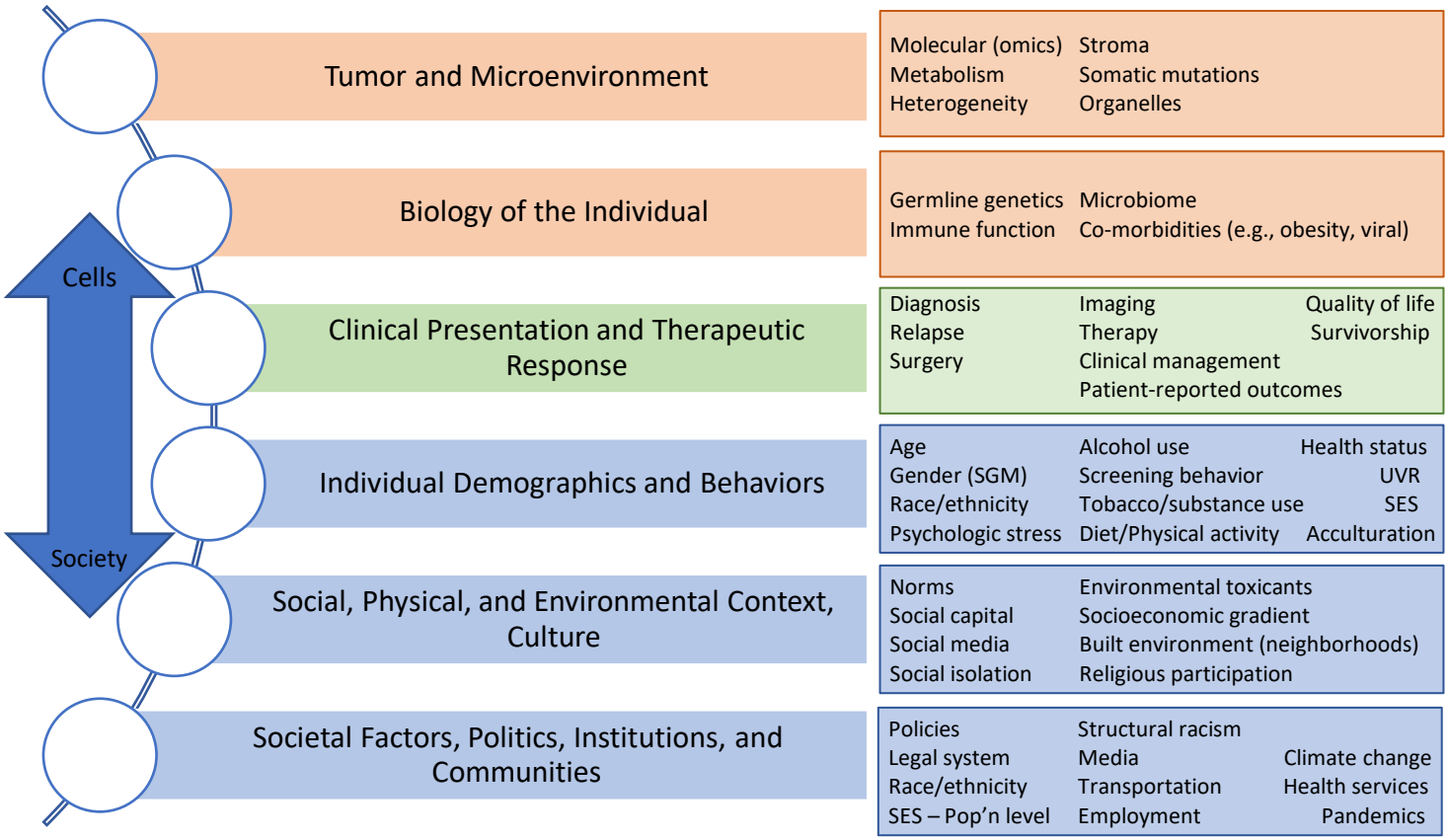


Figure: Schematic of Strategic Plan process leading to the overall roadmap: an iterative process with the framework document, provocative questions, and tactics.

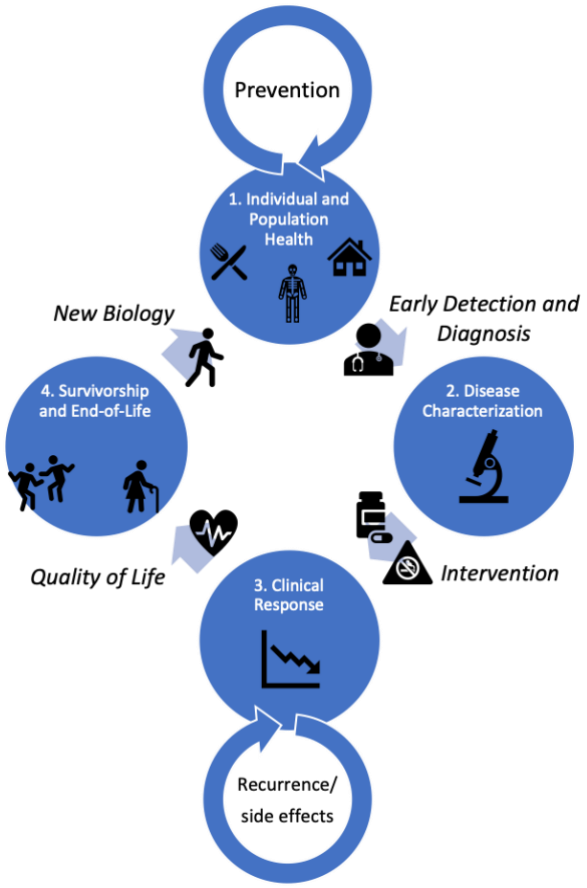
In order to define Center-wide mission, goals, research priorities, and provocative questions around which to provide institutional support, we developed the (1) **Transdisciplinary Framework** and (2) **Patient Experience Perspective Continuum** around which to organize the common themes and priorities. Combined into our overall Strategic Plan Framework, it will be used 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

This framework, by definition, promotes research questions, teams, and methodology that are cross-disciplinary, based on team science, and translational aligning with a "cells to society" model. Importantly, this merging also defines a "society to cells" pathway, by which the etiology of broader societal and demographic factors may be uncovered.



2. PATIENT EXPERIENCE PERSPECTIVE (CANCER CONTINUUM)



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.).

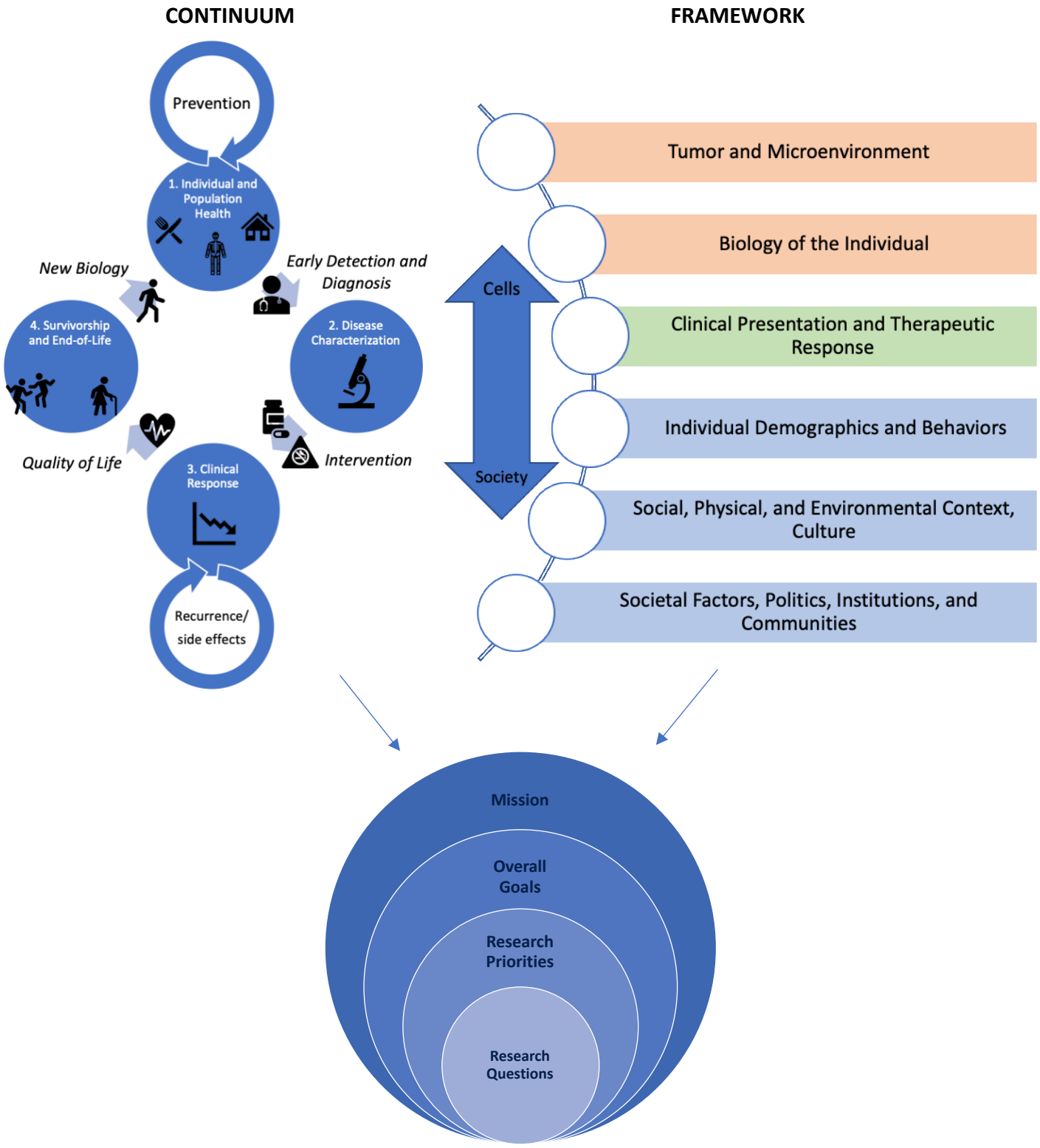
   → ***Quality of Life*** →

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)

II. OUTPUT: STRATEGIC GOALS ACROSS THE FRAMEWORK AT EACH STAGE OF THE CONTINUUM

By combining the Transdisciplinary Framework and the Cancer Continuum structures, we can define 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 Continuum, research goals and priorities were identified at each step of the Framework. By defining goals at these levels, we will be able to identify commonalities and define Center-wide strategic plans to support them.



1. Individual and Population Health

MISSION

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

OVERALL GOALS

At UCSF in 2030, data will be collected from a wide variety of sources, including patient-derived data sources, population-level data sets and predictions, and medical records.

At UCSF in 2030, 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).

At UCSF in 2030, cancer care will be coordinated, and clinicians and health care providers have the requisite expertise to deliver specific screening regimens (e.g., addressing preventive genomics).

At UCSF in 2030, effective communication strategies will be in place with members of all populations within the catchment areas of comprehensive cancer centers across the US to improve understanding and uptake of cancer prevention practices.

At UCSF in 2030, cancer research will be engaged in discovering and implementing proven approaches for reaching and maintaining healthy lifestyles and health behaviors across the cancer continuum (e.g., among the general population and vulnerable subpopulations, and among cancer survivors).

At UCSF in 2030, we will understand 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?

At UCSF in 2030, we will know more about modifiable risk factors that predispose to malignancies, and of ways to delay the evolution of malignancies of indeterminant potential and other precancerous conditions.

At UCSF in 2030, bioethicists will ensure that with the testing and dissemination of any new technology and collection of data via multiple platforms, appropriate safeguards are employed, underserved populations are not left behind, and research integrity and reputation is maintained.

BROAD RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- Detection and data collection (markers) of baseline host biology, including immune function/competence, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- 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)
- Move from single-cell to systems view/combinations of genes working together
- Use alterations in tumor and microenvironment metabolism as novel biomarkers and imaging modalities to track tumor growth, plasticity, aggressiveness, and response to therapeutics

Biology of the Individual

- Detection and data collection (markers) of baseline host biology, including immune function, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- Prioritize novel research and technologies for risk assessment, predictive biomarkers, and early detection based on host biology (e.g., imaging, polygenic risk scores)
- 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)
- Look across cancer type at co-morbidities including cardiovascular risk
- Move from single-cell to systems view and combinations of genes working together

Clinical Presentation and Therapeutic Response

- Detection and data collection (markers) of baseline host biology, including immune function, microbiome, organelles, metabolism, neonatal and pediatric markers, geriatric markers
- 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)
- Assessment of risk with new behaviors and etiologic factors (e.g., cannabis, genetics, and interactions)
- Generate hypothesis-driven collection and sharing of data and samples
- Focus on basic etiology of major cancers with limited prevention and early detection efforts (e.g., pancreas, ovary, prostate, brain)

Individual Demographics and Behaviors

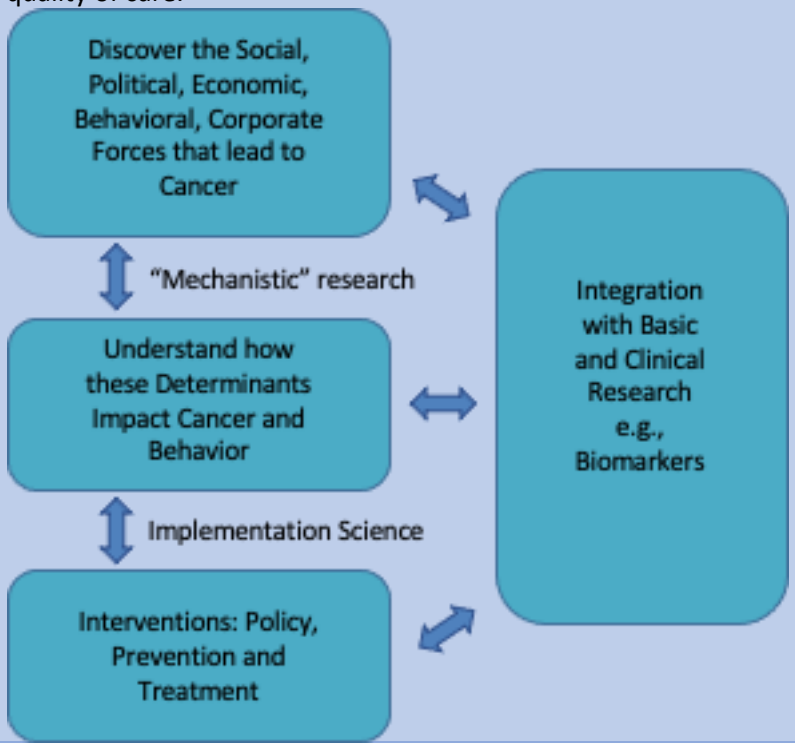
- GWAS studies focusing on risk factors, predictive biomarkers, host determinants of cancer
- Innovation in cancer etiology should focus on the root causes of cancer (including social, environmental, and behavioral determinants of health) and specifically tackle prevention as the translational goal (society to cells)
- Understand how behavior change can reduce risk and increase screening compliance
- Assessment of risk with new behaviors and etiologic factors (e.g., cannabis, genetic, diet and lifestyle)

Social, Physical, and Environmental Context, Culture

- 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)
- Studies will incorporate a core set of measures of social determinants of health and have a toolkit/box of individual- and community-level interventions that address the perpetual challenge of cancer health disparities
- New environmental exposures (e.g., pollution, chemical toxins, climate change) and corporate drivers (e.g., tobacco, sugar, pharma) are driving current efforts to improve cancer prevention and early detection interventions

Societal Factors, Politics, Institutions, and Communities

- Implementation science with increased emphasis on application of new knowledge and implementing effective preventative measures (e.g., screenings, interventions, behavior change, policy)
- Social and environmental determinants of health, with increasing recognition of upstream influences on cancer and health in general, including corporate or commercial drivers (e.g., tobacco, sugar, pharm)
- 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
- 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.



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?	**Research Highlight** • GWAS studies in prostate cancer (Witte) • Myeloma GWAS (Ziv) •
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?	**Research Highlight** • GWAS data for adult glioma risk, AGS (Wrensch) •
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?	**Research Highlight** • Tobacco Center: pulmonary and cardiovascular effects of tobacco • Screening for anal cancer/anal dysplasia clinic for high-risk patients (Palefsky) • Pre-diagnosis prostate cancer biobank (Shirohara) • Appropriate follow-up post-screening: quality of care, prevent loss to follow-up (Palmer) • UCSF PRHE - measuring exposures to environmental carcinogens/chemicals in pregnant people and children
Individual Demographics and Behaviors • GWAS studies in ethnic groups to correlate risk. • What is the influence of microbes on documented cancer social health disparities, and vice versa?	**Research Highlight** • WISDOM trial • Ziv, Witte • All of Us cohort - large cohort, multiple topics, cells to society (Hiatt) • Decision-making in African-American men (Palmer) • SF CAN • Environmental chemical exposure – prenatal, childhood (Woodruff)
Social, Physical, and Environmental Context, Culture • Do individuals respond to social media messaging promoting screening? • Capacity building • Implementation science	**Research Highlight** • Ling: tobacco prevention strategies • Gomez et al – GBACR • cancer patient navigation and leveraging technology to deliver navigation (rural, Asians) • SF CAN • UCSF PRHE - understanding populations vulnerable to environmental carcinogens (i.e., age, life stage, social stressors)
Societal Factors, Politics, Institutions, and Communities • Does the flavored tobacco ban influence smoking behavior?	**Research Highlight** • New opportunities to apply lessons learned from tobacco to other industries that affect cancer

• 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? • Capacity building	risk, including the food, chemical, oil, sugar, cannabis, and pharmaceutical industries (e.g., industry documents library) • SF CAN • Trade policy and health (Bialous) • Extending HDFCCC expertise in genetic counseling to safety net via remote channels of communication (Pasick) • Healthcare costs of tobacco and cannabis (Max) • Social gradients with cancer in CA (Hiatt)

2. Disease Characterization

MISSION

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.

OVERALL GOALS

At UCSF in 2030, 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 minority populations will be better understood (e.g., immune response, pharmacogenomics).

At UCSF in 2030, a multi-dimensional 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, and an evaluation of tumor heterogeneity and plasticity.

At UCSF in 2030, cancer research will be facilitated by new tools (e.g. single cell profiling, novel imaging and drug delivery systems) and advances in cell culture models that encompass the complexity of human organs, allowing the study of how cancer evolves in the context of the tumor microenvironment.

At UCSF in 2030, 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.

At UCSF in 2030, 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 allowing preventing the evolution of disease.

At UCSF in 2030, we will treat cancer as a tissue: a network of interacting cells.

At UCSF in 2030, we will know more about how 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.

BROAD RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- Biomarkers of tumor characteristics (e.g., heterogeneity, plasticity, metabolism, pathology) to improve risk stratification, diagnosis, and early detection through screening and regular wellness visits
- Microenvironment characterization and changes due to tumor onset and development
- Changes in cellular function: organelle biology, -omic characteristics of tumor (e.g., epigenome, metabolome, exposome)
- Continued research focused on synthetic lethality and "untargetable" genes/processes
- Increased focus on tumor as a community of cells through single-cell analysis
- Integrative analysis of multiomics data
- Interaction of the cancer genome (+ epigenetics) with host factors (e.g., immune system, microbiome, metabolism)

Biology of the Individual

- Effect of host factors (e.g., immune system, microbiome, metabolism) on tumor onset and progression
- Tumor-driven changes in host biology (e.g., immune function, microbiome, metabolism)
- Etiology of external determinants of health
- "Untargetable" genes/processes
- Multimodality imaging data collected from multiple sources, combined and analyzed using advanced AI approaches to provide diagnostic prognostic and predictive information
- Increased emphasis on understanding pre-neoplastic conditions to help with early detection
- Integrative analysis of multiomics data
- Development of a conceptual framework for defining the immune competence of a cancer patient
- Host variability will influence risk stratification, drug exposure, resistance, and toxicity

Clinical Presentation and Therapeutic Response

- Combinatorial data, including multimodality imaging data, biomarkers, *in vivo* and real-time screening, -omic, collected from multiple sources, combined and analyzed using advanced AI approaches to provide diagnostic prognostic and predictive information based on tumor, patient, and environmental characteristics
- 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
- Evaluation of benefits and risks (costs) of new screening tools (e.g., ctDNA, liquid biopsy, imaging)
- Effect of past interventions/prevention measures on current clinical presentation and predicted therapeutic response

Individual Demographics and Behaviors

- Correlation of demographics and behaviors with risk stratification, tumor development and progression
- Individual demographics and behaviors that affect intervention options and success
- Behavior change to improve risk stratification and early detection
- Understand the mechanisms by which tobacco and cannabis use causes and promotes cancer

Social, Physical, and Environmental Context, Culture

- Social and environmental factors that affect intervention options, risk stratification, early detection
- Data collection to inform diagnosis will include social, physical, environmental, culture context
- Outreach to communicate risk, importance of early detection, next steps, navigating a diagnosis

Societal Factors, Politics, Institutions, and Communities

- Societal and political factors that affect intervention options, risk stratification, early detection
- Data collection to inform diagnosis will include social, physical, environmental, culture context
- Implementation research on policies, infrastructure to improve early detection, seeking treatment, accessing care

RESEARCH QUESTIONS TO BE ANSWERED BY 2030

Tumor and Microenvironment
• 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
  ▪ e.g., diseases that have changed in etiology/demographics (colorectal)
	Research Highlight
	• 13C-Hyperpolarized Imaging - use of MRI to study various metabolites for in vivo studies of preclinical models and first-in-man clinical studies (Dan Vigneron, John Kurhanewicz, Pam Munster, Rahul Aggarwal, Andrei Goga, etc.)
	• Molecular characterization of different human cancer types to improve diagnostic subtyping (Pathology Dept.)
	• Methylation profiling for tumor classification (Solomon)
	• Monitoring heme malignancies at single-cell level using microfluidics and DNA sequencing (Cathy Smith)
	• PDX for colorectal drug testing (Atreya)
	• organoids in GI malignancies (Bob Warren)

Biology of the Individual • How does host biology change upon tumor development factors influence risk (e.g., microbiome, immune function, metabolism) and are these biomarkers for early detection? • 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?	**Research Highlight** • Targeted NGS panel (UCSF500) for cancer diagnosis and treatment (CCGL) • Microbiome in colorectal cancer patients (Atreya) • UCSF500 testing to provide precision medicine to pediatric patients
Clinical Presentation and Therapeutic Response • 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?”	**Research Highlight** • LoGlio (project in NeuroOnc SPORE) - imaging, molecular, clinical dataset • Hyperpolarized C-13 MRI in diagnosing aggressive prostate cancer (Kurhanewicz, Vigneron) • Hyperpolarized C-13 MRI in risk stratification of renal tumors (Jane Wang, Peder Larson) • Metagenomic sequencing for early cancer detection (Wei Gu, DeRisi • Cell of origin methylome profiling (Costello) • Mathematical model of breast cancer incidence (Hiatt)
Individual Demographics and Behaviors • How does tobacco use cause cancer? • What genetic variants are associated with disease progression and onset?	**Research Highlight** • Biomarkers of tobacco and cannabis use (Benowitz) • Nicotine and cancer biology (Glantz) • Whole-exome sequencing in Latinas (Ziv) • Assessment of racial/ethnic distribution of known genetic variants

Social, Physical, and Environmental Context, Culture • Etiology of social determinants of cancer	**Research Highlight** • Genetic vs. social determinants of cancer disparity (Cooperberg, Washington) • Social media tobacco cessation interventions (Ling)
Societal Factors, Politics, Institutions, and Communities • What societal determinants or policies affect early detection?	**Research Highlight** • SIREN (social interventions research and evaluation network) - collection of social determinants of health/social risk screening

3. Clinical Response

MISSION

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.

OVERALL GOALS

At UCSF in 2030, 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 minority populations will be better understood (e.g., immune response, pharmacogenomics).

At UCSF in 2030, interventions will be iterative, based on real-time monitoring of response and compliance to treatment regimens.

At UCSF in 2030, 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.

At UCSF in 2030, 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

At UCSF in 2030, 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.

At UCSF in 2030, 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.

At UCSF in 2030, 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.

At UCSF in 2030, we will coordinate care across systems (e.g., UCCCC, Fresno, John Muir, BCHO) with EHRs, multidisciplinary research, research application, health services.

BROAD RESEARCH PRIORITIES ACROSS THE FRAMEWORK

Tumor and Microenvironment

- Continued focus on "undruggable" targets
- Novel modeling paradigms
- Target identification and validation
- Etiology of tumor evolution of metastatic disease
- Minimal residual disease

Biology of the Individual

- Continued focus on "undruggable" targets
- Target identification and validation
- Pharmacogenomics, PK/PD
- Patient biology over the course of treatment – side-effects, toxicity
- Host variability will influence drug exposure, resistance, and toxicity
- Spatio-temporal stem cell interactions throughout disease
- Patient microbiota features will be incorporated into the growing array of clinical, tumor 'omics and microenvironment features analyzed for all cancer therapy selection and outcome expectations at UCSF
- We should determine with our methods, and in our patients, which microbial strains, genes and metabolites are associated with poor therapeutic responses, testing patient stool samples before and during treatment

Clinical Presentation and Therapeutic Response

- Combination therapies
- Diet and integrative oncology
- Pharmacogenomics
- Clinical response and patient-reported outcomes will be considered in intervention decisions
- Short- and long-term toxicity
- Creation of an "opt-out" consent structure
- Expansion of resources available for rapidly procuring specimens across our campuses through the Biospecimen Repository program.
- Multimodality imaging data collected from multiple sources, combined and analyzed using advanced AI approaches to provide diagnostic prognostic and predictive information
- Development of resistance is assumed and will be considered in all treatment regimens
- Combine tumor biology + individual (person) biology to inform treatment

Individual Demographics and Behaviors

- 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 Context, Culture

- Implementation science
- Tools to improve access to and compliance with interventions
- Environmental barriers to access and compliance (e.g., built environment, peer group support)

Societal Factors, Politics, Institutions, and Communities

- New models of ***industry collaborations*** will allow iterative and creative study design and more control of the pipeline
- Population-level interventions, including policy, screening guidelines
- Cost-effectiveness and health economics research
- Implementation science

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?	**Research Highlight** • A UCSF-based study has identified enrichment of specific bacterial species in the feces of healthy women versus women with DCIS versus invasive breast cancer, and is now positioned to use shotgun metagenomic sequencing and metabolomics to extend their observations into testable mechanistic hypotheses (McCune, et al). • clonal evolution (Costello, Bivona) • therapy for tumors with DDR (Dhaven, Assamal) • new approaches to CAR-T design and overcoming resistance (Parker Inst) • resistance mechanisms to targeted therapy in AML (Cathy Smith) • intratumoral drug levels (van t' Veer)
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?	**Research Highlight** • Manipulation of the immune system beyond checkpoint inhibitors • WISDOM trial • GWAS on patients on immunotherapy (Ziv) • pharm chem, development of new small molecules targeting protein homeostasis (Taunton) • P01 on structure of ABC transporters (Stroud) • microbiome effects on drug metabolism (Turnbaugh)
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?	**Research Highlight** • Clarity- and NLP-driven comprehensive outcomes database for urologic oncology (Odisho, Cooperberg) • mechanisms of resistance, targeted therapy in NSCLC (Bivona) • cohort study using a comprehensive geriatric assessment to predict outcomes after hematopoietic cell transplantation for hematologic malignancies (Olin)
Individual Demographics and Behaviors • How do tobacco, other toxins, affect response to interventions? • What behavior decreases individual compliance to an intervention regimen?	**Research Highlight** • WISDOM trial • Physical activity and diet impact on disease progression (Jo Chan) • Integrating tobacco cessation in cancer treatment (Tsoh)
Social, Physical, and Environmental Context, Culture • What characteristics of a patient's homelife (e.g., isolation, poverty, built environment) affect access to and compliance with interventions?	**Research Highlight** • Clinical trial access and enrollment disparities (Winestone) • Cost analysis of smoking cessation and immunotherapy
Societal Factors, Politics, Institutions, and Communities	**Research Highlight**

• What health care policies affect patient's access to and compliance with interventions? • How do do healthcare costs affect outcomes?	• Efficient means for safety net patients to obtain and benefit from HDFCCC clinical expertise (Pasick) • Community screening - meet patients where they are (Palmer)

4. Survivorship and End-of-Life

MISSION

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.

OVERALL GOALS

At UCSF in 2030, cancer research will need to reflect an aging population and a growing number of cancer survivors.

At UCSF in 2030, there will be greater 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.

At UCSF in 2030, 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.

At UCSF in 2030, 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.

At UCSF in 2030, 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.

At UCSF in 2030, 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.

At UCSF in 2030, there will be 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.

At UCSF in 2030, 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).

BROAD 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)
- Prevention and therapy of secondary neoplasms

Biology of the Individual

- Late effects and aging of the cancer population will mean that more survivors have multiple comorbidities
- Health outcomes research
- Patient-reported outcomes regarding physical symptoms, side effects

Clinical Presentation and Therapeutic Response

- Symptom science (including survivorship), patient-reported outcomes, and patient preferences will be incorporated into study design.
- 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 of multi-comorbidities
- Symptom management across the cancer treatment and advanced cancer trajectory (includes genetics and behavioral science)

Individual Demographics and Behaviors

- 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 Context, Culture

- Implementation science
- Tools to improve access to and compliance with interventions
- Environmental barriers to access and compliance (e.g., built environment, peer group support)

Societal Factors, Politics, Institutions, and Communities

- 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.

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?	**Research Highlight** • Disparities and outcomes in neuroendicrine neoplasms (CCR) (Bergsland)
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)?	**Research Highlight** • UCSF and many of its clinical partners are beginning to incorporate Patient Reported Outcomes (PROs) into their electronic health records systems, which should facilitate research on cancer risk and cancer disparities. • Childhood cancer survivorship study (ccss) - contributing site (Goldsby)
Clinical Presentation and Therapeutic Response • What therapeutic uses are there for cannabinoids, including use in supporting treatment of cancer patients? • Is the EHR part of the solution to better understanding of health outcomes or a distraction from the real work of improving outcomes? • What are the costs and benefits of new cancer therapeutic approaches in terms of the length and quality of survivorship for major cancer sites?	**Research Highlight** • Integrative Oncology research and care • SON emerging research focus on survivorship • Symptom management/toxicity management (Miaskowski) • understanding risk factors for cognitive decline after hematopoietic cell transplantations in older adults in hematologic malignancies (Olin) • Alliance multisite study of improving surgical care and outcomes in older cancer patients through implementation of an efficient pre-surgical tool kit (Finlayson)
Individual Demographics and Behaviors • How does supporting patients' end-of-life preferences improve quality of life? • 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 survivorship for major cancer sites? • What factors should be considered, and how, in the transition from active treatment to recovery and rehab post-treatment?	**Research Highlight** • NIA-funded focus group study to evaluate a best case/worst case communication tool for treatment discussions with older adults (Melisa Wong) • survivorship in GI malignancies (Van Blarigan)

Social, Physical, and Environmental Context, Culture • What characteristics of a patient's homelife (e.g., isolation, poverty, built environment) affect access to and compliance with interventions? • What family contexts play a role in survivorship? • Capacity building • How are plans and best practices best disseminated to different underserved populations?	**Research Highlight** • UCSF has a newly created Population Health Data Initiative which is enabling an analysis of geospatially coded clinical data in concert with other publicly available neighborhood data, and this is opening up new vistas for approaching health outcomes, implementation science, and policy research in cancer. • survivorship care plans and dissemination and best practices to underserved populations (Sarkar Gomez)
Societal Factors, Politics, Institutions, and Communities • What policies improve survivorship 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? • Capacity building	**Research Highlight** • Behavioral/psychosocial research not limited to symptom management (e.g., patient self-management, family caregiving, contexts for behaviors (e.g., rural contexts)) (Dept of Psychological Nursing)

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:**

> *Through discovery, clinical, and population science, we will understand the **person** and their social and physical **environment**, understand the **tumor**, and understand the **intervention**. We will translate this research into appropriate risk stratification, prevention, screening, diagnosis, interventions, and long-term care decisions, and **reduce inequities** in cancer care and treatment outcomes.*

Furthermore, our organization allows for the concept of HDFCCC-wide **Provocative Questions**, to be defined below, around which tactics can be deployed.

HDFCCC MISSION

Through discovery, clinical, and population science, we will understand the **person** and their social and physical **environment**, understand the **tumor**, and understand the **intervention**. We will translate this research into appropriate risk stratification, prevention, screening, diagnosis, interventions, and long-term care decisions, and **reduce inequities** in cancer care and treatment outcomes.

OVERALL GOALS

At UCSF in 2030, we will be developing and testing **highly individualized therapy based** on comprehensive knowledge of the biology of the tumor; the contributory features of the host; how the intervention being developed interacts with the host and tumor environment; and environmental, social, and political barriers to interventions.

At UCSF in 2030, we will undertake **a comprehensive multi-dimensional clinical evaluation** of every patient's cancer, including an understanding of the comprehensive genomic and immunologic characteristics of a cancer, the role of tumor heterogeneity, cancer plasticity, and the tumor microenvironment.

At UCSF in 2030, **the biologic, social, and environmental context** of the individual will be an integral component of the treatment paradigm.

At UCSF in 2030, discovery will be advanced by looking **across cancer types** and broadening the definition of cancer beyond the organ site in which a tumor develops.

At UCSF in 2030, data from basic, clinical, and population research will be **integrated** in an open and iterative flow, in order to inform appropriate risk stratification, prevention, screening, diagnosis, and interventions.

At UCSF in 2030, HDFCCC will be at the forefront of **comprehensive and universal data collection and analysis** with the goal of improving diagnosis, treatment, and ability to share across research studies.

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.

At UCSF in 2030, **translational research "hubs"** will be organized to bring complementary expertise to a research question, to link the tool-builders with the tool-users, and to dissolve boundaries around existing silos to allow iterative research design in the lab, in the clinic, and in the community.

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.

At UCSF in 2030, we will establish **formal relationships** with other comprehensive cancer centers regionally and nationally, and with global partners, and together use big data and artificial intelligence to identify individuals with elevated cancer risk or rare cancers, identifying opportunities for population health interventions as well as candidates for appropriately targeted cancer prevention and cancer therapy research.

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.

Biology of the Individual

- Includes patient-derived data sources (e.g., devices, 23andMe, etc.) and new technologies yet to be determined
- Link between what happens outside the body with what happens inside the body

Clinical Presentation and Therapeutic Response

- Avoid collecting data for the sake of having more data: how to use the wealth of information to make specific decisions about treatment and research for individual patients/populations
- 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

Social, Physical, and Environmental Context, Culture

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

Societal Factors, Politics, Institutions, and Communities

- Link between what happens outside the body with what happens inside the body
- 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 beyond UCSF. Our research will lead towards investigating the impact of integrative oncology approaches on survival among cancer patients and cost-effectiveness research.
- 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.