1. Protocol title:

The TREC@TAMU Cancer Prevention Registry and Repository (referred to hereafter as "Protocol") Version Date 11/01/2024:

2. Study team

Principal investigator:
Kenneth S. Ramos, MD, PhD
Alkek Chair of Medical Genetics
Center for Genomic and Precision Medicine
Professor of Translational Medical Sciences, Texas A&M College of Medicine
Executive Director, Texas A&M Institute of Biosciences and Technology
Associate Vice President, Texas A&M University Health Science Center
Assistant Vice Chancellor for Health Services, The Texas A&M University System
2121 W. Holcombe Blvd
Houston, TX. 77030
Tel. 713.677.7440
kramos@tamu.edu

Co-Investigator(s)

Gabriel Neal, MD
Gabriel Neal MD MA (Bioethics) FAAFP
Clinical Professor& Department Head
Chief Clinical Officer SOM
Texas A&M University | Primary Care and Rural Medicine

Rick Silva, PhD, MBA
Executive Director, Clinical | Translational | Industry Collaborations
Texas A&M Health Science Center
Assistant Professor, Department of Translational Medical Sciences

Marcia Ory, PhD
Regents & Distinguished Professor
Department of Environmental and Occupational Health School of Public Health
Core faculty, Center for Community Health and Aging

Fen Wang, PhD
Professor of Translational Medical Sciences, Texas A&M College of Medicine
Texas A&M Institute of Biosciences and Technology, Center for Translational Cancer Research

3. Objectives:

The Cancer Prevention Clinicogenomic Registry (CPCR) Core will support the Texas Regional Excellence in Cancer (T**REC) @TAMU Cancer Prevention Registry and Repository Program.** Documentation of the genetic, environmental, and lifestyle, dimensions is crucial to validation and implementation of cancer prevention and treatment strategies. This is often a critical unmet need at academic health centers which limits the ability of cancer investigators to

access biospecimens and complete in silico investigations. A discussion with TREC investigators and cancer researchers at Texas A&M University documented the many challenges they face accessing biospecimens with patient-matched clinical histories from other Texas Centers. Thus, a core facility is needed to provide prospective and retrospective collection and curation of specimens and clinical data from populations at-risk of cancer and those being screened for cancer at Texas A&M clinics. The service will be provided in partnership with the Health Hub and Family Medicine Clinics (located in Bryan and Navasota, Texas) of Texas A&M Health. (1, 2). The involvement of two clinical sites is facilitated by the overlapping coverage provided by TAMU clinicians at both clinical sites. All study participants will have an eCW medical record, but data curation from their medical records will be agnostic to the site providing care or the TAMU provider involved.

The immediate research aims of the TREC@TAMU Registry Program are to:

1) Measure the impact of a cancer screening program on overall patient satisfaction in at-risk populations.
2) Collect data on the socio-economic, environmental, and occupational determinants of cancer risk longitudinally.
3) Establish a biobank enabling case-matched histories with multi-omic bioanalysis for cancer biomarker discovery and validation.
4) Model determinants of cancer event rates across time.
5) Enable decision science, cohort discovery, and risk model training for cancer screening and chemoprevention programs.
6) Measure health economic outcomes in cancer at risk populations by analysis of billing and diagnosis entries into the subject's electronic health record in TAMU's family medicine clinic.

4. Background:

There are many predicates of clinicogenomic approaches to combine clinical annotation, registries, and biobanks to inform and refine clinical practice across communities of practice and organizational boundaries.

The Framingham Studies (FHS) provided a robust platform from which to build risk models that leverage biomarkers to prevent cardiovascular disease.(3) These seminal studies have led to marked reductions in mortality from cardiovascular disease over the last 50 years.(4) A major challenge to the implementation of chemoprevention strategies is the lack of reliable surrogate biomarkers of disease progression and resolution. (5) Using a definitive cancer diagnosis as a direct clinical endpoint renders most randomized controlled chemoprevention trials impractical due in part to a large study size and time requirements. Further, genetic, social, and environmental factors are difficult to study in the primary and community health settings.

In most academic medical centers and cancer center settings, where most robust clinicogenomic registries reside, the genetics of premalignant lesions (i.e., liquid biopsy material from blood) and the natural progression of disease are often not available. In addition, the study of social and environmental factors intertwined with genetics is limited because biospecimens are collected *after* a cancer diagnosis is made and retrospective analysis of health records is limited to data obtained within the oncology ecosystem. As such, typical registries and biobanks do not currently serve the needs of **Cancer Interception and Precision Prevention** programs, thus limiting hypothesis generation in that segment of the patient's journey.

A more complete understanding of cancer development, and the validation of strategies that prevent cancer in at-risk populations would be aided by use of the Framingham approach that takes advantage of digital tools available today to contextualize social and economic disparities and their interaction with genetic determinants of cancer outcomes. The first example of a longitudinal registry was the Bone Sarcoma Registry, providing both population level and case level understanding of bone sarcoma. (6) Dr. Codman's commentaries on the registry first published in 1924, provides a remarkable perspective on the utility of thoughtfully constructed, forward looking registry programs. Nearly a century later, the same opportunity exists for real world clinicogenomic data, but policy and industry structure constraints abound. Cancer biorepositories and registries do not provide a deep documentation of the clinical care across time, especially prior to the patient's entry into specialized oncology care. Most cancer registries curated by Public Health Cancer Control Programs in the US tend to be limited to demographic and census data. (7) Successful cancer prevention and treatment strategies require implementation of systems-based solutions that fully integrate the complexities of cancer.(5)

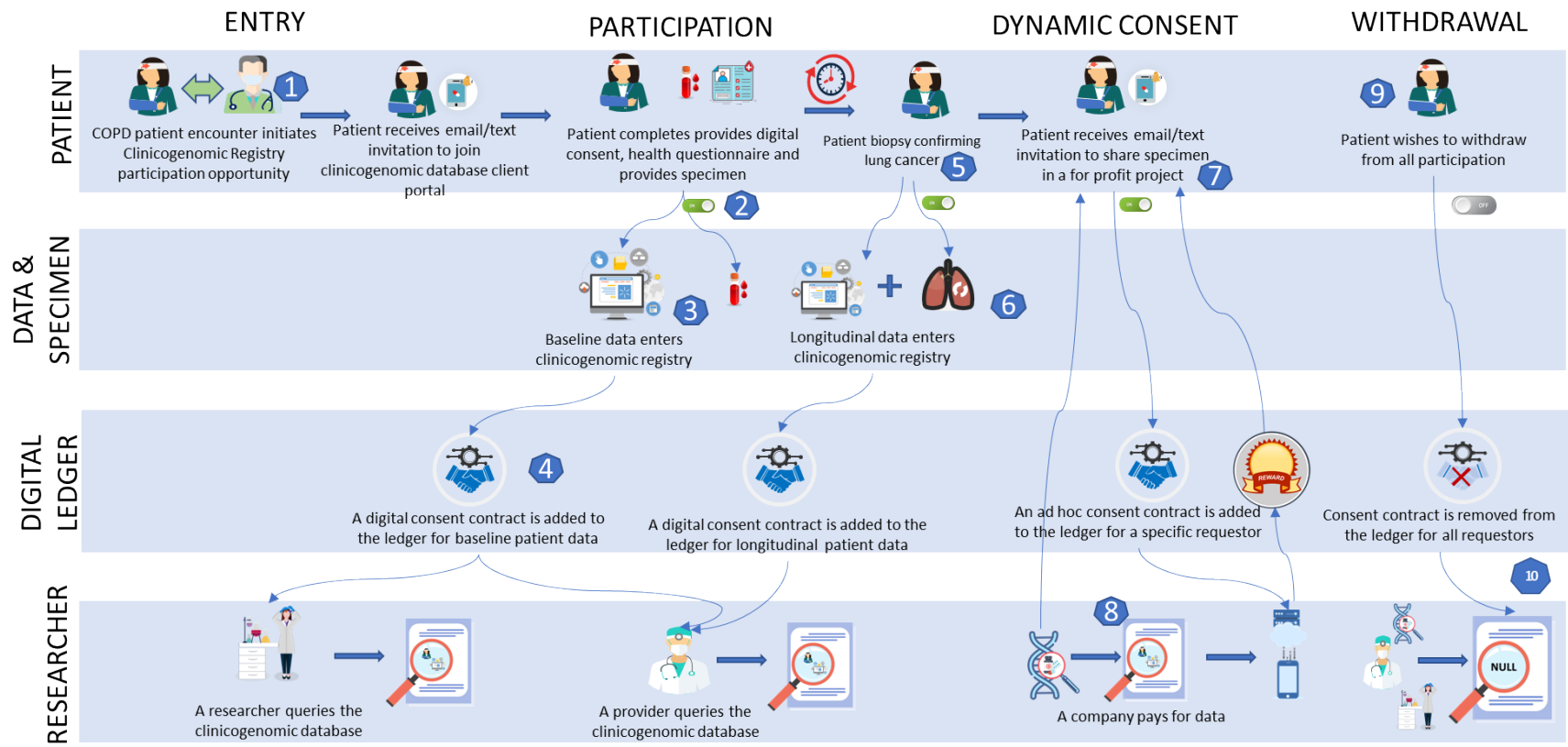
More recently, in part due to 21st Century Cures Legislation (8), tumor genotyping, treatment, and outcomes data have been generated widely in oncology practice even when patients are not participating in a clinical trial, rendering rich real-world data (RWD) and potential for real world evidence (RWE) to refine and validate the evolution of oncology practice and guide investments in clinical development of new technologies and drugs. (9) In the era of precision medicine, there is a paradox in that the more specific the criteria in a population of interest, the less likely a meaningful number can be found at a single institution. (10, 11) Nonprofit organizations like the ORIEN network, an alliance with 18 cancers centers across the US, using federated biobanking and data models, have emerged to empower cohort construction and enrichment across organization boundaries. (12) The ORIEN program utilizes the Total Cancer Care Protocol, pioneered by Dr. Bill Dalton in collaboration among the Moffitt Cancer Center and the James Cancer Center and numerous public and private sector partners. (12) The Total Cancer Care Protocol is framed as a 20 year longitudinal partnership between patient and research team (NCT03977402).

The private sector has invested heavily in cancer clinicogenomics since the rise of next generation sequencing (NGS). Foundation Medicine built a business model around targeted tumor sequencing in their CLIA lab. Flatiron Health built their business around a medical record abstracting service for community oncology clinics to bring unstructured case-level data into a computable and structured format. Both companies spawned data that reveal valuable demographic, phenotypic, and genetic aspects of cancer at population scale. (13) So much so that Roche purchased Foundation Medicine and Flatiron Health for $5.3B and $1.9B, respectively. However, the point of entry of patients into the Foundation Medicine and Flatiron Health is through oncology practice and their clinicogenomic databases provide only a keyhole view of the cancer patient journey, arguably the least tractable period for curative and preventative interventions. Tempus has become a major participant in the clinicogenomics industry recently due to founder Eric Lefkofsky's experience when his wife was treated for breast cancer at a number of prominent cancer centers in the US.(14) Lefkofsky cites data discontinuity, population scale clinicogenomic infrastructure, and institutional data practices as a constraint to leveraging big data in the fight against cancer. Tempus has worked upstream in its product and services model to engage populations in cancer screening and pharmacogenomics (both populations with chronic disease burden and high cancer risk). In all cases, these companies forged robust public-private partnerships with the NCI and NCI-designated Cancer Centers to enable their substantial contributions to medicine. Companies such as Truveta, Explorys, and Cerner have built business around clinical decision support and health analytics at the intersection of population scale EMR data and AI. Oracle-Cerner and Epic have both

implemented genomic clinical decision support functions that are AI driven and trained by data obtained across their universe of hospital system and provider customers. All examples are driven by the curation of case-level data from the EMR. A large community of practice studying and sharing knowledge of implementation in PGx has emerged. (2, 15, 16) Implementation science in clinicogenomics is largely about collection and curation of clinicogenomic data and then sharing that among the community of practice (industry, practitioners, health systems) to move towards standardization of bioanalytic methods, nomenclature, interoperable data formats, and workflows.

Biobank blind-spots: Clinical annotation of specimens in a biobank is correlated with the clinical relevance and utility of studies using those specimens. For example, the sequencing of 1000 lung tumors reveals neurotrophic tropomyosin/tyrosine kinase fusions in 300 cases. This information is of limited use by itself- as this is an epidemiological fact, but does not inform clinical actionability (11). However, if the medical records of those 1000 cases provide the researcher with treatments used and clinical outcomes, it becomes evident that certain drugs with kinase inhibitor activity delay tumor recurrence substantially. (10, 17) Now we can learn from the biobank which drugs might warrant clinical trials in patients with tumors that have these genetic features. What if molecular and cellular debris that are shed from these tumors can reveal the existence of these tumors very early in the disease process where surgery and chemotherapy are highly effective? Most cancer-related biobanks have a blind-spot: the timeframe before the patient is diagnosed with cancer. What if genetic anomalies like gene fusions were an early-stage screening biomarker that could be detected in a blood test? Consensus on the clinical benefits does not exist for most cancer types. (18) In fact, the population genomics company GRAIL has undertaken the largest prospective validation trials of pan cancer screening biomarker panels to date. Enrolling a population of patients that might develop tumors is an expensive undertaking and requires a high threshold of confidence. The merits of these approaches remain controversial, in large part because the positive predictive value of these approaches is expected to be low. (19) It is argued that mutant allelic fractions of circulating tumor DNA correlate with tumor size. (20) How does one know this in early-stage tumors without prospectively enrolling thousands of patients for a long observational period in expectation that a few dozen will have a disease trajectory that is informative.

In cancer screening and prevention, it becomes a challenge to study cancer biology without a tumor, but at the same time the tumor represents just a snapshot in time of the disease process and patient journey where social determinants of health (SDOH) and lifestyle factors also contribute to disease trajectory. Therein lies an opportunity for a thoughtfully designed longitudinal surveillance program in high-risk populations. General medical practice now has risk-based guidelines for screening for lung cancer, liver cancer, cervical cancer, and breast cancer, all areas where we have active programs. An idealized clinicogenomic registry works like a time machine and a teleportation machine (**Figure 1**). It provides biospecimens, genetic, and regulatory-grade clinical annotation longitudinally, across the patient journey, across time, and across organizational boundaries in the healthcare ecosystem.



Journal of Personalized Medicine

Silva, P.; Dahlke, D.V.; Smith, M.L.; Charles, W.; Gomez, J.; Ory, M.; Ramos, K. **An Idealized Clinicogenomic Registry to Engage Underrepresented Populations Using Innovative Technology**. *J. Pers. Med.* **2022**, *12*, x. https://doi.org/10.3390/xxxxx

Figure 1. Adapted from Silva et al., 2022. Annotating the systems factors in the cancer patient journey. **1)** COPD patient at high risk for developing lung cancer has periodic low-dose CT screening, screening for participation in the TREC@TAMU Cancer Prevention Registry and Repository Program. **2)** patient provides a digital and dynamic consent for routine banked specimens to be used for research when a need arises **3)** Consent is entered on the digital ledger and digital permission is effected through smart contract. **4)** data and specimen are now accessible on the Provenance Platform for research use within the scope of consent. **5}** the need arises: the patient is diagnosed with tumors and tumor specimens become available through the TREC@TAMU Cancer Prevention Registry and Repository research network with a cancer center the patient is referred to. **6)** patient provides a modified consent for tumor specimens (if available) to be added to the clinicogenomic registry. **7)** a specific research project identifies the patient for inclusion and digitally pings for project specific research consent appropriate for inclusion in a retrospective blood liquid biopsy cancer screening validation study. **8)** Modified consent is entered on the digital ledger and digital permission is effected through smart contract for a commercial user, participant may receive a digital reward for participation. **9)** Patient wishes to revoke all consent for research on their specimen, medical data, and genetic data in their portal on the Provenance Platform. **10)** the data associated with that patient is rendered as null in all successive queries.

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The registries associated with the FHS and the Bone Sarcoma Registry are case studies that show that predictive science requires patient data and patient participation. Participants, biospecimens, or individual clinical cases might be added to a study to build composite cohorts from multiple predecessor cohorts with information technology permitting this within a compressed timeframe. In early years of the FHS cohort, it was estimated it would take 20 years to accession enough coronary heart disease cases for a statistically significant subpopulation for common analysis strategies. (21) In many instances, inclusion of cases under the guise of broad, prospective patient consent and deidentified case level data may support study objectives and not require prospective enrollment or participation in a study. Such is the case with many of the subsequent studies of the FHS cohorts, thus enabling investigators to assemble a subpopulation cohort to test novel hypotheses or explore novel cardiovascular disease biomarkers. Biospecimens with robust clinical phenotyping and appropriate consent and documentation of provenance theoretically enable development of an FHS-like cohort using RWD in a much shorter period. In the present, computational science has an increasingly important role in improving care through information. (2) Artificial intelligence models increasingly underlie clinical decision-support (22) and have great potential to simplify the increasing complexity of medical practice. Artificial intelligence technology has also been qualified to build external control arms in silico. (23-25) The training of models that provide personalized and precision healthcare perspectives will require datasets that transcend organization boundaries. In many respects, the Framingham risk score was an early application of a predictive qualitative model trained by a retrospective data set. The emergence of RWD sources and machine learning technologies have great potential to accelerate and create more dynamic examples of the Framingham risk score.

Many health systems and research centric institutions have lagged industry in evolving and adapting practices to enable the assembly of population scale data sets, especially across organizational boundaries in federated collaboration models. The clinicogenomic registry presents data governance challenges that impede the flow of case level genomic data and case level clinical annotation from institutions to users such as policy agencies, researchers, drug developers, insurers, and the healthcare industry. Under current US policy frameworks, privacy and compliance are the primary constraints to constructing population scale, case-level data sets. There are two common workarounds: 1) de-identify the data to share it (this has been done at scale (10) albeit primarily in populations of European decent), 2) obtain broad and open-ended research authorization from research participants and research subjects. However, de-identified comprehensive case level data, particularly including specimens and DNA sequences, render the statutory concept of privacy difficult to impossible to preserve with high confidence when sharing data. These workarounds fall short in engaging populations where health disparities are greatest.

In the long term, the TREC@TAMU Registry will be a living laboratory built for RWD and RWE in cancer prevention leg of the patient journey, using digital technologies to enable a more dynamic model of patient centric data governance. Trust, patient agency, and data governance are currently major impediments to collection and curation of medical records and patient reported outcomes for many of the populations experiencing socio-economic, environmental, and occupational determinants of health disparities in cancer. We have implemented a Provenance Platform to digitize governance and address impediments related to longitudinal registry development. The PROVENANCE data platform became operational in July 2024, and includes dictionaries for medical record data, genomic data, coding for obscuring HIPAA identifiers/de-identification of data sets, and informed consent metadata.

The Provenance Platform will enable a staged transition toward dynamic, electronic, patient-centric clinic data governance. The TREC@TAMU Registry is modeled after the clinicogenomic approaches used elsewhere but adding a longitudinal view of patient outcomes and the underlying economics of healthcare utilization. TREC@TAMU Registry is intended to be a resource of myriad future hypothesis driven studies utilizing subsets of the data in the TREC@TAMU Registry.

5. Inclusion and Exclusion Criteria:

Inclusion
We plan to recruit as many participants as possible from the Texas A&M affiliated Family Medicine Clinics.

Participants will be:

- 18 years of age and older, and,
- People participating in the Cancer Prevention and Research Institute of Texas (CPRIT) A coordinated cancer screening research program in Bryan and Navasota Family Medicine Clinics (**Figure 2**), and,
- People with COPD, liver disease, cervical intraepithelial neoplasia (CIN) lesions, having had a colonoscopy or a low dose computed tomography (LDCT) lung scan or cervical exam in the last 12 months or scheduled for one, and,
- Able to give and comprehend the consent process, and,
- Able to consent to donate blood and urine samples, genetic material through buccal swabs for future research, and,
- Able to understand that their specimens, health record, and changes in health status will be followed for a five-year period and shared in deidentified form with the research community, and,
- All sexes and gender identities.

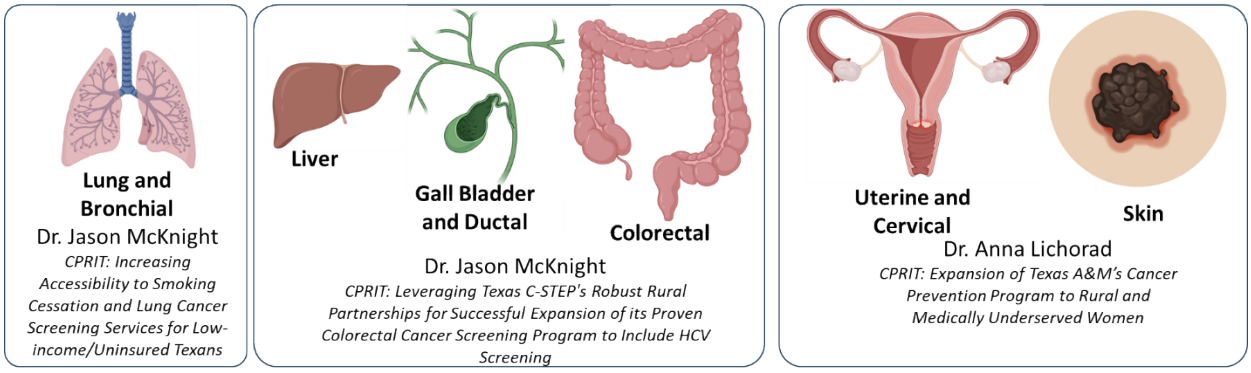
Exclusion

- Declines to participate or interact with staff/share their medical status.
- A diagnosis of Alzheimer's disease or related dementias in a medical record indicates a progressive, debilitating condition that impairs memory, thought processes, and functioning Individuals who are unable or unwilling to provide consent will be excluded.

As noted, the TREC@TAMU Registry will recruit as many participants as possible. The estimated enrollment in five years is expected to be 2500, but we will not limit recruitment if we exceed that number.

6. Geographic Reach of Research Activities:

Patients will be referred to the TREC@TAMU Registry from the Texas A&M Family Medicine Clinics located in Bryan and Navasota and the CPRIT Cancer Screening programs (Figure 2). The Bryan and Navasota programs have common providers and share the same medical record. Both sites participate in CPRIT Cancer Screening programs. Recruitment and consenting of patients will be conducted onsite or via a telemedicine encounter at a Texas A&M Health Family Care Clinic (Bryan and Navasota) or the Texas A&M Interprofessional Pharmacogenomics Clinic in Bryan (2). Clinical research staff that are a part of the practice plan workforce will scan appointments for TAMU Health patients meeting risk criteria. Additionally, patients coming in for cancer screening services under the CPRIT programs in Figure 2 will be



PI	Title	Cancer Site	Link
Anna Lichorad	Expansion of Texas A&M'S Cancer Prevention Program to Rural and Medically Underserved Women	Breast, Cervix Uteri, Colorectal, Gallbladder, Leukemia, Skin, Uterus	PP200070 — Cancer Prevention and Research Institute of Texas (state.tx.us)
Jason McKnight	Leveraging Texas C-STEP's Robust Rural Partnerships for Successful Expansion of its Proven Colorectal Cancer Screening Program to Include HCV Screening	Colorectal, Gallbladder, Liver and Intrahepatic Bile Duct	PP220013 — Cancer Prevention and Research Institute of Texas
Jason McKnight	Increasing Accessibility to Smoking Cessation and Lung Cancer Screening Services for Low-income/Uninsured Texans	Lung and Bronchus	PP210027 — Cancer Prevention and Research Institute of Texas (state.tx.us)

Figure 2 CPRIT Cancer Screening Programs

approached to participate. Data will be stored on the cloud (Amazon Web Services or BurstIQ) as described in section 9. Long term storage of specimens will be at the Texas A&M Institute of Bioscience and Technology (IBT) as described in section 9. Following immediate collection of samples, specimens will be temporarily stored at the Family Medicine Clinic in a dedicated cold storage refrigerator under the supervision of trained staff at 4°C until transport for temporary storage at the Reynolds building on the TAMU College Station campus by staff with appropriate training. Transport from the clinic to Reynolds will comply with the guidelines established in the TAMU Biosafety Manual for Risk Group 2. Samples will be processed and aliquoted into smaller quantities in a laboratory with biocontainment level 2 and then placed in liquid nitrogen tanks before shipping to the IBT in Houston for long-term storage in liquid nitrogen, as outlined in the protocol addendum. Shipment to Houston will be performed weekly by a FedEx on dry ice per their guidelines: Quality of life (QoL) surveys will be administered electronically such that participants can submit them online through an encrypted link to the patient portal for the TREC@TAMU Registry research data warehouse described in section 9.

All participating sites (Navasota and Bryan locations of TAMU Family Health Clinics) will have the most current version of the Protocol, informed consent documentation, and HIPAA authorization. All planned modifications to the Protocol will be communicated to the various primary care sites and implemented upon IRB approval, as required. All engaged participating clinics will safeguard data as required by their local information security policies and in compliance with HIPPA, CPRIT, and NIH Genomic Data Sharing (GDS) Policy. All non-

compliance with the study protocol or applicable requirements will be reported in accordance with TAMU HSPO policy, IRB approval, and as specified in the Protocol.

7. Study Timelines:

The duration of individual participation in the TREC@TAMU Cancer Prevention Registry and Repository is 5 years after the enrollment encounter (**Figure 1**) for follow-up data collection from the electronic medical record (EMR), biannual quality of life surveys, and outcome analysis. Patients will also consent to share the specified data from their EMR for the *1 year prior* to the enrollment date visit. Sometime prior to a patient reaching the 5-year milestone, they will be contacted with a digital invitation to participate in the Provenance Platform using BurstIQ which involves the use of blockchain tools and tokenization (turning a meaningful piece of data into a random set of characters without value if breached) to bring enhanced consent, trust, control, and transparency to the longitudinal linkage of health data and genomic data. The Provenance platform enables TAMU users to utilize the patient-centric (and IRB approved) data governance tools to document patient consent at the case level for use 1) collection of their EMR data, 2) use of their remaining specimen in the TREC@TAMU Cancer Prevention Repository, 3) sharing

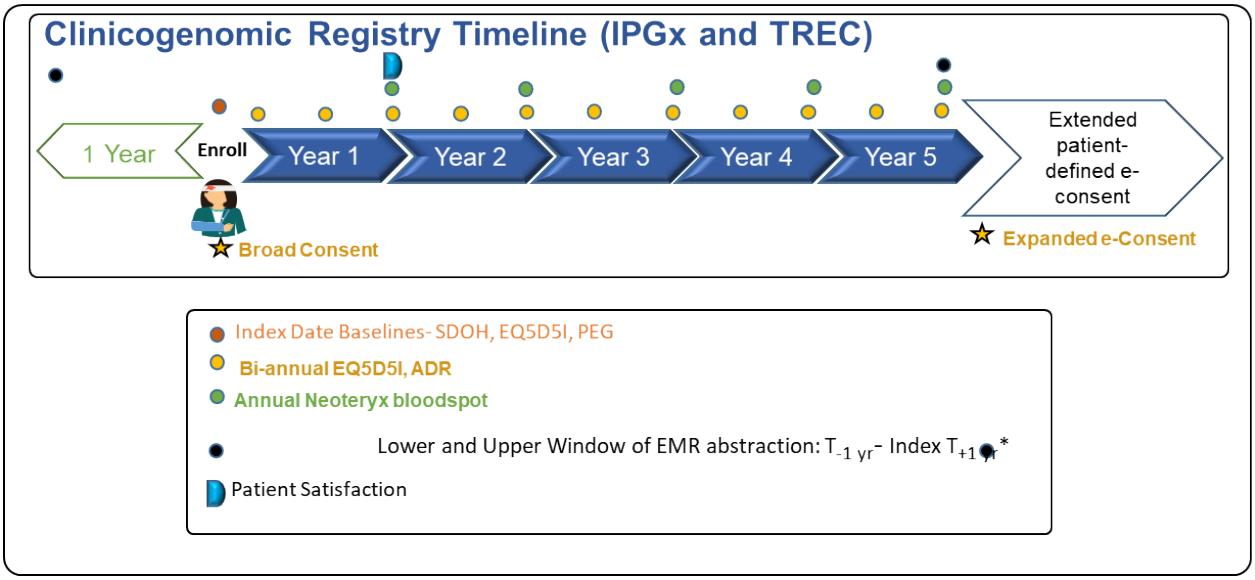


Figure 3. Timeline of participation, data collection, data accession, and extension of the TREC@TAMU Cancer Prevention Repository.

of their genetic data for research use. Consent for specimen use and further EMR data or claims data collection shall end at 5 years in the absence of an affirmative consent extension on the Provenance Platform. Use and analysis of data collected in this 5-year window of data collection will be available for analysis until 2044. Thus, data analysis within the parameters of the patient consent is expected to be ongoing until 2044. However patient case-level data from the electronic medical record will not be accessed after five years unless the patient opts into an extended and expanded consent Provenance Platform. The period of consent for analysis (until 2044) will allow the research team (listed investigators and people under their supervision) to engage in probabilistic or deterministic matching of claims data from commercial claims databases (like the All-Payer Claims Database or TX Medicaid databases) to assess their healthcare utilization and health outcomes that can be gleaned from health data. Sharing of

clinical data and specimens are clearly voluntary, but if the patient declines to share both, they will be excluded from the TREC REGISTRY. They, however, can still participate in other care protocols including the CPRIT cancer screening program they may be interacting with.

8. Procedures Involved & Variables and Outcome Measures:

Sample collection will be conducted by a licensed nurse or trained phlebotomist with standard precautions, surface sterilization, and sterile venipuncture. Approximately 35 mL of blood will be collected at enrollment. Subsequent blood collection will entail 10 μL microsamples using the Mitra Device. Samples will be stored at 4°C for a maximum of 6 hours and then processed in a biocontainment level 2 environment in the Reynolds Building in College Station, aliquoted, and frozen in a dedicated liquid nitrogen tank for transport to the IBT Biobank facility in Houston.

Collected in every patient at enrollment:

EQ-5D-5l with pain visualization (26) will be administered to every patient in the registry at every visit to the clinic and at least every 6 months for 5 years after enrollment either in-clinic (on the initial visit and if and when they visit the clinic) or electronically (every 6 months, see **Figure 3**) through an encrypted link to the patient research portal.

- Social determinants of health (SDOH) (EMR).
- Hospital admissions (abstracted from EMR, from questionnaire).
- Comorbidities (abstracted from EMR).
- Healthcare utilization (case level claims data abstracted from eCW or the All-Payer Claims Database).
- Four 8.5 mL (PAX RNA, PBMC, Plasma) and one 2.5 mL (PAX DNA) will be collected from a single needle stick, by phlebotomy-trained clinical staff.
- A urine sample.
- 2 buccal (cheek) swabs or saliva samples will be collected.

Self-collected in every patient biannually upon request:

- digitally administered EQ-5D-5L survey to gather data on health status and any significant changes.
- A home-based 10 μL patient sample collection of dried bloodspots (Neoteryx Mitra micro sampling) for additional analysis of blood chemistry. Subjects will be instructed to mail this sample to Texas A&M (at our expense) on the day of blood drop collection.

At the discretion of research team, per criteria:

- Georges' quality of life scale for patients with diagnosed COPD (27)
- Quality of Life (DQOL) questionnaire for patients with diagnosed diabetes (28)
- DSM-IV for patients with diagnosed depression (29)

We will not use all these instruments in any given patient, rather discretionary surveys will be collected as appropriate at scheduled check-ins. The TREC REGISTRY may collect relevant medical history that is not included the medical record at Texas A&M, which they can submit via a secure and encrypted portal online or when then visit a Texas A&M clinic or research site.

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There is no specific hypothesis being tested under this protocol. Data will be accessed for future studies approved by the TREC@TAMU Cancer Center of Excellence Leadership, subject to acceptable the data and specimen governance process in section 9

Table 1. Biospecimen collection for Registry.

Collection Media	Sample Type	Clinical Use Regulatory Context	Use Case	BioAnalytic Vendor	Bioanalyte	Bioanalysis Method	Methodology Protocol Reference	Storage	Aliquot
Sterile Sample Cups	Urine	LDT	Biobank	TBD	TBD	TBD		liquid N_2	@500 µL
Cotton Tipped Applicator	Buccal Swab	LDT	Biobank	TBD	TBD	ProbeArray		liquid N_2	Whole
Neoteryx Mitra	dried bloodspot	LDT/RUO	Biobank	TBD	TBD	TBD	Shen, X., Kellogg, R., Panyard, D.J. *et al.* Multi-omics microsampling for the profiling of lifestyle-associated changes in health. *Nat. Biomed. Eng* (2023).	liquid N_2	Whole
Vacutainer Purple top	Plasma, PBMC	RUO	Biobank	TBD	TBD Exosomes	TBD NGS; RNASeq; Proteomics	Posevitz-Fejfár, A., et al. (2014) "Effects of blood transportation on human peripheral mononuclear cell yield, phenotype and function: Implications for immune cell biobanking," PLoS ONE 9(12): e115920. doi:10.1371/journal.pone.0115920 Du K, Sun X, Tang X, et al. Effects of storage temperature and time on quality of plasma exosomes extracted by ExoQuick. Chinese Journal of Cellular and Molecular Immunology. 2020 Apr;36(4):330-336. PMID: 32519671.	liquid N_2 liquid N_2	@ 100 µL remainder @1000 µL x 1;
PAX RNA	Blood RNA	RUO	Biobank	TBD	TBD		Campbell R, Marmar CR, Hammamieh R, Jett M. Gene expression profiling of whole blood: A comparative assessment of RNA-stabilizing collection methods. PLoS One. 2019 Oct	liquid N_2	@200 µL x all
PAX DNA	ccfDNA	RUO	Biobank	TBD	TBD		Voss T, Ullius A, Schönborn M, Oelmüller U (2021) Sensitivity assessment of workflows detecting rare circulating cell-free DNA targets: A study design proposal. PLOS ONE 16(7): e0253401.	liquid N_2	
Vacutainer CPT Red/Green	PBMC	RUO	Biobank	TBD	TBD	RNA seq	Science of Blood for Peripheral Blood Mononuclear Cell (PBMC) Functional Applications. *Curr Pathobiol Rep* **7**, 17–27 (2019).	liquid N_2	@200 µL x all
BD P800 Blood Collection System	Stable Plasma Proteins	RUO	Biobank	TBD	TBD	Proteomics	Wynendaele E, De Spiegeleer B. Influence of Blood Collection Methods and Long-Term Plasma Storage on Quorum-Sensing Peptide Stability. ACS Omega. 2020 Jun 22;5(26):16120-16127.	liquid N_2	@200 µL x all
Vacutainer Yellow Top	Whole Blood	RUO	Biobank	TBD	TBD	TBD		liquid N_2	@500 µL x all
Cotton Tipped Applicator	Buccal Swab	RUO	Biobank	TBD	WGS/WES	NGS		liquid N_2	
Thermo Scientific™ SpeciMAX™ Saliva Collection Kit	Saliva	RUO	Biobank	TBD	TBD	TBD		liquid N_2	

LDT =Laboratory Developed Test

RUO=Research Use Only

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9. Biobanking and Clinicogenomic Protocol- Specimen and Data Management:

- See Addendum

10. Data Analysis:

Because this is a registry and biobank program, data analysis plans will be formulated in the future as testable hypotheses arise and are addressable using the data and clinical cases enrolled in TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository at the time.

Analyzed data (aggregated and deidentified data) may be published in accordance with informed consent when an analysis meets the standards for peer-reviewed publication. Raw case level data will not be openly published with the exception of genomic data to be shared in public repositories in accordance with NIH guidelines for sharing such data using practices we have previously published.(10, 11) To be clear, sharing of genomic data in NIH sponsored repositories will involve limited and deidentified clinical annotation. The TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository is expected to seek future funding from the NIH and CPRIT. Express patient consent will be sought separately for case reports that might be published.

Data from Wole Genome Sequencing will be uploaded to TAMUs AWS cloud enclave. WGS sequencing will be conducted on Illumina HiSeq at 30X coverage by the company that has done single cell sequencing for the TREC single cell core, Admera. **WGS data will be for research use only** and will not at any point be reported providers. These data will only be used as specified in the section on research data government in the biobanking addendum. Incidental findings will not be shared with participants. WGS data will only be accessible to the investigators listed herein or third-party research collaborators in accordance with IRB oversight of future proposed studies. Consent forms will be signed with a wet ink signature on a printed consent form or as a secure digital signature on the PDF file using the Adobe Sign function and attached to the PROVENANCE and WGS metadata using a script developed in the BurstIQ platform.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

11. Participant Safety:

Participation in the TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository poses minimal risk. The risks to subjects are of a low likelihood of harm and low magnitude of harm, limited to privacy risks.

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It is expected that most study participants will generally remain engaged with the primary care clinic from where they were referred. Clinical documentation will be monitored for consistency with the protocol by TREC research staff during enrollment, and as needed to ensure complete and quality documentation of registry associated outcomes data.

Data Safety Monitoring Plan.

Clinical study staff and investigators, under the supervision of the PI will review all data quarterly for data completeness and accuracy as well as protocol compliance. Drs. Ramos, Neal, and Silva will review the safety and progress of the study quarterly. Study reports, including patient recruitment, retention/attrition, will be produced following each of the quarterly reviews to ensure faithful adherence to the protocol.

12. Withdrawal of Participants:

It is not expected that the study team would need to remove a participant from the study. Attrition will only occur when a participant revokes their consent. Upon revocation of consent, the subjects' alphanumeric identifier will be reassociated with specimens, samples will be retrieved, and destruction will be documented and disposed of appropriately. Their clinical annotation data will be rendered unavailable on the Provenance Platform using existing functions of the BurstIQ data governance system.

15. Risks to Participants:

Risks and inconveniences involved:

- Time spent in clinic or responding to study related information requests.
- Phlebotomy, along with its associated risks ranging from ecchymoses, hematoma, nerve injury, infection. PL

Key
Probability P | Magnitude M | Duration D | Short S | Low L | Moderate M Extensive E

17. Potential Benefits to Participants:

Benefits for participating patients

The registry is designed in alignment with the principles of *Standards in the Conduct of Registry Studies for Patient-Centered Outcomes Research – Report to PCORI* [11].

We seek to understand how and when cancer risk becomes clinically actionable. This knowledge is unlikely to immediately evolve into clinical, care related benefits for participants in the present, but can benefit like patients in the future. The TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository has a high likelihood of helping a participating patient in the future by enabling matching of them with appropriate clinical trials if cases when cancer is developed.

Benefits of the study for the healthcare and scientific communities

The potential benefit and reason for requesting the TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository is to develop a cancer screening registry model that can account for the important environmental, occupational, genetic, and socio-economic determinants of cancer disparities. We might understand the impact of comorbidities such as obesity, cardiovascular disease, depression, or cognitive problems in cancer. These phenomena are major drivers of high healthcare utilization, with known and unknown genetic and social determinants. This registry strategy enables the collection of data underlying these factors and aids in understanding the scope and magnitude of these factors in cancer risk and outcomes following a cancer diagnosis. It can help inform more holistic clinical decision-making in cancer screening and cancer prevention and improve policies that can improve the quality of life (greater agency in managing cancer risk) and clinical outcomes for patients (improved preventive practices).

As the enrolled population and our database grow, we might identify novel blood biomarkers for screening that empower chemoprevention development and improve risk management through holistic cancer prevention programs. Our informed consent form, collaborative structure, and contracts will thoughtfully account for the best way to allow for compliant and deidentified sharing of the data collected under this protocol with the clinical and scientific communities of practice addressing an information gap in cancer prevention upstream of peer-reviewed publication.

18. Vulnerable Populations:

People with cancer may experience some degree of cognitive impairment, either associated with cancer, cancer treatment (36), or a somewhat independent covariate (37). The impacts of cognitive impairment are poorly understood and warrant study (36-38). Recruitment (40) and exclusion (41) of people with cognitive impairment are both ethically fraught approaches in clinical research. Patients with cognitive decline will be excluded per revised the exclusion criteria.

No minors, no prisoners will be recruited into this study.

19. Sharing of Results with Participants:

While the TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository is likely to attract industry partners willing to perform multi-omic bioanalysis at low or no cost, it is quite complicated to share that information with patients or physicians unequipped to interpret it. Most bioanalytic work TREC@TAMU Cancer Prevention Clinicogenomic Registry and Repository will not be conducted in a CLIA compliant setting. Consequently, there are no immediate plans to report findings back to patients as this would be highly impractical to achieve in a compliant, responsible, and ethical manner without significant investment in genetic and medical counseling, access to CLIA compliant testing, and highly specialized medical expertise. This is the expectation that will be set in the informed consent form.

20. Setting:

Texas A&M University. Research participants will be recruited from the patients referred to the primary care clinics of Texas A&M Health (Bryan and Navasota). Participants will be recruited

that have elevated risk of cancer, with priority on patients receiving cancer screening under CPRIT cancer prevention programs at Texas A&M. The patient consent will be performed by clinical or research staff at the clinic site designated by Texas A&M (or via telemedicine when that is the format of care delivery for that patient) but some bioanalytic, computational sample, and data analysis will occur offsite. Please see section 6 above regarding geographic distribution of research activities.

No community advisory review board other than what is customary for Texas A&M is considered currently. If the decision is made that a community advisory board is indicated, members might include those who represent the referring physicians, a community cancer patient advocate, and CPRIT designees.

21. Personnel and Resources Available:

Dr. Ramos MD, PhD, PharmB- Principal Investigator
Dr. Ramos is a licensed physician-scientist with training and certifications in clinical pharmacology, toxicology, forensic medicine, pulmonary and integrative medicine. He is an inductee in the National Academy of Medicine and a Lifetime Associate of the National Academy of Sciences. He is a tenured professor at Texas A&M Health Science Center. Dr. Ramos also is Associate Vice President at the Texas A&M University Health Science Center and Assistant Vice Chancellor for Health Services for the Texas A&M University System. Previously, Dr. Ramos was founding director of the University of Arizona Health Sciences Center for Applied Genetics and Genomic Medicine and chief medical and scientific officer of the Arizona Precision Medicine Initiative and has been instrumental in developing precision health strategies, diagnostic technology, and clinical data strategies to improve health care delivery. Dr. Ramos will be the Principal Investigator and be the ultimate decision-maker and have supervisory authority for the conduct of the protocol and management of the Registry. Dr, Ramos will also participate in data analysis and future research strategies and collaborations enabled by the Registry.

Dr. Gabriel Neal MD, Clinical Co-Investigator
Dr. Gabriel Neal is board certified in Family Medicine and received his MD from the University of Oklahoma in 2001. Dr. Neal first joined the Department of Family Medicine in 2008 and is faculty in the Texas A&M Family Medicine Residency. Over the past decade, he has taught in numerous pre-clinical and clinical courses for the College of Medicine. He is the Family Medicine Clerkship Director for the A&M Integrated Medicine Program at the Bryan-College Station College of Medicine Campus. His teaching illuminates applied evidence-based medical care and ethics. He was awarded Clinical Faculty Preceptor of the Year in 2011 and Outstanding Faculty in Family Medicine in 2019. Dr Neal holds several roles: Department Head, Primary Care and Rural Medicine; Clinical Professor; Chief Clinical Officer, Texas A&M School of Medicine; Family Medicine Clerkship Director, Texas A&M Integrated Medicine Program; Faculty, Texas A&M Family Medicine Residency and is involved in several clinical research projects. Dr. Neal will assist in the recruitment and consenting of patients who might be eligible for, and benefit from participation. Dr. Neal will also participate in data analysis and future research strategies and collaborations enabled by the Registry.

Rick Silva PhD, MBA Co-Investigator
Dr. Rick Silva is Executive Director Executive Director, Clinical | Translational | Industry Collaborations at Texas A&M Health Science Center. In addition, he holds an academic appointment as Assistant Professor of Translational Medical Sciences in the Texas A&M Institute of Biosciences and Technology. He has scientific training in physiology and

neuroendocrinology, with significant experience in implementing and managing clinical and translational research programs, including dimensions of regulatory science, diagnostic technology development, cohort strategy, and clinical data strategies in clinical translational collaborations among academic medical centers and industry. Dr. Silva will serve as coordinator of the Registry and implement its data strategy with the Family Medicine Clinics. Dr. Silva will also participate in data analysis and future research strategies and collaborations enabled by the Registry.

Fen Wang PhD, Co-Investigator
Dr. Wang earned his Bachelor of Science in Microbiology and Master of Science in Cell Biology degrees at Xiamen University, and his Ph.D. in Biochemistry and Cell Biology at Clarkson University at Potsdam, NY. He undertook postdoctoral studies for Cancer Research and Nutrition at Texas A&M University. Dr. Wang joined IBT as Assistant Professor where he was promoted to Associate Professor with tenure and Professor with tenure at the Texas A&M University System Health Science Center. Dr. Wang will serve as coordinator of the Biobank. Dr. Wang will also participate in data analysis and future research strategies and collaborations enabled by the Registry.

Marcia Ory PhD Co-Investigator
Is a Regents and Distinguished professor for the Department Environmental and Occupational Health at the Texas A&M School of Public Health. With a long-standing interest in aging and public health, Dr. Ory is the founding director of the university-wide Center for Population Health and Aging, chair of the SPH Health and Wellness Committee and academic partner for the Community Research Center for Senior Health with Baylor Scott and White Health. She chairs the HSC Opioid Task Force and is working with an interdisciplinary cross-campus group to foster innovative research, education and service projects emanating from the health Sciences Center. She co-leads Healthy Texas, a new system-wide effort to examine strategies for promoting health and wellness for all Texans. Dr. Ory was honored for her sustained commitment to her research, receiving The Association of Former Students' Distinguished Achievement Award in Research from Texas A&M University for 2021. Prior to coming to Texas, A&M University, Dr. Ory spent 20 years in federal service as chief of Social Science Research on Aging in the Behavioral and Social Research Program at the National Institutes of Health's National Institute on Aging. Dr. Ory received her Bachelor of Arts in sociology and psychology from the University of Texas, Master of Arts in sociology and human development from Indiana University, doctorate in family studies and human development from Purdue University and Master of Public Health in chronic disease epidemiology and behavioral sciences from John Hopkins University Bloomberg School of Public Health.

22. Prior Approvals

IRB approval of this registry protocol, and amendments hereto, will be obtained from Texas A&M IRB as the IRB of record, and any IRB of future collaborative health systems and research institutions.

23. Confidentiality

- *Where and how data or specimens will be stored locally?*

  At the point of enrollment, alpha-numeric specimen identifiers will be generated onsite using a HIPAA compliant true-randomizer like the Global Unique Identifier (GUID Tool). Keys will be assigned to a designated data steward or honest broker, barcodes

encoding alpha-numeric specimen identifiers will be linked to all records using BarTender software (Seagull Scientific), and specimens will be labeled with barcodes for long term storage.

- *How long the data or specimens will be stored locally*?
  Five years, unless the patient consents to an extended participation period **(Figure 3)**

- *Who will have access to the data or specimens locally*?

  Investigators and their designated staff will have access to the specimens locally. Researchers with approved protocols will have permissioned and password protected access to the TREC@TAMU Cancer Prevention Registry and Repository Research Data Warehouse.

- *Who is responsible for receipt or transmission of the data or specimens locally?*

  A clinical research staff member at the TAMU clinic will hand deliver or ship specimens to IBT via qualified courier. Researchers with approved protocols will have permissioned and password protected access to the TREC@TAMU Cancer Prevention Registry and Repository Research Data Warehouse through the Provenance Platform.

- *How data and specimens will be transported locally?*

  Local transport of specimens from the Family Medicine Clinic in Bryan to the IBT in Houston by a qualified courier. Clinical data will be stored in the eCW EMR on the cloud. This is 2015 Edition compliant and has been certified by an ONC-ACB in accordance with the applicable certification criteria adopted by the Secretary of Health and Human Services. Deidentified research data will be stored on the cloud (AWS).

24. Provisions to Protect the Privacy Interests of Participants:

We will obtain written informed consent for participation, interaction, and collection of medical data from a patient. No participant will be required to interact with anyone or share personal information with anybody other than their care team providers at their clinic and the TREC@TAMU research staff. See exclusion criteria about unwillingness to participate or consent. Participants will be made to feel at ease through open communication with TREC@TAMU staff and explanation of data use and data sharing and limitations thereof in the informed consent form. Participants should feel no more or less uncomfortable than when presenting to any general medicine clinic. There is nothing invasive beyond giving urine, blood, and a buccal swab. Discomfort about sharing DNA is addressed in the informed consent form and consultation, the consent for future use of specimens or forward-looking collection of data from the participant's ongoing medical record will be revocable in the Provenance Platform patient portal. Participants will be advised that their information will always be handled confidentially. Authorized members of the research and care team will have a password so that they can access the secured electronic health record and TREC@TAMU Registry Research Data Warehouse.

25. Compensation for Research-Related Injury

N/A

The registry is only intended to collect data and specimens. While observational outcome data will be collected, this protocol is not intended to evaluate or propose any experimental intervention.

26. Economic Burden to Participants

Patients are responsible for transportation to the clinic as they normally do for routine care. No elements of the patient encounter with the TREC@TAMU protocol will trigger reimbursement requests from insurance. The costs of the research use for blood testing will be covered by TREC research funds or provided cost-free by research partners. Cancer screening is covered by other CPRIT grant funds or insurance, not this study.

27. Recruitment Methods

(*Describe when, where, and how potential participants will be recruited*.)

We will work with the Texas A&M Health Family Medicine clinics (Bryan and Navasota) to refer participants who may meet criteria and benefit from cancer screening. The TREC@TAMU will be open to any Texas A&M family medicine, primary care clinics or specialty clinics that choose to refer their patients to the TREC@TAMU Registry program. Research recruiting will be performed by Texas A&M Family Medicine staff and qualified TREC@TAMU clinical or research staff.

Three recruitment collaterals are attached:

1) A telephone script.
2) A recruitment email.
3) A recruitment brochure.

Subject compensation not currently planned.

28. Consent Process

We will obtain consent in a basic informed consent form [**Appendix 1**].

An individual team member authorized by the principal investigator and IRB can obtain consent from potential participants. However, regardless of who is obtaining consent, the Principal Investigator is responsible for ensuring the correct procedures are carried out.

- How will consent for Spanish-speaking participants take place?

  To ensure that Spanish-speaking participants are effectively included in the study, it is essential to implement a clear and respectful process for consent and communication throughout the research.

  Staff Requirements

1. Bilingual Staffing: Where available we will utilize study staff members who are fluent in Spanish to communicate directly with participants. This will promote a comfortable environment and ensure accurate information exchange.

2. Qualified Interpreters: If bilingual staff members are unavailable, we will engage qualified interpreters who are experienced in medical contexts and culturally competent from an existing service used to interpret for care to Spanish speaking patients. These interpreters are currently available through the Family Medicine Clinic and will assist in all interactions with Spanish-speaking participants.

Consent Process

1. Informed Consent Documents: All consent documents have been be translated into Spanish, ensuring they are easily understandable and culturally relevant. These documents will be available to participants prior to consent discussions.

During the consent process, staff or interpreters will present the information in Spanish, allowing participants to ask questions and seek clarification as needed. Before obtaining consent, we will ensure that participants fully understand the study's purpose, procedures, risks, and benefits.

2. Documentation: We will document the consent process carefully, noting the use of interpreters when applicable, to maintain compliance with ethical guidelines and ensure transparency.

- Where will the consent process take place?

At the designated Family Care Clinic or IPGx (Interprofessional Pharmacogenomics Clinic), or virtually in all instances when telemedicine services are being provided to subjects in and out of Brazos Valley. In the case of virtual consent, a verbal recorded consent after reading the ICF will be obtained and backed up by an online digitally signed version of the informed consent form. The digital consent (eConsent) process will be set up using Adobe Acrobat Sign and validated to comply with FDA's 21 CFR Part 11 regulatory requirements. The study team will manage digital consent metadata for electronic medical record data and genomic data.

- Any waiting period available between informing the prospective participant and obtaining the consent?

It would be at the discretion of the participant to consent when they decide they are comfortable enrolling in the study.

- Any process to ensure ongoing consent?

No. Participants will be advised they are consenting for 5 years of prospective and 1 year of retrospective data collection **(Figure 3)** and may end their participation at any time either via email or phone. Revocation specifically would apply to consent for future use of specimens or forward-looking collection of data from the patient's ongoing

medical record. Revocation will be digitally enforced in the Provenance Platform patient portal. Any data in the Registry up to the date of revocation cannot currently be forgotten or removed. Specimens would be removed from the registry and destroyed upon revocation of ongoing consent. After 5 years, participants would need to affirmatively extend their consent to continue to participate in the registry.

- The role of the individuals listed in the application as being involved in the consent process.

  The role of the PI or Clinical Co-Investigator would include answering an enrollee's questions, discussing risk-benefit options and alternatives, reporting back to the investigator team, and answering questions in support of regulatory compliance.

- The time that will be devoted to the consent discussion.

  As much as needed. It is estimated that a half-hour will be sufficient.

- Steps that will be taken to minimize the possibility of coercion or undue influence.

  We will make it clear at the outset and in printed materials that TREC@TAMU Registry is completely voluntary and unrelated to the receipt of health care. The consent form will emphasize this point. Non-participation will not in any way jeopardize the patient's relationship with their doctor, provider, or any other individual. No financial inducements will be used.

- Steps that will be taken to ensure the participants' understanding.

  Participants will acknowledge in writing they understand what their participation in the study entails.

Waiver or Alteration of Consent Process:

NA.

Participants who are not yet adults (infants, children, teenagers)

Minors excluded. This study will focus on adults.

Cognitively Impaired Adults

Please refer to inclusion/exclusion criteria.

Adults Unable to Consent

Please refer to inclusion/exclusion criteria.

30. Process to Document Consent in Writing:

See **Appendix 1- Informed Consent Form**

31. Drugs or Devices:

Not relevant

32. Waiver of IND or IDE

Not relevant

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